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fMRI Correlates of Risky Decision-Making in Adolescent Alcohol Users:

The Role of Abstinence

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

Doctor of Philosophy

in

Clinical Psychology

by

Alissa Dyan Bazinet

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2013

The Dissertation of Alissa Dyan Bazinet is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego

San Diego State University

2013

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This work is being prepared for submission for publication as “fMRI Correlates of Risky Decision-Making in Adolescent Alcohol Users: The Role of Abstinence.” The dissertation author will be the primary author of this material along with co-authors Alan Simmons, Ph.D., Carmen Pulido, Ph.D., Susan Tapert, Ph.D., and Sandra Brown, Ph.D.

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- Bazinet, A.D.**, Squeglia, L., Riley, E.P., & Tapert, S.F. (in press, 2013). The effects of drug exposure on development. In: K.J. Sher (Ed.), *Oxford handbook of substance use disorders*. Oxford: University Press.
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Abstracts

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- (2008). Functional brain changes in children and adolescents with heavy prenatal alcohol exposure. Symposium conducted at the 36th International Neuropsychological Society meeting: Waikoloa, HI.
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 University of California, San Diego
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June 2010 – June 2012

Responsibilities: Conducted neuroimaging research in adolescents with histories of heavy alcohol use as well as non-users. Involved in data collection (scanner operation), image processing, data quality control, data analyses, and manuscript preparation. Dissertation involved an examination of the neural correlates of risky decision-making and the role of abstinence on neural functioning in adolescents with and without histories of heavy alcohol use. The project utilized functional magnetic resonance imaging (fMRI) methodology to assess participants at 3 time-points, over a six-week period of sustained abstinence.

Graduate Research Assistant
Center for Behavioral Teratology
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Advisor: Edward Riley, Ph.D.

August 2006 – May 2010

Responsibilities: Conducted neuroimaging research in children with fetal alcohol spectrum disorders (FASD) and/or attention-deficit/hyperactivity disorder (ADHD), as well as typically developing children. Involved in all phases of research, including: data collection (scanner operation), quality control and management of neuroimaging and neuropsychological data, image processing and data analyses, manuscript preparation, and grant writing. Involved in projects examining: 1) neural correlates of spatial working memory in children with and without FASD, and 2) motor activity and continuous performance test behavior in children with FASD and/or ADHD and controls. Also involved in writing chapters and review papers relevant to fetal alcohol research.

Research Assistant/Study Coordinator
Behavioral Tech Research, Inc, Seattle, WA.
Supervisor/PI: Linda Dimeff, Ph.D.

October 2003 – July 2006

Responsibilities: Coordinated two large studies examining the effect of training modality (computer-based vs. text vs. instructor-led) on skill acquisition, knowledge gains, and self-efficacy among community mental health providers trained to implement Dialectical Behavior Therapy (DBT). Responsible for subject recruitment, data collection, entry, and management, supervision of undergraduate research assistants, submission of materials to IRBs, and other administrative tasks. Also involved in data analyses, preparation of abstracts for research conferences, manuscript preparation, and grant writing. Assisted the PI with the development and psychometric evaluation of study outcome measures and coding manuals.

Undergraduate Research Assistant
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October 2003 – June 2006

Responsibilities: Coded parent-child interactions of 2.5 – 3.5 year-old children in laboratory settings and preadolescents in home settings, using a behavioral rating system. Also created and managed databases, and conducted all reliability analyses for the coding group. Developed and proposed a study for an undergraduate honors thesis investigating contextual risk, physiological reactivity (to frustrating and anxiety-eliciting tasks), and children's later adjustment outcomes (in the preadolescent sample).

TEACHING EXPERIENCE

Graduate Teaching Associate

August 2011 – May 2012

Department of Psychology, San Diego State University

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SUPERVISED CLINICAL EXPERIENCE

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August 2012 – August 2013

Psychology Intern

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Neuropsychology rotation

August 2012 - December 2012

PVAMC Neuropsychology Clinic

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Responsibilities: Conduct comprehensive neuropsychological and personality assessment of veterans in an outpatient hospital setting. Responsible for all phases of the evaluation process, including intakes, test administration, scoring and interpretation of results, report writing, and provision of feedback to patients and their families. Work with a primarily male adult population with a variety of neurological and neuropsychiatric disorders, including dementia, epilepsy, PTSD, depression, cerebrovascular disease, multiple sclerosis, primary progressive aphasia, and other cognitive disorders. Also co-facilitate a weekly "cognitive strategies" skills-based group for older veterans with mild cognitive impairment; skills taught include time management, organization, learning and memory

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Neuropsychology sub-rotation

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Responsibilities: Conduct comprehensive neuropsychological and personality assessment of adult patients in an outpatient medical setting. Responsible for test administration, scoring and interpretation of results, and report writing. Patient population includes young, middle-aged, and older adults (both male and female) with a variety of disorders, including epilepsy, cancer, psychiatric disorders, dementia, multiple sclerosis, and cerebrovascular disease.

Health Psychology rotation

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PVAMC/Hillsboro Community Based Outpatient Clinic

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Substance Abuse Treatment Program rotation

April 2013 – August 2013

PVAMC/Vancouver Community Based Outpatient Clinic

Supervisor: Veronica Rodriguez, Ph.D.

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Psychology Clinic

September 2011 – June 2012

San Diego State University

Practicum Student

Supervisor: Michael Taylor, Ph.D.

Responsibilities: Conducted assessments and provided individual outpatient psychotherapy services to adults in a university-based community clinic setting. Caseload consisted of diverse clients with mood and anxiety disorders (e.g., major depression, panic disorder, generalized anxiety). Interventions included cognitive-behavioral and acceptance and commitment therapy.

OEF/OIF Post-Traumatic Stress (PTSD) Clinic July 2010 – January 2011
Department of Veterans Affairs Medical Center, San Diego
Practicum Student

Supervisors: Martha Diaz, Ph.D., Nancy Lin, Ph.D., & Sonya Norman, Ph.D.

Responsibilities: Provided group and individual psychotherapy services in an outpatient setting to veterans returning from Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) service symptoms of PTSD. Comorbidities observed in this population included: obsessive-compulsive disorder, substance abuse, depression, generalized anxiety, traumatic brain injury, psychotic symptoms, and interpersonal difficulties. Treatments included cognitive processing therapy (CPT) and prolonged exposure (PE).

Child and Adolescent Psychiatric Service July 2009 – June 2010
University of California, San Diego
Practicum Student

Supervisor: Sandra J. Brown, Ph.D., ABPP/CN

Responsibilities: Completed psychodiagnostic and neuropsychological assessments of children and adolescents in an inpatient psychiatric hospital setting. Administered and scored tests and interpreted and wrote up results in an integrated report format. Also provided group psychotherapy for adolescents in a “process group” format, as well as individual psychotherapy services, utilizing cognitive-behavioral treatment approaches. Attended weekly multidisciplinary treatment team meetings with medical (psychiatry) and psychology staff. Presenting problems included severe mood disorders, substance abuse, psychosis, disruptive behavior disorders, developmental disorders, and other acute psychiatric conditions.

Neuropsychology Laboratory July 2009 – June 2010
University of California, San Diego
Practicum Student
Supervisor: Robert Heaton, Ph.D.

Responsibilities: Interpreted neuropsychological and personality test data from historical forensic cases. Formulated and wrote integrated reports for patients with psychiatric, neurological, or general medical conditions and known or suspected cerebral disorders. Discussed details of written reports within a small group supervision format.

Neuropsychological Assessment Unit July 2008 – June 2009
Department of Veterans Affairs Medical Center, San Diego

Practicum Student

Supervisors: Mark Bondi, Ph.D., ABPP/CN, Dean Delis, Ph.D., ABPP/CN, & Vince Filoteo, Ph.D.

Responsibilities: Conducted comprehensive neuropsychological assessments of veterans in an outpatient setting, utilizing a flexible battery, process approach. Administered and scored tests, presented cases in group supervision, and interpreted and wrote up results in an integrated report format. Also provided in-person feedback to patients and their families when requested. Patient population included young, middle-aged, and elderly adults with a variety of medical, neurological, and psychiatric disorders.

Psychology Clinic

July 2007 – June 2008

San Diego State University

Practicum Student

Supervisors: Nader Amir, Ph.D. & Alan Litrownik, Ph.D.

Responsibilities: Conducted assessments and provided individual and group outpatient psychotherapy services in a university-based community clinic setting. Treated clients with a variety of mental health issues, including: depression, bipolar disorder, generalized anxiety, obsessive compulsive disorder, eating disorders, substance abuse, behavioral problems, and marital stress. Treatments utilized were primarily cognitive-behavioral, with some interpersonal and mindfulness-based approaches used.

ABSTRACT OF THE DISSERTATION

fMRI Correlates of Risky Decision-Making in Adolescent Alcohol Users: The Role of Abstinence

by

Alissa Dyan Bazinet

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2013
San Diego State University, 2013

Professor Susan F. Tapert, Chair

A neurobiological model of risk-taking suggests that differential timing in the maturation of the brain networks associated with emotional processing and cognitive control may predispose adolescents to risky behavior, including alcohol and other substance use. Heavy alcohol use during adolescence has been shown to alter normative brain functioning, though it remains unknown whether alterations normalize with sustained abstinence or persist after cessation of use. The present study utilized fMRI to examine the effects of heavy alcohol use and short-term abstinence on adolescent neural functioning during a risky decision-making task.

Heavy drinking adolescents and non-users completed three neuroimaging assessments, spaced two weeks apart (baseline, +2weeks, +4weeks). Adolescents abstained from alcohol and other substances for the duration of the study, confirmed through regular urinalysis screenings. During scanning, participants completed a modified Balloon Analog Risk Task (BART) to inflate balloons by entering a fixed number of “pumps”. Adolescents earned 1cent/pump unless the balloon popped according to a predetermined value; a higher pump number represented a riskier choice. Relevant neuroanatomical regions of interest were identified for each phase of decision-making (assessment, anticipation, and evaluation of outcome) and between-group differences in blood oxygenated level dependent (BOLD) response were assessed at baseline. In addition, longitudinal analyses examined the main effects and interaction of Group and Time on BOLD response across the five-week period of abstinence.

At baseline, heavy drinkers showed *less* BOLD response in the right insula during anticipation [$t(1,39) = -2.89$, cluster = 324 μl , $p < .01$] and *more* BOLD response in the ventromedial prefrontal cortex [VMPFC; $t(1,39)$ cluster 1 = 3.17, 702 μl ; $t(1,39)$ cluster 2 = 3.24, 405 μl , $p_s < .01$] during evaluation of negative outcomes, compared to non-users. These differences were no longer evident at either follow-up time point. However, significant main effects of Group and interaction effects (Group X Time) were observed in other regions. Averaged across time, heavy drinkers showed *reduced* BOLD response in the dorsolateral prefrontal cortex (DLPFC) during the assessment phase [14 clusters, F -statistics (1,40) ranged from 7.65 to 9.85, volumes ranged from 378 μl to 1,782 μl , $p_s < .01$] and the left insula during anticipation [$F(1,40) = 8.25$, cluster = 297 μl , $p < .01$], and *greater* BOLD response in the left VMPFC during anticipation [$F(1,40) = 10.94$,

cluster = 756 μ l, $p < .01$], compared to non-users. For non-users, BOLD response in the right anterior cingulate increased across time during the assessment phase [$t(1,15) = -3.11$ when previous balloons popped; $t(1,15) = -3.48$ when previous balloons did not pop, $p_s < .01$], while for heavy drinkers, BOLD response increased across time in the right VMPFC/anterior cingulate during anticipation [$t(1,19) = -3.33$ when previous balloons popped; $t(1,19) = -3.54$ when previous balloons did not pop, $p_s < .01$].

Overall, these findings highlight differential neural functioning during risky decision-making in heavy drinking adolescents and non-users. While group differences in BOLD response observed at baseline were no longer apparent after two weeks of abstinence, other differences persisted across a five-week period of sustained abstinence. This pattern of results suggests that alterations in neural functioning commonly observed in adolescent alcohol users may result from a combination of acute changes related to use as well as pre-existing vulnerabilities. Conversely, some brain functioning abnormalities may reverse after longer periods of abstinence.

Introduction

Risk-taking behavior is prevalent in adolescence

It is well established that adolescents are more likely to engage in risky behaviors compared to adults or younger children, and that rates of behaviors such as substance use, unsafe sexual activity, dangerous driving, and involvement in criminal activity emerge, increase, and peak during adolescence (Boyer, 2006). Statistics from the Center for Disease Control and Prevention's (CDC, 2011) "*Youth Risk Behavior Surveillance Survey*" indicate that in 2011, 24% of adolescents in grades 9-12 knowingly rode in a car at least once with a driver who had been drinking alcohol, 22% of adolescents reported engaging in binge drinking activities (consuming five or more alcoholic drinks in one drinking episode for males, four or more drinks for females), and of the 34% of adolescents who defined themselves as "sexually active," 40% reported that they did not use a condom the last time they had sexual intercourse. Risk-taking is a complex and dynamic construct, yet not all adolescents are risk-takers. Studies have investigated individual differences in personality, sex, cognitive performance, and emotion regulation abilities, as well as complex socio-cultural influences in attempts to explain why some adolescents may be more likely to take risks than others. Recently, research has highlighted a neurobiological component that may underlie the trajectory of risk-taking commonly observed during adolescent development (Casey, Getz, & Galvan, 2008; Steinberg, 2008). This explanatory model derives from the rapidly changing nature of the adolescent brain, specifically in regions thought to play a role in risky decision-making and cognitive control.

Alcohol use increases dramatically during adolescence

Alcohol use is a behavior that goes hand in hand with risk-taking; thus, it is no surprise that rates of alcohol consumption also rapidly increase during adolescence, with 65% of 12th graders endorsing some alcohol use over the past year, compared to only 29% of 8th graders. Self-reports of past-year “drunkenness” also increase by more than 30% between 8th and 12th grades, with 12% of 8th graders and 44% of 12th graders endorsing this behavior (Johnson, O’Malley, Bachman, & Schulenberg, 2011). Heavy episodic drinking is common among this age group, with 25% of high school seniors reporting at least one binge drinking episode within the past two weeks. In addition to increased binge drinking behavior, substance-related clinical disorders begin to emerge during adolescence, with 5% of youth ages 12 to 17 meeting diagnostic criteria for an alcohol use disorder (AUD) (Substance Abuse and Mental Health Services Administration, 2008).

Risk-taking in adolescence has a neurobiological basis

Cognitive decision-making capacity has been implicated as an important mechanism in the development of adolescent risk-taking behavior. Moore and Gullone (1996) define a “risky” behavior as *“any behavior that involves potential negative consequences or loss, but is balanced in some way by perceived positive consequences or gain”*. A behavior is considered more “risky” if the potential negative consequences outweigh the perceived positive consequences. Cognitive theories attempting to explain adolescent risk-taking as the result of underdeveloped decision-making skills have found little, if any support, as studies demonstrate that adolescents show an adequate

understanding of the steps involved in the decision-making process, such as weighing pros and cons. In fact, children as young as 4 years old have some understanding of consequence probabilities (Acredolo, O'Connor, Banks, & Horobin, 1989; Schlottman, 2001) and adolescents and adults show equal levels of awareness of the consequences associated with risky behaviors (Beyth-Marom, Austin, Fischhoff, Palmgren, & Quadrel, 1993; Quadrel, Fischhoff & Davies, 1993). In some cases, adolescents may even *overestimate* their personal vulnerability to risk consequences compared to adults (Millstein & Halpern-Felsher, 2002). Further, interventions designed to provide adolescents with information about the risks of substance use, drinking and driving, and unprotected sex have proved largely unsuccessful and have done little to change adolescents' actual behavior (Bearman, Jones, & Udry, 1997). Simplified theories of "immature cognitive abilities" in adolescence are also inconsistent with a developmental perspective, as the increase in cognitive sophistication from childhood to adolescence would imply a decrease in risk-taking behaviors with age, rather than an increase (Boyer, 2006).

Steinberg (2004) proposes an alternative view of adolescent risk-taking behavior that is rooted in developmental neuroscience. Specifically, heightened risk-taking in adolescence is described as the product of a "competition" between a socioemotional network that is sensitive to social and emotional stimuli (such as reward), and a cognitive control network that is responsible for regulating executive functions such as planning, organization, response inhibition, and self-regulation. The socioemotional network relies on limbic and paralimbic structures such as the amygdala, ventral striatum, orbitofrontal cortex, ventromedial prefrontal cortex, and superior temporal sulcus, while the cognitive

control network consists of lateral prefrontal and parietal cortices as well as the anterior cingulate (Steinberg, 2008).

During adolescence, the brain undergoes significant structural, functional, neurochemical, and hormonal changes that directly impact the development of the socioemotional and cognitive control networks, among other regions. Specifically, synaptic pruning and myelination processes result in reduced gray matter volume and increased white matter volume by late adolescence/early adulthood (Giedd, 2004; Yakovlev & Lecours, 1967). Increases in white matter during adolescence are associated with greater structural connectivity and faster, more efficient neural communication between brain regions (e.g., Giedd et al., 1999; Hüppi & Dubois, 2006; Jernigan & Gamst, 2005; Luna & Sweeney, 2004). Evidence from neuroimaging studies note that dramatic changes occur in the brain's dopaminergic system at puberty, primarily in prefrontal and striatal regions (Spear, 2000). Specifically, dopamine activity shows substantial decreases in the nucleus accumbens, an important region of the ventral striatum well known for its role in reward processing. Dopamine has been implicated as a primary mechanism of affective and motivational regulation and is linked to the socioemotional network (Steinberg, 2008); thus, the sudden decrease in this neurochemical creates a "dopamine void" which may compel adolescents to seek out novel and risky behaviors to compensate (Spear, 2002). Changes in brain regions associated with the cognitive control network also take place in adolescence, including gray matter decreases and white matter increases in the prefrontal cortex, and an overall increase in synaptic connections among cortical and subcortical regions of the brain (Paus, 2005). In contrast to the acute changes that occur to socioemotional regions with

puberty, changes in the cognitive control network are gradual and typically continue into the mid-twenties.

As a result of timing differences in the developmental brain changes that occur during adolescence, there appears to be a “timing gap” between the maturation of the socioemotional network and the maturation of the cognitive control network. Greater motivational drives for novel and rewarding experiences combined with an immature cognitive control network may predispose adolescents to risky behavior, including substance use. This becomes especially relevant under conditions of high emotional arousal (e.g., in the presence of peers), where the socioemotional network is likely to become highly activated and the cognitive control network must “work harder” to override it (Chambers, Taylor, & Potenza, 2003).

Heavy drinking during adolescence is linked to cognitive impairments and brain abnormalities

While neurochemical modifications and other developmental brain changes may contribute to adolescents’ increased propensity for risk-taking (including alcohol use), it is paradoxical, as the brain may be especially vulnerable to the insult of alcohol during this critical time (e.g., Brown, et al., 2008; Durston et al., 2001; Gogtay et al., 2004; Schweinsburg, Nagel, & Tapert, 2005; Spear & Varlinskaya, 2005). A handful of studies have shown a deleterious effect of heavy alcohol use on adolescents’ neuropsychological performance in varied domains, including visuospatial abilities (e.g., Sher, Martin, Wood, & Rutledge, 1997), verbal and non-verbal retention (e.g., Brown, Tapert, Granholm, & Delis, 2000), attention and information processing (Tapert & Brown, 1999; Tapert & Brown, 2000; Tarter, Mezzich, Hsieh, & Parks, 1995), and language and academic

achievement (Moss, Kirisci, Gordon, & Tarter, 1994; Tapert & Brown, 2000; Tarter et al., 1995). Female adolescent alcohol users have also shown deficits on tasks of executive functioning, specifically those involving in planning, abstract reasoning, and problem-solving (Giancola, Shoal, & Mezzich, 2001; Moss et al., 1994). Post-drinking effects, such as hangover severity and withdrawal symptoms have been demonstrated to be important predictors of alcohol-related neurocognitive impairment, as greater self-reported withdrawal symptoms have been linked with poorer visuospatial functioning (Brown et al., 2000; Tapert & Brown, 1999; Tapert, Granholm, Leedy, & Brown, 2002) and poorer verbal and non-verbal retention (Brown et al., 2000).

Longitudinal studies have examined whether observed neurocognitive deficits in this population represent premorbid risk factors for use or consequences of heavy alcohol use. In one study, after controlling for recent alcohol use, age, education, practice effects, and baseline neuropsychological functioning, substance use over an 8-year follow-up period significantly predicted neuropsychological functioning at Year 8. Specifically, adolescents who reported continued heavy drinking and greater alcohol hangover or withdrawal symptoms showed impairment on tasks of attention and visuospatial functioning compared to non-using adolescents (Tapert et al., 2002). These findings were replicated in a prospective study that characterized at-risk adolescents prior to initiating alcohol use. For females, initiation of alcohol use over the follow-up period was associated with worsening visuospatial functioning, while greater hangover symptoms over the follow-up period predicted poorer sustained attention in males (Squeglia, Spadoni, Infante, Myers, & Tapert, 2009). Taken together, these studies suggest that heavy drinking during adolescence is associated with deficits in cognitive performance,

which likely result from, rather than predate, alcohol use. Other factors such as gender and family history of AUDs may moderate this relationship. Specifically, evidence suggests that females may be more vulnerable to the negative impact of heavy alcohol use in adolescence (Caldwell et al., 2005; Medina et al., 2008; Moss et al., 1994; Schweinsburg et al., 2003; Squeglia, Schweinsburg, Pulido, & Tapert, 2011; Squeglia et al., 2009), and a positive family history of AUDs has been associated with worse neurocognitive performance in adolescent heavy alcohol users, particularly in language and attention domains (e.g., Tapert & Brown, 2000).

Structural magnetic resonance imaging (MRI) studies provide evidence for anatomical brain abnormalities in adolescents with histories of heavy lifetime alcohol use, compared to their non-using peers. The hippocampus (critical for learning and memory functioning) appears to be one area of potential vulnerability, as decreased bilateral hippocampal volumes have been observed in adolescents meeting criteria for AUDs, with smaller hippocampi related to earlier onset and longer duration of the disorder (De Bellis, et al., 2000). Nagel, Schweinsburg, Phan, and Tapert (2005) found similar results, with smaller left hippocampal volumes observed in heavy alcohol-using adolescents compared to controls, even after excluding teens with co-occurring Axis I disorders. Hippocampal volume did not correlate with degree of alcohol use in this study, suggesting that between-group differences may be reflective of premorbid factors, and not solely the result of heavy alcohol use.

Another area of the brain that may be especially vulnerable to the effects of heavy alcohol use in adolescence is the prefrontal cortex. As a key component of both the cognitive control and socioemotional networks, this region is important to the study of

risk-taking. In a sample of adolescents with co-occurring psychiatric and AUDs, DeBellis and colleagues (2005) found significantly smaller prefrontal cortex volumes (both overall volume and white matter volume) in alcohol users compared to controls. These findings were replicated by Medina and colleagues (2008) in a sample of alcohol dependent adolescents without psychiatric disorders; however, a significant group by gender interaction was observed. Specifically, alcohol dependent females showed smaller prefrontal cortex and white matter volumes than female controls, and alcohol dependent males showed larger prefrontal and white matter volumes than male controls. In a cortical thickness study of adolescent binge drinkers, Squeglia, Sorg, and colleagues (2012) found alcohol use by gender interactions in four left frontal brain regions, where female binge drinkers had thicker cortices than female controls and male binge drinkers had thinner cortices than male controls. Thicker (i.e., less mature) frontal cortices corresponded with poorer visuospatial, inhibition, and attention abilities for females and worse attention abilities for males, providing further evidence that females may be especially vulnerable to brain changes brought on by heavy alcohol use in adolescence.

