THE ROLE OF PERSONAL AND FAMILIAL ALCOHOL MISUSE IN TEMPORAL DECISION MAKING AND WHITE MATTER MICROSTRUCTURAL DEVELOPMENT DURING ADOLESCENCE

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A DISSERTATION

Presented to the Department of Behavioral Neuroscience

and the Oregon Health & Science University

School of Medicine

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

September 2018

School of Medicine

Oregon Health & Science University

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Abbreviations

AFNI – Analysis of Functional NueroImages
AIC – Akaike Information Criterion
ALIC – Anterior Limb of the Internal Capsule
ANOVA – Analysis of Variance
ANT – Advanced Normalization Tools
AUC – Area under the Curve
AUD – Alcohol Use Disorder
BIC – Bayesian Information Criterion
CC – Corpus Callosum
CFA – Confirmatory Factor Analysis
CFC – Consideration of Future Consequences
DWI – Diffusion Weighed Imaging
FA – Fractional Anisotropy
FHD – Family History Density
FHN – Family History Negative
FHP – Family History Positive
FOQ – Future Orientation Questionnaire
FSL – FMRIB Software Library
IFOF – Inferior Fronto-Occipital Fasciculus
ILF – Inferior Longitudinal Fasciculus
IQ – Intelligence Quotient
LL – log-likelihood
ML – Maximum Likelihood
MNI – Montreal Neurological Institute
MRI – Magnetic Resonance Imaging
OLS – Ordinary Least Squares
NAc – Nucleus Accumbens
PLIC – Posterior Limb of the Internal Capsule
QA – Quality Assessment
RT – Reaction Time
SES – Socioeconomic Status
SFG – Superior Frontal Gyrus
SLF – Superior Longitudinal Fasciculus
SN – Substantia Niagra
VTA – Ventral Tegmental Area
ZTPI – Zimbardo Time Perspective Inventory

Acknowledgements

First and foremost, the deepest of gratitude and thanks goes to my mentor, Dr. Bonnie Nagel. Without her unfaltering support and encouragement I would have never made it through the first year of graduate school, let alone accomplish all of this work. Not only has Bonnie helped me design, execute and publish the work of this dissertation, but she has also provided me with limitless career and life advice that has and will continue to serve me well. She is an exemplar in what it is to be a mentor and scientist and I look forward to continuing my work with her.

I would like to express gratitude to my dissertation advisory committee, Dr. Suzanne Mitchell, Dr. Sarah Feldstein Ewing, and Dr. William Hoffman, for their time and guidance throughout my dissertation. Also, thanks to Dr. Sarah Karalunas for joining my oral examination committee and proving feedback on my dissertation manuscript. Dr. Mitchell is also deserved of a special thank you for introducing me to the world of temporal discounting and for providing a tremendous amount of support during the design and implementation of the discounting tasks utilized in this dissertation.

I would like to also acknowledge all members of the Developmental Brain Imaging Lab, past and present, who assisted with various aspects of this project. I am especially grateful for Hannah Scheuer, Sarah Alberti and Kristina Hernandez for their help with recruitment, data collection and data management, and Jesse Chiem and Gareth Harman for their technical support. I have also been fortunate enough to share an office with several outstanding people, Dr. Anita Cservenka, Dr. Gabriela Alarcón, Dr. Angelica Morales, Dr. Stephen Boyd, and Jordan Lueras, all of whom have provided a welcoming environment for critical discussion of this project. I would also like to acknowledge the Advance Imaging Research Center at OHSU for their support of the neuroimaging in this project, with special thanks to Daniel Schwartz for providing consultation on issues surrounding data processing. Further, I would also like to thank Dr. Joel Steele at Portland State University for this statistical consultation on this project.

This work would not have been possible without the participation of the many families in the Portland area who graciously offered up their time and energy for this study, and the various agencies and fellowships that funded myself and this research, including the National Institute on Alcohol Abuse and Alcoholism (R01 AA017664 to B.N. and T32 AA007468), OHSU Tartar Trust Research Fellowship (S.A.J.), Behavioral Neuroscience Ashworth Graduate Training Award (S.A.J.), American Psychological Association Dissertation Research Award (S.A.J.), and the ARCS Foundation Portland Chapter (S.A.J.).

Lastly, I would like to thank my friends and family whose names and contributions to my life could fill a whole book. My successes in life are all a testament to your love and support and for that I will forever be grateful.

Abstract

Adolescence is a time of significant neurobiological development and is characterized by many social, environmental, and behavioral changes. It is also a period of heightened risk-taking behavior, including the decision to drink. With up to 70% of adolescents having experimented with alcohol by the end of high school, understanding the neurobiological and behavioral processes that underlie adolescent decision making, such as the decision to drink, is crucial to the development of future intervention and prevention strategies targeted at youth. One significant predictor of future alcohol misuse is a family history of alcoholism. In adolescence, both personal and familial alcohol misuse have been shown to be associated with structural alterations in the brain, as well as greater impulsive choice – a temporal facet of decision making. Despite singular associations, the ways in which personal and familial alcohol misuse interact to alter brain structure, impulsive responding, and other temporal facets of decision making, such as the appreciation for future consequences, is unclear. Further, the persistence of these documented associations across adolescence, remains underexplored.

In this dissertation, a monetary gain discounting paradigm was used to investigate the interactive role that both personal and familial alcohol misuse play in the longitudinal development of impulsive choice across adolescence. Meanwhile, diffusion weighted imaging was used to investigate the interactive role of personal and familial alcohol misuse in the longitudinal development of fraction anisotropy, a measure of white matter microstructural maturation, across adolescence. Finally, a unique construct of decision making, the appreciation of future consequences, was assessed using self-report measures as well as a monetary loss discounting paradigm. The association between future

orientation and fractional anisotropy was assessed, as were the effects of personal and familial alcohol misuse on future orientation and the appreciation of future consequences.

These investigations suggested that early in adolescence, family history density of alcoholism was associated with greater impulsive choice, and lower fractional anisotropy in the superior frontal gyrus in all adolescents. However, this association with familial alcoholism dissipated by mid-to-late-adolescence for both impulsive choice (controls only) and fractional anisotropy (binge drinkers and controls). Meanwhile, adolescents who went on to binge drink, demonstrated comparable levels of impulsive choice as those who did not, at baseline, but failed to demonstrate the age-related decline in impulsive choice, shown by adolescents who remained largely alcohol-naïve. Finally, binge-drinking adolescents also demonstrated persistently greater fractional anisotropy in the posterior limb of the internal capsule throughout adolescence and lower future orientation and appreciation for future consequences in late-adolescence, with greater fractional anisotropy in the posterior limb of the internal capsule being associated with greater impulsive choice, throughout adolescence, and reduced future orientation in late-adolescence. Together, these findings suggest time-limited effects of familial alcoholism on both fractional anisotropy and impulsive choice in adolescence, while providing important neurobiological targets for future intervention and prevention strategies in binge-drinking adolescents.

Chapter 1. Introduction

(Portions of this chapter have been published in *Alcohol Research: Current Reviews* and *Birth Defects Research: Reviews*)

1.1 Defining adolescence

Adolescence can be loosely defined as the transitional stage between childhood and adulthood. It is a period of life associated with a myriad of social and environmental changes, including spending less time with parents and more time with peers, and a gaining of autonomy (Steinberg and Morris 2001). Associated with this, is an increase in risk-taking behavior and pattern of decision making that results in greater instances of substance use, risky sexual activity, unintentional injuries and other negative health consequences for many youth (Casey, Jones et al. 2008). While it is widely accepted that adolescence begins around the onset of puberty, when the activation of pubertal hormones trigger significant physical, psychological, and neurobiological changes (Blakemore, Burnett et al. 2010), the end of adolescence is less defined. Often characterized by a gaining of independence and a stable adult role, the end of adolescence is both highly culturally-dependent and prone to immense individual variability, with a delaying of traditional adult responsibilities becoming an emergent trend in contemporary societies (Furstenberg 2000). However, one thing is clear, neurobiological studies have repeatedly demonstrated continued neurodevelopment well into the third decade of life (Sowell, Thompson et al. 2001, Shaw, Kabani et al. 2008, Ostby, Tamnes et al. 2009, Giorgio, Watkins et al. 2010, Tamnes, Ostby et al. 2010, Lebel and Beaulieu 2011).

1.2 Structural neurodevelopment during adolescence

A wealth of studies using magnetic resonance imaging (MRI) have described both linear decreases and nonlinear changes in cortical and subcortical gray-matter volume and cortical thickness (Giedd, Blumenthal et al. 1999, Gogtay, Giedd et al. 2004, Shaw,

Kabani et al. 2008, Ostby, Tamnes et al. 2009, Giorgio, Watkins et al. 2010, Tamnes, Ostby et al. 2010, Pfefferbaum, Rohlfing et al. 2016). However, this development does not take place uniformly across the brain, but occurs in a region-specific manner, with sensory and motor cortices demonstrating peaks in gray matter volume and thickness earlier than regions necessary for higher executive function, such as the prefrontal cortex (Sowell, Thompson et al. 2001, Gogtay, Giedd et al. 2004, Shaw, Kabani et al. 2008). Further, the prefrontal cortex, also demonstrates protracted development compared to subcortical limbic structures (e.g. striatum and amygdala), important for emotion and reward processing (Mills, Goddings et al. 2014). While some have hypothesized that adolescent neurodevelopment is adaptive and renders adolescents capable of initiating behaviors important for survival (Sercombe 2014), prevailing literature suggest that the asynchronous development of the prefrontal cortex and emotional and reward circuitry results in increased risk-taking behavior, including alcohol use, during adolescence (Spear 2000, Crews, He et al. 2007).

Accompanying these changes in gray matter are widespread volumetric increases in white matter across adolescence (Giedd, Blumenthal et al. 1999, Giorgio, Watkins et al. 2010, Tamnes, Ostby et al. 2010, Lebel and Beaulieu 2011, Pfefferbaum, Rohlfing et al. 2016). Underlying these increases in white matter volume are changes in the microstructural properties of white matter fibers. Diffusion Weighted Imaging (DWI) is a structural MRI technique that indirectly characterizes the direction of water diffusion in the brain, in order to draw conclusions about the microstructural properties of white matter. One of the most common measurements obtained from DWI is fractional anisotropy (FA), a measurement of the degree of anisotropic (i.e. unidirectional) water

movement, which is thought to be a reflection of greater fiber density, axonal diameter, and myelination (Hagmann, Jonasson et al. 2006). Widespread linear increases in FA across adolescence have been repeatedly demonstrated (Barnea-Goraly, Menon et al. 2005, Giorgio, Watkins et al. 2010, Pfefferbaum, Rohlfing et al. 2016), with some studies suggesting that these changes may be non-linear, with peaks in FA occurring during late adolescence/young adulthood in a region-specific manner (Tamnes, Ostby et al. 2010, Lebel and Beaulieu 2011). A greater understanding of the microstructural development of white matter is crucial, as increases in FA across adolescence have been shown to be associated with several developing executive control processes, including lower impulsivity (Olson, Collins et al. 2009, Achterberg, Peper et al. 2016), greater inhibitory control (Seghete, Herting et al. 2013), and greater working memory capacity (Nagy, Westerberg et al. 2004). More importantly, FA has been shown to be a modifiable neurobiological feature during the treatment of various neurobiological disorders and cognitive impairments (Trivedi, Gupta et al. 2008, Keller and Just 2009, Prosperini, Fanelli et al. 2014). Therefore, a better understanding of the microstructural development of white matter and its relation to decision making, including the decision to binge drink during adolescence, is crucial for developing targeted intervention strategies for youth.

1.3 Binge drinking and structural neurodevelopment

Binge drinking is a pattern of alcohol use that raises a person's blood alcohol concentration to at least 0.08 grams percent, which amounts to consuming approximately 5 alcoholic drinks for men and 4 alcoholic drinks for women in about 2 hours (NIAAA 2004), and is the most common pattern of alcohol consumption in adolescents and young

adults. Recent reports suggest that 1.5 million adolescents ages 12–17 (6.1 percent) and 13.2 million young adults ages 18–25 (37.7 percent) in the United States reported binge drinking (SAMHSA 2015), with approximately 16% of high school seniors reporting binge drinking within the last two weeks (Johnston, O'Malley et al. 2016). Although binge drinking alone is insufficient to meet criteria for an alcohol use disorder (AUD) diagnosis, this pattern of alcohol misuse has been associated with neurobiological changes, as well as an increased risk of developing an AUD later in life (DeWit, Adlaf et al. 2000).

Binge drinking during adolescence has been associated with both greater (Howell, Worbe et al. 2013, Doallo, Cadaveira et al. 2014) and lesser (Howell, Worbe et al. 2013, Mashhoon, Czerkawski et al. 2014, Kvamme, Schmidt et al. 2016, Pfefferbaum, Rohlfing et al. 2016) gray matter volume and cortical thickness, particularly in frontal and striatal regions important for decision making. Recent longitudinal studies have been crucial in revealing the temporal nature of these changes, particularly given the non-linear development of gray matter volume and thickness. These studies have found that binge-drinking adolescents demonstrate reduced gray matter volumes and thickness prior to alcohol use initiation (Squeglia, Rinker et al. 2014, Whelan, Watts et al. 2014, Squeglia, Tapert et al. 2015) and show accelerated gray matter declines compared to alcohol-naïve controls (Luciana, Collins et al. 2013, Squeglia, Rinker et al. 2014, Whelan, Watts et al. 2014, Squeglia, Tapert et al. 2015). Similarly, when compared to alcohol-naïve controls, binge-drinking adolescents show reduced white-matter volume both before (Squeglia, Rinker et al. 2014) and following initiation of binge drinking (Luciana, Collins et al. 2013, Squeglia, Tapert et al. 2015).

While volumetric findings in binge-drinking adolescents, particularly in longitudinal studies, have been fairly parsimonious, varied differences in white-matter microstructure have been observed between binge-drinking adolescents and non-alcohol-using controls. First, a cross-sectional study found that binge-drinking adolescents had lower FA than control subjects in the corpus callosum (CC), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), anterior corona radiata, posterior corona radiata, posterior limb of the internal capsule (PLIC), external capsule, fornix and cerebellar peduncles (McQueeny, Schweinsburg et al. 2009). Similarly, in a second cross-sectional study, binge-drinking adolescents had lower FA than control subjects in the CC, SLF, ILF, cerebral peduncles, temporal-thalamic tract, occipital-frontal tract, and white matter regions of postcentral, superior temporal and inferior frontal gyri, with reduced FA in several of these regions associated with greater lifetime alcohol use (Bava, Frank et al. 2009). Conversely, the investigators also noted three regions, the SLF, anterior limb of the internal capsule (ALIC) and white matter regions of the occipital lobe, where FA was *greater* in binge-drinking adolescents than control subjects, and found that greater FA in these regions was associated with greater lifetime alcohol use (Bava, Frank et al. 2009). Finally, a third cross-sectional study found that binge-drinking adolescents, again, had lower FA than control subjects in the ILF, SLF, superior corona radiata, inferior fronto-occipital fasciculus (IFOF), and cerebellar peduncle; however, greater number of lifetime drinks was again associated with *greater* FA in the SLF (Jacobus, McQueeny et al. 2009).

Longitudinal studies of FA have attempted to reconcile this discrepancy, and have demonstrated that compared with control subjects, adolescent binge drinkers showed

significantly diminished normative increases in FA between baseline and follow-up visit in the dorsal caudate and IFOF (Luciana, Collins et al. 2013), and reduced FA in the CC, prefrontal thalamic fibers, and posterior corona radiata at follow-up, with no differences reported at baseline (Bava, Jacobus et al. 2013). Furthermore, a pair of studies examined FA in a group of adolescents with a history of binge drinking for at least 3 years and found that when compared to controls, binge-drinking adolescents showed significant, widespread declines in FA during this time (Jacobus, Squeglia et al. 2013), and that lower FA in the fornix and superior corona radiata at baseline predicted greater subsequent use at a year and a half follow-up visit, above and beyond baseline substance use (Jacobus, Thayer et al. 2013). Taken together, these findings suggest that binge drinking is largely associated with reduced FA throughout adolescence. However, conflicting findings, in regions such as the SLF and internal capsule, support the exploration of additional relevant variables, such as family history of alcoholism, as it has been previously suggested that personal and familial alcoholism interact to predict the severity of impairments in FA (Hill, Terwilliger et al. 2013).

1.4 Family history and structural neurodevelopment

It has been repeatedly demonstrated that family history of alcoholism is a significant risk factor associated with the development of AUDs (Schuckit, Goodwin et al. 1972, Goodwin 1985, Cloninger, Sigvardsson et al. 1986), and results in a three-to-five fold increase in the likelihood of developing an AUD (Cotton 1979). It has been estimated that roughly a quarter of adolescents in the United States have some degree of familial alcoholism (Grant 2000), with a greater density of familial alcoholism being

associated with a higher risk of AUD (Hill and Yuan 1999). While there are several ways of classifying individuals with a family history of alcoholism, most previous studies compare individuals who have at least one first degree relative with an AUD (family history positive; FHP) to individuals with no familial alcoholism (family history negative; FHN) or classify adolescents as high-risk or low-risk, based on whether they do or do not have multigenerational AUDs in their family.

Several studies have demonstrated volumetric alterations associated with familial alcoholism in adolescents with varying degrees of personal alcohol use. When compared to low-risk adolescents, high-risk adolescents had smaller amygdala (Hill, De Bellis et al. 2001, Hill, Wang et al. 2013), orbitofrontal cortex (Hill, Wang et al. 2009, Sharma and Hill 2017), inferior temporal gyrus, and insula (Sharma and Hill 2017) volumes, and greater cerebellum volumes (Hill, Muddasani et al. 2007, Hill, Wang et al. 2011). However, all of these studies were confounded by the fact that high-risk adolescents had greater rates of substance use than low-risk adolescents. Meanwhile, a recent study in largely drug- and alcohol-naïve adolescents, found that FHP adolescents had thinner medial and lateral orbitofrontal and superior parietal cortices compared to FHN adolescents, with the stronger difference present in early-adolescence, suggesting the association between family history of alcoholism and brain structure may be transient (Henderson, Vaidya et al. 2018).

In regards to white matter microstructure, three studies have been conducted in largely alcohol- and substance-naïve adolescents. First, relative to FHN adolescents, FHP adolescents have been shown to have lower FA in the superior, posterior, and anterior corona radiata, SLF, ALIC, IFOF, and superior fronto-occipital fasciculus (Herting,

Schwartz et al. 2010, Acheson, Wijtenburg et al. 2014), with the density of family alcoholism being negatively associated with FA in corona radiata, superior fronto-occipital fasciculus, and posterior thalamic radiation (Acheson, Wijtenburg et al. 2014). Conversely, relative to FHN adolescents, FHP adolescents have been shown to have greater FA in the SLF, ILF ALIC, anterior thalamic radiation, posterior corona radiata, and the body of the CC (Squeglia, Jacobus et al. 2014). Further, while cross-sectional reports suggest the effects of familial history on FA are stronger in adolescents than young adults (Acheson, Wijtenburg et al. 2014), no studies have longitudinally investigated the development of FA in adolescents with familial alcoholism, therefore it is unclear if these alterations in FA are persistent characteristics of familial alcoholism or represent transient, time-limited alterations in FA. Additionally, a previous study with an *a priori* region of interest, found that familial alcoholism may interact with personal alcohol use to predict more severe reductions in FA in the SLF and ILF (Hill, Terwilliger et al. 2013); however, whole-brain analyses are needed to confirm these results. This dissertation seeks to provide longitudinal insight into the effects of familial alcoholism on FA and explores this association in the context of personal alcohol use.

1.5 Risk taking and temporal decision making during adolescence

In addition to significant neurodevelopment, adolescence is characterized by many behavioral changes, including increases in executive functioning, emotional processing, working memory, mental flexibility, and behavioral inhibition with age (Luciana, Conklin et al. 2005, Crone, Bunge et al. 2006, Sullivan, Brumback et al. 2016). In support of the dual process model and the developmental mismatch of frontal-limbic

neurocircuitry, described previously (Mills, Goddings et al. 2014), adolescents also demonstrate increased risk-taking behavior (Eaton, Kann et al. 2012), which may partially explain why nearly 70% of adolescents have experimented with alcohol by the end of high school (Johnston, O'Malley et al. 2016). However, some hypothesize that the same developing neurobiological and behavioral processes that render an adolescent vulnerable to increased risk taking and substance use, may also provide an adaptive framework to help reduce risk taking and alcohol misuse later in adulthood (Cousijn, Luijten et al. 2018). As such, additional longitudinal work is necessary to understand the emergence and development of alcohol use in adolescence, and how it relates to the development of neurobiological and behavioral constructs of risk-taking behavior.

Risk taking is a complex behavior that may be composed of several separate but related constructs, including impulsive decision making, sensation seeking, behavioral inhibition, temperamental characteristics (e.g. negative affect), and genetic and environmental susceptibilities (Feldstein and Miller 2006). For example, during adolescence, there are age-related increases in self-reported sensation seeking and impulsivity; however, the correlation between these two constructs is non-significant, with substantial individual differences present (Harden and Tucker-Drob 2011). Additionally, the method of assessment may impact findings surrounding adolescent risk taking. For example, behavioral measures of risk-taking behavior (e.g. the balloon analogue risk task) have been shown to account for a significant amount of unique variance in real-world risk taking above and beyond self-reported measures alone (Aklin, Lejuez et al. 2005). Furthermore, the neurobiological underpinnings of risk taking may vary based on the form of risk-taking behavior (e.g. risky sexual activity vs. substance

misuse) (Feldstein Ewing, Ryman et al. 2016). Together, this highlights the importance of understanding individual constructs of adolescent risk taking, how they relate to specific behaviors (e.g. binge drinking), the neurobiological features associated with them, and the timing and temporal nature of these developmental processes.

When making the decision to drink, adolescents tend to do so with the potential for both immediate gains (e.g. subjective effects and acceptability among peers) and losses (e.g. getting in trouble with their parents/law) in mind. However, what adolescents often neglect to consider are long-term outcomes, particularly delayed negative consequences (e.g. health complications or AUD) associated with alcohol use. Self-report measures suggest that time perspective, as well as the capacity to plan ahead and show appreciation for future consequences, all increase across adolescence (Steinberg, Graham et al. 2009). The temporal nature surrounding the decision to drink (e.g. impulsive responding for immediate rewards or the devaluing of future consequences), is one component of risk taking that may partially explain adolescents' willingness to engage in binge drinking, despite the known risk associated with such behavior.

One behavioral model often used to look at delayed outcomes in decision making is intertemporal delay discounting. The most commonly employed version, gain discounting, sheds light on adolescents' tendency to discount larger future gains in favor of smaller immediate rewards and is often considered to be a measure of impulsivity or impulsive choice. Using this paradigm, impulsive choice has been shown to decrease during adolescence into young adulthood (Olson, Hooper et al. 2007, Steinberg, Graham et al. 2009, Water, Cillessen et al. 2014, Achterberg, Peper et al. 2016). Furthermore, this decrease in impulsive choice has been shown to be associated with white matter

microstructural maturation, particularly in frontal-limbic circuitry (van den Bos, Rodriguez et al. 2014, van den Bos, Rodriguez et al. 2015, Achterberg, Peper et al. 2016, Hampton, Alm et al. 2017). In a longitudinal study of white matter microstructure in adolescents, greater FA in several fronto-striatal white matter tracts was associated with a decrease in impulsive choice across adolescence (Achterberg, Peper et al. 2016). Similarly, using probabilistic tractography, greater medial striatal to dorsolateral prefrontal connectivity has been associated with less impulsive choice in young adults (van den Bos, Rodriguez et al. 2014), as well as adolescents (van den Bos, Rodriguez et al. 2015). However, this relationship remains somewhat unclear, as another study found that the structural connectivity between the ventral striatum and ventromedial prefrontal cortex was associated with greater impulsive responding in young adults (Hampton, Alm et al. 2017). Given this discrepancy in the directionality of the association between impulsive decision making and white matter microstructure, this dissertation seeks to expand upon this literature via a longitudinal whole-brain analyses of FA in adolescents with and without personal and familial alcohol misuse.

A lesser used version of intertemporal delay discounting paradigm, loss discounting, helps to address a different, but very important potential facet of decision making, the appreciation of delayed consequences, which develops across adolescence (Steinberg, Graham et al. 2009), and may uniquely influence the decision to drink. In fact, previous literature in adults suggests that loss discounting behavior differs significantly from that of gain discounting (Mitchell and Wilson 2010, Appelt, Hardisty et al. 2011, Han and Takahashi 2012, Hardisty, Appelt et al. 2013). Additionally, functional MRI studies have revealed greater neural activation during the discounting of

losses compared to gains in numerous prefrontal, parietal and subcortical brain regions (Xu, Liang et al. 2009), including networks that continue to develop during adolescence (Lenroot and Giedd 2006, Mills, Goddings et al. 2014) and have been shown to be particularly vulnerable to the neurotoxic effects of alcohol (Philpot, Wecker et al. 2009, Koss, Sadowski et al. 2012). While loss discounting behavior has never been assessed in an adolescent population, a previous study of risk taking in adolescence demonstrated that perceived risks affect risk-taking behavior more than perceived benefits (Rolison and Scherman 2002). Together, these findings suggest that the appreciation of future consequences may be a unique component of adolescent risk taking that may contribute to an adolescents' propensity to engage in binge drinking and warrants further investigation. This dissertation not only seeks to better characterize loss discounting behavior and the appreciation of future consequences, but it also seeks to investigate the association between white matter microstructure and these behaviors.

1.6 Effects of binge drinking on temporal decision making

While binge drinking during adolescence has been associated with impaired, or riskier, decision making (Goudriaan, Grekin et al. 2007) and decreased inhibition (Sanhueza, Garcia-Moreno et al. 2011), little research has been conducted into the association between binge drinking and the temporal components of decision making. Two studies, using a delayed gain discounting task, reported that binge-drinking adolescents demonstrated greater impulsive responding for alcohol (Field et al. 2007) and monetary (Sullivan, Brumback et al. 2016) rewards, compared to light drinkers. However, these cross-sectional reports fail to address the question of whether greater

impulsive responding predates initiation of binge drinking or result as a consequence of alcohol use itself. Further, it is unclear whether these observed greater rates of impulsive choice persist throughout adolescence in those who drink, or whether this behavioral phenomenon dissipates as adolescents show adaptive improvements in executive control. Similarly, using self-report measures, a previous study reported that binge drinking was associated with lower future time perspective in adolescents and young adults (Keough, Zimbardo et al. 1999). However, a thorough investigation into the association between binge drinking and the appreciation of future consequences has yet to be conducted in adolescents. This dissertation seeks to address these two areas of limitation, by longitudinally investigating the association between future binge drinking and impulsive choice, and by more rigorous assessment of the appreciation of future consequences via both self-report and behavioral measures in binge-drinking adolescents and controls.

