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Family History of Alcohol Use Disorders and Neuromaturation: A Functional Connectivity Study with Adolescents

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

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The Dissertation of Andrea D. Spadoni, M.S. is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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PUBLICATIONS

Peer-Reviewed Articles

1. Fryer, S.L., Tapert, S.F., Mattson, S.N., Paulus, M.P., **Spadoni, A.D.**, & Riley, E.P. (2007) Prenatal alcohol exposure affects frontal-striatal BOLD response during inhibitory control. *Alcoholism: Clinical and Experimental Research 31*:1415-24.
2. **Spadoni, A.D.**, Schweinsburg, A.D., & Tapert, S.F. (2008) Family history of alcohol use disorders and spatial working memory in adolescents. *Alcoholism: Clinical and Experimental Research 32*: 1135-45.
3. Fryer, S.L., **Spadoni, A.D.**, Frank, L.R., Nagel, B.J., Schweinsburg, A.D., Theilmann, R.J., & Tapert, S.F. (2008). Microstructural integrity of the corpus callosum linked with neuropsychological performance in adolescents. *Brain and Cognition 37*: 225-33.
4. Squeglia, L. M., **Spadoni, A. D.**, Infante, M. A., Myers, M. G., & Tapert, S. F. (in press). Initiating Moderate to Heavy Alcohol Use Predicts Changes in Neuropsychological Functioning for Adolescent Girls and Boys. *Psychology of Addictive Behavior*s.

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1. Fryer, S.L, McGee, C.L., **Spadoni, A.D.**, & Riley, E.P. (2006). Influence of alcohol on the structure of the developing human brain. In M.W. Miller (Ed), Brain Development. Normal Processes and the Effects of Alcohol and Nicotine. Oxford University Press: New York.
2. Tapert, S. F., Pulido, C., & **Spadoni**, A. (2007). Substanzgebrauch und Gehirnfunktion bei Jugendlichen (*Substance use and brain function of adolescents*). In K. Mann (Ed.), Jugendliche und Suchtmittelkonsum: Trends, Grundlage, Maßnahmen *(Youth and Drugs:Trends, Basics, Policies).* Lambertus Verlag: Freiburg, Germany.
3. **Spadoni, A.D.**, McGee, C.L., Fryer, S.L., Riley, E.P. (2007). Neuroimaging and fetal alcohol spectrum disorders. Neuroscience and Biobehavioral Reviews 31(2):239-45.

Abstracts and Posters

1. Hanson, K. L., **Spadoni, A. D.,** Gorlick, A. S., Medina, K. L., Nagel, B. J., Norman, A. L., & Tapert, S. F. (2008, June). Affective and behavioral correlates with hippocampal volumes in adolescents with and without a family history of alcoholism. Poster presented to the Research Society on Alcoholism Annual Meeting, Washington, D.C. (abstracted in Alcoholism: Clinical and Experimental Research 32, 104A).
2. Squeglia, L.M., **Spadoni A.D.**, Gorlick A.S., Norman A.L., Eberson S.C. & Tapert S.F. (June, 2008). Effects of Hangover on Neurocognition in Adolescents: A Prospective Study. Poster presented at the Research Society on Alcoholism, Washington, DC. (abstracted in Alcoholism: Clinical and Experimental Research 32, 178A).

3. **Spadoni, A.D.**, Squeglia, L., Norman, A.L., Tapert, S.F. (February, 2008): Utility of neurocognitive performance in predicting subsequent heavy drinking in adolescence. Poster presented at the annual meeting of the International Neuropsychological Society, Waikoloa, HI.
4. Hanson, K.L., Medina, K.L., Nagel, B.J., Norman, A.L., **Spadoni, A.D.**, & Tapert, S.F. (January, 2008): Hippocampal volumes in adolescents with and without a family history of alcoholism. Poster presented at the second International Conference on Applications of Neuroimaging to Alcoholism, New Haven, CT.
5. Norman, A.L., **Spadoni, A.D.**, Paulus, M.D., & Tapert, S.F. (January, 2008). An fMRI study of adolescent inhibitory processing prior to the initiation of substance use. Poster presented at the second International Conference on Applications of Neuroimaging to Alcoholism, New Haven, CT.
6. **Spadoni, A.D.**, Bazinet, S. Fryer, S.F. Tapert, S.N. Mattson, E. Riley (July, 2007): Prenatal alcohol exposure and spatial working memory in adolescents and pre-adolescents: an fMRI study. Presented at the annual meeting of the Research Society on Alcoholism, Chicago, IL (abstracted in Alcoholism: Clinical and Experimental Research 31:68A).
7. Fryer, S.L., Noonan, S.K., Tapert, S.F., Mattson, S.N., **Spadoni**, **A.D.**, Riley, E.P. (July, 2007): Examination of functional connectivity during response inhibition task performance in individuals with prenatal alcohol exposure. Presented at the annual meeting of the Research Society on Alcoholism, Chicago, IL (abstracted in Alcoholism: Clinical and Experimental Research 31:106A).
8. **Spadoni, A.D.**, Pulido, C., Norman, A.L., Tapert, S.F. (February, 2007): Do the effects of alcoholism family history on adolescent neuropsychological function depend on maternal education? Presented at the annual meeting of the International Neuropsychological Society, Portand, OR.
9. Fryer, S.L., Schweinsburg, B.C., Bjorkquist, O.A., Frank, L.R., Mattson, S.N., **Spadoni, A.D.**, Riley, E.P. (November, 2007): Evidence of global white matter microstructural damage in fetal alcohol spectrum disorders. Presentated at the annual conference of the Society for Neuroscience, San Diego, CA.
10. **Spadoni, A.D.**, Norman, A.L., Roesch, S.C., Pulido, C., and Tapert, S.F. (June, 2006): Neurocognitive factors discriminate alcohol use disorder family history status in adolescents: A discriminant function analysis. Presented at the annual meeting of the Research Society on Alcoholism, Baltimore, MD (abstracted in Alcoholism: Clinical and Experimental Research 30:150A).
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12. **Spadoni, A.D.**, Fryer, S.L., Frank, L.R., Tapert, S.F. (February, 2006): Adolescent neuropsychological performance predicts callosal microstructure. Presented at the annual meeting of the International Neuropsychological Society, Boston, MA.
13. **Spadoni, A.D.**, Schweinsburg, A.D., Caldwell, L., Tapert, S.F. (June, 2005): Family history of alcohol use disorders and spatial working memory in

adolescents: An fMRI study. Presented at the annual meeting of the Research Society on Alcoholism, Santa Barbara, CA (abstracted in Alcoholism: Clinical and Experimental Research 29:102A).

14. De Rosa, E., Murray, D., **Spadoni, A.D.**, Pfefferbaum, A., Sullivan, E.V. (June, 2004). Age enhanced interference from past learning on the present. Presented at the annual meeting of the Canadian Society for Brain, Behaviour and Cognitive Science, Newfoundland.
15. DeRosa, E., Murray, D., **Spadoni, A.D.**, Pfefferbaum, A., Sullivan, E.V. (November, 2003). Effect of normal and pathological aging on proactive interference using a nonverbal paired associate learning paradigm. Presented at the annual meeting of the Society for Neuroscience, New Orleans, LA.
16. Schulte, T., **Spadoni, A.D.**, Pfefferbaum, A., Sullivan, E.V. (June, 2002). Interhemispheric summation in alcoholics. Presented at the joint annual meeting of the Research Society on Alcoholism and ISBRA, San Francisco, CA (abstracted in Alcoholism: Clinical and Experimental Research 26:126A).

Presentations

1. **Spadoni, A.D.** Adolescent Brain Development Development and Substance Use: Workshop presented to the San Diego County Office of Education, December 2008.
2. **Spadoni, A.D.** Thinking and Drinking: Effects of Alcohol Abuse on the Brain and Cognitive Abilities: Guest lecture presented to SDSU undergraduate abnormal psychology students,October 2007.
3. **Spadoni, A.D.**, Bazinet, A., Fryer, S.L, Tapert, S.F, Mattson, S.N., and Riley, E.P. Fetal Alcohol Spectrum Disorders and Spatial Working Memory During Childhood and Adolescence: An fMRI study. Presented at the Fetal Alcohol Spectrum Disorders Study Group, satellite meeting to the annual meeting of the Research Society on Alcoholism, Chicago, IL, July 2007.
4. **Spadoni, A.D.** Adolescent Brain Development: Vulnerabilities and Opportunities. Workshop presented to the San Diego County Office of Education, May 2007.
5. **Spadoni, A.D.** Relapse Prevention, Seemingly Irrelevant Decisions & Craving. Single lectures presented to the San Diego Veterans' Affairs Alcohol and Drug Treatment Program. June 2007, March 2007, January 2007, December 2006.
6. **Spadoni, A.D.** Schweinsburg, A.D., Tapert, S.F. Effects of Alcohol on the Brain and Body presented to UCSD Peer Education Group, October 2006.
7. **Spadoni, A.D.** Schweinsburg, A.D., Tapert, S.F., Effects of Substance Use on the Brain and Body presented to UCSD Peer Education Group, October 2006.
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ABSTRACT OF THE DISSERTATION

Family History of Alcohol Use Disorders and Neuromaturation:
A Functional Connectivity Study with Adolescents

by

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Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2009
San Diego State University, 2009

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BACKGROUND: A positive family history (FHP) of alcohol use disorders (AUD) is linked to increased risk for personal AUD, but mechanisms behind this risk are unclear. FHP adolescents tend to be different from family history negative (FHN) youth on electrophysiological, brain volumetric, and neuropsychological measures. These differences diminish by young adulthood, suggesting that a subtle neurodevelopmental lag may contribute to AUD risk.

METHODS: Neural networks of blood oxygen level dependent (BOLD) response to a spatial working memory (SWM) task were examined for markers of neuromaturational delay across FH groups. It was hypothesized that FHP adolescents

(*n*=24, ages 12-14), as compared to matched FHN youth (*n*=26, ages 12-14), would show less similarity to brain activity patterns observed in older adolescents (OA; *n*=35, ages 16-20). Structural equation modeling tested the fit of brain response in FH groups against the OA model. The influence of physiological noise was also examined using a filter to isolate task related response.

RESULTS: Connectivity between key regions for SWM response was similar between FH groups, but FHN connectivity resembled OA patterns more than FHP adolescents did. FHP youth demonstrated higher bilateral association between right posterior and left frontal brain regions (*r*s=.49 v .22, $p<.05$) than FHN youth, and had a link between more superior posterior activation and poorer SWM accuracy ($r=-.40$, $p<.05$, $r^2=.16$) not observed in other groups. Applying filters to model sources of noise did not alter results.

CONCLUSIONS: Developmental stage of adolescence and FH status influenced functional connectivity to a SWM task. A bilateral brain connection was characteristic of FHP young adolescents but not to OA model fit, suggesting this as a less mature brain response pattern, and providing additional support for the notion of a neuromaturational lag in FHP youth. Protracted neuromaturation may be a mechanism by which FH increases risk for alcohol dependence, and this less mature neural connectivity pattern may provide a novel endophenotype for identifying youth at risk for drinking problems.

FAMILY HISTORY OF ALCOHOL USE DISORDERS AND NEUROMATURATION: A FUNCTIONAL CONNECTIVITY STUDY WITH ADOLESCENTS

INTRODUCTION

Recent national surveys and community studies report that alcohol use is highly prevalent in the youth of America (L. Johnston, O'Malley, Bachman, & Schulenberg, 2005; L. D. Johnston, O'Malley, Bachman, & Schulenberg, 2009). For youths ages 12 to 17, past month alcohol use was 16% in 2007. Binge and heavy drinking rates for this age group were 10% and 2% (NSDUH, 2007), respectively. Heavy use of alcohol in adolescence increases risk for developing myriad secondary disorders such as psychopathology (Fidalgo, da Silveira, & da Silveira, 2008; Kandel, et al., 1997; Rohde, 2001), physical problems (Aarons, 1999; Clark, Lynch, Donovan, & Block, 2001), cognitive decrements (Squeglia, Spadoni, Infante, Myers, & Tapert, in press; Tapert, Granholm, Leedy, & Brown, 2002), impaired social development (Baumrind & Moselle, 1985; Maggs, Patrick, & Feinstein, 2008), and substance dependence (Englund, Egeland, Oliva, & Collins, 2008; Grant & Dawson, 1997). Early identification of youth at greatest risk for developing AUD will facilitate intervention development and implementation.

One of the most robust risk factors for developing an AUD is a positive family history of AUD (Capone & Wood, 2008; Cloninger, Sigvardsson, Reich, & Bohman, 1986; Goodwin, 1979; King, et al., 2009; I. C. Liu, et al., 2004; Sartor, Agrawal, Lynskey, Bucholz, & Heath, 2008; Sartor, Lynskey, Heath, Jacob, & True, 2007; Schuckit, 1985). Risk of developing an AUD rises with increased family history density, or multiple generations of AUD (Capone & Wood, 2008; Dawson & Grant, 1998; S. Y. Hill, Shen,

Lowers, & Locke, 2000; Little, Handley, Leuthe, & Chassin, 2009; Nurnberger, et al., 2004; Peterson, Finn, & Pihl, 1992; Sher, Bartholow, & Wood, 2000). Because many individuals with AUD are FHP, understanding the neural characteristics of FHP youth may help determine potential premorbid abnormalities in brain functioning of alcohol dependent individuals.