Diffusion tensor imaging (DTI) studies have yielded corroborating evidence of altered brain development in adolescent heavy alcohol users. In one study, adolescents with histories of binge drinking (but not meeting criteria for an AUD) showed decreased white matter integrity in 18 major fiber tract pathways, specifically in the frontal, cerebellar, temporal, and parietal regions (McQueeney et al., 2009). Another study found reduced white matter integrity in the corpus callosum of youth with AUDs, particularly in the posterior aspect (the splenium). In addition, reduced white matter integrity in this region was related to longer durations of heavy drinking, larger quantities of recent

alcohol consumption, and greater alcohol withdrawal symptoms (Tapert, Theilmann, & Schweinsburg, 2003). There is evidence that poorer white matter integrity may be both a consequence of adolescent alcohol use and a predisposing risk factor for use.

Specifically, in a study of 11- to 15-year-old alcohol naïve youth, Herting, Schwartz, Mitchell, & Nagel, (2010) found that youth with a positive family history of AUDs had poorer white matter integrity in several brain regions, along with slower reaction time on a task of delay discounting, when compared to youth without a family history of AUDs. In addition, Jacobus, Thayer, Trim, Bava, and Tapert (in press, 2012) found that poorer white matter integrity measured in 16- to 19-year old adolescents was related to more self-reported substance use and delinquency/aggression at an 18-month follow-up.

In fMRI studies, altered neural processing has been observed in heavy drinking adolescents during cognitive tasks of spatial working memory (SWM), verbal encoding, and visual working memory (VWM). Tapert and colleagues (2004) found that adolescents with a history of heavy drinking over the past 1-2 years showed increased blood oxygen level-dependent (BOLD) response in bilateral parietal regions during a SWM task, but decreased BOLD activation in the occipital and cerebellar regions compared to lighter drinkers. In addition, BOLD activation abnormalities were associated with more withdrawal, hangover symptoms, and greater lifetime alcohol consumption. Similarly, in a study of verbal encoding, Schweinsburg, McQueeny, Nagel, Eyler, and Tapert (2010) showed that adolescent binge drinkers had more BOLD response in the right superior frontal and bilateral posterior parietal regions but less BOLD response in the occipital cortex, compared to non-drinkers. Control adolescents also showed significant activation in the left hippocampus during novel encoding,

whereas binge drinkers did not. A 2011 follow-up to this investigation found increased dorsal frontal and parietal BOLD response among 16- to 18-year-old binge drinkers, and decreased inferior frontal response during verbal encoding (Schweinsburg, Schweinsburg, Nagel, Eyler, & Tapert, 2011). Squeglia, Pulido, and colleagues (2012) found comparable results during a VWM task, in that heavy drinking adolescents showed more BOLD response compared to matched controls in right inferior parietal, right middle and superior frontal, and left medial frontal regions, but less BOLD response in left middle occipital regions. Notably, this investigation included a longitudinal component with a separate sample of adolescents in which the brain areas showing group differences in BOLD response to the VWM task (outlined above) were identified as ROIs. Adolescents were scanned at baseline before they ever used alcohol or drugs and then scanned again at a 3-year follow-up time point. Adolescents from this sample who transitioned into heavy drinking during the follow-up period showed less BOLD response to the VWM task compared to continuous non-drinkers in frontal and parietal regions at baseline; in addition, BOLD response in these regions increased significantly over the follow-up period for the heavy drinkers, while controls' BOLD response did not change significantly over time. Finally, less BOLD activation at baseline predicted subsequent substance use, above and beyond age, family history of AUDs, and baseline externalizing behaviors. Taken together, results from these studies suggest that the adolescent brain is indeed sensitive to the insult of excessive alcohol use, and structural alterations and neural reorganization may result from continued heavy drinking. In turn, this altered brain development may trigger cognitive, emotional, and behavioral changes, leading to further alcohol use and other risk-taking behaviors.

As the majority of fMRI studies of adolescent alcohol users to date are cross-sectional in nature, it is difficult to determine whether the observed neural abnormalities predate the onset of alcohol use, or are consequences of alcohol use. However, results of the Squeglia, Pulido et al. (2012) study suggest that a combination of both explanations may be most accurate. Specifically, neural functioning differences may be evident prior to the initiation of drinking, but early alcohol use may also change the trajectory of normative brain development observed in adolescence, leading to less efficient neural processing over time. It remains unknown whether neural abnormalities stimulated by early heavy alcohol use persist throughout the lifespan or revert to normative patterns after periods of short or long-term abstinence.

Risky decision-making has neural functioning correlates

fMRI studies provide a framework for understanding the regions of the brain associated with risky decision-making. The process of making a decision involves three distinct stages: 1) the assessment and formation of preference among options; 2) the selection and execution of an action; and 3) the experience or evaluation of an outcome (Ernst & Paulus, 2005). Areas that reliably activate in fMRI tasks of risk-taking and reward-based decision-making include both cognitive and affective brain areas, such as the orbitofrontal/ventromedial, and dorsolateral prefrontal cortices, anterior cingulate, ventral striatum (particularly the nucleus accumbens), amygdala, and insula (Bjork et al., 2004; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Ernst et al., 2005; Eshel, Nelson, Blair, Pine, & Ernst, 2007; Galvan et al., 2006; Galvan, Hare, Voss, Glover, & Casey, 2007; Knutson, Fong, Adams, Varner, & Hommer, 2001; Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003). However, some fundamental differences in BOLD activation

patterns are observed in adolescent populations completing these tasks, compared to adults and children. Specifically, adolescents display an increased BOLD response in the nucleus accumbens in response to rewarding outcomes compared to both adults (Ernst et al., 2005; Galvan et al., 2006; 2007) and children (Galvan et al., 2006). There is also some evidence of reduced BOLD activation in the amygdala when experiencing decision outcomes, relative to adults (Ernst et al., 2005). This finding is of interest because the amygdala is involved in responding to negative stimuli and can function as a “behavioral brake”, signaling individuals to retreat from potentially dangerous situations (LeDoux, 2000). Adolescents also engage prefrontal regulatory structures (e.g., dorsolateral prefrontal cortices, dorsal anterior cingulate) to a lesser extent than do adults when making risky decisions (Eshel et al., 2007; Galvan et al., 2006), and these findings can be interpreted as underdeveloped cognitive control systems, relative to socioemotional networks (Galvan et al., 2006). Neural functioning during risky decision-making has also been linked to adolescent self-reports of their risky behaviors in real life as well as task performance on cognitive measures of risk-taking. Specifically, in the Galvan et al. (2007) study (cited above), adolescents’ BOLD response in the nucleus accumbens during reward anticipation was correlated with an increased level of self-reported risky behavior, and Eshel and colleagues (2007) found that risk-taking performance during a decision-making task was negatively associated with BOLD response in regions associated with cognitive control, including the ventrolateral prefrontal and anterior cingulate regions.

One known study to date has examined neural correlates of affective decision-making in adolescent alcohol users. Specifically, Xiao and colleagues (in press, 2012)

used a modified version of the Iowa Gambling Task (IGT) with adolescents in the early stages of binge drinking as well as age-matched controls. They found that compared to controls, the binge drinkers showed increased BOLD response in the left amygdala and bilateral insulae during decision-making; in addition, BOLD response in the insulae was positively correlated with drinking severity, while BOLD response in the orbitofrontal cortex was negatively correlated with drinking severity. Of note, binge drinkers also performed more poorly on the task compared to non-drinkers (i.e., they were more likely to select from “riskier” decks of cards, leading to increasing losses and lower overall scores). This finding is important as differences in task performance often contribute to observed differences in neural functioning.

The Balloon Analogue Risk Task (BART) (Lejuez et al., 2002) is one laboratory-based measure of risky decision-making where participants are required to “pump up” balloons (typically earning points or money per pump) that can ultimately explode; the larger a participant inflates the balloon, the greater the risk he/she is willing to take. Behavioral studies using this measure with adults and adolescents have shown that risky decision-making on the BART correlates with scores on self-report of risky behavior (e.g., substance use, delinquency) as well as scores on personality constructs related to risk-taking (e.g., sensation seeking, impulsivity). Rao, Korkczykowski, Pluta, Hoang, and Detre (2008) first examined use of the BART within an fMRI context. Participants were healthy adults and the task was manipulated to measure both active decision-making (i.e., participants made their own choices) and passive/involuntary decision-making (participants observed the computer making choices for them). In both conditions, increasing risk correlated with neural activation in bilateral visual pathways, including

occipital, fusiform, and parietal cortices, which likely reflects increased attention to or processing of visual information as the balloon inflated to larger sizes. In the active decision-making condition only, increasing risk correlated with neural activation in the ventral tegmental area, striatum, anterior insula, anterior cingulate cortex/medial prefrontal cortex, and dorsolateral prefrontal cortex, suggesting that these regions are directly implicated in risky decision-making. While no known studies have yet used the BART in an fMRI context with adolescents, let alone heavy drinking adolescents, one study has used the task in a sample of young adults, aged 18-23, with a range of alcohol consumption behaviors (from modest use to alcohol dependence). Results indicated that during inflation, as the probability of a balloon exploding increased (in other words, as behavior became more “risky” with a greater number of pumps), participants showed decreasing BOLD response in the medial prefrontal cortex and anterior cingulate. In addition, during successful inflation outcomes (i.e., while receiving feedback that balloons had not popped) BOLD response in the medial prefrontal cortex/anterior cingulate was greater when the probability of that balloon exploding had been higher. This may indicate that outcomes (unpopped balloons) were viewed as more rewarding (as indicated by greater medial prefrontal cortex activity) when it took riskier behavior (i.e., a greater number of pumps) to achieve the outcome. Finally, decreasing medial prefrontal cortex/anterior cingulate BOLD response during riskier inflation and increasing BOLD response in the same regions during successful riskier inflation outcomes was correlated with higher alcohol use and trait disinhibition, and lower IQ (Bogg, Fukunaga, Finn & Brown, 2012).

Abstinence from alcohol may lead to recovery in cognitive and neural functioning

Little, if any longitudinal information is currently available on the effects of short or long-term abstinence on rates or patterns of change in cognitive or neural functioning in heavy-drinking adolescents. However, it is well established that in adults, abstinence from alcohol leads to some recovery of neurocognitive functioning, with the rate and pattern of recovery depending on several factors, such as age, baseline cognitive ability, length of abstinence, and peak level of alcohol use. During the acute detoxification period, broad cognitive impairment is common, with memory, executive functioning, gait and balance coordination, and visuospatial skills among those domains most affected (e.g., Fein, Bachman, Fisher, & Davenport, 1990; Moselhy, Georgiou, & Kahn, 2001). With several weeks to months of sobriety, impairments in attention and concentration, reaction time, gait and balance, and selected executive, visuospatial, and memory abilities tend to improve, but mild to moderate difficulties in components of working memory, processing speed, non-verbal skills, and postural stability can remain (Brandt, Butters, Ryan, & Bayog, 1983; Parsons, 1983; Sullivan, Rosenbloom, Lin, & Pfefferbaum, 2000). After several years of abstinence, adults appear to recover most neuropsychological abilities, although spatial processing may remain affected (Fein, Torres, Price, & DiSclafani, 2006). In addition to some lasting cognitive impairment, abstinent adults may demonstrate externalizing behavioral symptoms, social deviance, and reward-related decision-making deficits, associated with prior peak alcohol use (e.g., Oscar-Berman & Hutner, 1993; Parsons, Butters, & Nathan, 1987; Sullivan, 2000).

Structural brain dysmorphology and altered neural functioning has also been observed in adults with persisting alcohol dependence, even among those individuals free

of alcohol-related brain syndromes (i.e., Korsakoff's syndrome). In terms of dysmorphology, the brain structures most consistently affected include the corpus callosum (Estruch et al., 1997; Pfefferbaum, Lim, Desmond, & Sullivan, 1996), pons (Sullivan, Deshmukh, De Rosa, Rosenbloom, & Pfefferbaum, 2005; Sullivan & Pfefferbaum, 2001) and the cerebellar hemispheres and vermis (Sullivan, Deshmukh, Desmond, Lim, & Pfefferbaum, 2000). In addition, both cortical gray matter and white matter sustain widespread volume loss, especially in the prefrontal cortex (Fein et al., 2002; Kubota et al., 2001; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997).

Functional neuroimaging studies provide evidence of neural processing inefficiencies in adults with AUDs, which complement associated cognitive and structural findings. Pfefferbaum and colleagues (2001) found that alcohol dependent adults showed less BOLD activation in prefrontal regions compared to controls and more activation in posterior and inferior regions while performing a SWM task. In another study of verbal working memory, alcohol dependent adults demonstrated task performance equivalent to that of matched controls, but required increased BOLD activation in the left prefrontal cortex and right superior cerebellum to reach an effective level of performance (Desmond et al., 2003). In a study of proactive interference (where participants are trained to make a certain kind of response when a stimulus is presented, and then asked to make a new response to the same stimulus), alcohol dependent adults engaged frontal systems to a higher degree than did controls; while controls activated lower-level subcortical systems to carry out the same task (De Rosa, Desmond, Anderson, Pfefferbaum, & Sullivan, 2004). Collectively, these fMRI results suggest that alcohol dependent adults recruit cerebellar activity to carry out functions that otherwise

would be frontal lobe tasks, and frontal lobe activity to carry out functions that otherwise would be lower-level tasks. One interpretation is that the additional activation is “compensatory”, enabling alcohol dependent adults to achieve normal levels of performance, despite cerebellar and/or frontal dysmorphology (Rosenbloom & Pfefferbaum, 2008). As the cerebellar and prefrontal regions are among those most structurally affected in alcoholism, these observations point to a disruption in frontocerebellar circuitry as one primary mechanism of the behavioral impairments characteristic of chronic alcohol use (Sullivan & Pfefferbaum, 2005).

Although longitudinal findings of the effects of long-term abstinence on the brains of adults with chronic alcohol dependence are not yet available, some recent longitudinal studies of short-term abstinence have provided promising results. These studies suggest that structural brain damage is at least partially reversible, with increases in gray matter observed after 1 month of abstinence from alcohol (Pfefferbaum et al., 1995); white matter has also been noted as amenable to recovery with abstinence (O’Neill, Cardenas, & Meyerhoff, 2001; Shear, Jernigan & Butters, 1994). Of interest to the study of risk-taking and reward, one study showed significantly greater volumes in the nucleus accumbens of adults with alcohol dependence who had achieved one month of sobriety, compared to alcohol dependent adults who continued drinking. In addition, the volume loss observed in the actively drinking group was greater than that typically observed in Korsakoff’s patients (Sullivan, Deshmukh, De Rosa, Rosenbloom, & Pfefferbaum, 2004).

In adolescents, preliminary results from three studies using the same sample as is proposed in this dissertation provide promising evidence that a similar pattern of

cognitive and neural recovery may occur for heavy drinking adolescents after a short period of abstinence. Pulido and colleagues (2010) conducted an fMRI study of alcohol cue reactivity in heavy drinking adolescents and controls, assessed across three time points over a five-week period of abstinence. They found that compared to controls, heavy drinking adolescents showed greater baseline BOLD response to pictures of alcohol-related stimuli (vs. non-alcohol-related stimuli) in six brain regions, including the right superior frontal gyrus, the left medial frontal/striatum, bilateral cerebellum, left cingulate, left pre and post-central gyrus, and the left middle temporal gyrus. After two to three weeks of monitored abstinence, the heavy drinkers evidenced BOLD responding patterns similar to that of controls in five out of the six brain regions that previously showed differences, showing increased BOLD response to alcohol cues only in the right superior frontal gyrus. After four to five weeks of monitored abstinence, no significant group differences in BOLD response related to alcohol cue reactivity were seen in any brain region. Another study (Hanson, Bekman, Tapert, Lejuez, & Brown, 2011) assessed risk-taking behavior using the BART task (outside of an fMRI environment). At the baseline assessment, heavy drinking adolescents had fewer “wins” (unpopped balloons) compared to controls, but when assessed after five weeks of abstinence, the two groups were equivalent on this measure. In addition, heavy drinkers had a higher number of balloon pumps on the last half of the task (an indicator of riskier decision-making) than did controls, and again, this difference disappeared after drinkers had been abstinent for five weeks. Finally, the number of balloon pumps during the second half of the task was positively correlated with self-report of recent and lifetime substance use. In the third study, Winward and colleagues (2009) used a modified computer version of the Paced

Auditory Serial Addition Test (PASAT) to measure distress tolerance levels during the task. Findings indicated that although the control adolescents outperformed heavy drinkers across the three time points on the PASAT task itself, there was a significant group by time interaction on self-reported levels of happiness and frustration before and after PASAT administration. Specifically, heavy drinkers showed greater increases in frustration and greater decreases in happiness compared to control adolescents at baseline and after two to three weeks of abstinence; however, this difference disappeared at the third time point (four to five weeks of abstinence). The results of these three studies, although preliminary, provide support for the idea that heavy alcohol use in adolescence may lead to cognitive changes and concurrently, altered neural processing. In addition, these abnormalities may normalize with sustained abstinence, which in turn, could reduce risk-taking behavior and associated negative consequences.

The current study aimed to supplement these findings by examining neural functioning during a risky decision-making fMRI task in heavy drinking adolescents and matched controls across a five-week period of abstinence. The goals were to (a) identify brain regions where activation to a risky decision-making task differed between heavy drinking adolescents and controls, (b) examine whether neural activity associated with risky decision-making changed across a five-week period of abstinence and whether trajectories of change over time differed for heavy drinkers vs. controls, and (c) determine whether neural activation in regions showing baseline group differences during risky decision-making predicts differences in neuropsychological functioning (i.e., executive functioning), risk-taking performance, or self-report of risk-taking behavior and impulsivity. Understanding the impact of heavy alcohol use on adolescents' brain

functioning during risky decision-making is an important step in clarifying factors which may further risk-taking behavior in adolescence. In addition, measuring longitudinal changes in brain functioning over a period of sustained abstinence from alcohol can elucidate whether observed alterations in neural functioning associated with heavy alcohol use normalize with abstinence or persist after cessation of use.

Hypotheses

Primary aim. The primary aim of this study was to understand differences in neural functioning between adolescents with histories of heavy lifetime alcohol use vs. non-using controls by measuring BOLD response during the BART, a risky decision-making fMRI task, cross-sectionally (at baseline) and longitudinally (over a 5 week period of abstinence).

Hypothesis 1. It was hypothesized that adolescents with histories of heavy lifetime alcohol use would show abnormalities in BOLD response to a risky decision-making task at baseline, compared to non-using adolescents. Specifically, heavy drinking adolescents were expected to show decreased BOLD response in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) regions during the pre-response assessment stage of decision-making, as well as increased BOLD activation in the ventral striatum, ventromedial prefrontal cortex (VMPFC), and insula during the anticipatory stage of decision-making, as compared to non-drinking controls. During the outcome evaluation stage of decision-making, it was expected that heavy drinking adolescents would show increased BOLD response in the ventral striatum and VMPFC during both “win” and “loss” conditions, and decreased BOLD response in the amygdala when reward was omitted (“loss” condition), as compared to controls.

Hypothesis 2. It was hypothesized that between-group BOLD activation differences observed at baseline in the regions of interest (ROIs) described above would attenuate across the three assessment periods, and differences were expected to be non-significant by the third time point.

Hypothesis 3. Finally, it was hypothesized that baseline BOLD activation patterns in the specified ROIs would be linked to poorer performance on neuropsychological measures of executive functioning and risk-taking at the same time point, as well as to self-report of risk-taking and impulsive behavior. Specifically, we expected that less BOLD response at baseline in the DLPFC and ACC regions during the pre-response assessment stage of decision-making would be linked to poorer performance on the BART task, as well as on the D-KEFS Trails and Color-Word Interference subtests. In addition, we expected that greater BOLD response in the VMPFC, ventral striatum and insula during the anticipatory stage of decision-making, greater BOLD response in the VMPFC and ventral striatum during the outcome evaluation stage, and less BOLD response in the amygdala during reward omission (at baseline) would be linked to poorer performance on the BART task as well as to increased levels of self-reported risk-taking and impulsive behavior.

This work is being prepared for submission for publication as “fMRI Correlates of Risky Decision-Making in Adolescent Alcohol Users: The Role of Abstinence.” The dissertation author will be the primary author of this material along with co-authors Alan Simmons, Ph.D., Carmen Pulido, Ph.D., Susan Tapert, Ph.D., and Sandra Brown, Ph.D.

Methods

Participants

Participants ($N = 46$; 27 heavy drinking adolescents, 19 controls) were part of a larger longitudinal study (3 time points: baseline, +2weeks, +4weeks) examining the effects of five weeks of sustained abstinence on neurocognitive functioning (i.e., structural and functional brain changes and neuropsychological and behavioral correlates) in adolescents with histories of heavy recent alcohol use (Brown R21 AA017321). Participants were primarily recruited through flyers handed out at local high schools in the San Dieguito Union High School District; these included a description of the study, basic inclusion and exclusion criteria, financial compensation amounts, and contact information. Interested adolescents were asked to contact the research office, and those who responded completed extensive screening procedures before being selected for the study. Background data including information about psychological history, family history of drug/alcohol use, and past/current alcohol and substance use were obtained from each adolescent as well as from one biological parent. The study protocol was executed in accordance with the standards approved by the University of California, San Diego Human Research Protections Program (UCSD IRB approval #071697).

Sixty-nine adolescents (43 heavy drinkers, 26 controls) were screened into the study and completed baseline assessments. Of the 69, 18 did not complete the neuroimaging portion of the study due to ineligibility (e.g., braces or other non-removable metal, left-handedness) or refusal to participate, and therefore, completed only

the neuropsychological and behavioral assessments. Fifty-one adolescents (32 heavy drinkers, 19 controls) completed the initial neuroimaging session; of these, four heavy drinkers were dropped from all analyses due to evidence of continued substance use gleaned from toxicology results (i.e., use that occurred shortly after initiation of the study), and one heavy drinker was dropped due to reports of prenatal alcohol exposure. Forty-six adolescents ages 16 to 18 years (average age = 17.85 years [$SD = 0.67$]) were included in the final sample. For the baseline time point, 41 participants had valid neuroimaging data (25 heavy drinkers, 16 controls); 4 participants (2 heavy drinkers, 2 controls) were excluded due to technical difficulties with the scanner or imaging software, and 1 control participant was excluded due to excessive head motion during the imaging task. At the +2weeks time point, 39 participants (21 heavy drinkers, 18 controls) had valid neuroimaging data; 1 control participant was excluded for excessive head motion, and 6 heavy drinking participants were excluded (1 for excessive motion, 1 for image artifacts, 1 for technical difficulties, 1 for voluntary drop-out, and 2 for toxicology confirmed substance use). At the +4weeks time point, 36 participants (20 heavy drinkers, 16 controls) had valid neuroimaging data; 2 control participants were excluded for excessive motion, and 8 heavy drinking participants were excluded (4 for technical difficulties, 2 for voluntary drop-out, and 2 for toxicology confirmed substance use).

Adolescents in the control group ($n = 19$) endorsed very minimal alcohol use (average lifetime drinking episodes = 0.79 [$SD = 2.34$], average lifetime binges = 0.05 [$SD = 0.23$]) and reported no history of alcohol withdrawal symptoms or other alcohol related problems. Adolescents in the heavy drinking group ($n = 27$) endorsed high rates of lifetime and recent alcohol exposure (average lifetime drinking episodes = 188.03 [SD

= 137.30], average drinks per month = 63.40 [$SD = 61.66$], average binge drinking episodes in prior 90 days = 15.52 [$SD = 12.25$]), and had experienced at least one symptom of alcohol withdrawal in the prior 90 days. In order to reduce potential confounds introduced by exposure to substances other than alcohol, rates of exposure to tobacco, cannabis, and other illicit drugs were kept to a minimum in both groups. See Table 1 for complete demographic characteristics of study participants, and Table 2 for complete substance use characteristics.

