

University of Arkansas, Fayetteville

ScholarWorks@UARK

Psychological Science Undergraduate Honors
Theses

Psychological Science

5-2023

Adolescents With Family History of Alcohol-Use Disorders Have Reduced Structural Coherence of Anterior Insula to Nucleus Accumbens Tract

Grace Wood

University of Arkansas, Fayetteville

Follow this and additional works at: <https://scholarworks.uark.edu/psycuht>



Part of the [Developmental Neuroscience Commons](#), [Developmental Psychology Commons](#), and the [Psychological Phenomena and Processes Commons](#)

Citation

Wood, G. (2023). Adolescents With Family History of Alcohol-Use Disorders Have Reduced Structural Coherence of Anterior Insula to Nucleus Accumbens Tract. *Psychological Science Undergraduate Honors Theses* Retrieved from <https://scholarworks.uark.edu/psycuht/38>

This Thesis is brought to you for free and open access by the Psychological Science at ScholarWorks@UARK. It has been accepted for inclusion in Psychological Science Undergraduate Honors Theses by an authorized administrator of ScholarWorks@UARK. For more information, please contact scholar@uark.edu, uarepos@uark.edu.

**Adolescents With Family History of Alcohol-Use Disorders Have Reduced Structural
Coherence of Anterior Insula to Nucleus Accumbens Tract**

An Honors Thesis submitted in partial fulfillment of the requirements of Honors Studies in
Psychology

By

Grace Wood

Spring 2023

Psychology

Fulbright College of Arts and Sciences

The University of Arkansas

Acknowledgements

The completion of this thesis could not have been possible without the expertise of Dr. Josiah Leong, my thesis advisor. Words cannot express my gratitude for all the time and effort he put into guiding me through this project. I also could not have undertaken this project without the help of my defense committee, who generously gave their time and effort to aid me in my endeavors and provide valuable feedback. I am immensely thankful for all the help from research associate Ethan Ellis as well, who was a massive help alongside Josiah with my analyses in the lab.

I'd like to thank my classmates and everyone else on campus for their help in my revisions. Their feedback was incredibly helpful, and I would not have been able to complete this project without them. I would also like to thank my coworkers at Washington Regional, who were always supportive and available for advice and expertise.

Lastly, I want to thank my parents and my best friend Emma, who were supportive, loving, and kind despite me annoying them with discussions and rants about my thesis. Their emotional support through this entire process was invaluable and I could not ask for a better support system.

Table of Contents

ACKNOWLEDGEMENTS	2
ABSTRACT.....	4
INTRODUCTION.....	5
EXPERIMENTAL PROCEDURES	8
DWI ANALYSIS.....	10
RESULTS	10
DISCUSSION	13
REFERENCES.....	18

Abstract

Genetics play a significant role in predisposition towards alcohol use disorders. Analyzing the neural phenotypes related to alcohol use disorder development could allow researchers to predict one's predisposition. The anterior insula (AIns) contributes to binge drinking tendencies while exhibiting downstream signaling towards the nucleus accumbens (NAcc). Recent research has examined this relationship simultaneously with alcohol consumption, but the genetic effect of the AIns and NAcc functional relationship prior to alcohol consumption has yet to be examined. In this study, we used data from the Adolescent Brain Cognitive Development (ABCD) study to analyze the structural coherence of the AIns to NAcc tract in adolescents with and without family history of alcohol use disorders. We found that adolescents with family history of alcohol use disorders have reduced structural coherence of the AIns to NAcc tract in the first 25% of the tract in the left hemisphere only. Furthermore, when controlling for socioeconomic status, these findings were only significant in the low socioeconomic status group. Overall, these findings contribute to alcohol use disorder prevention methods by providing insight into one of the many possible factors that lead to alcohol use problems.