Neuroimaging studies have helped shed some light on the mechanisms underlying this increase in risk taking and impulsivity in binge-drinking adolescents. Structurally, greater impulsivity in adolescent binge drinkers has been shown to be associated with smaller dorsolateral prefrontal cortex and inferior parietal lobule volumes and greater dorsal cingulate and precuneus volumes (Banca, Lange et al. 2015), whereas reduced FA in the fornix of binge-drinking adolescents has been shown to predict greater amounts of risky behavior a year and a half later (Jacobus, Thayer et al. 2013). This dissertation seeks to extend upon these findings via investigation of alcohol's effects on the association between impulsive choice and appreciation for future consequences and FA during adolescence.

1.7 Effects of family history on temporal decision making

In addition to FHP adolescents demonstrating reduced behavioral inhibition, another potential facet of risk-taking behavior (Nigg, Glass et al. 2004, Saunders, Farag et al. 2008), when compared to FHN adolescents, several studies have investigated the effects of family history status on temporal decision making. Using a gain discounting task, studies in largely drug- and alcohol-naïve adolescents and young adults found that FHP individuals made more impulsive choices (Acheson, Vincent et al. 2011, Dougherty, Charles et al. 2014, Henderson, Vaidya et al. 2018) than FHN individuals. In another study, FHP and FHN individuals showed no difference in impulsive responding, but FHP adolescents had significantly slower reaction times (RTs), than FHN adolescents, suggesting a greater difficulty in making these temporal reward-based decisions (Herting, Schwartz et al. 2010). Despite this rather parsimonious body of literature, all of these studies are cross-sectional and fail to assess whether this association between family history and impulsive choice persists throughout adolescence. A longitudinal investigation in early- to mid-adolescence found that the effect of familial history of alcoholism on impulsive choice dissipated by mid-adolescence (Dougherty, Lake et al. 2015). Thus, this dissertation seeks to longitudinally examine the development of impulsive choice across a wide age-range of adolescents, in order to gain a better understanding of this window of vulnerability associated with familial alcoholism. Additionally, the association between family history of alcoholism and the appreciation of future consequences remains unknown, and will be explored in this dissertation.

Regarding neurobiological development, lower FA in the ILF has been shown to mediate the relationship between FH status and slower RTs (Herting, Schwartz et al.

2010), while in FHN adolescents there appears to be a negative association between impulsive choice and parietal lobe thickness (Henderson, Vaidya et al. 2018). While these findings are limited, group differences in behavioral inhibition between FHP and FHN adolescents (Nigg, Glass et al. 2004, Saunders, Farag et al. 2008) have also been shown to be related to global white matter volume (Silveri, Tzilos et al. 2008). Together, these findings suggest that alterations in white matter may at least partially underlie the effect of family history on adolescent temporal decision making; however, how this pertains to consideration for future consequences, and how this effect may vary based on personal binge drinking is unclear and are questions this dissertation seeks to address.

1.8 Summary

In summation, previous literature demonstrates that during adolescence, there are behavioral decreases in impulsive decision making (as measured using gain discounting paradigms) (Olson, Hooper et al. 2007, Steinberg, Graham et al. 2009, Water, Cillessen et al. 2014, Achterberg, Peper et al. 2016) and self-reported increases in future orientation and consideration for future consequences (Steinberg, Graham et al. 2009), two potentially unique facets of decision making. Associated with changes in impulsive choice are significant underlying neurodevelopmental changes, specially increases in frontal-limbic white matter microstructure (as measured using FA) with age (van den Bos, Rodriguez et al. 2014, van den Bos, Rodriguez et al. 2015, Achterberg, Peper et al. 2016, Hampton, Alm et al. 2017). However, the association between FA and the appreciation of future consequences remains unexplored. Further, alterations in FA have been repeatedly demonstrated in both binge-drinking adolescents (Bava, Frank et al.

2009, Jacobus, McQueeny et al. 2009, McQueeny, Schweinsburg et al. 2009, Bava, Jacobus et al. 2013, Jacobus, Squeglia et al. 2013, Jacobus, Squeglia et al. 2013, Luciana, Collins et al. 2013), as well as those with a family history of alcoholism (Herting, Schwartz et al. 2010, Acheson, Wijtenburg et al. 2014, Squeglia, Jacobus et al. 2014), compared to alcohol-naïve adolescents without a family history. However, the temporal nature of these findings requires greater exploration, as some studies support the notion of a positive feedback loop, with neurobiological differences prior to alcohol use that are subsequently exacerbated (Squeglia, Rinker et al. 2014, Whelan, Watts et al. 2014, Squeglia, Tapert et al. 2015), while other studies suggest that the risk associated with familial alcoholism and its effect on neurobiology may be time-limited and dissipate as adolescents "age-out" of this vulnerable window (Acheson, Wijtenburg et al. 2014, Henderson, Vaidya et al. 2018). A better understanding of the potential interactive effect of both personal and familial alcohol misuse, may provide additional clarity. Similarly, while both personal and familial alcohol misuse are associated with impaired impulsive choice (Field, Christiansen et al. 2007, Herting, Schwartz et al. 2010, Acheson, Vincent et al. 2011, Dougherty, Charles et al. 2014, Sullivan, Brumback et al. 2016), whether this persists throughout adolescence, and whether this precedes initiation of binge-drinking or is as a consequence of it, is not certain. The association between personal and familial alcohol misuse and the appreciation of future consequences has also not been investigated and may help provide novel insight into adolescents' decision to drink.

1.9 Dissertation aims

Given previous findings, this dissertation seeks to address three specific aims: 1) Chapter 3 investigates the interactive role that both personal and familial alcohol misuse

play in the development of impulsive choice across adolescence. 2) Chapter 4 investigates the interactive role that both personal and familial alcohol misuse play in the development of FA across adolescence, and whether alterations in FA mediate the relationship between personal/familial alcohol misuse and the development of impulsive choice. 3) Chapter 5 investigates the interactive role of both personal and familial alcohol misuse on future orientation and the appreciation of future consequences and assess whether future orientation is associated with FA in adolescents with and without personal and familial alcohol misuse. Specific hypotheses for each aim are included in the introduction section of Chapters 3-5.

Chapter 2. General approach

(Portions of this chapter have been published in *Addiction* and *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*)

2.1 Participant recruitment and exclusionary criteria

Adolescent participants, aged 10-16 at baseline (n = 153), were recruited from the local community (Portland, OR and surrounding suburbs), as part of an ongoing longitudinal study on adolescent neurodevelopment. Following a telephone prescreen to determine initial eligibility, adolescents and their parents provided written consent and assent, respectively, followed by participation in separate comprehensive screening interviews. As the goals of the ongoing longitudinal study are to investigate the emergence of mental illness and psychopathology during development, baseline exclusionary criteria included a likely diagnosis of a DSM-IV psychiatric disorder [Diagnostic Interview Schedule for Children Predictive Scales (Lucas, Zhang et al. 2001)], serious medical problems (including head trauma), mental retardation or learning disability, psychotic illness in a biological parent, known prenatal drug and/or alcohol exposure, left-handedness [Edinburgh Handedness Inventory (Oldfield 1971)], MRI contraindications, and inability to obtain family history information. Adolescents were also excluded at baseline if they endorsed prior drug and alcohol use that exceeded >10 lifetime alcohol drinks, >2 drinks on any one occasion, >5 uses of marijuana, >4 cigarettes per day, or any other drug use [Brief Lifetime version of the Customary Drinking and Drug Use Record (Brown, Myers et al. 1998)].

2.2 Baseline participant characterization

Socioeconomic status

Previous studies have demonstrated that lower socioeconomic status (SES) is associated with impairments in future orientation (Nurmi 1987), and behavioral inhibition

(Spielberg, Galarce et al. 2015), in adolescence. Therefore, to assess SES, adolescents' parents completed the Hollingshead Index of Social Position, a measure based on the educational attainment and occupation of each parent (Hollingshead and Redlich 1958). Education and occupation scores range from 1 to 7, with 1 specifying attainment of a professional degree or professional occupation and 7 specifying less than seven years of education or unskilled work. To calculate a final score, occupation scores are multiplied by 7 and education scores are multiplied by 4, and then combined, resulting in a score ranging from 11 (upper class) to 77 (lower class). For the following studies, the Hollingshead Index of Social Position score for adolescents' head of household (the parent who earns a higher income) are reported.

General intelligence

Lower intellectual functioning (IQ) has been associated with greater discounting of delayed rewards and impairments in behavioral inhibition (Olson, Hooper et al. 2007). Thus, to estimate overall intellectual functioning, adolescents were administered the 2-subtest version (including Vocabulary and Matrix Reasoning) of the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999). A Full-Scale IQ score was calculated for all adolescents with higher scores indicating greater estimated intellectual functioning.

Pubertal development

Given the drastic changes in delay discounting rates and future orientation across adolescence (Steinberg, Graham et al. 2009), self-assessment of puberty was obtained using a modified line drawing version of the Tanner's Sexual Maturation Scale (Taylor,

Whincup et al. 2001), with drawings ranging from stage 1 (pre-adolescent) through stage 5 (adult-like maturation).

Family history density

To evaluate family history of alcoholism, a family history density (FHD) score was calculated using the Family History Assessment Module (Rice, Reich et al. 1995), as has been used in prior studies (Herting, Schwartz et al. 2010, Cservenka and Nagel 2012, Cservenka, Casimo et al. 2014, Cservenka, Fair et al. 2014). FHD was based on the number of adolescents' relatives with an AUD; parents contributed 0.5 each, grandparents 0.25 each, and aunts and uncles a weighted ratio of 0.25 divided by the number of their siblings, with higher scores indicating greater prevalence of familial history.

2.3 Follow-up procedure and binge-drinking criterion

After recruitment and collection of all baseline measures, follow-up phone interviews were conducted with adolescents approximately every 90 days, for the remainder of their enrollment in the study. During these interviews, the Customary Drinking and Drug Use Record and 90-day Timeline Followback (Sobell, Brown et al. 1996) were administered to assess substance abuse. Adolescents were brought back in for re-assessment if they reported 3 or more occasions of binge drinking (more than 5 drinks for males or 4 drinks for females, in one occasion) within the last 90 days[1]. This criterion is in accordance with National Institute on Alcohol Abuse and Alcoholism guidelines of binge drinking (NIAAA 2004) and has been utilized previously (Cservenka, Jones et al.

[1] For analyses in Chapter 5, 5 subjects had 2 binge-drinking episodes, and 5 subjects had 1 binge-drinking episode, in the last 90 days.

2015, Jones, Cservenka et al. 2016). For every participant that met binge-drinking criterion, a time-since-baseline, sex- and age-matched largely drug- and alcohol-naïve control (not exceeding baseline drug and alcohol use criteria) was also brought in for re-assessment 1-3 times. Furthermore, additional controls were brought in for re-assessment as part of an ongoing longitudinal investigation of sex differences in adolescent neurodevelopment (Alarcon, Cservenka et al. 2014).

This design resulted in a total of 272 visits among 33 binge-drinking adolescents and 83 largely drug- and alcohol-naïve controls, collected between July 2008 and May 2016, for longitudinal analyses investigating the development of impulsive choice (Chapter 3), and 246 visits among 45 binge-drinking adolescents and 68 controls, collected between November 2009 and July 2016, for longitudinal analyses investigating white matter microstructural development (Chapter 4). Furthermore, 66 additional visits (14 baseline, 52 re-assessment) from 34 binge-drinking adolescents and 32 controls were collected between December 2016 and April 2018 and were used for cross-sectional investigations of loss discounting behavior and the appreciation of future consequence (Chapter 5). While most subjects contributed data to at least two of the current studies, the results presented in Chapter 5 utilized an independent set of visits that were collected after the completion of the analyses presented in Chapters 3 and 4 (Figure 1).

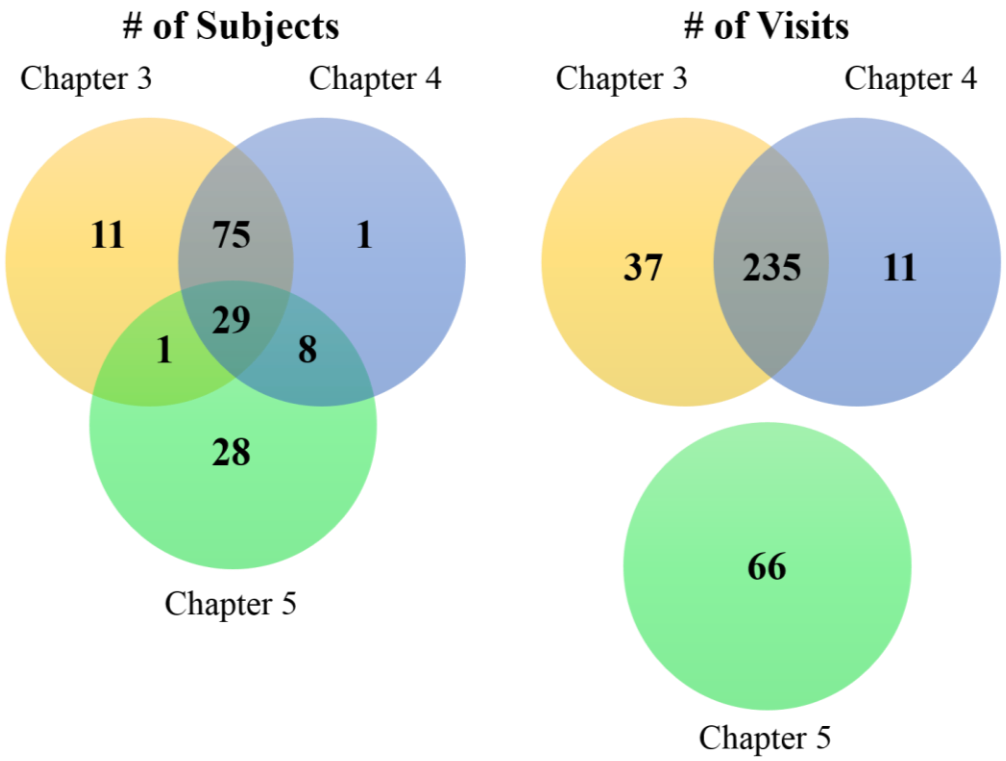

Figure 1. Participants breakdown by study
Breakdown of participants' contributions to each of the three studies in regards to overall number of subjects and total number of visits.

2.4 Temporal decision making

Gain discounting paradigm

For the studies outlined in Chapters 3 and 4, a computerized, and self-paced, version of the gain discounting paradigm, described previously (Mitchell 1999, Herting, Schwartz et al. 2010), was administered to adolescents during all in-person visits. Briefly, the task presented adolescents with the choice between a variable monetary reward ($0 to $10.50) available immediately, or a set monetary reward ($10) available after a delay (0, 7, 30, 90, 180, or 365 days). Choice pairs, consisting of one immediate variable reward and one delayed set reward, were presented in random order to make up a total of 138 questions. Participants were asked to choose the option they preferred from each choice pair. To enhance the saliency of the task, participants were informed that one of their choices would be randomly selected, following the task, and money would be awarded based on their choice during the task.

Indifference points, the point at which a person switched from choosing the immediate reward to choosing the delayed reward, were calculated for each delay length. Using these indifference points, the rate of discounting (k) was calculated by fitting a hyperbolic discounting function: $V = A/(1 + kD)$. In this equation, V represents the value of the $10 reward (the indifference point) at a given delay length (D), and A represents the amount of the set delayed reward ($10). Using this equation, greater k values represent lower indifference points, or a greater preference for more immediate rewards.

Loss discounting paradigm

For the study outlined in Chapter 5, a computerized, and self-paced, modified version of the loss discounting paradigm (Mitchell and Wilson 2010) was administered to

a subset of adolescents. During the task, participants were asked, "At this moment, what would you prefer?" and were given the choice between paying a variable amount of money "now" ($20 to $180), or a set amount of money ($100) after a delay (7, 30, 90, 180, and 365 days). Values higher than the fixed delay amount were included, as previous studies have demonstrated that some individuals display a tendency towards "negative" discounting (i.e. selection of an immediate loss despite it being greater than the delayed option) (Hardisty, Appelt et al. 2013). Allowing for negative discounting behavior also produces a broader distribution of behavior from which to assess the effects of binge drinking and family history of alcoholism. Choice pairs, consisting of one immediate payment and delayed set payment, were presented in random order to make up a total of 125 questions. Prior to the task, participants were told to answer all questions as if they were actually going to lose money; however, no money was taken from them. Hypothetical losses were used due to the problematic nature of taking money away from participants after a delay. While no comparisons have been made between real and hypothetical losses in delay discounting, studies have found no differences in behavior (Johnson and Bickel 2002, Madden, Begotka et al. 2003, Bickel, Pitcock et al. 2009) or brain activation (Baker, Johnson et al. 2003), between real and hypothetical rewards. Further, previous studies have indicated no behavioral differences in risk taking between real or hypothetical consequences such as rejection (Spector, Cohen et al. 1976), or time and effort (Wiseman and Levin 1996).

Indifference points were calculated for each delay length; however, given little is known regarding loss discounting behavior in adolescence, and due to the problematic nature of log transforming negative k-values, a specific discounting function was not fit

for loss discounting behavior. Instead another common measure in temporal discounting, area under the curve (AUC), was calculated for each participant, with lower AUC values representing greater discounting, and values greater than 1 representing negative discounting.

2.5 Summary of analytic strategy

This dissertation focused on the role of personal and familial alcohol misuse in temporal decision making and white matter microstructural development. To address the first set of aims (described in Chapter 1.9), Chapter 3 utilized a longitudinal design and multilevel modeling to test 1a) whether personal binge-drinking status and degree of familial alcoholism were associated with an altered trajectory of impulsive choice during adolescence, and 1b) whether greater lifetime alcohol use was associated with greater impulsive choice across age, in adolescents who went on to binge drink. To address the second set of aims, Chapter 4 utilized voxel-wise multilevel modeling 2a) to identify regions of the brain where binge-drinking status and degree of familial alcoholism were associated with altered white matter microstructural development, and then used mediation analyses 2b) to determine whether alterations in the development of white matter microstructure in these regions mediate the effects of personal binge-drinking status or degree of familial alcoholism on impulsive choice. To address the third set of aims, Chapter 5 used ordinary least squares (OLS) regression and multilevel modeling to 3a) determine whether personal binge-drinking status and degree of family alcoholism were associated with self-reports and behavioral measures of appreciation of future consequences and 3b) whether appreciation for future consequences were related to white matter microstructure, in those with personal and/or familial alcohol abuse, and then 3c)

used mediation analyses to determine whether alterations in white matter microstructure mediated the effects of personal binge-drinking status and/or degree of familial alcoholism on the appreciation of future consequences.

Chapter 3. Binge drinking and family history of alcoholism are associated with an altered developmental trajectory of impulsive choice across adolescence

(Portions of this chapter have been published in *Addiction*)

3.1 Introduction

Using delay discounting paradigms, alcohol-dependent individuals discount (or devalue) delayed rewards to a greater degree than non-dependent individuals (Vuchinich and Simpson 1998, Petry 2001, Mitchell, Fields et al. 2005). That is, when forced to choose, alcohol-dependent individuals are more likely to select smaller immediate rewards over larger delayed rewards, thus making what is often considered an impulsive choice. However, the temporal nature of this relationship between alcohol use and impulsive choice (i.e. discounting rates) remains unclear. While some speculate that greater impulsive choice leads to the initiation of alcohol use, others argue that alcohol use itself alters underlying neural mechanisms responsible for increases in impulsive choice. It is also possible that these two behaviors are both products of some underlying risk phenotype, and share a common genetic component (Mitchell 2011). Adolescence is a critical period during which many first initiate alcohol use, and a time during which impulsive choice develops, as evidenced by both human and rodent studies. For example, as noted in Chapter 1.5, both cross-sectional and longitudinal work in human adolescents has shown that impulsive choice decreases across adolescence and into young adulthood (Olson, Hooper et al. 2007, Steinberg, Graham et al. 2009, Water, Cillessen et al. 2014, Achterberg, Peper et al. 2016). Meanwhile, cross-sectional pre-clinical models have found that adolescent rodents exhibit more impulsive responding for food rewards than adults (Adriani and Laviola 2003, Pinkston and Lamb 2011, Doremus-Fitzwater, Barreto et al. 2012). Thus, adolescence is an important period for investigating the development of impulsive choice.

Previous cross-sectional work in humans and rodents has established that both alcohol use and a familial history of alcoholism are associated with altered impulsive choice. Compared to light drinkers, heavy-drinking human adolescents show greater impulsive choice for monetary and alcohol rewards (Field, Christiansen et al. 2007, Sullivan, Brumback et al. 2016). Meanwhile, alcohol exposure has a greater impact on impulsive choice in adolescent rodents than adults (Mejia-Toiber, Boutros et al. 2014). Further, as noted in Chapter 1.7, studies in drug- and alcohol-naïve human adolescents and young adults found that FHP adolescents made more impulsive choices (Acheson, Vincent et al. 2011, Dougherty, Charles et al. 2014, Henderson, Vaidya et al. 2018) and had significantly slower RTs (Herting, Schwartz et al. 2010), than FHN adolescents. Similarly, alcohol-naïve rodents bred to consume high levels of alcohol demonstrate more impulsive responding for food and sucrose rewards than those bred for low levels of alcohol consumption (Wilhelm and Mitchell 2008, Oberlin and Grahame 2009, Perkel, Bentzley et al. 2015). In combination, these findings suggest that both alcohol use and a family history of alcoholism may predispose adolescents to be more impulsive.

Despite evidence supporting the influence of both alcohol use and family history on impulsive choice, few studies have investigated their effects concurrently. In a cross-sectional study, impulsive choice correlated with age in light-drinking adults, but not heavy drinkers, and in light drinkers, those with a FHP showed greater impulsive choice (Smith, Steel et al. 2015). Further, another study in adults found that higher rates of impulsive choice partially mediated the relationship between greater parental substance use and greater alcohol consumption (VanderBroek, Acker et al. 2016). However, these studies were both in adult populations, and thus were unable assess the combined

associations of alcohol use and family history of alcoholism with the development trajectory of impulsive choice. Understanding the association of this combined effect with development is crucial, as binge drinking and familial alcoholism have been shown to interact and are associated with impaired neuropsychological functioning during adolescence (Tapert and Brown 2000).

The current study focused on the developmental trajectory of impulsive choice across adolescence. The longitudinal design allowed for the assessment of whether binge drinking and degree (i.e. density) of familial alcoholism are associated with an altered trajectory of impulsive choice during this critical period. Further, this study aimed to test whether greater lifetime alcohol use (i.e. lifetime drinks) is associated with greater impulsive choice across age, in binge-drinking adolescents. While many studies utilize family history status (based on alcoholism in at least one parent), for this study, a continuous FHD score was calculated based on the number and degree of relatives with an AUD (see Chapter 2.2), to improve effect sizes, power, and measurement reliability (MacCallum, Zhang et al. 2002). Based on previous literature, it was hypothesized that alcohol-naïve adolescents would show a decrease in impulsive choice across age, and that this relationship would be diminished in adolescents who ultimately engaged in binge drinking. Furthermore, it was hypothesized that greater FHD would be associated with greater impulsive choice prior to alcohol consumption, and that FHD would interact with binge-drinking status across age. For this interaction effect, non-drinking adolescents with low FHD were expected to show the greatest age-dependent decrease in impulsive choice compared to binge drinkers and those with higher FHD, similar to the behavioral pattern found in previous neuropsychological work (Tapert and Brown 2000).

Additionally, it was hypothesized that among binge-drinking adolescents there would be a positive association between lifetime drinks and impulsive choice across age.

3.2 Methods

3.2.1 Baseline participant characteristics

All statistical analyses were carried out using R (v 3.2.3). Baseline demographic variables (see Chapter 2.2) were examined for outliers (> 2.5 SD from the mean) and normal distribution and were compared between binge-drinking adolescents and controls, using independent-samples *t*-tests, or Mann-Whitney and chi-square tests where appropriate.

3.2.2 Modeling the effects of binge-drinking status and family history density on impulsive choice

Prior to multilevel modeling, *k* values were log transformed due to non-normal distribution; this also reframed the outcome measure, such that the estimated impacts of the predictor variables represent percent change in impulsive choice. Age was re-centered at the average baseline age (~14 years) to aid in interpretation of the results.

To address the first aim of this study, a series of multilevel models were used to test the effects of binge-drinking status and FHD on the association between age and discounting rate using full maximum likelihood (ML). This approach is similar to a mixed repeated-measures ANOVA design, modeling within- and between-subjects factors simultaneously, and helps account for individual level growth or change by accounting for the nested nature of longitudinal data. First, an unconditional means model

(Model A), analogous to a traditional one-way ANOVA, was fit to determine how much of the observed variation in the outcome could be attributed to between-subjects differences[2]. Next, a linear slope was added to create an unconditional growth model (Model B), which accounted for both within-individual changes in discounting rates over time, as well as between-individual differences in change over time, and estimated a unique baseline and slope over time, for each participant. This model was a necessary step to determine whether adolescents' discounting rates varied across age, and additionally, provided an estimate of between-individual variability, which represents a second level of differences from those estimated over time within individuals. The variance estimates from this model, both among individual starting points, or intercepts, and among individual trajectories of change, or slopes, served as a baseline model for testing the effects of level-2 predictors. Subsequent models included the addition of level-2 predictors to account for the estimated differences from Model B; these included binge-drinking status (Model C), and FHD (Model D), separately, and in combination (Model E).

3.2.3 Modeling dose-related effects of alcohol use on impulsive choice

To further examine dose-related associations between alcohol use and impulsive choice, and to address the second aim of this study, a separate series of linear models were fit in the binge-drinking adolescents only. These models allowed for a more thorough examination of the influence of other important predictors that were unique to this group of adolescents (i.e. lifetime drinks) and followed a similar modeling

[2] A common metric computed from this model is the intra-class correlation coefficient (ICC), which represents the percentage of variance in the outcome explained by inter-individual differences.

progression as the earlier analysis. After fitting the unconditional means (Model F) and unconditional growth (Model G) models, individuals' number of lifetime drinks was added to the model as a time-varying covariate (Model H) to estimate the dose-related relationship between drinking and impulsive choice.

3.2.4 Assessing model fit

A chi-square test comparing deviance statistics was used to assess the goodness-of-fit of each nested model. Furthermore, effect sizes for all predictors in the final model of each aim (Model E and H) were reported as either Cohen's d (for categorical predictors), standardized regression estimates (for continuous variables), or differences scores between standardized regression estimates (for interactions of categorical and continuous variables). To obtain standardized regression estimates, all continuous variables were first z-transformed, and then the final model was rerun using these z-transformed variables.

3.3 Results

3.3.1 Participant characteristics

A summary of ages at each visit, for all participants is depicted in Figure 1, and participant baseline demographics for all subjects included in the final neuroimaging analysis are presented in Table 1. To ensure valid and consistent discounting behavior, indifference points were examined to determine nonsystematic discounting behavior outliers. That is, adolescents' discounting data was excluded if any indifference point was greater than the indifference point at the previous delay length by 20% of the larger later

amount (i.e. $2.00) (Johnson and Bickel 2008). Thus, 11 data points were excluded for nonsystematic discounting behavior, and 19 were excluded due to missing data. The remaining 242 data points (across 33 binge-drinking adolescents and 81 non-drinking controls) were included in multilevel modeling.