Exclusion criteria. Adolescents were excluded from the study if they met any of the following criteria: (1) history of any DSM-IV Axis I psychiatric disorder (including conduct disorder or oppositional defiant disorder) (2) history of any neurological disorder (e.g., meningitis, migraines, seizures) or head trauma with loss of consciousness > 2 minutes; (3) history of chronic medical illness; (4) history of learning disability or mental retardation; (5) history of complicated or premature birth (<33 weeks of gestation); (6) current use of medications potentially affecting the brain or cerebral blood flow (e.g. psychotropic medications); (7) history of prenatal alcohol exposure (>7 drinks in a week or >4 drinks a day) or any illicit drug exposure; (8) colorblindness or non-correctable vision, hearing, or other sensory problems; (9) left handedness, as brain lateralization for these individuals differs from that of right-handed individuals; (10) pregnant on day of scanning; (11) inadequate comprehension of English, since this limits ability to participate in the assessment process; (12) claustrophobia; (13) irremovable metal, such as orthodontic braces or retainers, and; (14) adolescent and parent/guardian failure to provide informed assent and consent, respectively.

Measures

Screening. At first contact with a prospective participant, a five-minute Initial Youth Screening was conducted via phone. The study was described in detail, including the required 42-day abstinence period and toxicology screen procedures; the inclusion and exclusion criteria were not shared in order to minimize motivation to alter responses. Participants were asked to answer IRB-approved basic screening questions to ascertain eligibility and demographic information (e.g., age, ethnicity, handedness, irremovable metal, vision/hearing problems, yes/no questions about nicotine, alcohol and other drug use). Parents of interested youth were then contacted and informed of the purpose of the study, procedures, potential risks and benefits, and confidentiality, and screened with questions regarding potential exclusionary criteria (e.g., adolescent's history of medication use, neurological dysfunction, head injury, use of mental health services, learning disability) from a five-minute Initial Parent Screening. Assent for further screening was then mailed to adolescents who remained eligible and informed consent was mailed to their parents. For 18-year-old participants, informed consent was mailed directly to the adolescent as well as to the parent requesting their participation as a collateral informant. Three days after mailing the consents, a trained lab assistant called the family to review the consent/assent forms and answer any questions. Parents were informed at the time of initial contact that they would not receive information regarding the adolescent's group assignment, toxicology screening results, or any other information provided in confidence.

After signed consents were received, eligible adolescents were administered the Modified Lifetime version of the Customary Drinking and Drug Use Record (CDDR) (Brown et al., 1998) by phone to assess lifetime and recent use of alcohol, nicotine,

marijuana, and other drugs, as well as ages of first use and regular use for each substance. The CDDR has been demonstrated to have good psychometric properties with adolescents, for both in-person and phone administration. As part of this interview, adolescents were administered the six-item *Fagerstrom Test for Nicotine Dependence* to assess symptoms of nicotine dependence (Heatherton, Kozlowski, Frecker & Fagerstrom, 1991). Based on adolescents' responses on the CDDR, they were tentatively classified at the end of the interview as either: 1) Controls (non-users), or 2) Heavy Drinkers, or they were excluded from the study.

Adolescents still eligible for the study after the CDDR interview then completed a *Detailed Teen Screening*. This screening included the *Diagnostic Interview Schedule for Children 4.0 Predictive Scales* (DISC-PS-4.32b; Lucas et al., 2001; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) to eliminate participants with probable psychiatric disorders (other than substance use disorders) and the *Family History Assessment Module* (FHAM; Rice et al., 1995) to collect information regarding family history of alcohol or substance use disorders in all first and second-degree relatives as well as history of mood, anxiety, psychotic, and personality disorder symptoms in first-degree relatives. Family density of AUDs was calculated by adding 0.5 for each biological parent and 0.25 for each biological grandparent (Zucker, Ellis, & Fitzgerald, 1994) when endorsed by either adolescents or their parents. The detailed screening took 75 minutes on average and adolescents received \$20 for completion of this interview.

Parents or guardians of adolescents who continued to meet eligibility criteria following the *Detailed Teen Screening* were administered a *Detailed Parent Screening*, which collected information on the adolescent's prenatal and infant development,

childhood behavior, parent education and occupation, and family history. To improve the reliability of adolescent reports, the parent version of the DISC-PS-4.32b was administered. Adolescents were excluded from the study if either their report or their parent's report indicated a probable psychiatric disorder. Socioeconomic background information (i.e., educational attainment, occupation, and salary of each parent) was obtained from parents and converted to a Hollingshead Index of Social Position score, with higher scores indicating lower socioeconomic status (Hollingshead, 1965). Parents received \$20 for completion of this 60-minute interview.

Neuropsychological testing. Adolescents who remained eligible after all screening was completed were scheduled for a baseline neuropsychological (NP) testing appointment. Measures of working memory, attention, visuospatial functioning, executive functioning, learning and memory, language, and academic achievement were administered by a trained bachelor's level psychometrician at each of the 3 time points. Alternate versions were used whenever feasible to minimize practice effects. For purposes of this dissertation, the following NP tests were of interest for analyses: 1) Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary subtest, 2) Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test, 3) D-KEFS Color-Word Interference Test, and 4) behavioral BART task. The WASI Vocabulary subtest measured adolescents' knowledge of word definitions and was used primarily for descriptive purposes, as a proxy for verbal intellectual functioning. The D-KEFS Trail Making Test number-letter switching condition measured cognitive flexibility and was used in Hypothesis 3 analyses as a measure of executive functioning. Similarly, the D-KEFS Color-Word Interference test measures inhibition and set shifting and was used as

a second measure of executive functioning in Hypothesis 3 analyses. Finally, the behavioral BART task (identical to the BART task used during fMRI scanning and described later) was used as a measure of risk-taking performance in Hypothesis 3 analyses.

Substance use measures. Adolescents reported on the frequency, quantity, and type of substances used before and during the study. The modified *Timeline Followback* (TLFB; Sobell & Sobell, 1992) was used to collect detailed information about substance use quantity and frequency. The TLFB uses a calendar format, and for each day adolescents indicated whether they drank or used drugs, and if so, how much. Temporal cues (e.g., holidays, special events) were used to aid recall. The TLFB was administered twice during the study: 1) at the initial NP testing appointment to obtain use information for the prior 30 days prior, and, 2) at the end of the study, to re-confirm that substances were not used during the period of abstinence. The TLFB has excellent reliability and validity, and the modified version assesses nicotine and caffeine use in addition to alcohol and other substance use (Brown et al., 1998). The *Participant Last Use Scale* (PLUS; designed specifically for this study) recorded the cumulative number of days that passed since participants' last use of alcohol and other substances; this measure was administered at all three time points, during the neuroimaging appointments.

Participants also completed a breathalyzer and urine toxicology screening at each of the six scheduled appointments (3 NP testing sessions, 3 neuroimaging sessions). Participants completed additional urine toxicology screens once every weekend, and once during the week in weeks where they did not have scheduled appointments. Participants completed 12 toxicology screens in total throughout the duration of the study. These

screenings verified that adolescents were not acutely intoxicated at any of their NP or scanning appointments, and provided objective evidence of abstinence from alcohol and other substances across the study's five-week period.

Mood and Behavior. Self-report mood questionnaires were collected at each neuroimaging appointment. Current depression and anxiety levels (measured over the past week) were assessed with the examiner-administered *Hamilton Depression Scale* (Hamilton, 1960), and *Hamilton Anxiety Scale* (Hamilton, 1959). The “state” portion of the *Spielberger State-Trait Anxiety Inventory (STAI)* (Spielberger, Gorsuch, & Lushene, 1970) assessed acute anxiety levels immediately prior to scanning, as anxiety has been associated with altered cerebral metabolism and could therefore influence fMRI results (Harris & Hoehn-Saric, 1995). The *Karolinska Sleepiness Scale (KSS)* (Åkerstedt & Gillberg, 1990) assessed levels of alertness and fatigue before and after scanning. The *Youth Self Report (YSR)* (Achenbach & Rescorla, 2001) was administered once during the study as a self-report measure of adolescents' psychopathological symptoms. Subscales of interest for this dissertation project included rule-breaking behavior (as this subscale is thought to be closely related to risk-taking behavior) and overall levels of externalizing and internalizing problems.

Development. The *Pubertal Development Scale* (Petersen, Crockett, Richards, & Boxer, 1988) was used as a self-report measure of pubertal maturation. This measure correlates significantly with physician ratings and self-ratings on the Sexual Maturation Scale (Miller, Tucker, Pasch, & Eccles, 1988). This is a five-item measure for males (score range: 5–20) and four-item measure for females (score range: 4–16); higher scores indicated greater maturity.

Personality. Two self-report measures of personality were utilized in this dissertation. First, a shortened version of the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ-CC) (Aluja, et al., 2006) was used to measure the five personality dimensions captured in the Alternative Five-Factor Model (neuroticism-anxiety, activity, sociability, impulsivity/sensation seeking, and aggression-hostility). The impulsivity/sensation seeking subscale was of particular interest, as this subscale is thought to be related to risk-taking behavior. Second, the BIS/BAS scales (Carver & White, 1994) measured individual differences in traits associated with the behavioral activation system (BAS, thought to be related to reward sensitivity and approach motivation) and behavioral inhibition system (BIS, thought to be related to punishment sensitivity and avoidance motivation).

Procedures

General procedures. Adolescents accepted into the study were scheduled for six separate assessment appointments, spread out across a period of five weeks. In weeks 1 (baseline), 3 (+2weeks), and 5 (+4weeks), subjects completed a 3-hour long NP testing session at our laboratory on the UCSD Medical School campus as well as a 2-hour long neuroimaging session at the UCSD Keck Center for fMRI. The neuroimaging sessions took place within 1-2 days following the NP testing sessions. In addition to these six appointments, subjects were administered toxicology screenings each Sunday for the five-week duration of the study, and on an additional randomly selected day during the two weeks where no NP or neuroimaging sessions took place. Participants earned up to \$485 for completion of all study elements, plus an additional \$6-\$48, depending on performance on the BART task (administered six times total; once at each NP and

neuroimaging session).

Maintaining abstinence. Adolescents were asked to maintain abstinence from alcohol and other substances (aside from tobacco) from the time they completed their CDDR; the initial appointment was scheduled to coincide with 4-10 days of abstinence. This ensured that any cognitive impairment observed in the heavy drinkers could not be indicative of acute alcohol withdrawal and detoxification. Adolescents completed a TLFB at their first NP appointment to gather information about alcohol and substance use that may have occurred in the time after completion of the CDDR. Although adolescents typically provide valid self-reports of alcohol and other drug use (Winters, Stinchfield, Henly, & Schwartz, 1990), self-report of abstinence was verified with breathalyzer and urine toxicology screens (as described above; Redwood Toxicology Lab, San Diego, CA). If an adolescent came up with a positive result for any alcohol or drug use, a trained research assistant discussed the finding with the participant and sought verification of use from the adolescent. A TLFB was used to assist the adolescent in recall. If adolescents acknowledged use but reported continued interest in the study, they were allowed to continue, provided they remained abstinent for the number of days that passed since their first NP assessment plus the number of days that they reported being abstinent prior to their first NP assessment. No additional compensation was offered for additional time in the study. A Motivational Interviewing protocol was employed when necessary, which assisted participants in maintaining their abstinence throughout the duration of the protocol.

Imaging. All imaging data were collected from the 3.0 Tesla General Electric (3T GE) short bore Excite-2 MR system with an eight-channel phase-array head coil located

at the UCSD Keck fMRI Center. Eight high bandwidth receivers for ultra-short repetition time (TR) reduced signal distortions and signal dropout. Scan sessions collected: 1) localizer scans to assure good head placement and slice selection to cover the Whole brain (13 seconds); 2) a high resolution 3d T1-weighted sequence obtained using a sagittally acquired spoiled gradient recalled sequence (field of view [FOV] 24 cm, 256 x 256 x 192 matrix, .94 x .94 x 1 mm voxels, 176 slices, TR = 20 ms, echo time [TE] = 4.8 ms; flip angle 12°, 7:26 minutes) to allow volumetric analyses of brain structures and the defining and outlining of regions of interest (ROIs); 3) a T2-weighted axially acquired echo-planar imaging sequence measured BOLD signal (FOV=24 cm, 64 x 64 matrix, 3.75 x 3.75 x 3.8 mm voxels, 32 slices, TR = 2000ms, TE=30 ms, flip angle 90°, ramped bandwidth 250 KHz) during the BART task; 4) field map scans employed two different echo times to assess field inhomogeneities and signal distortions under the same parameters used in the echo-planar sequence (2:16 minutes); these were applied to the fMRI acquisitions to minimize warping and signal dropout. fMRI task stimuli were back projected from a laptop to a screen at the foot of the scanner bed visible via an angled mirror attached to the head coil. Responses were recorded using a fiber-optic trackball mouse (Current Designs, Pittsburgh, PA).

BART Task. All participants were administered the same BART task during fMRI acquisition. The task utilized a rapid event-related design in order to measure changes in the hemodynamic response corresponding to the three stages of decision-making (formation of preference, execution of action, evaluation of outcome). Twenty balloons trials were presented one at a time on the screen, each with a predetermined, random “explosion point”. Participants were asked to “pump up” each balloon by

responding to a series of six phases; a status bar was present throughout the task, which indicated which phase of the task was currently active. In the “*Think*” phase, participants viewed a question mark on the screen and were asked to think about the number of pumps they would like to enter. In the “*Pump*” phase, participants manually entered their chosen number of pumps, between 1-128. In the “*Wait*” phase, participants viewed the uninflated balloon on the screen and waited for the task to continue. In the “*Inflate*” phase, participants watched the balloon slowly expand as they waited to receive the outcome of their decision. In the “*Pop or Win*” phase, participants found out whether or not they earned money for the trial. If the chosen number of pumps was greater than the predetermined explosion point, the balloon on the screen “popped” at the end of the inflation period, and no money was earned. If the chosen number was less than the explosion point, participants “won” that balloon, and the inflated balloon remained on the screen for a moment, as a counter box in the lower right-hand corner displayed the amount of money earned for that trial (one cent per pump). Last, in the “*Rest*” phase, balloons were removed from the screen, and participants viewed a blank screen and waited for the next balloon trial to begin. The task consisted of 241 repetitions in all, with a total run time of 8 minutes and 2 seconds (see Figure 1 for screenshots of the BART task).

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Data Analyses

Image Processing

All neuroimaging data were processed and analyzed using Analysis of Functional NeuroImages (AFNI; Cox, 1996). Each repetition of each slice was examined for artifact and atypical signal levels, using an automated program developed by the UCSD Laboratory of Cognitive Neuroimaging. Motion in the time series data were corrected by registering each acquisition to the maximally stable base volume with an iterated least squares algorithm (Cox & Jesmanowicz, 1999) to estimate 3 rotational (roll, pitch, yaw) and 3 displacement (superior-to-inferior, left-to-right, posterior-to-anterior) parameters for each participant, which were used in the model to control for spin history effects (Bandettini, Jesmanowicz, Wong, & Hyde, 1993; Friston et al., 1996). To evaluate task-related motion, the reference vector was correlated with the six motion parameters generated for each individual dataset. Datasets with significant task-correlated or bulk motion were excluded from analyses. Trained raters then manually examined the time series data, and omitted any repetitions containing excessive head movements. If more than 20% of repetitions in a task were discarded, the participant was excluded. Two participants were excluded from each time point due to excess motion (1 heavy drinker and 1 control were excluded from both the baseline and +2weeks time points, while 2 controls were excluded from the third time point). For the remaining participants in the sample, 89% or greater repetitions were retained.

Deconvolution was conducted on time series data with a reference function which

coded the alternating task conditions and convolved the behavioral stimuli with a hemodynamic response model (Cohen, 1997), while covarying for linear trends and the degree of motion correction applied. As the specific task stimuli are unique each time the task is run, according to each participant's performance (i.e., balloons either pop or stay inflated depending on the number of pumps chosen), separate customized reference functions were created for each run and each participant. This resulted in fit coefficients for each voxel representing the change in BOLD signal across the task conditions (think, pump, wait, anticipation, outcome, and rest), as well as percentage signal change and threshold statistics.

Standardization transformations were made for each high-resolution anatomical image (Talairach & Tournoux, 1988), and functional datasets were warped in accordance to these images, to manage individual anatomical variability. Functional data were resampled into isotropic voxels (3mm^3), and a spatial smoothing Gaussian filter (full-width half maximum = 5.0 mm) minimized the influence of individual anatomic variability. Co-registration of structural to functional images was performed with a mutual information registration program (Cox & Jesmanowicz, 1999) that robustly handles images with different signal characteristics and spatial resolutions.

ROI masks were created for each hypothesized ROI using the TT_Daemon brain atlases available in AFNI. As there were no pre-existing DLPFC and VMPFC masks, these were created by adding together masks from relevant Brodmann areas (BA 10, 11, 32, and 47 for the VMPFC and BA 08, 09, 44, 45, and 46 for the DLPFC). Six planned contrasts allowed for the examination of BOLD response unique to the three phases of decision-making modeled in the task (pre-response assessment, anticipation, outcome

evaluation), and to the effect of “winning” (unpopped balloons) vs. “losing” (popped balloons). Active task conditions (i.e., “Think”, “Inflate”, and “Pop or Win”) were contrasted against control task conditions (i.e., “Rest” and “Wait”). The six contrasts included: 1) “Think” trials where the previous balloon popped (“Think-Pop”) vs. “Rest”, 2) “Think” trials where the previous balloon did not pop (“Think-Win”) vs. “Rest”, 3) “Inflate” trials where the previous balloon popped (“Inflate-Pop”) vs. “Wait”, 4) “Inflate” trials where the previous balloon did not pop (“Inflate-Win”) vs. “Wait”, 5) “Pop or Win” trials where the balloon popped (“Outcome-Pop”) vs. “Wait”, 6) “Pop or Win” trials where the balloon did not pop (“Outcome-Win”) vs. “Wait”. ROI masks were applied separately to these six planned contrasts, which enabled the extraction of fit coefficients averaged across each ROI for each participant; these were imported into SPSS for use in further analyses.

Statistical Analyses

Demographics. To determine if group differences existed on demographic measures, independent samples *t*-tests were conducted on quantitative variables (i.e., age, socioeconomic status, family history of alcoholism, education, grade point average, pubertal development, YSR externalizing & internalizing problems), and chi-square analyses were conducted on categorical variables (i.e., gender, race, ethnicity).

Substance use. Adolescents’ responses on the CDDR were analyzed primarily for descriptive purposes. Independent samples *t*-tests were also conducted to characterize group differences on these variables. In addition, reported number of days of abstinence from alcohol and other substances were calculated for the heavy drinking group at each scanning time point, for descriptive purposes.

Mood and alertness day-of-scan. Independent samples *t*-tests were utilized to determine if group differences existed on self-report measures of mood (depression and anxiety) across the prior week, acute “state” anxiety levels immediately prior to scanning, or alertness levels pre and post scan.

BART task performance. Independent samples *t*-tests determined if group differences existed on performance task variables collected from participants’ responses during the “Pump” phase of the task across the 20 balloon trials. Variables collected included: total number of popped and unpopped balloon trials, total number of “too slow” results, mean number of pumps entered (overall mean across all 20 trials, mean on trials following “popped balloons”, and mean on trials following “unpopped balloons”), total number of “risky” (>64), “conservative” (<64), and “safe” (=64) pump entries (overall, on trials following “unpopped balloons”, and on trials following “popped balloons”), mean number of pumps entered on trial 1 of the task, mean number of pumps entered on the 1st “pop” trial, and mean number of pumps entered on the trial immediately adjacent to the 1st “pop” trial. Task performance variables were calculated separately for each of the three time points.

Hypothesis testing. Hypothesis 1 was tested using the AFNI program 3dttest++, with group (heavy drinkers vs. controls) as the between-subjects variable, to determine the effect of group on baseline BOLD response during active vs. control task conditions for each of the six planned contrasts, averaged across each ROI. There were a total of 6 ROIs identified using AFNI-based atlases, with 2 relevant to the pre-response assessment phase of decision-making (ACC, DLPFC), 3 relevant to the anticipation phase (insula, ventral striatum, VMPFC), and 3 relevant to the outcome evaluation phase (amygdala,

ventral striatum, VMPFC). For each ROI, AFNI program 3dClustSim determined the number of contiguous voxels (each with an effect of $p < .01$) necessary within a given area of activation (i.e., a “cluster”), to keep the family-wise alpha level at 0.05 within the ROI. Cluster sizes were identified as 5 voxels (135 μ l) for the amygdala, 9 voxels (243 μ l) for the ventral striatum, 10 voxels (270 μ l) for the anterior cingulate, 11 voxels (297 μ l) for the DLPFC and insula, and 12 voxels (324 μ l) for the VMPFC. In addition to testing the six contrasts of interest originally identified *a priori* (described above), two additional contrasts were tested: 1) “Inflate” trials where the previous balloon popped vs. “Rest”, 4) “Inflate” trials where the previous balloon did not pop vs. “Rest”; these contrasts were added because of the hypothesized overlap between the active “Inflate” condition and the control “Wait” condition. Specifically, as the “Wait” condition takes place immediately after participants input their chosen pump number, it is likely that participants are “anticipating” the outcome of their decision during “Wait” trials before viewing the visual cue of an inflating balloon during the “Inflate” trials. Thus, to more effectively separate out changes in BOLD response related to the anticipation phase of decision-making, the “Inflate” trials were contrasted with the other control condition, “Rest.” These two contrasts were also examined in Hypothesis 2 and the exploratory whole-brain analysis. There were a total of 22 tests run for Hypothesis 1 (2 contrasts x 2 ROIs for the pre-response assessment phase of the task, 4 contrasts x 3 ROIs for the anticipation phase, 1 contrast x 3 ROIs during evaluation of negative outcomes, and 1 contrast x 2 ROIs during evaluation of positive outcomes).

Hypothesis 2 was tested using AFNI program 3dLME (Chen, Saad, Britton, Pine, & Cox, 2013) to run a mixed-model 2 x 3 ANOVA with group (heavy drinkers vs.

controls) as the between-subjects factor, time (baseline, +2weeks, +4weeks) as the within-subjects factor, and subjects as a random factor, to determine main effects of group and time, as well as interaction effects between group and time on BOLD response during active conditions vs. control task conditions in the 8 planned contrasts in specified ROIs. Contrasts and ROIs with between-group differences at baseline were first tested to assess changes in BOLD activation patterns over time in these regions as specified in Hypothesis 2. To do this, masks were created representing the specific clusters within an ROI that showed significant between-group differences in BOLD activation. In addition, all other contrasts and ROIs (see Hypothesis 1) were tested for interaction and main effects in order to assess any other patterns of change in BOLD response across time that may exist other than the expected pattern of change (attenuation of baseline between-group differences over time). Significant interaction effects were followed up with pairwise comparisons as well as visual inspection of the data, in order to characterize the direction of between and within-group differences. Cluster sizes determined by 3dClustSim were again used (see above, in Hypothesis 1), to keep the family-wise alpha level at 0.05 within each ROI. There were a total of 25 tests run for Hypothesis 2 (3 baseline regions were tested, plus 2 contrasts x 2 ROIs for the pre-response assessment phase of the task, 4 contrasts x 3 ROIs for the anticipation phase, 1 contrast x 3 ROIs during evaluation of negative outcomes, and 1 contrast x 2 ROIs during evaluation of positive outcomes).

