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White Matter Integrity, Substance Use, and Risk Taking in Adolescence

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

in

Clinical Psychology

by

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The Dissertation of Joanna Jacobus is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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2006 – 2008	M.S.	San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology.
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MEMBERSHIPS & SERVICE

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RESEARCH EXPERIENCE

2007 – present **Graduate Student, Joint Doctoral Program in Clinical Psychology at University of California, San Diego and San Diego State University.**
Laboratory Research Objectives: Determine the impact of substance use (e.g., cannabis, alcohol) on adolescent brain functioning utilizing neuroimaging methods such as FMRI and DTI; evaluate adolescent brain and cognitive development over time in healthy youths and youths at risk for substance use disorders.
Dissertation Research: Examine the influence of white matter tissue integrity and neurocognitive functioning on real-world risk taking behaviors in adolescence.
Graduate Research Responsibilities: Conduct neuropsychological testing, MRI scan acquisition, FMRI, DTI, and ASL data processing, analysis of multimodal neuroimaging data, manuscript writing, NRSA grant preparation.
Advisor: Susan F. Tapert, Ph.D.

2006 – 2007 **Graduate Student, Joint Doctoral Program in Clinical Psychology at University of California, San Diego and San Diego State University.**
Laboratory Research Objectives: Study the structural and functional brain correlates of substance abuse, both in the presence and absence of HIV.
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Supervisors: Brian C. Schweinsburg, Ph.D., Igor Grant, M.D.

2004 – 2006 **Research Specialist in Cognitive and Addictions Neuroscience, Department of Psychiatry, University of Illinois, Chicago**.
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Supervisor: Eileen Martin, Ph.D.

2003 – 2004 **Research Assistant/Psychometrist, Geriatric Neuropsychology, Veteran's Affairs Ann Arbor Healthcare System.**
Responsibilities: Administering and scoring a baseline neuropsychological screening battery to all newly admitted Veterans in the Extended Care Center.
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CLINICAL EXPERIENCE

2010-2011 **Psychology Intern, Posttraumatic Stress Disorder Clinical Team (PCT), VA San Diego Healthcare System.**
Conduct individual mental health diagnostic interviews and individual and group Cognitive Processing Therapy for Veterans with PTSD; weekly supervision and case presentation.
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2010-2011 **Psychology Intern, Neuropsychological Assessment Service, University of California, San Diego Medical Center**
Conduct flexible neuropsychological assessment batteries with individuals diagnosed with neurological, medical, and psychiatric disorders; specialized experience in transplant assessments and pre- and post-operative neuropsychological assessments with epilepsy patients; written integrated reports; weekly supervision and case presentations.
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2009 – 2010 **Psychology Trainee, Neuropsychological Assessment Service, VA San Diego Healthcare System.**
Conducted flexible 5-6 hour batteries of neuropsychological functioning, clinical interviews, written integrated reports, and feedback sessions for Veterans referred for cognitive complaints; twice-weekly supervision and biweekly case presentations.
Supervisors: Dean Delis, Ph.D., Mark Bondi, Ph.D., Vincent Filoteo, Ph.D.

2009 – 2010 **Neuropsychology Practicum Student, SDSU/UCSD Joint Doctoral Program in Clinical Psychology.**
Weekly supervision, discussion of timely issues in neuropsychology, preparation of written integrated reports, and case presentations as assigned.
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2008 – 2009 **Psychology Trainee, Substance Abuse Mental Illness (SAMI) Program, VA San Diego Healthcare System.**
Conducted integrated group therapy using cognitive behavioral treatment for Veterans with depression and substance dependence and Seeking Safety for Veterans with PTSD and substance dependence, as well individual diagnostic interviews; weekly supervision, and case presentation.
Supervisors: Susan F. Tapert, Ph.D., John McQuaid, Ph.D., Sonya Norman, Ph.D., Martha Diaz, Ph.D., Ryan Trim, Ph.D.

2007 – 2008 **Psychotherapy Trainee, Psychology Clinic at San Diego State University.**
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PUBLICATIONS

Peer-Reviewed Data-Based Articles

1. Bava, S., Boucquey, V., Goldenberg, D., Ward, M., **Jacobus, J**. & Tapert, S.F. Sex differences in adolescent white matter architecture. (2011). *Brain Research*, *1375*, 41-48.

2. Mahmood, O., **Jacobus, J.,** Bava, S., Scarlett A., & Tapert, S.F. (2010). Learning and memory performance in adolescent users of alcohol and marijuana: interactive effects. *Journal of Studies on Alcohol and Drugs, 71*, 885-894.

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6. **Jacobus, J.,** McQueeny, T., Bava, S., Schweinsburg, B.C., Frank, L.R., Yang, T. T., & Tapert, S.F. (2009). White matter integrity in adolescents with histories of combined binge drinking and marijuana use. *Neurotoxicology and Teratology, 31,* 349-355.

7. McQueeny, 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.

8. Gongvatana, A., Schweinsburg, B.C., Taylor, M.J., Letendre, S., Alhassoon, O.M., **Jacobus, J**., Woods, S.P., Jernigan, T.L., Ellis, R.J., Frank, L., & Grant, I. (2009). White matter tract injury and cognitive impairment in HIV-infected individuals. *Journal of NeuroVirology, 15*, 187-195.

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1. **Jacobus, J.,** Bava, S., Cohen-Zion, M., Mahmood, O., & Tapert, S.F. (2009). Functional consequences of marijuana use in adolescents. *Pharmacology, Biochemistry, and Behavior, 92*(4), 559-565.

2. Squeglia, L.M., **Jacobus, J.,** & Tapert, S.F. (2009). The influence of substance use on adolescent brain development. *Clinical EEG and Neuroscience, 40*(1), 31-38.

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1. Trim, R., Mrnak-Meyer, J., **Jacobus, J.,** & Tapert, S.F. (2009). Integrated Cognitive Behavioral Treatment of Depression and Substance Dependence. VA San Diego Healthcare System.

Abstracts

1. **Jacobus, J**., & Tapert, S.F. (2009). Neuroimaging markers of substance use and risk behavior in adolescents. Presented at the annual meeting of the Research Society on Alcoholism, San Diego, CA (abstracted in Alcoholism: Clinical and Experimental Research 33: 295A).

2. **Jacobus, J.,** McQueeny, T., Bava, S., Schweinsburg, B.C., & Tapert, S.F. (2008). White matter integrity in adolescents with histories of binge drinking and marijuana use. Presented at the annual meeting of the Research Society on Alcoholism, Washington, D.C. (abstracted in Alcoholism: Clinical and Experimental Research 32: 104A).

3. **Jacobus, J**., Schweinsburg, B.C., Theilmann, R.J., Taylor, M.J., Woods, S.P., Harrison, T.B., Gongvatana, A., Franklin, D.R., Letendre, S.L., Ellis, R.J., Heaton, R.K., Frank, L.R., Grant, I., & Jernigan, T.L. (2008). Neurocognitive performance predicts altered white matter fractional anisotropy in HIV-infected individuals. Presented at the annual meeting of the International Neuropsychological Society, Waikoloa, HI (abstracted in International Neuropsychological Society 36th Annual Meeting Program & Abstracts, 149).

4. **Jacobus, J**., Schweinsburg, B.C., Taylor, M.J., Alhassoon, O.M., Harrison, T.B., Gongvatana, A., & Grant, I. (2008). Altered brain metabolism in alcoholic individuals with self-reported history of withdrawal seizure. Presented at the International Conference on Applications of Neuroimaging to Alcoholism, New Haven, CT.

5. Schweinsburg, B.C., **Jacobus, J.,** Harrison, T.B., Theilmann, R. J., Taylor, M.J., Woods, S.P., Harrison, T.B., Gongvatana, A., Franklin, D.R., Letendre, S.L., Ellis, R.J., Heaton, R.K., Frank, L.R., Grant, I., & Jernigan, T.L. (2008). Neurochemical markers of cellular integrity predict white matter anisotropy in HIV infection. Presented at the annual meeting of the International Neuropsychological Society, Waikoloa, HI (abstracted in International Neuropsychological Society 36th Annual Meeting Program & Abstracts, 243).

6. Harrison, T.B., Schweinsburg, B.C., **Jacobus, J.**, Theilmann, R.J., Taylor, M.J., Woods, S.P., Gongvatana, A., Franklin, D.R., Letendre, S.L., Ellis, R.J., Heaton, R.K., Frank, L.R., Grant, I., & Jernigan, T.L. (2008). Abnormal white matter signal and lower CD4 nadir independently predict lower white matter fractional anisotropy in HIV-infected individuals. Presented at the annual meeting of the International Neuropsychological Society, Waikoloa, HI (abstracted in International Neuropsychological Society 36th Annual Meeting Program & Abstracts, 146).

7. McQueeny, T., Schweinsburg, B.C., Schweinsburg, A.D., **Jacobus, J.,** Frank, L.R., & Tapert, S.F. (2008). Altered white matter fiber integrity in adolescent binge drinkers. Presented at the International Conference on Applications of Neuroimaging to Alcoholism, New Haven, CT.

8. Gongvatana, A., Schweinsburg, B.C., Taylor, M.J., Theilmann, R.J., Letendre, S.L., Alhasson, O.M., **Jacobus, J**., Woods, S.P., Franklin, D.R., Jernigan, T.L., Frank, L.R., & Grant, I. (2008). HIV-associated white matter tract injury and neurocognitive impairment in the HAART Era. Presented at the annual meeting of the International Neuropsychological Society, Waikoloa, HI (abstracted in International Neuropsychological Society 36th Annual Meeting Program & Abstracts, 145).

9. **Jacobus, J.,** Schweinsburg, B.C., Schweinsburg, A.D., Taylor, M.J., & Grant, I. (2007). The interactive effects of age and alcoholism on brain response to spatial working memory. Presented at the annual meeting of the International Neuropsychological Society, Portland, OR (abstracted in International Neuropsychological Society 35th Annual Meeting Program & Abstracts, 209).

10. Gonzalez, R., **Jacobus, J.,** Rodriguez, J.W., Fakhoury, E.H., & Martin, E.M. (2007). Nondeclarative memory among HIV+ and HIV- individuals with substance dependence. Presented at the annual meeting of the International Neuropsychological Society, Portland, OR (abstracted in International Neuropsychological Society 35th Annual Meeting Program & Abstracts, 181).

11. Gonzalez, R., **Jacobus, J.,** Vassileva, J., & Martin, E.M. (2007). Effects of cannabis dependence and HIV on procedural learning performance. Presented at the annual conference of the American Psychological Association, San Francisco, CA.

12. **Jacobus, J.,** Gonzalez, R., O'Neill, J.R., Kohnke, M.L., Sworowski, L., & Martin, E.M. (2006). Ecstasy use is associated with prospective memory deficits. Presented at the annual meeting of the International Neuropsychological Society, Boston, MA (abstracted in International Neuropsychological Society 34th Annual Meeting Program & Abstracts, 207).

13. Gonzalez, R., **Jacobus, J.,** & Martin, E.M. (2006). HIV and severity of substance use have interactive effects on procedural learning. Presented at the annual conference of the

American Psychological Association, New Orleans, LA.

14. Gonzalez, R., **Jacobus, J.,** & Martin, E.M. (2006). Procedural memory and decision-making among HIV+ and HIV- individuals with substance dependence: Preliminary data. Presented at the NIDA Research Training Institute, Bethesda, Maryland.

15. Gould, F., **Jacobus, J.,** & Martin, E.M. (2006). The relationship between subjective memory rating and performance objective measures in midlife HIV+ women. Presented at the annual meeting of the International Neuropsychological Society, Boston, MA (abstracted in International Neuropsychological Society 34th Annual Meeting Program & Abstracts, 146).

16. Gonzalez, R., **Jacobus, J.,** Bechara, A., Pitrak, D.L., Nunnally, G., Novak, R.M., & Martin, E.M. (2005). Factors affecting gambling task performance among substance dependent individuals with HIV. Presented at the annual meeting of the International Neuropsychological Society, St Louis, MO (abstracted in International Neuropsychological Society 33rd Annual Meeting Program

ABSTRACT OF THE DISSERTATION

White Matter Integrity, Substance Use, and Risk Taking in Adolescence

by

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Doctor of Philosophy in Clinical Psychology

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San Diego State University, 2011

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White matter (WM) development is important for efficient communication between brain regions and higher order neurocognitive functioning. Adolescents have a higher propensity for engaging in risky behaviors such as substance misuse and delinquent acts, yet few studies have explored associations between WM integrity, neurocognitive functioning, and risk taking during adolescent development. This study evaluated baseline indices from diffusion tensor imaging (DTI) to examine the influence of WM microstructural integrity and executive functioning on subsequent real-world risk taking. Altered WM integrity in fiber tracts at baseline was suspected to be related to risk taking behaviors measured at 18-month follow-up, and neurocognitive functioning was proposed to mediate this relationship.

Adolescent substance users (e.g., predominately marijuana and alcohol misuse; *n*=47) and controls (*n*=49) received DTI and comprehensive neuropsychological testing at baseline (ages 16-19), and risk taking measures at both baseline and an 18-month

follow-up (i.e., ages 17-20). Brain regions of interest were: fronto-occipital fasciculus, superior longitudinal fasciculus, fornix, superior corona radiata, and genu of the corpus callosum.