Introduction

Adolescents whose biological family members have a history of Alcohol Use Disorders (AUD) have a 40-60% chance of developing an alcohol use disorder themselves, which is nearly double the probability of development for those with no family history of alcohol related problems (Amark, 1951). Twin and adoption studies demonstrate that genes contribute to risk for an AUD (Cloninger et al., 1981; Merikangas, 1990). However, the genetic risk can also be exacerbated by environmental stressors (Jacob et al., 2003). To develop strategies for preventing onset of AUD, researchers must understand how the genetic and environmental factors contribute to risk for AUD (Cloninger, 1983). While researchers have focused on genetic, behavioral phenotypic, and environmental risk factors for AUD, researchers have only recently begun to explore the neural phenotypes that signal risk for AUD.

Recent research examines how structural differences within the brain are associated with a variety of substance abuse tendencies; a study on the brain structure of heroin addicts found that craving changes could be predicted by changes in white matter integrity (Lu et al., 2023). Similarly, analysis of subjects with damage to specific reward centers of the brain exhibited unusual disruptions to their addiction patterns (Naqvi et al., 2007). Studies such as these are crucial for understanding the role that brain structure plays in substance use behaviors. However, relating to alcohol use specifically, there are few studies that observe how structural differences affect AUD predisposition since there is little research on which parts of the brain are significant for this problem (Oscar-Berman & Marinkovic, 2003).

To understand which parts of the brain to focus on, we must understand how alcohol use tendencies are related to the brain. Researchers have theorized that the genetics related to AUD development lead to an imbalance in the homeostasis of the nervous system, where the ingestion

of alcohol temporarily alleviates this imbalance (Begleiter & Porjesz, 1999). Neuroimaging research suggests that this imbalance is partially associated with mesolimbic structures within the brain, including the anterior insula (AIns) which regulates motivational and sentence processes and could possibly be used to predict future alcohol use (Chung & Clark, 2014; Serafini et al., 2020; Namkung et al., 2017). The AIns plays an important role in decision making processes and is one of the most prevalent predictors of alcohol problems when observed simultaneously with alcohol ingestion (Schuckit et al., 2016). Using an emotional face recognition task, researchers were able to observe functional magnetic resonance imaging (fMRI) data of subjects who consumed alcohol alongside a control group (Schuckit et al., 2016). By comparing groups with both low and high response levels to alcohol, researchers were able to conclude that the insula was not only a significant area for reactions to alcohol stimuli, but also has a downstream influence on the nucleus accumbens (NAcc) which exhibits reward related behaviors that may be pertinent to AUD development (Salgado & Kaplitt, 2015; Schuckit et al., 2016).

The nucleus accumbens not only plays a significant role in motivational processes but is also implicated in a variety of neurological disorders (Salgado & Kaplitt, 2015). In a study using fMRI on the NAcc, researchers found a significant relationship between NAcc activity during decision-making and the age of onset for youth binge drinking (Morales et al., 2020). When observing the NAcc simultaneously with alcohol consumption, it was found that weaker functional connectivity between the NAcc and the AIns is associated with greater alcohol consumption levels (Veer et al., 2019). This demonstrates the importance of communication between the AIns and the NAcc when observing response levels to alcohol and provides insight into how those areas contribute to AUD development. However, this process does not provide information on how the AIns or the NAcc behave prior to alcohol ingestion as well as their

relationship to genetic predisposition towards AUD development. By observing adolescents prior to alcohol ingestion, one could analyze the relationship between brain structure and AUD predisposition prior to structural conformations caused by consumption of alcohol, placing more emphasis on genetic influences.

Furthermore, diffusion data analysis shows that white matter density in family history positive subjects is significantly lower in certain sections of the brain when compared to family history negative subjects for all substance use disorders, not just alcohol (Acheson et al., 2014). Multiple experiments show that fractional anisotropy (FA) values differed significantly in over 18 different white matter clusters, suggesting that a family history of AUDs has a direct genetic effect on white matter density in specific areas of the brain (Squeglia et al., 2014; Acheson et al., 2014). In addition, research shows that white matter integrity mediates the relationship between family history status and slowed reactions times, which demonstrates the effect that family history plays on adolescent neurodevelopment (Herting et al., 2010). By understanding the relationship that family history has with specific sections of the brain that control risk-taking or motivational processes, we can further understand what neurological characteristics are associated with AUD predisposition.