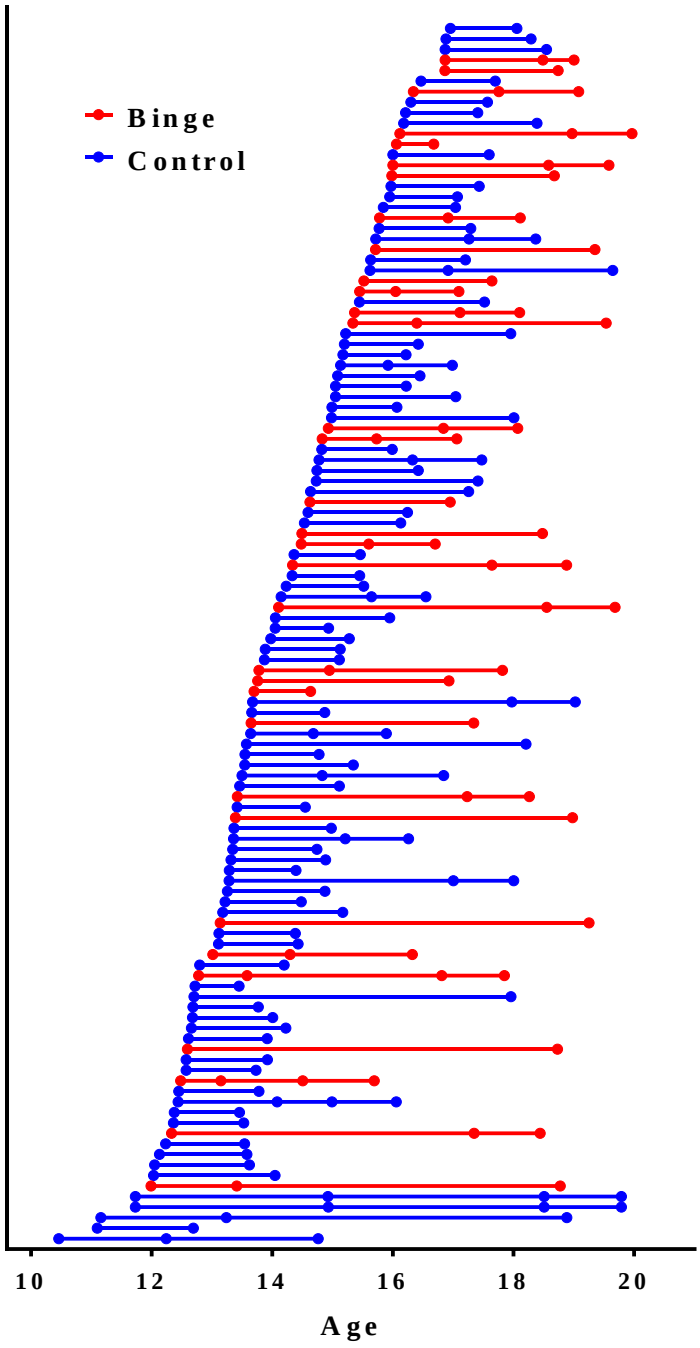

Figure 1. Distribution of participant visits

Ages for all scans depicted within subject and separated by binge-drinking status. There were a total of 272 total visits, divided amongst 33 binge-drinking adolescents (88 visits) and 83 controls (184 visits). There was a median of 1.35 years between visits (range = 0.51-6.14 years) and a median of 1.74 years between first and last visit (range = 0.62-8.06 years).

Table 1. Baseline demographics

	Bingers (n = 33) M (SD)	Controls (n = 83) M (SD)	Significance test
Sex (male/female)	19/14	43/40	$X^2 = 0.32$
Age	14.52 (1.39)	13.97 (1.47)	$t_{114} = 1.85$
Pubertal stage	4.00 (1.04) [a]	3.75 (1.07) [b]	$U_{103} = 952.0$, $Z = -1.13$
IQ	112.82 (9.01)	110.70 (10.38) [c]	$t_{113} = 1.03$
SES	27.12 (12.62)	31.63 (13.81)	$t_{114} = 1.62$
FHD	0.39 (0.32)	0.39 (0.33)	$U_{103} = 1354.5$, $Z = -0.09$

[a] n = 29 due to missing data; [b] n = 76 due to missing data; [c] n = 82 due to outliers. There were no statistically significant differences between groups on any variables

3.3.2 Effects of binge-drinking status and family history density on impulsive choice

Results from the multilevel models investigating the effects of binge-drinking status and FHD on the development of discounting rates, addressing the first aim of this study, are presented in Table 2. Model A demonstrated that roughly half the variation in discounting rates was between subjects ($\rho = 0.532$), supporting the need for the addition of both within- (age) and between-subjects (drinking status and FHD) predictors. Next, Model B demonstrated a significant decrease in discounting rates across age. The addition of age to the model decreased the amount of within subject variance by 22%, and was an improved model compared to Model A [$\chi^2(3) = 13.71$, $p < 0.05$].

Next, Model C (including binge-drinking status) revealed a significant association between binge-drinking status and change in discounting rate across age. Discounting rates decreased significantly across age in control adolescents ($b = -0.420$, $p < .05$); however, this slope differed significantly in binge-drinking adolescents, with an estimated greater rate of change across age ($b = 0.394$, $p < .05$), compared to controls. The combined estimates resulted in a slight (but non-significant) decrease in discounting rates across age ($b = -0.026$) estimated for binge-drinking adolescents. Further, Model D (including FHD), revealed a significant association between FHD and baseline discounting rates (~age 14); greater FHD was associated with greater baseline discounting rates ($b = 1.401$, $p < .05$). Only Model C was a significantly improved model, compared to model B [$\chi^2(2) = 7.56$, $p < 0.05$]; however, due to the significance of FHD as a predictor of adolescents' discounting rates, and the extent of literature suggesting an association between familial alcoholism and discounting rates (Oberlin and Grahame

2009, Herting, Schwartz et al. 2010, Dougherty, Charles et al. 2014, VanderBroek, Acker et al. 2016), it was retained for Model E.

Model E, the final model (including binge-drinking status, FHD, and their interaction), revealed the interaction of FHD and binge-drinking status was significantly associated with discounting rates across age (b = 1.090, $p < 0.05$, $\Delta\beta$ = 0.298). For control adolescents, higher FHD resulted in a significantly steeper decrease in discounting rates across age (b = -0.633, $p < 0.05$, β = -0.173). This relationship was significantly different in binge-drinking adolescents, such that higher FHD was associated with a slight, non-significant increase in the slope of discounting rates across age (b = 0.457, p = 0.24, β = 0.125). It is important to note that when binge-drinking status was reverse-coded, FHD had no effect on the rate of change of discounting rates in binge-drinking adolescents, suggesting that the binge drinking-by-FHD interaction was driven by an effect of FHD on discounting rates in control adolescents, but not binge-drinking adolescents. Additionally, greater FHD was also associated with higher discounting rates at baseline in controls (b = 1.530, $p < 0.05$, β = 0.204), an effect that did not differ based on ultimate binge-drinking status. However, due to the significant binge-by-FHD-by-age effect, by age 18, FHD was no longer associated with impulsive choice in control adolescents, but a significant group-by-FHD interaction existed (b = 3.739, $p < 0.05$, $\Delta\beta$ = 0.499), with binge-drinking adolescents demonstrating a positive association between FHD and impulsive choice (b = 2.692, p = 0.06, β = 0.359). To aid in the interpretation of these findings, Figure 2 depicts prototypical trajectories for an individual falling 1 SDs above/below the mean FHD. Comparing models, demonstrated that Model

E, explained significantly more variation in discounting rates than Model B [$\chi^2(6) = 17.34$, $p < 0.05$], Model C [$\chi^2(4) = 9.78$, $p < 0.05$], and Model D [$\chi^2(4) = 12.67$, $p < 0.05$].

Table 2. Parameter estimates of discounting rates in all subjects

		Model A	Model B	Model C	Model D	**Model E**
Fixed Effects						
Initial Status	Intercept	-4.981[a] (0.198)	-4.628 [a] (0.218)	-4.573 [a] (0.248)	-5.199 [a] (0.339)	**-5.210 [a] (0.383)**
	BINGE			-0.205 (0.475)		**0.069 (0.764)**
	FHD				1.401 [c] (0.645)	**1.530 [c] (0.725)**
	BINGE*FHD					**-0.699 (1.452)**
Rate of Change	Intercept		-0.242 [b] (0.077)	-0.420 [a] (0.098)	-0.142 (0.120)	**-0.177 (0.148)**
	BINGE			0.394 [b] (0.147)		**0.020 (0.225)**
	FHD				-0.245 (0.256)	**-0.633 [c] (0.309)**
	BINGE*FHD					**1.090 [c] (0.495)**
Variance Components						
Level 1	Within-person	2.707	2.122	2.237	2.136	**2.256**
Level 2	Initial status	3.072	3.089	2.804	2.838	**2.573**
	Rate of change		0.142	0.078	0.137	**0.047**
	Covariance		-0.247	-0.127	-0.209	**-0.037**
Goodness-of-fit						
	Deviance	1064.7	1051.0	1043.5	1046.4	**1033.7**
	AIC	1070.7	1063.0	1059.5	1062.4	**1057.7**
	BIC	1081.2	1084.0	1087.4	1090.3	**1099.6**

[a] $p < 0.001$; [b] $p < 0.01$; [c] $p < 0.05$; standard errors are in parentheses. Model A is an unconditional means model; Model B is an unconditional growth model (including AGE); Model C includes the effects of binge-drinking status (BINGE) on both initial status and rate of change (BINGE*AGE); Model D includes the effects of FHD on both initial status and rate of change (FHD*AGE); Model E includes the effects of BINGE and FHD, as well as the effects of the interaction of the two predictors (BINGE*FHD) on both initial status and rate of change (BINGE*AGE, FHD*AGE, BINGE*FHD*AGE). The final, most parsimonious model is in bold text.

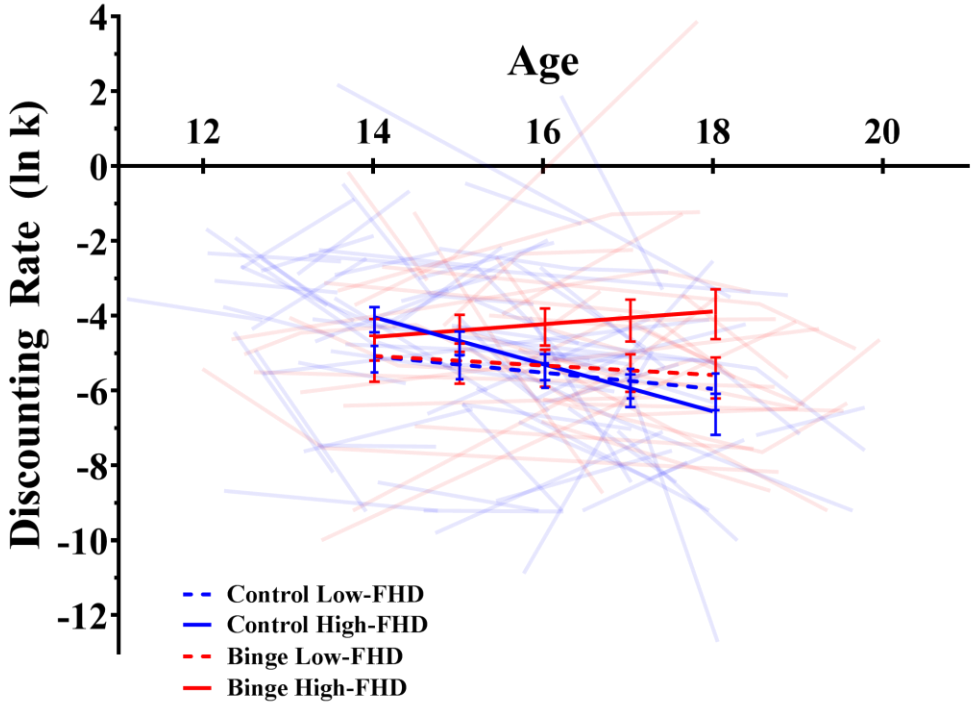

Figure 2. Binge-drinking status and family history density interact with age to predict discounting rates

Prototypical trajectories of discounting rates (ln k ± SEM) across age are plotted for binge-drinking adolescents and controls with a high (+1 SDs from the mean) and low FHD (-1 SDs from the mean). Binge-drinking (light red) and control (light blue) adolescents' individual discounting rates (ln k) across age are plotted in the background. For reference, the prototypical trajectory of high-FHD individuals is one with a FHD of 0.72, or roughly the equivalent of having at least one parent with an AUD, similar to the definition of FHP in prior research (Herting, Schwartz et al. 2010, Acheson, Vincent et al. 2011, Dougherty, Charles et al. 2014). Meanwhile, the prototypical trajectory of a low-FHD individual is one with a FHD of 0.06, or an individual with AUD only in a second-degree relative.

3.3.3 Dose-related effects of alcohol use on impulsive choice

To address the second aim of this study and examine the dose-related association between binge drinking and discounting rates, a separate set of models was created in only the binge-drinking adolescents, depicted in Table 3. Results from Model F (unconditional means model) and Model G (unconditional growth model) are in line with the previous models, suggesting that binge-drinking adolescents show a non-significant change in discounting rates across age. Model H (including lifetime drinks) revealed that adolescents who had a greater number of drinks at baseline had lower baseline discounting rates (b = -0.012, $p < 0.05$, β = -0.776), and those who showed a greater escalation of drinking also had a significantly greater increase in discounting rates across age (b = 0.002, $p < 0.05$, β = 0.295). Also, the addition of lifetime drinks improved upon Model G, albeit at a trend level [$\chi^2(2) = 5.37$, $p = 0.07$].

Table 3. Parameter estimates of discounting rates in binge drinkers

		Model F	Model G	**Model H**
Fixed Effects				
Initial Status	Intercept	-4.866 [a] (0.301)	-4.635 [a] (0.374)	**-4.663 [a] (0.380)**
	DRINKS			**-0.012 [c] (0.005)**
Rate of Change	Intercept		-0.094 (0.156)	**-0.046 (0.161)**
	DRINKS			**0.002 [c] (0.001)**
Variance Components				
Level 1	Within-person	2.752	0.833	**0.744**
Level 2	Initial status	1.845	3.101	**3.145**
	Rate of change		0.587	**0.490**
	Covariance		-0.539	**-0.468**
Goodness-of-fit				
	Deviance	360.0	348.3	**342.9**
	AIC	366.0	360.3	**358.9**
	BIC	373.3	375.0	**378.5**

[a] $p < 0.001$; [c] $p < 0.05$; standard errors are in parentheses. Model F is an unconditional means model; Model G is an unconditional growth model (including AGE); Model H includes the effects of lifetime drinks (DRINKS) on both initial status and rate of change (DRINKS*AGE). The final, most parsimonious model is in bold text.

3.4 Discussion

The first aim of this study was to investigate the effects of binge-drinking status and FHD on the development of impulsive choice across adolescence. This is the first study to use a prospective longitudinal design with data both before and after initiation of binge drinking. The results suggest that as hypothesized, the interaction between FHD and binge drinking is associated with an altered developmental trajectory of impulsive choice across adolescence. More specifically, higher FHD was associated with a greater decline in impulsive choice across age in adolescents who remained largely alcohol-naïve, but not in adolescents who went on to binge drink. This suggests that if adolescents refrain from binge drinking, greater FHD may be developmentally protective, at least with respect to reducing impulsive decision making.

This study is not the first to suggest that FHD may be protective in those that do not drink. Studies of children of alcoholics suggest that many individual and social factors may contribute to an adolescents' resilience against binge drinking (for review, see Park and Schepp 2015). Additionally, there could be a biological explanation behind this resilience. For example, a previous study found that FHP adults, but who themselves were not alcoholics, had greater dopamine D2 receptor availability in the caudate and ventral striatum than FHN individuals (Volkow, Wang et al. 2006), suggesting that greater D2 receptor levels could protect against alcoholism by regulating brain regions involved in behavioral inhibition and impulsivity (for review, see Trifilieff and Martinez 2014). Another possible explanation is that not all heritable predispositions toward high-alcohol drinking are associated with impulsive choice. That is, there is some degree of phenotypical variability in FHP adolescents that causes some to engage in more

impulsive choice and others less. For example, when comparing a high alcohol-consuming and alcohol-seeking strain of mice to a high-consuming but moderate-seeking strain, high alcohol-seeking animals had greater discounting rates, suggesting that impulsive choice may be more closely associated with a propensity to drug seek than to consume (Beckwith and Czachowski 2014). In humans, this is supported by findings that novelty seeking is a significant predictor of alcohol dependence in FHP individuals, but not FHN individuals (Grucza, Cloninger et al. 2006). Additional work is necessary to determine the mechanism behind the association between the interaction of binge drinking and FHD, and impulsive choice.

Another benefit of this longitudinal study was that the multilevel modeling analytic strategy allowed for investigation of the association between binge-drinking status and FHD and impulsive choice at the intercept (placed at the average age at baseline), when all adolescents were alcohol naïve. As hypothesized, these results showed that higher FHD was associated with more impulsive choices at baseline, prior to alcohol consumption. This is in line with previous studies in both humans (Herting, Schwartz et al. 2010, Acheson, Vincent et al. 2011, Dougherty, Charles et al. 2014) and rodents (Wilhelm and Mitchell 2008, Oberlin and Grahame 2009, Perkel, Bentzley et al. 2015). Additionally, these findings suggest that despite those with greater FHD initially demonstrating greater impulsive choice, this effect becomes negligible, and may in fact reverse, across development in those that remain alcohol-naïve. This is consistent with longitudinal work showing that the association between family history of alcoholism and greater impulsive choice diminished across early-adolescence in alcohol-naïve individuals (Dougherty, Lake et al. 2015). Further, these results showed that ultimate

binge-drinking status on its own, or in interaction with FHD, was not associated with baseline impulsive choice. This suggests that adolescents who later go on to drink have comparable levels of impulsive choice to controls prior to alcohol initiation and supports the notion that alcohol use may alter underlying neural mechanisms involved in impulsive choice. To further strengthen this notion, the second aim of this study investigated the dose-related association between alcohol use and impulsive choice. Results showed that an escalation of drinking was associated with a greater increase in impulsive choice across adolescence, suggesting that the greater rates of impulsive choice previously observed in drinking adolescents (Field, Christiansen et al. 2007, Sullivan, Brumback et al. 2016) may be the result of alcohol use, as opposed to a premorbid risk phenotype; however, the temporal nature of this association cannot be definitely claimed and additional studies are necessary to confirm this.

This study is not without limitation. First, as mentioned, there is a possibility that the association between greater FHD and more impulsive choice over time could be driven by a third variable (e.g. sensation seeking) (Weiland, Welsh et al. 2013). While investigation into this is beyond the scope of this study, it should be explored in future experiments. Second, this study did not investigate sex differences. While one meta-analysis suggests that there are no sex differences in delay discounting behavior (Cross, Copping et al. 2011), another suggests a very small effect (r = 0.058) (Silverman 2003), with studies in humans and rodents suggesting this depends largely on task and the sample used (Weafer and de Wit 2014). Further, whether this changes in the context of alcohol use is unclear. Unfortunately, with only 14 binge-drinking females, this study lacks power to detect potential three-way interactions between predictor variables;

however, this is also an important future direction. Third, in light of the effect of binge drinking on impulsive choice, it is unclear if abstinence returns binge-drinking adolescents to a trajectory similar to that of non-drinking adolescents, given that abstinence has been shown to reduce some of the behavioral consequences of alcohol use in adolescents (Winward, Hanson et al. 2014), it is also uncertain in binge-drinking adolescents will maintain continued drinking, or will show reductions in substance use and potentially reductions in impulsive choice. Finally, while this study utilized a longitudinal dataset, the analyses were primarily correlational in nature and thus causality cannot be inferred (discussed in greater detail in Chapter 6). That said, while the lack of group differences at baseline and the dose-dependent association between alcohol use and impulsive choice would suggest that alcohol may be altering the development of impulsive choice, additional longitudinal studies will be necessary to sufficiently support this claim.

In conclusion, these findings demonstrate that FHD interacts with binge drinking during adolescence and is associated with an altered developmental trajectory of impulsive choice. While greater FHD may be protective in adolescents who remain alcohol naïve, this effect is not present in adolescents who go on to binge drink. Furthermore, in binge-drinking adolescents, escalated drinking was associated with a greater increase in impulsive choice across adolescence. Understanding how alcohol use is associated with the development of impulsive choice may inform intervention strategies, such as episodic future thinking (Snider, LaConte et al. 2016), in an effort to reduce rates of both impulsive choice and alcohol consumption. Knowledge of the interaction between FHD and binge drinking in relation to impulsive choice may help

identify which individuals will benefit the most from behavioral intervention. Future work is important to understand what mechanism(s) may be responsible for this association between alcohol use and FHD and the development of impulsive choice across adolescence.

Chapter 4. Altered frontal and striatal white matter microstructure is associated with impulsive choice, familial alcoholism, and future binge drinking in adolescence

(Portions of this chapter have been submitted for publication)

4.1 Introduction

Neurodevelopment during adolescence is highlighted by extensive volumetric changes, including decreases in gray matter and increases in white matter with age (Giedd, Blumenthal et al. 1999, Gogtay, Giedd et al. 2004, Paus 2005, Shaw, Kabani et al. 2008, Ostby, Tamnes et al. 2009, Tamnes, Ostby et al. 2010), as noted in Chapter 1.2. Underlying these volumetric changes, particularly in white matter, are changes in the microstructural properties of white matter fibers, including widespread increases in FA (Barnea-Goraly, Menon et al. 2005, Giorgio, Watkins et al. 2010, Lebel and Beaulieu 2011, Pfefferbaum, Rohlfing et al. 2016), which is thought to be a reflection of greater fiber density, axonal diameter, and myelination (Hagmann, Jonasson et al. 2006). Further, increases in FA across adolescence have been shown to be associated with several developing executive control processes, including lower impulsivity (Olson, Collins et al. 2009, Achterberg, Peper et al. 2016), greater inhibitory control (Seghete, Herting et al. 2013), and greater working memory capacity (Nagy, Westerberg et al. 2004), highlighting the relevance of FA as a neurobiological marker for cognitive maturation in adolescents.

Both personal and familial alcohol misuse have been associated with alterations in FA during adolescence. As noted in Chapter 1.3, binge drinking has been repeatedly associated with widespread reductions in FA in numerous projection, association, and commissural white matter tracts throughout the brain (Bava, Frank et al. 2009, Jacobus, McQueeny et al. 2009, McQueeny, Schweinsburg et al. 2009, Bava, Jacobus et al. 2013, Luciana, Collins et al. 2013); however, in some regions, such as the SLF and internal capsule, greater FA has been reported in binge-drinking adolescents compared to controls

(Bava, Frank et al. 2009). Meanwhile, as noted in Chapter 1.4, adolescents free of personal substance use, but with a family history of alcoholism, also have demonstrated lower FA, including in fronto-striatal regions, such as the anterior corona radiata and ALIC (Herting, Schwartz et al. 2010, Acheson, Wijtenburg et al. 2014); however, contradictory findings have again been reported, with FHP adolescents demonstrating greater FA than FHN adolescents in the SLF, ILF, ALIC, posterior corona radiata, CC, and anterior thalamic radiation. This begs the question of whether alterations in white matter microstructure evident in binge-drinking adolescents are present prior to alcohol use and represent a developmentally transient or sustained predisposition associated with familial alcoholism or are consequences of alcohol use itself. Further, it is also possible that alterations in FA related to familial alcoholism precede binge drinking and are further exacerbated by alcohol use. Longitudinal studies in binge-drinking adolescents have begun to help elucidate this issue. As noted in Chapter 1.3, it has been shown that adolescents who go on to binge drink demonstrate significant FA decreases with time, including in frontal and striatal white matter tracts, when compared to alcohol-naïve adolescents, despite having comparable levels of FA at baseline, prior to alcohol use initiation (Bava, Jacobus et al. 2013, Luciana, Collins et al. 2013). However, no study has investigated the longitudinal association between FA and familial alcoholism in either alcohol-naïve or binge-drinking adolescents.

Earlier (Chapter 3) it was demonstrated that there is an interaction effect of binge-drinking status and FHD on the development of impulsive choice. That is, a greater FHD was associated with a lack of normative decline in impulsive choice in adolescents who went on to binge drink but was protective (i.e. resulted in a greater decline in impulsive

choice with development) in adolescents who remained alcohol naïve. While the neural underpinnings of this effect are unclear, as noted in Chapter 1.5, several previous studies have shown that individual differences in impulsive decision making are associated with differences in fronto-striatal white matter connectivity and microstructure. However, greater FA and structural connectivity (via tractography) in fronto-striatal white matter tracts has been associated with both lesser(van den Bos, Rodriguez et al. 2014, van den Bos, Rodriguez et al. 2015, Achterberg, Peper et al. 2016), and greater (Hampton, Alm et al. 2017) impulsive choice in adolescents and young adults. Furthermore, the association between FA and impulsive choice has yet to be investigated in the context of both binge drinking and familial history of alcoholism across adolescent development.

Given that both personal and familial alcohol misuse are associated with alterations in fronto-striatal FA, it's plausible that such alterations underlie the developmental trajectories of impulsive choice shown earlier (in Chapter 3). Thus, the current study had two aims. First, to address previous discrepancies in the directionality of the association between both binge-drinking status and family history of alcoholism and FA, this study sought to longitudinally investigate the association of binge-drinking status, FHD, and their interaction, with FA development using voxel-wise multilevel modeling. Based on previous findings, it was hypothesized that binge-drinking adolescents would show an altered course of white matter maturation, characterized by age-related reductions in FA compared to alcohol-naïve controls. Further, it was hypothesized that a greater FHD would be associated with greater reductions in FA with age in binge-drinking adolescents, but not controls, particularly in fronto-striatal tracts. Second, this study aimed to determine whether alterations in the development of FA

mediated binge-drinking and family history-related alterations in impulsive choice. It was hypothesized that impairments in FA in fronto-striatal regions would also be associated with greater impulsive choice, and that lower FA would mediate the effects of binge drinking and FHD on impulsive choice.

4.2 Methods

4.2.1 Baseline participant characteristics

All baseline demographic variables outlined in Chapter 2.2 were collected. Baseline demographic variables were examined for outliers (> 2.5 SD from the mean) and normal distribution and were compared between binge-drinking adolescents and controls, using independent-samples *t*-tests, or Mann-Whitney and chi-square tests where appropriate.

4.2.2 Image acquisition

During baseline and follow-up visits, all participants were scanned on a 3T Siemens Magnetom Tim Trio with a 12-channel head coil. DWI images were collected using a whole-brain, high-angular resolution, echoplanar imaging sequence (repetition time = 9,100 ms, echo time = 88 ms, field of view = 256 mm^2, slices = 72, slice thickness = 2mm). Gradient encoding pulses were applied in 30 directions with a b-value of 1,000 s/mm^2, with six additional images collected with a b-value of 0 s/mm^2 at the beginning of each DWI run. Participants received either three (n = 168; scan time = 16:52) or two (n = 88; scan time = 11:24) DWI runs. A diffusion field map was also acquired (repetition time = 790 ms, echo time 1 = 5.19 ms, echo time 2 = 7.65 ms, flip angle = 60°, field of

view = 240 mm2, slices = 72, slice thickness = 2 mm, scan time = 3:13) to correct DWIs for eddy current-induced field distortions.