Regression analyses evaluating direct and indirect relationships were carried out in Mplus. In the user group (n=47), decreased WM integrity at baseline in the fornix and superior corona radiata predicted 12% of the variability in follow-up substance use, and fornix integrity predicted 7% of the variability in follow-up delinquent behaviors, above and beyond personality, emotional functioning, family history of an alcohol use disorder, and baseline risk taking behaviors, which were included as covariates (ps < .05). WM integrity was not significantly linked to executive functioning in users or controls above and beyond covariates, and executive functioning did not mediate the relationship between WM integrity and risk taking.

Overall, findings suggest that poorer integrity or maturation in distinct WM pathways is linked to a greater propensity for increased risk taking behaviors into late adolescence, among those youth with heavy levels of substance use by mid-adolescence. Most notable were relationships between limbic system fibers and future substance use frequency. It is possible that an imbalance between the maturation levels in cognitive control and reward systems may disadvantage the resistance to engage in risk taking behaviors during adolescence.

INTRODUCTION

Macrostructural Evidence of White Matter Development in Adolescence

Total brain volume typically reaches adult size by six years, but brain structures continue to show dynamic cellular changes throughout human development (Giedd et al., 2009; Lenroot & Giedd, 2006). Early cross-sectional and longitudinal conventional magnetic resonance imaging studies (MRI) have shown maturational changes in brain structures such as progressive increases in white matter (WM) and decreases in grey matter volume often explained by myelination and synaptic organization (Paus et al., 2001). Postmortem histological studies and MRI in infants reveal extensive WM changes occurring in the first few years of life (Barkovich et al., 1988; Yakovlev & Lecours, 1967), but many reports also suggest subtle WM changes continuing throughout adolescence and well into young adulthood (Benes et al., 1994; Giedd, 2004; Giedd et al., 1999; Pfefferbaum et al., 1994).

WM development is purported to follow a temporal and regional developmental specificity pattern, as frontal-parietal regions are largely found to develop last (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997; Yakovlev & Lecours, 1967). Such changes are often described as increased myelin development and synaptic pruning in higher order association areas (Sowell et al., 1999; Sowell et al., 2001) along with continued development of non-cortical circuitry that likely has effects on frontal WM fibers and corresponding cognitive functioning (Pujol et al., 1993).

Microstructural Evidence of White Matter Development in Adolescence

Diffusion tensor imaging (DTI) is an *in vivo* imaging technique of microstructural WM development allowing us to expand on the macrostructural information provided by

MRI. As follows, DTI measures reflect the degree of molecular water diffusion in brain tissue, or more specifically, alterations in tissue density, coherence, compactness, and fiber diameter (Le Bihan et al., 2001; Suzuki et al., 2003; Taylor et al., 2004). The developmental microstructural properties of WM at different stages of myelin development are important for the smooth, efficient, and integrated connections between WM fiber pathways, and thus neuronal transmission and cognitive functioning.

Childhood DTI studies have been fairly well studied and find progressive *increases* in estimated diffusion parameters such as fractional anisotropy (FA; a measure of the directionality of water movement within axons) and *decreases* in mean diffusivity (MD; a measure of the overall displacement of water molecules) with advancing age (Cascio et al., 2007; Giorgio et al., 2008; Mukherjee et al., 2001; Mukherjee et al., 2002). Although most studies have focused on changes in FA and MD to reveal potential WM fiber changes in overall integrity and myelination (Barnea-Goraly et al., 2005; Fryer et al., 2008; Klingberg et al., 1999; Meutzel et al., 2008; Schmithorst et al., 2002; Snook et al., 2005), axial diffusivity (AD; a measure of diffusivity parallel to the axon) and radial diffusivity (RD; a measure of diffusivity perpendicular to the axon) may help describe microstructural integrity in late adolescence and early adulthood. While the mechanism by which changes in FA and MD occur over the course of development is still unclear (Ashtari et al., 2007), many studies have found evidence for *decreases* in RD across adolescence (Asato et al., in press; Bava et al., 2010; Bonekamp et al., 2007; Eluvathingal et al., 2007; Giorgio et al., 2010; Lebel et al. 2008; Liston et al., 2006; Qiu et al., 2008; Snook et al., 2005; Suzuki et al., 2003). These indices in combination provide a slightly more precise characterization of how tissue microstructure may change (e.g., myelination

vs. axonal changes, see Figure 1). For example, RD is restricted by myelin sheaths decreasing water mobility in a perpendicular direction with minimal or less influence on AD (Beaulieu, 2002; Hasan et al., 2007; Song et al., 2002).

Likewise, studies are only beginning to understand the relationship of microstructural integrity to neurocognitive functioning (e.g., working memory, attention, language, response inhibition) and clinical disorders in adolescent populations (Bava et al., 2010; Fryer et al., 2008; Hertling et al., 2010; Li et al., 2005; Liston et al., 2006; Mabbott et al., 2006; Madsen et al., 2010; Muetzel et al., 2008; Nagy et al., 2004; Qiu et al., 2008; Schmithorst et al., 2005; Silveri et al., 2006). These studies have reported correlations between neurocognitive functioning and diffusion indices in areas ranging from corpus callosum, frontal-striatum, and frontal-parietal regions. More recently, Olson and colleagues (2009) found associations between white matter pathways in the prefrontal, parietal, and temporal cortices and preference for delayed rewards in adolescents. Alterations in white matter fiber tracts have also been found in youth with behavioral problems, such as disruptions in the superior longitudinal fasciculus in teenagers with disruptive behavior disorder (Li et al., 2005).

Development of Executive Abilities in Adolescence

In general, brain regions subserving primary functions (e.g., motor) appear to mature first, and higher order cortical association areas continue to develop into early adulthood (Gogtay et al., 2004; Sowell et al., 2004). "Executive functioning" refers to various complex higher-order cognitive abilities such as sustained attention, inhibitory control, cognitive flexibility, planning ahead, and decision-making (Baddeley & Hitch, 1974; Jurado & Rosselli, 2007; Lezak, 2004), abilities comprised of many integrated

subcomponents critical for carrying out goal-directed behaviors, adapting to new situations, and quickly weighing rewards and risks in decision-making. Animal and human studies of early cognitive development show executive abilities still immature in childhood (Bechara et al., 1994; Becker et al., 1987; Chelune & Baer, 1986; Diamond & Doar, 1989; Diamond & Goldman-Rakic, 1989; Diamond et al., 2002; Gerstadt et al., 1994; Hale, 1990; Levin et al., 1991b; Luciana & Nelson, 1998, 2002; Passler et al., 1985; Welsh et al., 1991; Zald & Iacono, 1998). These studies have primarily focused on the differences in executive functioning between children and adults. However, recent investigations show gradual improvement in executive functioning when the transitional time between childhood and young adulthood is examined, along with regional brain changes in prefrontal cortical areas (e.g., dorsolateral prefrontal cortex) and subcortical connectivity that parallel subtle increases in cognitive control capacity (Anderson, 2001; Anderson et al., 2001; Bunge et al., 2002; Conklin et al., 2007; Eluvathingal et al., 2007; Fuster, 1993; Jurado & Rosselli, 2007; Klingberg et al., 2002; Leon-Carrion et al., 2004; H. S. Levin et al., 1991b; Luna et al., 2004; Luna et al., 2010; Luna & Sweeney, 2001; Rubia et al., 2006; Steinberg et al., 2008; Tamm et al., 2002; van Leifenhorst et al., 2010).

The executive subcomponent of attention, comprised of both sustained attention and response inhibition (Anderson, 2002) has been shown to progress through adulthood (Adelman et al., 2002; Anderson, 2001; Anderson et al., 2001; Bjorklund & Harnishfeger, 1995; Brocki & Bohlin, 2004; Case, 1992; Casey et al., 2002, 2005a, 2005b; Dempster, 1992; Diamond, 1990; Diamond et al., 2002; Harris, 1974; Leon-Carrion et al., 2004; Levin et al., 1991a; Piaget, 1954; van der Stelt et al., 1998; Williams

et al., 1999). Problem solving, another executive subcomponent, is defined as taking steps to organize the elements necessary to achieve a goal (Lezak, 2004). Problem solving or planning abilities can be found as young as three (Hudson et al., 1995) and also continue to develop into early adulthood (Romine & Reynolds, 2005). Cognitive flexibility refers to the ability to shift efficiently and quickly between response sets and gradually develops from early childhood throughout adolescence (Anderson, 2002; Zelazo & Frye, 1998). Further, verbal fluency, the ability to retrieve and produce words that begin with a specific phoneme in a limited amount of time, is suggested to be one of the most sensitive executive tasks to frontal lobe functioning and shown to involve inhibitory processes. Performance on verbal fluency tests is one of the last cognitive skills to reach adult levels during development (Jurado & Rosselli, 2007; Matute et al., 2004; Riva et al., 2000; Stuss & Benson, 1986). Sustained attention, response inhibition, problem solving, and cognitive flexibility are integrated components necessary for achieving abstract reasoning which is transforming into adulthood (Graber & Petersen, 1991), as well as for adaptive and responsible functioning in adolescence (Anderson, 2001; Spear, 2000).

Recent research has emphasized the importance of efficient and integrated projections from subcortical regions to the frontal lobes as contributors to these executive functioning capabilities (Royall et al., 2002). Continuous development of projections to and from prefrontal and limbic regions during adolescent system maturation (e.g. increased myelin) likely reflects efficiency of neuronal communication and brain circuitry, coinciding with top-down control of behavior implicated in problem solving

strategies, inhibition, flexibility, and attention (Barnea-Goraly et al., 2005; Ben Bashat et al., 2005; Eluvathingal et al., 2007; Paus et al., 2001; Schmithorst et al., 2005).

Emergence of Risk Taking in Adolescence

Teenagers are frequently categorized as reward and sensation seekers and risk-takers. In fact, over 50% percent of deaths among individuals ages 10-24 are from behaviors that contribute to unintentional injuries and violence (Centers for Disease Control and Prevention, 2008). The study of risk taking is not novel (Boyer, 2006; Slovic, 1966), but few measures adequately capture the concept of risk taking. Many studies have used various self-report measures (Barratt, 1985; Zuckerman et al., 1978), but an abundance of risk taking research has shifted from self-report to behavioral assessment of risk taking utilizing hypothetical dilemmas, lab-based decision-making paradigms, and behavioral measures of risk taking to assess risky behaviors during adolescence (Bechara et al., 1994; Benthin et al., 1993; Byrnes & McClenny, 1994; Crone et al., 2005; Grant et al., 2000; Huizenga et al., 2007; Petry, 2001). Developmental findings have been varied, with some studies showing adolescent decision-making capabilities comparable to adults, and others finding performance differences (Boyer, 2006). The construct validity of these tasks with self-reported risk taking is not always consistent (Gullone & Moore, 2000; Mitchell, 1999; Pack et al., 2001; Petry, 2001; Vitaro et al., 1999; White et al., 1994).

Behavioral measures of risk taking with adolescents have been more consistent (Lejuez et al., 2002), however the relationship between behavioral tasks of risk taking and decision-making are not conclusive (Lejuez et al., 2003). As follows, some suggest that varied findings may be the result of differences in methodologies, experimental settings, or task sensitivities, as adolescents may take more time to weigh risk-benefit

ratios in the laboratory than they do in everyday environments (Keating, 1990; Steinberg, 2004). Additional research is needed to expand on the relationships between self-report and objective measures of risk taking, the complex constructs of decision-making and executive functioning, and the predictive validity to actual real-world behaviors. Furthermore, it may simply be the case that basic measures of cognitive control (e.g., attention, impulsivity) may help predict risk behavior in adolescents (Steinberg, 2008; White et al., 1994), given the progressive development of WM prefrontal association fibers known to underlie executive function capabilities (Eluvathingal et al., 2007). Limited studies (Berns et al., 2009) have explored the utility of such constructs to predict real-world risky behaviors, and currently there have been no longitudinal studies that have looked at the relationship between white matter health and risk taking.

In a cross-sectional study, Berns and colleagues (2009) found that increased white matter integrity (or more mature white matter fibers) predicted risk taking behaviors, particularly rebellious behaviors (e.g., taking drugs). It is unclear if executive functioning, along with progressive white matter fiber development, may aid in predicting self-reported real-world behaviors during this unique developmental time span.

Biological Underpinnings of Risk Taking in Adolescence

Risk taking (i.e., any behavior associated with some probability of undesirable results) is a complex and dynamic construct, influenced by individual factors such as emotion, personality, sex, cognition, and socio-cultural influences (Boyer, 2006; Galvan et al., 2007; Ready et al., 2001; Steinberg, 2004). Interestingly, risk taking seems to change nonlinearly across the lifespan (Steinberg, 2004). Adolescents are more susceptible to engaging in risky behaviors compared to children and adults, therefore

recent research has focused on the unique trajectory of adolescent development (commonly defined as 12 to 18 years of age, and sometimes up to 21 or 25) as compared to childhood and adulthood (Spear, 2000).

Notably, research has highlighted a large neurobiological component to the trajectory of risk taking in adolescent development (Casey et al., 2008; Steinberg, 2008). In further support of a physiological contribution, animal models of adolescence show a corresponding increase in novelty seeking (Laviola et al., 2003), while regions important for cognitive control undergo maturation until young adulthood in humans (e.g., impulsivity and dorsolateral prefrontal cortex) (Giedd, 2004; Gogtay et al., 2004; Liston et al., 2006). Changes in the progressive development (or integration) of two neural systems during these years, prefrontal (control) and limbic (reward), have been postulated to leave adolescents with a distinct vulnerability to risk taking behaviors (Casey et al., 2008; Ernst et al., 2005; Galvan et al., 2007; Galvan et al., 2006; Steinberg, 2004, 2008).