Socioeconomic status (SES) also moderates FA values; a previous experiment found that family income moderates the relationship between cognitive functioning and white matter density (Ursache et al., 2016). A meta-analysis on white matter integrity disparities between family history positive and family history negative subjects found that for those with lower SES, family history negative subjects tend to have higher FA values than their family history positive peers, while for subjects of high SES backgrounds, data exhibits either the opposite trend or simply no significant relationship at all (Cservenka, 2016; Squeglia et al., 2014). To fully

understand the genetic relationship between family history and white matter integrity, SES must be controlled for.

While researchers have investigated the differences in white matter density overall for family history positive and family history negative youths (Acheson et al., 2014; Squeglia et al., 2014), there is currently a lack of exploration into the tract connecting the AIns to the NAcc and how this specific connection plays a role in predicting AUD development. Since the AIns has a significant relationship with the NAcc regarding genetic inheritance of substance use disorders (Schuckit et al., 2016; Manuweera et al., 2022), the structure of the tract between the two structures could provide insight into the ability to predict AUD inheritance in alcohol-naïve adolescents.

We investigated the ability to predict future AUD development in adolescents using FA data from the white matter tract projecting from the AIns to the NAcc. Since white matter density is affected by not only genetic trends but also SES (Cservenka, 2016; Acheson et al., 2014), we predicted that FA values for family history positive subjects would be significantly lower than family history negative subjects. We also predicted that when controlling for SES, the low SES participants would have a larger difference in mean FA values between family history positive and family history negative than the high SES participants. Furthermore, since past research shows that the AIns has a stronger relationship with alcohol use prediction than the NAcc (Schuckit et al., 2016; Morales et al., 2020), we predict that FA values based on family history will be more significant in the section of the tract that is closer to the AIns.

Experimental Procedures

Data was sourced from the Adolescent Brain Cognitive Development (ABCD) Study. From the ABCD data, we selected 3,822 adolescents for the study who have sufficient family history of substance use data as well as diffusion weighted imaging (DWI) data for the AIns to NAcc tract. Data from 269 of these participants were excluded due to head motion $>1.85\text{mm}$ during DWI acquisition, leaving 3,553 subjects (1,691 females) with a mean age of 9.52 years ($S.D. = 0.50$, range = 9-10 years). Participants were separated into family history negative (FH-) and family history positive (FH+) groups based on self-reported family history of alcohol use disorders. Subjects were asked to respond with either “yes” or “no” to a series of questions regarding the details of their substance use histories (criminal record, marriage problems, rehabilitation, etc.). Subjects who have either one or both biological parents with reported alcohol related problems were placed in the FH+ group, while subjects whose biological parents both have no history of alcohol related problems were placed in the FH- group. Each participant has data from 100 imaging slices between the AIns and the NAcc. FA data for each participant was segmented into the first 25%, middle 50%, and last 25% of the white matter tract by taking the mean values for the first 25, middle 50, and last 25 slices respectively. These values were analyzed for the right and left hemisphere separately, excluding outliers by removing values that are not within 1.5 times the interquartile range of data.

For socioeconomic status, participants were grouped based on self-reported demographic data on family income and employment. Out of our 3,553 subjects, approximately 39% were considered higher SES ($n = 1,383$), while the remaining 61% were considered lower SES ($n = 2,170$). After dividing participants into their respective SES groups, we repeated the same analysis as before, with FH- and FH+ groups separated and segmented by area of the NAcc-AIns tract.

DWI Analysis

For preprocessing, the T1-weighted images were converted into anterior and posterior commissures (AC-PC) aligned space using a rigid-body transformation guided by anatomical landmarks defined in both the AC-PC and midsagittal plane. Each image was then aligned with the mean of a set of non-diffusion-weighted ($b = 0$) reference images with corrected motion. Mean values of motion for the diffusion-weighted images were determined using these reference images after alignment. Images were filtered by a mean-motion parameter of 1.85 mm or less to correct for excess motion during scans.