BACKGROUND

Neural Features Linked to FHP

FHP youth commonly perform differently from FHN controls on neurocognitive measures. Non-AUD FHP adolescents, especially males, tend to perform worse on tests of executive cognitive functioning (M. Corral, Holguin, & Cadaveira, 2003; Dolan, Bechara, & Nathan, 2008; Giancola, Martin, Tarter, Pelham, & Moss, 1996; Harden & Pihl, 1995; Nigg, et al., 2004) working memory, (M. M. Corral, Holguin, & Cadaveira, 1999; Dolan, et al., 2008; Harden & Pihl, 1995; T. Ozkaragoz, Satz, & Noble, 1997), perseveration (Giancola, Peterson, & Pihl, 1993), nonverbal memory (Sher, Walitzer, Wood, & Brent, 1991), organization of new information (Peterson, et al., 1992), visuospatial skills (Berman, 1995; M. M. Corral, et al., 1999; Garland, 1993; T. Ozkaragoz, et al., 1997; T. Z. Ozkaragoz & Noble, 1995; Sher, et al., 1991), language functioning and academic achievement (Giancola, et al., 1993; Hegedus, Alterman, & Tarter, 1984; Najam, Tarter, & Kirisci, 1997; Poon, Ellis, Fitzgerald, & Zucker, 2000; Sher, et al., 2000; Tarter, Hegedus, Winsten, & Alterman, 1984; Viken, Kaprio, Koskenvuo, & Rose, 1999), and attention (Tarter, Jacob, & Bremer, 1989). Multigenerational transmission of alcohol dependence (Conrod, Pihl, & Ditto, 1995; LeMarquand, Benkelfat, Pihl, Palmour, & Young, 1999; Peterson, et al., 1996; R. Pihl & Bruce, 1995), high familial density (S. Y.

Hill, et al., 2000), early age of alcoholism onset in father (Tarter, et al., 1989), active paternal alcoholism (T. Ozkaragoz, et al., 1997), behavioral disinhibition (Lovallo, Yechiam, Sorocco, Vincent, & Collins, 2006), and genotypic features (Berman, 1995; Edenberg, et al., 2004; Enoch, et al., 2009; Schumann, et al., 2008) may increase the strength in relationship between FHP and NP functioning. However, some studies reported no neurocognitive differences (Bates & Pandina, 1992; Bjork, Knutson, & Hommer, 2008; Finn & Justus, 1999; Schuckit, Butters, Lyn, & Irwin, 1987), or effect of intelligence via genotype (Petrill, et al., 1997) between FHN and FHP participants. In sum, these findings raise the possibility that some neurocognitive deficits previously reported in alcoholics may predate the onset of heavy drinking.

A positive FH has also been linked to different patterns of brain activation during functional neuroimaging tasks. FHP youth had less brain response in the inferior frontal gyrus during response inhibition (Schweinsburg, et al., 2004), as well decreased activation in the middle temporal gyrus and inferior frontal gyrus while judging facial expressions (S. Y. Hill, et al., 2007). FHP youth also had relatively greater neural activation in the anterior cingulate cortex and caudate nucleus during a gambling task (Acheson, Robinson, Glahn, Lovallo, & Fox, 2009), and more activation in the orbital frontal gyrus in response to affective stimuli (Heitzeg, Nigg, Yau, Zubieta, & Zucker, 2008) than FHN peers in recent neuroimaging studies. Similar studies have also failed to isolate FH effects from behavioral undercontrol (Glahn, Lovallo, & Fox, 2007), or found no FH group differences (Bjork, et al., 2008). Taken together, these findings may suggest that a positive FH influences neural correlates of behavioral and affective regulation and, in turn, risk for personal AUD.

Decreases in intracranial and amygdala volume have also been evidenced in FHP individuals. FHP adolescents and young adults have demonstrated smaller volume of the right amygdala (S. Y. Hill, et al., 2001). Smaller intracranial volume and skull growth in children of alcoholics with AUD may indicate that reduced brain growth, whether by genetic or environmental mechanisms, increases risk for developing AUD in the offspring of problem drinkers (Gilman, Bjork, & Hommer, 2007). Since amygdala and intracranial volume tends to increase over childhood and adolescence, reduced volumes in FHP youth may indicate a developmental lag.

In addition to differences in NP performance, brain activation, and decreased intracranial and amygdala volumes, neurophysiological abnormalities have also been found in FHP youth (H. Begleiter, Porjesz, & Bihiari, 1987; R. Pihl & Bruce, 1995; R. O. Pihl, Peterson, & Finn, 1990; Tarter, et al., 1984). The P300 component of the event-related potential (ERP), which serves as an indicator of rapid shifts in allocation of cognitive resources, has shown reduced amplitude in FHP children and adults (Almasy, et al., 1999; H. Begleiter, Porjesz, Bihari, & Kissin, 1984; Polich, Pollock, & Bloom, 1994; Porjesz, et al., 1998) as well as in heavy drinkers, suggesting an endophenotype of alcoholism (Hesselbrock, 2001). This feature is most consistently displayed in FHP individuals under age 18. After this age, FHP individuals begin to resemble FHN peers, suggesting an inherited developmental lag (Polich, et al., 1994). Aberration in P300 amplitude among FHP individuals also supports the developmental delay hypothesis. Delayed maturation of postural sway (S. Y. Hill, et al., 2000) as evidenced by abnormalities in the cerebellum and basal ganglia has also been implicated in FHP youth.

Spatial Working Memory Involves Shared Abnormalities in AUD and FHP

Spatial working memory refers to the maintenance of spatial locations for further manipulation (Baddeley, 1986). The neural mechanism of these processes has been reliably demonstrated to involve a frontoparietal network including the dorsolateral prefrontal cortex (DLPFC), posterior parietal cortices, and cingulate cortex (Casey, et al., 1997; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Goldman-Rakic, 1987; McCarthy, et al., 1996; Ricciardi, et al., 2006; van Asselen, et al., 2006). While the frontal regions of the brain are linked to executive control, parietal cortices are thought to be recruited for tasks requiring accuracy and effort (Nelson, 2000; van Asselen, et al., 2006). Disorganization of source density maps of the P300 may indicate abnormalities of the frontal and prefrontal cortex in non-drinking FHP individuals (Hada, 2001). Rangaswamy and colleagues (2004) postulate that dysfunction of the frontoparietal circuit underlies the low P300 amplitude in FHP individuals (Rangaswamy, Porjesz, Ardekani, et al., 2004). This suggests that in fMRI studies of alcoholics, the observed reorganization of frontoparietal pathways used to complete spatial working memory tasks (Pfefferbaum, et al., 2001; Tapert, et al., 2001; Tapert, et al., 2004) may be moderated by premorbid FH effects.

Maturation of the Neural Mechanisms Supporting Spatial Working Memory

The organization of spatial working memory is also theorized to change during pre- to post-adolescent development (Klingberg, 2006; Klingberg, Forssberg, & Westerberg, 2002a; Nelson, 2000; Schweinsburg, Nagel, & Tapert, 2005; Thomas, et

al., 1999; Thomason, et al., 2009). Brain activation in the DLPFC appears more bilateral in younger children than older children (Tsujii, Yamamoto, Masuda, & Watanabe, 2009) and adults, who progressively demonstrate activation in predominantly right prefrontal regions (Thomas, et al., 1999). This right greater than left pattern of activation is consistently observed in adults (Courtney, Ungerleider, Keil, & Haxby, 1997; Jonides, et al., 1993; Smith, Jonides, & Koeppe, 1996). Children also show increased activity in prefrontal areas as compared to adults, who show greater volumes of parietal activity (Thomas, et al., 1999).

Work from our lab indicates that typically developing adolescents show a positive relationship between age and brain activation of prefrontal and inferior parietal regions, and a negative relationship between age and superior parietal cortices (Schweinsburg, Nagel, et al., 2005). This evidence suggests that the underlying neural mechanisms of SWM develop over adolescence, shifting more posterior and lateralizing to the right side, and that the inferior parietal lobe becomes more important by late adolescence. Studies have also demonstrated correspondence between working memory ability and activity in the intraparietal cortex (Todd & Marois, 2004; Vogel & Machizawa, 2004), which corresponds to the increase in SWM capacity over development (Issacs & Vargha-Khadem, 1989; Logie & Pearson, 1997). Greater SWM task accuracy has been shown to be correlated with increasing activation in the inferior and intra-parietal cortices in conjunction with frontal cortices (Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002). Therefore, changes in brain activation over adolescence may reflect a shift in strategy, cortical organization, or a combination of the two processes (Edin, Macoveanu, Olesen, Tegner, & Klingberg,

2007; Klingberg, 2006; Schweinsburg, Nagel, et al., 2005; Thomas, et al., 1999). Examination of these activation patterns in FHP youth may ascertain whether they differ from that of FHN youth and show a less mature pattern of neural response.

Studies examining the integrity of underlying anatomical connections also suggest that white matter increases occur in a specific temporal and spatial manner that is consistent with improved SWM functions (Klingberg, 2006). White matter tracts and the degree to which they are anisotropic, or constrict the motion of fluid in the direction parallel to the fiber, increase with brain development (Giedd, Blumenthal, Jeffries, Rajapakse, et al., 1999; Paus, et al., 2001). Changes in anisotropy are attributed to myelination, or the process of oligodendrocytes insulating axon fibers (Beaulieu, 2002), which is thought to improve the speed and efficiency of cortico-cortical communication (Felts, Baker, & Smith, 1997; C. Liston, et al., 2006; Waxman, 1977). During adolescence, age related increases in total white matter volume are prominent (Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996; Giedd, et al., 1996; Hasan, et al., 2007; Hua, et al., 2009; Jernigan, et al., 1991; Pfefferbaum, et al., 1994; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Sowell, et al., 1996), with demonstrated rapid increases from ages 12 to 15, and slowed continued increases through approximately age 30 (Courchesne, et al., 2000). The largest increase in anisotropy seems to occur between early and late adolescence (Qiu, Tan, Zhou, & Khong, 2008; Snook, Paulson, Roy, Phillips, & Beaulieu, 2005). Changes in connective fibers including the superior longitudinal fasciculus, which connects the frontal and parietal lobes, have been demonstrated to occur in older adolescents (Bava, Jacobus, Thayer, Frank, & Tapert, in preparation; Fair, et al., 2008;

Snook, et al., 2005). Eluvathingal and colleagues (2007) examined youth aged 6 to 17 years and found higher anisotropy in all areas of the *left* fasciculus, except within the *right* frontoparietal segment of the fasciculus, suggesting a developmental process occurring specifically in the region where there are predicted age-related FH group differences (Eluvathingal, Hasan, Kramer, Fletcher, & Ewing-Cobbs, 2007). Additionally, in a study examining fMRI BOLD response in relation to white matter (Olesen, Nagy, Westerberg, & Klingberg, 2003), SWM scores were positively related to BOLD response in the inferior parietal lobe after controlling for age, and anisotropy values in frontoparietal white matter were also correlated with BOLD response in nearby gray matter in the superior frontal sulcus and inferior parietal lobe, suggesting coordinated development of an underlying SWM network.

Functional Connectivity Can Help Elucidate Altered Systems of Complex Cognitive Tasks

The relationship between neuromaturation and brain activation has yet to be fully understood. Change in PFC blood oxygen level dependent (BOLD) activation has been demonstrated to both increase (Casey, et al., 1997; Klingberg, Forssberg, & Westerberg, 2002b) and decrease with age (Adleman, et al., 2002). Because BOLD is only a proxy for neural activation in response to a task (Kim, et al., 2004; Logothetis, 2002; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), there is no direct measure of brain activity that can conclusively relate task response to activation of specific brain regions. Activation maps are also subject to multiple interpretations. Developmental literature typically associates focal increases and reduced extent of

activation with greater functional maturation (Kwon, Reiss, & Menon, 2002), while clinical studies commonly interpret increased activation as indicative of compensatory neural recruitment and neural inefficiency (Desmond, et al., 2003; Pfefferbaum, et al., 2001; Tapert, et al., 2004).

Explaining brain activity in terms of the volume and direction of activations may ignore connectivity of these regions. Yet, the manner in which brain areas work in concert to perform the task can provide useful information as to neural integrity (Y. Liu, et al., 2008; Supekar, Menon, Rubin, Musen, & Greicius, 2008) and efficiency (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006), and may be assessed by examining networks of activation (Stricker, Brown, Wetherell, & Drummond, 2006). For example, a recent study used functional connectivity to assess the age-related changes in the brain's default network (Fair, et al., 2008) which is anti-correlated with brain activation to cognitively challenging tasks (Fox, et al., 2005), and found that this network is minimally functionally connected at approximately 8 years of age, but that continued integration of these regions into a unified network occurs over development. As in functional imaging research, there is also evidence that patterns of connectivity change with age, some areas decreasing and other increasing in integration, allowing for improved efficiency (Fair, et al., 2007; M. C. Stevens, Kiehl, Pearlson, & Calhoun, 2007). Functional connectivity analyses examining brain network dynamics during error commission, inhibition, and resting states have described neurobiological discrepancies between adolescent and adult networks (Fair, et al., 2007; M. C. Stevens, et al., 2007; M. C. Stevens, Kiehl, Pearlson, & Calhoun, 2009; M. C. Stevens, Pearlson, & Calhoun, 2009). The conclusions of resting state-based studies suggest

that within network connectivity becomes stronger, and between network interactions become weaker. The authors interpreted these findings as indicating more flexible intra-network processing capacity (M. C. Stevens, Kiehl, et al., 2009; M. C. Stevens, Pearlson, et al., 2009). Additionally, examination of inhibitory processes implicates increased participation of higher order cortices with increasing development (M. C. Stevens, et al., 2007). Therefore, while most studies assess functional specialization of brain regions, providing information in terms of a region's contribution to a given behavior, they fail to characterize communication between these regions (Lee, Harrison, & Mechelli, 2003). By characterizing brain activity in terms of connectivity, or "the influence that one neural system exerts over another directly or indirectly" (Friston, 1994), valuable clinical information may be gleaned. For instance, the influence of age and FH can be specified as increasing or decreasing the strength of communication between brain regions, or altering the influence one region has upon another. Connectivity changes as a function of FH could perhaps provide a "quantifiable marker of genetic risk (Bullmore & Sporns, 2009)," or endophenotype, for AUD.