4.2.3 Image processing

Visual inspection and quality assessment

Prior to image processing, all DWI runs underwent strict visual inspection for motion and scanner-related artifacts, as described previously (Roalf, Quarmley et al. 2016). Artifacts identified during visual inspection were either scanner-related, potentially due to issues in gradient performance, or a result of signal dropout, caused by the interaction of subject and motion and diffusion encoding. For each run, all 36 volumes were visually inspected and runs were classified into one of three categories based on the number of volumes containing artifact: 1) "Poor" if 7 or more volumes (>20%) contained artifact; 2) "Good" if 1 to 6 volumes contained artifact; and 3) "Excellent" if no volumes were found to contain artifacts. Furthermore, four quality assessment (QA) metrics (temporal signal-to-noise, mean voxel outlier count, maximum voxel outlier count, and mean relative motion) were obtained for each DWI run. Results from this visual inspection and QA were in line with previous findings (Roalf, Quarmley et al. 2016); approximately 7% of the data were labeled Poor, 32% Good and 61% Excellent, and there were significant differences between the three categories on all four QA measures (Table 1).

Table 1. Quality assessment values for raw diffusion images

	Poor	Good	Excellent
DWI Runs	44	207	397
TSNR, mean (SD)	5.19 (0.54) [a,b]	5.88 (0.42) [a]	6.06 (0.35)
MAXVOX, mean (SD)	10,887 (7,779) [a,b]	4,540 (6,023) [a]	1,416 (882)
MEANVOX, mean (SD)	1,924 (949) [a,b]	1,046 (377) [a]	828 (115)
MOTION, mean (SD)	0.59 (0.59) [a,b]	0.24 (0.23) [a]	0.12 (0.06)

Diffusion Weighted Imaging (DWI); temporal signal-to-noise ratio (TSNR); maximum outlier voxel count (MAXVOX); mean voxel outlier count (MEANVOX); mean relative motion (MOTION); [a] $p < 0.001$ (Bonferroni-corrected) as compared to Excellent group; [b] $p < 0.001$ (Bonferroni-corrected) as compared to Good group.

Volume censoring

Inclusion of Poor data, as defined above, has been shown to result in significantly altered diffusion metrics, particularly in developmental samples (Roalf, Quarmley et al. 2016). Therefore, in order to retain the maximum amount of data possible, volumes deemed to contain motion or scanner-related artifact were censored for subjects with Good and Poor data. In the current study, participants received 2-3 runs of the same diffusion sequence (with the same 30 diffusion directions) during a single imaging session. Therefore, a single volume could be censored from one run, while still retaining information about that diffusion direction from the other acquired runs within that imaging session. However, excluding diffusion directions entirely from a DWI session (either at random, or worse, when clustered in a similar direction) also results in overestimation of several diffusion metrics, including FA (Chen, Tymofiyeva et al. 2015). Thus, if the same direction/volume was removed from all DWI runs for an individual scan, that scan was excluded from further analyses. Based on this procedure, 10 scans were excluded for excessive motion, 5 scans were excluded for scanner-related artifacts, and 2 scans were excluded for errors in image acquisition (i.e. incomplete whole-brain coverage). This resulted in a final sample of 109 individuals with 229 total scans.

In addition to this volume censoring procedure, QA metrics were obtained for each imaging session (all DWI runs within a scan combined) and compared within-subject before and after volume this censoring. This comparison demonstrated that the volume censoring procedure resulted in significant improvements in temporal signal-to-noise ($t(123) = 5.840$, $p < 0.001$), maximum voxel outlier count ($t(123) = 2.481$, $p <$

0.05), mean voxel outlier count ($t(123) = 2.685$, $p < 0.01$), and mean relative motion ($t(123) = 4.332$, $p < 0.001$), in the raw data of scans with one or more censored volumes ($n = 124$). Furthermore, final QA metrics for each imaging session (after volume censoring), were not associated with binge-drinking status or FHD (all p's > 0.05)

Fractional anisotropy

DWI data were processed using a combination of FMRIB Software Library (FSL; v. 5.0.9) and Analysis of Functional NeuroImages (AFNI; v. 17.1.03). First, for each imaging session, the diffusion field map was affine registered to the first volume of the first DWI run (Saad, Glen et al. 2009). Next, to align all volumes while properly adjusting the gradient table, all DWI runs within an imaging session were concatenated, then correction for eddy current distortion, intensity inhomogeneities, head motion, and subsequent adjustment of the gradient table was conducted using FSL's newest eddy correction algorithm (Andersson and Sotiropoulos 2016). Then, FSL's dtifit (Smith, Jenkinson et al. 2004) was used to calculate the diffusion tensor, and identify the eigenvalues of the tensor, for each voxel. These eigenvalues were used to calculate FA using FSL's non-linear computational algorithm.

Image registration

After obtaining individual FA maps, Advanced Normalization Tools (ANTs) algorithms (Avants, Epstein et al. 2008) were used to register participants to standard space, prior to group-level analysis. An independent analysis found this algorithm to provide superior registration compared to 13 similar registration algorithms (Klein, Andersson et al. 2009). With specific regards to registration of FA images, it has been

demonstrated that ANTs produces better results than similar processes in FSL (i.e. tract-based spatial statistics) (Schwarz, Reid et al. 2014, Tustison, Avants et al. 2014).

Registration to standard space was carried out on individuals' FA maps, following procedures outlined previously (Schwarz, Reid et al. 2014). First, data were eroded to remove the bright ring of voxels surrounding the brain caused by eddy current induced distortion in cerebrospinal fluid voxels (Bastin 1999, Jones and Cercignani 2010). Next, to avoid processing bias and overestimation of effect sizes (Reuter, Schmansky et al. 2012), subjects were registered to an unbiased within-subject template using 4 iterations of affine registration (Avants and Gee 2004). Then, a study-specific template was created using the within-subject templates of all individuals. This template was created using an initial rigid registration, followed by four nonlinear registration iterations (Avants and Gee 2004, Avants, Tustison et al. 2011). The study-specific template was then transformed to Montreal Neurological Institute (MNI) space using ANTS-SyN nonlinear warping algorithm. For all subjects, registration of FA images to within-subject space, the study-specific template, and the MNI template were combined in a single transformation to reduce interpolation error. In order to restrict analyses to white matter, a binary white matter mask was created and included only voxels where mean FA was greater than 0.3 across subjects. Finally, a Gaussian blur (sigma = 1mm) was applied to all individual FA images (Ashburner and Friston 2000).

4.2.4 Group-level analyses

To address the first aim of this study, voxel-wise analyses were carried out for FA using AFNI's 3dLME (Chen, Saad et al. 2013) and were fit using ML estimation to allow

for direct comparison of models with different fixed effects structures (Singer and Willett 2003). First, an intercept-only model (FA ~ 1), analogous to a traditional one-way ANOVA, was fit to serve as a baseline model containing no between- or within-individual predictors. Next, a linear growth model (FA ~ Age) was fit, which accounted for both within-individual changes in FA over time, as well as between-individual differences in baseline FA (i.e. random intercepts). Due to the limited number of subjects with 3 time points of imaging data (< 25%), it was deemed inappropriate to allow for between-individual differences in change over time (i.e. random slopes) (Singer and Willett 2003)[3]. Finally, to assess the effects of FHD and binge-drinking status on FA, four additional models were fit: a main-effects model (FA ~ Age + Binge + FHD), and three interaction models looking at the effects of binge-drinking status controlling for FHD (FA ~ Age * Binge + FHD), FHD controlling for binge-drinking status (FA ~ Age * FHD + Binge) and the interaction of the two (FA ~ Age * Binge * FHD).

To compare the overall fit of the aforementioned models, a deviance map was created between the model of interest (i.e. saturated model), and a reduced model using the log-likelihood (LL) values, estimated voxel-wise for each model, based on the following equation: deviance = -2*(LLreduced model - LLsaturated model). A voxel-wise threshold ($p < 0.01$) was then applied to these deviance maps using the $\chi 2$ and degrees of freedom difference between the two models (Reiss, Abrams et al. 1996). To correct for multiple comparisons, and estimate the probability of false positive clusters, AFNI's 3dClustsim (Forman, Cohen et al. 1995) was employed using the spatial

[3] In post-hoc analyses, models (including all fixed effects) failed to converge when attempting to model between-individual differences in change over time.

autocorrelation function parameters (Cox, Chen et al. 2017) obtained from the residuals of the current model ($\alpha < 0.01$).

Using these deviance maps, first, brain regions where FA showed significant development with age in all adolescents were identified by comparing the fit of the intercept-only model and the linear growth model [voxel $\chi2(1) > 6.635$, cluster size > 500 voxels]. Second, to assess the effects of binge-drinking status and FHD on baseline FA only, the main-effects model was compared to the linear growth model [voxel $\chi2(2) > 9.210$, cluster size > 498 voxels]. Third, to assess the independent effects of binge-drinking status and FHD on both baseline and change and FA, interaction models including binge-drinking status controlling for FHD [voxel $\chi2(3) > 11.345$, cluster size > 505 voxels], or FHD controlling for binge-drinking status [voxel $\chi2(3) > 11.345$, cluster size > 511 voxels] were independently compared to the linear growth model. If any region identified in these interaction models overlapped with region(s) identified in the main-effects model, the main-effects and interaction models were compared voxel-wise to determine the best fitting, most parsimonious model. Finally, to assess the interaction effect of binge-drinking status and FHD on baseline FA and change in FA with age, an interaction model with both FHD and binge-drinking status was compared to the linear growth model [voxel $\chi2(6) > 16.812$, cluster size > 518 voxels]. Again, if this model identified any overlapping region(s) with any of the previous model(s), they were compared voxel-wise.

Comparing a taxonomy of models in this way ensured that final fixed effects were interpreted only in regions of the brain where the final model(s) serve as the best fitting model when compared to a reduced model (i.e. intercept-only or linear age model). This

method is statistically superior to previous developmental imaging studies using 3dLME, which simply interpret the fixed effects of whole-brain multilevel models, without comparing them to a potentially more parsimonious, alternative, or null model, a practice that has been traditionally discouraged in multilevel modeling approaches (Bliese and Ployhart 2002, Singer and Willett 2003).

4.2.5 Post-hoc analyses

FA values were extracted from all significant regions for model confirmation, interpretation of fixed effects, and for assessing the association between white matter microstructural development and delay discounting rates, using the nlme package (Pinheiro, Bates et al. 2009) in R (v. 3.4.2). Prior to multilevel modeling, *k* values were log transformed due to non-normal distribution, and age was re-centered at age 14 (approximately the median baseline age) or age 18 (approximately the median follow-up age) in order to aid in interpretation of the intercept. These represent ages where estimates were obtained based on data from at least half of our subjects, as opposed to interpreting effects at age 12 and 20 (the range of our data) where estimates are less reliable, due to few subjects contributing data to the estimates at that point. Further, FHD and FA values were mean centered for all models where they served as predictor variables. In all final models, effect sizes were reported in text as either Cohen's d (for categorical predictors), standardized regression estimates (for continuous predictors), or the difference between two standardized regression estimates (for interactions between continuous and categorical predictors). All models fit at the voxel-wise level were refit using extracted region-of-interest values from all significant clusters and the most

parsimonious model was confirmed by statistically comparing deviance statistics between nested models ($p < 0.01$) and by quantitative comparison of Akaike information criterion (AIC) and Bayesian information criterion (BIC) values between non-nested models (Singer and Willett 2003).

Finally, to determine if FA mediated the previously demonstrated relationship between binge-drinking status and FHD on the development of delay discounting rates (in Chapter 3), and to address the second aim of this study, a series of models were fit allowing FHD and binge-drinking status to interact with both baseline delay discounting rates and change in delay discounting rates with age (see Chapter 3 for more details). Once a final model was identified, FA from each significant cluster was added to the model to assess associations between FA and the development of delay discounting rates. To determine whether FA mediated the relationship between binge-drinking status or FHD and discounting rates, Z-tests were used to compare all significant fixed effects between models before and after the addition of FA (Paternoster, Brame et al. 1998).

4.3 Results

4.3.1 Participant characteristics

Participant baseline demographics are presented in Table 2. There were no significant differences between binge-drinking adolescents and controls on any baseline demographic variables.

Table 2. Baseline demographics.

	Bingers (n = 45) M (SD)	Controls (n = 68) M (SD)	Significance test
Sex (male/female)	25/20	34/34	$X^2(1) = 0.15$, $p = 0.699$
Age	14.55 (1.42)	14.17 (1.45)	$t_{111} = 1.39$, $p = 0.167$
Pubertal stage	3.84 (1.17)	3.72 (1.12)	$U = 1418$, $p = 0.496$
IQ	111.78 (10.57)	110.54 (10.06)	$t_{111} = 0.63$, $p = 0.533$
SES	26.95 (13.97) [a]	31.19 (13.25) [b]	$U = 1760$, $p = 0.084$
FHD	0.38 (0.30)	0.45 (0.36)	$U = 1688$, $p = 0.350$

[a] n = 44 due to missing data; [b] n = 67 due to missing data.

4.3.2 Effects of binge-drinking status and family history density on the development of fractional anisotropy

Results from the voxel-wise analysis revealed a single widespread white matter cluster (283,866 voxels) where a linear growth model provided a significantly better fit than an intercept-only model (Figure 1A). In this cluster, there was a significant increase in FA with age in all subjects ($b = 0.006$, $\beta = 0.655$, $p < 0.001$).

When binge-drinking status and FHD were added to the model and allowed to interact with baseline FA (the intercept), there were two regions where this main-effects model provided a significantly better fit than the linear growth model, in the left (2593 voxels) and right (3022 voxels) midbrain/PLIC (Figure 1A).

When the interaction model, including the effects of binge-drinking status with age (controlling for FHD) was fit, two regions in the midbrain/PLIC (left: 2,305 voxels; right: 2,762 voxels) were identified 96% of which overlapped with the two clusters identified in the main-effects model. Voxel-wise comparison of the main-effects and interaction models in this region (6,282 combined voxels) found no significant clusters where the interaction model fit significantly better than the main-effects model; therefore, the main-effects model was retained.

Similarly, when the interaction effect of FHD with age (controlling for binge-drinking status) was modeled, two regions, in the midbrain/PLIC (left: 2,305 voxels; right: 2,762 voxels) were identified 87% of which overlapped with the two clusters identified in the main-effects model, Voxel-wise comparison of the main-effects and interaction models in this region (5,794 combined voxels) found no significant clusters where the interaction model fit significantly better, thus the main-effects model was again

retained. Additionally, there was one new cluster identified by the FHD interaction model, located in the left superior frontal gyrus (SFG) white matter (540 voxels) (Figure 1A).

Lastly, when the interaction effect of binge-drinking status and FHD were modeled, two clusters in the midbrain/PLIC (left: 1,812 voxels, right: 2,087 voxels) were identified, 83% of which overlapped with those in the main-effects model. Again, voxel-wise analysis found no significant clusters (6,277 combined voxels) where this interaction model fit significantly better than the main-effects model. In total, three clusters in the left and right midbrain/PLIC and SFG white matter were carried into post-hoc analyses for interpretation of fixed effects.

Post-hoc modeling confirmed that the main-effects model was the most parsimonious model in the left and right midbrain/PLIC. Since the location, directionally and significance of the fixed effects for the two midbrain regions were the same, they were combined to produce a single bilateral cluster (Table 3, Model C). In this region, there was a significant association between binge-drinking status and FA throughout adolescence, when controlling for FHD (Figure 1B), such that FA was significantly greater in binge-drinking adolescents compared to controls ($b = 0.024$, $p < 0.001$, $d = 0.843$), while all adolescents showed a significant increase in FA with age ($b = 0.002$, $p < 0.05$, $\beta = 0.134$). Further, post-hoc modeling confirmed that an interaction model looking at the effects of FHD on baseline FA and change in FA with age, controlling for binge-drinking status, proved to be the best fitting model in the SFG (Table 4, Model E). In this region, greater FHD was associated with reduced FA at baseline ($b = -0.042$, $p < 0.001$, β

= -0.497), but a greater increase in FA with age (b = 0.006, p < 0.001, β = 0.148), such that FHD had little effect on FA by age 18 (Figure 1C).

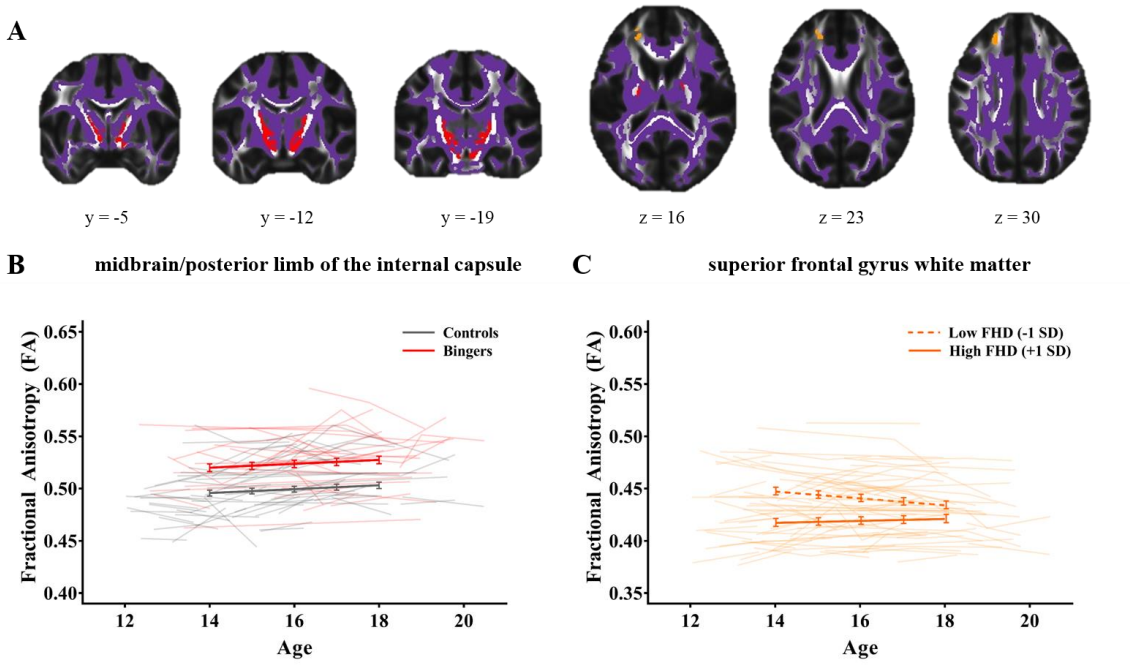

Figure 1. Regions showing significant effects of age, binge-drinking status and family history density on fractional anisotropy

(A) There was a single widespread cluster (violet) where the linear growth model provided the best fitting model, one cluster in the bilateral midbrain/PLIC (red) where a main-effects model including binge-drinking status and FHD of alcoholism provided the best fitting model, and one cluster in the SFG (orange) where an interaction model including the effect of FHD on baseline and change in FA, controlling for binge-drinking status, was the best fitting model. (B) Group means (±SEM) across age for binge-drinking adolescents (red) and controls (gray) are overlaid on top of individual measures of FA in the midbrain/PLIC. (C) Prototypical trajectories for individuals falling one standard deviation above (High FHD = 0.78) and below (Low FHD = 0.09) the mean FHD are overlaid on top of individual measures of FA in the SFG white matter.

Table 3. Parameter estimates for fractional anisotropy in the bilateral midbrain/PLIC

		Model A	Model B	**Model C**	Model D	Model E	Model F
Fixed Effects							
Initial Status	Intercept	0.508 [a] (0.003)	0.505 [a] (0.003)	**0.496 [a] (0.003)**	0.494 [a] (0.003)	0.496 [a] (0.003)	0.494 [a] (0.003)
	BINGE			**0.024 [a] (0.005)**	0.028 [a] (0.005)	0.024 [a] (0.005)	0.028 [a] (0.005)
	FHD			**-0.002 (0.006)**	-0.002 (0.006)	-0.001 (0.007)	0.003 (0.008)
	BINGE*FHD						-0.009 (0.015)
Rate of Change	Intercept		0.002 [a] (0.001)	**0.002 [a] (0.001)**	0.003 [a] (0.001)	0.002 [b] (0.001)	0.003 [a] (0.001)
	BINGE				-0.002 (0.001)		-0.003 (0.001)
	FHD					-0.001 (0.002)	0.001 (0.002)
	BINGE*FHD						-0.004 (0.004)
Variance Components							
Level 1	Within-person	1.45E-04	1.39E-04	**1.39E-04**	1.34E-04	1.39E-04	1.34E-04
Level 2	Initial status	6.15E-04	5.65E-04	**4.29E-04**	4.30E-04	4.28E-04	4.13E-04
Goodness-of-fit							
	df	3	4	**6**	7	7	10
	AIC	-1122.7	-1133.9	**-1156.9**	-1158.9	-1155.0	-1156.8
	BIC	-1112.3	-1120.2	**-1136.3**	-1134.9	-1131.0	-1122.4
	Deviance	-1128.7	-1141.9	**-1168.9**	-1172.9	-1169.0	-1176.8
	Test		A vs B	**B vs C**	C vs D	C vs E	C vs F
	Δ Deviance		13.227 [a]	**26.951 [a]**	4.086	0.142	7.917

[a] $p < 0.001$; [b] $p < 0.01$; standard errors are in parentheses. Model A is an unconditional means model; Model B is an unconditional growth model (including AGE); Model C includes the effects of binge-drinking status (BINGE) and FHD on initial status; Model D includes the effect of BINGE on initial status and rate of change (BINGE*AGE), controlling for FHD; Model E includes the effect of FHD on initial status and rate of change (FHD*AGE), controlling for BINGE; Model F includes the effects of BINGE and FHD, and their interaction (BINGE*FHD) on initial status and rate of change (BINGE*AGE, FHD*AGE, BINGE*FHD*AGE). The final, most parsimonious model is in bold text.

Table 4. Parameter estimates for fractional anisotropy in the left SFG

		Model A	Model B	Model C	Model D	**Model E**	Model F
Fixed Effects							
Initial Status	Intercept	0.430 [a] (0.003)	0.432 [a] (0.003)	0.429 [a] (0.003)	0.428 [a] (0.003)	**0.429 [a] (0.003)**	0.428 [a] (0.003)
	BINGE			0.008 (0.005)	0.010 (0.005)	**0.008 (0.005)**	0.007 (0.005)
	FHD			-0.032 [a] (0.007)	-0.032 [a] (0.007)	**-0.042 [a] (0.008)**	-0.034 [a] (0.009)
	BINGE*FHD						0.002 (0.017)
Rate of Change	Intercept		-0.001 [b] (4.49E-04)	-0.001 [b] (4.49E-04)	-2.95E-04 (6.74E-04)	**-0.001 [b] (4.21E-04)**	-0.001 (0.001)
	BINGE				-0.002 (0.001)		-2.22E-04 (0.001)
	FHD					**0.006 [a] (0.001)**	0.001 (0.002)
	BINGE*FHD						-0.001 (0.003)
Variance Components							
Level 1	Within-person	9.12E-05	8.47E-05	8.45E-05	8.14E-05	**7.26E-05**	7.09E-05
Level 2	Initial status	7.37E-04	7.46E-04	6.03E-04	6.05E-04	**6.09E-04**	6.13E-04
Goodness-of-fit							
	df	3	4	6	7	**7**	10
	AIC	-1164.3	-1170.4	-1188.3	-1190.9	**-1204.6**	-1201.0
	BIC	-1154.0	-1156.7	-1167.7	-1166.9	**-1180.6**	-1166.7
	Deviance	-1170.3	-1178.4	-1200.3	-1204.9	**-1218.6**	-1221.0
	Test		A vs B	B vs C	C vs D	**C vs E**	C vs F
	Δ Deviance		8.092 [b]	21.937 [a]	4.581	**18.264 [a]**	2.441

[a] $p < 0.001$; [b] $p < 0.01$; standard errors are in parentheses. Model A is an unconditional means model; Model B is an unconditional growth model (including AGE); Model C includes the effects of binge-drinking status (BINGE) and FHD on initial status; Model D includes the effect of BINGE on initial status and rate of change (BINGE*AGE), controlling for FHD; Model E includes the effect of FHD on initial status and rate of change (FHD*AGE), controlling for BINGE; Model F includes the effects of BINGE and FHD, and their interaction (BINGE*FHD) on initial status and rate of change (BINGE*AGE, FHD*AGE, BINGE*FHD*AGE). The final, most parsimonious model is in bold text.

4.3.2 Relationship between impulsive choice and fractional anisotropy in regions associated with binge-drinking status and family history density

When assessing the effects of binge-drinking status and FHD on the development of delay discounting rates, the best fitting, most parsimonious model was one where binge-drinking status was allowed to interact with both baseline delay discounting rates, and change in delay discounting rates with age, controlling for FHD (Table 5, Model C). This model revealed that while discounting rates decreased significantly across age in control adolescents (b = -0.521, $p < 0.001$, $\beta = 0.453$), this slope differed significantly in binge-drinking adolescents, with an estimated greater rate of change across age (b = 0.405, $p < 0.01$, $\Delta\beta = 0.352$), compared to controls (Figure 2). The combined estimates resulted in a non-significant change in discounting rates across age estimated for binge-drinking adolescents (b = -0.116), and thus, binge-drinking adolescents had greater discounting rates than controls by age 18 (b = 1.473, $p < 0.01$, $d = 0.627$).

When the main effect of midbrain FA was added to this model as a time-varying predictor (Table 5, Model D), it resulted in a slight model improvement ($\chi 2(1) = 4.458$, $p < 0.05$), and greater FA was associated with greater discounting rates throughout adolescence (b = 14.855, $p < 0.05$, $\beta = 0.181$); however, there were no significant change in the effect of binge-drinking-status-by-age on discounting rates ($Z = 0.269$) or the effect of binge-drinking status on discounting rates present at age 18 ($Z = 0.446$) between the two models. This suggests that while midbrain FA is associated with delay discounting rates, it serves as an independent predictor and does not mediate the age-related effects of binge-drinking status on impulsive choice. Models where the effect of midbrain FA was allowed vary with age (Table 5, Model E), or interact with binge-drinking status or FHD,

revealed no significant model improvement. Lastly, when FA in the SFG was added to the delay discounting model, it resulted in no model improvement, and was not associated with delay discounting rates, thus mediation was not tested for this cluster.