FreeSurfer software (<http://surfer.nmr.mgh.harvard.edu/>, Fischl, 2012) was used to process each subject's weighted image after AC-PC alignment to define anatomical volumes of interest (VOIs). For the anterior insula VOIs, the Destrieux cortical parcellation atlas was used by combining short gyrus and anterior insula parcellations (Destrieux et al., 2010). For the nucleus accumbens, VOIs were identified from probabilistic subcortical tissue classification established by a manually labeled training set (Fischl et al., 2002). FreeSurfer was used to identify the border between the white and grey matter by utilizing a binary mask to restrict fibers to white-matter volume only.

Results

First, we tested the hypothesis that presence of AUD within family history leads to decreased white matter volumes by using an independent samples t-test. We analyzed fractional anisotropy values singled out from the anterior insula tract (Figure 1).

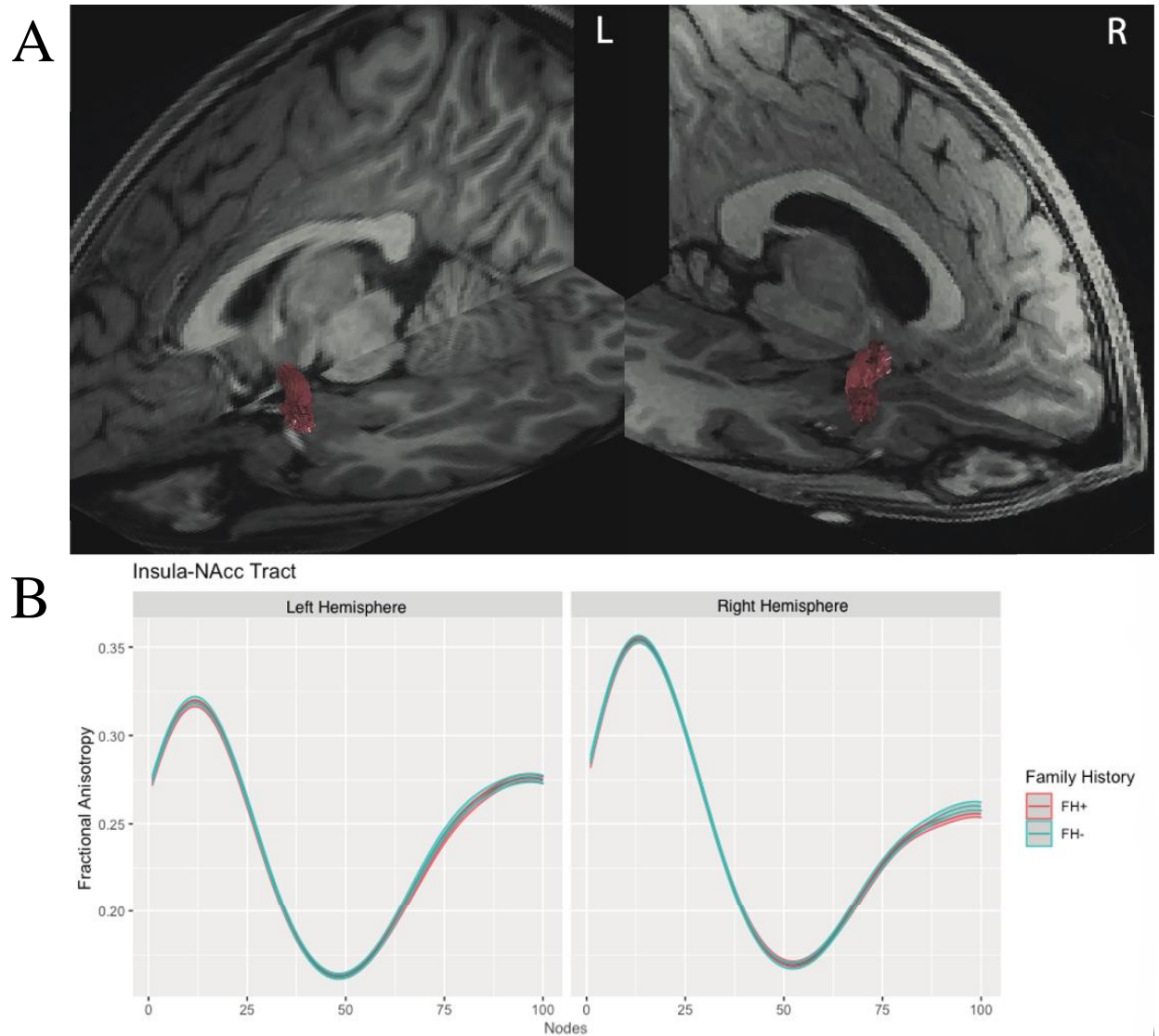


Figure 1: Anterior Insula to Nucleus Accumbens Tractography. (A) Anatomy of AIns to NAcc tract in left and right hemisphere of a representative subject. (B) Tract profile of AIns to NAcc tract between family history positive and negative groups in both right and left hemispheres.

Fractional anisotropy data was sectioned by taking the average of the values for the first 25%, middle 50%, and last 25% of the white matter tract. Results showed that family history positive youth have significantly lower FA values in the first 25% of the AIns-NAcc tract on the left side only (Table 1).

Table 1: AIns-NAcc tract fractional anisotropy (FA) values for overall subject pool

Tract Section	Mean FA values		Significance	
	FH+	FH-	T-score (df)	P-value
Left Hemisphere				
first 25%	0.294	0.298	1.82 (3019.9)	0.034
middle 50%	0.187	0.190	1.47 (2924.4)	0.071
last 25%	0.260	0.262	0.70 (2995.8)	0.242
Right Hemisphere				
first 25%	0.329	0.330	0.53 (3124.1)	0.299
middle 50%	0.196	0.196	0.40 (2933.9)	0.344
last 25%	0.239	0.242	0.87 (2996.6)	0.192