Structural Equation Modeling

Structural equation modeling (SEM) techniques are part of the general linear model (GLM) family, can be used with latent variables and observed variables alike, and serve both confirmatory and exploratory analyses (Kline, 2005b). However, for models as those specified in these analyses, where no variable is both predictor and outcome of another variable (recursive) and is over-identified (the number of free

parameters is less than the number of observations), multiple regression can be used to complete the path analysis and will have practically identical results as the maximum likelihood estimation procedures used in SEM (Kline, 2005b). However, there are distinct advantages of performing a path analysis with SEM instead of with multivariate regression. Most importantly, SEM requires the *a priori* designation of models based on established data gleaned from neuroanatomical, neuropsychological, and functional neuroimaging studies of the brain (Friston, 1994). Therefore, SEM can be used to evaluate functional neuroimaging models generated by the researcher by testing their fit against observed patterns of brain activation. Also, SEM provides multiple indices of overall model fit necessary to delineate the best of competing models. These indices are not output by regression programs. Also, in the case that our hypothesized model does not fit, re-specification of the model with non-recursive (bidirectional) pathways could not be evaluated using multiple regression (Kline, 2005b).

In addition to a SEM approach, functional connectivity has also been ascertained using a variety of other methods, such as dynamic causal modeling (Friston, Harrison, & Penny, 2003), seed voxel analyses (Cordes, et al., 2000), and various multivariate analyses (R. G. Schlosser, Wagner, G., Sauer, H., 2005). Where SEM and dynamic causal modeling use BOLD response to characterize regional interactions, dynamic causal modeling also attempts to make inferences regarding relationships at the neural level by exploiting knowledge of well-known neuroanatomical correlates of direct sensory input and concurrent cognitive functioning (R. G. Schlosser, Wagner, G., Sauer, H., 2005). Mapping the neural

coordinates of cognition with input that requires more complex processing than visual or auditory stimuli (i.e., working memory) may be too theoretical for dynamic causal modeling (R. G. Schlosser, Wagner, G., Sauer, H., 2005).

In direct contrast to SEM and dynamic causal modeling approaches, seed voxel analysis does not begin with an *a priori* model of neural interactions. Instead, based on the selection of a start point, or "seed voxel," one creates correlation maps to examine the relationships between signal in the chosen voxel and other voxels in the brain (Cordes, et al., 2000). Finally, multivariate approaches such as principle components analyses (Friston, Frith, & Frackowiak, 1993; Mikula & Ernst, 2007), independent component analyses, and partial least squares (Della-Maggiore, et al., 2000) may be used for data reduction and to compare models across groups. These approaches may produce similar solutions but do not offer summary indices of model fit necessary for comparing the utility of competing models. The SEM approach was therefore selected to allow testing a carefully reasoned a priori model, to examine the influence of each node in the specified model, and to provide model fit indices.

Physiological Filtering

Changes in BOLD signal depend on blood oxygenation, volume, and flow during neural activity (Kwong et al., 1992). The percent of signal change that occurs in brain regions during engagement, such as an experimental task compared to a baseline condition, are very small in measure, usually between 1% and 5% (Huettel et al., 2004). Detection of task induced neural activity can be affected by a host of non-neural influences such as thermal noise, variation due to scanner hardware, participant

movement, and several physiological processes. Filtering is traditionally used in signal detection processes to help refine a signal. If the signal of interest and noise occur at discrete frequencies, methods to attenuate undesired frequencies will increase signal to noise ratio. While small variations caused by gross subject movement can be corrected for with relative ease (Cox & Jesmanowicz, 1999), fluctuations due to physiological processes are not as easily ameliorated.

The two chief sources of physiological variance affecting BOLD signal are cardiovascular and respiratory. Cardiovascular induced pulsations in blood can result in signal change in regions of the brain near highly vascularized regions (e.g., middle cerebral artery (Dagli, Ingeholm, & Haxby, 1999; Lowe, Mock, & Sorenson, 1998), and in cerebral spinal fluid (e.g., ventricles, edges of brain) as well as gray matter, especially near blood vessels (Jezzard & Song, 1996; Weisskoff, et al., 1993) where task-induced signal is localized. Change in arterial level of carbon dioxide (CO_2) during respiration can also result in task correlated signal variation in gray matter (Stillman, Hu, & Jerosch-Herold, 1995; Weisskoff, et al., 1993). Noise has also been detected in regions containing predominantly white matter (Stillman, et al., 1995; Weisskoff, et al., 1993).

Physiologic noise can be especially problematic in functional connectivity analyses of resting state BOLD signal (Biswal, DeYoe, & Hyde, 1996; Cordes, et al., 2001) because it cannot easily be distinguished from neurally generated signal (R. M. Birn, Diamond, Smith, & Bandettini, 2006). Low frequency fluctuations (<0.1 Hz) are thought to result from a coordinated and structurally coherent network most active during rest. This “default network” includes the anterior cingulate and parts of medial

prefrontal cortex, extending inferiorly into orbitofrontal cortices (Greicius, Krasnow, Reiss, & Menon, 2003; Greicius & Menon, 2004; Hampson, Peterson, Skudlarski, Gatenby, & Gore, 2002; Raichle, et al., 2001). Reliably isolating respiratory or cardiac induced signal from neural based resting signal can be problematic because the fMRI sampling rate, or TR, is usually about 2 seconds while average breathing rate is about every 4 seconds. While a 2-second sampling rate is optimal for capturing peak BOLD signal (e.g., 1/TR, or .5 Hz (Menon, Hu, Mitra, Ogawa, & Ugurbil, 1994), it does not accurately sample high frequency physiological influences (e.g., ~.3 Hz respiration or ~1-2 Hz cardiac influence (Lowe, et al., 1998). Cardiac and respiratory signal is subsequently aliased, or displaced, to lower frequencies (<.08 Hz) and thus difficult to isolate from signal of interest, especially when examining resting brain activity (Lowe et al., 1998). Fluctuations due to inspiration depth have also been shown to occur at very low frequencies (~0.03 Hz) and are therefore also very difficult to separate from resting brain-based activity (R. M. Birn, et al., 2006).

Several problems may result from ignoring physiological fluctuations in BOLD data. For example, when error is not independent or normally distributed, standard deviations may be falsely deflated, and statistical inference may be generously biased (Lund, Madsen, Sidaros, Luo, & Nichols, 2006). Wise and colleagues demonstrated that changes in CO_2 during normal breathing have been shown to be significantly correlated with BOLD signal (Wise et al., 2004); therefore changes in breathing that are task related could falsely inflate effects (R. M. Birn, et al., 2006). In addition, regions of the default network also overlap with areas shown to be most influenced by fluctuations in CO_2 (R. M. Birn, et al., 2006). Similarly, aliased

physiologic noise can increase correlations between non-default network (i.e., bilateral precentral gyri and right inferior parietal lobule) regions of interest sensitive to the physiological signal (Lowe, et al., 1998). Conversely, physiologic-related fluctuations can decrease sensitivity to task-induced BOLD variation, obscuring very small percentages of task-induced change with noise (Lund, et al., 2006). More obvious effects might result such as image artifact or non-uniform intensity (Glover, Li, & Ress, 2000). Also, because physiological noise depends on the total signal strength, it may constitute a larger fraction of the total noise with signal increases (Kruger & Glover, 2001; Triantafyllou, et al., 2005) and increased magnetic field strength (e.g., 1.5T v. 3T) (Shmueli, et al., 2007). Therefore, while the final influence of physiological noise may be small, depending upon the experimental condition, region of interest, and field strength, separation of physiological signal from task-related signal may be vital for valid conclusions.

Although the influence of high frequency physiological fluctuations has been well defined, methods by which to best deal with their influence are less clearly established. Physiological noise correction can be done in either spatial domain (e.g., highlighting areas most likely to contain noise) or in the temporal domain, which incurs targeting suspect waveforms in the fMRI time course. Early attempts were k-space corrections that used scanner-obtained information but were spatially non-specific (Glover, et al., 2000; Hu, Le, Parrish, & Erhard, 1995; Wowk, McIntyre, & Saunders, 1997). The use of a fixed bandpass filter was also proposed to reject noise at cardiac and respiratory frequencies (Biswal, DeYoe, & Hyde, 1995), but such a filter can only produce meaningful results if the physiological noise is adequately sampled

(e.g., short TR) and not aliased to lower (and harder to approximate) frequencies (Shmueli, et al., 2007). Additionally, if the signal of interest is within the band of rejected frequencies, such as in resting state functional connectivity analyses, such correction cannot be applied without losing task-relevant information (Shmueli, et al., 2007).

In attempts to increase specificity of physiological noise correction, retrospective corrections based on parallel measures of respiration and cardiac activity collected with additional monitoring equipment have been developed (e.g., RETROICOR) (Glover, et al., 2000). These parallel measures have also been used to model the effects of physiological noise, and used nuisance regressors in the general linear model, reducing non-normality of residuals and bolstering validity statistical conclusions (Lund, et al., 2006). This regression method does not interfere with the signal extraction of functional activation is therefore preferred to a rejection filter (Deckers, et al., 2006). However, many noise reduction methods assume a stable cardiac cycle, and rely on this stability and its relationship in timing to fMRI sampling (A. D. Liston, et al., 2006; Vogt, Ibinson, Small, & Schmalbrock, 2006). Researchers have found that they could explain an additional 1% of BOLD signal by including heart rate fluctuation measures in the general linear model above and nuisance regressors based on parallel measures of cardiac and respiration (Shmueli, et al., 2007). Mapping a response function for both respiration volume (R.M. Birn, Smith, Jones, & Bandettini, 2008) and heart rate (Chang, Cunningham, & Glover, 2009) in relation to BOLD and including these simultaneously in the model has also been demonstrated to increase subsequent functional connectivity in the default network

(Chang, et al., 2009), suggesting that inclusion of physiological noise and its relation to BOLD may be important to functional connectivity analysis.

Parallel physiological measurements are not always possible to collect or available to researchers. Authors have also attempted to create generalizable filters based on an average of physiological data (Beall & Lowe, 2007; Chuang & Chen, 2001). However, their estimates require that a researcher pre-plan to use a suggested prescription (Beall & Lowe, 2007; Murphy, Birn, Handwerker, Jones, & Bandettini, 2009), or that the sampling rate be shorter than is typically optimal in fMRI (Chuang & Chen, 2001; Murphy, et al., 2009). Data reduction analyses (principal component analyses (PCA), or independent component analyses (ICA)) have been used to estimate noise (McKeown, et al., 1998). PCA clusters spatially and temporally correlated information across multiple scans of the same subject, but tends to overlap with regions that are active during resting states, complicating analysis in resting functional connectivity studies (Beall & Lowe, 2007). ICA also attempts to isolate non-task related (non-Gaussian) sources of variation into separable components (Beckmann, DeLuca, Devlin, & Smith, 2005; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006; McKeown, et al., 1998). However, evidence that these components do not contain neurally induced signal is lacking, in addition to the method's failure to address aliasing problems (Beall & Lowe, 2007). Other ICA methods with greater specificity require parallel cardiac and respiratory monitoring (Beall & Lowe, 2007).

As the influence of physiological noise has been shown to be potentially deleterious in functional connectivity analyses, a method of physiological noise

correction was included in the current analyses. No parallel physiological data were collected along with fMRI data, and therefore the type of correction that can be applied is limited. Therefore, a spatial filtering method, based on filtering signal from regions of non-interest (i.e., white matter) was applied (A. N. Simmons, et al., 2008; Strigo, Simmons, Craig, & Paulus, 2006). The benefits of this method are the ability to apply it retrospectively without measured physiological data, the reduced risk of affecting signal from the regions of interest in the gray matter, and its individual specificity. Because physiological sources of noise are increased at higher field strengths (Kruger, Kastrup, & Glover, 2001; Triantafyllou, et al., 2005) this correction will only be applied to the OA sample, which was collected on a 3T magnet. Functional connectivity analyses were carried out on these data with and without the correction for comparison.

Specific Hypotheses

This study tests the hypothesis that risk for AUD in FHP youth is moderated by a subtle lag in neuromaturation. The age range of interest (12 to 14) is prior to the time at which many alcohol dependent young adults typically began drinking. Importantly, neurodevelopmental processes, such as synaptic refinement of the frontal regions and gray matter pruning, are heightened between the ages of 12 and 14 years of age (Giedd, Blumenthal, Jeffries, Castellanos, et al., 1999; Gogtay, et al., 2004; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999), making this an ideal window to capture developmental differences between groups. These results will also aid in interpreting whether deficits of spatial working memory in youth with AUD resulted

from alcohol involvement or were associated with premorbid factors such as FH. Using SEM, neural networks in young adolescents (aged 12 to 14) employed during a SWM paradigm using fMRI BOLD data will be compared between 1) youth with at least one parent who has a history of AUD (FHP), and 2) youth with no parent or grandparent with any history of a substance use disorder (FHN), and against 3) older adolescents (OA; aged 16 to 20) without histories of alcohol or drug abuse. This third comparison group of older adolescents ensures that a valid baseline of "mature SWM network" is established.