In adolescence, developmental changes occur in regions involving corticolimbic circuitry, including the prefrontal cortex, which interacts with other structures to mediate attention and behavioral inhibition (Bechara et al., 2000; Cunningham et al., 2002), among myriad other functions. Behavioral and functional magnetic resonance imaging (FMRI) studies of risk taking and reward-related processing implicate brain regions such as the amygdala, hippocampus, orbital-frontal cortex, dorsolateral prefrontal cortex, ventromedial prefrontal cortex, ventral tegmental area, anterior cingulate gyrus, nucleus accumbens, and parietal cortex (Bechara et al., 1994; Buchel et al., 1999; Elliott et al., 2000; Elliott et al., 1999; Ernst et al., 2002; Ernst et al., 2003; Ernst et al., 2005; Ernst et al., 2004).

Studies often show increases in subcortical (e.g., nucleus accumbens) activation when making risky choices during adolescence as well as more diffuse and immature prefrontal recruitment (Brown et al., 2005; Bunge et al., 2002; Casey et al., 1997, 2002; Crone et al., 2006; Galvan et al., 2006; Moses et al., 2002; Tamm et al., 2002). The prefrontal cortex may not provide sufficient top down control resulting in less influence of prefrontal systems, and delayed WM maturation and functional connectivity between these prefrontal and limbic areas may lead to impulsive and risky behaviors (Casey et al., 2008; Steinberg, 2008; Van Leijenhorst et al., 2010) Adolescent drug taking may further alter these developmental processes (Tapert et al., 2004a, 2004b, 2007). The link between the biological underpinnings and actual real-world behaviors has yet to be clearly defined. Therefore it is important to expand on the literature by exploring the purported biological underpinnings with self-reports of risk behaviors (drug use, school misconduct) during adolescence.

Proposed Model: Adolescent WM Integrity Predicts Changes in Risk Taking Behavior

Significance of proposed research. Early studies of progressive white matter (WM) development in infancy through adolescence have shown increased myelination and organization of fiber tracts into tight coherent bundles (Benes et al., 1994; Brody et al., 1987; Yakovlev & Lecours, 1967). Cellular maturation of WM improves conductivity between connecting brain regions, so subtle alterations in the microstructure of WM fibers during development may affect neurocognitive capabilities and behavior (Cascio et al., 2007). Given chronological and regional patterns of WM development in childhood (Huttenlocher, 1979; Sowell et al., 2002; Yakovlev & Lecours, 1967), it was suspected that poorer WM integrity would predict poorer cognitive functioning in teenagers. As

adolescents are more likely to engage in risk taking behaviors than children or adults (Arnett, 1992; Galvan et al., 2007; Steinberg et al., 2008), variability in WM integrity may help predict their likelihood of engaging in risky behaviors (e.g., substance use, rule violation). It is important to note the broad conceptualization of risk taking (e.g., financial risks vs. substance use), and certain risk taking is likely to be adaptive for social growth and social status, exploration of the environment, and opportunity for future successes (Spear, 2010). However, this study will focus on the negative and potential harmful effects of adolescent risky behaviors (Centers for Disease Control and Prevention, 2008), defined as engaging in behaviors with a significant probability of negative consequence or unintentional injury.

The relationship between brain structure and risk taking behavior is only beginning to be explored in late adolescence, and most studies have either focused on white matter and risk taking, or focused on impulsivity in the context of cognitive performance (e.g., Berns et al., 2009; Liston et al., 2006; Silveri et al., 2006;); however there have been no studies that have examined the mediational relationship between all three constructs. Therefore, this investigation examined influence of WM fiber integrity on neurocognition and real-world risk taking behaviors in adolescents ages 16-19 at baseline. It was expected that WM fiber integrity, measured using diffusion tensor imaging (DTI), would predict performance on measures of executive functioning, particularly impulsivity, attention, cognitive flexibility, and problem solving. Four DTI measures sensitive to WM tract integrity, as described above, are FA, MD, RD, and AD, which index WM fiber organization and coherence. Further, this investigation examined the degree to which variation in indices of diffusion predicted changes in real-world risky

behaviors (e.g., increased substance use, rule-breaking) over an 18-month follow-up period.

Hypotheses. The specific aim of this research plan was to determine the influence of white matter microstructural integrity on neurocognitive functioning and real-world risk taking behaviors during adolescence in a sample of 96 adolescents (see Figure 2 for conceptual model). This investigation will help inform whether WM microstructure relates to neurocognition and expansion of risk taking behaviors, which often have negative consequences during adolescent neurodevelopment. The first hypothesis predicted that lower FA and higher MD would prospectively predict greater risk taking behaviors at the 18-month follow-up, above and beyond variability accounted for by baseline risk taking behaviors, and any demographic factor linked to 18-month risk taking. Furthermore, in brain regions in which FA or MD significantly predicted follow-up risk taking behaviors (i.e., summary *T*-score of risk taking), increased radial (RD) but not axial (AD) diffusivity would predict changes in risk taking behaviors, representing differences in myelination as opposed to axonal damage. If Hypothesis 1 was supported, baseline neurocognitive performance (i.e., a summary *T*-score of executive functioning) was proposed to mediate the relationship between baseline white mater integrity (i.e., FA, MD, AD, RD) and 18-month risk taking behaviors.

METHODS

Participants

Participants were part of an ongoing longitudinal adolescent drug use research project (R01 DA021182 FMRI and Cognition in Adolescent Cannabis Users, PI: Tapert). The ages of interest (16-19) correspond with the time at which many adult substance users typically began using substances and engaging in risk taking behaviors such as delinquency and rule-breaking (Spear, 2000). Importantly, WM microstructural changes still occur during adolescence, particularly in frontal brain regions (Klingberg et al., 1999). Therefore, late adolescence is an ideal period to capture subtle changes in WM development that can contribute to both neurocognitive dysfunction and behavioral manifestations of risk taking.

Ninety-six adolescents are included in the present study. Informed consent and assent was obtained from all teens and parents at project intake and at later follow-up time points. Adolescents who were over 18 years of age at follow-up consented for their own participation, while parents were separately consented for a collateral informant interview. Consent was approved by the University of California, San Diego Human Research Protections Program.

Procedures

Adolescents were recruited by flyers distributed at local schools. The project has district-level approval for recruitment from San Diego Unified Schools. After making arrangements with the high school principal, project staff distributed the approved flyer, typically during the lunch hour.

Participants were asked questions to ascertain eligibility for the parent study. Teens were classified as substance users (SU) by the parent project if they had >200 lifetime experiences with cannabinoids, and as controls (CON) if they had <10 lifetime experiences with cannabinoids. The present study includes 47 SU and 49 CON teens from the parent study (see Tables 1 and 2). For both groups, alcohol use was limited to not meeting Cahalan and colleagues' criteria for heavy drinking (Cahalan et al., 1969) at project entry.

Teens were excluded for history of a DSM-IV Axis I psychiatric disorder, learning disability, neurological disorder (e.g., meningitis, migraine, or HIV), head trauma with loss of consciousness >2 minutes, serious physical health problem; complicated or premature birth; sensory impairments; non-fluency in English; left handedness; MRI contraindications (claustrophobic symptoms, irremovable metal such as braces or permanent retainers, or positive pregnancy test); use of medications that affect the brain or cerebral blood flow; and drug or heavy alcohol use (>3 drinks on an occasion) in the 28 days preceding the baseline assessment.

Eligible adolescents were scheduled to begin a 28-day monitored abstinence period. If adolescents maintained abstinence, they received a neuropsychological evaluation followed by a diffusion tensor imaging scan session. Brief telephone follow-up interviews assessed recent substance use and life functioning 6 and 12 months later (99% and 95% follow-up rates, respectively, for the parent study). Approximately 15 months after completing the protocol, participants were invited to repeat the study for an 18-month follow-up visit.

Measures

Substance use. Alcohol, marijuana, and other drug use histories were assessed using the Customary Drinking and Drug Use Record (CDDR) (Brown et al., 1998). The CDDR obtains lifetime and past 3-month information on use of tobacco, alcohol (beer, wine, liquor), and other drugs (cannabinoids, amphetamines, barbiturates, hallucinogens, cocaine, inhalants, opioids, misuse of prescription medications, and other substances not previously specified); detailed alcohol and drug withdrawal symptomatology, abuse and dependence criteria (DSM-IV), and substance-related related life problems were also assessed. Past-month substance use was assessed in detail with the Timeline Followback (Sobell & Sobell, 1992) to index the number of days of use in the 28 days before the mandatory 28 days abstinence period. In addition, a collateral version of the TLFB was administered to parents, and breathalyzers and urine toxicology screen data were collected at each in-person follow-up visit (9 over 28 days) to confirm abstinence. If self-report and collateral data were discrepant data were coded to reflect the presence of substance use. The number of days of substance use (i.e., alcohol, illicit drugs, or misuse of prescription drugs to get high) from the Timeline Followback was used to create a *T*-score of substance use-related risk behavior (RTsu) used in subsequent analyses.

*Other Risk Taking Behaviors***.** The Child Behavior Checklist (CBCL; ages 6-18), Youth Self Report (YSR; ages 11-18), and Adult Self Report (ASR; ages 18-59) instruments provide indices of psychopathological syndromes that include real-world risk taking behaviors, including rule-breaking and aggression (Achenbach & Rescorla, 2001). The CBCL was given to all participants' parents at baseline for reports on youths' behavioral problems for the previous six months. By the 18-month follow-up, all

participants were age 18 or older; thus, the YSR (for ages ≤ 18) or ASR (for ages ≥ 19) self-report forms were given, with questions regarding past 6-month behavioral status parallel to the CBCL. This well validated assessment system has shown excellent reliability and validity. Cross-informant agreement (e.g., child/parent) on reports of externalizing behaviors show large effect sizes (Pearson *r*s= .48-.55) (Achenbach et al., 1987; Achenbach & Rescorla, 2001).

To most accurately create an index of risk taking from the Achenbach assessment instruments administered at baseline and follow-up time points, individual items from these assessments were selected *a priori* to best reflect youth and young adult risk taking behaviors, defined as engaging in behaviors with a significant probability of negative consequence or unintentional injury (Boyer, 2006; Centers for Disease Control and Prevention, 2008). The Achenbach assessment instruments each yield *T*-scores on eight syndrome subscales (Withdrawn, Somatic, Anxious/Depressed, Social, Thought, Attention, Rule Breaking/Delinquency, Aggression) that encompass both internalizing and externalizing behaviors. In constructing the index of risk taking behaviors for this project, individual items from the Aggression, Delinquency/Rule Breaking, Attention, Social, and Thought scales were selected that most reflected non-substance use teenage risk taking behaviors (RTns). Internal consistency of the selected items was assessed for all three CBCL, YSR, and ASR risk taking scales with standardized Cronbach's α coefficients, and all coefficient levels were ≥.80 (see Table 3). Scores on these items (e.g., CBCL and ASL or YSR) were used to compute *T*-scores based on sample means and standard deviations to index non-substance use risk taking behavior at baseline and 18-month follow-up. Separate risk taking *T*-scores were created from the substance use

items to disentangle substance use from other forms of rule breaking and aggressive behaviors (e.g., fighting, stealing).

Executive functioning. Standardized neuropsychological tests of response inhibition, attention, cognitive flexibility, verbal fluency, and problem solving were administered at baseline using: 1) Delis-Kaplan Executive Function System (D-KEFS) Tower Test (TWT), 2) D-KEFS Trail Making Test (TMT), 3) D-KEFS Verbal Fluency Test (VFT), 4) D-KEFS Color-Word Interference (CWI), and 5) Digit Vigilance Test (DVT) (Delis et al., 2004; Lewis & Rennick, 1979). Thirty-one subjects did not receive D-KEFS Color-Word Interference and Digit Vigilance Test (it was added to the protocol later). *T*-scores based on the means and standard deviations from the sample were calculated for each measure, and a summary *T*-score of executive functioning was computed for all participants (N=96) by computing an average *T*-score of all five measures (n=65 individuals,) and of three measures (i.e., TMT, VFT, and TWT) for n=31 participants, based on means and standard deviations in the sample. Participants who received D-KEFS Color-Word Interference and Digit Vigilance Test were statistically similar (ps > .05) to those who did not on demographic, diffusion, and substance use, but scored higher on the Beck Depression Inventory-II and Spielberger State-Trait Anxiety Inventory-State scale, $p < .05$), so these measures of depression and anxiety were used as covariates in all analyses.

Tower Test (Delis et al., 2004; Shallice, 1982), was developed to identify impairment in planning and problem solving. Disks have to be moved from a starting configuration on three sticks of equal height to a target arrangement in a minimum number of moves. Subjects were asked to rearrange the disks on the sticks so that their

positions match the target stimulus (presented as a colored drawing). The starting position of the disks is varied so a solution can only be reached in a minimum number of moves. The goal of the task is to solve the problem with the minimum number of translocations. The outcome variable total achievement raw score takes into account points earned for correctly completing a tower within a specified number of moves.

Trail Making Test number-letter switching condition is also part of the D-KEFS (Delis et al., 2004). The test measures cognitive flexibility and participants are required to switch between connecting numbers and letters in order as quickly as possible without error. Raw scores are based on seconds to completion.