Hypothesis 3 was tested using hierarchical regressions to examine if baseline BOLD responding in specified ROI regions predicted baseline NP performance on executive functioning and risk-taking tasks or self-reported risk-taking behavior. Only

ROIs with significant group differences at baseline were used as predictors in these analyses. As the DLPFC and ACC ROIs during the pre-response assessment phase of decision-making at baseline did not evidence significant group differences, the impact of baseline BOLD response in these regions on baseline NP performance during executive functioning tasks (i.e., D-KEFS Color-Word Interference and Trails subtests) was not examined as originally planned in Hypothesis 3. However, baseline BOLD response in the insula and VMPFC ROIs during the anticipation and outcome evaluation stages of decision-making, respectively, were examined in relation to dependent measures of risk-taking (i.e., performance on the BART task and self-reported risk-taking behavior). Dependent measures of BART performance included: total number of “wins” and “pops”, mean number of pumps (overall, on trials following “unpopped balloons”, and on trials following “popped balloons”), and number of pumps on trial 1, on the first “pop” trial, and on the trial immediately after the first “pop” trial. Dependent measures of self-reported risk-taking behavior included: the Rule-Breaking subscale of the YSR, the Impulsivity/Sensation Seeking subscale of the ZKPQ, and the “Drive”, “Reward Responsiveness”, “Approach total”, and “Inhibition total” scales from the BIS/BAS.

Separate regression analyses were run for each dependent variable and each ROI (insula or VMPFC). Relevant covariates thought to affect risk-taking performance and self-report of risk-taking were entered as covariates on Block 1 of the regression analyses. These included: age, family history of alcoholism, average # of alcoholic drinks per month, # of binge episodes in the prior 3 months, # of days/month of cannabis use in prior 3 months. BOLD response signal change variables for each ROI (insula during “Inflate-Pop” contrast, and VMPFC during “Outcome-Pop” contrast) were entered

on Block 2. The $R^2\Delta$ for the second step represented the degree to which BOLD activation was associated with baseline risk-taking performance or self-report of risk-taking behavior, above and beyond the covariates listed in Step 1. There were a total of 28 tests run for Hypothesis 3 (2 ROIs x 14 dependent variables of interest). Alpha was set at 0.05 for each test, as this was the first fMRI study of risk-taking in adolescent alcohol users and the analyses for Hypothesis 3 were considered exploratory. However, it should be noted that the probability of Type I error is increased due to the large number of tests that were run.

Follow-up analyses of covariance. Analysis of Covariance (ANCOVA) was used to assess the impact of cannabis use and verbal intellectual functioning on the significant findings uncovered in Hypotheses 1 and 2. As the heavy drinkers showed significantly greater cannabis use and significantly lower WASI vocabulary scores than controls, it was important to determine whether these differences could account for the observed group differences in BOLD response. Only the “lifetime cannabis use” variable was entered as a covariate, as recent cannabis use (“# of days of cannabis use per month, in past 90 days”) did not correlate with any BOLD response variable.

Whole-brain analysis. An exploratory whole-brain analysis was conducted to examine if additional brain regions (aside from those identified in ROIs) showed between-group BOLD response differences to active vs. control conditions within 8 planned contrasts at baseline (Hypothesis 1) or if additional brain regions showed significant interaction effects of group x time or main effects of group or time on BOLD response to active vs. control task conditions within 8 planned contrasts in the mixed-model analyses (Hypothesis 2). 3dClustSim determined the appropriate cluster size (each

voxel showing an individual alpha level of $p < .01$) to be 25 voxels (675 μl) in this analysis, to maintain a family-wise alpha of $p = .05$.

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Results

Demographics. Groups did not differ on age, gender, race, ethnicity, socioeconomic status, family history of alcoholism, education, pubertal development, or self-reported internalizing problems. Heavy drinkers reported a higher level of externalizing problems on the YSR than did controls ($p < .05$). In addition, controls had higher scores on average on the WASI Vocabulary subtest than did heavy drinkers ($p < .05$). Controls also showed a trend ($p = .06$) for higher grade point averages compared to heavy drinkers (see Table 1).

Substance use. As expected, groups significantly differed on all lifetime and recent alcohol use variables ($p_s < .01$). In addition, the heavy drinking group showed significantly greater lifetime and recent nicotine and cannabis use compared to controls ($p_s < .05$). Groups did not differ on tobacco dependence scores or lifetime or recent use of other substances (see Table 2). With regard to cumulative days of abstinence from alcohol in the heavy drinking group, abstinence periods ranged from two to 21 days at the baseline scan ($M = 7.88$), 11 – 34 days at the +2weeks scan ($M = 20.86$), and 23 – 49 days ($M = 35.15$) at the +4weeks scan. In those heavy drinkers who reported using marijuana, abstinence from marijuana ranged from two to 243 days at baseline ($M = 68.54$), 13 – 355 days at +2weeks ($M = 72.24$), and 29 – 369 days at +4weeks ($M = 83.37$). For all other substances (aside from alcohol, marijuana, and nicotine), abstinence was reported as six days or greater at the baseline scan.

Mood and alertness day-of-scan. Heavy drinkers had significantly higher levels of self-reported past-week depression compared to controls at the baseline and +2weeks time point scans ($p_s < .05$); depression scores were equivalent across groups at the +4weeks scan. Heavy drinkers had significantly higher levels of past-week anxiety compared to controls at all three scanning time points ($p_s < .02$). Acute “state” anxiety levels measured immediately prior to scanning did not significantly differ between-groups at any time point, though there was a trend for higher levels of “state” anxiety in the heavy drinking group at the baseline scan only ($p = .06$). Levels of alertness measured pre and post scan did not significantly differ between groups at any time point.

BART task performance. At baseline, groups did not significantly differ on any BART task performance variable. However, there was a trend for heavy drinkers to have a greater number of “pop” trials compared to controls ($p = .08$). At the second time point (+2weeks), heavy drinkers inputted a greater number of pumps on trial 1 as well as a greater number of pumps on the trial directly adjacent to the first “pop” trial compared to controls ($p_s < .05$). Heavy drinkers also showed trends for a greater mean number of pumps after “pop” trials and fewer conservative pumps following “pop” trials compared to controls ($p_s < .10$). At the third time point, there were no significant group differences on any of the task performance variables (see Table 3).

Hypothesis 1: Baseline BOLD response. Groups showed significant differences in BOLD response patterns to active vs. control task conditions in two contrasts, and two ROIs. Specifically, during “Inflate” trials where the previous balloon popped (“Inflate-Pop”), heavy drinkers had significantly less BOLD response than controls in the right

insula region [$t(1, 39) = -2.89$, cluster = 324 μl , $p < .01$]. Single-sample analyses of each group revealed that controls showed more activation during “Inflate-Pop” trials compared to “Rest” trials, while heavy drinkers showed less activation during “Inflate-Pop” trials vs. “Rest” trials. In addition, during “Outcome” trials where balloons popped (“Outcome-Pop”), heavy drinkers showed significantly more BOLD response contrast than controls in bilateral clusters in the VMPFC [left inferior VMPFC: $t(1, 39) = 3.17$, cluster = 702 μl ; right medial VMPFC: $t(1, 39)$, cluster = 3.24, 405 μl , $p_s < .01$]. Single-sample t-tests showed this was due to heavy drinkers’ higher BOLD response during the “Outcome- Pop” trials than during “Wait” trials, while controls showed less BOLD response during “Outcome- Pop” than “Wait” trials. Between-group differences in baseline BOLD response for all other contrasts and ROIs (i.e., “Think-Pop” vs. “Rest”: DLPFC, ACC; “Think-Win” vs. “Rest”: DLPFC, ACC; “Inflate-Pop” vs. “Wait”: insula, ventral striatum, VMPFC; “Inflate-Win” vs. “Wait”: insula, ventral striatum, VMPFC; “Inflate-Win” vs. “Rest”: insula, ventral striatum, VMPFC; “Outcome-Pop” vs. Wait: amygdala; “Outcome-Win” vs. “Wait”: ventral striatum, VMPFC) were non-significant (see Table 4 and Figure 2).

Hypothesis 2: Longitudinal analyses of BOLD response across time. In the brain regions and contrasts where groups differed at baseline (i.e., bilateral VMPFC during “Outcome-Pop” and the right insula during “Inflate-Pop”), no significant between-group differences were observed at the +2weeks or +4weeks time points, and no significant interaction or main effects of group or time emerged. However, significant interaction and main effects of group were seen in several other contrasts and ROIs. No contrast or ROI showed any significant main effects of time.

Interaction effects were observed in the right anterior cingulate for the “Think-Pop” vs. “Rest” [$F(2, 40) = 5.89$, cluster = 324 μ l, $p < .01$] and “Think-Win” vs. Rest [$F(2, 40) = 6.34$, cluster = 675 μ l, $p < .01$] contrasts, as well as in the right VMPFC/anterior cingulate for the “Inflate-Pop” vs. “Wait” [$F(2, 40) = 6.00$, cluster = 513 μ l, $p < .01$] and “Inflate-Win” vs. “Wait” [$F(2, 40) = 5.96$, cluster = 648 μ l, $p < .01$] contrasts, and the left VMPFC for the “Outcome-Win” vs. “Wait” [$F(2, 40) = 5.66$, cluster = 702 μ l, $p < .01$] contrast. Follow-up analyses for the anterior cingulate ROIs during the “Think-Pop” and “Think-Win” contrasts revealed that the control group showed more BOLD activation at +4weeks than at baseline [$t(1, 15) = -3.11$ for “Think-Pop”, $t(1, 15) = -3.48$ for “Think-Win”, $p_s < .01$], while BOLD activation patterns during these contrasts remained the same across time for heavy drinkers. In addition, heavy drinkers showed significantly less BOLD response than controls during “Think-Pop” trials at the +4weeks time point [$t(1, 34) = -2.71$, $p_s < .01$]. For the VMPFC/anterior cingulate ROI during the “Inflate-Pop” and “Inflate-Win” (vs. “Wait”) contrasts, BOLD response increased between baseline and +4weeks for heavy drinkers [$t(1, 19) = -3.33$ for “Inflate-Pop”; $t(1, 19) = -3.54$ for “Inflate-Win”, $p_s < .01$]; controls did not show changes in BOLD response for these contrasts over time. None of the between-group pairwise comparisons were significant for these two contrasts. For the VMPFC ROI during the “Outcome-Win” vs. “Wait” contrast, BOLD response decreased from the +2weeks to the +4weeks time points for the control group only [$t(1, 16) = 2.86$, $p < .01$]; in addition, there was a significant between-group difference at the +2weeks time point, in that controls showed greater BOLD response compared to heavy drinkers [$t(1, 37) = -2.84$, $p < .01$]. For the

heavy drinking group, BOLD response did not change across time in this contrast (see Table 5 and Figures 3&4).

Main effects of group were observed within bilateral regions of the DLPFC for the “Think-Pop” vs. “Rest” [7 clusters, F -statistics (1, 40) ranged from 8.07 to 9.76, volumes ranged from 1,080 μ l to 378 μ l, $p_s < .01$] and “Think-Win” vs. “Rest” [7 clusters, F -statistics (1, 40) ranged from 7.65 to 9.85, volumes ranged from 1,782 μ l to 486 μ l, $p_s < .01$] contrasts, in the left insula, for the “Inflate-Win” vs. “Rest” contrast [F (1, 40) = 8.25, cluster = 297 μ l, $p < .01$], in the right VMPFC for the “Inflate-Pop” vs. “Rest” [F (1, 40) = 10.00, cluster = 405 μ l, $p < .01$] contrast, and the left VMPFC for the “Inflate-Win” vs. “Wait” [F (1, 40) = 10.94, cluster = 756 μ l, $p < .01$] contrast. Specifically, averaged across time, controls showed more BOLD activation in the DLPFC during “Think-Pop” and “Think-Win” (vs. “Rest”) trials, than heavy drinkers. Similarly, controls showed more BOLD activation in the insula during “Inflate-Win” (vs. Rest) and in the VMPFC during “Inflate-Pop” (vs. “Rest”) trials than heavy drinkers, averaged across time. During “Inflate-Win” (vs. “Wait”) trials, heavy drinkers showed more BOLD activation in the VMPFC than controls, averaged across time (see Table 6).

Hypothesis 3: Baseline BOLD response as a predictor of risk-taking task performance and self-reported risk-taking/impulsive behavior. Regression results for all BART task performance measures were non-significant. Neither of the specified models (covariates only, covariates plus BOLD response variables) accounted for a significant degree of variance in risk-taking performance on the BART. For self-report measures of risk-taking and impulsivity, greater BOLD response in bilateral regions of the VMPFC during the “Outcome-Pop” (vs. “Wait”) contrast at baseline predicted higher

scores on the Rule Breaking subscale of the YSR, $F(6, 32) = 2.94$, $p = .017$ ($R^2\Delta = 12\%$, $p = .05$, $\beta_s = .36$ for the left inferior VMPFC cluster, .17 for the right middle VMPFC cluster). Regression results for the other measures of self-reported risk-taking and impulsive behavior (i.e., ZKPQ Impulsivity/Sensation Seeking subscale, BIS/BAS scales) were non-significant. BOLD response in the right insula during the “Inflate-Pop” (vs. “Rest”) contrast at baseline did not predict either risk-taking task performance or self-report of risk-taking/impulsive behavior.

Follow-up analysis of covariance. Findings from Hypotheses 1 and 2 remained significant when lifetime cannabis use and WASI vocabulary score variables were entered into the model as covariates.

Whole-brain analyses.

Baseline group differences. Results of the exploratory whole-brain analysis of baseline BOLD responding uncovered significant group differences between heavy drinkers and controls in four of the eight specified contrasts (“Inflate-Pop”, “Inflate-Win”, “Outcome-Pop”, and “Outcome-Win”, vs. “Wait”), in brain regions not identified in the ROI analyses. Clusters already described above in the ROI analyses are not described again here and are not included in the exploratory whole-brain analysis tables of results. Within “Inflate-Pop” trials, controls showed greater baseline BOLD response compared to heavy drinkers in the right middle frontal gyrus [$t(1, 39) = -3.07$, cluster = $1,107\mu\text{l}$, $p < .01$]. The same pattern was observed within the “Inflate-Win” trials in the left anterior cingulate [$t(1, 39) = -2.92$, cluster = $864\mu\text{l}$, $p < .01$]. During the outcome evaluation phase of the BART task, heavy drinkers showed greater baseline BOLD responding compared to controls in seven clusters located in five brain regions during

“Outcome-Pop” trials, and in two clusters/brain regions during “Outcome-Win” trials. Significant “Outcome-Pop” clusters were located in bilateral regions of the middle temporal gyrus [3 clusters: $t(1, 39) = 2.85, 2.88, \text{ and } 2.98$, volumes = $810\mu\text{l}, 702\mu\text{l}$, and $675\mu\text{l}$, $p_s < .01$] and cingulate gyrus [1 cluster: $t(1, 39) = 3.05$; volume = $702\mu\text{l}$, $p < .01$], as well as regions of the right inferior frontal gyrus [1 cluster: $t(1, 39) = 3.15$; volume = $729\mu\text{l}$, $p < .01$], right precentral gyrus [1 cluster: $t(1, 39) = 2.88$; volume = $1,107\mu\text{l}$, $p < .01$], and right supramarginal gyrus [1 cluster: $t(1, 39) = 3.02$; volume = $1,917\mu\text{l}$, $p < .01$], while “Outcome-Win” clusters were located in regions of the right supramarginal gyrus [1 cluster: $t(1, 39) = 2.93$; volume = $864\mu\text{l}$, $p < .01$] and right medial frontal gyrus [1 cluster: $t(1, 39) = 3.14$; volume = $702\mu\text{l}$, $p < .01$] (see Table 7). For the majority of clusters where groups differed at baseline, differences did not persist at the +2weeks and +4weeks time points. Two exceptions to this were: 1) the right middle frontal gyrus during “Inflate-Pop” trials, which showed group differences across all three time points and is included as a main effect of group (below), and 2) the right medial frontal gyrus during “Outcome-Win” trials, which showed a significant interaction effect and is described as such below.

Interactions of Group X Time. Exploratory whole-brain results for BOLD responding across the three time points revealed several significant interaction effects between group and time as well as main effects of group and time in brain regions not identified as ROIs. Interaction effects were observed during anticipation and outcome evaluation phases of the BART task, in “Inflate-Pop” (vs. “Rest” and “Wait”), “Inflate-Win” (vs. “Rest” and “Wait”), and “Outcome-Win” (vs. “Wait”) contrasts. Brain regions showing significant interaction effects during “Inflate-Pop” trials included the left

superior frontal gyrus [$F(2, 40) = 6.68$, cluster = 756 μ l, $p < .01$] and the left middle frontal gyrus [$F(2, 40) = 5.73$, cluster = 702 μ l, $p < .01$] when contrasted with “Rest” trials, and the left anterior cingulate [$F(2, 40) = 6.23$, cluster = 2,835 μ l, $p < .01$] and right medial frontal gyrus [$F(2, 40) = 5.87$, cluster = 1,350 μ l, $p < .01$] when contrasted with “Wait” trials. For “Inflate-Win” trials, a significant interaction was observed in the left superior frontal gyrus [$F(2, 40) = 6.00$, cluster = 891 μ l, $p < .01$] when contrasted with “Rest” trials, and in the left anterior cingulate [$F(2, 40) = 5.94$, cluster = 2,862 μ l, $p < .01$] when contrasted with “Wait” trials. In “Outcome-Win” trials (vs. “Wait”), significant interactions emerged in regions of the right middle temporal gyrus [$F(2, 40) = 6.04$, cluster = 1,053 μ l, $p < .01$], right inferior temporal gyrus [$F(2, 40) = 6.70$, cluster = 1,026 μ l, $p < .01$], right insula [$F(2, 40) = 5.71$, cluster = 810 μ l, $p < .01$], and right medial frontal gyrus [$F(2, 40) = 5.79$, cluster = 675 μ l, $p < .01$].

Follow-up pairwise comparisons for the “Inflate-Pop” (vs. “Rest”) contrast revealed that BOLD response in the left superior frontal gyrus increased between the +2weeks and +4weeks time points for the control group only [$t(1, 16) = -3.22$, $p < .01$]; heavy drinkers’ BOLD response did not change across time for this region and no between-group differences were evident. In the left middle frontal gyrus, controls showed the same within-group pattern as described above [$t(1, 16) = -3.34$, $p < .01$], while heavy drinkers showed a greater BOLD response to “Inflate-Pop” trials compared to controls at the +2weeks time point only [$t(1, 37) = 3.12$, $p < .01$]; an identical pattern was observed in the left superior frontal gyrus during the “Inflate-Win” (vs. “Rest”) contrast [$t(1, 16) = -3.49$; $t(1, 37) = 2.85$, $p_s < .01$]. In both “Inflate-Pop” and “Inflate-Win” (vs. “Wait”) contrasts, BOLD response increased across time for the heavy drinkers only, in that

activation during the +4weeks time point was significantly greater than activation during the baseline time point in regions of the left anterior cingulate [“Inflate-Pop” $t(1, 19) = -3.15$; “Inflate-Win” $t(1, 29) = -3.54, p_s < .01$] and right medial frontal gyrus [“Inflate-Pop” $t(1, 19) = -2.86, p < .01$]. For the control group, BOLD activation did not significantly differ across time points in these regions/contrasts. In the “Outcome-Win” (vs. “Wait”) contrasts, controls showed greater BOLD activation at the +4weeks time point compared to the +2weeks time point in the right middle/inferior temporal gyrus [2 clusters: $t(1, 16) = 2.95, 3.15, p < .01$] and right insula [$t(1, 16) = 2.78, p < .01$] while heavy drinkers did not show changes in their BOLD response across time points. No between-group differences were observed in these brain regions. In the right medial frontal gyrus, heavy drinkers showed increased BOLD response compared to controls at baseline (described earlier); in addition, controls showed greater BOLD response at the +2weeks time point compared to baseline [$t(1, 16) = -2.74, p < .01$] (see Table 8).

Main effects of Group. Main effects of group emerged in six of the eight specified contrasts. In the “Think-Pop” (vs. “Rest”) trials, controls showed greater BOLD response compared to heavy drinkers in 13 clusters across regions of the frontal, parietal, and temporal lobes, including bilateral middle/inferior frontal [5 clusters; F -statistics (1, 40) ranged from 8.46 to 9.55, volumes ranged from 675 μ l to 1,350 μ l, $p_s < .01$], bilateral cingulate gyrus [2 clusters; F -statistics (1, 40) = 8.02, 8.52; volumes = 756 μ l, 918 μ l; $p_s < .01$], bilateral inferior parietal [2 clusters; F -statistics (1, 40) = 10.41, 8.71; volumes = 2,997 μ l, 2,970 μ l; $p_s < .01$], bilateral medial temporal [2 clusters; F -statistics (1, 40) = 9.23, 8.38; volumes = 20,034 μ l, 1,134 μ l; $p_s < .01$], right thalamus [1 cluster; $F(1, 40) = 7.85$, volume = 1,242 μ l, $p < .01$], and right superior frontal gyrus [1

cluster; $F(1, 40) = 8.59$, volume = 6,777 μ l, $p < .01$] areas (see Table 9a). Similarly, in the “Think-Win” (vs. “Rest”) trials, controls showed greater BOLD response than heavy drinkers in 10 clusters located across bilateral regions of the inferior parietal lobule [3 clusters; F -statistics (1, 40) ranged from 8.85 to 10.27, volumes ranged from 5,266 μ l to 24,948 μ l, $p_s < .01$] and inferior/middle frontal gyrus [2 clusters; F -statistics (1, 40) = 8.69, 9.44; volumes = 918 μ l, 1,593 μ l; $p_s < .01$], as well as regions of the left middle temporal gyrus [1 cluster; $F(1, 40) = 9.05$, volume = 1,647 μ l, $p < .01$], left precuneus [1 cluster; $F(1, 40) = 8.68$, volume = 1,620 μ l, $p < .01$], left precentral gyrus [1 cluster; $F(1, 40) = 8.76$, volume = 6,804 μ l, $p < .01$], left superior frontal gyrus [1 cluster; $F(1, 40) = 9.22$, volume = 15,606 μ l, $p < .01$], and right thalamus [1 cluster; $F(1, 40) = 8.11$, volume = 1,620 μ l, $p < .01$] (see Table 9b).

During the anticipation phase of decision-making, heavy drinkers showed greater BOLD response compared to controls in 4 clusters, and decreased BOLD response in 1 cluster during “Inflate-Pop” (vs. “Wait”) trials. During “Inflate-Win” (vs. “Wait”) trials, heavy drinkers had greater BOLD response compared to controls in 7 clusters. Areas of greater activation for heavy drinkers during “Inflate-Pop” trials included the left cuneus [1 cluster; $F(1, 40) = 8.58$, volume = 2,565 μ l, $p < .01$], left middle frontal gyrus [1 cluster; $F(1, 40) = 10.43$, volume = 1,053 μ l, $p < .01$], left cingulate gyrus [1 cluster; $F(1, 40) = 8.75$, volume = 837 μ l, $p < .01$], and right postcentral gyrus [1 cluster; $F(1, 40) = 9.75$, volume = 1,458 μ l, $p < .01$]; while lesser activation was observed in the right middle frontal gyrus [1 cluster; $F(1, 40) = 8.50$, volume = 675 μ l, $p < .01$]. For “Inflate-Win” trials, areas of greater activation for heavy drinkers included bilateral regions of the middle/inferior frontal gyrus [3 clusters; F -statistics (1, 40) ranged from 8.08 to 9.85,

volumes ranged from 729 μ l to 2,781 μ l, $p_s < .01$] and cingulate gyrus [3 clusters; F -statistics (1, 40) ranged from 8.17 to 9.16, volumes ranged from 675 μ l to 1,458 μ l, $p_s < .01$], and the right postcentral gyrus [1 cluster; F (1, 40) = 9.09, volume = 837 μ l, $p < .01$] (see Table 9c).