To test whether brain regions work together differently in youth with a positive family history, models of brain activity during SWM were developed. Specifically, the OA model was developed to include brain regions that best approximate patterns previously reported for older adolescents and adults in response to an SWM fMRI task. It is hypothesized that activation networks of FHN young adolescents will more closely resemble those of the OA comparison group than will the FHP youth, and that statistical comparison of SWM functional connectivity models will differentiate FHN and FHP youth (Figure 1). Regions of interest (ROIs) included: 1) right inferior parietal lobule, 2) right superior parietal lobule, 3) right middle frontal gyrus, and 4) left middle frontal gyrus, based on evidence that these regions are (a) integral to SWM functions (Casey, et al., 1997; Courtney, et al., 1998; Goldman-Rakic, 1987; McCarthy, et al., 1996; Ricciardi, et al., 2006; van Asselen, et al., 2006), (b) sensitive to shifts in cortical organization or change in strategies that accompany adolescent development (Edin, et al., 2007; Klingberg, 2006; Klingberg, et al., 2002a; Nelson, 2000; Schweinsburg, Nagel, et al., 2005; Thomas, et al., 1999; Thomason, et al.,

2009), and (c) susceptible to FH effects (Hada, 2001; Rangaswamy, Porjesz, Ardekani, et al., 2004). The hypothesized relationships between these regions are specified below, but ultimately, will depend on the fit of the OA model.

1) FHP youth have been shown to recruit neural resources more heavily from bilateral DLPFC (right and left middle frontal gyri) (Thomas, et al., 1999). Therefore, in FHP youth, it is predicted that the right middle frontal gyrus will have a weaker, positive influence on the left middle frontal gyrus, as compared to the FHN and OA youth, whose right middle frontal gyri will exert a greater positive influence on the left middle frontal gyri.
2) Activation to this SWM task in the superior parietal lobule has been shown to be negatively correlated with increased age, while activation in the inferior parietal lobule shows a positive relationship with age (Schweinsburg, Schweinsburg, et al., 2005). It may be that as the inferior parietal lobule comes online, activation in the superior parietal region is no longer crucial for efficient task performance. Therefore, it is predicted that FHP subjects will rely more heavily on the superior parietal lobule and less in the inferior parietal lobule for SWM processing, thus producing a strong, negative influence of the inferior parietal lobule on the superior parietal lobule. OA and FHN negative youth will show the opposite relationship between parietal regions, and will demonstrate increasing inferior parietal activation with decreasing superior parietal response, thus also show a negative (though weaker) relationship.
3) Relative decrease in the activation of the superior parietal lobule in FHN and OA youth will lead to a relatively weak, negative influence of this region on

the right middle frontal gyrus. The opposite pattern is predicted for the FHP youth.

4) A right greater than left pattern of activation is consistently observed in adults in response to SWM tasks (Courtney, et al., 1997; Jonides, et al., 1993; Smith, et al., 1996; Thomas, et al., 1999). If there is increased response in the right middle frontal gyrus and concomitant increase in the right inferior parietal lobe in OA and FHN youth, a strong, positive relationship between these regions is proposed, thus mimicking the right greater than left pattern established in adults. The FHP youth will alternatively demonstrate a negative relationship between these two regions, owing to their comparatively decreased response of the inferior parietal lobule and simultaneously greater response of the superior parietal lobule. In FHP youth, the inferior parietal lobule will have a comparatively weaker and negative influence on the right inferior frontal gyrus.
5) It was hypothesized that if improved SWM performance is positively related to connectivity associated with mature neural networks, then delayed neuromaturation in FHP youth gains further support as a risk factor for AUD.

It was also hypothesized that the physiological correction would not meaningfully change the outcome of group comparisons, chiefly due to the location of the regions of interest as well as the frequency of their signal. The majority of research has found that physiological noise is most detrimental to resting state neural activation, as is not the case in the current study. Also, the brain regions most affected

by physiologic noise are midline and ventrolateral orbitofrontal regions of the default network, dissimilar to the current more dorsal regions of interest. However, due to the relative paucity of physiologic correction in studies of functional connectivity in these dorsal areas, it was thought to be an important comparison to document.

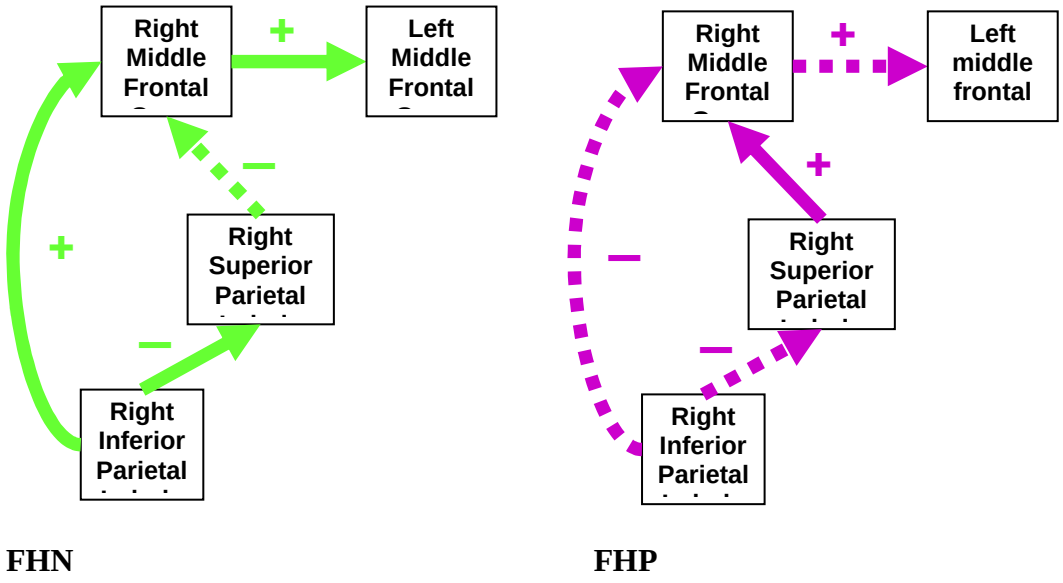


Figure 1. Hypothesized Models. Relationships for OA and FHN youth depicted in green; relationships for FHP in purple. Dashed lines: Pathways expected to demonstrate weaker correlations relative to the other group. Solid lines: Pathways expected to show stronger correlations within each group. Expected positive and negative relationships are depicted with "+" and "-".

METHODS

Participants

Participants were sampled from two larger studies on neurocognition 1) youths at risk for AUD (R01 AA13419, PI: Tapert), and 2) older adolescent cannabis users and matched healthy controls (R01 DA021182, PI: Tapert). In both studies, adolescents are recruited by distributing flyers at local middle and high schools. Youths or parents responded by phone and were preliminarily screened for age, left-handedness, MRI contraindications (e.g., braces, metal implants), and sensory

problems following parental informed verbal consent and youth assent. The current study includes only youth with limited personal substance use histories.

Early adolescents (*N*=50) were between the ages of 12 and 14, were 83% Caucasian, and 56% male (see Table 1). FHP (*n*=24) and FHN (n=26) groups were statistically equivalent on parental education, annual salary, and pubertal development. On average, parents were generally well educated and affluent. In terms of physical maturation, females as a group were just past the midpubertal stage and males were just under the midpubertal mark (Petersen, Crockett, Richards, & Boxer, 1988). Scores on measures of internalizing, externalizing, and depression were not clinically significant in any participant, and were statistically equivalent between groups. FHP youth were slightly more extraverted that FHN youth, but this difference was not clinically significant. Adolescents had minimal exposure to alcohol, cigarettes and marijuana.

Subjects were excluded for a lifetime history of greater than 1 cigarette per month, or 10 cigarette *or* marijuana uses total. The maximum number of lifetime drinking episodes (defined as at least one full drink) was 4 episodes in one FHN youth, and 5 for one FHP youth. The maximum number of drinks consumed during a single time period (over the past 3 months) was 4 drinks in one FHN subject and 5 drinks in one FHP subject. The average number of lifetime uses of alcohol was less than one instance for each group. These youth had negligent other substance use histories.

The youth was considered to have a positive family history of AUD if one or more parents was assessed to have a lifetime history of AUD based on the results of

the Family History Assessment Module screener (FHAM) (Andreasen, Rice, Endicott, Reich, & Coryell, 1986) and Schuckit's Problem List (Schuckit et al., 1985). Of the FHP (*n*=24) group, 100% had a parent with an AUD history, 79% had a multigenerational history, 63% had a biological father with a history of AUD, 46% had a biological mother with a history of AUD, 8% had positive history in both parents, and one subject had a history of AUD solely in their biological mother. FHN youth (*n*=26) had no history of any substance use disorder in either parent or any grandparent. History of maternal AUD was confirmed as occurring before or after mothers' pregnancies to avoid including subjects with fetal alcohol exposure.

OA youth (n=35) were between the ages of 16 and 20, were 67% Caucasian, and 74% male (see Table 2). On average, parents attained 15 years of education and came from families with $116K annual salaries. A measure of depression indicated totals in the normal range (*M*=2.37, SD=3.44). OA youth also had minimal exposure to alcohol, cigarettes, and marijuana use. Subjects were qualitatively non-drinkers or light, social drinkers. The maximum number of lifetime drinking episodes (defined as at least one full drink) was $\leq$54 episodes and the maximum number of drinks consumed during a single time period (over the past 3 months) was <4 drinks. No participants met diagnostic criteria for an AUD; the average number of lifetime uses of alcohol was ~2 instances. Youth had negligible other substance use history. A youth was considered to have a positive family history if one or more parent was determined to have a lifetime history of AUD based on the results of the Family History Assessment Module screener (FHAM) (Andreasen, et al., 1986) and Schuckit's Problem List (Schuckit et al., 1985). Of the OA group, 14% had a parent with an AUD

history, and 11% had a multigenerational history. Youth with a spectrum of FH backgrounds were included, as literature suggests that FH effects diminish by adulthood (Polich, et al., 1994). As with younger adolescents, history of maternal AUD was confirmed as occurring before or after mothers' pregnancies to avoid including subjects with fetal alcohol exposure.

Table 1. Characteristics of adolescent participants (*N*=50)
ANOVA and Chi-square comparing FH across categories

	FHN *n*=26 M (*SD*) or %	FHP *n*=24 M (*SD*) or %	F/χ^2	*p*-value
Sex (% Male)	46%	67%	2.15	.14
Age in years (range 12-14)	13.16 (0.82)	13.25 (0.86)	.17	.70
Boys' age in years	13.50 (0.68)	13.34 (0.85)	1.02	.32
Pubertal Development Scale				
Girls (*n*=24)	3.20 (1.15)	3.13 (0.64)	.29	.87
Boys (*n*=28)	2.38 (0.77)	2.88 (0.72)	3.14	.09
Ethnicity (% Caucasian)	79%	88%	.72	.40
Conduct disorder diagnosis	11%	29%	2.83	.09
Father education	16.64 (1.83)	15.64 (2.50)	2.70	.11
Mother education	15.75 (1.82)	14.63 (2.34)	3.81	.06
Parental annual salary ($K)	127.27 (53.46)	125.38 (94.05)	.01	.93
CBCL internalizing *T*-score	45.87 (6.20)	47.38 (7.29)	.61	.44
CBCL externalizing *T*-score	44.93 (4.60)	46.87 (6.22)	1.55	.22
Beck Depression Inventory total	3.04 (3.35)	3.13 (3.39)	.01	.93
Spielberger State Anxiety *T*-score	27.96 (6.56)	30.67 (7.84)	1.83	.18
Junior Eysenck Personality Inventory				
Extraversion total	16.64 (3.69)	18.75 (3.14)	4.82	.03*
Neuroticism total	6.07 (5.89)	8.52 (5.55)	2.26	.14
Alcohol Expectancy Questionnaire				
Global Positive Expectancies	38.16 (8.45)	39.13 (8.78)	.16	.69
Lifetime uses of alcohol	0.39 (1.07)	0.63 (1.41)	.46	.50
Maximum drinks per episode	4.00	5.00	.09	.77
Lifetime uses of cigarettes	0.11 (0.32)	0.04 (0.21)	.69	.41
Lifetime uses of marijuana	0.18 (0.67)	0.22 (0.67)	.04	.84

* $p < .05$

Table 2. Characteristics of older adolescent (OA) participants (*N*=35)

	M (*SD*) or %
Sex (% Male)	74%
Age in years (range 16-20)	17.69 (1.07)
Ethnicity (% Caucasian)	67%
Conduct disorder diagnosis	0%
Father education	15.12 (3.27)
Mother education	14.35 (3.64)
Parental annual salary ($K)	116.00 (71.41)
CBCL internalizing *T*-score	44.66 (3.79)
CBCL externalizing *T*-score	44.23 (4.57)
Beck Depression Inventory total	11.00 (2.39)
Spielberger State Anxiety *T*-score	38.03 (7.94)
NEO Extraversion total *T*-score	44.82 (7.18)
Lifetime uses of alcohol	1.86 (9.23)
Maximum drinks per episode last 3 months	4.00 (0.34)
Number of cigarettes past month	0.54 (3.21)
Lifetime uses of marijuana	0.54 (1.27)

For youth aged 12 to 14, eligible adolescents were administered the computer assisted version of the Diagnostic Interview Scale for Children Predictive Scales (DPS)(Lucas, et al., 2001); Shaffer et al., 2000) to rule out history of DSM-IV Axis I psychiatric diagnoses. The Lifetime version of the Customary Drinking and Drug use Record (Brown, et al., 1998) was administered to assess previous alcohol, nicotine, and other drug use. Presence or absence of conduct disorder was assessed with the Conduct Disorder Questionnaire, a structured interview that ascertains DSM-III-R and DSM-IV criteria for conduct disorder (Brown, Gleghorn, Schuckit, Myers, & Mott, 1996). The Short Michigan Alcoholism Screening Test (Selzer, Vinokur, & Van Rooijen, 1976), modified for reporting on fathers and mothers (Crews & Sher, 1992), was administered to enhance accuracy of FH information by multiple informant report (Andrews, Tildesley, Hops, & Li, 2002). To assess psychosocial functioning and health history (fetal and infant development, childhood behavior, psychosocial functioning, family characteristics, and parent education and occupation) a clinical

interview was administered separately to the parent and adolescent.