Table 5. Parameter estimates for delay discounting rates

		Model A	Model B	Model C	**Model D**	Model E
Fixed Effects						
Initial Status	Intercept	-5.003 [a] (0.209)	-4.518 [a] (0.227)	-4.442 [a] (0.281)	**-4.191 [a] (0.305)**	-4.140 [a] (0.316)
	BINGE			-0.148 (0.457)	**-0.570 (0.498)**	-0.652 (0.516)
	FHD			0.888 (0.554)	**0.911 (0.554)**	0.893 (0.555)
	midbrain FA				**14.855 [c] (7.083)**	17.865 [c] (8.597)
Rate of Change	Intercept		-0.294 [a] (0.067)	-0.521 [a] (0.098)	**-0.574 [a] (0.101)**	-0.587 [a] (0.103)
	BINGE			0.405 [b] (0.133)	**0.442 [a] (0.133)**	0.479 [b] (0.146)
	midbrain FA					-1.627 (2.617)
Variance Components						
Level 1	Within-person	2.505	2.348	2.251	**2.171**	2.170
Level 2	Initial status	3.133	2.739	2.483	**2.504**	2.492
Goodness-of-fit						
	df	3	4	7	**8**	9
	AIC	918.2	901.7	895.0	**892.5**	894.1
	BIC	928.2	915.1	918.4	**919.2**	924.18
	Deviance	912.2	893.7	881.0	**876.5**	876.1
	Test		A vs B	B vs C	**C vs D**	D vs E
	Δ Deviance		18.47 [a]	12.738 [b]	**4.458 [c]**	0.399

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; standard errors are in parentheses. Model A is an unconditional means model; Model B is an unconditional growth model (including AGE); Model C includes the effect of binge-drinking status (BINGE) on initial status and rate of change (BINGE*AGE), controlling for the main effect of FHD; Model D includes the effects of BINGE on initial status and rate of change (BINGE*AGE), and the main effect of midbrain fractional anisotropy (FA), controlling for the main effect of FHD; Model E includes the effect of BINGE on both initial status and rate of change (BINGE*AGE), and the effect of midbrain FA on initial status and the rate of change (FA*AGE), controlling for the main effect of FHD. The final, most parsimonious model is in bold text.

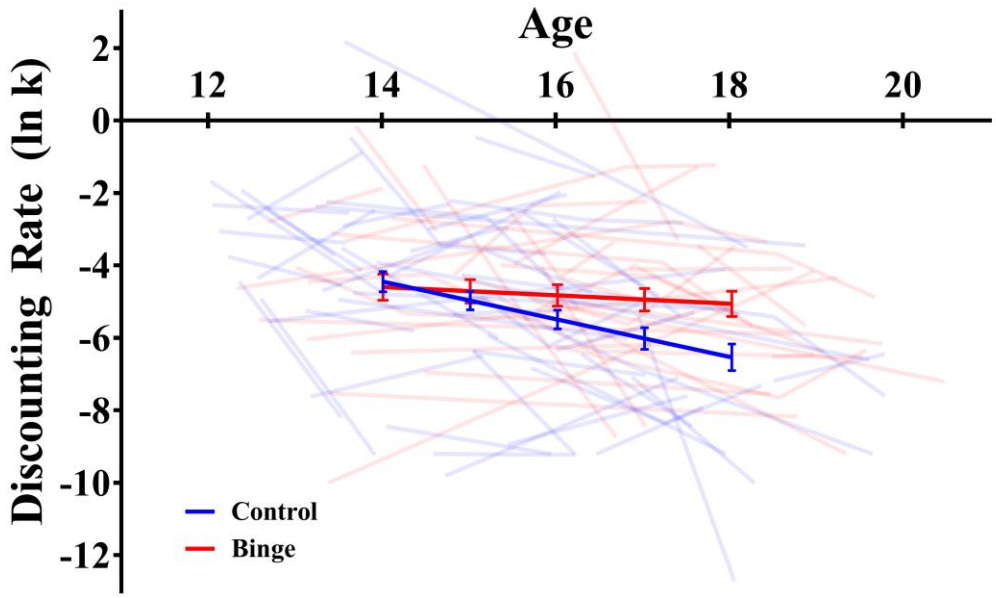

Figure 2. Significant association between binge-drinking status and delay discounting rates

Fixed effects trajectories of delay discounting rates across age are plotted for binge-drinking adolescents and controls, controlling for FHD. Binge-drinking (light red) and control (light blue) adolescents' individual delay discounting rates across age are plotted in the background.

4.4 Discussion

The goals of this study were to investigate the association of binge-drinking status and family history of alcoholism on FA development, and to determine whether alterations in the development of FA were associated with alterations in impulsive choice development. This is the first study to use a longitudinal design to investigate the combined effects of binge-drinking status and family history of alcoholism on the development of FA, and the first to investigate the association between FA and impulsive choice in binge-drinking adolescents.

As hypothesized, binge-drinking adolescents had altered FA in fronto-striatal tracts important for impulsive reward-based decision making, however, contrary to what was originally hypothesized, FA values in the midbrain were persistently *greater* in adolescents who went on to binge drink. While a majority of studies suggest that binge drinking during adolescence is associated with widespread reductions in FA, these studies have found that differences largely occur after an adolescent has engaged in alcohol use, with little difference being shown prior to initiation of use (Bava, Jacobus et al. 2013, Luciana, Collins et al. 2013), suggesting that these reductions in FA may be a result of alcohol's neurotoxic effect on the brain. The findings of the current study, however, demonstrated premorbid differences in FA prior to alcohol use initiation in those who went on to binge drink, and may represent neural alterations that could be used to distinguish adolescents who go on to engage in binge drinking from those who remain alcohol-naïve. This finding is in line with an early cross-sectional study that found binge-drinking adolescents had greater FA in the internal capsule, albeit in a slightly different location (anterior vs. posterior) (Bava, Frank et al. 2009). Greater levels of FA in striatal

white matter (including the internal capsule) of binge-drinking adolescents may represent stronger connectivity within mesolimbic dopaminergic pathways from the substantia niagra (SN)/ventral tegmental area (VTA) to nucleus accumbens (NAc), dorsal striatum, and prefrontal cortex, key pathways in the development of addiction (Koob and Volkow 2010).

This argument is further strengthened by the positive association found between midbrain FA and impulsive choice, regardless of age, drinking status, or FHD. These findings are in line with previous literature in healthy adolescents and young adults that have shown significant positive associations between impulsive choice and structural connectivity in reward-related white matter tracts, such as those connecting the ventral medial prefrontal cortex and ventral striatum as well as the amygdala and ventral striatum (van den Bos, Rodriguez et al. 2014, Hampton, Alm et al. 2017), regions that partially overlap with those found in the current study. The findings of this study extend those results and suggest that this association exists in both alcohol-naïve controls and binge-drinking adolescents and those with varying degrees of familial alcohol misuse. Taken together, these findings support the conclusion that binge-drinking adolescents have greater FA in regions where FA is positively associated with impulsive responding for rewards, and could provide one explanation for why these adolescents went on to engage risk-taking behavior, such as binge drinking, as impulsivity is thought to dominate the early stages of the addiction cycle (Koob and Volkow 2010).

While FHD did not interact with binge-drinking status in its association with FA, greater FHD was independently associated with reduced FA in the SFG at baseline, an effect that dissipated with age. This finding corroborates a previous report that found

reduced FA in FHP adolescents (FHD > 0.5) compared to those without familial alcoholism, in dorsal medial regions of the prefrontal cortex (Herting, Schwartz et al. 2010). However, the current findings suggest that these alterations, may be transient and diminish with age, both in adolescents who go on to binge drink and those who remain largely alcohol naïve. This finding is also in agreement with functional MRI studies that have found that FHP youth, compared to FHN youth, had reduced brain activation in the SFG during response inhibition (Schweinsburg, Paulus et al. 2004), and that reduced brain activation in the SFG during response inhibition predicted which adolescents would go on to binge drink (Norman, Pulido et al. 2011). While FA in the SFG in this study was not associated with future binge-drinking status, its negative association with FHD prior to alcohol use does suggest it may be indirectly involved in the increased risk for future alcohol misuse that accompanies this genetic and/or environmental predisposition.

These findings provide novel insight into the association between personal and familial alcohol misuse and FA, however, there are several limitations. First, while these results strongly suggest that the observed differences in FA between binge-drinking adolescents and controls are in dopaminergic pathways projecting up from the VTA/SN, it cannot be ruled out that other fiber tracts make up portions of this cluster, be it top-down control pathways from the prefrontal cortex or corticospinal tract fibers more involved in motor control (see Chapter 6 for more discussion). Follow-up tractography analyses may be helpful in addressing this possibility. Second, this analysis failed to replicate the interaction effects of FHD and binge-drinking status on impulsive choice development, as seen in Chapter 3. However, the effect of the three-way interaction in this sample was in the same direction as in Chapter 3, despite not reaching statistical

significance (b = 0.734, p = 0.13, $\Delta\beta$ = 0.210). Further, the effect sizes in Chapter 3 ($\Delta\beta$ = 0.298) and here ($\Delta\beta$ = 0.210) reflect small to medium effects, that may be impacted by slight alterations in sample size or sample makeup, as is the case in the current analysis, with many subjects being excluded between Chapter 3 and this analysis due to missing or unusable DWI data. Third, this analysis failed to identify any regions of the brain where the association between FHD and FA varied based on future binge-drinking status. While this may suggest that personal and familial alcoholism are independently associated with FA development, this null finding may also be a result of one or more methodological restrictions including, sample size, the number of within-subject time points, lack of non-linear modeling, or the voxel-wise modeling strategy itself. Future studies in larger samples will be necessary to substantiate this novel analytic strategy and further explore the interactive effects of personal and familial alcohol misuse. Fourth, it cannot be ruled out that control participants will not initiate alcohol use at a later time, or that current binge drinkers may cease drinking later in adolescence, two possibilities that must be taken into account when considering these findings as risk markers for future alcohol misuse (see Chapter 6 for more discussion). Lastly, given the sample size, this study did not have adequate power to report on additional important variables, such as sex differences, which have been reported in both white matter development (Simmonds, Hallquist et al. 2014), as well as in rates of impulsive decision making (Silverman 2003, Weafer and de Wit 2014).

In conclusion, these findings provide novel insight into the development of FA in adolescents with personal and familial alcohol misuse and demonstrated that those who went on to drink had greater FA in white matter tracts important for impulsive decision

making. These findings also demonstrated that greater FHD was transiently associated with lower FA in the frontal white matter in all adolescents. These findings suggest that over maturation of white matter fibers in the midbrain may be indicative of a hyperactive mesolimbic dopamine pathway, prior to alcohol use in adolescents who later go on to engage in binge drinking, and that alterations in frontal white matter early in adolescence are associated with a genetic and/or environmental susceptibility to developing an AUD. Future studies will be necessary to confirm this association between greater FA in midbrain white matter and hyperactivity in reward networks, at which point this may serve as a useful neurobiological marker for identifying adolescents prone to engage in impulsive behavior and initiate binge drinking.

Chapter 5. The role of personal and familial alcoholism in the appreciation of future consequences in adolescence

5.1 Introduction

It is well-documented that adolescence is a time of extensive neurobiological development (for review, see Chapter 1.2), resulting in a period of increased plasticity and vulnerability to the neurotoxic effects of alcohol (Crews, He et al. 2007). Pre-clinical models suggest that adolescent rodents are more vulnerable to the neurotoxic effects of alcohol (Crews, Braun et al. 2000), especially in regions demonstrating protracted development, such as the prefrontal cortex (Koss, Sadowski et al. 2012). Meanwhile, as noted in Chapter 1.3, numerous MRI studies in binge-drinking human adolescents have demonstrated structural differences in brain volume and thickness (Howell, Worbe et al. 2013, Luciana, Collins et al. 2013, Doallo, Cadaveira et al. 2014, Mashhoon, Czerkawski et al. 2014, Squeglia, Rinker et al. 2014, Whelan, Watts et al. 2014, Squeglia, Tapert et al. 2015, Kvamme, Schmidt et al. 2016) and white matter microstructure (Bava, Frank et al. 2009, Jacobus, McQueeny et al. 2009, McQueeny, Schweinsburg et al. 2009, Bava, Jacobus et al. 2013, Jacobus, Squeglia et al. 2013, Jacobus, Thayer et al. 2013), when compared to controls. As noted in Chapter 1.5, adolescents also demonstrate increased risk-taking behavior (Eaton, Kann et al. 2012), likely due to the changes in impulsivity (see Chapter 3), behavioral inhibition (Seghete, Herting et al. 2013) and future orientation (Steinberg, Graham et al. 2009), during this period of development. Further, earlier findings (in Chapter 3) confirmed previous literature (Field, Christiansen et al. 2007, Sullivan, Brumback et al. 2016), that binge drinking during adolescence is associated with elevated impulsivity, while findings in Chapter 4, suggested these impairments may be associated with alterations in white matter microstructure in striatal regions such as the PLIC. While a previous report suggested that binge-drinking adolescents and young

adults may also show less future orientation (as noted in Chapter 1.6) (Keough, Zimbardo et al. 1999), it is unclear if this, too, is associated with underlying alterations in white matter microstructure. A more thorough understanding of this association is crucial as the appreciation of future consequences represents an under-explored facet of risk-taking behavior, which may uniquely influence the decision to drink (see Chapter 1.5).

In addition to the associations between binge drinking and elevated impulsivity, familial alcohol use has also been associated with increased impulsivity (as noted in Chapter 1.7), with FHP adolescents demonstrating greater impulsive choice than FHN (Acheson, Vincent et al. 2011, Dougherty, Charles et al. 2014, Henderson, Vaidya et al. 2018). However, it is unclear if a family history of alcoholism, itself, is associated with reduced future orientation and appreciation of future consequences, nor is it clear if binge drinking and family history of alcoholism have any interaction effect on the consideration of future consequences, like has been demonstrated previously for impulsive choice (see Chapter 3). As the decision to drink requires the weighing of both potential gains and losses (see Chapter 1.4), a better understanding of the effects of binge drinking, familial alcoholism, and their interaction on future orientation and the consideration for future consequences is warranted.

Further, earlier findings (in Chapter 4) confirmed previous reports that family history of alcoholism is also associated with altered white matter microstructure (Herting, Schwartz et al. 2010, Acheson, Wijtenburg et al. 2014, Squeglia, Jacobus et al. 2014), particularly in fronto-striatal regions shown to be associated with the development of impulsive choice (van den Bos, Rodriguez et al. 2014, van den Bos, Rodriguez et al. 2015, Achterberg, Peper et al. 2016, Hampton, Alm et al. 2017); however, no interaction

effect between binge drinking and familial alcoholism on FA was observed, despite a previous study suggesting familial alcoholism and personal alcohol use may combine to result in greater alterations of FA (Hill, Terwilliger et al. 2013). Little is known about the underlying changes in neurobiology that are associated with future orientation, and more specifically the appreciation of future consequences, neither in regards to normative development nor in the context of personal or familial alcohol use. Using a temporal discounting paradigm, previous studies have demonstrated that discounting of delayed gains and discounting of delayed losses are associated with differential neural activation (Xu, Liang et al. 2009). This further suggests that future orientation and the appreciation of future consequences may represent unique constructs of risk taking and may be differentially associated with underlying neurobiology.

The current study aimed to explore future orientation and the appreciation of future consequences both via self-report and behavioral measures (e.g. loss discounting), in binge-drinking and control adolescents with varying degrees of familial alcoholism. Further, it aimed to investigate the association between FA and the appreciation of future consequence and how this may vary as a function of personal and familial alcohol misuse. Based on previous studies demonstrating reduced future time perspective in high school and college aged youth is associated with greater alcohol use (Keough, Zimbardo et al. 1999), it was hypothesized that adolescents in this study would also demonstrate reduced future orientation and appreciation of future consequences via measures of self-report and discounting of delayed losses. Further, as it was shown earlier (see Chapter 3) that family history of alcoholism has a differential role in impulsive choice depending on binge-drinking status, it was hypothesized that family history of alcoholism would be

associated with less future orientation in binge-drinking adolescents, but greater future orientation in control adolescents. Further, it was hypothesized that greater future orientation would be associated with greater FA in midbrain white matter tracts (similar to earlier findings related to impulsive choice; see Chapter 4), as well as greater FA in white matter tracts connecting salience regions in the brain, such as ALIC and the SLF (Wakana, Jiang et al. 2004), regions shown to be more heavily recruited during the discounting of delayed losses as compared to gains (Xu, Liang et al. 2009). Lastly, it was hypothesized that binge-drinking status and family history of alcoholism would be associated with disruptions in the relationship between FA and future orientation.

5.2 Methods

5.2.1 Participant characteristics

As noted in Chapter 2.3, 66 adolescents (14 baseline, 52 re-assessment), including 34 binge-drinking adolescents and 32 controls, were recruited for this study. This cross-sectional study included adolescents ages 14-22, with a median age of 18.7, suggesting that over half of the adolescents in this sample were older than the median follow-up age in Chapters 3 and 4. All demographic variables outlined in Chapter 2.2 were collected, examined for outliers (> 2.5 SD from the mean) and normal distribution and, compared between binge-drinking adolescents and controls, using independent-samples *t*-tests, or Mann-Whitney and chi-square tests where appropriate.

5.2.2 Behavioral and self-report measures

Future Orientation Questionnaire

To obtain a general measure of future orientation, all adolescents received the Future Orientation Questionnaire (FOQ). The FOQ is a 15-item self-report measure that consists of three, 5-item subscales (Time Perspective, Planning Ahead and Anticipation of Future Consequences (Steinberg, Graham et al. 2009). Investigation into the inter-correlations among these sub-scales suggests that they represent three related, but not identical aspects of future orientation, all of which increase across adolescence (Steinberg, Graham et al. 2009).

Zimbardo Time Perspective Inventory

In order to directly compare future orientation to present (and past) orientation, all participants were administered the Zimbardo Time Perspective Inventory (ZTPI). The ZTPI is a 56-item, self-report measure of individual differences in time-orientation, with a specific focus on the temporal (past, present or future) component (Zimbardo and Boyd 2015). The questionnaire consists of 5 reliable subscales (Past Negative, Past Positive, Present Hedonistic, Present Fatalistic, and Future), which have been validated in several diverse populations, included adolescents (Keough, Zimbardo et al. 1999, Díaz-Morales 2006, Sircova, V. Mitina et al. 2007, Worrell and Mello 2007, Zimbardo and Boyd 2015).

Consideration of Future Consequences

To focus specifically on negative outcomes, and simultaneously assess concern for immediate and future consequences, all participants were administered the Consideration of Future Consequences (CFC) questionnaire. The CFC is a validated and reliable measure of individual differences in the extent to which one considers immediate

consequences versus distant (or delayed) consequences (Strathman, Gleicher et al. 1994, Toepoel 2010). Using the original twelve-item questionnaire, previous studies suggest a two-factor solution (i.e. two subscales) relating to consideration for either immediate (7 questions) or future (5 questions) consequences (Joireman, Balliet et al. 2008, Adams 2012). However, the reliability of the five-item CFC-Future subscale has been shown to be poor (Joireman, Balliet et al. 2008). Therefore, the current study utilized a modified fourteen-item scale (including the original 12 questions, with 2 additional questions added to the CFC-Future subscale), which has also been show to support the presence of two highly reliable factors (Joireman, Shaffer et al. 2012). This allowed for the assessment of concern for both immediate and future consequences, independently, as opposed to treating them as opposite ends of a continuum.

Loss discounting

To obtain a behavioral measure of appreciation for future consequence, a subset of individuals (22 binge-drinking adolescents and 17 controls) were administered a novel loss discounting task (described in detail, in Chapter 2.4).

5.2.3 Image acquisition

All participants were scanned on a recently upgraded scanner platform resulting in slightly modified acquisition parameters from those reported in Chapter 4.2.2. Here, participants were scanned on a 3T Siemens Magnetom Prisma with a 20-channel head coil. DWI sequences parameters were similar to those in Chapter 4.2.2 and participants received either three (n = 3; scan time = 16:52) or two (n = 52; scan time = 11:24) DWI runs. A modified diffusion field map was also acquired (repetition time = 701 ms, echo

time 1 = 4.92 ms, echo time 2 = 7.38 ms, flip angle = 60°, field of view = 256 mm^2, slices = 72, slice thickness = 2 mm, scan time = 3:02) to correct DWIs for eddy current-induced field distortions. Thirteen participants in the current study did not receive a DWI scan due to time constraints.

5.2.4 Image processing

Quality assessment and volume censoring

Prior to image processing, all DWI runs underwent strict visual inspection for motion and scanner-related artifacts, and four image QA metrics were calculated for each run (see Chapter 4.2.3 for details). Based on this procedure, only 2 runs were deemed as being Poor. This is significantly fewer than has been seen previously (see Chapter 4.2.3 for details) and is likely a result of lower degrees of motion in the older age range included in this analysis. All volumes deemed to contain motion or scanner-related artifacts were censored; however, if the same direction/volume was excluded from all DWI runs within a single imaging session, that entire scan was excluded (see Chapter 4.2.3 for details). This procedure led to the exclusion of 2 participants and resulted in a final sample of 28 binge-drinking adolescents and 25 controls.

Fractional anisotropy

DWI data were processed using a combination of FSL and AFNI, and consisted of affine registration of the diffusion field map (Saad, Glen et al. 2009), concatenation of all DWI runs within a scan, and correction for eddy current distortion, intensity inhomogeneities, head motion, and subsequent adjustment of the gradient table (Andersson and Sotiropoulos 2016). FSL's dtifit (Smith, Jenkinson et al. 2004) was used

to calculate the diffusion tensor, identify the eigenvalues of the tensor, and calculate FA, for each voxel (see Chapter 4.2.3 for details).

Image registration

After obtaining individual FA maps, ANTs algorithms (Avants, Epstein et al. 2008) were used to register participants to standard space. These procedures were similar to those outlined previously, in Chapter 4.2.3; however, there was no registration to a within-subject template, due to the cross-sectional nature of the current analyses.

5.2.5 Statistical analyses

Future orientation and appreciation for future consequences

First, to investigate future orientation more broadly, OLS regression was utilized to look at the effects of binge-drinking status and FHD on total scores on the FOQ. An unrestricted model including binge-drinking status, FHD, and their interaction, with age as a covariate (Total FOQ ~ Group * FHD + age), was tested and then compared to several reduced models. If any model provided significant results, then this final model was applied to the three subscales to aid in further interpretation of the findings.

Second, to directly compare future orientation to present and past orientation, and to investigate the association between binge-drinking status and FHD and time perspective, all subscales on the ZTPI were assessed. As there is no overall (i.e. total) score on the ZTPI, to properly incorporate the within-subject nature of the subscales into a single statistical test, multilevel modeling with subscales nested within individual, and included as a fixed effect, was utilized. This allowed for the exploration of interaction effects of binge-drinking status and FHD with subscale, that is, where binge drinking or

FHD was associated with differences in one subscale but not the other. Further, the multilevel modeling framework allowed for the inclusion of random effects (i.e. random intercepts), which help better account for between-individual differences in overall ZPTI scores. A series of multilevel models were fit using ML, which allowed for direct statistical comparison of several models with different fixed effects structures.

Third, to focus more specifically on consequences, the association between binge-drinking status and FHD and consideration for immediate and future consequences (as assessed using the CFC) was investigated. First, OLS regression was utilized to model the effect of binge drinking, FHD, and their interaction, with age as covariate on CFC total scores (Total CFC ~ Group * FHD + age). Then, since previous studies have suggested that the Immediate and Future subscales measure two independent constructs (Joireman, Balliet et al. 2008, Adams 2012, Joireman, Shaffer et al. 2012), multilevel modeling, similar to what was utilized for the ZTPI, was conducted with the two subscales of the CFC (Future Consequences and Immediate Consequences) nested within individuals and explored as fixed effects, while allowing for individual differences in CFC scores via the random effects structure.

Lastly, to investigate the effects of binge-drinking status and FHD on loss discounting behavior, a series of unrestricted and reduced OLS regressions were fit for the AUC measures obtained from the loss discounting task (see Chapter 2.4 for more details). An unrestricted model including binge-drinking status, FHD, and their interaction (AUC ~ Group * FHD), was tested and then compared to several reduced models. Further, given that effects of family history on RTs during gain discounting have been shown previously (Herting, Schwartz et al. 2010), RTs (the time between

presentation of the choice pair and the subject's response) were collected for each trial. Previous studies suggest that choices made near an individual's indifference point (regardless of delay length) require greater deliberation, and thus, have longer RTs (i.e. "hard" choices), than choices made farther from an individual's indifference point (i.e. "easy" choices) (Robles and Vargas 2007, Hoffman, Schwartz et al. 2008, Robles and Vargas 2008). Therefore, for the purposes of exploratory analyses, RTs were classified in two ways: 1) based on whether they corresponded to a delay choice selection vs. immediate choice selection, or 2) based on whether they corresponded to choices near the indifferences point vs. choices further from the indifference point. For the current study, choices made near the indifference point included any choice that occurred on either side of a "switch point". That is, the choice amount within any given delay length where an adolescent switched from selecting the immediate payment to the delayed payment, or vice versa. In line with previous analyses in this study, to assess the effects of binge-drinking status and FHD on RTs a series of multilevel models were fit that included delay length (7, 30, 90, 180, and 365 days) and trial type (delay vs. immediate or near indifference point vs. not) nested within subject (RT ~ Group * FHD * delay length * trial type).

Principal components analysis

To reduce the number of self-report measures, and to obtain a single measure of future orientation in which to correlate with FA, a confirmatory factor analysis (CFA) was run utilizing all subscales from each of the three self-report measures. A CFA with a three-factor solution was tested to create latent variables for "past," "present," and "future" orientation. ZTPI-Past Negative and ZTPI-Past Positive were used as measures

of past orientation, CFC-Immediate, ZTPI-Present Hedonism, and ZTPI-Present Fatalism were used as measures of present orientation, and FOQ-Planning Ahead, FOQ-Time Perspective, FOQ-Anticipation of Future Consequences, CFC-Future, and ZTPI-Future were used as measures of future orientation. There was a significant correlation between all measures within the present (all $p < 0.001$), future (all $p < 0.001$), and past ($p < 0.05$) variables (Figure 1), providing statistical support for a theoretically-driven three-factor solution. The CFA model was fit using the lavaan package (Rosseel 2012) in R using ML estimation, with full information maximum likelihood (FIML) for missing data, using standardized scores from each subscale. In order to further assess the appropriateness of this model, the three-factor solution was compared to a CFA model with a single latent factor, and a three-factor model where the covariance between latent variables was set to zero (i.e. the three latent factors treated as independent). Lastly, regression factor scores (for the future orientation latent variable) were extracted from the three-factor CFA model and the effects of binge-drinking status and FHD, controlling for age, on future factor scores were assessed.