During the outcome evaluation phase of decision-making, heavy drinkers again showed greater BOLD responding compared to controls in both “Outcome-Pop” (6 clusters) and “Outcome-Win” (8 clusters) trials. Areas where heavy drinkers showed greater activation when receiving feedback that balloons had popped included the right middle frontal gyrus [2 clusters; F -statistics (1, 40) = 8.31, 8.55; volumes = 972 μ l, 1,296 μ l; $p_s < .01$], right inferior parietal [2 clusters; F -statistics (1, 40) = 8.69, 8.82; volumes = 1,512 μ l, 2,997 μ l; $p_s < .01$], right superior temporal [1 cluster; F (1, 40) = 10.03, volume = 1,323 μ l, $p < .01$] and right thalamus [1 cluster; F (1, 40) = 8.86, volume = 810 μ l, $p < .01$] regions. When receiving feedback that balloons had not popped, heavy drinkers showed greater activation across time points in bilateral middle/inferior frontal [4 clusters; F -statistics (1, 40) ranged from 8.32 to 10.08, volumes ranged from 729 μ l to 3,699 μ l, $p_s < .01$], right middle temporal [2 clusters; F -statistics (1, 40) = 9.21, 10.13; volumes = 1,053 μ l, 2,025 μ l; $p_s < .01$], right inferior parietal [1 cluster; F (1, 40) = 9.85, volume = 1,188 μ l, $p < .01$], and left cuneus [1 cluster; F (1, 40) = 8.89, volume = 1,242 μ l, $p < .01$] regions (see Table 9d).

Main effects of Time. Main effects of time were observed in four of the eight specified contrasts. Specifically, regardless of group, participants showed greater BOLD response in the +4weeks time point compared to the +2weeks and baseline time points in temporal, occipital, and frontal regions while engaged in the anticipation phase of

decision-making. During “Inflate-Pop” trials (vs. “Rest”), this pattern was observed in 2 clusters: the right parahippocampal gyrus [$F(2, 40) = 5.96$; volume = 837 μ l, $p < .01$] and the right lingual gyrus [$F(2, 40) = 6.04$; volume = 837 μ l, $p < .01$]. During “Inflate-Pop” trials (vs. “Wait”), this pattern was evident in 4 clusters within bilateral regions of the parahippocampal gyrus [2 clusters; F -statistics (2, 40) = 5.96, 5.76; volumes = 1,998 μ l, 1,836 μ l; $p_s < .01$] and areas of the left middle frontal gyrus [2 clusters; F -statistics (2, 40) = 5.99, 5.39; volumes = 1,404 μ l, 675 μ l; $p_s < .01$]. During “Inflate-Win” (vs. “Wait”) trials, the pattern was observed in bilateral regions of the middle frontal gyrus [3 clusters; F -statistics (2, 40) ranged from 6.15 to 6.50, volumes ranged from 1,296 μ l to 2,187 μ l, $p_s < .01$], as well as the left caudate [$F(2, 40) = 6.23$; volume = 2,025 μ l, $p < .01$] and left parahippocampal gyrus [$F(2, 40) = 6.83$; volume = 675 μ l, $p < .01$]. When receiving feedback that balloons had not popped (“Outcome-Win” vs. “Wait), both heavy drinking and control group participants showed greater BOLD response in 3 clusters during the baseline and +2weeks time points compared to the +4weeks time points. These clusters were located in the right middle temporal gyrus [$F(2, 40) = 6.64$; volume = 2,646 μ l, $p < .01$], right superior frontal gyrus [$F(2, 40) = 6.01$; volume = 2,619 μ l, $p < .01$], and left medial frontal gyrus [$F(2, 40) = 5.80$; volume = 891 μ l, $p < .01$] (see Table 10).

This work is being prepared for submission for publication as “fMRI Correlates of Risky Decision-Making in Adolescent Alcohol Users: The Role of Abstinence.” The dissertation author will be the primary author of this material along with co-authors Alan Simmons, Ph.D., Carmen Pulido, Ph.D., Susan Tapert, Ph.D., and Sandra Brown, Ph.D.

Discussion

The goals of this study were to use fMRI to: (1) identify brain regions where neural activation associated with three separate stages of risky decision-making differed between heavy drinking adolescents and controls; (2) examine whether neural activity associated with risky decision-making changed across a five-week period of abstinence and whether the trajectory of change over time differed for heavy drinkers vs. controls; and (3) determine whether neural activation in regions showing baseline group differences during risky decision-making could predict differences in neuropsychological functioning (i.e., executive functioning), risk-taking performance, or self-report of risk-taking behavior and impulsivity. Both ROI and whole-brain analyses were conducted to examine neural functioning in brain regions expected to activate during risky decision-making as well as brain regions not implicated as fundamental, but which may still be relevant.

With regard to group differences in neural activation patterns in ROIs at baseline (Hypothesis 1), heavy drinkers showed less BOLD response relative to controls in the right insula during the anticipation phase of decision-making when previous balloon trials had popped. Although it was originally hypothesized that heavy drinking adolescents would show increased activation in the insula during this stage of decision-making, the finding of reduced activation fits with previous investigations that suggest the insula is primarily involved in the experience of loss avoidance (as opposed to having a direct role in reward seeking; Fukunaga, Brown, & Bogg, 2012; Krawitz, Fukunaga, & Brown,

2010; Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003). With this interpretation, it may be that heavy drinkers were less concerned with avoiding further losses than controls, even when faced with a reminder of loss from the previous trial. During the experience of negative outcome evaluation (i.e., while observing balloons popping), heavy drinkers showed increased activation in bilateral regions of the VMPFC compared to nondrinkers. This result is consistent with expectation given the widely replicated findings outlining the VMPFC as central to reward processing (Rushworth, Noonan, Boorman, Walton & Behrens, 2011). Specifically, studies have suggested that the VMPFC is involved in encoding the reward value of a choice (e.g., Lebreton, Jorge, Michel, Thirion, & Pessiglione, 2009), with greater activation associated with appraisals of a higher valued item or result (Plassman, O'Doherty, & Rangel, 2007). While it was expected that heavy drinkers would show increased activation in the VMPFC relative to controls during evaluation of both “win” and “loss” outcomes, this effect was only observed during the evaluation of “loss” outcomes. Thus, it is possible that heavy drinkers and controls experience “winning” similarly; however, heavy drinkers may be less affected by negative outcomes, finding them more rewarding. This explanation is consistent with findings from Bogg and colleagues’ (2012) study, in which participants with greater recent alcohol consumption showed greater medial prefrontal cortex activity while experiencing outcomes achieved through riskier behavior (i.e., inflating balloons to a larger size).

With regard to changes in BOLD activation during the stages of risky decision-making across the five-week period of abstinence (Hypothesis 2), findings were mixed. In brain regions where differences in BOLD activation were observed at baseline (the

right insula during anticipation when previous balloons had popped and bilateral VMPFC during the experience of negative outcomes), no between-group differences were evident after two to three weeks of abstinence. This pattern of change was anticipated, though group differences were not expected to be nonsignificant until the third time point (+4weeks). However, the observed pattern is consistent with results of the preliminary study by Pulido and colleagues (2010), in which baseline BOLD activation differences between heavy drinkers and controls to an alcohol cue reactivity task were non-existent in most brain regions (with the exception of the superior frontal gyrus) after two to three weeks of abstinence. On the other hand, some surprising group differences in the trajectory of BOLD response to risky decision-making across the five-week abstinence period were seen. Specifically, controls showed increasing activation over time in the right anterior cingulate during the pre-response assessment phase of decision-making, while heavy drinkers did not show changes over time in this region during this phase of decision-making. Instead, heavy drinkers showed increasing activation over time in the right ventromedial prefrontal cortex/anterior cingulate during the anticipation phase of decision-making, while controls did not show this change. The anterior cingulate has been linked with a variety of separate functions at different stages in the decision-making process. Specifically, during the pre-response assessment phase of decision-making, it has been shown to have a primary role in cognitive control processes such as error and performance monitoring (Gehring & Knight, 2000; Holroyd & Coles, 2002). During anticipation of reward and reward evaluation, the anterior cingulate has also shown high reactivity, particularly when there is a higher degree of effort that must be undertaken to “earn” a reward (Croxson, Walton, O’Reilly, Behrens, & Rushworth, 2009). Other

studies have suggested that, like the insula, the anterior cingulate is associated with loss aversion during the anticipation of risks, with greater activation observed as the probability of a negative outcome increases (Fukunaga et al., 2012). Thus, increasing BOLD response in the anterior cingulate over time during the pre-response assessment phase may be indicative of learning, or an increased attention to cognitive strategies for optimal performance on the task as participants become increasingly comfortable with the task format. As controls showed this pattern but heavy drinkers did not, it is possible that heavy drinkers did not increase attention to cognitive strategies/performance monitoring over repeated assessments to the same degree as controls. Similarly, increased BOLD response in the VMPFC/anterior cingulate during the anticipation phase of decision-making may be indicative of increasing loss aversion or greater attention to the probability of loss with increasing abstinence. As the heavy drinkers showed this pattern but controls did not, this suggests that alcohol may alter brain functioning in regions responsible for aversion to loss which in turn, could contribute to greater risk-taking; in addition, short-term abstinence may contribute to neural recovery in these regions.

Other regions of the brain demonstrated main effects of group on BOLD response averaged across time points, indicating that some neural functioning differences between heavy drinkers and controls persisted across the abstinence period. Specifically, heavy drinkers had less BOLD response relative to controls in bilateral regions of the DLPFC during the pre-response assessment phase of the task (this occurred whether balloons on the previous trials had popped or not), in the left insula during anticipation (when balloons on the previous trials had not popped), and in the right VMPFC during

anticipation (when balloons on the previous trial had popped). Heavy drinkers also had more BOLD response compared to controls in the left VMPFC during anticipation (when balloons on the previous trial had not popped). The finding that heavy drinkers exhibited hyporeactivity relative to controls in the DLPFC during pre-response assessment is consistent with expectation as well as with previous studies indicating that adolescents engage the DLPFC to a lesser extent than do adults during risky decision-making (Eshel et al., 2007; Galvan et al., 2006). In addition, hyporeactivity in widespread brain regions during a risky decision-making task has been observed in a sample of adolescent males with substance use problems who had been abstinent from substances for at least 30 days. It is important to note that all adolescents in this sample had comorbid conduct disorder, so it is impossible to determine whether the observed neural abnormalities resulted from substance use, psychiatric factors, or both.

The finding that heavy drinkers displayed decreased left insular activity averaged across time points (vs. controls) during anticipation (when balloons on the previous trial had not popped) is consistent with between-group differences in baseline BOLD response observed in this study, where heavy drinkers showed decreased right insular activity during anticipation, when previous balloons had popped. However, it is interesting that differences in right insular activity did not persist across the abstinence period as is observed in the left insula. This may be because the left insular activity was observed after previous “winning” trials (unpopped balloons) while the right insular activity was observed after previous “loss” trials (popped balloons). If insular activity represents a marker for loss aversion, it may be that loss aversion is triggered more quickly when the memory of loss is more salient. In other words, heavy drinkers may continue to be less

averse to loss during anticipation of an uncertain outcome when the memory of a recent reward is more salient. The finding that heavy drinkers showed increased left VMPFC activity averaged across time points during anticipation (when previous balloons did not pop) is consistent with the idea that adolescent heavy alcohol users may pay greater attention to the potential rewarding properties of an uncertain outcome compared to nondrinkers. This interpretation also fits with the possibility that alcohol use may alter neural functioning patterns related to reward sensitivity, and that these alterations may persist for longer periods than do alterations related to loss aversion. However, the finding that controls had greater BOLD response than heavy drinkers averaged across time in the right VMPFC during anticipation (when previous balloons popped) is somewhat surprising as we might expect the opposite pattern.

With regard to baseline BOLD response as a predictor of executive functioning, risk-taking task performance, and self-report of risk-taking and impulsive behavior (Hypothesis 3), baseline BOLD response during risky decision-making was not associated with executive functioning performance or performance on the risk-taking task. However, greater activation in the VMPFC during negative outcome evaluation was predictive of self-report of greater risk-taking in the naturalistic environment. This is consistent with other studies that have reported similar relationships between BOLD response and ratings of risk-taking in adolescents. For example, Galvan and colleagues (2007) found that BOLD response in the nucleus accumbens (part of the ventral striatum) during a reward processing task was positively correlated with adolescents' ratings of both the likelihood of engaging in risky behaviors in the near future and ratings of anticipated positive consequences as a result of such risky behavior. Nucleus accumbens

activity was negatively correlated with ratings of anticipated negative consequences of risky behavior.

Findings from the exploratory whole-brain analysis suggest that heavy drinkers and controls may show differential neural response to risky decision-making in regions not identified as ROIs. During the baseline anticipation phase, heavy drinkers showed *less* BOLD response than controls in the right middle frontal gyrus (when balloons on previous trials had popped) and left anterior cingulate (when balloons on previous trials had not popped). During the baseline outcome evaluation phase, heavy drinkers showed *greater* BOLD response than controls in bilateral middle temporal and cingulate gyrus, right supramarginal gyrus, inferior/medial/superior frontal, and precentral gyrus areas. These baseline group differences were not evident after two to three weeks of abstinence, except for the right middle frontal gyrus during anticipation, where BOLD response was greater for controls, averaged across time points. During the pre-response assessment phase of decision-making, controls showed greater BOLD response than heavy drinkers averaged across time points, in widespread regions including bilateral medial temporal, inferior parietal, inferior/middle/medial frontal, anterior cingulate, right thalamus, and right superior frontal areas. In contrast, during the anticipation phase, heavy drinkers showed more BOLD response relative to controls averaged across time points in bilateral cingulate cortices, middle/inferior frontal regions, and occipital areas. During outcome evaluation, heavy drinkers showed greater BOLD response relative to controls averaged across time points in bilateral inferior/middle/medial frontal, right inferior parietal, right superior temporal, left occipital, and left thalamic regions. Overall, results of the whole-brain analysis provide evidence that there are other regions (aside from those identified as

ROIs) implicated in the stages of risky decision-making, which show neural functioning differences between heavy drinkers and controls. Some neural functioning differences in these areas appear to resolve after two to three weeks of abstinence, while others persist for at least 4+ weeks.

Some limitations should be mentioned. First, among the heavy drinking adolescents, there was considerable variability in the reported length of abstinence from alcohol prior to entering the study. Although the ideal length of abstinence at study entrance was between 4-10 days, some subjects reported much longer periods of abstinence (up to 21 days), while others reported shorter periods (as little as 2 days). Although the mean number of days of reported abstinence in the heavy drinking group was consistent with the ideal length of abstinence (7.88 days) it is possible that the variability may have skewed the results.

The rapid event-related design of the BART fMRI task created some special challenges for analysis. Because the task moved very quickly through the *Think, Pump, Wait, Inflate, Pop or Win, and Rest* conditions (with some conditions lasting only 2 seconds), it is possible that there was overlap of the hemodynamic response across task conditions. However, the deconvolution process (completed during image processing) is generally effective at disentangling the individual hemodynamic response functions so that the BOLD response pattern specific to each task condition can be appropriately measured. Rapid event-related designs are also limited by a lower signal-to-noise ratio, compared to blocked designs or slower event-related designs. This ultimately leads to a loss of statistical power. Also, some of the task conditions may not have been perceived as separate, distinct events to participants, and thus BOLD response may not be

qualitatively different between these conditions. For example, the “Wait” control condition occurred immediately after subjects inputted their number of pumps. Although the active “Inflate” condition was designed to measure the anticipation stage of decision-making, the “Wait” condition may have captured some anticipatory response as well. The visual display of a balloon inflating likely added an element of anticipation above and beyond the “Wait” phase (where participants just looked at the uninflated balloon on the screen); however, both “Rest” and “Wait” conditions were used as control conditions for the “Inflate” (anticipation) conditions, in order to address this issue.

It is somewhat surprising that heavy drinkers and controls showed very few differences on BART task performance variables. This contrasts with previous studies using BART paradigms which have found group differences between adolescent smokers and non-smokers (Lejuez, Aklin, Bornovalova, & Moolchan, 2005) and adolescents with “serious substance use and conduct problems” and controls (Crowley, Raymond, Mikulich-Gilbertson, Thompson, & Lejuez, 2006). However other studies have not shown differences between adolescent substance users and non-users (e.g., Gonzalez et al., 2012). One reason for the lack of performance differences may be that the version of the BART used in this study differs from the original design of the task where participants are asked to sequentially input discrete pumps, one by one, to pump up the balloons (rather than inputting a single number of pumps). It may be that inputting each pump separately allows for anticipation to build to higher levels, leading to an increased response to reward or loss which may further risk-taking performance on the task. Some studies have also analyzed the first and second half of the BART separately, to examine group differences in risky decision-making as the task progresses. A preliminary study of

the BART in the current sample (outside of the fMRI setting) used this method and found that heavy drinking adolescents had a greater number of pumps on the second half of the task compared to controls, though after 5 weeks of abstinence, the groups were equivalent (Hanson et al., 2011). In addition, at baseline, number of pumps on the second half of the task was positively correlated with number of recent alcohol binges and number of drinks per day. Although the lack of group differences in BART task performance within the current study allows for easier interpretation of the fMRI data, it is also important to consider the real-world generalizability of any laboratory measure of an abstract concept like risky decision-making.

Another limitation to this study and all fMRI studies is that other variables may have affected the magnitude of the BOLD response other than the construct of interest (alcohol use). For example, heavy drinkers and controls differed in their use of cannabis and nicotine. However, findings remained unchanged after controlling for cannabis use. While tobacco use was not controlled for in this study, the level of use in the heavy drinking group was relatively low, and no participants met criteria for tobacco dependence. Therefore it is unlikely that tobacco use could have accounted for variability in BOLD response. Heavy drinkers and controls also differed in terms of verbal intellectual functioning and level of externalizing problems. Findings remained unchanged after controlling for verbal intellectual functioning. However, level of externalizing problems was not controlled for, primarily because the difference observed on this variable was thought to represent a naturally occurring difference between adolescents who use substances (in and of itself an “externalizing behavior”) and those who do not. Cerebral blood flow was not measured in this study and is known to have

some effect on BOLD response. As resting state perfusion can affect the magnitude of the BOLD response (Brown et al., 2003; Stefanovic, Warnking, Rylander, & Pike, 2006), it is possible that differences in cerebral blood flow could explain BOLD response differences between heavy drinkers and controls. A recent study by Jacobus and colleagues (2012) found that for heavy adolescent marijuana users, cerebral blood flow was reduced in four cortical regions and increased in one region at baseline (relative to controls); however, after four weeks of abstinence, no between-group differences in cerebral blood flow were found. In extrapolating these findings to adolescent heavy alcohol users, it seems possible that cerebral blood flow could have an impact on the baseline between-group differences in BOLD response in this study, but may be less likely to impact BOLD response differences at the +2weeks and +4weeks time points.

The issue of test-retest reliability of the BOLD response should be considered. There has been some controversy about this topic in the literature, as some studies have found high test-retest BOLD signal reliability (Aron, Gluck, & Poldrack, 2006; Fernandez et al., 2003; Friedman et al., 2008; Specht, Willmes, Shah, & Jancke, 2003), and others have reported considerable within-subject variation in BOLD signal change across scan sessions (Marshall et al., 2004; Tjandra et al., 2005; Zandbelt et al., 2008). Changes in BOLD signal response across different scan sessions for the same subject can occur for several reasons, such as fluctuating mood/anxiety/alertness states (Bishop, Duncan, & Lawrence, 2004; Harris & Hoehn-Saric, 1995), levels of effort (Specht et al., 2003), motion, scanner drift (Gunter et al., 2009), physiological changes (respiration, cerebral blood flow) (Menon, 2002; Petridou, Schäfer, Gowland, & Bowtell, 2009; Tomasi & Caparelli, 2007), and developmental maturation. Many of these variables were

measured and controlled for in this study. Specifically, acute anxiety and alertness were found to be equivalent between groups and are therefore unlikely to affect results. In addition, subpar effort was controlled for by removing subjects with five or more “Too Slow” outcomes within a given scan session, as it was assumed that subjects with a high degree of “Too Slow” responses were not adequately engaged in the task. Excess motion was controlled for by removing participants with more than 20% repetitions containing excessive head motion. Field maps applied to the fMRI acquisitions also helped to control the BOLD signal stability across scans, as this process minimizes warping and signal dropout, as well as reduces mislocalization errors, especially in frontal regions. Physiological changes and scanner drift were more difficult to control for and thus there is a small probability that these variables could have affected the reliability of the BOLD signal across repeated assessments in this study.

Finally, the probability of Type I error in this study is likely higher than desired due to the large number of tests that were run within each hypothesis. Although Hypotheses 1 and 2 included corrections for multiple comparisons *within* each ROI (i.e., predetermined “cluster sizes” indicating the number of contiguous voxels which must be significantly activated to keep a family-wise alpha level of .05), there was no comparable correction for the number of comparisons examined *across* ROIs (i.e., within each hypothesis). Hypothesis 3 also did not employ any multiple comparison corrections, and these analyses (as well as the whole-brain analyses) should be considered exploratory.

Taken together, the results of this study suggest that heavy drinkers display abnormalities in neural functioning during risky decision-making compared to their nondrinking peers, particularly in the right insula during anticipation and the

ventromedial prefrontal cortex during evaluation of negative outcomes. Abnormalities in these regions appear to resolve after two to three weeks of abstinence. In addition, heavy drinkers showed some changes in BOLD response across repeated assessments (i.e., the anterior cingulate during anticipation), which provide further support for a neural recovery hypothesis. However, after five weeks of abstinence, heavy drinkers and controls show some differences in neural functioning that persist across time. This suggests that other regions of the brain may take longer to fully recover, or, that there are pre-existing differences in these regions, which could represent vulnerabilities for future substance use. In addition, this study suggests that differences in neural functioning in reward-related regions can effectively predict real-world report of risk-taking behavior. These findings are important as they suggest that neural functioning may be used as a potential biomarker for risk-taking vulnerability in the future.

Future directions for this study should first include replication within a larger sample, to increase confidence in the findings. Second, an examination of the effect of length of abstinence from alcohol prior to study entry on BOLD response in the heavy drinking group will be necessary to determine whether variability in length of abstinence may have contributed to the between-group differences observed in this study. It would also be informative to analyze the first and second half of the BART task separately, as Hansen and colleagues (2011) did with the non-fMRI BART task. In addition, an examination of gender differences could be important, given results from previous studies suggesting that females may be especially susceptible to the effects of heavy alcohol use. Measures of hangover severity and withdrawal effects could also be investigated as possible moderating factors of group differences in BOLD response to risky decision-

making, as these have been implicated as significantly related to performance on cognitive tasks in heavy alcohol users. The ultimate goal of this study and others like it should be to disseminate findings to youth and families, and to provide psychoeducation through the creation of prevention materials and public service campaigns. By understanding how the brain responds to risky decision-making after recent alcohol use, and how the brain's circuitry may "repair" itself with sustained abstinence, adolescents could become motivated to remain abstinent from alcohol, which ultimately, would reduce the rates of accidents and deaths in this age group as a result of risky behavior.