The biological mother of an eligible youth was administered the FHAM (Andreasen, et al., 1986) to assess for AUD and other substance use disorders (SUD), antisocial personality disorder, bipolar disorder, and schizophrenia in the youth's first and second degree biological relatives. Youths' psychopathology reports were augmented by administering the parent version of the DPS (Lucas, et al., 2001).

The Computerized Diagnostic Interview Schedule for DSM-IV (Robins, Cottler, Bucholz, & Compton, 1996) modules of Antisocial Personality, Alcohol Dependence and Abuse, and Drug Dependence and Abuse were administered to both the biological father and biological mother. The FHAM (Andreasen, et al., 1986) was administered to both parents to ensure all of the child's biological first and second-degree relatives (i.e., the child's other parent, siblings, maternal and paternal aunts, uncles, and grandparents) are assessed. Socioeconomic status was determined with the Revised Socioeconomic Index of Occupational Status (G. Stevens & Featherman, 1981). The youth and participating family members were financially compensated for participation.

Exclusionary criteria were: history of head injury with loss of consciousness >2 min, neurological or medical problems, learning disabilities, psychiatric disorder, current psychotropic medication use, significant maternal drinking or drug use during pregnancy, left-handedness, sensory deficits, MRI contraindications; and parental history of bipolar I, psychotic disorder, or antisocial personality disorder (E. M. Hill, Stoltenberg, Burmeister, Closser, & Zucker, 1999; Ichiyama, Zucker, Fitzgerald, & Bingham, 1996; Poon, et al., 2000).

Youth aged 16 to 20 were screened in a similar manner, except that parents were not administered the DIS regarding their psychiatric histories, and the Diagnostic Interview schedule was used for youth aged 18 or older who lived independently from parents, in place of the DPS.

Measures

Mood assessments. State measures are collected at the time of scanning. Current level of depression is assessed with the Beck Depression Inventory (BDI)(Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), which has been validated with 12 to 14 year-olds (Steer, Kumar, Ranieri, & Beck, 1998). The state portion of the Spielberger State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970) is administered to assess anxiety and ensure that youth are not experiencing any nervousness that could influence fMRI results (Harris & Hoehn-Saric, 1995).

Pubertal Development Scale. The Pubertal Development Scale is a self-report measure of pubertal status (Petersen, et al., 1988). Youth select one of five, sex-specific, descriptive statements ranging from “has not begun yet” to “seems complete” to indicate current level of pubertal development. Multiple domains (i.e., presence of body hair, breast growth/voice change, menstruation/facial hair growth) are sampled in order to most closely ascertain their current Tanner-based stage of development. Pubertal staging is important to measure, as between group differences in Tanner stage could account for developmental differences in brain activation. This measure was not collected in the OA sample as it was assumed there would be a near ceiling effect.

Potential confounds. While FH is a robust risk factor in development of AUD,

externalizing and internalizing psychopathological traits (Siewert, Stallings, & Hewitt, 2004; Windle & Davies, 1999), personality attributes (Anderson, et al., 2005; McGue, Iacono, Legrand, Malone, & Elkins, 2001; Tarter & Vanyukov, 1994), and positive attitudes about alcohol use (Brown, Christiansen, & Goldman, 1987; Brown, Creamer, & Stetson, 1987; Brown & Munson, 1987) have also been shown as important risk factors. To assess these constructs in our sample, performance on the Junior Eysenck Personality Inventory (JEPI) (Eysenck, 1963), Child Behavioral Checklist (CBCL) (Achenbach & Rescorla, 2001) and Alcohol Expectancy Questionnaire (AEQ) (Brown, Christiansen, et al., 1987) were collected as potential covariates in the models specified.

Procedures

Functional neuroimaging. Adolescents were assessed and scanned at the VA San Diego Healthcare System (youth aged 12 to 14 years; 1.5T) and the UCSD Keck fMRI Center (youth aged 16 to 20; 3T). Participants were trained on the SWM task. Once positioned in the scanner, the participant's head was stabilized to minimize motion. The MRI technologist localized the head position, ensured that the participant could fully view the display screen, and asked the participant to test the four-button opto-isolated response box in the right hand. Task stimuli were presented from a laptop computer through a data projector to a screen in the MRI room positioned near the foot of the scanner bed. The participant views stimuli through a mirror mounted on the head coil.

Spatial Working Memory task. The spatial working memory task was chosen to explore the neural substrates of spatial working memory functioning and to probe the integrity of these brain regions in adolescents with a family history of AUD. The task (Kindermann, Brown, Zorrilla, Olsen, & Jeste, 2004; Tapert, et al., 2001) was adapted from McCarthy and colleagues (McCarthy, et al., 1994). The spatial working memory task (Figure 2) consists of 18 20-sec blocks alternating between experimental (spatial working memory) and baseline (vigilance) conditions. Blocks of rest were in the beginning, middle, and end of the task, during which a fixation cross appeared in the center of the screen. In the spatial working memory condition, figures appear one at a time in one of eight locations. Stimuli and locations were chosen to minimize verbal labeling (i.e., stimuli were abstract line drawings and were not presented in the four compass positions). Participants were to press a button when a design appears in a location already occupied in that block. On average, 3 of the 10 stimuli in each block were repeat locations, and repeats were 2-back. In the vigilance condition, the same stimuli were presented in the same locations, but a dot appeared above figures on 30% of trials. Participants were to press a button when a dot appeared. The purpose of the baseline is to control for simple motor and attention processes involved in the experimental condition. In both conditions, stimuli were presented for 1000 ms, and each interstimulus interval is 1000 ms (20 sec/block, repetition time (TR) = 3000 ms, 156 repetitions). Accuracy and response times were recorded.

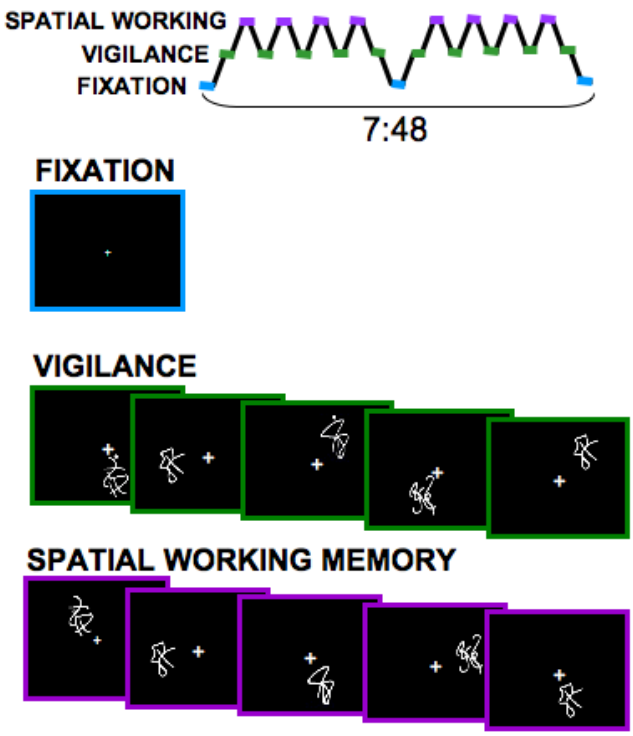


Figure 2: Spatial Working Memory task design.

Scanning parameters. For youth aged 12 to 14, 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 three-dimensional spiral fast-spin echo sequence (repetition time = 2,000 ms, echo time = 16 ms, field of view = 240 mm, resolution = 0.9375 mm x 0.9375 mm x 1.328 mm) (Wong, Luh, Buxton, & Frank, 2000). Functional imaging was collected in the axial plane using T2-weighted spiral gradient recall echo imaging (156 repetitions, repetition time = 3000 ms, echo time = 40 ms, flip angle = 90°, field of view = 240 mm, 20 continuous 7 mm slices, in-plane resolution = 1.875 mm x 1.875 mm).

For youth aged 16 to 20, images were acquired on a 3T General Electric Excite

MR system with an 8-channel phase-array head coil (General Electric Medical System, Milwaukee, WI, USA). A scout scan ensured good head placement and whole-brain coverage. A high-resolution anatomical SPGR image was acquired sagittally (TR = 7.784 ms, TE = 2.988 ms, flip angle = 12º, 1 mm^3 voxels, FOV 240 mm, matrix 256x192, slice thickness 1mm, 176 slices, bandwidth 31.25, acquisition time 7 minutes and 19 seconds). Functional imaging was collected in the axial plane using T2-weighted gradient echo imaging (156 repetitions, repetition time = 3000 ms, echo time = 30 ms, flip angle = 90°, field of view = 240 mm, 32 continuous 3.8 mm slices, matrix 64 x 64, in-plane resolution = 3.75 mm x 3.75 mm, total time 7 minutes 48 seconds). EPIs were unwarped with two field map acquisitions (each 1 minute and 8 seconds acquisition time; TR: 1000 ms, flip angle 60, FOV 240 mm, 32 contiguous axial slice s each 3.8 mm thick, matrix 64 x 64, echo times 3.2 and 5.5 ms).

Data Analysis and Statistics

Image processing. 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 selected repetition with an iterated least squares algorithm (Cox & Jesmanowicz, 1999) to estimate three rotational and three displacement parameters for each participant. Subjects were excluded if more than 17% of repetitions were removed due to motion, or if SWM accuracy performance was less than 71% (n=3). An output file specifying adjustments made was subsequently used to control for spin history effects (Friston, Williams, Howard, Frackowiak, & Turner, 1996). In addition, applied adjustments were

compared between groups, and correlation with the task reference vector to see if motion indices need to be corrected in subsequent analyses.

The time series data were deconvolved with a reference vector that coded the hypothesized BOLD signal for the alternating task conditions across the time series of the task while covarying for linear trends and the degree of motion correction previously applied (Bandettini, Jesmanowicz, Wong, & Hyde, 1993). The reference vector was convolved with a vector that modeled the typical hemodynamic response (Cohen, 1997). All data were transformed into standardized space (Talairach & Tournoux, 1988). The functional data were resampled into 3 mm cubic voxels, and a spatial smoothing Gaussian filter (full-width half maximum = 5 mm) was applied. These steps resulted in a fit coefficient for each voxel, representing BOLD response to SWM relative to the vigilance baseline condition. Activations that consisted of at least 49 contiguous significantly (α =.025) activated voxels (1,323 µl) in the younger adolescent group will be interpreted, as well as activations that consist of at least 49 contiguous significantly (α =.025) activated voxels (1,323 µl) in the OA.

For determining whether motion during the spatial working memory task differed between groups, each participant's absolute mean for each of the six motion parameters across the time series data were examined, and determined to be non-contributory ($\leq$.8 mm and <.5 degrees). For estimating task-correlated motion, the six parameters were correlated with the task reference vector across the time series for each participant. These correlations were judged to be non-contributory since there was very little bulk motion.

Physiological filtering. The data from the OA sample were re-processed to minimize the influence of brain signal originating from regions outside those of interest. While gray matter is principally composed of neural cell bodies and dendrites that are responsible for relaying information through synaptic activity resulting in stimulus response, white matter is composed of myelinated nerve cell axons that connect gray matter areas of the brain to each other. Therefore, SWM related brain activity is chiefly localized to gray matter, and white matter is of less interest in the current analysis. Based on this logic, nuisance regressors were created using an in-house pre-programmed procedure to censor-out signal originating in each individual's white matter (http://mri.ucsd.edu/wiki/index.php/BuildMask (A.N. Simmons, 2007; A. N. Simmons, et al., 2008; Strigo, et al., 2006). First, intensity-defined gray matter, white matter, and whole brain masks were created for each subject from the high-resolution anatomical brain scans. A histogram of the intensity values was then used to delineate gray from white matter. The gray matter time series, or corresponding measurements of gray matter signal in response to the SWM task, was then subtracted from the whole brain mask resulting in response specific to white matter. To reduce the influence of this "extra" signal, each individual's white matter time series were used in the general linear model as nuisance regressors with the goal of better isolating SWM related activity.

Hypothesis testing. To compare how FH might affect the maturation of functional networks in the samples of younger adolescents, it was imperative that the model be correctly specified to reflect how connectivity changes with age. Therefore a validation sample of older adolescents (OA; *N*=35) ages 16 to 20 (see Table 2 for

group characteristics) was used to establish a model of "mature" functional connectivity in the frontoparietal network. It was hypothesized that the FHN pattern would resemble the OA model than the FHP group. Specifically, FHP youth would show greater bilateral prefrontal and superior parietal lobule activation in BOLD response to SWM paradigm than FHN youth, and FHN youth would show more right lateralized frontal and inferior parietal lobule activation than FHP youth. In terms of connectivity, it was hypothesized that FHN youth, as compared to FHP youth, would demonstrate increased positive influence of the right middle frontal gyrus on the left middle frontal gyrus, and the right inferior parietal lobule on the right middle frontal gyrus, as well as an increased negative influence of the right inferior parietal lobule on the superior parietal lobule (see model depicted in Figure 1).