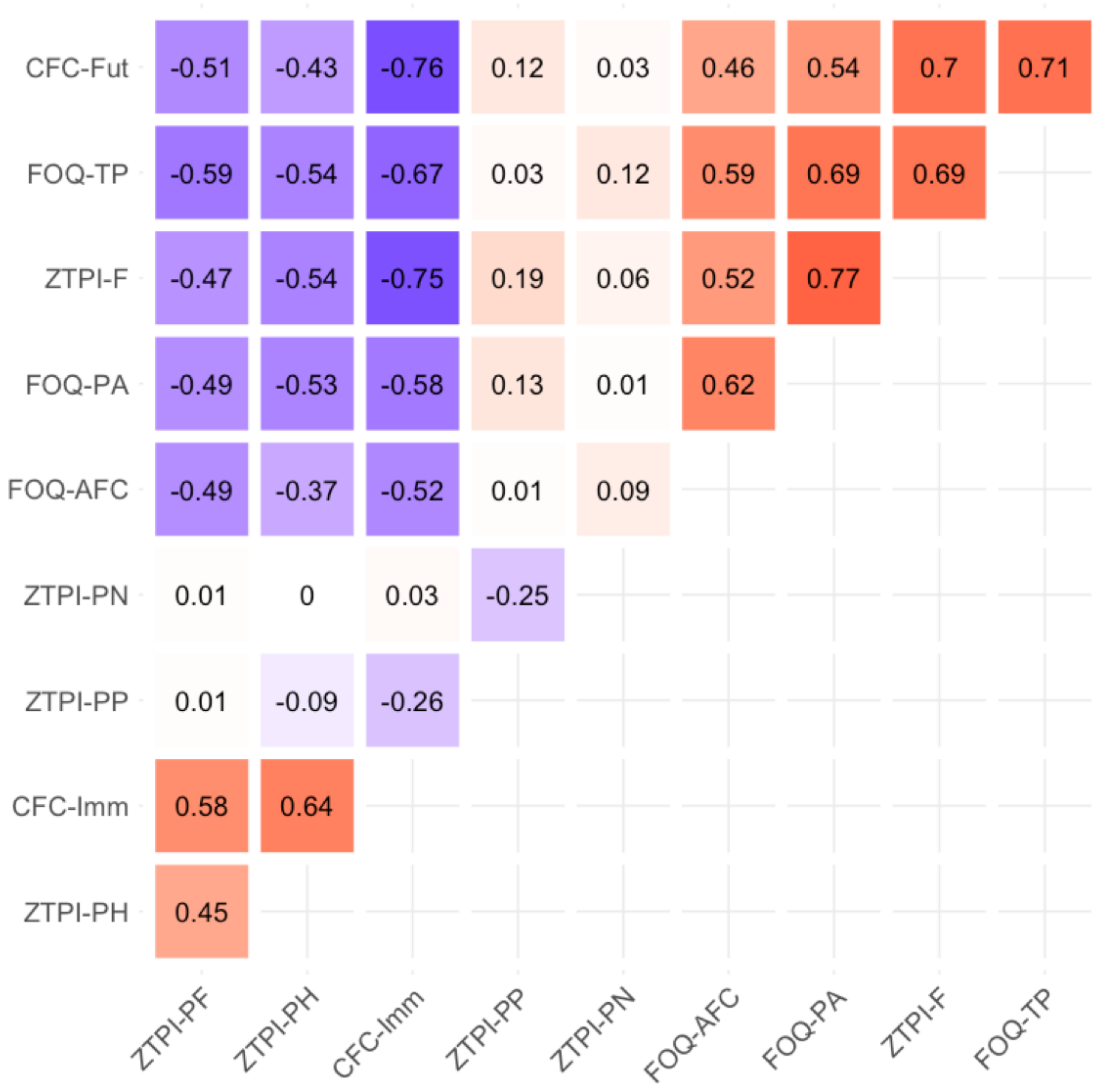

Figure 1. Correlation matrix for all self-report measures
Correlations for subscales on the Future Orientation Questionnaire (FOQ), Consideration of Future Consequences (CFC) and Zimbardo Time Perspective Inventory (ZTPI). There were three "present" subscales (ZTPI-Fatalism, ZTPI-Present Hedonism and CFC-Immediate) that were highly inter-correlated ($p < 0.001$), five "future" subscales (FOQ-Anticipation of Future Consequences, FOQ-Planning Ahead, FOQ-Time Perspective, ZTPI-Future and CFC-Future) that were highly inter-correlated ($p < 0.001$), and two "past" subscales (ZTPI-Past Positive and ZTPI-Past Negative) that were inversely correlated ($p < 0.05$). Positive correlations are in red and negative correlations are in blue.

Associations with white matter microstructure

To investigate the association between future orientation and FA, "future orientation" factor scores were utilized in a voxel-wise white matter analysis. All predictors (e.g. binge-drinking status, FHD, and age) that proved to be significantly associated with these factor scores were included as predictors (and allowed to interact with the future orientation latent variable) in voxel-wise regression using AFNI's 3dttest++. Similar to previous analyses (see Chapter 4.2.3), this voxel-wise regression was carried out in a whole brain white matter mask, with a voxel-wise threshold ($p < 0.01$) applied to each of the individual fixed effects in the model. To correct for multiple comparisons, and estimate the probability of false positive clusters, AFNI's 3dClustsim (Forman, Cohen et al. 1995) was employed using the spatial autocorrelation function parameters (Cox, Chen et al. 2017) obtained from the residuals of this regression model ($\alpha < 0.01$), similar to analyses in Chapter 4.2.4. For all significant clusters, average FA values were extracted in order to interpret the directionality of findings and for inclusion in post-hoc analyses.

5.3 Results

5.3.1 Participant characteristics

Participant demographics for each analysis are presented in Table 1. As binge-drinking adolescents were significantly older than controls, age was tested as a covariate in all analyses of self-report measures and diffusion imaging and included in any final analysis where it served as a significant predictor or resulted in improvements in model fit.

Table 1. Demographics for analyses of self-reports, loss discounting and diffusion weighted imaging

	Bingers: *M* (SD)	Controls: *M* (SD)
Self-report measures		
Total N	34	32
Sex (male/female)	14/20	15/17
Age	19.32 (1.36)	17.45 (2.23) [a]
IQ	113.35 (12.10)	113.25 (6.62)
SES	27.66 (15.38)	26.91 (12.01)
FHD	0.38 (0.25)	0.37 (0.29)
Loss discounting		
Total N	22	17
Sex (male/female)	9/13	8/9
Age	19.07 (0.96)	18.32 (2.11)
IQ	113.05 (12.37)	113.94 (7.81)
SES	26.55 (13.91)	30.88 (14.67)
FHD	0.33 (0.27)	0.36 (0.28)
Diffusion weighted imaging		
Total N	28	25
Sex (male/female)	10/18	12/13
Age	19.30 (1.44)	17.41 (2.21) [a]
IQ	111.21 (10.79)	112.80 (7.04)
SES	28.11 (12.22)	29.68 (15.85)
FHD	0.38 (0.28)	0.40 (0.27)

[a] $p < 0.05$

5.3.2 Effects of binge-drinking status and family history density on the appreciation for future consequences

Future Orientation Questionnaire

Fitting an unrestricted model for Total FOQ scores (Total FOQ ~ Group * FHD + age) resulted in a model that was significantly better than the null model [$F(4,60) = 3.316$, $p < 0.05$, Adjusted-$R^2 = 0.127$], with significant effects of binge-drinking status ($b = -0.434$, $p < 0.01$) and age ($b = 0.086$, $p < 0.05$); however, the effects of FHD and the binge-drinking-status-by-FHD interaction were not significant. When compared to a reduced model (Total FOQ ~ Group + age), the unrestricted model failed to provide an improvement ($df = 2$, $SS = 0.231$, $F = 0.454$, $p = 0.637$) over a reduced model, and this reduced model, also proved to be significantly better than the null model [$F(2,62) = 6.289$, $p < 0.01$, Adjusted-$R^2 = 0.142$]. This reduced model demonstrated that binge-drinking adolescents had significantly lower FOQ scores than controls ($b = -0.451$, $p < 0.01$), when controlling for the significant effect of age ($b = 0.094$, $p < 0.01$). When this reduced model was used to analyze the FOQ subscales, binge-drinking adolescents had lower planning ahead ($b = -0.541$, $p < 0.01$), time perspective ($b = -0.384$, $p < 0.05$) and appreciation of future consequences ($b = -0.425$, $p < 0.01$) scores, when controlling for the effects of age (Figure 2).

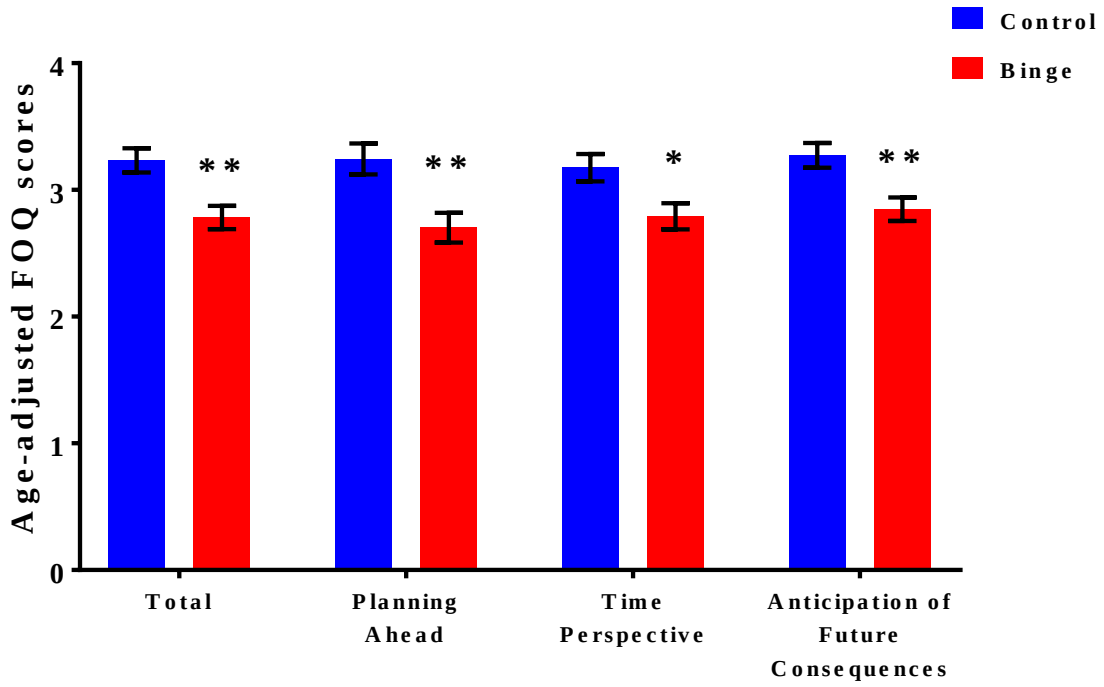

Figure 2. Binge-drinking adolescents have reduced future orientation.
Compared to controls, binge-drinking adolescents demonstrate reduced future orientation, as assessed using the Future Orientation Questionnaire (FOQ) Total Scores, as well as Planning Ahead, Time Perspective, and Anticipation of Future Consequences subscale scores. Age-adjusted scores (means and standard errors) are depicted for binge-drinking adolescents (red) and controls (blue). * $p < 0.05$ compared to controls; ** $p < 0.01$ compared to controls.

Zimbardo Time Perspective Inventory

For the ZTPI, when comparing a series of multilevel models, there were several models, including binge-drinking status, FHD and their interactions with each other and by subscales (controlling for age), that proved significantly better than the null model. However, a reduced model including only the main effect of subscale was the most parsimonious model that proved to be significantly better than the null model [$\chi^2(1) = 142.907$, $p < 0.001$], while failing to be improved by the addition of any other predictors (e.g. binge-drinking status, FHD, or age). In this model, all adolescents regardless of binge-drinking status or FHD, demonstrated lower Present Fatalistic scores when compared to all other subscales (all $b \geq -0.597$, $p < 0.001$), and reduced Past Negative scores compared to all subscales except Present Fatalistic (all $b \geq -0.484$, $p < 0.001$). Furthermore, while the model investigating binge-drinking-status-by-subscale interactions was not a significantly better model, there were significant subscale-by-group interaction when comparing the Future subscale to both the Present Fatalistic ($b = 0.437$, $p < 0.05$) and Present Hedonistic ($b = 0.456$, $p < 0.05$) scales. That is, binge-drinking adolescents appear to have lower Future scores and greater Present Hedonistic and Present Fatalistic scores (Figure 3), though none of those simple linear contrasts reached statistical significance.

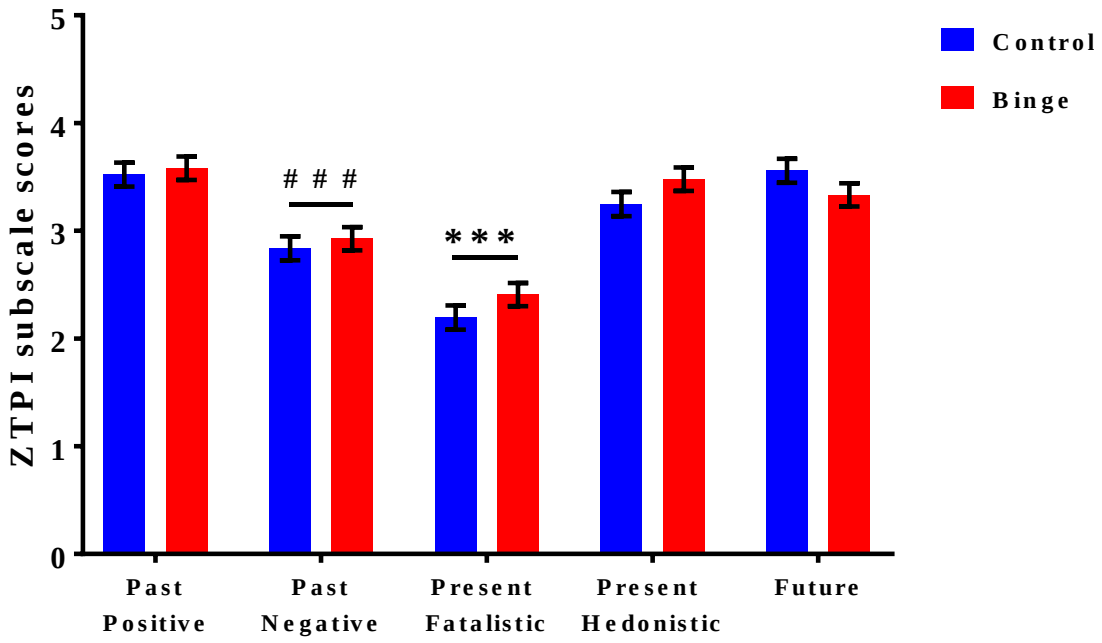

Figure 3. All adolescents demonstrate reduced past negative and present fatalistic time perspective.
Overall all adolescents had lower Present Fatalistic scores compared to all other subscales, and lower Past Negative scores compared to all subscales except Present Fatalistic. There were no main effects of binge-drinking status or binge-drinking status by subscale interactions. *** $p < 0.001$ compared to all other subscales; ### $p < 0.001$ compared to Past Positive, Present Hedonistic and Future.

Considerations for Future Consequences

Fitting an unrestricted model for Total CFC scores (Total CFC ~ Group * FHD + age) resulted in a model that was not significantly better than the null model [$F(4,61) = 2.390$, $p = 0.061$, Adjusted-$R^2 = 0.079$]; however, significant binge-drinking status ($b = -0.537$, $p < 0.05$) and age ($b = 0.164$, $p < 0.05$) effects were again present. When a reduced model was fit (Total CFC ~ Group + age), this model proved to be significantly better than the null model [$F(2,63) = 4.588$, $p < 0.05$, Adjusted-$R^2 = 0.099$], and demonstrated that binge-drinking adolescents had significantly lower CFC scores than controls ($b = -0.562$, $p < 0.05$), when controlling for the significant effect of age ($b = 0.176$, $p < 0.01$) (Figure 4). However, multilevel modeling failed to demonstrate any significant binge-drinking-status-by-subscale interactions, with only a model including subscale as a significantly fixed effect providing any improvement over the null model [$\chi^2(1) = 66.950$, $p < 0.001$], with all adolescents demonstrating greater scores on consideration for future consequences compared to immediate consequences ($b = 1.658$, $p < 0.001$).

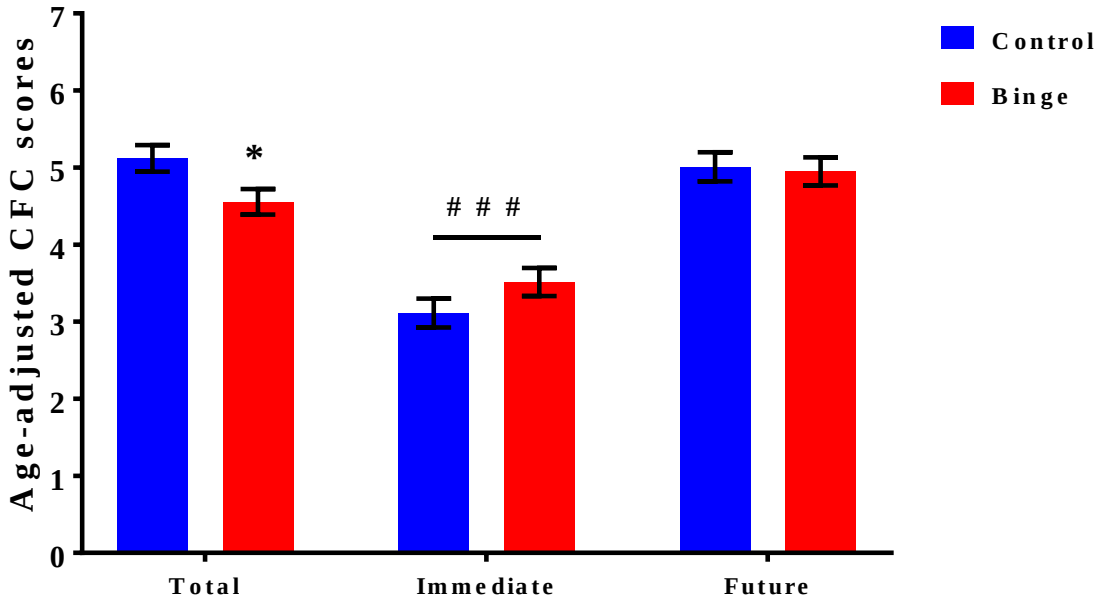

Figure 4. Binge-drinking adolescents demonstrate reduced consideration of future consequences

Binge-drinking adolescents demonstrate lower CFC-Total scores when compared to controls. No significant group effects were evident in the subscales; however, all adolescents demonstrated reduced CFC-Immediate scores than CFC-Future scores. * $p < 0.05$ compared to controls; ### $p < 0.001$ when compared to CFC-Future scores.

Loss discounting task

When investigating the effects of binge-drinking status and FHD on AUC measures from the loss discounting task, the unrestricted model, as well as all reduced models failed to provide a significantly better model than the null model, suggesting that there were no effects of binge-drinking status or FHD on loss discounting rates in this sample. Prior to analyses of RTs, data from 5 subjects were excluded due to having RTs that were more than 3 SDs above the mean at multiple delay lengths. After excluding these participants there were still no effects of binge-drinking status or FHD on AUC measures. Exploratory analyses of RTs, when classified based on correspondence to immediate vs delay selections found that on average, adolescents had longer RTs when making delay selections vs. immediate selections ($b = 155.410$, $p < 0.001$, $d = 0.423$) and demonstrated greater RTs as a function of delay length (longer RTs for longer delay lengths) ($b = 0.687$, $p < 0.001$, $\beta = 0.243$) (Figure 5A). A model including delay length and selection type as main effects proved significantly better than the intercept only model [$\chi^2(2) = 57.893$, $p < 0.001$], as well as reduced models including only delay length [$\chi^2(1) = 26.385$, $p < 0.001$] or choice selection [$\chi^2(1) = 34.299$, $p < 0.001$]. Follow-up Bonferroni-corrected ($p < 0.01$) paired t-tests found that RTs were greater at delay lengths of 30 days ($t(31) = 4.615$, $p < 0.001$) and 90 days ($t(31) = 3.506$, $p < 0.01$) (Figure 5A). Further, when RTs were calculated based on whether they surrounded the indifference point or not, multilevel modeling revealed that, on average, adolescents demonstrated longer RTs when making selections around the indifference point than when not ($b = 305.583$, $p < 0.001$, $d = 0.629$), and again, RTs were greater as a function of delay length ($b = 0.516$, $p < 0.01$, $\beta = 0.139$) (Figure 5B). Again, this model including

delay length and selection type as main effects proved to be significantly better than the intercept only model [$\chi^2(2) = 54.347$, $p < 0.001$], as well as reduced models including only delay length [$\chi^2(1) = 46.248$, $p < 0.001$] or selection type [$\chi^2(1) = 9.487$ $p < 0.01$]. Follow-up Bonferroni-corrected ($p < 0.01$) paired t-tests found that RTs were greater at delay lengths of 7 days ($t(31) = 2.973$, $p < 0.01$) and 90 days ($t(31) = 4.909$, $p < 0.001$) (Figure 5B). Binge-drinking status and FHD had no effect on RTs in either analysis.

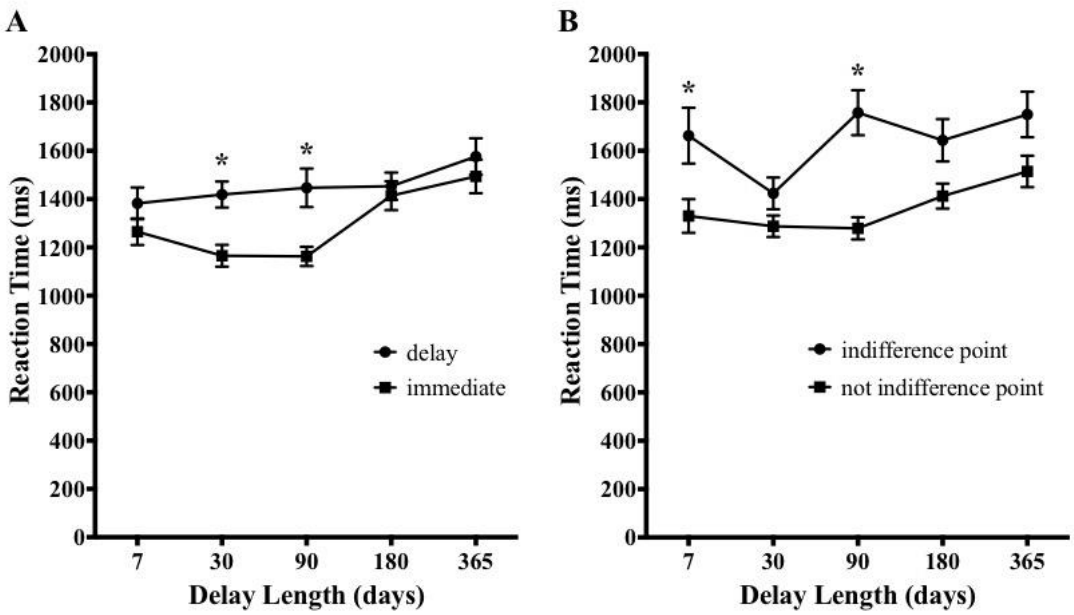

Figure 5. Reaction times on the loss discounting task.
(A) Adolescents had significantly longer RTs when making delay choices compared to immediate choices at delay lengths of 30 and 90 days. (B) Adolescents had significantly longer RTs when making selections around their indifference point compared to selections not around their indifference point at delay lengths of 7 and 90 days. * $p < 0.01$ (Bonferroni-corrected)

5.3.3 A three-factor solution of time perspective

When fitting a CFA model to the self-report measures of time perspective, the model fit for the three-factor solution was acceptable, but not excellent (TLI = 0.914, RMSEA = 0.099); however, given the small sample size, and relatively low degrees of freedom, RMSEA values may be artificially inflated (Kenny, Kaniskan et al. 2015), suggesting the fit of this model may be better than these values indicate. Further, the three-factor model fit the data significantly better than a single-factor solution [$\chi^2(3) = 10.440$, $p < 0.05$] and a three-factor solution treating the latent factors as independent [$\chi^2(3) = 73.897$, $p < 0.001$]. All indicators loaded significantly on Future and Present orientation latent factors, but not the Past orientation latent factor (Figure 5), and there was a significant negative correlation ($r = -0.690$, $p < 0.001$) between the immediate and future orientation latent factors, suggesting that individuals with high future orientation have lower present orientation (Figure 6).

Assessing the effects of binge-drinking status and FHD (controlling for age) on Present, Future, and Past latent variables confirmed previous findings. Binge-drinking adolescents had lower future orientation ($b = -0.763$, $p < 0.01$) compared to controls, and there was a positive association between future orientation and age across all subjects ($b = 0.189$, $p < 0.01$), but no effects of FHD [$F(2,63) = 6.524$, $p < 0.01$, Adjusted-$R^2 = 0.145$]. Similarly, binge-drinking adolescents showed greater present orientation ($b = 0.715$, $p < 0.01$) compared to controls, and there was a significant negative association between present orientation and age across all subjects ($b = -0.177$, $p < 0.01$), but no effects of FHD [$F(2,63) = 5.673$, $p < 0.01$, Adjusted-$R^2 = 0.126$]. There were no effects of either binge-drinking status or FHD on past orientation.

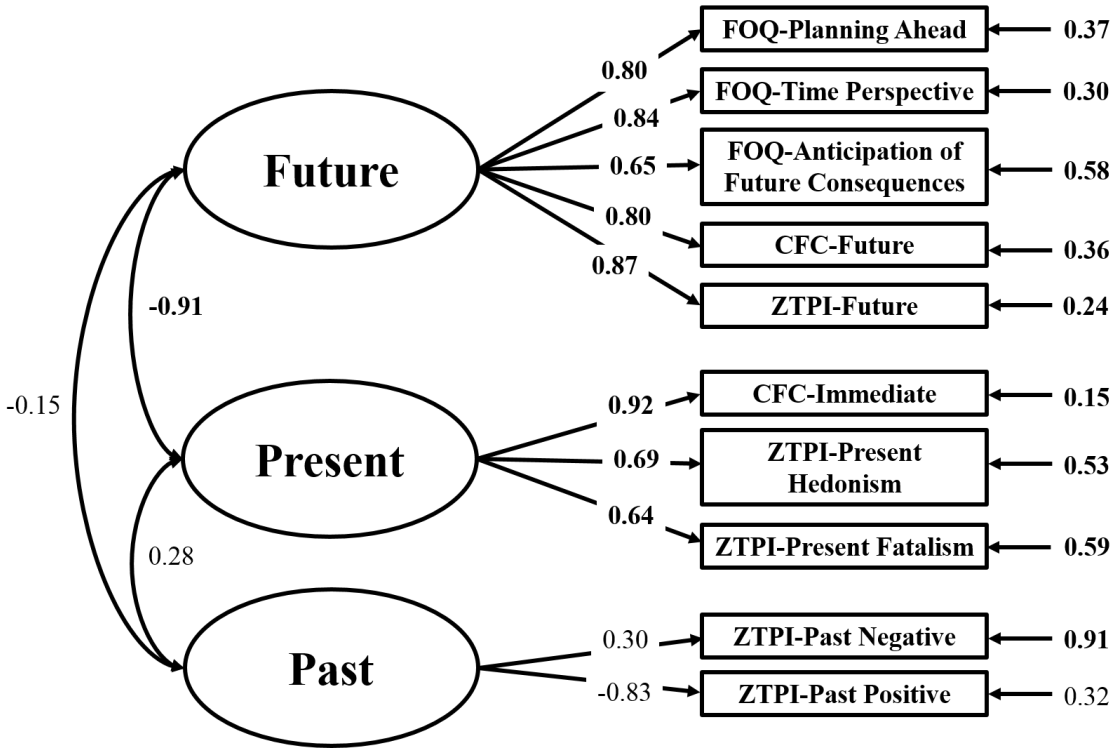

Figure 6. A three-factor solution for time perspective.
Significant loadings are in bold font; all factors for the "Future" and "Present" latent variables loaded positively and significantly ($p < 0.001$) on their respective latent variables.