The letter fluency condition of the D-KEFS Verbal Fluency test measures the ability to orally generate words beginning with a specific letter in 60 seconds. There are three trials in which the examinee is given the letters F, A, and S. Raw scores are based on number of total correct responses from all three trials (Delis et al., 2004).

Color-Word Interference (Delis et al., 2004; Stroop, 1935) measures an individual's ability to inhibit a prepotent response. The test consists of pages of words printed in black and white, congruent colors, and incongruent colors. In the inhibition condition, the participant is required to name the color of the ink as quickly as possible of words printed in incongruent colors. A raw inhibition score reflecting ability to inhibit an over-learned response is derived from seconds to complete.

Digit Vigilance Test (DVT) is designed to assess vigilance and alertness during rapid visual tracking, providing a measure of sustained visual attention. Subjects are asked to cross out target 6's which appear randomly in 59 rows of single digits (Lewis & Rennick, 1979) time to completion is the summary variable for this task.

The Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary subtest and Wide Range Achievement Test, Third Edition (WRAT-III) provided estimates of intellectual capacity (Wechsler, 1999; Wilkinson, 1993).

Personality. The NEO-Five Factor Inventory (Costa & McCrae, 1985) was used to account for individual variance in risk taking behaviors at 18-month follow-up. It is a 60-item personality scale measure of neuroticism, openness, extraversion, agreeableness, and conscientiousness administered at the baseline assessment.

Mood. The Beck Depression Inventory-II and Spielberger State-Trait Anxiety Inventory (Beck et al., 1961; Spielberger et al., 1970) were used to assess level of depression and anxiety at baseline.

Family background. Family History Assessment Module (FHAM) was used to assess family history of substance use disorders and other major mental health problems. (Rice et al., 1995). The FHAM was administered to both adolescent and parent, and whole reports were composited; any relative reported by either respondent to have a history of psychopathology was coded as positive. Socioeconomic status was based on the two-factor Hollingshead scale that combines parental education and occupation (Hollingshead, 1965).

Pubertal development. The Pubertal Development Scale (PDS) is a self-report measure to assess physical development stage (Peterson et al., 1988). Adolescents indicated which statements best characterize their current level of development, and all participants in this project met criteria for midpuberty, late puberty, or postpubertal stage (i.e., Stages III, IV, or V).

Diffusion Tensor Imaging.

Image acquisition. DTI is a safe, noninvasive imaging method that does not require the same level of participant compliance as FMRI, making it very useful in pediatric populations. Participants were imaged in a 3.0-Tesla General Electric CXK4 short bore Excite-2 magnetic resonance system with an 8-channel phase-array head coil. A scout scan was acquired to assure good head placement in the scanner, check for artifacts, and select slices to be acquired during diffusion scanning. A high-resolution anatomical MRI was acquired using a T1-weighted spoiled gradient recalled acquisition (SPGR) sequence (echo time = minimum full, flip angle = 12º, field of view = 24 cm, resolution = 1 mm^3, 176 continuous slices, acquisition time = 7:26 minutes). The DTI echo planar imaging sequence was optimized for minimum echo time and included a single-shot dual spin echo excitation (Reese et al., 2003) to reduce eddy current artifacts (repetition time = 12,400 ms, echo time = 93.4 ms, 4 averages, 15 directions, b ≈ 2000s/mm^2, field of view = 24 cm, matrix 128 x 128, voxel resolution = 1.875 mm x 1.875 x 3 mm^3, 36 slices, acquisition time = 13:39 minutes). Diffusion weighted images were acquired along 15 diffusion directions, in addition to the normalization image with no diffusion encoding (b=0) (Frank, 2001). Four volumes were acquired and averaged for each direction. Two field map sequences were collected for unwarping (repetition time = 1,000 ms, echo time = minimum full for the first field map, echo time = 5.5 ms for the second field map, flip angle = 60º, same spatial dimensions as the DTI acquisition, acquisition time for each = 2:12 minutes).

Image processing. Image analyses were processed with Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Package

(FSL)(Parker, 2004) and Analysis of Functional NeuroImages (AFNI) library (Cox, 1996). DTI acquisitions were unwarped with two field maps using FMRIB's Phase Region Expanding Labeler for Unwrapping Discrete Estimates (PRELUDE, Jenkinson, 2003) and FMRIB's Utility for Geometrically Unwarping EPIs (FUGUE, Jenkinson & Smith 2001). A six-degree of freedom affine motion correction for head motion and a linear alignment to reduce the effects of gradient coil eddy currents were conducted using tools from FMRIB software library (FMRIB's Diffusion Toolbox (FDT), Smith et al., 2004; FMRIB's Linear Image Registration Tool (FLIRT), Jenkinson et al., 2002). Each image was visually inspected for quality, and non-brain voxels removed from analysis by the AFNI program 3dAutomask. FA, MD, RD, and AD values (see Figure 1) were calculated using a log-linear estimation procedure that fits a diffusion tensor model at each voxel via FDT within FSL (Smith et al., 2004).

Regions of interest. Given evidence for microstructural changes in frontal brain regions in relation to impulsivity and risk behavior (Asato et al., in press; Berns et al., 2009; Li et al., 2005; Liston et al., 2006; Silveri et al., 2006), and neurobiological models of adolescent risk taking (Steinberg, 2008), five regions of interest (ROIs) were extracted: 1) the fronto-occipital fasciculus, 2) superior longitudinal fasciculus, 3) body of the fornix, 4) superior corona radiata, and 5) genu of the corpus callosum. The following strategy was used for all four ROI placements (see Stricker et al., 2009). The ICBM-DTI-81 stereotaxic white matter parcellation map within FSL (Mori et al., 2008) was used to pre-define the white matter ROIs and guide placement of each ROI in each subject's diffusion dataset (i.e., FA, MD, RD, AD). Each subject's diffusion and anatomical image was then linearly transformed into MNI-152 space using the method of Oxford FSL

FLIRT (Evans et al., 1992; Jenkinson et al., 2002) to achieve alignment between the diffusion images, anatomical images, and white matter parcellation map. Next, a white matter mask was created from each subject's high-resolution anatomical image using FSL's Automated Segmentation Tool (FAST; Zhang et al., 2001); this white matter mask was subsequently applied to each diffusion image to ensure only white matter was included in each ROI. Finally, the diffusion file was multiplied by the parcellation map to extract the average diffusion value for each ROI.

All white matter ROIs were positioned bilaterally, inspected by careful reference to landmarks and coordinates identified by the white matter parcellation map, and further verified by the white matter anatomical atlas (Mori et al., 2005, 2008; Schmahmann & Pandya, 2006). ROIs were defined as follows: 1) fronto-occipital fasciculus (FOF): this region begins in the inferior medial frontal cortex, travels above the caudate nucleus, and terminates in the medial parietal area; 2) superior longitudinal fasciculus (SLF): beginning in the dorsomedial frontal lobe and continuing to the superior lateral side of the putamen through the arcuate fasciculus and along the superior edge of the insula until termination in the parietal lobe; 3) body of the fornix (FX): located along the inferior edge of the septum pellucidum, and followed posteriorly to the crura of the fornix, located inferior to the corpus callosum; 4) superior corona radiata (SCR): located anterior and superior to the corpus callosum; and 5) genu of the corpus callosum (GCC) which encompasses the anterior portion of the corpus callosum. Average FA, MD, RD, and AD coefficients were extracted for each ROI (see Figure 3), and imported into Mplus statistical software version 5.1 (Muthén & Muthén, 2008) for mediational analyses.

Data Analysis

Demographics and Covariates. ANOVA's and chi-square tests were used to examine between-group differences on demographic, substance use, and neuropsychological variables. Significant differences were interpreted if $p<.05$. Since participants were part of a larger sample from the parent project consisting of both substance users and controls, if SU and CON were found to differ on demographic variables, cognition, or white matter integrity, models were evaluated in each group separately. Pearson's *r* correlation coefficients were used to identify demographic variables related to 18-month risk taking ($p < .05$). If a variable was significantly correlated with 18-month taking, it was included as a covariate in all analyses.

Mediation. Risk taking items from the CBCL, YSR, or ASR (RTns) and scores indexing days per month of substance use (i.e., alcohol, marijuana, other illicit drugs, and intoxicating medications used other than as prescribed) in the past month (RTsu), as assessed by the Timeline Followback, were used to compute *T*-scores of real-world risk taking (based on means and standard deviations of the sample to ensure equivalent metric across measures) for each participant at baseline and 18-month follow-up. An executive functioning summary *T*-score was computed by summing scores from all five measures of executive functioning based on the means and standard deviations from the sample; these five scores include total seconds to completion on the DVT (inverted so higher scores equal better performance), the inhibition condition raw score from the D-KEFS Color-Word Interference test (inverted), the D-KEFS Trail Making Test switching condition raw score (inverted), the D-KEFS Verbal Fluency letter condition raw score,

and the total achievement raw score on the D-KEFS Tower Test. Statistical analyses were conducted to test whether neurocognitive functioning mediated the effects of WM integrity on risk taking behavior.

A contemporary approach to mediation was utilized in this study. A product-of-coefficients (*ab*) test using the distribution of the product (MacKinnon et al., 1995) involves calculating the product of two path coefficients, between the independent variable (WM integrity) and the hypothesized mediator (executive functioning), and between the same mediator and the dependent variable (risk taking). The product of the path coefficients is then divided by the standard error of the product, and 95% confidence intervals (adjusting for the asymmetric distribution of the product) are calculated to provide a more accurate estimate of the range of potential values for the mediated effect. These analyses were conducted in Mplus software version 5.1 (Muthén & Muthén, 2008) using robust maximum likelihood estimation. This contemporary analytic approach offers increased power to detect a mediated effect, and does not require that all "causal steps" be significant to confirm such indirect effects (MacKinnon et al., 2007).

For each ROI, four regression models were run to test whether the relationship between white matter integrity and 18-month risk taking (RTsu and RTns) was mediated by executive functioning (controlling for baseline risk taking and covariates as appropriate). Direct paths were specified between white matter integrity and 18-month risk taking, executive functioning and 18-month risk taking, and white matter integrity and executive functioning. An indirect path from white matter integrity and 18-month risk taking via executive functioning was specified to test for mediation. The values in the 2.5^{th} and 97.5^{th} percentile were examined to determine the lower and upper limits of

the 95% confidence interval; mediation would be supported if the confidence interval of the indirect path estimate did not contain zero.

Post-hoc Analyses. If evidence was present for significant relationships between WM integrity and executive functioning, or executive functioning and 18-month risk taking, the direct relationship was re-analyzed, replacing the executive functioning summary score with *T*-scores from each test of executive functioning (e.g., TMT, TWT, VFT, CWI, DVT). A Bonferroni correction was applied to control for Type I error, as alpha was divided by the number of cognitive tasks used to calculate the executive functioning summary score ($\alpha = .05/5$, $p < .01$).

Secondary Analyses: Gender. To explore model differences that may exist between males and females, significant relationships from above were run within each gender group separately. *Risk taking relationships.* RTsu and RTns were correlated with measures of academic, occupational, and psychosocial functioning to evaluate the relationship between risk taking construction and real-world functioning.

RESULTS

Demographic Information

The sample consisted of 96 adolescents (66% male, 65% Caucasian) with a mean age of 17 (SD 1; range 16 to 19) at project intake (see Table 1 and 2 for demographic and substance use information of participants). No between-group differences were found in any of the diffusion indices (all *p*s > .05), and this did not change after controlling for age differences between the groups. However, group differences were found between SU and CON in age [$F(1,95) = 4.5$; $p = .04$], family history of a substance use disorder, $\chi^2(1) = 9.2$; $p < .01$, GPA [$F(1,95) = 5.9$; $p = .02$], anxiety [$F(1,95) = 6.6$; $p = .01$], neuroticism [$F(1,92) = 10.5$; $p < .01$], openness [$F(1,92) = 4.0$; $p = .04$], lifetime drinking occasions $F(1,94) = 36.5$; $p < .01$], lifetime marijuana use episodes [$F(1,95) = 84.8$, $p < .01$], lifetime other drug use episodes [$F(1,95) = 5.3$; $p = .02$], days since last use of alcohol [$F(1,95) = 20.5$; $p < .01$] or marijuana [$F(1,62) = 23.2$; $p < .01$] use at baseline, days of substance use in the past month (RTsu) at baseline [$F(1,95) = 77.1$; $p < .01$] and follow-up [$F(1,95) = 37.3$; $p < .01$], RTns at follow-up [$F(1,95) = 6.0$; $p = .02$], and cigarettes smoked at baseline [$F(1,95) = 4.8$; $p = .03$] and follow-up [$F(1,95) = 8.1$; $p < .01$]. Given the between-group differences observed, regression models were run for each group separately.

Bivariate Relationships

The following variables were assessed for contribution to variance in 18-month risk taking scores: age, pubertal development (from the PDS), gender, intellectual functioning (WASI Vocabulary), Hollingshead SES, family history of substance use disorders, personality scores (NEO-FFI), and mood (BDI and STAI). To accurately

identify covariates to include in the mediational models, a summary *T*-score of risk taking was computed (RTsu and RTns) to examine bivariate relationships between demographics and risk taking in the overall sample. Self-reported depressive symptoms (Pearson's $r = .30$, $p < .01$), family history of an alcohol use disorder (Pearson's $r = .21$, $p = .04$), and personality scores on the NEO neuroticism (Pearson's $r = .34$, $p < .01$), conscientiousness (Pearson's $r = -.27$, $p = .01$), and agreeableness (Pearson's $r = -.33$, $p < .01$) subscales were found to be related to 18-month risk taking. These variables, in addition to baseline risk taking and self-reported anxiety symptoms (see Methods), were included as covariates in all analyses.