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References

- Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for the ASEBA School-Age Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.
- Acredolo, C., O'Connor, J., Banks, L., & Horobin, K. (1989). Children's ability to make probability estimates: Skills revealed through application of Anderson's functional measurement methodology. *Child Development*, 60, 933-945.
- Åkerstedt, T., & Gillberg, M. (1990). Subjective and objective sleepiness in the active individual. *International Journal of Neuroscience*, 52, 29-37.
- Aluja, A., Rossier, J., Garcia, J.F., Angleitner, A., Kuhlman, M., & Zuckerman, M. (2006). A cross-cultural shortened form of the ZKPQ (ZKPQ-50-cc) adapted to English, French, German, and Spanish languages. *Personality and Individual Differences*, 41, 619-628.
- Aron, A. R., Gluck, M. A., & Poldrack, R. A. (2006). Long-term test-retest reliability of functional MRI in a classification learning task. *NeuroImage*, 29, 1000-1006.
- Bandettini, P. A., Jesmanowicz, A., Wong, E. C., & Hyde, J. S. (1993). Processing strategies for time-course data sets in functional mri of the human brain. *Magnetic Resonance in Medicine*, 30(2), 161-173.
- Bearman, P., Jones, J., & Udry, J.R. (1997). *The National Longitudinal Study of Adolescent Health: Research Design*. Chapel Hill, N.C.: Carolina Population Center.
- Beyth-Marom, R., Austin, L., Fischhoff, B., Palmgren, C., & Quadrel, M.J. (1993). Perceived consequences of risky behaviors: Adults and adolescents. *Developmental Psychology*, 29, 549-563.
- Bishop, S. J., Duncan, J., & Lawrence, A. D. (2004). State anxiety modulation of the amygdala response to unattended threat related stimuli. *Journal of Neuroscience*, 24, 10364-10368.
- Bjork, J., Knutson, B., Fong, G., Caggiano, D., Bennett, S., & Hommer, D. (2004). Incentive-elicited brain activation in adolescents: Similarities and differences from young adults. *The Journal of Neuroscience*, 24, 1793-1802.
- Bogg, T., Fukunaga, R., Finn, P. R., & Brown, J. W. (2012). Cognitive control links alcohol use, disinhibition, and reduced cognitive capacity: Evidence for medial prefrontal cortex dysregulation during reward-seeking behavior. *Drug and Alcohol*

Dependence, 122, 112-118.

Boyer, T. (2006). The development of risk-taking: A multi-perspective review. *Developmental Review*, 26, 291-345.

Boynton, G.M., Engel, S.A, Glover, G.H., & Heeger, D.J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. *The Journal of Neuroscience*, 16, 4207-4221.

Brandt, J., Butters, N., Ryan, C., & Bayog, R. (1983). Cognitive loss and recovery in long-term alcohol abusers. *Archives of General Psychiatry*, 40, 435-442.

Brown, G. G., Eyler Zorrila, L. T., Georgy, B., Kindermann, S. S., Wong, E. C., & Buxton, R. B. (2003). BOLD and perfusion response to finger-thumb apposition after acetazolamide administration: Differential relationship to global perfusion. *Journal of Cerebral Blood Flow & Metabolism*, 23, 829-837.

Brown, S.A., McGue, M., Maggs, J., Schulenberg, J., Hingson, R., & Swartzwelder, S. (2008). A developmental perspective on alcohol and youths 16 to 20 years of age. *Pediatrics*, 121, S290-S310.

Brown, S. A., Myers, M. G., Lippke, L., Tapert, S. F., Stewart, D. G., & Vik, P. W. (1998). Psychometric evaluation of the Customary Drinking and Drug Use Record (CDDR): A measure of adolescent alcohol and drug involvement. *Journal of Studies on Alcohol*, 59, 427-438.

Brown, S. A., Tapert, S. F., Granholm, E., & Delis, D. C. (2000). Neurocognitive functioning of adolescents: Effects of protracted alcohol use. *Alcoholism: Clinical and Experimental Research*, 24, 164-171.

Caldwell, L. C., Schweinsburg, A. D., Nagel, B. J., Barlett, V. C., Brown, S. A., & Tapert, S. F. (2005). Gender and adolescent alcohol use disorders on BOLD (blood oxygen level dependent) response to spatial working memory. *Alcohol & Alcoholism*, 40, 194-200.

Carver, C., & White, T.L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. *Journal of Personality and Social Psychology*, 67, 319-333.

Casey, B. J., Getz, S., & Galvan, A. (2008). The adolescent brain. *Developmental Review*, 28, 62-77.

Center for Disease Control and Prevention (2011). Youth risk behavior surveillance – United States. *Morbidity and Mortality Weekly Report*, 61(4), 1-168.

Chambers, R., Taylor, J. & Potenza, M. (2003). Developmental neurocircuitry of

motivation in adolescence: A critical period of addiction vulnerability. *American Journal of Psychiatry*, 160, 1041-1052.

Chen, G., Saad, Z.S., Britton, J.C., Pine, D.S., & Cox, R.W. (2013). Linear mixed-effects modeling approach to fMRI analysis. *Neuroimage*, 73, 176-190.

Cohen, M. S. (1997). Parametric analysis of fMRI data using linear systems methods. *NeuroImage*, 9, 508-515.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, 29, 162-173.

Cox, R. W., & Jesmanowicz, A. (1999). Real-time 3D image registration for functional MRI. *Magnetic Resonance in Medicine*, 42, 1014-1018.

Crowley, T.J., Raymond, K.M., Mikulich-Gilbertson, S.K., Thompson, L.L., & Lejuez, C.W. (2006). A risk-taking "set" in a novel task among adolescents with serious conduct and substance problems. *Journal of the American Academy of Child & Adolescent Psychiatry*, 45, 175-183.

Croxson, P. L., Walton, M. E., O'Reilly, J. X., Behrens, T. E. J., & Rushworth, M. F. S. (2009). Effort-based cost-benefit valuation in the human brain. *The Journal of Neuroscience*, 29, 4531-4541.

De Bellis, M. D., Clark, D. B., Beers, S. R., Soloff, P. H., Boring, A. M., Hall, J.,...Keshavan, M.S. (2000). Hippocampal volume in adolescent-onset alcohol use disorders. *American Journal of Psychiatry*, 157, 737-744.

De Bellis, M. D., Narasimhan, A., Thatcher, D. L., Keshavan, M. S., Soloff, P., & Clark, D. B. (2005). Prefrontal cortex, thalamus, and cerebellar volumes in adolescents and young adults with adolescent-onset alcohol use disorders and comorbid mental disorders. *Alcoholism: Clinical & Experimental Research*, 29, 1590-1600.

Delgado, M., Nystrom, L.E., Fissell, C., Noll, D.C., & Fiez, J. (2000). Tracking the hemodynamic responses to reward and punishment in the striatum. *Journal of Neurophysiology*, 84, 3072-3077.

De Rosa, E., Desmond, J.E., Anderson, A.K., Pfefferbaum, A., & Sullivan, E.V. (2004). The human basal forebrain integrates old and the new. *Neuron*, 41, 825-837.

Desmond, J.E., Chen, S.H., De Rosa, E., Pryor, M.R., Pfefferbaum, A., & Sullivan, E.V. (2003). Increased frontocerebellar activation in alcoholics during verbal working memory: An fMRI study. *NeuroImage*, 19, 1510-1520.

Durston, S., Hulshoff Pol, H. E., Casey, B. J., Giedd, J. N., Buitelaar, J. K., & van

- Engeland, H. (2001). Anatomical MRI of the developing human brain: What have we learned? *Journal of the American Academy of Child and Adolescent Psychiatry*, 40, 1012–1020.
- Ernst, M., Nelson, E., Jazbec, S., McClure, E., Monk, C., Leibenluft...Pine, D.S. (2005). Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *NeuroImage*, 25, 1279-1291.
- Ernst, M. & Paulus, M. (2005). Neurobiology of decision-making: A selective review from a neurocognitive and clinical perspective. *Biological Psychiatry*, 58, 597-604.
- Eshel, N., Nelson, E., Blair, J., Pine, D., & Ernst, M. (2007). Neural substrates of choice selection in adults and adolescents: Development of the ventrolateral prefrontal and anterior cingulate cortices. *Neuropsychologia*, 45, 1270-1279.
- Estruch, R., Nicolas, J.M., Salamero, M. Aragon, C., Sacanella, E., Fernandez-Sola, J., & Urbano-Marquez, A. (1997). Atrophy of the corpus callosum in chronic alcoholism. *Journal of Neurological Society*, 146, 145-151.
- Fein, G., Bachman, L., Fisher, S., Davenport, L. (1990). Cognitive impairments in abstinent alcoholics. *Western Journal of Medicine*, 152, 531-537.
- Fein, G., Di Sclafani, V., Cardenas, V.A., Goldmann, H., Tolou-Shams, M., & Meyerhoff, D.J. (2002). Cortical gray matter loss in treatment-naïve alcohol dependent individuals. *Alcoholism: Clinical and Experimental Research*, 26, 558-564.
- Fein, G., Torres, J., Price, L.J., & Di Sclafani, V. (2006). Cognitive performance in long-term abstinent alcoholics. *Alcoholism: Clinical and Experimental Research*, 30, 1538-1544.
- Fernandez, G., Specht, K., Weis, S., Tendolkar, I., Reuber, M., Fell, J.,...Elger, C.E. (2003). Intrasubject reproducibility of presurgical language lateralization and mapping using fMRI. *Neurology*, 60, 969-975.
- Friedman, L., Stern, H., Brown, G. G., Mathalon, D. H., Turner, J., Glover, G. H.,...Potkin, S.G. (2008). Test-retest and between-site reliability in a multicenter fMRI study. *Human Brain Mapping*, 29, 958-972.
- Friston, K. J., Williams, S., Howard, R., Frackowiak, R. S. J., & Turner, R. (1996). Movement-related effects in fMRI time-series. *Magnetic Resonance in Medicine*, 35, 346-355.
- Fukunaga, R., Brown, J. W., & Bogg, T. (2012). Decision making in the Balloon Analogue Risk Task (BART): Anterior cingulate cortex signals loss aversion but not the infrequency of risky choices. *Cognitive, Affective, and Behavioral Neuroscience*, 12,

479-490.

Galvan, A., Hare, T., Parra, C., Penn, J., Voss, H., Glover, G., & Casey, B.J. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *The Journal of Neuroscience*, 25, 6885-6892.

Galvan, A., Hare, T., Voss, H., Glover, G., & Casey, B. J. (2007). Risk-taking and the adolescent brain: Who is at risk? *Developmental Science*, 10, F8-F14.

Gehring, W.J., & Knight, R. T. (2000). Prefrontal – cingulate interactions in action monitoring. *Nature Neuroscience*, 3, 516-520.

Giancola, P. R., Shoal, G. D., & Mezzich, A. C. (2001). Constructive thinking, executive functioning, antisocial behavior, and drug use involvement in adolescent females with a substance use disorder. *Experimental and Clinical Psychopharmacology*, 9(2), 215-227.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A.,...Rapaport, J.L. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, 2, 86 1-863.

Giedd, J. N. (2004). Structural magnetic resonance imaging of the adolescent brain. *Annals of the New York Academy of Sciences*, 1021, 77-85.

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C.,...Rapaport, J.L. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences*, 101, 8174-8179.

Gonzalez, R., Schuster, R.M., Mermelstein, R.J., Vassileva, J., Martin, E.M., & Diviak, K.R. (2012). Performance of young adult cannabis users on neurocognitive measures of impulsive behavior and their relationship to symptoms of cannabis use disorders. *Journal of Clinical and Experimental Neuropsychology*, 34, 962-976.

Gunter, J. L., Bernstein, M. A., Borowski, B. J., Ward, C. P., Britson, P. J., Felmlee, J. P.,...Jack, C.R. (2009). Measurement of MRI scanner performance with the ADNI phantom. *Medical Physics*, 36, 2193-2205.

Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology*, 32, 50-55.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, & Psychiatry*, 23, 56-62.

Hanson, K.L., Bekman, N.M., Tapert, S.F., Lejuez, C.W., & Brown, S.A. (June 2011). Elevated risk-taking among binge drinking adolescents decreases with abstinence. Poster

presented at the Research Society on Alcoholism: Atlanta, GA.

Harris, G. J., & Hoehn-Saric, R. (1995). Functional neuroimaging in biological psychiatry. In J. Panksepp (Ed.), *Advances in biological psychiatry* (pp. 113-160). Greenwich, CT: JAI Press.

Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., & Fagerstrom, K.O. (1991). The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. *Addiction*, 86, 1119-1127.

Herting, M. M., Schwartz, D., Mitchell, S. H., & Nagel, B. J. (2010). Delay discounting behavior and white matter microstructure abnormalities in youth with a family history of alcoholism. *Alcoholism: Clinical & Experimental Research*, 34, 1590-1602.

Hollingshead, A.B. (1965). *Two-factor index of social position*. New Haven, CT: Yale University Press.

Holroyd, C. B., & Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, 109, 679-709.

Hüppi, P. S., & Dubois, J. (2006). Diffusion tensor imaging of brain development. *Seminars in Fetal and Neonatal Medicine*, 11, 489-497.

Jacobus, J., Goldenberg, D., Wierenga, C. E., Tolentino, N. J., Liu, T. T., Tapert, S. F. (2012). Altered cerebral blood flow and neurocognitive correlates in adolescent cannabis users. *Psychopharmacology*, 222, 675-684.

Jacobus, J., Thayer, R.E., Trim, R., Bava, S., & Tapert, S. F. (in press, 2012). White matter integrity, substance use, and risk taking in adolescence. *Psychology of Addictive Behaviors*.

Jernigan, T. L., & Gamst, A. C. (2005). Changes in volume with age—consistency and interpretation of observed effects. *Neurobiology of Aging*, 26, 1271-1278.

Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2011). *Monitoring the Future national results on adolescent drug use: Overview of key findings, 2010*. Bethesda, MD: National Institute on Drug Abuse.

Knutson, B., Fong, G., Adams, C.M., Varner, J.L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport*, 12, 3683-3687.

Krawitz, A., Fukunaga, R., & Brown, J. W. (2010). Anterior insula activity predicts the influence of positively framed messages on decision making. *Cognitive, Affective, and*

Behavioral Neuroscience, 10, 392-405.

Kubota, M., Nakazaki, S., Hirai, S., Saeki, N., Yamaura, A., Kusaka, T., (2001). Alcohol consumption and frontal lobe shrinkage: Study of 1432 non-alcoholic subjects. *Journal of Neurology, Neurosurgery, & Psychiatry*, 71, 104-106.

Lebreton, M., Jorge, S., Michel, V., Thirion, B., & Pessiglione, M. (2009). An automatic valuation system in the human brain: Evidence from functional neuroimaging. *Neuron*, 64, 431-439.

LeDoux, J.E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, 23, 55-184.

Lejuez, C. W., Aklin, W., Bornovalova, M., & Moolchan, E. (2005). Differences in risk-taking propensity across inner-city adolescent ever- and never-smokers. *Nicotine & Tobacco Research*, 7, 71-79.

Lejuez, C. W., Read, J. P., Kahler, C.W., Richards, J. B., Ramsey, S. E., Stuart, G.L.,...Brown, R.A. (2002). Evaluation of a behavioural measure of risk-taking: the Balloon Analogue Risk Task (BART). *Journal of Experimental Psychology: Applied*, 8(2), 75-84.

Lucas, C. P., Zhang, H., Fisher, P. W., Shaffer, D., Regier, D. A., Narrow, W. E.,...Friman, P. (2001). The DISC Predictive Scales (DPS): Efficiently screening for diagnoses. *Journal of American Academy of Child & Adolescent Psychiatry*, 40, 443-449.

Luna, B., & Sweeney, J. A. (2004). The emergence of collaborative brain function: fMRI studies of the development of response inhibition. *Annals of the New York Academy of Sciences*, 1021, 296-309.

Marshall, I., Simonotto, E., Deary, I. J., MacLulich, A., Ebmeier, K. P., Rose, E. J.,...Chappell, F.M. (2004). Repeatability of motor and working-memory tasks in healthy older volunteers: Assessment at functional MR imaging. *Radiology*, 233, 868-877.

McQueeney, T., Schweinsburg, B. C., Schweinsburg, A. D., Jacobus, J., Bava, S., Frank, L. R., & Tapert, S. F. (2009). Altered white matter integrity in adolescent binge drinkers. *Alcoholism: Clinical and Experimental Research*, 33, 1278-1285.

Medina, K. L., McQueeney, T., Nagel, B. J., Hanson, K. L., Schweinsburg, A. D., & Tapert, S. F. (2008). Prefrontal cortex volumes in adolescents with alcohol use disorders: Unique gender effects. *Alcoholism: Clinical & Experimental Research*, 32, 386-394.

Menon, R. (2002). Post acquisition suppression of large-vessel BOLD signals in high-resolution fMRI. *Magnetic Resonance Imaging*, 47, 1-9.

- Miller, C. L., Tucker, M. L., Pasch, L., & Eccles, J. S. (March, 1988). Measuring pubertal development: A comparison of different scales and different sources. *Paper presented at the biennial meeting of the Society for Research in Child Development, Alexandria, VA.*
- Millstein, S. & Halpern-Felsher, B. (2002). Perceptions of risk and vulnerability. *Journal of Adolescent Health, 31*, 10-27.
- Moore, S. & Gullone, E. (1996). Predicting adolescent risk-taking behavior using a personalized cost-benefit analysis. *Journal of Youth and Adolescence, 25*, 343-359.
- Moselhy, H.F., Georgiou, G., & Kahn, A. (2001). Frontal lobe changes in alcoholism: A review of the literature. *Alcohol and Alcoholism, 36*, 357-368.
- Moss, H. B., Kirisci, L., Gordon, H. W., & Tarter, R. E. (1994). A neuropsychologic profile of adolescent alcoholics. *Alcoholism: Clinical & Experimental Research, 18*, 159-163.
- Nagel, B. J., Schweinsburg, A. D., Phan, V., & Tapert, S. F. (2005). Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. *Psychiatry Research: Neuroimaging, 139*, 181-190.
- O'Neill, J., Cardenas, V.A., & Meyerhoff, D.J. (2001). Effects of abstinence on the brain: Quantitative magnetic resonance imaging and magnetic resonance spectroscopic imaging in chronic alcohol abuse. *Alcoholism: Clinical and Experimental Research, 25*, 1673-1682.
- Oscar-Berman, M., & Hutner, N. (1993). Frontal lobe changes after chronic alcohol ingestion. In: Hunt, W.A., Nixon, S.J. (Eds.), *Alcohol-Induced Brain Damage. NIAAA Research Monographs #22*. National Institutes of Health, Rockville, MD, 121-156.
- Parsons, O.A. (1983). Cognitive dysfunction and recovery in alcoholics. *Substance and Alcohol Actions/Misuse, 4*, 175-190.
- Parsons, O.A., Butters, N., & Nathan, P.E. (1987). *Neuropsychology of alcoholism: implications for diagnosis and treatment*. Guilford Press, New York.
- Paulus, M., Rogalsky, C., Simmons, A., Feinstein, J. & Stein, M. (2003). Increased activation in the right insula during risk-taking decision-making is related to harm avoidance and neuroticism. *NeuroImage, 19*, 1439-1448.
- Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. *TRENDS in Cognitive Sciences, 9*(2), 60-68.
- Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence,*

17(2), 117-133.

Petridou, N., Schäfer, A., Gowland, P., & Bowtell, R. (2009). Phase vs. magnitude information in functional magnetic resonance imaging time series: toward understanding the noise. *Magnetic Resonance Imaging*, 27, 1046-1057.

Pfefferbaum, A., Desmond, J.E., Galloway, C., Menon, V., Glover, G.H., Sullivan, E.V. (2001) Reorganization of frontal systems used by alcoholics for spatial working memory: An fMRI study. *NeuroImage*, 14, 7-20.

Pfefferbaum, A., Lim K.O., Desmond, J., & Sullivan, E.V. (1996). Thinning of the corpus callosum in older alcoholic men: a magnetic resonance imaging study. *Alcoholism: Clinical and Experimental Research*, 20, 752-757.

Pfefferbaum, A., Sullivan, E.V., Mathalon, D.H., & Lim, K.O. (1997). Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcoholism: Clinical and Experimental Research*, 21, 521-529.

Pfefferbaum, A., Sullivan, E.V., Mathalon, D.H., Shear, P.K., Rosenbloom, M.J., & Lim, K.O. (1995). Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. *Alcoholism: Clinical and Experimental Research*, 19, 1177-1191.

Plassman, H., O'Doherty, J. O., & Rangel, A. (2007). Orbitofrontal cortex encodes willingness to pay in everyday economic transactions. *Journal of Neuroscience*, 27, 9984-9988.

Pulido, C., Wagner, C., Winward, J.L., Bekman, N.M., Hanson, K.L., Bazinet, A.,... Brown, S.A. (August, 2010). Adolescent heavy drinkers heightened cue reactivity decreases with abstinence. *Poster presented at the 118th convention of the American Psychological Association: San Diego, CA.*

Quadrel, M.J., Fischhoff, B., & Davis, W. (1993). Adolescent (in) vulnerability. *American Psychologist*, 48, 102-116.

Rao, H., Kordzykowski, M., Pluta, J., Hoang, A., & Detre, J. (2008). Neural correlates of voluntary and involuntary risk taking in the human brain: an fMRI study of the Balloon Analog Risk Task (BART). *NeuroImage*, 42, 902-910.

Rice, J. P., Reich, T., Bucholz, K. K., Neuman, R. J., Fishman, R., Rochberg, N.,...Begleiter, H. (1995). Comparison of direct interview and family history diagnoses of alcohol dependence. *Alcoholism: Clinical and Experimental Research*, 19, 1018-1023.

Rosenbloom, M.J., & Pfefferbaum, A. (2008). Magnetic resonance imaging of the living brain: Evidence for brain degeneration among alcoholics and recovery with abstinence.

Alcohol Research and Health, 31, 362-376.

Rushworth, M. F. S., Noonan, M. P., Boorman, E. D., Walton, M. E., & Behrens, T. E. (2011). Frontal cortex and reward-guided learning and decision-making. *Neuron*, 70, 1054-1069.

Schlottman, A. (2001). Children's probability intuitions: Understanding the expected value of complex gambles. *Child Development*, 72, 103-122.

Schweinsburg, B. C., Alhassoon, O. M., Taylor, M. J., Gonzalez, R., Videen, J. S., Brown, G. G., . . . Grant, I. (2003). Effects of alcoholism and gender on brain metabolism. *American Journal of Psychiatry*, 160, 1180-1183.

Schweinsburg, A. D., McQueeny, T., Nagel, B. J., Eyler, L. T., & Tapert, S. F. (2010). A preliminary study of fMRI response during verbal encoding among adolescent binge drinkers. *Alcohol*, 44, 111-117.

Schweinsburg, A. D., Nagel, B. J., & Tapert, S. F. (2005). fMRI reveals alteration of spatial working memory networks across adolescence. *Journal of the International Neuropsychological Society*, 11, 631-644.

Schweinsburg, A. D., Schweinsburg, B. C., Nagel, B. J., Eyler, L. T., & Tapert, S. F. (2011). Neural correlates of verbal learning in adolescent alcohol and marijuana users. *Addiction*, 106, 564-573.

Shaffer, D., Fisher, P., Lucas, C. P., Dulcan, M. K., & Schwab-Stone, M. E. (2000). NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): Description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39, 28-38.

Shear, P.K., Jernigan, T.L., & Butters, N. (1994). Volumetric magnetic resonance imaging quantification of longitudinal brain changes in abstinent alcoholics. *Alcoholism: Clinical and Experimental Research*, 18, 172-176.