5.3.4 Associations between future orientation and fractional anisotropy

Voxel-wise analyses revealed one cluster (740 voxels), in the left PLIC (Figure 7), where there was a significant binge-drinking-status-by-future orientation interaction on FA, when controlling for age (b = -0.020, $p < 0.001$, β = -1.202). In this region, binge-drinking adolescents demonstrated a significant negative association between future orientation and FA (b = -0.009, $p < 0.01$, β = -0.525), while control adolescents demonstrated a significant positive association between future orientation and FA (b = 0.011, $p < 0.001$, β = 0.677) (Figure 7). However, post-hoc analyses revealed that this association was not unique to future orientation. In this region, there was also a significant binge-drinking-status-by-present orientation interaction when controlling for age; however, in the inverse direction (b = 0.017, $p < 0.001$, β = 1.045). That is, binge-drinking adolescents had a significant positive association between present orientation and FA (b = 0.008, $p < 0.05$, β = 0.492), while control adolescents had a significant negative association between present orientation and FA (b = -0.009, $p < 0.01$, β = -0.553).

To test whether FA mediates the effects of binge-drinking status on future (and present) orientation, separate linear models were conducted with and without the inclusion of FA (and its interaction with binge-drinking status) and the effect of binge-drinking status was compared between models (analogous to analysis described in Chapter 4.2.5). Similar to the findings in Chapter 4.3.2, there was no significant change in the effect of binge-drinking status on either future or present orientation, suggesting that while FA is associated with present and future orientation, it serves as an

independent predictor and does not mediate the effects of binge-drinking status on future or present orientation.

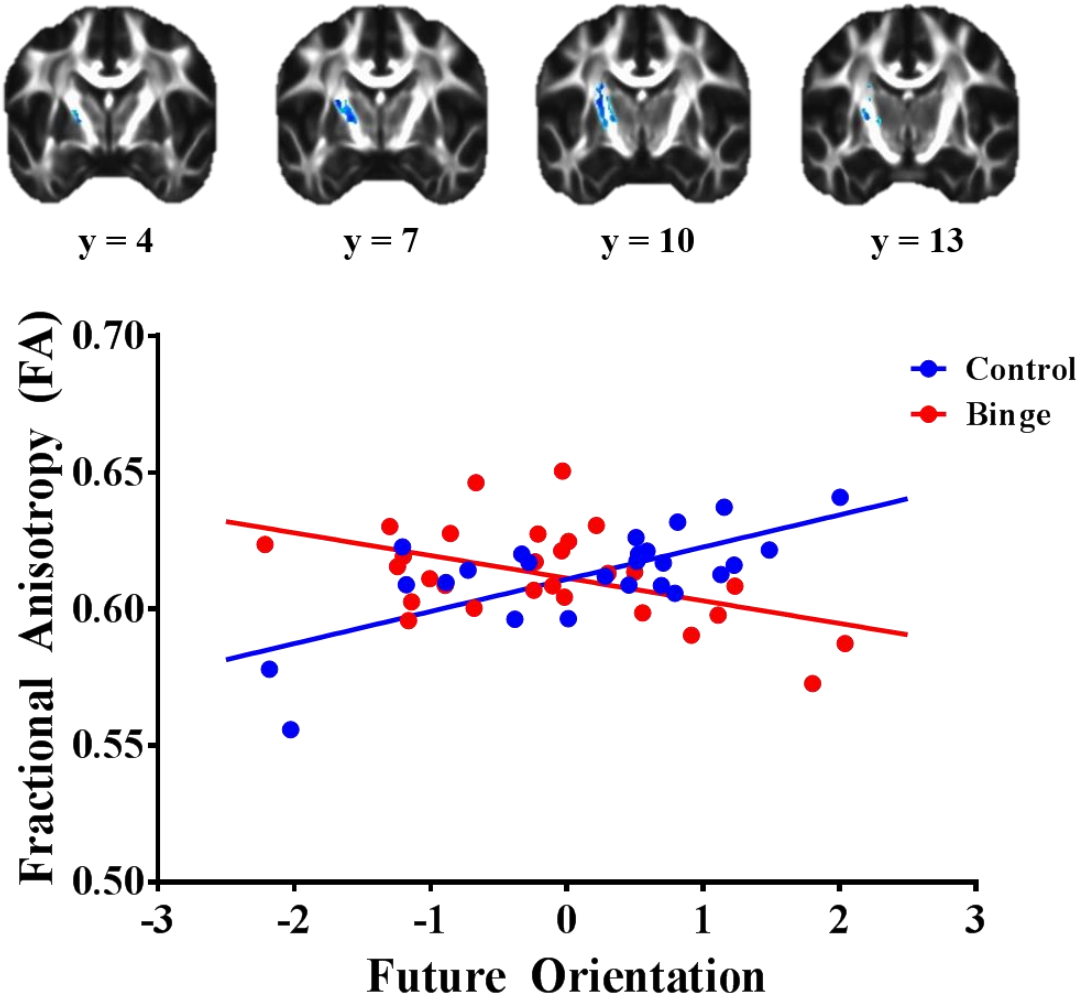

Figure 7. Significant association between future orientation and fractional anisotropy in the PLIC.
Binge-drinking adolescents demonstrated a negative association between future orientation and FA, whereas controls demonstrated a positive association between future orientation and FA, resulting in a significant group-by-future orientation interaction in the right PLIC.

5.4 Discussion

This study had two aims, to examine the association between personal and familial alcohol misuse and future orientation in adolescents, and to examine the association between future orientation and FA. Results demonstrated that binge-drinking adolescents have reduced future orientation and appreciation for future consequences, as measured via self-report scales, but there was no association between FHD and future orientation. CFA suggested the presence of a three-factor model that included future, present, and past latent variables. Voxel-wise analyses demonstrated one region, in the PLIC where future orientation was differentially associated with FA, based on binge-drinking status, with binge-drinking adolescents demonstrating a negative association between future orientation and FA and controls a positive association. Together, these findings suggest that binge drinking during adolescence is associated with less future orientation, and future orientation is differentially associated with FA in striatal regions of the brain, compared to controls.

This study confirmed previous reports of reduced future time perspective in binge-drinking adolescents/young adults (Keough, Zimbardo et al. 1999) and supported the hypothesis that binge-drinking adolescents have reduced future orientation and appreciation for future consequences. However, contrary to the original hypothesis, this study suggested no associations between familial history and future orientation. While there are no previous studies that would imply an association between family history of alcoholism and future orientation, given the previously demonstrated association between family history and impulsive choice, a behavioral measure of greater present orientation and reduced future orientation (see Chapter 3), and the strong anti-correlation between

present and future orientation demonstrated in this study, it could be expected that family history would associated with altered future orientation as well. Nonetheless, previous studies suggest that the effect of family history on impulsive choice dissipates by late-adolescence (Dougherty, Lake et al. 2015), as do the findings in the group of largely alcohol-naïve adolescents in Chapter 3. Thus, given that adolescents in the current study were older than in previous reports (mean age ~18), these null findings do not raise significant concern, as earlier findings (in Chapter 4) also suggested that the neurobiological alterations associated family history also dissipated across adolescence. However, additional investigation into the effects of family history on future orientation are warranted.

Despite significant effects of binge drinking on self-report measures of future orientation and the consideration of future consequences, there were no significant effects of binge-drinking status or FHD on loss discounting behavior. This is surprising, as binge-drinking adolescents have shown alterations in gain discounting paradigms both here (Chapter 3) and elsewhere (Field, Christiansen et al. 2007, Sullivan, Brumback et al. 2016). However, it is important to note that this was the first study to investigate loss discounting behavior in adolescents, with several studies in adults suggesting that varying parameters, such as gain/loss magnitude (Hardisty, Appelt et al. 2013), may impact discounting behavior (discussed further in Chapter 6). Nonetheless, this study did find that adolescents (regardless of binge-drinking status or FHD) had slower RTs when choosing to delay a loss, and when making selections near their indifference point, with these effects being the most robust during delay lengths of 90 days or less. A more thorough investigation of loss discounting behavior in adolescents may be warranted to

further refine this task, in hopes of potentially teasing apart effects of binge drinking (and familial alcoholism) on loss discounting behavior.

In addition to these behavioral findings, this study is the first to demonstrate an association between future orientation and FA, and further demonstrates that this association is altered in binge-drinking adolescents. The fact that more FA in the PLIC was associated with less future orientation (and more immediate orientation), in binge-drinking adolescents, complements findings from Chapter 4, which demonstrated greater FA in binge-drinking adolescents, and a positive association between FA and impulsive choice, in a partially overlapping region of the PLIC (see Chapter 6 for more discussion). Both preclinical and clinical studies suggest that damage to the PLIC results in motor impairments (Puig, Pedraza et al. 2011, Blasi, Whalen et al. 2015), emphasizing its role in the corticospinal tract and its connectivity with the motor/premotor cortex. Further, tractography analyses suggest that the PLIC serves as a primary region involved in the connectivity of the SN and thalamus to the premotor and sensori-motor cortices (Kwon and Jang 2014). Therefore, altered FA in the PLIC may represent changes in the integrity of circuitry responsible for the motivation and drive to obtain ethanol (i.e. orbitofrontal cortex-dorsal striatum-motor cortex), a hypothesized neurobiological marker for the transition into addiction (Volkow and Baler 2014). However, as future (and present) orientation were also associated with FA in the PLIC in control participants (albeit in the opposite direction), future studies will be necessary to tease apart the relationship between future orientation and white matter microstructure in this region.

While this study presented several novel findings concerning future orientation in binge-drinking adolescents, limitations are again present. First, while the extent of the FA

cluster identified in this study falls within the PLIC, this is a very large white matter tract, likely composed of fibers extending from several subcortical regions (including the striatum, VTA, NAc, SN, and thalamus) to various regions of the cortex (Kwon and Jang 2014). More complex tractography studies may be necessary to gain a better idea of which pathways are most important for future orientation in adolescents. Also, the findings of this study were purely associative in nature. That is, while binge drinking during adolescence was associated with reduced future orientation, and alterations in its association with FA, it is unclear if these were results of alcohol use itself or may represent premorbid behavioral and neurobiological alterations prior to alcohol use (discussed further in Chapter 6). Lastly, many of the analyses and findings in this chapter are preliminary and were exploratory in nature. Replication of these findings will be important.

In conclusion, this study demonstrates that binge-drinking adolescents and young adults have reduced future orientation and appreciation of future consequences compared to largely drug- and alcohol-naïve controls. Further, binge-drinking adolescents showed alterations in the relationship between future orientation and FA in striatal regions of the brain such as the PLIC. While these findings failed to find the appreciation of future consequences as a neurobiologically unique facet of risky decision making, they do extend previous findings regarding greater impulsive choice in binge-drinking adolescents (see Chapter 3) and suggest that these impairments extend to other facets of time perspective, including future orientation. Further, they provide neurobiological convergence, with the PLIC serving as a region significantly associated with both present and future time perspective. Further investigation into this rather novel construct of

decision making may help aid in future intervention and prevention strategies targeted at adolescents.

Chapter 6. General discussion

6.1 Summary of goals and results

This dissertation sought to address three major aims: 1) Investigate the role of personal and familial alcohol misuse in the development of impulsive choice across adolescence. 2) Determine whether the development of FA is affected by personal and/or familial alcohol misuse, and whether FA mediates the effects of personal and familial alcohol misuse on the development of impulsive choice. 3) Assess the effects of personal and familial alcohol misuse on the consideration of future consequences and its potential association with FA.

Findings in Chapter 3 demonstrated that both personal and familial alcohol misuse were associated with alterations in impulsive choice. Adolescents who went on to binge drink showed comparable levels of impulsive choice a baseline (~age 14) compared to controls but failed to demonstrate the same age-related declines in impulsive choice as those who remained largely drug- and alcohol-naïve. Furthermore, a greater FHD was associated with greater age-related increases in impulsive choice in adolescents who went on to binge drink, but less impulsive decision making in adolescents who remained largely alcohol naïve. Findings in Chapter 4 demonstrated that future binge drinking and FHD was associated with alterations in FA at baseline (prior to alcohol use) in frontal and striatal white matter tracts. These binge-drinking-related increases persisted in the PLIC, whereas the FHD-related reductions in the SFG were transient and diminished by late-adolescence (~age 18). Further, impulsive choice was associated with FA in the PLIC, but FA in this region did not mediate the effect of personal alcohol use

on impulsive choice. Lastly, findings in Chapter 5 demonstrated that future orientation (and the appreciation of future consequences) was reduced in binge-drinking adolescents compared to controls and was differentially associated with FA in the PLIC. Findings from this dissertation are summarized in Table 1. Together, these findings provide novel insight into the role of personal and familial alcohol misuse in temporal decision making during adolescence (both in terms of impulsive choice and appreciation of future consequences) and highlight the importance of understanding the neurobiology underlying these associations.

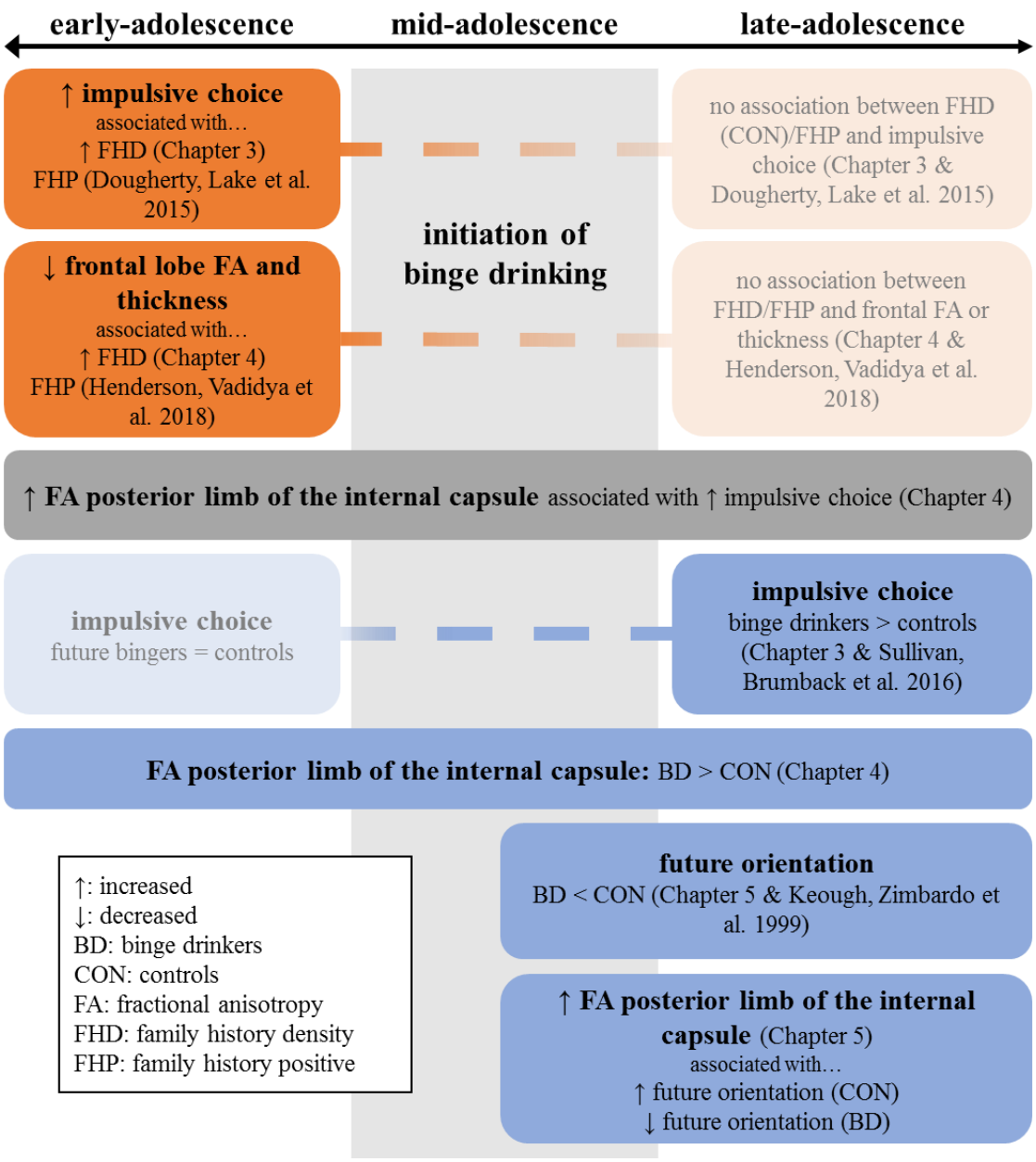

Figure 1. Summary of previous relevant literature and dissertation findings
The effects of family history of alcoholism (orange) and binge drinking (blue) on impulsive choice and brain structure are depicted in early-adolescence through late-adolescence with persistent, transient, and emergent effects present. Chapters, as well as previous literature, where these findings occur are noted.

6.2 Personal and familial alcohol misuse in temporal decision making

As noted in Chapter 1.5, risk taking represents a complex behavior that is composed of several features (e.g. impulsivity, inhibition, sensation seeking), as well as temperamental characteristics (such as negative affect) and genetic and environmental influences (Feldstein and Miller 2006). This dissertation sought to focus on the role time perspective plays in adolescents' risk-taking behavior, specifically the decision to drink. Deciding to drink is a complex process in which an adolescent must make a choice (consciously or unconsciously) regarding the outcome they expect to achieve by drinking or not drinking (Kuntsche, Knibbe et al. 2005). When adolescents report on their drinking motives, much of their focus is on immediate benefits or consequences, and can include positive reinforcement, such as drinking to experience/enhance positive mood and drinking for positive social outcomes, or negative reinforcement, such as drinking to cope with, avoid, or regulate negative emotions and to avoid negative social outcomes (Cox and Klinger 1988, Cox and Klinger 1990). However, what are often overlooked are the long-term negative outcomes associated with repeated alcohol misuse (i.e. AUD and the personal and societal burden that accompanies it), and theoretically, the positive outcomes that one may experience by not drinking (i.e. improved physical and emotional well-being). To further explore this notion, this dissertation used a temporal decision-making task – the delay discounting of both gains and losses – as well as self-report measures of time perspective, to assess the association between binge drinking during adolescence and this temporal component of decision making.

Adolescents who binge drink tend to discount or devalue future rewards in favor of immediate ones (Field, Christiansen et al. 2007, Sullivan, Brumback et al. 2016), as

noted in Chapter 1.6. However, the nature of this relationship is rather complex, and prior to this dissertation, it was largely unclear if the greater discounting rates (i.e. greater impulsive choice) observed in binge-drinking adolescents were behavioral consequences of alcohol use itself (potentially due to altered underlying neurobiology) or if they represented a predisposition to engage in impulsive decision-making behavior prior to initiation of alcohol use, due to some form of genetic or environmental influence earlier in life. As noted in Chapter 1.7, this latter notion is supported by the findings that adolescents with a family history of alcoholism – a significant predictor of future alcohol use (Schuckit, Goodwin et al. 1972, Cotton 1979, Goodwin 1985, Cloninger, Sigvardsson et al. 1986) – tend to also devalue or discount delayed rewards, despite having no history with alcohol use themselves (Acheson, Vincent et al. 2011, Dougherty, Charles et al. 2014, Henderson, Vaidya et al. 2018). Chapter 3 of this dissertation attempted to provide further insight into this complexity by, for the first time, assessing the effects of both binge-drinking status and family history of alcoholism on impulsive choice in a longitudinal fashion. Meanwhile, Chapter 5 provided a greater understanding of time perspective and the appreciation of future consequences in binge-drinking adolescents, with varying degrees of familial alcoholism, all of which may impact the way in which an adolescent makes decisions. These findings reveal several important things (summarized in Figure 1): 1) early on in adolescence, when all adolescents were alcohol-naïve, there appeared to be a positive association between FHD and impulsive choice, regardless of an adolescent's future binge-drinking status; however 2) adolescents who later went on to binge drink showed comparable levels of impulsive choice at baseline. 3) As adolescents aged, those that went on to binge drink maintained elevated levels of impulsive choice,

while adolescents who remained alcohol-naïve demonstrated expected age-related declines in this behavior, and 4) the role family history plays in this process is complex, as it was associated with non-significant increases in impulsive choice in those who emerged into binge drinking, and significant decreases in impulsive choice in those who remained alcohol naïve. Finally, 5) future orientation (including the consideration of future consequences) was lower, and present orientation was greater, in binge-drinking adolescents, when compared to controls.

Personal alcohol misuse

In regard to the association between binge drinking and impulsive choice, these results clearly demonstrated that adolescents who went on to binge drink showed no differences in impulsive choice, as measured by delay discounting, prior to alcohol use. These findings would suggest that, at the very least, impulsive choice (on its own) may not serve as a phenotypical trait-like variable that could be used to predict which adolescents go on to engage in binge drinking. As such, either initiation of alcohol use and impaired impulsive choice development are a co-occurring phenomenon or altered development of impulsive choice is a direct consequence of alcohol use itself. In support of this finding, preclinical models of impulsive decision making in rodents, found that acute alcohol administration dose-dependently increased impulsive responding for food rewards, and that rats that showed a stronger effect of acute alcohol on impulsive responding went on to consume greater levels of alcohol, irrespective of baseline levels of impulsive responding (Poulos, Parker et al. 1998). This sort of positive feedback or "loss-of-control drinking" has long been hypothesized as one mechanism for the development of alcoholism (Ludwig, Wikler et al. 1974, Field, Wiers et al. 2010). This is

further supported by the finding of a dose-related effect on impulsive choice in Chapter 3; binge-drinking adolescents who showed a greater lifetime drinks also demonstrated greater increases in impulsive choice, with age. However, these finding do not align with all previous literature. For example, preclinical models suggest greater impulsive responding for food rewards predicted a greater level of alcohol consumption in a later test (Poulos, Le et al. 1995). Additionally, a longitudinal study in early human adolescents (ages 12-15) found that greater impulsive choice predicted greater alcohol use six months later (Fernie, Peeters et al. 2013); however, this sample had low rates of alcohol use (< 1 alcohol drinking day in the last month), below the cutoff utilized in this dissertation. Additional longitudinal studies with larger samples and greater temporal resolution will be necessary to further address this discrepancy (further discussed in Chapter 6.5).

While not necessarily adding to the longitudinal understanding of temporal decision making, the findings in Chapter 5 provide support for those in Chapter 3 and add novel insight into the role of time perspective in decision making during adolescence. These findings (in Chapter 5), suggested that binge drinking during adolescence (mean age 18 – roughly the same age as the average age of follow-up in Chapter 3), was associated with greater present time perspective, and lower future orientation, with preliminary findings suggesting lower levels of appreciation for future consequences, specifically, among binge-drinking adolescents. These extend previous findings of reduced future time perspective in heavy-drinking adolescents and young adults (Keough, Zimbardo et al. 1999) and suggested that greater levels of impulsive choice in binge-drinking adolescents may be associated with, or potentially driven by, lower levels of

future orientation or greater levels of present orientation, compared to controls. Furthermore, the findings of this dissertation suggest that future orientation and present orientation are highly anti-correlated and may represent two ends of a temporal continuum both in regards to behavior and neurobiology (see Chapter 5.3). Early views of time perspective consisted of this idea of a cognitive-spatial temporal continuum (Nuttin and Lens 1985), and self-report measures, such as the CFC (Strathman, Gleicher et al. 1994), were designed with a single one-factor solution for consideration of both present and future consequences. However, recent studies suggest a highly reliable two-factor solution for present and future consequences (Joireman, Shaffer et al. 2012), while measures such as the ZTPI (Zimbardo and Boyd 2015) were designed with separate constructs for past, present, and future time. This has led to the hypothesis that when making a decision, individuals may consider the immediate consequences, future consequences, or both (Shipp, Edwards et al. 2009). While the CFA in this study does indeed support the notion of three separate time perspectives, further research will be necessary to assess the potential independence of these constructs, as the results of this dissertation suggest that present and future orientation are significantly inversely related.

Familial alcohol misuse

The role of family history of alcoholism in the development of impulsive choice, as observed in Chapter 3, provides additional insight into the association between intertemporal decision making and binge drinking. The findings of this dissertation, particularly that greater FHD was associated with greater impulsive choice at baseline (~age 14), confirm previous reports that familial alcoholism is associated with greater impulsive choice in early-adolescence (Acheson, Vincent et al. 2011, Dougherty, Charles

et al. 2014, Henderson, Vaidya et al. 2018). Furthermore, this finding is in line with preclinical models that demonstrate that rodents bred to consume high amounts of alcohol demonstrate greater impulsive responding for food and sucrose rewards than rodents bred to consume low amounts of alcohol (Wilhelm and Mitchell 2008, Oberlin and Grahame 2009, Perkel, Bentzley et al. 2015). As a family history of alcoholism is associated with greater impulsive choice, and both greater impulsive choice and a family history of alcoholism have been associated with binge drinking (see Chapter 3), it is possible that impulsive decision making and alcohol misuse share a common neurobiological phenotype, or genetic variation, whereby impulsive choice mediates the effects of familial alcoholism on adolescent binge drinking. For example, genetic variation in GABAR2 (the alpha subunit of the gamma-aminobutyric acid receptor) has been shown to be related to alcoholism (e.g. Covault, Gelernter et al. 2004), is associated with impulsive responding on an incentive delay task in a sample enriched for alcoholism (Villafuerte, Heitzeg et al. 2012), and impulsiveness has been shown to mediate the effects of GABAR2 on alcohol-related problems in individuals with familial alcoholism (Villafuerte, Strumba et al. 2013). Together, these findings suggest that early in adolescence, a family history of alcoholism may result in greater impulsive choice and thus a greater risk for engaging in future alcohol misuse. However, this increased risk may be time-limited and dissipate by late-adolescence if one is able to remain alcohol-naïve (as is seen for the effect of FHD on impulsive choice in Chapter 3). Future studies will be necessary to confirm this hypothesis, as the effects of familial alcoholism on adolescent alcohol use are not purely genetic, and likely consists of gene-by-environment effects (Rose, Dick et al. 2001).

Interaction of personal and familial alcohol misuse

More interestingly, findings in Chapter 3 demonstrated that the association between FHD and impulsive choice varies as a function of both age and future binge-drinking status. In binge-drinking adolescents, there was a non-significant exaggeration of these findings (the association between FHD and impulsive choice became greater); however, among non-drinkers, FHD appeared to be protective (i.e. FHD was associated with a greater decline in impulsive choice with age). As noted in Chapter 3.4, this is not the first study to suggest that a family history of alcoholism may be protective in adolescents who refrain for alcohol use. Studies in children of alcoholics have demonstrated that many individual and social factors may contribute to an adolescent's resilience against alcohol use (Park and Schepp 2015). Furthermore, underlying differences in neurobiology may explain why some adolescents with a familial alcoholism do not go on to drink. For example, FHP adults, but who themselves are not alcoholics, show greater D2 receptor availability in the caudate and ventral striatum than FHN individuals (Volkow, Wang et al. 2006), suggesting that greater D2 receptor levels could be protective by regulating brain regions involved in impulsivity (Trifilieff and Martinez 2014).