Data preparation. A three-step process was used to identify relevant activations for analysis as outlined by Stricker and colleagues (Stricker, et al., 2006). First, a stereotaxic brain atlas (Talairach Daemon (Cox, 1996; Lancaster, et al., 2000) was used to create a mask defining the a priori ROIs stated in the models (based on areas shown to be critical for SWM, their changes as a result of neuromaturation, and susceptibility to FH effects). Second, significant clusters of activation ($\alpha = .025$; volume $\geq$ 1,323 µL) were identified for each group using AFNI 3dttest within the regions defined in the prior step. Third, the peak activation within each significant cluster was extracted for each participant, representing the each subject's maximal contrast between the SWM and baseline vigilance conditions of the areas that are active to this task within the specified ROIs. Peak values were used instead of average BOLD response values to avoid problems related to restricted range (Stricker, et al.,

2006). Peak activation has been demonstrated to be as valid and reliable as averaged activation in indicating activity within a selected ROI (Goncalves & Hall, 2003). Also, the likelihood that these values are falsely representative was reduced because they were chosen from the hypothesis-driven search regions, and met the predetermined volume threshold criterion (Stricker, et al., 2006).

Data quality. Many fMRI studies do not report on whether their data meet basic assumptions important for the validity and success of their analyses. Peak values extracted from the ROIs were screened for multivariate outliers and non-normal distribution. Regression diagnostic statistics indicate the distance in standard deviations between a set of scores for an individual case and the sample means for all variables. Cases where $\geq$3/5 of these criteria (i.e., Mahalanobis distance $p<.001$, leverage >3*number of predictors/*n*, standardized residuals >3SD, DFFITS >1SD, DFBETAS >1SD) were met were considered as outliers and removed from the analysis (n=3). The proposed estimation procedures require normality of distributions of the peak BOLD signal values and there were no extremely skewed or kurtotic distributions, or significant heteroscedasticity. There was also a similar ratio between the largest and smallest variance of the ROIs. Because these steps were taken in data preparation one can have more confidence in the stability of the solutions and the probability increases that results are due to real effects and are not artifacts of chance (Kline, 2005b). The Satorra-Bentler scaled chi-square statistic was used to correct for lesser degrees of non-normality. The correction adjusts the model fit chi-square statistic (downward) and the standard errors for parameter estimates (upward) based

on the degree of non-normality in the data thereby reducing the type 1 error rate for individual parameter estimate tests (UofT, 2009).

Statistical analyses. SEM analysis uses covariances of these peak values, computed across subjects among the predetermined ROIs, and thus examines the extent to which the areas most associated with the task covary (Stricker, et al., 2006). It also indicates the discrepancy between the hypothesis-driven path models specified for each group by testing them against the observed data. EQS software (Bentler & Wu, 1995) was used to assess the fit of these hypothesized models. In EQS, Maximum Likelihood was specified as the estimation procedure to reduce error in the predicted covariance structure relative to the specified models. Root Mean Square Error of Approximation (RMSEA) and Akaike's Information Criterion (AIC) were consulted to for overall model fit between the observed data's variance/covariance matrix with the predicted model's matrix. RMSEA indicates overall model fit given the variability in the data, the parsimony of the model, and the number of subjects. Values below 0.05 (range 0.0-1.0) indicate excellent model fit, while values above 0.1 indicate poor model fit (Browne & Cudeck, 1993) . The lower and upper bound 90% confidence intervals were documented to help assess the degree of uncertainty associated with RMSEA. However, RMSEA confidence intervals are sensitive to small sample size and were therefore very wide in these analyses. AIC, which is widely employed throughout SEM literature, adjusts fit by weighting values by the number of parameters estimated. Smaller values indicate better model fit. Therefore, the results of this analysis illustrate the difference found in overall model fit with the data where FH and age are considered.

Follow-up analyses examined the strength of the specified connections and allowed us to infer the importance of particular connections to the overall model fit. A high amount of covariation between particular areas may indicate that these regions are correlated with SWM-related demands, and that these regions are interacting with each other as part of effective SWM functioning. As in interpreting multiple regression coefficients, the unstandardized coefficients were compared between groups to assess the relative magnitude of variance accounted for by each ROI in its respective pathway, while holding other sources of variance constant.

After good model fits were obtained, the importance of each path to overall model fit was examined by removing paths from the good fitting model one at a time with replacement and re-running the structural equation analysis. The change in model fit when each connection is left out provided a descriptive indicator of that connection's importance to overall model fit. This is akin to using Lagrange Multipliers, but expressed in terms of model fit indices instead of chi-square values (Kline, 2005a; Loehlin, 2004). The relative increase in RMSEA indicates each connection's contribution to the model's ability to fit the data. In other words, a smaller increase in RMSEA suggests that pathway is less important to overall model fit. Also, a significant change in S-B χ^2 (based on a χ^2 distribution, with appropriate applied correction because S-B χ^2 does not follow a chi-square distribution) between the less restrictive model (or nested model) and the more restrictive model (the one with a greater number estimated pathways and thus fewer degrees of freedom) suggests that the nested model is not equivalent to the restricted model, and is thus

unlikely to explain the data sufficiently if the more restrictive model (i.e., more specified paths) is a good fit. Smaller changes in S-B χ^2 suggest that a particular pathway is less important to the model, or perhaps that the nested model (i.e., fewer paths) is a more parsimonious way to explain the data (Byrne, 2006). The magnitude of the change in the Comparative Fit Index (CFI), which provides an index of the target model's improved fit over the null model, and AIC is also used as a proxy of model change, with a *decrease* in CFI indicating poorer fit and an *increase* in AIC suggesting that a nested model is less likely to replicate in a separate sample. Partial model invariance (Byrne 1989) can also be statistically evaluated using a multi-group analysis, wherein shared pathways are constrained to be equal and LaGrange Multiplier tests of equality provide S-Bχ^2 values for comparisons. Evidence for non-invariance across groups is indicated by S-Bχ^2 values less than p=.05 (Byrne, 2006).

Several analyses were performed to ensure results are not to due to confounding variance. Task-correlated motion and between-group ANOVA of bulk motion confirmed these parameters were not unduly influencing model fit per group. Importantly, stage of pubertal development is matched between FH (12 to 14 year-old) groups. Performance on the task (percentage of correctly identified stimuli) as well as reaction time has been assessed for differences between groups.

RESULTS

Behavioral performance and group membership

A 3-way ANOVA compared performance of group by SWM and vigilance conditions (Table 3). Tukey's post-hoc tests demonstrated that OA youth performed significantly better than FHN youth on all measures, and better than FHP on vigilance reaction time (rt). FHP youth performed significantly better than FHN youth on SWM accuracy.

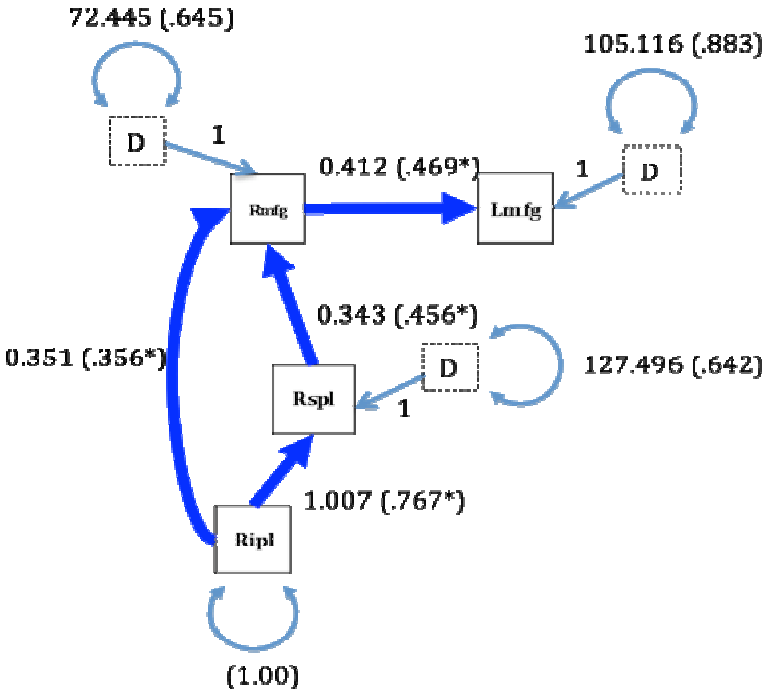
Table 3. SWM performance of adolescent and young adult participants across SWM and vigilance conditions.

	FHN (*n*=26) M (*SD*) %	FHP (*n*=24) M (*SD*) %	OA (*n*=35) M(*SD*) %	*F*-, *p*-values
Vigilance accuracy (%)*	95.52 (2.13)	95.63 (2.17)	96.70 (1.49)	3.34, .04
Vigilance rt (ms) *	656.32 (60.94)	654.42 (53.67)	605.50 (62.76)	5.60, .01
SWM accuracy *	88.29 (7.62)	93.23 (4.23)	92.79 (5.01)	6.63, .00
SWM rt (ms) *	622.67 (77.32)	576.38 (74.92)	558.49 (64.16)	5.68, .01

* $p < .05$

Model Fit in Young Adult Sample

In terms of model specification, the hypothesized model fit the OA validation sample well statistically (S-Bχ^2 [2, N=35]=1.85, p=.40 and descriptively (CFI=1.00, RMSEA= .00, $CI_{90\%}$ =.00-.33). All standardized path coefficients were ranged from .356 to .767 and were statistically significant (ps<.05).



Effect size per path	(r^2)
Rmfg → Rspl → Lmfg	.58
Rmfg → Rspl	.22
Rspl → Ripl	.59

Figure 3. The results of fitting the covariance matrix to the proposed model in OA youth. Pathways labeled with unstandardized (standardized) coefficients (p<.05) and (standard) error terms for endogenous variables.
(Rmfg = right middle frontal gyrus; Lmfg = left middle frontal gyrus; Rspl = right superior parietal lobule; Ripl = right inferior parietal lobule.)

Primary Analyses: Results of FHN and FHP Adolescents samples

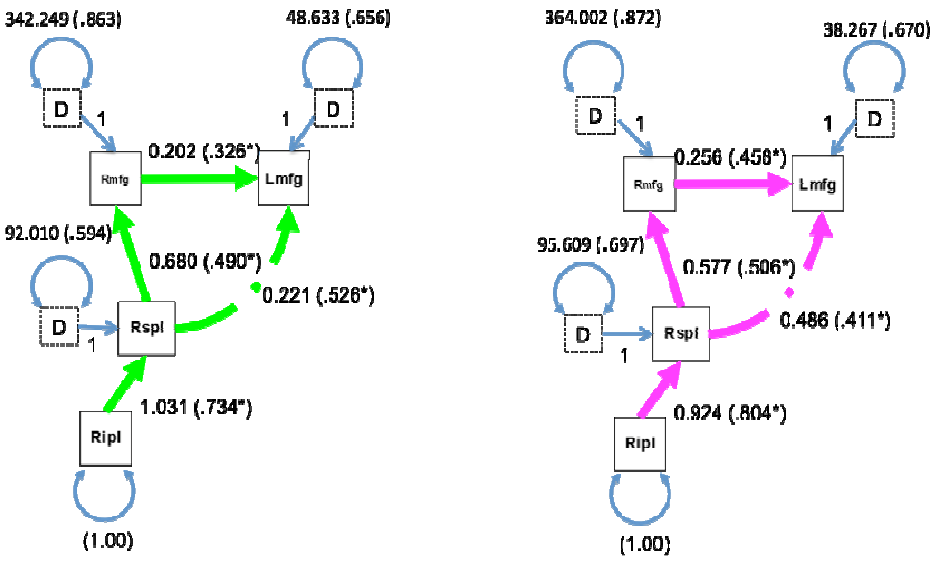
The originally hypothesized model (Figure 1) tested on data from the OA (aged 16 to 20) validation sample fit well statistically and descriptively. To determine how this model changes over FH samples, these groups were constrained to the OA model. It was proposed that the FHN sample would fit the best fitting model generated from the OA validation sample better than the FHP adolescents, indicating more mature SWM networks (see Hypotheses for details). Covariance matrices for FHP

(*n*=24) and FHN (*n*=26) adolescents (ages 12 to 14) were generated and model fit indices were examined. The specified model did not fit either group statistically (FHN S-Bχ^2 [2, N=26]=6.153, *p*=.046; FHP S-Bχ^2 [2, N=24]=8.451, *p*=.015). The residual matrices for both groups indicated that the greatest amount of variance missing was from omitted bilateral connections, particularly between the right superior parietal lobule and the left middle frontal gyrus (e.g., standardized residual was .40 in FHP and .28 in FHN, indicating greater variance unaccounted for in the FHP group). The addition of a bilateral path from the right superior parietal lobule and left middle frontal gyrus (see Figure 3) greatly improved statistical fit (FHN S-Bχ^2 [1, N=26]=0.133, *p*=.716; FHP S-Bχ^2 [1, N=24]=0.891, *p*=.345) and was not statistically redundant (FHN RMSEA= 0.000 with $CI_{90\%}$ =.000-.392; FHP RMSEA = 0.000 with $CI_{90\%}$ =.000-.528). However, the path from the right superior parietal lobule and right middle frontal gyrus was not significant in either FH group of young adolescents. For FHN participants, the remaining standardized path coefficients were statistically significant (*p*s<.05) and ranged from .378 to .796. For the FHP group, connections between the right superior parietal lobule and right middle frontal gyrus, *and* right superior parietal lobule to left middle frontal gyrus were not significant, and remaining loadings ranged from .326 to .734, indicating less good fit to the mature model.