Sher, K. J., Martin, E. D., Wood, P. K., & Rutledge, P. C. (1997). Alcohol use disorders and neuropsychological functioning in first-year undergraduates. *Experimental and Clinical Psychopharmacology*, 5, 304-315.

Sobell, L. C., & Sobell, M. B. (1992). Timeline Follow-back: A technique for assessing self-reported ethanol consumption. In J. Allen & R. Z. Litten (Eds.), *Measuring Alcohol Consumption: Psychosocial and Biological Methods* (pp. 41-72). Totowa, NJ: Humana Press.

- Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience & Biobehavioral Reviews*, 24, 417-463.
- Spear, L. P. (2002). The adolescent brain and the college drinker: Biological basis of propensity to use and misuse alcohol. *Journal of Studies on Alcohol, Suppl. 14*, 71-81.
- Spear, L. P., & Varlinskaya, E. I. (2005). Adolescence: Alcohol sensitivity, tolerance, and intake. *Recent Developments in Alcoholism*, 17, 143-159.
- Specht, K., Willmes, K., Shah, N., & Jancke, L. (2003). Assessment of reliability in functional imaging studies. *Journal of Magnetic Resonance Imaging*, 17, 463-471.
- Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.
- Squeglia L.M., Pulido C, Wetherill R.R., Jacobus J, Brown G.G., & Tapert S.F. (2012). Brain response to working memory over three years of adolescence: Influence of initiating heavy drinking. *Journal of Studies on Alcohol and Drugs*, 73, 749-60.
- Squeglia, L. M., Schweinsburg, A. D., Pulido, C., & Tapert, S. F. (2011). Adolescent binge drinking linked to abnormal spatial working memory brain activation: Differential gender effects. *Alcoholism: Clinical and Experimental Research*, 35, 1831-1841.
- Squeglia, L. M., Sorg, S. F., Schweinsburg, A. D., Wetherill, R. R., Pulido, C., & Tapert, S. F. (2012). Binge drinking differentially affects adolescent male and female brain morphometry. *Psychopharmacology*, 220, 529-539.
- Squeglia, L. M., Spadoni, A. D., Infante, M. A., Myers, M. G., & Tapert, S. F. (2009). Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. *Psychology of Addictive Behaviors*, 23, 715-722.
- Stefanovic, B., Warnking, J. M., Rylander, K. M., & Pike, G. B. (2006). The effect of global cerebral vasodilation on focal activation hemodynamics. *Neuroimage*, 30, 726-734.
- Steinberg, L. (2004). Risk-taking in adolescence: What changes, and why? *Annals of the New York Academy of Sciences*, 1021, 51-58.
- Steinberg, L. (2008). A social neuroscience perspective on adolescent risk-taking. *Developmental Review*, 28, 78-106.
- Substance Abuse and Mental Health Services Administration (SAMHSA), Office of Applied Studies, (2008). *Results from the 2007 National Survey on Drug Use and Health: National Findings* (NSDUH Series H-34, DHHS Publication No. SMA 08-4343). Rockville, MD.

Sullivan, E.V. (2000). Human brain vulnerability to alcoholism: evidence from neuroimaging studies. In: Noronha, A., Eckardt, M., Warren, K. (Eds.), *Review of NIAAA's neuroscience and behavioral research portfolio*. NIAAA Research Monograph #34, National Institutes of Health, Bethesda, MD, 473-508.

Sullivan, E.V., Deshmukh, A., De Rosa, E., Rosenbloom, M.J., & Pfefferbaum, A. (2004). Striatal volume deficits in alcoholism with and without Korsakoff's Syndrome. *Neuropsychopharmacology*, 29 (Supplement 1): S188.

Sullivan, E.V., Deshmukh, A., De Rosa, E., Rosenbloom, M.J., & Pfefferbaum, A. (2005). Striatal and forebrain nuclei volumes: Contribution to motor function and working memory deficits in alcoholism. *Biological Psychiatry*, 57, 768-776.

Sullivan, E.V., Deshmukh, A., Desmond, J.E., Lim, K.O., & Pfefferbaum, A. (2000). Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: Relation to ataxia. *Neuropsychology*, 14, 341-352.

Sullivan, E.V., & Pfefferbaum, A. (2001). Magnetic resonance relaxometry reveals central pontine abnormalities in clinically asymptomatic alcoholic men. *Alcoholism: Clinical and Experimental Research*, 25, 1206-1212.

Sullivan, E.V., & Pfefferbaum, A. (2005). Neurocircuitry in alcoholism: A substrate of disruption and repair. *Psychopharmacology*, 180, 583-594.

Sullivan, E.V., Rosenbloom, M.J., Lim, K.O., & Pfefferbaum, A. (2000). Longitudinal changes in cognition, gait, and balance in abstinent and relapsed alcoholic men: relationships to changes in brain structure. *Neuropsychology*, 14, 178-188.

Talairach, J., & Tournoux, P. (1988). *Coplanar stereotaxic atlas of the human brain. Three-dimensional proportional system: An approach to cerebral imaging*. New York: Thieme.

Tapert, S. F., & Brown, S. A. (1999). Neuropsychological correlates of adolescent substance abuse: Four-year outcomes. *Journal of the International Neuropsychological Society*, 5, 481-493.

Tapert, S. F., & Brown, S. A. (2000). Substance dependence, family history of alcohol dependence and neuropsychological functioning in adolescence. *Addiction*, 95, 1043-1053.

Tapert, S. F., Granholm, E., Leedy, N. G., & Brown, S. A. (2002). Substance use and withdrawal: Neuropsychological functioning over 8 years in youth. *Journal of the International Neuropsychological Society*, 8, 873-883.

Tapert, S. F., Schweinsburg, A. D., Barlett, V. C., Brown, S. A., Frank, L. R., Brown, G. G., & Meloy, M. J. (2004). Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. *Alcoholism: Clinical & Experimental Research*, 28, 1577-1586.

Tapert, S. F., Theilmann, R. J., & Schweinsburg, A. D. (2003). Reduced fractional anisotropy in the splenium of adolescents with alcohol use disorder. *Proceedings of the International Society of Magnetic Resonance Medicine*, 11(8217).

Tarter, R. E., Mezzich, A. C., Hsieh, Y.C., & Parks, S. M. (1995). Cognitive capacity in female adolescent substance abusers. *Drug and Alcohol Dependence*, 39, 15-21.

Tjandra, T., Brooks, J. C., Figueiredo, P., Wise, R., Matthews, P. M., & Tracey, I. (2005). Quantitative assessment of the reproducibility of functional activation measured with BOLD and MR perfusion imaging: implications for clinical trial design. *NeuroImage*, 27, 393-401.

Tomasi, D. G., & Caparelli, E. C. (2007). Macrovascular contribution in activation patterns of working memory. *Journal of Cerebral Blood Flow & Metabolism*, 27, 33-42.

Ward, B. D. (2000). Simultaneous inference for fMRI data. Retrieved March 23, 2009, from <http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim>.

Winters, K. C., Stinchfield, R. D., Henly, G. A., & Schwartz, R. (1990). Validity of adolescent self-report of alcohol and other drug involvement. *International Journal of the Addictions*, 25(11A), 1379-1395.

Winward, J. L., Bekman, N. M., Hanson, K. L., Jordan, S. J., Tapert, S. F., & Brown, S. A. (June, 2009). Distress tolerance among heavy drinking adolescents during sustained abstinence. Poster presented at the Research Society on Alcoholism: San Diego, CA.

Xiao, L., Bechara, A., Gong, Q., Huang, X., Li, X., Xue, G., ...Anderson Johnson, C. (in press, 2012). Abnormal affective decision making revealed in adolescent binge drinkers using a functional magnetic resonance imaging study. *Psychology of Addictive Behaviors*.

Yakovlev, P. I., & Lecours, A. R. (1967). The myelogenetic cycles of regional maturation of the brain. In A. Minkowski (Ed.), *Regional development of the brain in early life*. (pp. 3-70). Oxford: Blackwell Scientific.

Zandbelt, B. B., Gladwin, T. E., Raemaekers, M., van Buuren, M., Neggers, S. F., Kahn, R. S., & Vink, M. (2008). Within-subject variation in BOLD-fMRI signal changes across repeated measurements: quantification and implications for sample size. *NeuroImage*, 42, 196-206.

Zucker, R.A., Ellis, D.A., & Fitzgerald, H.E. (1994). *Developmental evidence for at least two alcoholisms: I. Biopsychosocial variation among pathways into symptomatic difficulty*. New York, NY: The New York Academy of Sciences.

Tables and Figures

Table 1. Demographic Characteristics of Study Participants (N = 46)

Variable	Heavy Drinkers (HD) (n=27) M (SD) or %	Controls (CON) (n=19) M (SD) or %
Age, years	17.96 (0.65)	17.70 (0.68)
Female gender	52%	42%
Race, White	85%	63%
Ethnicity, Hispanic	30%	26%
Familial alcoholism density (range 0-2)	0.18 (0.25)	0.14 (0.29)
Hollingshead Index of Social Position score	23.30 (9.39)	20.32 (8.07)
Education, years	11.30 (0.82)	11.11 (0.65)
Grade point average †	3.39 (0.61)	3.74 (0.56)
WASI Vocabulary age scaled score *	55.11 (6.58)	63.05 (6.39)
Females' Pubertal Development Scale total	16.00 (1.41)	16.00 (1.41)
Males' Pubertal Development Scale total	17.17 (1.80)	16.45 (1.44)
YSR Externalizing Problems T-score *	55.70 (7.26)	50.11 (7.18)
YSR Internalizing Problems T-score	45.30 (10.03)	45.58 (6.90)

Notes: YSR = Youth Self Report; WASI = Wechsler Abbreviated Scale of Intelligence

*Heavy drinkers ≠ controls, $p < .05$

†trend for heavy drinkers ≠ controls, $p < .10$

Table 2. Substance Use Characteristics of Study Participants (N = 46)

Variable	Heavy Drinkers (HD) (n=27) M (SD); Min-Max	Controls (CON) (n=19) M (SD), Min-Max
Lifetime alcohol use occasions**	188.03 (137.30); 56 - 730	0.78 (2.34); 0-10
Average drinks per month, past 3 months**	61.66 (11.86); 15-288	0.80 (0.18); 0-3
Peak drinks on an occasion, past 3 months**	11.04 (4.22); 4-24	0.80 (0.18); 0-3
Lifetime binge episodes**	99.44 (80.16); 6-410	0.05 (0.22); 0-1
Binge episodes, past 3 months**	15.52 (12.24); 2-60	0 (0); 0-0
Lifetime nicotine use (# cigarettes)*	231.81 (469.93); 0-2000	0 (0); 0-0
# Cigarettes, past month*	5.33 (9.511); 0-30	0 (0); 0-0
FTND Score	0.41 (0.88); 0-3	0 (0); 0-0
Lifetime cannabis use occasions**	38.81 (47.60); 0-208	0.05 (0.22); 0-1
Cannabis use days/month, past 3 months**	1.93 (3.05); 0-15	0 (0); 0-0
Lifetime cocaine use occasions	1.22 (3.54); 0-15	0 (0); 0-0
Lifetime amphetamine use occasions	1.70 (5.31); 0-20	0 (0); 0-0
Lifetime hallucinogen use occasions	0.22 (0.64); 0-3	0 (0); 0-0
Lifetime ecstasy use occasions	1.15 (3.12); 0-13	0 (0); 0-0
Lifetime opiate use occasions	0.89 (2.15); 0-10	0 (0); 0-0
Lifetime other drug use occasions	0.92 (2.35); 0-10	0 (0); 0-0

Notes: FTND = Fagerstrom Test for Nicotine Dependence; "Other" drugs = inhalants, benzodiazepines, somas, prescription medications, over-the counter medications

**Heavy drinkers ≠ controls, $p < .01$; *Heavy drinkers ≠ controls, $p < .05$

Table 3. BART Task Performance at Baseline, +2 weeks, and +4 weeks

Variable: M (SD) or %	Baseline ($N = 41$)		+2 weeks ($N = 39$)		+4 weeks ($N = 36$)	
	HD ($n = 25$)	CON ($n = 16$)	HD ($n = 21$)	CON ($n = 18$)	HD ($n = 20$)	CON ($n = 16$)
Total “wins”	9.92 (1.77)	10.75 (1.65)	10.10 (1.89)	10.22 (1.86)	10.50 (1.39)	10.88 (2.09)
Total “pops”	8.96 (1.59)	8.00 (1.86) [†]	9.10 (1.54)	8.61 (1.72)	8.80 (1.73)	8.25 (1.48)
Total “too slow”	1.12 (1.48)	1.25 (1.34)	0.81 (1.20)	1.17 (1.68)	0.70 (1.12)	0.88 (1.54)
Mean # pumps/trial	62.29 (8.76)	58.38 (7.23)	63.36 (7.51)	59.44 (10.13)	62.79 (8.45)	60.98 (9.42)
Mean # pumps following “win”	62.05 (9.88)	58.75 (10.65)	60.20 (8.34)	59.20 (12.23)	60.94 (10.10)	60.60 (9.49)
Mean # pumps following “pop”	62.43 (13.04)	57.49 (9.88)	66.25 (11.22)	58.81 (12.90) [†]	64.35 (10.78)	60.82 (12.20)
# “Risky” (>64) pumps	6.96 (4.19)	6.38 (3.66)	7.95 (4.58)	6.44 (3.72)	6.85 (4.26)	6.38 (3.81)
# “Safe” (=64) pumps	2.76 (4.65)	1.94 (3.62)	3.05 (5.29)	2.56 (3.82)	4.05 (5.27)	4.69 (5.85)
# “Conservative” (<64) pumps	9.16 (5.29)	10.44 (5.16)	8.19 (5.50)	9.83 (5.78)	8.40 (5.95)	8.06 (5.90)
% “Risky” pumps after wins	36%	35%	35%	32%	35%	35%
% “Safe” pumps after wins	13%	11%	17%	14%	22%	23%
% “Conservative” pumps after wins	51%	54%	48%	54%	43%	42%
% “Risky” pumps following pop	39%	31%	50%	36%	36%	32%
% “Safe” pumps following pop	16%	10%	15%	12%	21%	26%
% “Conservative” pumps after pops	45%	59%	35%	52% [†]	43%	42%
# Pumps on trial 1	56.90 (17.51)	58.00 (20.16)	64.75 (17.46)	49.60 (17.23)*	61.85 (15.10)	63.53 (9.23)
# Pumps on 1st “pop” trial	67.56 (13.97)	59.81 (20.29)	71.14 (16.05)	63.11 (15.76)	65.50 (15.78)	65.94 (13.79)
# Pumps on trial after 1 st “pop” trial	58.72 (23.16)	59.40 (17.84)	63.00 (11.68)	49.94 (21.26)*	62.90 (18.93)	54.14 (19.84)
Total earnings (\$)	5.59 (1.25)	5.67 (0.88)	6.00 (0.88)	5.65 (1.17)	6.30 (0.70)	6.44 (1.23)

* Heavy drinkers ≠ controls, $p_s < .05$; [†]trend for heavy drinkers ≠ controls, $p_s < .10$

Table 4. Hypothesis 1: Between-Group Differences in BOLD Activation Within ROIs at Baseline

Contrast	ROI	Brodmann		Talairach coordinates ^a				<u>BOLD activation, $M(SD)$^b</u>		d
		area	Volume μl	x	y	z	Heavy Drinkers	Controls		
“Inflate-Pop” ¹	R Insula	13	324	-40.5	-4.5	+14.5	-0.49 (0.77)	0.28 (0.54)	1.19	
“Outcome-Pop” ²	R VMPFC (Medial)	10	405	-16.5	-61.5	-6.5	0.29 (0.38)	-0.38 (0.71)	1.23	
“Outcome-Pop” ²	L VMPFC (Inferior)	47	702	+28.5	-22.5	+15.5	0.41 (0.48)	-0.16 (0.33)	1.42	

Notes: R = right; L = left.

¹ Control condition = “Rest”;

² Control condition = “Wait.”

^a Coordinates refer to location of peak group difference during active (“Inflate-Pop” or “Outcome-Pop”) vs. control task conditions during risky decision-making.

^b BOLD activation values represent mean standardized coefficients for each group (averaged across the ROI; either insula or VMPFC).

Table 5. Hypothesis 2: Interaction Effects of Group X Time on BOLD Activation Within ROIs Across Time Points

Contrast	ROI	Brodmann		Talairach coordinates ^a				F-statistic	Pairwise comparisons		η^2
		area	Volume μ l	x	y	z			comparisons		
“Think-Pop” ¹	R ACC	32	324	-13.5	-37.5	+5.5		5.89	C3 > HD3; C1 < C3		.26
“Think-Win” ¹	R ACC	32	675	-13.5	-37.5	+5.5		6.34	C1 < C3		.31
“Inflate-Pop” ²	R VMPFC (ACC)	32	513	-4.5	-37.5	-3.5		6.00	HD1 < HD3		.32
“Inflate-Win” ²	R VMPFC (ACC)	32	648	-4.5	-40.5	-3.5		5.96	HD1 < HD3		.25
“Outcome-Win” ²	L VMPFC (Middle)	10	702	+34.5	-55.5	+2.5		5.66	C2 > HD2; C2 > C3		.36

Notes: R = right; L = left; C1 = Controls, baseline time point; C2 = Controls, +2weeks time point; C3 = Controls, +4weeks time point; HD1 = heavy drinkers, baseline time point; HD2 = heavy drinkers, +2weeks time point; HD3 = heavy drinkers, +4weeks time point.

¹Control condition = “Rest”;

²Control condition = “Wait.”

^aCoordinates refer to location of peak group difference during active (“Think-Pop”, “Think-Win”, “Inflate-Pop”, “Inflate-Win”, or “Outcome-Win”) vs. control task conditions during risky decision-making.

Table 6. Hypothesis 2: Main Effects of Group on BOLD Activation Within ROIs Across Time Points

Contrast	ROI	Brodmann		Talairach coordinates ^a				F-statistic	Group	η^2
		area	Volume μl	x	y	z				
“Think-Pop” ¹	R DLPFC (Inferior)	45	1,080	-46.5	-19.5	+14.5		9.21	CON > HD	.16
“Think-Pop” ¹	R DLPFC (Middle)	08	1,053	-40.5	-25.5	+41.5		9.00	CON > HD	.35
“Think-Pop” ¹	R DLPFC (Inferior)	09	675	-49.5	-10.5	+26.5		9.76	CON > HD	.33
“Think-Pop” ¹	R DLPFC (Medial)	08	675	-4.5	-25.5	+47.5		8.51	CON > HD	.22
“Think-Pop” ¹	R DLPFC (Middle)	09	594	-46.5	-7.5	+38.5		8.51	CON > HD	.36
“Think-Pop” ¹	L DLPFC (Middle)	09	540	+31.5	-22.5	+32.5		8.07	CON > HD	.24
“Think-Pop” ¹	L DLPFC (Middle)	08	378	+25.5	-22.5	+38.5		8.33	CON > HD	.31
“Think-Win” ¹	R DLPFC (Superior)	08	1,782	-1.5	-25.5	+50.5		9.21	CON > HD	.38
“Think-Win” ¹	R DLPFC (Middle)	08	1,107	-40.5	-25.5	+41.5		9.00	CON > HD	.36
“Think-Win” ¹	L DLPFC (Middle)	08	945	+49.5	-10.5	+41.5		9.76	CON > HD	.33
“Think-Win” ¹	L DLPFC (Precentral)	44	837	+43.5	-16.5	+8.5		8.51	CON > HD	.28
“Think-Win” ¹	R DLPFC (Inferior)	45	594	-46.5	-19.5	+14.5		8.51	CON > HD	.19
“Think-Win” ¹	L DLPFC (Middle)	09	513	+40.5	-19.5	+29.5		8.07	CON > HD	.25
“Think-Win” ¹	R DLPFC (Inferior)	09	486	-49.5	-10.5	+26.5		8.33	CON > HD	.33
“Inflate-Pop” ¹	R VMPFC (Middle)	10	405	-43.5	-55.5	+8.5		10.00	CON > HD	.29
“Inflate-Win” ¹	L Insula	13	297	+31.5	-13.5	-3.5		8.25	CON > HD	.60
“Inflate-Win” ²	L VMPFC (Middle)	10	756	+31.5	-43.5	+23.5		10.94	HD > CON	.18

Notes: R = right; L = left; CON = controls; HD = heavy drinkers. ¹Control condition = “Rest”; ²Control condition = “Wait.”

^aCoordinates refer to location of peak group difference during active (“Think-Pop”, “Think-Win”, “Inflate-Pop”, or “Inflate-Win”) vs. control task conditions during risky decision-making.

Table 7. *Exploratory Whole-Brain Analysis: Baseline BOLD Response*

Contrast	Anatomical region	Brodman		Volume μl	Talairach coordinates ^a			BOLD activation, $M(SD)$ ^b		
		n area			x	y	z	Heavy Drinkers	Controls	d
“Inflate-Pop” ²	R Middle frontal gyrus	06		1,107	-22.5	-22.5	+50.5	-0.45 (0.43)	0.18 (0.72)	1.09
“Inflate-Win” ²	L Anterior cingulate	24		864	+4.5	-34.5	+2.5	-0.38 (0.52)	0.20 (0.46)	1.18
“Outcome-Pop” ²	R Supramarginal gyrus	40		1,917	-43.5	+49.5	+29.5	0.50 (0.58)	-0.40 (0.87)	1.24
“Outcome-Pop” ²	R Precentral gyrus	06		1,107	-31.5	-1.5	+23.5	0.14 (0.70)	-0.63 (0.63)	1.15
“Outcome-Pop” ²	L Middle temporal gyrus	19		810	+34.5	+64.5	+20.5	0.30 (0.79)	-0.59 (0.70)	1.19
“Outcome-Pop” ²	R Inferior frontal gyrus	46		729	-46.5	-43.5	+2.5	0.11 (0.26)	-0.24 (0.37)	1.11
“Outcome-Pop” ²	R Middle temporal gyrus	39		702	-40.5	+58.5	+23.5	0.37 (0.64)	-0.43 (0.81)	1.10
“Outcome-Pop” ²	L/R Cingulate gyrus	24		702	+1.5	+10.5	+23.5	0.26 (0.54)	-0.40 (0.58)	1.17
“Outcome-Pop” ²	L Middle temporal gyrus	21		675	+52.5	+10.5	-12.5	0.33 (0.62)	-0.39 (0.50)	1.28
“Outcome-Win” ²	R Supramarginal gyrus	40		864	-46.5	+49.5	+32.5	0.65 (0.58)	-0.19 (0.99)	1.07
“Outcome-Win” ²	R Medial frontal gyrus	10		702	-13.5	-58.5	-3.5	0.44 (0.55)	-0.23 (0.56)	1.20

Notes: R = right; L = left.

²Control condition = "Wait".^aCoordinates refer to location of peak group difference during active ("Inflate-Pop", "Inflate-Win", "Outcome-Pop", or "Outcome-Win") vs. control task conditions during risky decision-making. ^bBOLD activation values represent mean standardized coefficients for each group (averaged across each cluster).