While the association between FHD and greater age-related declines in impulsive choice may be interpreted as protective, a closer look at Figure 1 in Chapter 3, and consideration of the interaction between FHD and binge-drinking status, may point to an alternative interpretation. It is important to note that by late adolescence (~age 18), FHD was only associated with impulsive choice in binge-drinking adolescents. As such, based on the findings in Chapter 3, one could hypothesize that, FHD predisposes an adolescent

to binge drink through increased impulsive choice (as described above) and that those that go on to binge continue to show elevated impulsive choice, particularly those with greater genetic/environmental predisposition (through a positive feedback loop). However, if adolescents refrain from alcohol use, the significant risk (of increased impulsive choice) associated with having familial alcoholism, declines to the point of being negligible. That is, as opposed to being protective, adolescents may simply age out of this vulnerable window. This is supported by previous findings which also demonstrated transient effects of familial alcoholism on impulsive choice in adolescence (Dougherty, Lake et al. 2015). This line of reasoning may help explain the lack of effects of familial alcoholism on future orientation in Chapter 5, as many of the participants in that sample were in late adolescence and age-related changes were not present/assessed. This is also supported by the neurobiological findings of Chapter 4, as well as previous cross-sectional reports (Acheson, Wijtenburg et al. 2014), which suggest that the effects of FHD on FA dissipate by late adolescence (see Chapter 6.3 for more discussion).

If this hypothesis holds, it then begs the question: what causes an adolescent to remain alcohol naïve despite demonstrated increases in impulsive choice in association with familial alcoholism? First, as mentioned above, it must be considered that family history of alcoholism carries with it both a genetic and an environmental component. For example, genetic variations in GABRA2, CHRM2 (muscarinic cholinergic receptor 2), and ADH4 (alcohol dehydrogenase 4 pi subunit) have all been linked to familial risk for alcoholism, and replicated in multiple samples (for review, see Edenberg and Foroud 2006). Conversely, the homes of children with alcoholic parents are often characterized by marital conflict, parent-child conflict, and poor parental adaptive functioning when

compared to the homes of children without alcoholic parents (Reich, Earls et al. 1988). Furthermore, when comparing adolescents with alcohol-related problems to those without, all of whom had a family history of alcoholism, it was found that adolescents with alcohol-related problems had more perceived parental rejection and less emotional warmth, and were more likely to associate with substance-using peers (Barnow, Schuckit et al. 2002). Most likely, then, familial alcohol carries with it both genetic and environmental aspects that interact to affect an adolescents' propensity to engage it alcohol use (Rose, Dick et al. 2001).

Second, as noted above, risk-taking behavior, including the decision to drink, may be influenced by a variety of factors beyond simply impulsive choice. That is, as noted in Chapter 3.4, there is likely a degree of phenotypical variability in FHP adolescents that render some more likely to drink than others. For example, preclinical models demonstrate that impulsive responding may be more closely associated with a propensity to drug seek than to consume (Beckwith and Czachowski 2014). Meanwhile, studies in humans, suggest that sensation seeking – an important component of risk-taking behavior (Feldstein and Miller 2006) – is a significant predictor of alcohol dependence in FHP individuals, but not FHN individuals (Grucza, Cloninger et al. 2006). While not related to familial history, the current study found that time perspective, both present and future (including future consequences), were related to adolescent binge drinking. Meanwhile, previous studies have shown that avoidance of negative affect, or drinking to cope (an example of an immediate consequences), are often related to patterns of heavy drinking (Cooper, Agocha et al. 2000) and greater alcohol-related problems (Windle 1996). Additionally, social environment may play an important role in adolescent risk taking and

binge drinking, as the presence of peers has been shown to increase impulsive choice (Weigard, Chein et al. 2014), while having delinquent peers can predicted heavier alcohol use (Feldstein Ewing, Filbey et al. 2015). Together, these findings highlight the importance of developing a more encompassing understanding of the numerous behavioral, social, and environmental variables that contribute to adolescents' decision to drink.

6.3 The neurobiology of time perspective and the effects of personal and familial alcohol misuse

As noted in Chapter 1.2, the adolescent brain undergoes drastic structural neurodevelopment (Giedd, Blumenthal et al. 1999, Gogtay, Giedd et al. 2004, Barnea-Goraly, Menon et al. 2005, Paus 2005, Shaw, Kabani et al. 2008, Ostby, Tamnes et al. 2009, Giorgio, Watkins et al. 2010, Tamnes, Ostby et al. 2010, Lebel and Beaulieu 2011, Pfefferbaum, Rohlfing et al. 2016), which occurs asynchronously, with striatal regions, important for reward and emotional reactivity, developing prior to frontal regions, important for cognitive and emotional control (e.g. Mills, Goddings et al. 2014). Given the well-established role of fronto-striatal circuitry in the formation of addiction (for review, see Koob and Volkow 2010), many MRI studies in adolescents have investigated the role binge drinking and familial alcoholism play in the development of fronto-striatal circuitry. As noted in Chapters 1.3 and 1.4, binge drinking and familial alcoholism are associated with alterations in fronto-striatal gray and white matter volumes and thickness (Hill, De Bellis et al. 2001, Hill, Wang et al. 2009, Hill, Wang et al. 2013, Howell, Worbe et al. 2013, Luciana, Collins et al. 2013, Doallo, Cadaveira et al. 2014, Mashhoon,

Czerkawski et al. 2014, Squeglia, Rinker et al. 2014, Whelan, Watts et al. 2014, Squeglia, Tapert et al. 2015, Kvamme, Schmidt et al. 2016, Sharma and Hill 2017, Henderson, Vaidya et al. 2018) and alterations in white matter microstructure (Bava, Frank et al. 2009, Jacobus, McQueeny et al. 2009, McQueeny, Schweinsburg et al. 2009, Herting, Schwartz et al. 2010, Bava, Jacobus et al. 2013, Jacobus, Squeglia et al. 2013, Jacobus, Thayer et al. 2013, Acheson, Wijtenburg et al. 2014, Squeglia, Jacobus et al. 2014). However, there has been a lack of longitudinal investigations into the effects of binge drinking and familial alcoholism (and their interaction) and discrepancies in the directionality of previous literature. This, combined with the notion that neurobiological plasticity may be adaptive in adolescence, and result in resilience to the proposed feedforward addiction cycle (Sercombe 2014, Cousijn, Luijten et al. 2018), highlights the need for additional longitudinal research investigating the association between binge drinking and familial alcohol and adolescent neurobiological development.

To address this concern and assess whether future binge drinking, familial alcoholism and their interaction are associated with persistent or transient alterations in the development of FA, Chapter 4 utilized longitudinal modeling in a sample of emergent binge-drinking adolescents and controls with varying degrees of familial alcoholism. Further, as noted in Chapter 1.5, fronto-striatal FA has been previously associated with impulsive choice development in adolescents (van den Bos, Rodriguez et al. 2014, van den Bos, Rodriguez et al. 2015, Achterberg, Peper et al. 2016, Hampton, Alm et al. 2017). Therefore, to aid in the understanding of time perspective and temporal decision making and their association with FA, this dissertation explored the role of impulsive choice (Chapter 4) in regions associated with binge drinking and familial alcoholism, as

well as the association between future orientation (Chapter 5) and FA as a function of personal and familial alcohol misuse. These findings revealed that, 1) future binge drinking during adolescence was associated with persistently greater FA in the PLIC, 2) family history of alcoholism was associated with transient reductions in FA in the SFG, which dissipated by late-adolescence, 3) FA in the PLIC was significantly associated with impulsive choice throughout adolescence and present/future orientation in late-adolescence, and 4) binge drinking during late-adolescence was associated with an altered relationship between PLIC FA and present and future orientation (summarized in Figure 1).

Personal alcohol misuse

In Chapter 4, binge-drinking status was associated with persistently greater FA in the PLIC. This finding is in line with early cross-sectional literature (Bava, Frank et al. 2009), and is one of the first studies to suggest that binge-drinking adolescents demonstrate alterations in FA prior to initiation of alcohol use. This is supported by volumetric findings which report reduced gray and white matter volume and gray matter thickness prior to alcohol use (Squeglia, Rinker et al. 2014, Whelan, Watts et al. 2014, Squeglia, Tapert et al. 2015). Greater FA in the PLIC could represent several things. First, the PLIC, particularly in inferior regions of the tract (see Figure 1A of Chapter 4.3) may carry fibers from midbrain regions, such as the SN/VTA, to the NAc, striatum and prefrontal cortex (Coenen, Panksepp et al. 2012, Chowdhury, Lambert et al. 2013). These regions all make up the mesolimbic dopaminergic pathway, a key pathway in the development of addiction, particularly early binge/intoxication phases that are characterized by elevated impulsivity (Koob and Volkow 2010). Greater FA in this tract

could represent an early strengthening of that circuitry prior to the initiation of alcohol use. This is further supported by longitudinal functional MRI work, which has found that greater NAc activation during decision making involving risk and reward was predictive of greater risk-taking behavior and an early age of onset of alcohol use in adolescents (Morales, Jones et al. 2018), and that young adults that escalated drinking during a 12-month period had greater frontal activation during inhibition than those who maintained stable levels (Worhunsky, Dager et al. 2015). Though it must be noted that greater activation in specific brain regions does not necessarily result in greater connectivity of adjacent white matter tracts, one might expect that greater neuronal activation in a particular brain region would be associated with greater synaptic strengthening, and thus, greater fiber density and myelination of the white matter tracts that subserve that region, as has been demonstrated previously (e.g. Toosy, Ciccarelli et al. 2004). Future multimodal studies will be necessary to provide strength to this argument.

Alternatively, the PLIC also contains a large portion of fibers in the corticospinal tract, which connects the brain stem to the motor/premotor cortex and serves as a primary region involved in the connectivity between the SN and thalamus to the premotor cortex (Kwon and Jang 2014). This pathway also plays a role in the addiction process, as activation of the dorsal striatum-motor cortex has been shown to play a role in the motivation and drive to obtain alcohol (Volkow and Baler 2014). This explanation is also supported by longitudinal functional MRI work, which found that during behavioral inhibition, greater premotor cortex activation during failure to inhibit responding served as a significant risk factor for adolescents who later when on to engage in binge drinking (Whelan, Watts et al. 2014). However, again, future studies utilizing both MRI modalities

will be necessary to strengthen understanding of these structural/functional relationships, as several studies suggest functional connectivity may reflect structural connectivity, but that functional connectivity may be present in regions with no direct structural connections (for review, see Damoiseaux and Greicius 2009). While its exact involvement in the addiction cycle is unclear, the effect of greater FA in the PLIC (in Chapter 4) preceded binge drinking and represents an alteration in neurobiology that may render adolescents more likely to engage in binge drinking and help explain the elevated impulsive choice observed in binge-drinking adolescents in Chapter 3.

In support of the above conclusion, findings in Chapters 4 and 5 found that impulsive choice and time perspective (both present and future orientation) were associated with FA in the PLIC. While the findings of Chapter 4 and 5 are in slightly different regions of the PLIC, they reside in the same white matter tract, suggesting they may be two portions of the same fiber pathway. In Chapter 4, it was found that greater impulsive choice was persistently associated with greater FA in the PLIC in all subjects, though FA did not mediate the association between binge-drinking status and impulsive choice. These findings are extended in Chapter 5, to suggest that greater present orientation and less future orientation are also associated with greater FA in this region (particularly in late-adolescence), at least in binge-drinking adolescents, suggesting a potential relationship between time perspective and impulsive choice, through a common neurobiological pathway. However, the inverse association between FA and future/present orientation was present in control subjects. Given the size of the cluster identified in Chapter 5 and its location on both medial and lateral portions of the PLIC (see Figure 6), this bivariate association between FA and time perspective in binge-

drinking adolescents and controls could be due to associations with different fiber pathways within the same white matter cluster. In support of this notion, previous neuroimaging studies have found that greater FA and structural connectivity in fronto-striatal pathways with age is associated with both greater (Hampton, Alm et al. 2017) and lesser (van den Bos, Rodriguez et al. 2014, van den Bos, Rodriguez et al. 2015, Achterberg, Peper et al. 2016) impulsive choice, depending on the exact frontal and striatal regions assessed. More nuanced tractography work, using DWI protocols with a greater number of directions, will be necessary to further elucidate this finding.

Finally, the longitudinal nature of these findings (in both Chapters 3 and 4) raise two important points. First, the findings in Chapter 4 suggest neurobiological alterations at baseline that predate binge drinking initiation and are associated with impulsive choice behavior, whereas the behavioral findings demonstrated in Chapter 3 suggest that behavioral differences between binge-drinking adolescents and controls do not manifest until initiation of binge drinking has occurred. This highlights the utility of neuroimaging work in identifying adolescents at risk for binge drinking above and beyond self-report and behavioral measures alone. Second, while emergent behavioral findings were present in Chapter 3, the neurobiological analysis in Chapter 4 failed to find any regions of the brain where there were emergent effects of binge drinking (or familial alcoholism) during adolescence. That is, the findings in this dissertation suggest that the most significant neural alterations that occur in binge-drinking adolescents may be present prior to alcohol use. As such, caution must be taken when interpreting cross-sectional findings as being a direct result of alcohol use itself.

Familial alcohol misuse

Although findings were limited, Chapter 4 provided additional information regarding the association between family history of alcoholism and FA, with greater FHD associated with reduced FA in the SFG in early-adolescence (regardless of future binge-drinking status), an effect that dissipated with age and was negligible by late-adolescence. This confirms previous findings of reduced FA in the prefrontal cortex of FHP adolescents, when compared to FHN adolescents (Herting, Schwartz et al. 2010). Further, functional MRI findings suggest that FHP adolescents have reduced functional connectivity of the prefrontal cortex (including connectivity to reward-relevant regions such as the NAc) compared to FHN adolescents (Herting, Fair et al. 2011, Wetherill, Bava et al. 2012, Cservenka, Casimo et al. 2014). Together, these findings suggest that (at least early in adolescence) familial alcoholism is associate with structural and functional impairments in the prefrontal cortex, potentially leaving adolescents vulnerable to a myriad of psychopathologies associated with decreased frontal control, including substance use.

Additionally, the findings in Chapter 4 suggest that the effect of FHD on frontal FA dissipates with age. Previous longitudinal work has also show that FHP adolescents had thinner prefrontal cortices compared to FHN adolescents, but that this effect was stronger in early-adolescence (Henderson, Vaidya et al. 2018). Further, it also been shown that FHP adolescents demonstrated reduced FA compared to FHN adolescents in more regions than when FHP young adults were compared to FHN young adults, again suggesting that the effects of familial alcoholism may be stronger in early-adolescence (Acheson, Wijtenburg et al. 2014). Similarly, findings in Chapter 3 suggest that the

association between greater FHD and greater impulsive dissipates across age in control adolescents, a finding that has also been reported previously (Dougherty, Lake et al. 2015). Together, these findings suggest that the effects of FHD on adolescent behavior and neurobiology may be transient and may dissipate with age, particularly if adolescents remain free of personal substance use. This may help explain why no association was found between FHD and time perspective in Chapter 5, as adolescents in this sample were on average older than those in earlier chapters.

6.4 Clinical implications

Taken together, the findings of this dissertation provide novel information that may be beneficial to the intervention and prevention of risky substance use during adolescence. In regards to binge drinking, the findings in this dissertation suggest that while impulsive choice, on its own, may not be a behavioral predictor of substance use (see Chapter 3), neuroimaging findings, such as greater FA in white matter regions of the brain important for the formation of addiction (see Chapter 4), may be neurobiological targets for prevention. For example, several previous studies have demonstrated that FA is a modifiable neurobiological construct that can be altered via behavioral intervention (Trivedi, Gupta et al. 2008, Keller and Just 2009, Prosperini, Fanelli et al. 2014). As FA in the PLIC was persistently associated with impulsive choice in adolescents (Chapter 4), if FA in this region were reduced, it is possible that normative declines in impulsive choice may be achieved in adolescents, potentially reducing the degree of substance use during this time as well.

Once adolescents initiate drinking, behavioral intervention may help reduce impulsive choice. Rodent work suggests that simple exposure to delayed rewards may

reduce impulsive responding (Renda and Madden 2016, Renda, Rung et al. 2018) and alter subsequent alcohol intake (Stein, Johnson et al. 2013). Other interventions focusing on enhancing time perspective, such as episodic future thinking, have been shown to reduce impulsive choice and smoking rates in humans (Stein, Wilson et al. 2016), and may be extended to alcohol use as well. Meanwhile, training working memory has also been shown to reduce discounting rates, potentially due to an increase in cognitive resources (Bickel, Yi et al. 2011). Furthermore, while impulsive choice may not predict *onset* of alcohol use, previous studies in humans adolescents suggests that delay discounting rates can predict substance abuse (Stanger, Ryan et al. 2012) and smoking (Krishnan-Sarin, Reynolds et al. 2007) treatment outcomes, in adolescents already engaging in such behaviors. Thus, having measures of impulsive choice and neuroimaging, as well as a knowledge of how they develop in adolescents who do and do not drink, may help identify adolescents most amenable to treatment.

In addition, the findings in adolescents with a familial history of alcoholism, particularly those that remain alcohol-naïve, are encouraging. In this dissertation (and elsewhere) it was shown that, early in adolescence, familial alcoholism was associated with greater impulsive choice (Chapter 3) and lower frontal FA (Chapter 4) – a neurobiological marker that has also been associated with greater alcohol use (Chung, Pajtek et al. 2013), as well as other psychopathologies, such as depression (LeWinn, Connolly et al. 2014), and anxiety (Liao, Yang et al. 2014), in adolescents. However, as adolescents age, the effects of familial alcoholism dissipate, particularly if an adolescent remains free of personal drug and alcohol use. This suggests there is heightened importance in early targeting of drug and alcohol prevention strategies at youth with

familial alcoholism, for if they can remain free of personal use during early-adolescence, they may see their risk of substance use (and other psychopathologies) significantly decline. Further, behavioral strategies geared toward improving frontal white matter microstructure or reducing impulsive choice (as described above), if employed in early-adolescence, may further reduce this time-limited window of vulnerability.

6.5 Caveats and future directions

While the findings of this dissertation produced several novel results, there are several caveats that warrant future investigation in order to further aid in the understanding of familial and personal alcohol misuse and their role in intertemporal decision making and neurobiological development. 1) While much of the data utilized in this dissertation are longitudinal, many of the analyses are associative in nature, and thus causal conclusions are limited and more nuanced longitudinal analyses are warranted. 2) Due to study design, the analyses in this dissertation cover a broad age range, during which adolescents experience numerous heterogeneous social and environmental changes, in addition to the behavioral and neurobiological changes observed here, which may impact these findings. 3) Findings regarding loss discounting behavior were limited, due to a sparsity of literature regarding the discounting of delayed losses in adolescents; a more thorough investigation of loss discounting behavior in "typically developing" adolescents will be necessary. 4) Due to the limited sample size and the desire to investigate the interaction effect of binge drinking and familial alcoholism, there are several additional variables (sex, sensation seeking, negative affect, involvement with

peers, etc.) that this dissertation did not have the power to investigate. These caveats, and methods for addressing them in the future, are each discussed in turn:

1) Longitudinal data were utilized for analyses in Chapters 3 and 4, with subjects contributing 2-4 time points of data. However, the time between visits, as well as the age at each visit varied widely between subjects. As such, multilevel modeling was utilized to assess the effects of between-subject factors (such as binge-drinking status and FHD) while properly accounting for the nested within-subject nature of the data. Therefore, effects both at a predetermined intercept (age 14 & 18) and across age could be assessed; however, this form of modeling is in essence an extension of simpler regression analyses, and thus all findings are associative in nature. While some findings, such as persistently elevated FA in binge-drinking adolescents (see Chapter 4), provide fairly straightforward interpretations, other findings still hold a degree of temporal ambiguity. For example, in Chapter 3, while there was no effect of binge drinking at the intercept (age 14), the exact timing of the initiation of binge drinking and impairments in impulsive choice development across age is unclear, and whether impulsive choice at one time point can predict alcohol use at a later time point is still largely unknown. To further probe the temporal nature of these developing processes, a more time-structured data set will be necessary, at which point path analyses (or structural equation modeling), like those used previously (Fernie, Peeters et al. 2013), can be used to assess whether impulsive choice predicts binge drinking, and whether this effect changes as a function of age.

2) As stated previously, in Chapter 2.1, the adolescents selected for this dissertation were part of an ongoing longitudinal investigation of adolescent neurodevelopment. To take advantage of this wealth of longitudinal data, the analysis conducted in Chapters 3 and 4 utilized adolescents that had, or were in the process of completing, multiple follow-up visits. These follow-up visits were collected after an adolescent had emerged into binge drinking (see Chapter 2.3), which could have occurred at any point during follow-up. Thus, the baseline and follow-up ages for adolescents in Chapters 3 and 4 varied widely (ages 10-19). Furthermore, to assess the association between binge drinking (and familial alcoholism) and future orientation/appreciation for future consequences, recruitment for participants in Chapter 5 took advantage of the sample already at hand, and thus future orientation and loss discounting behavior were assessed in a sample of older adolescents (ages 16-22). As such, the entire sample for this dissertation ranges in age from 10 to 22, and the cross-sectional analysis in Chapter 5 did not span a similar age range as Chapters 3 & 4. While this fact limits the associability of results between chapters, it does allow for unique conclusions to be drawn at specific time-intervals in adolescence. This should all be considered when interpreting the findings of this dissertation, as there are many theories as to which periods of adolescence carry the greatest vulnerabilities. For example, it has been hypothesized that as adolescents further mature, and cognitive control systems develop, they may demonstrate a reduction in risk-taking behavior, and de-escalation of substance use (Cousijn, Luijten et al. 2018), with substance use and risk taking following an inverted-U shaped

trajectory. This suggests that some adolescents in this study, who are currently binge drinking (and demonstrating elevated impulsivity), may eventually reduce their alcohol intake (and potentially demonstrate age-related declines in impulsive choice) during late-adolescence/young adulthood, while others may continue/escalate drinking. Meanwhile, others suggest that onset of regular drinking before age 21 can lead to chronic alcohol problems, but that no one period during adolescence is more sensitive than another (Guttmannova, Bailey et al. 2011). As it relates to this dissertation, there is a high degree of heterogeneity within groups of adolescents (binge-drinking adolescents and controls) in regards to developmental trajectories of impulsive choice (Chapter 3, Figure 2) and FA (Chapter 4, Figures 1B & 1C). This could suggest that some control adolescents have a greater potential for emerging into binge drinking. Furthermore, while future orientation appears to increase across adolescence, it's possible that individuals may demonstrate a dip in time perspective and the anticipation for future consequences in young adulthood (Steinberg, Graham et al. 2009), potentially due to a change of environment and social structure, as young adults leave college and enter the workforce, with some viewing emerging adulthood (ages 18-25) as a fundamentally distinct period from adolescence and young adulthood (Arnett 2000). To add a final layer of complexity to the matter, while the delaying of traditional adult responsibilities has become an emergent trend in contemporary western societies (Furstenberg 2000), some suggest that the behavioral and substance use patterns observed in adolescents are not being similarly stretched to older ages (Hayford and Furstenberg 2008). While

disentangling all of these effects is too grand of an endeavor for one single study, ongoing consortium-based work, collecting several time points of data on thousands of adolescents, will go a long way in furthering our understanding of this complex period of life.

3) Previous studies, mostly in adult participants, have demonstrated that intertemporal discounting is a complex behavior. In regards to gain discounting, simple variations in the magnitude of outcomes (Mitchell and Wilson 2010, Hardisty, Appelt et al. 2013), the delay to immediate reward (e.g. double delay procedures) (Scholten and Read 2013), or the framing of outcome options (Appelt, Hardisty et al. 2011, Scholten and Read 2013), can have an impact on discounting behavior. Furthermore, these same manipulations alter loss discounting in a different manner than gain discounting (Mitchell and Wilson 2010, Appelt, Hardisty et al. 2011, Hardisty, Appelt et al. 2013, Scholten and Read 2013). While no effects of binge drinking or family history of alcoholism were observed for the loss discounting task in Chapter 5, there have been no previously publish reports of loss discounting in adolescents from which to model a task. Assessment of RTs during loss discounting suggest that longer delay lengths require greater thought, as do choice pairs closer to an individual's indifference point. While these findings help validate the current task, it is unclear whether a manipulation of task parameters would create discounting behavior more amenable to observing differences as a function of binge drinking or familial alcoholism. A more thorough investigation into loss discounting behavior in adolescents is warranted.

4) In addition to the factors explored in this dissertation, there are many other relevant variables associated with adolescent binge drinking, impulsive choice, and structural brain development. For example, it has been suggested that there are sex differences in impulsivity (Silverman 2003, Weafer and de Wit 2014) and the development of FA (Simmonds, Hallquist et al. 2014) in adolescence. Meanwhile, social contexts, such as the presence of peers, can increase impulsive choice (O'Brien, Albert et al. 2011), and the presence of delinquent peers may increase trajectories of substance use (Feldstein Ewing, Filbey et al. 2015). Furthermore, variations in temperament (such as greater negative affect) may be associated with heavier drinking (Windle 1996, Cooper, Agocha et al. 2000). Lastly, marijuana, which is often used concomitantly with alcohol in adolescence may be differentially associated with impulsive choice (Romer, Duckworth et al. 2010, Dougherty, Mathias et al. 2013) and FA (Jacobus, McQueeny et al. 2009, Jacobus, Squeglia et al. 2013, Jacobus, Squeglia et al. 2013). These are just several examples of additional variables that could be explored as predictors, or mediators of the effects outlined in this study. Unfortunately, as the overall goal of this study was to assess the interactive effects of personal binge drinking and familial alcoholism on impulsive choice, future orientation, and FA, this study was not powered to assess the presence of such three- or four-way interactions. Each of these variables and others may be addressed in future analyses.

6.5 Conclusions

In summation, this dissertation sought to explore the effects of binge drinking and familial alcoholism on impulsive choice, the appreciation of future consequences and their association with the development of white matter microstructure during adolescence. Findings of this dissertation demonstrate that early in adolescence, greater familial alcoholism is associated with greater impulsive choice and reductions in FA in the SFG, while future binge-drinking status was not associated with differences in impulsive choice but was associated with greater FA in the PLIC. However, these effects changed across age, such that by later adolescence, familial alcoholism was not associated with FA, nor was it associated with alterations in impulsive choice in adolescents who remain largely alcohol-nave, though it was still associated with greater impulsive choice in binge-drinking adolescents. Meanwhile, binge-drinking adolescents continued to show greater FA in late adolescence in the internal capsule, demonstrated greater rates of impulsive choice and present orientation, and lower future orientation compared to largely alcohol-naïve peers, and greater impulsive choice, greater present orientation, and reduce future orientation were associated with greater FA in the internal capsule. Together these findings suggest that time perspective and impulsive choice may share some underlying neurobiological systems and may be associated with structural alterations in white matter tracts important for the development of addiction. Future longitudinal work will be necessary to further assess the causal nature of these findings.

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