Exploratory Analyses: Model Modification

Theoretical and statistical criteria were used to identify models where all paths were statistically significant for both FHN and FHP groups. It was thought that if the

less mature SWM networks rely on greater bilateral connectivity, then anterior-posterior gradients might be of lesser importance. Similarly, multivariate model modification indices, which approximate the improvement in model fit for the deletion (i.e., Wald Test) or addition (i.e., La Grange Multipliers) of a pathway, suggested that deletion of the right superior parietal lobule to the right middle frontal gyrus path (which was non-significant in both groups in both the original and newer model with the added bilateral connection) would improve overall model fit in FHN and FHP samples. Deletion of the right inferior parietal lobule to right middle frontal gyrus resulted in good overall fitting models for both groups (i.e., FHN S-Bχ^2 [2, N=26]=0.113, *p*=.945; FHP S-Bχ^2 [2, N=24]=2.124, *p*=.346) was statistically parsimonious and more likely to replicate (FHN RMSEA= 0.000 with $CI_{90\%}$ =.000-.149; FHP RMSEA = 0.000 with $CI_{90\%}$ =.000-.387). Standardized path coefficients were statistically significant (*p*s<.05) across groups and ranged from .326 to .734 and .411 to .804, respectively (Figure 4).



Effect size per path (r^2)	FHN	FHP
Rmfg → Rspl → Lmfg	.569	.552
Rmfg → Rspl	.256	.240
Rspl → Ripl	.647	.539

Figure 4. Best fitting FHN youth mode (green, left); Best fitting FHP youth model (purple, right); Pathways labeled with unstandardized (standardized) coefficients (*p<.05) and (standard) error of endogenous variables.
(Rmfg = right middle frontal gyrus; Lmfg = left middle frontal gyrus; Rspl = right superior parietal lobule; Ripl = right inferior parietal lobule.)

Partial model invariance was established for OA and FH groups. Three of 4 pathways in each groups' final model (right middle frontal gyrus to left middle frontal gyrus, right superior parietal lobule to right middle frontal gyrus, and right inferior parietal lobule to right superior parietal lobule) (ps>.172) were statistically comparable. Comparison of FH groups on their shared final model indicated invariance on the pathway added from the right superior parietal lobule to the left

middle frontal gyrus (χ^2 =4.75, *p*=.029; dashed line Figure 4). This pathway was redundant in the OA model.

SWM Performance and Connectivity

It was hypothesized that if improved SWM performance is positively related to connectivity associated with mature neural networks, then delayed neuromaturation in FHP youth gains further support as a risk factor for AUD. When SWM accuracy scores were included in each samples' model of best fit, as related to each region of interest, and re-run one relationship at a time, increased SWM accuracy scores were significantly and negatively related to activation of the right superior parietal node in the FHP sample (FHP S-Bχ^2 [5, N=24]=7.135, *p*=.211, RMSEA= 0.000 with $CI_{90\%}$ =.000-.279). The standardized factor loading between the right superior parietal lobule and SWM accuracy was negative (-.401) and statistically significant (*p*<.05). The effect size was small (r^2=.16). The remainder of the standardized loadings were positive and statistically significant (*p*s<.05) and ranged from .326 to .734. SWM accuracy was not significantly related to any other region of interest in this sample, and was not significantly associated with any nodes in the FHN or OA samples.

Covariance of SWM performance across sample comparisons did not affect the previously described outcomes. Also, differences in sample size may have contributed to the greater influence of SWM accuracy in the smallest group. Furthermore, when the path between the right superior parietal lobule and SWM accuracy scores was constrained to be equal across family history groups the relationship was statistically

invariant across groups. In consideration of the small effect size of the path in the FHP group, differences in sample size, and invariance between groups, the influence of SWM accuracy on the overall model fit was judged to be insignificant.

Follow-Up Analyses of Primary Hypotheses

Model fit was calculated after each path was removed one at a time. The change in model fit gives an estimation of the importance of the pathway to the model. As Table 4 illustrates, removal of the right superior parietal lobule to right middle frontal gyrus connection has the least impact on the overall OA model fit. This path was not statistically significant in either FH group. The next least important connection was between right middle frontal gyrus and left middle frontal gyrus. Across all three models, the most robust relationship was between the right superior parietal lobule and the right inferior parietal lobule. Indeed, the right superior parietal lobule was the only node across all 3 models that was (negatively) statistically associated with improved SWM accuracy in the FHP sample. Of note, removal of the right superior parietal lobule to left middle frontal gyrus pathway, the connection that was statistically different between FH groups, decreased overall model fit much more in FHP than FHN models, underscoring the magnitude of group differences

Table 4. Summary of Goodness of Fit Statistics: Overall fit indices for each group's final best fitting model and respective changes with removal of each pathway.

Model	S-B χ^2	*p*-value	df	¥AIC	¥CFI	SRMR	¥RMSEA	¥RMSEA90%CI	Δ¥S-Bχ^2	Δdf	Δ¥CFI	ΔAIC
OA best fit	1.85	.40	2	-2.15	1.00	.03	.00	.00 - .33	--	--	--	--
Lmfg → Rmfg	--	--	0	--	--	--	--	--	--	--	--	--
Rspl → Rmfg	9.56	.02	3	3.56	.83	.08	.25	.08 - .44	7.34*	-1	-.17	5.71
Ripl → Rmfg	5.91	.12	3	-.09	.92	.06	.17	.00 - .37	4.82*	-1	-.08	2.06
Ripl → Rspl	20.51	.00	3	14.51	.58	.24	.41	.25 - .58	15.66*	-1	-.42	18.81
FHN best fit	.11	.95	2	-3.89	1.00	.01	.00	.00 - .15	--	--	--	--
Lmfg → Rmfg	4.50	.21	3	-1.50	.96	.11	.14	.00 - .38	3.51	-1	-.04	2.39
Rspl → Rmfg	7.00	.07	3	1.00	.90	.23	.23	.00 - .45	35.74*	-1	-.10	4.89
Ripl → Rspl	--	--	0	--	--	--	--	--	--	--	--	--
Rspl → Lmfg	4.70	.20	3	-1.30	.96	.11	.15	.00 - .39	11.09*	-1	-.04	2.59
FHP best fit	2.12	.35	2	-1.88	1.00	.01	.05	.00 - .41	--	--	--	--
Lmfg → Rmfg	4.01	.26	2	-1.99	.98	.10	.12	.00 - .38	1.52	-1	-.02	-.11
Rspl → Rmfg	9.84	.02	2	3.84	.78	.26	.32	.11 - .53	7.63*	-1	-.22	5.72
Ripl → Rspl	--	--	0	--	--	--	--	--	--	--	--	--
Rspl → Lmfg	9.79	.02	2	3.79	.78	.19	.31	.11 - .53	5.47*	-1	-.22	5.67

* statistically significant ΔS-Bχ^2 $p<.05$; ¥ S-B = corrected values.

Physiological Noise Filtering

Data from the OA (aged 16 to 20) validation sample were subjected to physiological filtering to determine how the model would potentially change. Covariance matrices for OA were generated with the filtered data, and model fit indices were similar and slightly more robust than the non-filtered dataset (OA-filtered S-Bχ^2 [2, N=35]=.575, *p*=.75; RMSEA= .00, $CI_{90\%}$ =.00-.23). Standardized residuals ranged from .00 to .06, where largest residual was between the left middle frontal gyrus and the right superior parietal lobule. Standardized path coefficients were significant (*p*s<.05) and ranged from .429 to .735. The change in chi-square was not significant between the filtered and non-filtered models; tests of invariance were also non-significant. Comparisons between the filtered OA dataset and the FH groups yielded the same results as previously described.

Summary of Findings and Original Hypotheses

This is the first functional connectivity study of SWM, therefore, the hypothesized models of both "mature" and "immature" pathways were based on regional BOLD activation of adults and youth, and not necessarily how these regions interacted. Despite this, many of the proposed hypotheses describing "mature" and "immature" model relationships were supported and add to the validity of the current findings.

1) It was predicted that the right middle frontal gyrus would have a weaker, positive influence on the left middle frontal gyrus in FHP youth as compared to

the FHN youth and OA groups. Examination of the unstandardized coefficients suggested that, as predicted, the influence of the right middle frontal gyrus was stronger in the OA model than both FH groups. There was no qualitative difference between FH groups, and differences between all three groups were not judged to be statistically different in formal tests of model invariance.

2) It was predicted that FHP subjects would rely more heavily on the superior rather than inferior parietal lobule, producing a strong, negative influence of the inferior parietal lobule on the superior parietal lobule. Present results did not support this prediction. Instead, the superior parietal lobule demonstrated the strongest, *positive* connection across all three groups' models, and this relationship was crucial for overall model fit. It was also hypothesized that the inferior parietal lobule would increase in importance with greater adolescent development. In line with this prediction, the connection between the right inferior parietal lobule and right middle frontal gyrus was only significant in the OA model. Additionally, it was predicted that as activation in the right inferior parietal lobule increased, superior parietal input would no longer crucial for efficient task performance in OA youth. This hypothesis was not supported. However, right superior parietal lobule activation was weakly and negatively related to SWM accuracy in FHP youth. In other words, for FHP youth, increasing activation in the right superior parietal lobule was related to poorer SWM accuracy. SWM was not related to any other brain region in FHP youth, and was not related to any region at all across the other groups, perhaps suggesting that decreased involvement of the right superior parietal lobule

during SWM with maturing brain networks. However, group differences could also be influenced by sample size, though sizes were very similar.

3) It was also thought that a relative decrease in the activation of the superior parietal lobule in OA and FHN youth would lead to a relatively weak, negative influence of this region on the right middle frontal gyrus. This relationship was in fact *positive* across all groups, and although it was weaker in young adolescent groups than OA, this was not a significant different.
4) Increased response in the right middle frontal gyrus and concomitant increase in the right inferior parietal lobe in OA and FHN youth was proposed to create a strong, positive relationship between these regions, thus mimicking the right greater than left activation pattern established in adults. These results partially supported this hypothesis and demonstrated that the pathway between the right inferior parietal lobule and the right middle frontal gyrus was additive in the OA model but extraneous in the FH groups.
5) As hypothesized, physiological filtering of the OA dataset neither resulted in meaningful change in model fit or substantive change of between group comparisons.

DISCUSSION

Previous research suggests that a neurobiological mechanism may contribute to the increased risk that youth with positive family histories of AUD have for future problem drinking. Therefore, the primary goal of this study was to characterize SWM functions in youth with and without positive family histories via functional

connectivity models of SWM. “Mature” SWM functional connectivity was first established by modeling brain interactions on a group of demographically similar 16 to 20 year-olds, and youth between the ages of 12 and 14 with and without FH risk factors were compared to this baseline “mature” model.

It was proposed that the FHN young adolescents would demonstrate a pattern of functional connectivity that was more similar to the OA model than that of their FHP peers. Examination of the overall fit indices and relative strengths of the models’ connections within each group sample illustrated that both developmental stage (early versus late adolescence) and FH status influenced the pattern of interactions within the specified SWM network. Age independently influenced model fit, as the younger adolescents’ best fitting models required, 1) the addition of a bilateral pathway between the right superior parietal lobule and the left middle frontal gyrus, and 2) the deletion of the connection between the right middle frontal gyrus and right inferior parietal lobule, as compared to the young adult model of best fit. These findings are consistent with previous studies of localized BOLD response, citing increased right lateralized SWM in adults as compared to more bilateral SWM processes in children, and suggests increased specialization of SWM processing with age and experience.

Differences between the FH groups also suggest that a family history of AUD influences brain networks in a manner consistent with the developmental delay hypothesis. The main FH comparison demonstrated that youth without dense family histories of AUD produced a network of brain activity that resembled the OA model more than that of the FHP comparison group. Specifically, FHP youth demonstrated a statistically significant stronger regression coefficient for the bilateral pathway, which

was an age-invariant connection, and therefore demonstrated less right-lateralized brain activity. Removal of the pathway between the right superior parietal lobule to left middle frontal gyrus from the FHP model also decreased overall fit indices much more than when it was removed from the FHN group, underscoring the extent of group differences. The difference between FHN and FHP remained unchanged after controlling for SWM performance, which was slightly superior in FHP youth (means = 88% v 92%), suggesting that this difference is not mediated by SWM performance. These data contribute to the growing evidence that familial history of AUD may influence neurobehavioral correlates and thus contribute to increased rates of problem drinking in FHP youth.

The disparate relationship of SWM accuracy to brain networks across groups also provide support for subtle FH-related developmental differences. Improved SWM accuracy was weakly and negatively associated with activation in the right superior parietal lobule, but only in FHP youth. There was no relationship between the superior parietal lobule and SWM accuracy in either FHN or OA samples, demonstrating less involvement of this region during task performance. This is consistent with the expectation that the right superior parietal lobule would become less crucial for successful SWM performance with brain development (adolescent stage), and potentially suggests decreased involvement of the right superior parietal lobule during SWM as brain networks mature as previous studies have suggested (Schweinsburg, Schweinsburg, et al., 2005). However, the small effect size of this relationship and difference in sample size between groups precludes any strong conclusions regarding this finding.