Direct and Indirect Relationships.

Results indicated that executive functioning did not mediate the relationship between white matter integrity and RTsu or RTns (i.e., all 95% confidence intervals included zero, all *p*s > .05) in the user group. However, direct relationships were found between white matter integrity and 18-month risk taking.

In the user group (n=47), a direct relationship was found between 18-month RTsu and FA in SLF ($\beta = -.27$, $p < .03$), FX ($\beta = -.42$, $p < .01$), SCR ($\beta = -.40$, $p < .01$), and GCC ($\beta = -.29$, $p = .01$), with lower FA values in these white matter fiber tracts associated with more days of substance use at 18-month follow-up (see Figure 4). Similarly, lower FA values in the FX ($\beta = -.26$, $p = .01$) were related to more RTns (i.e., delinquent and aggressive behaviors) at follow-up. Unexpectedly, higher MD values in the GCC ($\beta = -.28$, $p = .03$) and higher RD values in the FOF ($\beta = -.24$, $p = .03$) were related to less RTns (see Figure 5).

To identify if the diffusion indices contributed to a significant *R*-square change in the models above and beyond the covariates, an *F*-change statistic was calculated for all direct relationships (see Figures 4-5). Diffusion parameters were found to contribute to significant model change in three models. FA in the FX (ΔR^2 = .12, *F(1,37)* = 7.0, *p* =.01) and SCR (ΔR^2 = *.12, F(1, 37)* = 6.7 , *p* = .01) contributed to a significant model change in RTsu. FA in the FX also contributed to variance in 18-month RTns beyond the covariates (ΔR^2 = .07, *F(1,37)* = 4.7, *p* =.03).

Poorer executive functioning performance in the user group was related to lower FA (β = .28, *p* = .01), higher MD (β =-*.25, p* = .03), and higher RD (β =-.30, *p* = .03*)* in the FOF. Poorer executive functioning was also associated with higher RD values in the SCR among the user group (β =-.25, *p* = .04) (see Figure 6), and a trend was found between lower executive functioning and lower FA values in the SLF (β =.20, *p* = .05).

In terms of relationships between executive functioning and subsequent risk taking, the executive functioning summary *T*-score was significantly associated with RTns (β = -.27, *p* = .03) in the user group (i.e. poorer functioning: more risk taking).

Similar to the user group, executive functioning did not mediate the relationship between white matter integrity and RTsu or RTns among the control group (*n*=49); all 95% confidence intervals contained zero and all *p*s > .05. In contrast to the user group, controls showed no direct relationship between white matter integrity and risk taking behavior at 18-month follow-up (RTsu or RTns). However, direct relationships were found between diffusion indices and executive functioning performance. Surprisingly, poorer executive functioning was linked to lower RD in the FOF (β = .29, *p* = .01)

and higher AD (β = -.27, p = .01) and lower RD (β = .22, p = .02) in the GCC in the control group (see Figure 7).

The executive functioning T-score was not linked to RTsu or RTns in the CON group (all ps > .05).

Follow-up Analyses to Executive Functioning

To follow-up the direct relationships between diffusion indices and executive functioning performance measured by the summary *T*-score, alpha levels were corrected for multiple comparisons by dividing alpha by the number of executive functioning subtests (α = .05/5, p < .01). In the user group, only FA in the FOF was related to TMT (β = .49, p < .01); however, trends were noted between RD in the FOF (β = -.36, p = .01) and RD in the SCR (β = -.26, p = .01) and the TMT.

In the control group, unexpectedly, better TWT performance was linked to higher RD in the FOF (β = .34, p < .01), and a similar unexpected trend was found linking poorer performance on VFT and higher AD in the GCC (β = -.24, p = .01).

Additional analyses were explored to evaluate if any individual executive functioning subtests were directly related to RTns in the user group, controlling for all covariates as indicated above. Corrected alpha levels were maintained at p < .01. Although significance testing did not meet the alpha corrected p < .01, significant trends were noted between VFT (β = -.24, p = .02) and DVT (β = -.30, p = .01), and 18-month RTns; as anticipated, poorer performance on these tests was associated with more risky, aggressive, and delinquent behaviors in the users.

Gender

As part of an exploratory analysis to better understand if significant models from above were similar in both male (*n*=28) and female (*n*= 19) users, and male (*n*=36) and female (*n*=13) controls, the significant direct effects between white matter integrity and risk taking, white matter integrity and executive functioning, and executive functioning and risk taking were analyzed within each gender and user group separately. Within both the male (β = -.56, $p < .01$) and female users (β = -.42, $p = .01$), FA in the FX was related to RTsu. The relationship between RTsu and FA values in the SCR was also significant in both male (β = -.42, $p < .01$) and female (β = -1.2, $p < .01$) users. However, the association between RTsu and FA values in the SLF (β = -.33, $p = .02$) and GCC (β = -.42, $p < .01$) remained significant in the male users only when groups were evaluated separately. The relationship between FA in the FX and RTns was significant in male (β = -.56, $p < .01$) and female (β = -.42, $p = .01$) users, and the relationship between MD values in the GCC and RTns was also significant for both male (β = -.30 $p = .03$) and female (β = -.57, $p < .01$) users. The relationship between RTns and RD values in the FOF was only significant in the male users (β = -.41, $p = .02$).

There were significant relationships between executive functioning and MD (β = -.43, $p < .01$) and RD (β = -.47, $p = .01$) in the FOF in the male users, while trends between executive functioning performance and FA in the FOF (β = .29, $p = .06$), and RD in the SCR (β = -.30, $p = .05$) were noted in this gender group. However, in both the male (β = .49, $p < .01$) and female (β = .52, $p = .01$) users, lower FA values in the FOF were linked to poorer performance on the TMT.

The relationship between executive functioning and RD in the FOF (β = .39, $p < .01$) and RD in the GCC (β = .24, $p = .01$), was significant in the male controls; while in

the female controls, the relationship between executive functioning and AD in the GCC was significant (β = -.64, p < .01). RD values in the FOF were also related to performance on TWT (β = .40 p < .01) in the male controls.

Risk Taking Relationships

To evaluate if RTsu and RTns were related to occupational, psychosocial, and academic functioning at 18-month follow-up, risk taking constructs were examined in relationship to the number of hours worked at a job, involvement in sports, hobbies, or other recreational activities (e.g., never, rarely, occasionally, frequently), grade point average, and long term career plans (e.g., no degree, high school degree, vocational school, college or graduate study). Relationships between these constructs and RTns and RTsu were supported. In the user group, RTns was related to GPA (Pearson's r = -.33, p = .02). In the control group, RTsu was related to hours worked at a job (Pearson's r = -.36, p = .01).

DISCUSSION

In this sample of adolescents, white matter integrity was found to be a potential marker of risk taking behaviors in substance using youth. We evaluated the predictive relationship between white matter integrity and executive functioning measured at a baseline time point during mid-adolescence in relation to risk taking measured 18 months later. This study did not find evidence to support the mediational hypothesis, as the relationship between white matter integrity and risk-taking behaviors in 16-19 year-olds did not appear to be explained by executive functioning. However, evidence for a direct relationship between white matter integrity and risk taking (substance use related and other aggressive/delinquent behaviors), and white matter integrity and executive functioning, were found in the user group; in the control group, associations were seen only between white matter integrity and executive functioning. Follow-up analysis revealed relationships between specific executive functioning tasks (e.g., TMT, TWT) and WM integrity in users and controls, and support for unique relationships within each gender group was also present.

In the user group, FA values in the FX were related to RTsu and RTns, as more microstructural coherence in the FX was associated with less risky behaviors at 18-month follow-up. Notably, *higher* FA values in the FX were associated with *less* risky substance use and delinquent behaviors, and this relationship was present in both males and females. White matter integrity in this brain region was not associated with executive functioning, and diffusion values in this region were not related to either risk taking or executive functioning in the control group. The fornix is believed to develop earlier in life and DTI studies show that this bundle is one of the earliest to reach maturity, as it is

likely to be in more advanced stages of maturation by adolescence (Dubois et al., 2008). The FX has been implicated in memory (D'Esposito et al., 1995; Gaffan et al., 1991; Papanicolaou et al., 2007; Poreh et al., 2006; Rudebeck et al. 2009; Tsivilis et al., 2008) and this major fiber bundle plays a large role in limbic system interconnections as it projects from the hippocampus to regions such as the mammillary bodies and hypothalamus, and sends connections to prefrontal cortical areas (Haines, 2008). The limbic system is important in adolescent development and risk taking, with involvement in reward processing and connections to later developing cortical regions such as striatal and prefrontal circuits (Ernst & Fudge, 2009). Previous studies have found low FA values in the FX among adolescents with clinical behavior disorders (Davenport et al., 2010), and our findings provide additional evidence that decreased white matter microstructural integrity (i.e., lower FA) in limbic system connections may be related to more impulsivity and risky behaviors, above and beyond indicators of emotional functioning and personality (e.g., agreeableness, conscientiousness). Alteration in FA values in this region may be related to less coherently organized fiber bundles that result in less efficient limbic system communication with prefrontal systems.

Similar to the FX, baseline FA values in the SCR also predicted follow-up RTsu in the user group above and beyond baseline RTsu and covariates. *Higher* FA values were associated with *fewer* days of substance use at 18-month follow-up in both male and female users. While others have found age-related diffusion changes in this white matter tract during adolescence (Bonkeamp et al., 2007; Snook et al., 2005), a recent investigation by Giorgio and colleagues (2010) found that age-related increases in FA in the superior corona radiata were driven mostly by changes in RD. While current findings

did not identify a relationship between RD and RTsu in this brain region, decreased RD values in the SCR were related to better executive functioning performance in the user group, and follow-up analysis revealed a trend with decreased RD and better performance on the TMT, a test of number-letter switching. RD has been suggested to reflect myelination processes in the maturing brain in a number of studies (Eluvathingal et al., 2007; Lebel et al., 2008; Madsen et al., 2010; Qiu et al., 2008; Snook et al., 2005, Song et al., 2002). Liston and colleagues (2006) found that decreased radial diffusivity was related to cognitive control capacity measured by performance on a go/no-go paradigm. However, alterations in diffusivity indices (e.g. FA, RD) may reflect varied microstructural tissue alterations, as many water compartments within the intra/extracellular space can influence diffusion measurements (e.g., neurofilaments, microtubules, number and coherence of axons, myelin thickness) (Johansen-Berg & Behrens, 2009). Likewise, the corona radiata contains crossing fibers, and such complex geometric configuration may also influence DTI parameters. The regions of the corona radiata evaluated in this study contain reciprocal frontal-striatal connections and projection fibers (e.g., motor and thalamic pathways), pathways important for both higher order cognitive processing as well as motor functioning. Microstructural alterations in these fiber tracts may account for the relationship between white matter integrity and propensity to engage in future substance use behaviors observed in the user group, along with changes in performance on the Trail Making Test.

While the remaining direct relationships were independent predictors of risk taking or executive functioning, they were not significant above and beyond the included covariates. Lower FA in the SLF was associated with *more* days of substance use at 18-

month follow-up in the user group, and when evaluated separately in each gender group, this relationship was significant only for male users. While there was a trend between better executive functioning and increased FA values in this white matter region, we did not find the SLF to be related to executive functioning in either users or controls, or risk taking constructs in the control group.

The SLF is an association fiber tract that connects the frontal and parietal cortices and has shown to be important for higher-order motor functioning, visuospatial cognition, and language (Makris et al., 2005). Investigations have shown decreased FA values in the SLF in adolescents and adults with disruptive behavior and attention-deficit hyperactivity disorder compared to matched controls (Davenport et al., 2010; Hamilton et al., 2008; Li et al., 2008; Makris et al., 2008); another study found decreased FA and AD values along with increased RD values in adolescents with substance use disorders compared to matched controls (Thatcher et al., in press), providing some evidence that changes in the microstructural architecture of this fiber bundle (e.g., delayed myelination) may disrupt neural connections and result in increased propensity for substance use and engagement in impulsive behavior, or be particularly susceptible to the neurotoxic effects of substance use during adolescent development. Studies have clearly shown this fiber bundle continues to develop through adolescence (Bonekamp et al., 2007; Lebel et al., 2008, Schmithorst et al., 2002), and previous studies from our laboratory have also found differences in frontal-parietal regions in both functional and structural studies in adolescent marijuana and alcohol users (Bava et al., 2009; McQueeny et al., 2009; Schweinsburg et al., 2008; Tapert et al., 2007).

Likewise, in the GCC, FA values predicted RTsu in the user group, as decreased FA values were related to more days of substance use at follow-up; when evaluated in each gender group separately, this relationship was present for male users only. Surprisingly, higher MD values in the GCC (along with higher RD values in the FOF) were related to decreased delinquent and aggressive behaviors at follow-up in both males and females. GCC values were not related to executive functioning in the user group, and again, unexpectedly, decreased AD and increased RD were associated with better executive functioning performance in the control group. In a younger sample of adolescents, Silveri and colleagues (2006) found that higher FA values in the GCC were associated with better performance on the interference condition of a Stroop task in female adolescents; however, the authors found the opposite relationship with a measure of emotional aspects of impulsivity, as lower FA was associated with better impulse control in healthy male adolescents. Another cross-sectional study conducted by Berns and colleagues (2009) found that increased white matter integrity in the GCC as well as the SCR was associated with more rebellious behaviors (e.g., substance use). Findings from these two studies together suggest distinct pathways underlying inhibition and neurocognitive control.