Participants were divided by SES following the initial analysis to control for effects of socioeconomic stressors; an independent samples t-test was performed within both the high and low SES groups for each section of the AIns to NAcc tract in both hemispheres. When only observing participants of low socioeconomic status, the difference in FA values between family history positive and family history negative groups increased slightly for the first 25% of the tract in the left hemisphere for low socioeconomic status participants, while there were no significant differences in FA values for any other areas of the tract (Table 2). When observing participants of high socioeconomic status, there were no significant differences in any areas of the tract whatsoever.

Table 2: AIns-NAcc tract FA values based on socioeconomic status

	Mean FA Values	Significance

Tract Section		FH+	FH-	T-score (df)	P-value
High SES					
Left Hemisphere					
first 25%		0.297	0.298	0.38 (1188.4)	0.351
middle 50%		0.189	0.190	0.50 (1174.5)	0.308
last 25%		0.263	0.260	-0.55 (1229.1)	0.708
Right Hemisphere					
first 25%		0.332	0.329	-0.64 (1185.5)	0.739
middle 50%		0.196	0.197	0.70 (1145.1)	0.243
last 25%		0.240	0.241	0.32 (1176.2)	0.376
Low SES					
Left Hemisphere					
first 25%		0.292	0.297	2.03 (1827.4)	0.021
middle 50%		0.187	0.190	1.48 (1745.1)	0.070
last 25%		0.258	0.263	1.29 (1765.7)	0.099
Right Hemisphere					
first 25%		0.327	0.330	1.22 (1936.1)	0.112
middle 50%		0.196	0.196	-0.04 (1786.4)	0.516
last 25%		0.239	0.242	0.86 (1818.3)	0.1963

Discussion

Our goal was to observe the effect that family history of alcohol use has on white matter integrity in adolescents. We hypothesized that adolescents with family history of AUDs would have lower fractional anisotropy values than adolescents with no family history of AUDs. We also hypothesized that socioeconomic status would have a moderating effect on the relationship between family history and white matter integrity. In line with our hypothesis, our results

showed that there are significant differences in white matter integrity between subjects with and without family history of alcohol use disorders, specifically in the first 25% of the AIns to NAcc tract in the left hemisphere. Our findings also support research showing that socioeconomic status also partially influences white matter integrity (Ursache et al., 2016); while there were no significant results for the high SES group, the hypothesis that the low SES group would have lower FA values for the family history positive group was supported by our results, suggesting that family history of AUDs has a much more significant effect on adolescents in lower SES groups.