Results of these analyses suggest that age impacts brain networks supporting effective SWM performance. It was predicted that the right inferior parietal lobule would become more integrated with age. Accordingly, young adults invoked an additional pathway for efficient SWM performance between the right inferior parietal lobule to the right middle frontal gyrus, which suggests that with ongoing neurodevelopment, changing strategy, or environmental experience, the right inferior parietal lobule asserts greater influence in more mature SWM networks. Indeed, increased white matter integrity of pathways connecting the frontal and parietal lobules (e.g, superior longitudinal fasciculus) has been demonstrated to occur in older adolescents (Bava, et al., in preparation; Eluvathingal, et al., 2007; Olesen, et al., 2003; Qiu, et al., 2008), suggesting development of an underlying microstructural network supporting SWM. Of note, deletion of this path in the young adult model had the least impact on overall model fit, suggesting that this pathway might not yet have reached its maximum utility. Longitudinal studies of white matter integrity and functional connectivity of BOLD activation might determine whether this connection becomes increasingly important to SWM networks with age. While the connection between the right inferior parietal lobule and right middle frontal gyrus was more important in the OA sample, the observation that the connection from the right superior parietal lobule to the right inferior parietal lobule was by far the strongest pathway across all groups suggests persisting importance of the right superior parietal lobule throughout adolescence into young adulthood.

A key finding was that FHP youth had a stronger bilateral connection between the right superior parietal lobule and the left middle frontal gyrus than the FHN cohort.

Since this connection was not observed in the young adult sample, a weaker connection between these regions may describe more fully developed SWM supportive processes in the FHN youth. FHP youth also demonstrated relatively more involvement of the right superior parietal lobule in SWM performance accuracy than other groups, which may also suggest developmental differences. Evidence of poorer performance on neurocognitive measures, aberrant neurophysiological indices (i.e., reduced amplitude of the P300 component, increased resting beta frequency, reduced intracranial volume, increased postural sway, and their relationship to genotypic features such as $GABA_A$ receptor genes) suggest a relationship between FHP and neurobiological risk factors, at least before the age of 18, when these differences are most robust. Therefore, understanding the neural characteristics of FHP youth may help determine potential interventions to reduce risk for future AUD.

The mechanism of FHP-related neurodevelopmental delay may be partially explained by genetic influence of gamma-aminobutyric acid (GABA) interneurons. Genetic links between $GABA_A$ receptor genes, the primary inhibitory neurotransmitter in the brain, have been linked to increased resting EEG beta frequency in the offspring of alcoholics (Bauer & Hesselbrock, 1993; Finn & Justus, 1999; Pollock, Earleywine, & Gabrielli, 1995; Rangaswamy, Porjesz, Chorlian, et al., 2004). Because the coordination of inhibitory inter-neurons and excitatory pyramidal cells depends on the action of $GABA_A$ (Whittington, Traub, Kopell, Ermentrout, & Buhl, 2000), alcoholics and their children who demonstrate increased beta activity (electrophysiological characteristic which seems to underscore differential P300 event-related potentials) may have a suboptimal balance between excitation and inhibition (Porjesz &

Rangaswamy, 2007). Variations in $GABA_A$ receptor genes (e.g., GABRA2) may influence neural excitability (Covault, Gelernter, Hesselbrock, Nellissery, & Kranzler, 2004; Edenberg, et al., 2004) and predispose youth for alcoholism and related disinhibitory disorders (H. Begleiter & Porjesz, 1999). Deficits in GABA benzodiazepine receptors in individuals with a family history of AUD have also been observed in neuroimaging studies (Volkow, et al., 1995), supporting the role of GABAergic systems in risk for AUD.

However, abnormal GABA interneuron action, like reduced P300 frequencies which are characteristic of many disinhibitory conditions (e.g., anti-social personality disorder, conduct disorder, and attention deficit hyperactivity disorder (Porjesz, et al., 2005), is also linked to a number of developmental disorders such as childhood schizophrenia (Lewis, Cruz, Eggan, & Erickson, 2004), Tourette's syndrome (Kalanithi, et al., 2005), and autism (Belmonte, et al., 2004). Although the mechanism underlying organization of cortical GABAergic synapses is poorly understood, it is thought that errors in the process may have a profound impact cortical processing and plasticity (Di Cristo, 2007). Specificity aside, an initial genetic disturbance (no matter how minimal) will influence the developmental trajectory and in all subsequent interactions with external stimuli (Di Cristo, 2007). Therefore, differences in neurobiological development due to FH effects may have a small but important impact on how FHP youth respond to increased risk factors for future AUD during adolescence.

CONCLUSIONS

These findings support the neurodevelopmental delay hypothesis, which suggests

that protracted neuromaturation is a potential mechanism through which a positive FH increases risk for alcohol dependence. Developmental literature suggests that with increasing skill in cognitive resources such as inhibition, processing speed, and working memory (Luna, Garver, Urban, Lazar, & Sweeney, 2004; Luna, et al., 2001), children and adolescents improve their mastery in tasks that require these component processes. Mastery and integration of each subcomponent improves overall cognitive control of behavior. A subtle deficit in one or more of these cognitive elements may lead to reduced complex cognitive control and postponed mastery of interdependent neurocognitive functions. Therefore, an adolescent with a subtle lag in fronto-parietal neuromaturation may also suffer a concomitant delay in achieving inhibitory control (Cloninger, Sigvardsson, & Bohman, 1988; McGue, Slutske, Taylor, & Iacono, 1997; Porjesz, et al., 2005; Tarter, 1988).

The potential influence of suboptimal cognitive behavioral control on teens exposed to high-risk situations is self-evident. In the context of many risk factors, neuromaturational lags may substantially increase transition to AUD. Recent national surveys estimate approximately 17% of youth between the ages of 12 to 17 have used alcohol in the past month(SAMHSA, 2008). Use of alcohol in adolescence increases the risk for developing secondary problems such as psychopathology (Rohde, 2001), physical problems (Aarons, 1999), impaired social development (Baumrind & Moselle, 1985), and substance dependence (Grant & Dawson, 1997). Alcohol consumption is also estimated to be responsible for roughly 4% of worldwide disease burden (Guilbert, 2003), which is comparable to rates of disease linked to hypertension (Room, Graham, Rehm, Jernigan, & Monteiro, 2003). Early identification of youth at greatest risk for developing AUD could

substantially reduce global rates of alcohol-related disease. Early identification will facilitate intervention development and implementation. Finally, these findings suggest that interventions need address the potentially protracted neurodevelopment of FHP youth.

Strengths

Theoretically driven analyses. A particular strength of the present study is its theoretically driven nature. As opposed to the majority of existing functional connectivity studies that use data-driven methods to compose models (e.g., functional connectivity via ICA or PCA) the current models were chosen based on literature describing the brain regions supporting SWM and how these brain regions may change and interact with brain development. Independent selection of regions of interest aids decreases the selection bias of whole brain correlational analyses, the subject of much recent scrutiny (e.g., (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009)Vul et al., 2009), and guards against false inflation of secondary analysis.

Data preparation. Unlike many fMRI studies, the current study employed multivariate regression diagnostics to ensure that assumptions important to the stability and validity of subsequent analyses were adequately met. ROIs were screened for multivariate outliers and non-normal distribution, and the Satorra-Bentler scaled chi-square statistic was used to correct for lesser degrees of non-normality. Improved data preparation increases the probability that these results are artifacts of noise.

Sample quality. Adolescents were screened for a large number of potentially confounding influences. Across a large range of parameters, from developmental problems and demographic factors, to current substance use and mental health indices,

these youth were extremely similar across groups and unaffected by factors that might confuse final conclusions (e.g., current substance abuse, parental education). Additionally, because samples were so well-matched and free from confounding influences, the fact that we found differences between groups is even more remarkable, and speaks to the robustness of these findings.

Limitations

Differences between scanners. The younger cohort was scanned on a 1.5T field strength magnet while the older cohort was imaged on a 3T system, which could potentially influence these findings. Stronger magnet strength improves signal to noise ratio, making it more likely to detect signals of interest. However, increased magnet strength also increases the sampling of non-random noise, such as cardiac, cerebral blood flow, and respiratory related influences. Although data was collected on disparate field strengths the relative relationships between the regions of interest should be proportionately scaled. Furthermore, FH history groups were collected on the same scanner, helping to ensure observed differences were due to the variable of interest. No parallel physiological data were collected along with fMRI data, however, when retrospective physiological filtering was applied to data collected on the 3T system, the relationships of interest remained unchanged.

Generalizability. The demographic make-up of our sample may attenuate FH effects on functional connectivity. Most participants are from relatively affluent areas of San Diego and have highly educated parents. Genetic risk for AUD is less likely to be expressed in such environments. For example, adoptees with a high genetic

predisposition for AUD were found to develop alcoholism more often when reared in low-socioeconomic (high-risk) environments (Sigvardsson, Bohman, & Cloninger, 1996). Sampling a greater number of participants with increased risks for AUD, such as adverse childhood events, lower socioeconomic status, and conduct disorder, a well-known risk factor for the development of AUD, might increase the likelihood of finding FH effects on neuromaturation. On the other hand, such a sample would be more likely to carry confounding factors. Similarly, these results will only generalize to youth who match the inclusion and sizable exclusion criteria for our study, with either a strong positive FH, or no first or second degree relatives with AUD.

Power and sample size. Although functional connectivity studies with much smaller samples have been published (Buchel & Friston, 1997; Hampson, Driesen, Skudlarski, Gore, & Constable, 2006; R. Schlosser, et al., 2003) our sample size is small by traditional SEM standards. SEM was designed for use in large samples, where *large* is loosely defined as N > 200 cases and *small* is anything less than *N* = 100 (Kline, 2005b). While results calculated from larger samples have less sampling error and greater power to detect small effects, there is considerable variability in what has been suggested as adequate sample size. One factor confusing the issue is that SEM has been traditionally carried out on latent variables, composed of many observations, which vary in reliability. For these types of analyses, thousands of cases may be necessary to ensure close model fit and large power (MacCallum, Browne, & Sugawara, 1996), though Kline suggests that the minimum ratio of number of cases to free parameters is 5:1 (Kline, 2005b). However, SEM can also be used to test path models that do not contain latent variables. In this role, SEM can measure the fit

between hypothesis-driven path models and the actual data, which may be more reliable in the case of fMRI. Furthermore, in fMRI, the number of observations *at the voxel level* meets the criteria proposed by MacCallum and colleagues (MacCallum, et al., 1996). Additionally, simulation studies examining the effect of sample size on the validity and reliability of model fit and relative strength in connections support the adequacy of smaller size (Boucard, Marchand, & Nogues, 2007; Protzner & McIntosh, 2006). For example, Boucard and colleagues (2007) found that very high validity and reliability can be achieved with $N \geq 25$, and that sample sizes $N \geq 20$ retain the accuracy of the relative strengths of coefficients 90% of the time (Boucard, et al., 2007). Protzer and McIntosh (2006) similarly advocate that the relative strength of most path coefficients is maintained with a sample size $N \geq 20$ (Protzner & McIntosh, 2006). These findings suggest that the current SEM study is adequately powered to detect valid and reliable FH effects.

Task design. This analysis was carried out on fMRI data collected with a block design. Although an event-related design would provide more information on the effects of successful or unsuccessful recognition of spatial locations, a block design has the advantage of greater statistical power (Friston, Zarahn, Josephs, Henson, & Dale, 1999). Also, many of the studies that the model was derived from were collected using a block design, thus maintaining the consistency of the patterns of response to SWM.

Temporal precedence. Temporal precedence, or whether activity in ROI "A" occurs prior to activity in ROI "B," may be obscured at the hemodynamic level due to the delay between change at the synaptic level and hemodynamic response.

Covariances of BOLD activation are averaged over groups from a block design, which in and of itself requires averaging of responses. Therefore, temporal sequencing of ROI activations cannot be addressed using this approach.

Directional inference. Connectivity equations are recursive, while cerebral physiology is bidirectional. Analysis of functional connectivity suggests that linear estimates can adequately represent observed changes in cerebral blood flow (Friston, 1994). However, models are made recursive as even one bidirectional effect enormously complicates the analysis (Kline, 2005). Failure to include bidirectional relationships between regions of interest limits our ability to accurately represent neural networks.

Models are underdetermined. Only a select few changes in observed voxels are used to characterize many voxels. Therefore the validity of such analyses depends on the validity of the model. Our simple model expresses the hemodynamic change at one voxel as a weighted sum of changes in regions hypothesized to be connected to an ROI being investigated (Friston, 1994). The weights of the path coefficients describe the degree of connectivity. Undoubtedly, this is a simplification of reality but hopefully captures an important mechanism by which we can improve identification of youth at greatest risk for AUD.

Cross-sectional study. Longitudinal follow-up data in early adulthood will be needed to fully test the neuromaturational lag hypothesis, to examine whether the FHP youth do indeed catch up to the FHN youth, evidenced by having the same model fit for connectivity of these frontal and parietal regions 6-8 years after the baseline imaging data evaluated here.

Future Directions

Sampling a greater number of participants with a greater number of risk factors, such as adverse childhood events, and especially, conduct disorder, a well-known risk factor for the development of AUD (Sartor, et al., 2007) might increase the likelihood of finding FH effects on neuromaturation, although consideration of confounds (e.g., history of head trauma and psychiatric comorbidity) would be critical.

The validity and reliability of these models can be further tested with ongoing research in our lab. As this study is part of a larger ongoing longitudinal study, our group can verify that changes in networks are due to neuromaturational changes with follow-up data. It will also be possible to compare functional networks by examining the quality of connective white matter tracts (using diffusion tensor imaging data) to anatomically inform connectivity models. Other investigators will hopefully seek to replicate the model with independent samples. This final step is necessary to ascertain the reliability of the networks described in the work.

The influence of protracted neuromaturation within a larger constellation of risk factors for AUD has yet to be understood. Longitudinal studies need to address the contribution of neurodevelopment in order to understand the interplay of factors predicting AUD. Finally, future studies on individuals with AUD need to account for FH as a potential moderator of neurotoxic effects.

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