While the current findings in this region are inconsistent and not particularly strong, the role of the GCC in risk and/or cognitive control is still unclear. It is possible that distinct fiber tracts within the GCC are separately involved in both processes, have a less substantial role in either process, or that significant variability within this tract may account for the discrepancies. The GCC is important for the transfer of information via frontal interhemispheric connections, and some literature suggests an opposite temporal

development pattern of the corpus callosum, with anterior portions (e.g., genu) developing earlier (Giedd et al., 1999). During adolescence, studies have shown age-related changes in FA and MD in the splenium and body of the corpus callosum more frequently than the genu (Ashtari et al., 2007; Barnea-Goraly et al., 2005; Bonekamp et al., 2007; Fryer et al., 2008; Muetzel et al., 2008).

Although the majority of studies find relationships between diffusion indices and cognitive functioning in the anticipated direction (e.g., increased MD and decreased cognitive performance) (Muetzel et al., 2008; Nagy et al., 2004; Olson et al., 2009; Qiu et al., 2008); recent publications from our laboratory have observed some similar unexpected relationships between diffusion indices and neurocognitive functioning in non-users of substances (Bava et al., 2009, 2010). Such findings are not novel (for review see Schmithorst & Yuan, 2009), and it is important to note that they may simply relate to the continued pruning of the neocortex and associated maturational processes in healthy adolescents that may affect diffusion measurements within pathways such as the GCC.

In the FOF, increased FA and decreased MD and RD values were related to better executive functioning performance in the user group, and this relationship appeared to be stronger in the male users. Yet in both genders, better performance on the TMT was related to increased FA values in the user group, highlighting the potential role of the FOF in executive cognitive control. Another unexpected relationship was found with controls in this region, as higher RD values were associated with better executive functioning performance, particularly TWT performance, which may be associated with continued neurodevelopmental processes as mentioned above. The FOF is an association

fiber bundle connecting parietal and prefrontal regions, and shown to be related to higher-order visuospatial processing (Makris et al., 2007).

While this study did not find associations between a summary score of executive functioning and RTsu, increased RTns was related to decreased executive functioning in the user group, particularly performance on measures of attention and verbal fluency. A recent study conducted by Ernst and colleagues (2010) found that performance on the Iowa Gambling Task *did not* predict individuals who initiated substance use over a four-year follow-up period; executive functioning may not have as much predictive validity in adolescents and may be more effective in predicting behavior later in life after longer periods of heavier substance use.

Overall, this study found notable support for the predictive relationships between RTsu and RTns and limbic and projection fiber pathways in the FX and SCR in both males and females, above and beyond measures of personality, emotion, baseline risk taking behaviors, and family history of alcohol use, which has recently shown to be related to white matter integrity in teens (Herting et al., in press). While some trends were also found between association fibers (e.g., SLF and FOF), risk taking, and executive functioning, these relationships were not as strong. Findings support previous studies (Berns et al., 2009; Silveri et al., 2006) suggesting distinct pathways for neurocognitive control and risk taking and reward-related behavior. Given that findings were less remarkable between white integrity and executive functioning compared to limbic and subcortical projection fibers and risk taking behaviors, it is possible that immature cortical association fiber connections and more rapidly maturing subcortical limbic connections may represent an imbalance in these two systems, thereby further supporting

the dual-systems model (Steinberg et al., 2008) recently evidenced in structural and functional imaging studies (Asato et al., in press; Van Leigenhorst et al., 2010). The discrepancy between limbic and subcortical white matter tracts and developing cortical connections necessary to efficiently modulate behavioral control in this group may be more pronounced in the user group due to the purported neurotoxic effects of alcohol and marijuana on white matter tissue development (Ashtari et al., 2009; Bava et al., 2009; Jacobus et al., 2009; McQueeny et al., 2009). It is likely that heavy alcohol and marijuana use reported by the user group has altered more developed subcortical fibers, and further weakened immature neuronal networks necessary to efficiently monitor and regulate risky behavior. In addition to structural brain changes, neurochemical changes, specifically excess dopamine that is the result of changes in the mesolimbic and mesocortical dopaminergic system may also contribute to reward seeking behavior during adolescence (Wahlstrom et al., 2010).

Although groups did not differ on diffusion indices, it is still possible that age played a role in the different outcomes between the models, as the user group was slightly older than controls. It may be that the user group has incurred more complete white matter maturation, while the slightly younger controls are still undergoing maturational processes, which yields unexpected relationships. There may be genetic and hormonal differences in these groups that influence white matter development in addition to other macrostructural and neurochemical processes (Asato et al., in press; Wahlstrom et al., 2010), and genetic influences may also interact with previous exposure to substances. Psychosocial stressors may also play a role, as adolescents that use drugs may be susceptible to increased in conflict in the home and school which may influence future

substance use and risk taking; these environmental effects may likely further interact with genetic traits. Future studies should evaluate these models in youths that transition to substance use over time.

The predictive validity of combined structural imaging data with cognitive assessment to real-world risk taking in typically developing adolescents has not been well studied. Risk taking is a complex and clinically important construct that likely results from the interaction of biological, neurochemical, and environmental influences. This study seeks to clarify how one biological marker (i.e., WM integrity in the context of development) mediates propensity to engage in risk taking behavior, operationalized here primarily as increased substance use and rule-breaking behavior. As histopathological studies have shown DTI to be related to white matter abnormalities (Concha et a1., 2010), characterizing structure-function relationships between risk taking, neurocognitive performance, and WM development will begin to bridge a gap in the literature linking microstructural brain tissue integrity, cognitive performance, and everyday adaptive functioning in adolescent populations.

Limitations

An inherent limitation to this study is that all factors that contribute to risk taking cannot be controlled; however, the purpose of this investigation was to examine one potential biological component of risk taking behavior. Self-reported risk taking behaviors were collected, including substance use, and additional sources of information (biological samples and parent reports) improved the validity of self-report measures. Temporal precedence must also be considered when inferring causation, and both indices of white mater integrity and neurocognitive performance were assessed at the same time,

limiting any conclusion about causal effects. The age range was limited to late adolescence and focuses on risk taking as it relates to substance use, delinquency, and aggressive behaviors. Risky sexual activity, gambling, and tobacco use also have serious consequences and should be the focus of future research. Further, while the vast majority of controls reported engaging in some risky behaviors (84%), it is also possible that fewer risky behaviors in this group (e.g., substance use) contributed to a lack of significant findings. The focus of this project was on risk taking in the context of negative consequence. Risk taking can also increase opportunity for successful outcomes in life (e.g., wealth, social status). Future longitudinal research should further explore the advantages of adaptive risk taking behaviors, underlying neurobiological models, and related functional outcomes in teens and young adults.

DTI is a useful tool for studying white matter, but has some limitations. For example, quantifying diffusion in multiple fiber orientations (i.e., crossing white matter tracts) within a single voxel, signal distortion, dropout, and motion artifact can influence indices of diffusion (Huettel et al., 2004). Furthermore, the primary aims of this investigation were not to disentangle the causes behind alterations in WM during adolescence (e.g., slow maturation, drug/toxin exposure), although this likely will be the focus of future studies. Yet, irrespective of the direct cause of WM integrity or injury, this study will help identify potential structure-function relationships between WM and real-world behavior in adolescence.

The CBCL, YSR, and ASR contain many items that appropriately represent risk taking behaviors common to young people, and this assessment system relies on reliable parent and child reports. The benefits include information from multiple informants, but

inconsistencies between parent and child may introduce some degree of measurement error that can bias regression coefficients. However, as can be seen from Table 3, the behaviors queried on each form are quite similar.

The project excluded individuals unable to remain abstinent prior to testing, as well as teens with histories of head injury, psychiatric disorders, and learning disabilities. Risk taking should be examined closely in these higher-risk individuals, and findings from this investigation may not generalize to adolescents that have been excluded from study.

Implications

If support exists for structure-function associations, microstructural predictors such as diffusion indices may be used in accordance with other assessment tools (e.g., neuropsychological, personality, socio-cultural) and imaging modalities (FMRI) to better understand behavioral manifestation of real-world risk taking. Understanding the biological component behind real-world behavioral manifestation of risk taking has implications for not only clinical assessment, but for designing intervention and prevention programs that take into account developmental differences in cognitive control capacities during the transitional window between childhood and adulthood. For example, identification of teens at increased risk for dangerous behaviors can help mental health providers select intervention strategies that work to limit risk taking opportunity and encourage healthier outlets (e.g., community activism, recreational activities) requiring less effective utilization of cognitive control; this may be more effective than targeting maladaptive cognitions about risky behaviors (e.g., drug use will lead to social acceptance). In the future, multi-domain risk taking assessment (e.g., imaging,

personality) may be used to guide high-risk teenagers, which could advantageously influence healthcare and criminal justice systems, and society as a whole.

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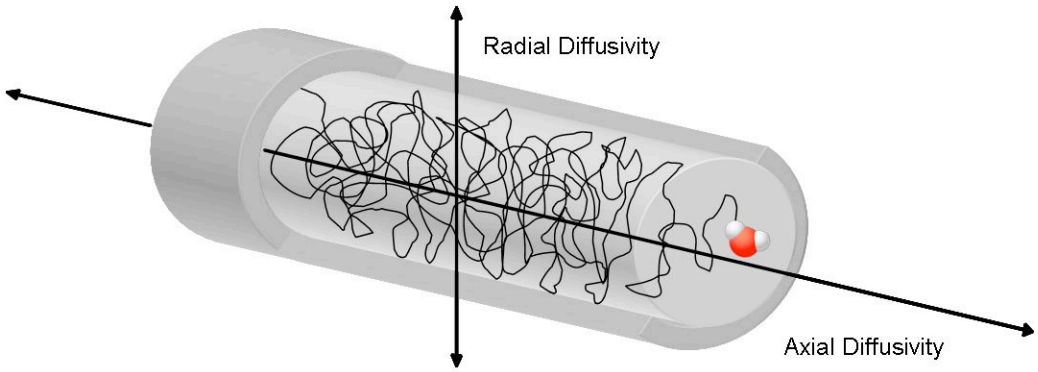


Figure 1. Illustration depicting axial (AD) and radial (RD) diffusivity.

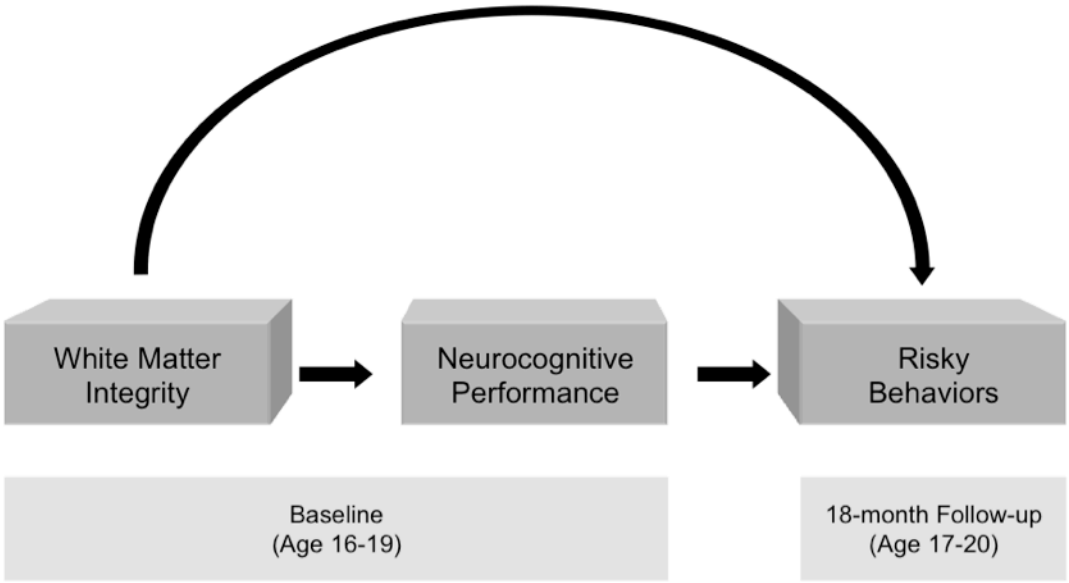


Figure 2. Hypothesized model.