Table 8. Exploratory Whole-Brain Analysis: Interaction Effects of Group X Time on BOLD Activation Across Time Points

Contrast	Anatomical region	Brodmann area	Volume μ l	Talairach coordinates ^a				F-stat	Pairwise comparisons
				x	y	z			
“Inflate-Pop” ¹	L Superior frontal gyrus	09	756	+13.5	-52.5	+38.5		6.68	C3 > C2
“Inflate-Pop” ¹	L Middle frontal gyrus	08	702	+31.5	-40.5	+41.5		5.73	HD2 > C2; C3 > C2
“Inflate-Win” ¹	L Superior frontal gyrus	08	891	+34.5	-31.5	+50.5		6.00	HD2 > C2; C3 > C2
“Inflate-Pop” ²	L Anterior cingulate	32	2,835	+7.5	-31.5	+2.5		6.23	HD3 > HD1
“Inflate-Pop” ²	R Medial frontal gyrus	06	1,350	-16.5	-1.5	+56.5		5.87	HD3 > HD1
“Inflate-Win” ²	L Anterior cingulate	24	2,862	+7.5	-28.5	+2.5		5.94	HD3 > HD1
“Outcome-Win” ²	R Middle temporal gyrus	21	1,053	-52.5	+4.5	-21.5		6.04	C2 > C3
“Outcome-Win” ²	R Inferior temporal gyrus	20	1,026	-52.5	+31.5	-15.5		6.70	C2 > C3
“Outcome-Win” ²	R Insula	13	810	-43.5	+10.5	+14.5		5.71	C3 > C2
“Outcome-Win” ^{2*}	R Medial frontal gyrus	10	675	-16.5	-64.5	-0.5		5.79	HD1 > C1; C1 < C2

Notes: R = right; L = left; C1 = Controls, baseline time point; C2 = Controls, +2weeks time point; C3 = Controls, +4weeks time point; HD1 = heavy drinkers, baseline time point; HD2 = heavy drinkers, +2weeks time point; HD3 = heavy drinkers, +4weeks time point.

¹Control condition = “Rest”;

²Control condition = “Wait.”

* = Cluster was significant at baseline and listed in Table 7.

^aCoordinates refer to location of peak group difference during active (“Inflate-Pop”, “Inflate-Win”, or “Outcome-Win”) vs. control task conditions during risky decision-making.

Table 9a. Exploratory Whole-Brain Analysis: Main Effects of Group on BOLD Activation in “Think-Pop” vs. “Rest” Contrast Across Time Points

Anatomical Region	Brodmann area	Volume μ l	Talairach coordinates ^a				F-statistic	Group
			x	y	z			
R Fusiform gyrus	37	20,034	-43.5	+46.5	-6.5		9.23	CON > HD
R Superior frontal gyrus	06	6,777	-10.5	-25.5	+56.5		8.59	CON > HD
L Supramarginal gyrus	40	2,997	+49.5	+43.5	+32.5		10.41	CON > HD
R Inferior parietal	40	2,970	-46.5	+40.5	+38.5		8.71	CON > HD
R Inferior/middle frontal	47	1,350	-43.5	-34.5	-6.5		9.46	CON > HD
R Thalamus	--	1,242	-7.5	+16.5	-0.5		7.85	CON > HD
L Parahippocampal gyrus	19	1,134	+40.5	+43.5	-3.5		8.38	CON > HD
L Medial frontal gyrus	06	1,107	+7.5	+22.5	+56.5		9.55	CON > HD
L Middle frontal gyrus	06	1,080	+37.5	+4.5	+47.5		8.92	CON > HD
R Middle frontal gyrus	10	945	-46.5	-55.5	+8.5		8.86	CON > HD
L Cingulate gyrus	24	918	+4.5	+13.5	+35.5		8.52	CON > HD
R Cingulate gyrus	24	756	-10.5	+19.5	+32.5		8.02	CON > HD
L Middle frontal gyrus	08	675	+43.5	-10.5	+41.5		8.46	CON > HD

Notes: R = right; L = left; CON = controls; HD = heavy drinkers.

^aCoordinates refer to location of peak group difference during active (“Think-Pop”) vs. control task conditions during risky decision-making.

Table 9b. Exploratory Whole-Brain Analysis: Main Effects of Group on BOLD Activation in “Think-Win” vs. “Rest” Contrast Across Time Points

Anatomical Region	Brodmann area	Volume μ l	Talairach coordinates ^a				F-statistic	Group
			x	y	z			
R Supramarginal gyrus	40	24,948	-46.5	+40.5	+38.5		8.85	CON > HD
L Superior frontal gyrus	06	15,606	+7.5	-25.5	+53.5		9.22	CON > HD
R Fusiform gyrus	37	13,419	-46.5	+43.5	-6.5		9.41	CON > HD
L Precentral gyrus	44	6,804	+43.5	-16.5	+8.5		8.76	CON > HD
L Supramarginal gyrus	40	5,266	+49.5	+43.5	+32.5		10.27	CON > HD
L Middle temporal gyrus	21	1,647	+52.5	+31.5	-6.5		9.05	CON > HD
R Thalamus	--	1,620	-7.5	+7.5	+8.5		8.11	CON > HD
L Precuneus	31	1,620	+13.5	+55.5	+35.5		8.68	CON > HD
R Inferior/middle frontal	47	1,593	-43.5	-34.5	-6.5		9.44	CON > HD
R Middle frontal gyrus	10	918	-43.5	-52.5	-9.5		8.69	CON > HD

Notes: R = right; L = left; CON = controls; HD = heavy drinkers.

^aCoordinates refer to location of peak group difference during active (“Think-Win”) vs. control task conditions during risky decision-making.

Table 9c. Exploratory Whole-Brain Analysis: Main Effects of Group on BOLD Activation in “Inflate-Pop” and “Inflate-Win” vs. “Wait” Contrasts Across Time Points

Contrast	Anatomical Region	Brodmann		Talairach coordinates ^a					F-statistic	Group
		area	Volume μl	x	y	z				
“Inflate-Pop”	L Cuneus	23	2,565	+13.5	+73.5	+11.5	8.58	HD > CON		
“Inflate-Pop”	R Postcentral gyrus	01	1,458	-58.5	+25.5	+41.5	9.75	HD > CON		
“Inflate-Pop”	L Middle frontal gyrus	08	1,053	+43.5	-28.5	+41.5	10.43	HD > CON		
“Inflate-Pop”	L Cingulate gyrus	24	837	+16.5	+1.5	+32.5	8.75	HD > CON		
“Inflate-Pop”*	R Middle frontal gyrus	06	675	-22.5	-22.5	+53.5	8.50	CON > HD		
“Inflate-Win”	L Medial frontal gyrus	09	2,781	+25.5	-34.5	+20.5	9.85	HD > CON		
“Inflate-Win”	L Inferior frontal gyrus	09	1,566	+25.5	-7.5	+26.5	8.14	HD > CON		
“Inflate-Win”	L Cingulate gyrus	24	1,458	+19.5	+22.5	+32.5	8.17	HD > CON		
“Inflate-Win”	R Postcentral gyrus	01	837	-58.5	+25.5	+41.5	9.09	HD > CON		
“Inflate-Win”	R Middle frontal gyrus	09	729	-28.5	-28.5	+26.5	8.08	HD > CON		
“Inflate-Win”	R Cingulate gyrus	24	702	-16.5	+1.5	+32.5	8.81	HD > CON		
“Inflate-Win”	L Cingulate gyrus	23	675	+1.5	+13.5	+23.5	9.16	HD > CON		

Notes: R = right; L = left; CON = controls; HD = heavy drinkers.

* = Cluster was significant at baseline and listed in Table 7.

^aCoordinates refer to location of peak group difference during active (“Inflate-Pop” & “Inflate-Win”) vs. control task conditions during risky decision-making.

Table 9d. Exploratory Whole-Brain Analysis: Main Effects of Group on BOLD Activation in “Outcome-Win” and “Outcome-Pop” vs. “Wait” Contrasts Across Time Points

Contrast	Anatomical Region	Brodmann		Talairach coordinates ^a					F-statistic	Group
		area	Volume μl	x	y	z				
“Outcome-Pop”	R Inferior parietal lobule	40	2,997	-37.5	+37.5	+29.5	8.82	HD > CON		
“Outcome-Pop”	R Parahippocampal gyrus	37	1,512	-22.5	+43.5	-18.5	8.69	HD > CON		
“Outcome-Pop”	R Superior temporal	22	1,323	-34.5	+52.5	+23.5	10.03	HD > CON		
“Outcome-Pop”	R Middle frontal gyrus	10	1,296	-31.5	-37.5	+14.5	8.31	HD > CON		
“Outcome-Pop”	R Middle frontal gyrus	09	972	-28.5	-19.5	+29.5	8.55	HD > CON		
“Outcome-Pop”	R Thalamus	--	810	-4.5	+16.5	+20.5	8.86	HD > CON		
“Outcome-Win”	L Inferior frontal gyrus	44	3,699	+55.5	-13.5	+14.5	10.08	HD > CON		
“Outcome-Win”	R Middle frontal gyrus	09	3,402	-34.5	-16.5	+26.5	9.71	HD > CON		
“Outcome-Win”	R Middle temporal gyrus	22	2,025	-52.5	+46.5	-0.5	9.21	HD > CON		
“Outcome-Win”	L Cuneus	30	1,242	+10.5	+70.5	+11.5	8.89	HD > CON		
“Outcome-Win”	R Inferior frontal gyrus	13	1,188	-43.5	-25.5	+5.5	9.85	HD > CON		
“Outcome-Win”	R Inferior parietal lobule	40	1,161	-55.5	+31.5	+29.5	7.99	HD > CON		
“Outcome-Win”	R Middle temporal gyrus	39	1,053	-37.5	+55.5	+23.5	10.13	HD > CON		
“Outcome-Win”	L Medial frontal gyrus	09	729	+19.5	-37.5	+20.5	8.32	HD > CON		

Notes: R = right; L = left; CON = controls; HD = heavy drinkers.

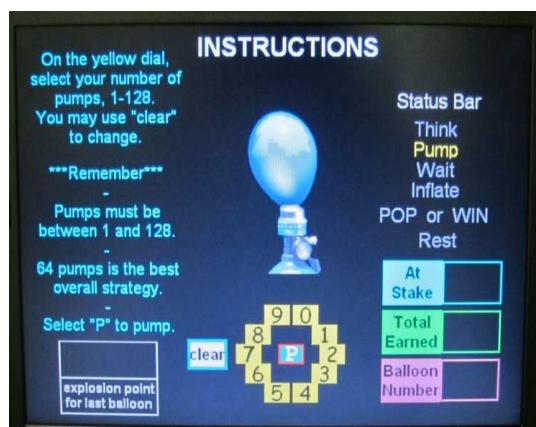
^aCoordinates refer to location of peak group difference during active (“Outcome-Pop” & “Outcome-Win”) vs. control task conditions during risky decision-making.

Table 10. Exploratory Whole-Brain Analysis: Main Effects of Time on BOLD Activation Across Time Points

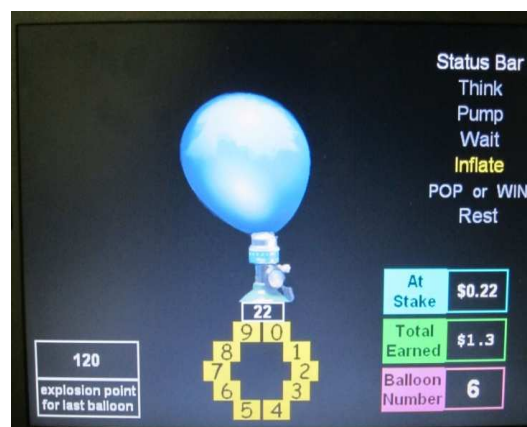
Contrast	Anatomical Region	Brodmann Volume		Talairach coordinates ^a				F-statistic	Time
		area	μl	x	y	z			
“Inflate-Pop” ¹	R Parahippocampal gyrus	19	837	-28.5	+46.5	-0.5		5.96	T3 > T1/T2
“Inflate-Pop” ¹	R Lingual gyrus	19	729	-25.5	+61.5	-3.5		6.04	T3 > T1/T2
“Inflate-Pop” ²	L Parahippocampal gyrus	36	1,998	+31.5	+34.5	-6.5		5.96	T3 > T1/T2
“Inflate-Pop” ²	R Parahippocampal gyrus	19	1,836	-22.5	+61.5	-3.5		5.76	T3 > T1/T2
“Inflate-Pop” ²	L Middle frontal gyrus	06	1,404	+7.5	+16.5	+26.5		5.99	T3 > T1/T2
“Inflate-Pop” ²	L Middle frontal gyrus	06	675	+22.5	+1.5	+56.5		5.39	T3 > T1/T2
“Inflate-Pop” ²	L Middle frontal gyrus	06	2,187	+22.5	+1.5	+56.5		6.50	T3 > T1/T2
“Inflate-Pop” ²	L Caudate	--	2,025	+10.5	+16.5	+20.5		6.23	T3 > T1/T2
“Inflate-Pop” ²	R Middle frontal gyrus	06	1,890	-28.5	+7.5	+56.5		6.51	T3 > T1/T2
“Inflate-Pop” ²	R Middle frontal gyrus	06	1,296	-28.5	-13.5	+53.5		6.15	T3 > T1/T2
“Inflate-Pop” ²	L Parahippocampal gyrus	36	675	+31.5	+34.5	-6.5		6.83	T3 > T1/T2
“Outcome-Win” ²	R Middle temporal gyrus	21	2,646	-58.5	+19.5	-12.5		6.64	T1/T2 > T3
“Outcome-Win” ²	R Superior frontal gyrus	09	2,619	-16.5	-40.5	+38.5		6.01	T1/T2 > T3
“Outcome-Win” ²	L Medial frontal gyrus	10	891	+1.5	-67.5	+11.5		5.80	T1/T2 > T3

Notes: R = right; L = left; T1 = baseline time point; T2 = +2weeks time point; T3 = +4weeks time point.

^aCoordinates refer to location of peak group difference during active (“Inflate-Pop”, “Inflate-Win”, “Outcome-Pop”, “Outcome-Win”) vs. control (“Rest”, “Wait”) task conditions during risky decision-making.



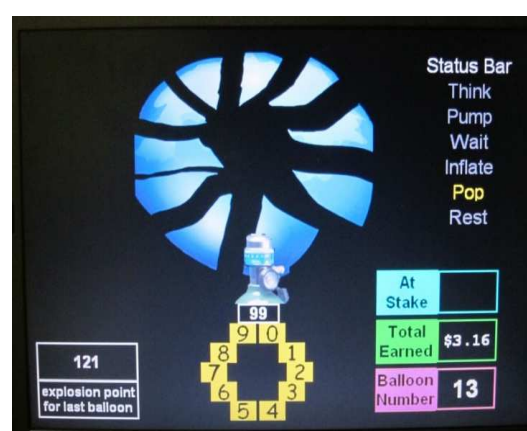
"Pump" Condition.



"Inflate" Condition.



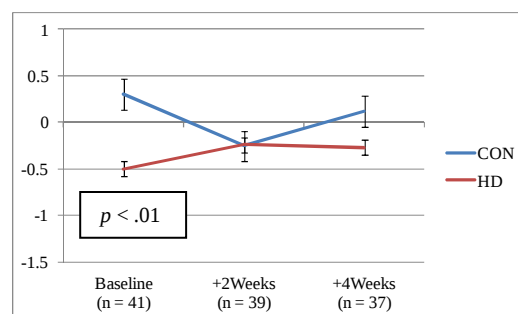
"Pop vs. Win" Condition: WIN



"Pop vs. Win" Condition: POP

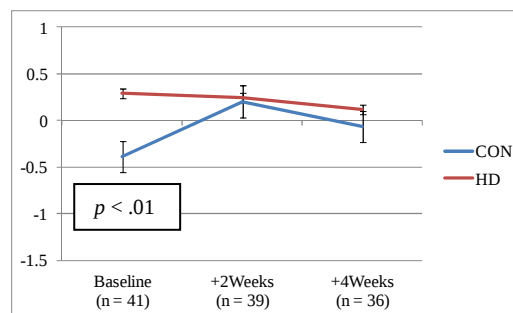
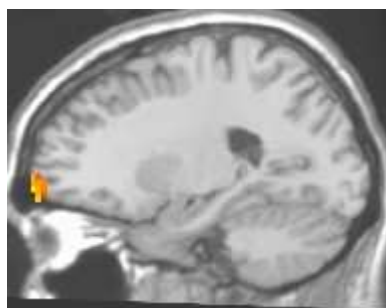
Figure 1. BART task screenshots

Inflate-Pop” vs. “Rest”: Right Insula



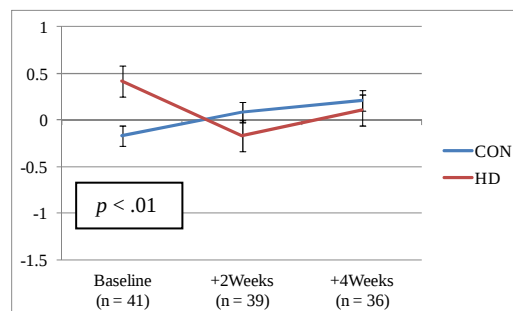
Significant between-group difference at baseline only ($t = 2.71$).
No differences observed between-groups at +2Weeks and +4Weeks

“Outcome-Pop” vs. “Wait”: Right VMPFC



Significant between-group difference at baseline only ($t = 2.71$).
No differences observed between-groups at +2Weeks and +4Weeks.

“Outcome-Pop” vs. “Wait”: Left VMPFC



Significant between-group difference at baseline only ($t = 2.71$).
No differences observed between-groups at +2Weeks and +4Weeks

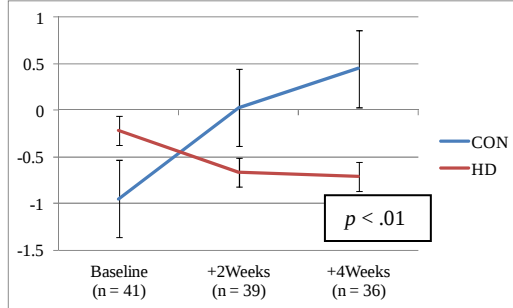
Deactivation (HD < CON)

Activation (HD > CON)



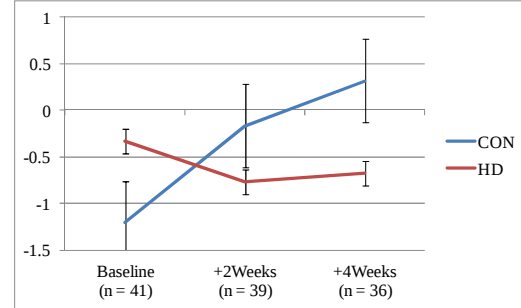
Figure 2. Hypothesis 1: Baseline between-group differences in BOLD response in ROIs.

“Think-Pop” vs. “Rest”: Right ACC



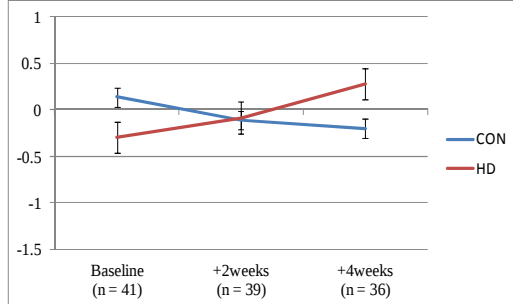
Significant Group X Time interaction ($F = 5.89$). Follow-up tests indicate significant between-group difference at +4weeks (CON > HD) and within group difference for control group only (+4weeks > Baseline; $p < .01$).

“Think-Win” vs. “Rest”: Right ACC



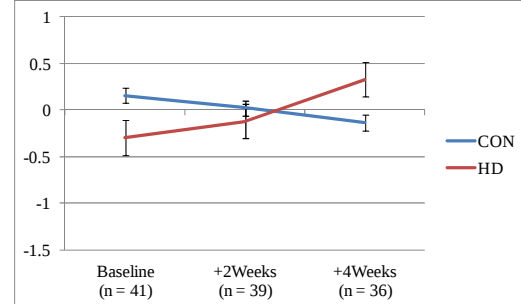
Significant Group X Time interaction ($F = 6.34$). Follow-up tests indicate no significant between-group differences and a significant within group difference for control group only (+4weeks > Baseline; $p < .01$).

“Inflate-Pop” vs. “Wait”: Right VMPFC/ACC



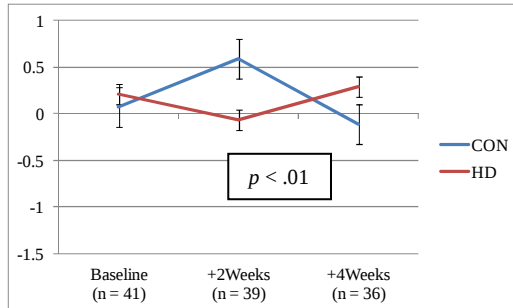
Significant Group X Time interaction ($F = 6.00$). Follow-up tests indicate no significant between-group differences and a significant within group difference for heavy drinking group only (+4weeks > Baseline; $p < .01$).

“Inflate-Win” vs. “Wait”: Right VMPFC/ACC



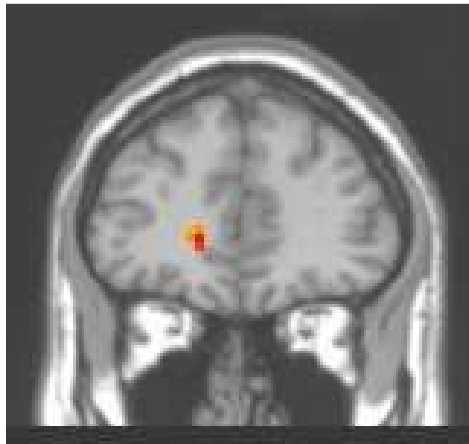
Significant Group X Time interaction ($F = 5.96$). Follow-up tests indicate no significant between-group differences and a significant within group difference for heavy drinking group only (+4weeks > Baseline; $p < .01$).

“Outcome-Win” vs. “Wait” – Left VMPFC

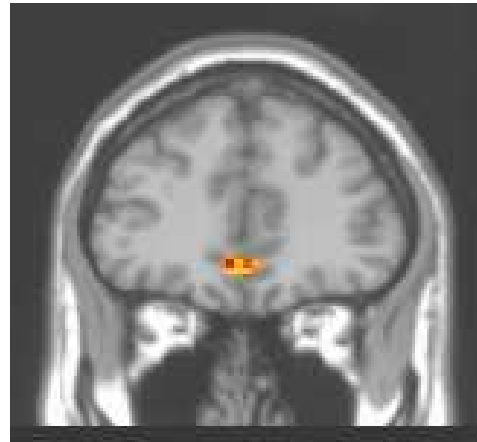


Significant Group X Time interaction ($F = 5.66$). Follow-up tests indicate significant between-group difference at +2weeks (CON > HD) and within group difference for control group only (+4weeks > +2weeks; $p < .01$).

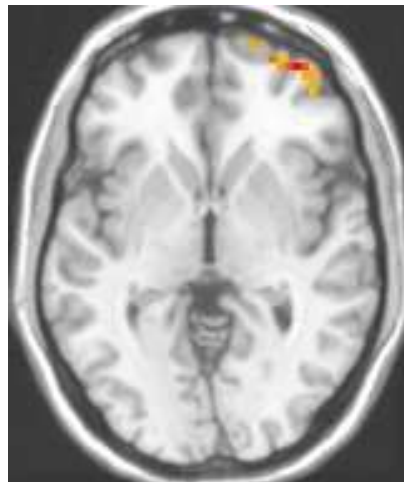
Figure 3. Hypothesis 2: Interaction effects of Group X Time on BOLD response in ROIs.



Right ACC: Think vs. Rest
(CON 4weeks > CON Baseline)



Right VMPFC/ACC: Inflate vs. Wait
(HD 4weeks > HD Baseline)



Left VMPFC: Outcome-Win vs Wait
(CON 2weeks > HD 2weekCON 2weeks > CON 4weeks)

Figure 4. Hypothesis 2: Locations of Significant Group X Time Interaction Effects