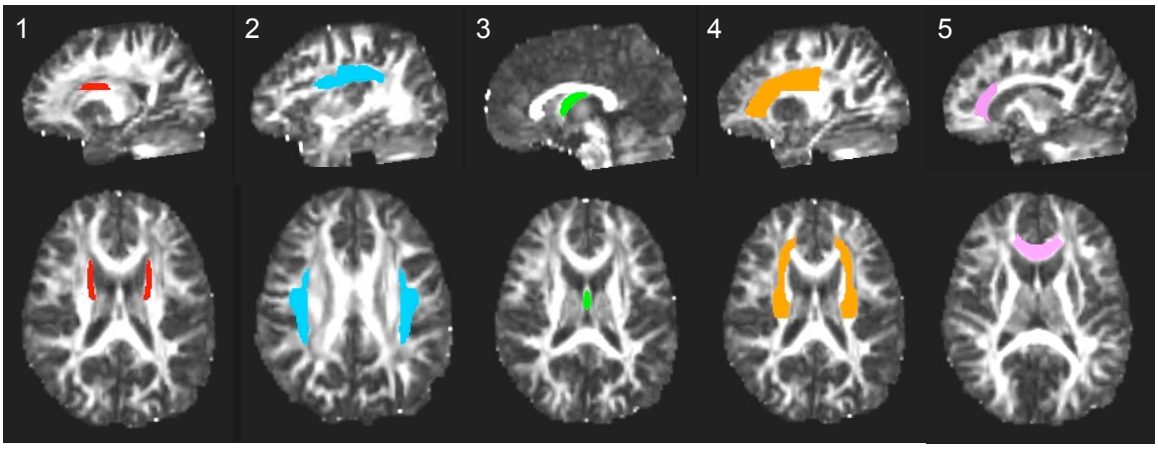


Figure 3. Regions of interest on ICBM-DTI-81 white matter atlas (from left):1) fronto-occipital fasciculus (FOF, highlighted in red), 2) superior longitudinal fasciculus (SLF, highlighted in blue, 3) fornix (FX, highlighted in green), 4) superior corona radiata (SCR, highlighted in light yellow), and 5) genu of the corpus callosum (GCC, highlighted in purple).

Table 1. Demographic, substance use, and neurocognitive characteristics of participants at baseline (BL) and 18-month follow-up (18mo)

	BL (*N*=96) M (SD; Range)	18mo (*N*=96) M (SD; Range)
Age (range: 16.2 to 19.1)	17.8 (0.8; 16.2-19.1)	19.2 (0.9; 17.4-20.9)
% Male	66%	-
% Caucasian	65%	-
% Family history negative for SUD [a]	69%	-
% Family history negative for AUD [a]	41%	-
% Postpubertal	40%	-
Grade point average	3.2 (0.7; 0.5-4.5)	3.2 (0.5; 1.8-4.8)
Hollingshead socioeconomic index	29.2 (16.4; 11.0-77.0)	-
WASI Vocabulary *T*-score	58.0 (9.4; 25.0-76.0)	-
Risk-Taking: non-substance (RTns) *T*–score [b]	49.3 (10.8; 39.2-80.5)	49.6 (8.6; 39.2-80.0)
Spielberger State Anxiety *T*-score	38.4 (7.1; 30.0-71.1)	-
Beck Depression Inventory total	2.7 (3.2; 0.0-15.0)	-
NEO-FFI Neuroticism	29.1 (7.2; 12.0-48.0)	-
NEO-FFI Extroversion	44.9 (5.7; 28.0-57.0)	-
NEO-FFI Openness	43.1 (6.0; 28.0-57.0)	-
NEO-FFI Agreeableness	41.7 (6.0; 27.0-56.0)	-
NEO-FFI Conscientiousness	42.0 (6.8; 27.0-57.0)	-
Lifetime drinking occasions	128.1 (196.3; 0.0-1210.0)	-
Lifetime marijuana use episodes	231.3 (342.6; 0.0-1800.0)	-
Lifetime other drug use episodes [c]	22.9 (100.0; 0.0-835.0)	-
Days since last alcohol use [d]	188.7 (326.7; 2.0-1000.0)	-
Days since last marijuana use [d]	155.9 (256.8; 2.0-1095.0)	-
Days of substance use (RTsu), past month [e]	6.4 (8.8; 0.0-28.0)	8.3 (9.4; 0.0-28.0)
Cigarettes smoked, past month [d]	15.6 (72.0; 0.0-600.0)	8.3 (9.4; 0.0-28.0)
DKEFS Tower Achievement (SS)	9.8 (1.7; 6.0-15.0)	-
DKEFS Trail Making Switching (SS)	10.7 (1.9; 4.0-14.0)	-
DKEFS Verbal Fluency (SS)	12.4 (3.2: 6.0-19.0)	-
DKEFS Color-Word Inhibition (SS)	11.1 (2.1; 4.0-16.0)[f]	-
Digits Vigilance Test (seconds)	163.0 (29.2; 96.0-225.0)[f]	-

[a] No first-degree or second-degree biological relative with alcohol or other substance use disorder.
[b] Excludes substance use
[c] Other than marijuana, alcohol, and nicotine
[d] Reported prior to DTI scan session
[e] Reported prior to 28-day abstinence period
[f] $n = 65$

Table 2. Demographic and substance use characteristics of controls (CON) and substance users (SU)

	CON (*n*=49) M (SD; Range)	**SU (*n*=47) M (SD; Range)**
Age (range: 16.2 to 19.1)[*†]	17.6 (0.8; 16.2-19.1)	18.0 (0.9; 16.4-19.1)
% Male	73%	59%
% Caucasian	65%	65%
% Family history negative for SUD [a,†]	83%	54%
% Family history negative for AUD [a,]	47%	35%
% Postpubertal [*]	33%	47%
Grade point average[*†]	3.4 (0.6; 1.9-4.5)	3.1 (0.8; 0.5-4.0)
Grade point average at 18 months[**†]	3.3 (0.5; 2.0-4.3)	3.0 (0.6; 1.8-4.8)
Hollingshead socioeconomic status index[*]	40.0 (16.7; 11.0-77.0)	27.5 (16.2; 11.0-73.0)
WASI Vocabulary *T*-score[*]	59.7 (9.2; 43.0-76.0)	56.2 (9.5; 25.0-75.0)
RTns *T*–score[*b]	48.7 (9.2; 41.3-78.7)	51.4 (10.4; 41.0- 80.5)
RTns *T*-score[**b,†]	47.6 (7.5; 39.2-77.8)	51.8 (9.2; 39.8-80.0)
Spielberger State Anxiety *T*-score[*†]	36.7 (6.5; 30.0-71.1)	40.4 (7.4; 30.0-62.0)
Beck Depression Inventory total[*]	2.1 (2.6; 0.0-11.0)	3.4 (4.0; 0.0-15.0)
NEO-FFI Neuroticism[*†]	26.9 (6.6; 12.0-40.0)	31.5 (7.2; 16.0-48.0)
NEO-FFI Extroversion[*]	45.6 (5.8; 28.0-57.0)	44.3 (5.6; 29.0-56.0)
NEO-FFI Openness[*†]	42.0 (6.2; 28.0-57.0)	44.4 (5.7; 33.0-55.0)
NEO-FFI Agreeableness[*]	42.7 (6.9; 27.0-56.0)	41.0 (4.9; 31.0-51.0)
NEO-FFI Conscientiousness[*]	43.3 (6.8; 28.0-55.0)	40.9 (6.8; 27.0-57.0)
Lifetime drinking occasions[*†]	25.5 (37.6; 0.0-196.0)	233.1 (234.7; 4.0-1210.0)
Lifetime marijuana use episodes[*†]	1.4 (2.4; 0.0-9.0)	471.0 (357.1; 5.0-1800.0)
Lifetime other drug use episodes[*c,†]	0.4 (1.9; 0.0-13.0)	46.5 (139.8; 0.0-835.0)
Days since last alcohol use[*d,†]	323.4 (408.8; 13.0-1000.0)	48.5 (82.0; 2.0-410.0)
Days since last marijuana use[*d,†]	385.2 (317.3; 30.0- 1076.0)[e]	77.9 (177.7; 2.0-1095.0)
RTsu [*g,†]	0.7 (1.3; 0.0-6.0)	12.6 (9.4; 0.0-28.0)
RTsu [**g,†]	3.5 (5.2; 0.0-26.0)	13.6 (10.2; 0.0-28.0)
Cigarettes smoked, past month[*g,†]	0.1 (0.6; 0.0-4.0)	31.8 (101.0; 0.0-600.0)
Cigarettes smoked, past month[**g,†]	0.2 (0.9; 0.0-6.0)	53.2 (130.7; 0.0-600.0)
DKEFS Tower Achievement (SS)[*]	9.9 (1.5; 7.0-14.0)	9.9 (2.0; 6.0-15.0)
DKEFS Trails Switching (SS)[*]	11.1(1.7; 5.0-14.0)	10.3 (2.2; 4.0-14.0)
DKEFS Verbal Fluency (SS)[*]	12.2 (3.4; 6.0-19.0)	12.7 (3.2; 7.0-19.0)
DKEFS Color-Word Inhibition (SS)[*]	11.2 (1.9; 9.0-15.0)[h]	11.0 (2.4; 4.0-16.0) [i]
Digits Vigilance Test (SS)[*]	158.4 (23.9; 122.0-211.0)[h]	167.9 (32.7; 96.0-225.0) [i]

[†] Group difference, $p < .05$

[*] Baseline visit

[**] 18-month follow-up visit

[a] No first-degree or second-degree biological relative with alcohol or other drug use disorder.

[b] Excludes substance use

[c] Other than marijuana, alcohol, and nicotine

[d] Days prior to DTI scan session

[e] $n = 16$

[f] $n = 27$

[g] Reported prior to 28-day abstinence period; [h] *n=30;* [i] *n=35*

Table 3. *C*omparable risk taking items from the Child Behavior Checklist (CBCL), Youth Self-Report (YSR), and Adult Self-Report (ASR)

CBCL Cronbach's α = .91	**YSR** Cronbach's α = .90	**ASR** Cronbach's α = .80
3. Argues a lot [b]	3. I argue a lot [b]	28. I get along badly with my family [b]
4. Fails to finish things he/she starts [d]	4. I fail to finish things I start [d]	53. I have trouble planning for the future [d]
16. Cruelty, meanness to others [b]	16. I am mean to others [b]	16. I am mean to others [b]
21. Destroys things belonging to his /her family [b]	21. I destroy things belonging to others [b]	21. I destroy things that belong to others [a]
22. Disobedient at home [b]	22. I disobey my parents [b]	76. My behavior is irresponsible [a]
23. Disobedient at school [b]	23. I disobey at school [b]	23. I break rules at work or elsewhere [a]
28. Break rules at home, school, or elsewhere [a]	28. I break rules at home, school, or elsewhere [a]	122. I have trouble keeping a job [a]
36. Gets hurt a lot, accident prone [c]	36. I get accidently hurt a lot [c]	36. I accidently get hurt a lot, accident prone [e]
37. Gets in many fights [b]	37. I get in many fights [b]	37. I get in many fights [b]
39. Hangs around with others who get in trouble [a]	39. I hand around with other kids that get in trouble [a]	39. I hang around other people that get in trouble [a]
41. Impulsive or acts without thinking [d]	41. I act without stopping to think [d]	41. I am impulsive or act without thinking [a]
43. Lying or cheating [a]	43. I lie or cheat [a]	43. I lie or cheat [a]
57. Physically attacks people [b]	57. I physically attack people [b]	57. I physically attack people [b]
61. Poor school work [d]	61. My schoolwork is poor [d]	61. My work performance is poor [d]
67. Runs away from home [a]	67. I run away from home [a]	114. I fail to pay debts or meet other financial responsibilities [a]
72. Sets fires [a]	72. I set fires [a]	89. I rush into things without considering the risks [d]
81. Steals at home [a]	81. I steal at home [a]	82. I steal [a]
82. Steals outside the home [a]	82. I steal from other places [a]	92. I do things that may cause problems with the law [a]
90. Swearing or obscene language [a]	90. I swear or use dirty language [a]	122. I have trouble keeping a job [a]
95. Temper tantrums or hot temper [b]	95. I have a hot temper [b]	95. I have a hot temper [b]
97. Threatens people [b]	97. I threaten to hurt people [b]	97. I threaten to hurt people [b]
99. Smokes tobacco [a]	99. I smoke tobacco [a]	124. Tobacco use [a]
101. Truancy, skips school [a]	101. I cut classes or skip school [a]	101. I skip work [d]
94.Teases a lot [b]	94. I tease others a lot [b]	121. I tend to be late for appointments [d]
104.Unusally loud [b]	104. I am louder than other kids [b]	120. I drive too fast [a]
68. Screams a lot [b]	68. I scream a lot [b]	17. I have trouble managing my money or credit card [a]
106. Vandalism [a]	-	-

*Numbers represent individual item numbers from assessment forms and letters represent item subscale; [a] Rule Breaking Scale; [b] Aggression Scale; [c] Social Problems Scale; [d] Attention Problems Scale; [e] Thought Problems Scale

Relationship	*ß*	*p-value* [a]	ΔR^2
FX FA → 18-month RTsu	-.42	< .01	.12[b]
SCR FA → 18-month RTsu	-.40	< .01	.12[b]
GCC FA → 18-month RTsu	-.29	.01	.07
SLF FA → 18-month RTsu	-.27	.03	.06

[a] *p*-value for beta coefficient controlling for covariates
[b] Significant model change (p<.05) after diffusion indices added to model

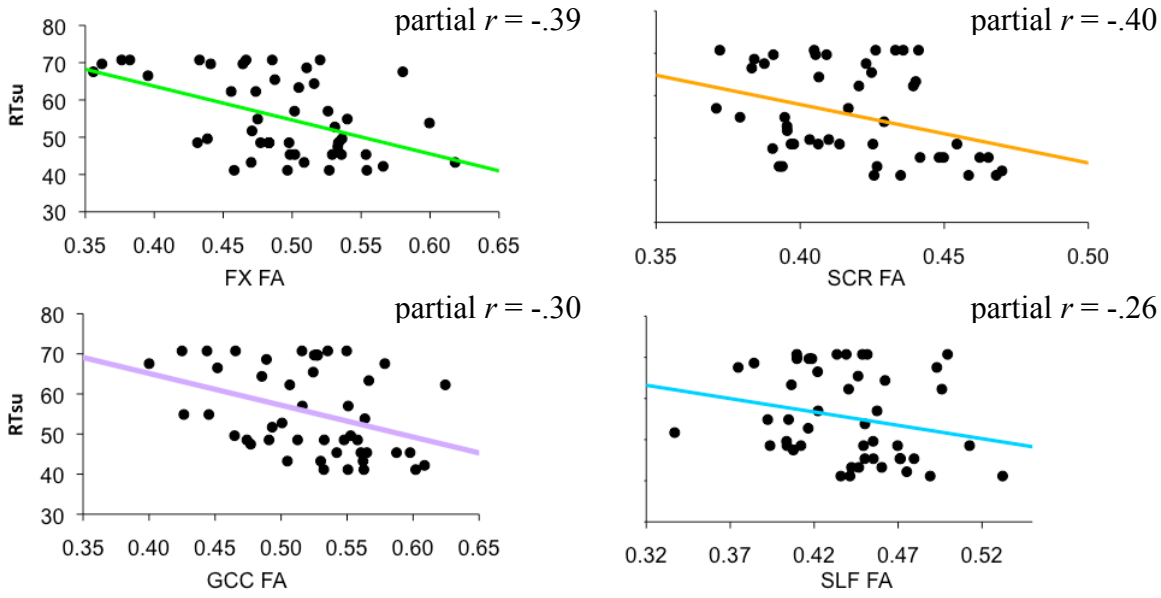


Figure 4. Direct relationships between baseline white matter integrity and 18-month **substance use** in the **user group** (partial *r* values take into account covariates as described above).

Notes: FX: fornix body; SCR: superior corona radiata; GCC: genu of corpus callosum; SLF: superior longitudinal fasciculus; FA: fractional anisotropy.

Relationship	*ß*	*p-value* [a]	ΔR^2
FX FA → 18-month RTns	-.26	.01	.07[b]
GCC MD → 18-month RTns	-.28	.03	.06
FOF RD → 18-month RTns	-.24	.03	.06

[a] *p*-value for beta coefficient controlling for covariates
[b] Significant model change ($p < .05$) after diffusion indices added to model

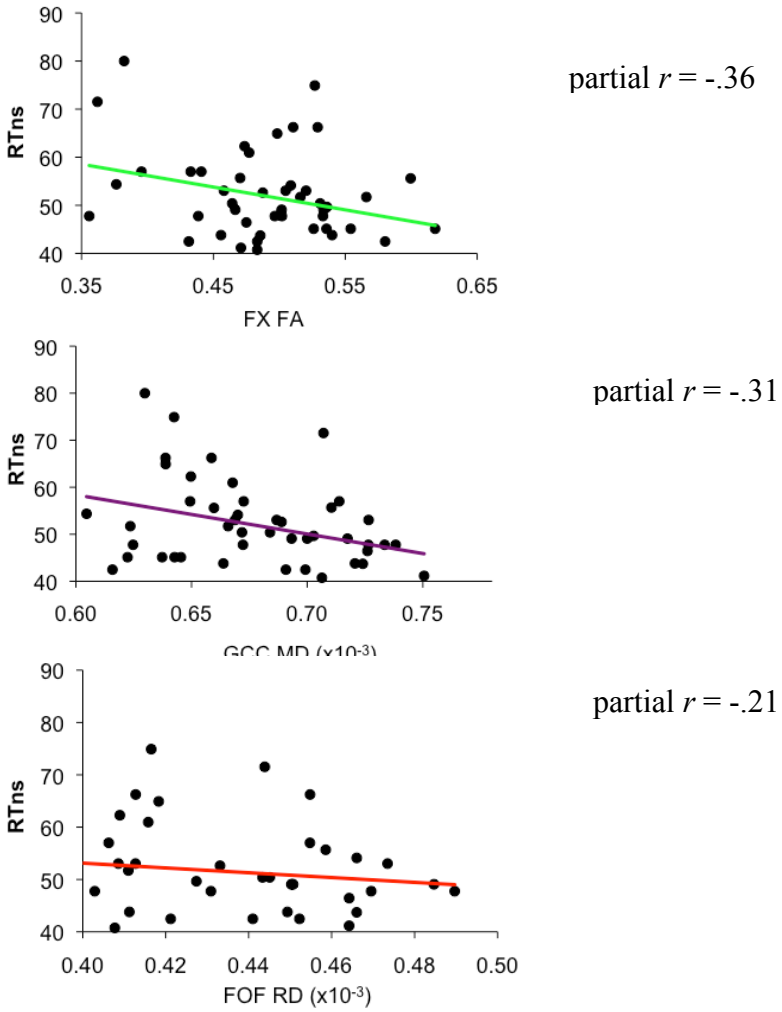


Figure 5. Direct relationships between baseline white matter integrity and 18-month **non-substance use risk taking behaviors** (RTns) in **user group** (partial *r* values take into account covariates as described above).

Notes: FX: fornix; GCC: genu of corpus callosum; FOF: fronto-occipital fasciculus; FA: fractional anisotropy; MD: mean diffusivity; RD: radial diffusivity.

Relationship	*ß*	*p-value* [a]	ΔR^2
FOF FA → Ex. Functioning	.28	.01	.06
FOF MD → Ex. Functioning	-.25	.03	.05
FOF RD → Ex. Functioning	-.30	.03	.06
SCR RD → Ex. Functioning	-.25	.04	.04

[a] *p*-value for beta coefficient controlling for covariates

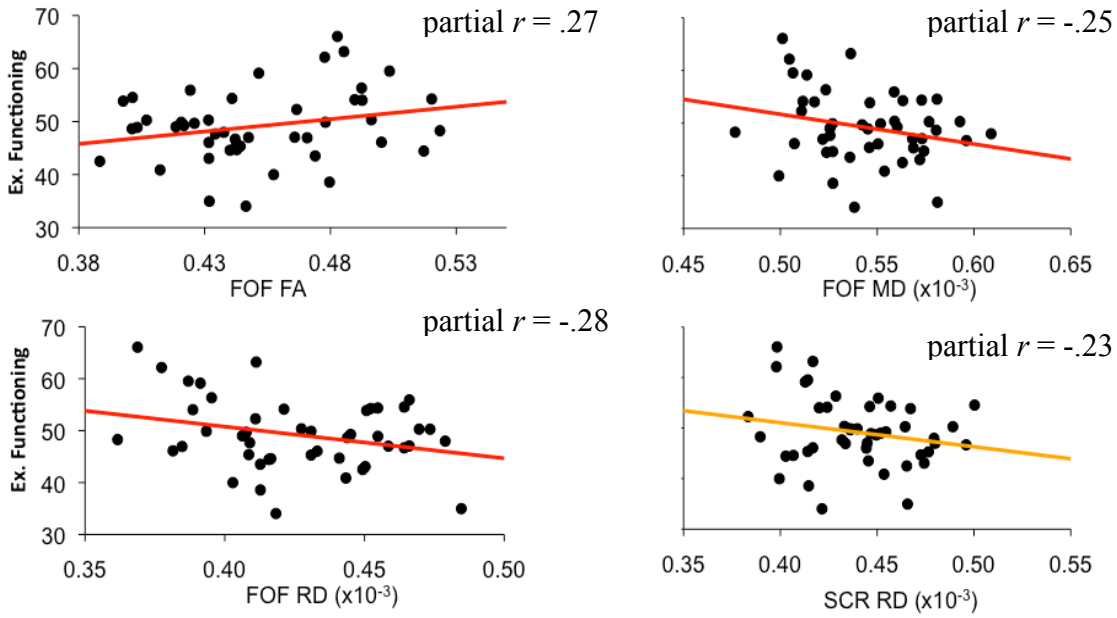
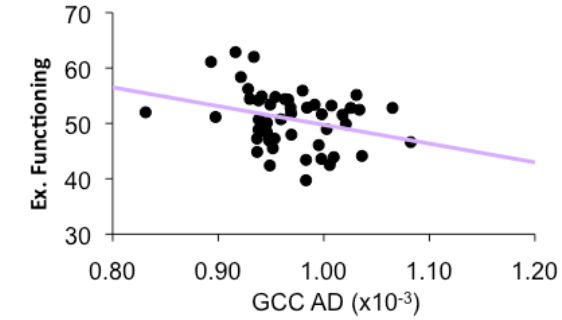


Figure 6. Direct relationships between baseline white matter integrity and baseline **neuropsychological performance** in the **user group** (partial *r* values take into account covariates as described above).

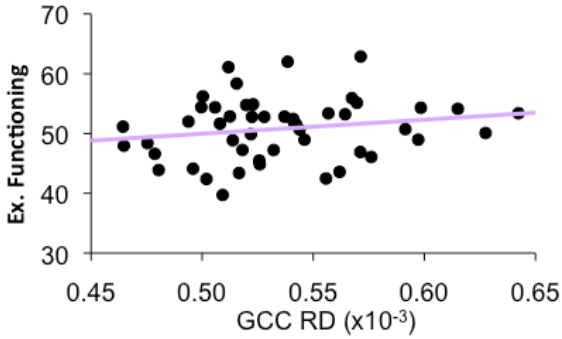
Notes: FOF: fronto-occipital fasciculus; SCR: superior corona radiata; FA: fractional anisotropy; MD: mean diffusivity; RD: radial diffusivity.

Relationship	*ß*	*p-value* [a]	ΔR^2
GCC AD → Ex. Functioning	-.27	.01	.06
GCC RD → Ex. Functioning	.22	.02	.05
FOF RD → Ex. Functioning	.29	.01	.08

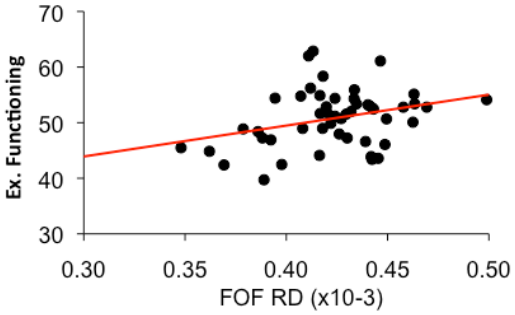
[a] *p*-value for beta coefficient controlling for covariates



partial *r* = -.27



partial *r* = -.23



partial *r* = .30

Figure 7. Direct relationship between baseline white matter integrity and baseline **neuropsychological performance** in the **control group** (partial *r* values take into account covariates as described above).

Notes: GCC: genu of corpus callosum; FOF: fronto-occipital fasciculus; AD: axial diffusivity; RD: radial diffusivity.

Table 4. Diffusion characteristics of participants (all *p*s > .05)

	CON (*n*=49) M (SD; Range)	**SU (*n*=47) M (SD; Range)**
FA FX	0.50 (0.05; 0.37-0.61)	0.49 (0.05; 0.35-0.61)
FA SCR	0.42 (0.02; 0.37-0.47)	0.41 (0.02; 0.37-0.47)
FA SLF	0.44 (0.02; 0.38-0.52)	0.44 (0.03; 0.33-0.53)
FA FOF	0.45 (0.03; 0.36-0.52)	0.45 (0.03; 0.36-0.52)
FA GCC	0.53 (0.04; 0.42-0.62)	0.52 (0.05; 0.42-0.62)
MD FX†	1.20 (0.21; 0.79-1.76)	1.13 (0.18; 0.80-1.68)
MD SCR†	0.56 (0.02; 0.52-0.62)	0.57 (0.02; 0.51-0.63)
MD SLF†	0.58 (0.02; 0.54-0.62)	0.58 (0.03; 0.53-0.69)
MD FOF†	0.54 (0.02; 0.49-0.61)	0.54 (0.03; 0.47-0.60)
MD GCC†	0.68 (0.03; 0.60-0.74)	0.67 (0.03; 0.60-0.75)
AD FX†	1.57 (0.17; 1.24-1.94)	1.50 (0.15; 1.20-1.88)
AD SCR†	0.82 (0.02; 0.76-0.89)	0.82 (0.03; 0.76-0.91)
AD SLF†	0.81 (0.02; 0.75-0.87)	0.82 (0.02; 0.75-0.88)
AD FOF†	0.77 (0.03; 0.71-0.90)	0.77 (0.04; 0.69-0.87)
AD GCC†	0.96 (0.04; 0.83-1.08)	0.96 (0.06; 0.84-1.11)
RD FX†	1.00 (0.23; 0.58-1.63)	0.93 (0.21; 0.56-1.55)
RD SCR†	0.43 (0.02; 0.39-0.49)	0.44 (0.02; 0.38-0.50)
RD SLF†	0.45 (0.02; 0.40-0.51)	0.47 (0.04; 0.41-0.59)
RD FOF†	0.42 (0.02; 0.34-0.49)	0.42 (0.03; 0.36-0.48)
RD GCC†	0.53 (0.04; 0.46-0.64)	0.52 (0.04; 0.43-0.62)

† All values 10^{-3}

Notes: FA: fractional anisotropy; MD: mean diffusivity; AD: axial diffusivity; RD: radial diffusivity; FX: body of fornix; SCR: superior corona radiata; SLF: superior longitudinal fasciculus; FOF: fronto-occipital fasciculus; GCC: genu of corpus callosum.