The finding that adolescents with a family history of alcohol use disorders have significantly lower fractional anisotropy values near the anterior insula is significant because it suggests that there may be underlying structural differences caused by genetics that contribute to the increased risk of alcohol use disorders in individuals with a family history, especially since the anterior insula is also thought to play a role in regulating impulsive behavior and decision-making (Chung & Clark, 2014; Serafini et al., 2020; Namkung et al., 2017). These structural differences may increase susceptibility to impulsive behavior and decision-making, which are risk factors for alcohol use disorders (Rose, 1998). These findings show that white matter FA values for tracts near the anterior insula could be a significant factor when predicting possible future alcohol related problems in adolescents. Also, outside the scope of AUDs, these results provide insight on genetic behavioral tendencies. With more extensive and longitudinal analysis, researchers could use the idea that genetics play a role in white matter integrity near the anterior insula and nucleus accumbens to examine the role that genetics play in the susceptibility to other behavioral issues such as mental health or other substance use disorders.

Since previous research shows that individuals from lower SES backgrounds tend to have lower FA values in several sections of the brain, it was necessary for us to control for the differing SES backgrounds of our participants (Cservenka, 2016; Squeglia et al., 2014). By testing the FA differences between family history positive and family history negative of low SES separately from those of high SES, we can conclude that our results are not solely due to reduced FA from differences in socioeconomic status. A possible explanation for this trend could also be the fact that low SES subjects tend to be prone to more negative reactions to stressors when compared to high SES subjects (Lovallo et al., 2018). Studies have shown that those with family history of AUDs tend to be less resilient when exposed to adversity, which could explain the trends seen in our results as well (Lovallo et al., 2018).

Regarding the lack of difference in FA values within the high SES group, it is possible that those of higher SES backgrounds have greater access to resources that may prevent white matter damage such as healthier food options, safer environment, or less exposure to stressors overall. This suggests that genetics are not necessarily the sole factor in FA value differences and may possibly have environmental stressors as a contributor as well, which lines up with previous research on the effects of socioeconomic status on white matter integrity; research found that heritability of white matter integrity differed between socioeconomic classes, suggesting that environmental factors play a significant role (Chiang et al., 2011). Furthermore, research shows that lower SES also leads to more rapid brain aging—such as accelerated cortical thinning—at younger ages (Colich et al., 2020), which illustrates the importance of considering environment in coordination with genetics. These findings suggest that it is crucial to observe genetic differences alongside environmental factors simultaneously to understand the full scope of AUD predisposition.

Together, these findings could lead to significant advancements in AUD prevention measures; they suggest that there may be differences in brain structure that contribute to increased susceptibility to impulsive behavior and decision-making, which could help to better inform prevention and intervention efforts. When analyzed alongside other white matter integrity studies, researchers can develop strategies to target specific structural differences in the brain that are associated with AUD development. Understanding the relationship that the anterior insula plays in AUD predisposition brings research one step closer to understanding the genetic factors that play into the development of these tendencies. To solidify these findings, however, we must be able to observe the future alcohol use tendencies of our adolescent subjects to see whether these structural differences truly have a future effect on their behaviors. We must also be able to consider environmental stressors at varying stages of life that could affect brain aging.

Our study has both strengths and limitations. Our study included a large, diverse sample of adolescents who have no history of alcohol use. Therefore, it is unlikely that the findings were a consequence of prior substance use to any degree. Also, the adolescents we analyzed were all very close in age, so the findings were also unlikely to be a result of brain aging differences purely based on relative ages. Limitations to our study include a lack of prospective data for the adolescents we followed. Given the time constraints, these subjects—while currently being followed longitudinally—have not been observed long enough to determine whether their differences in FA values will truly lead to corresponding alcohol use tendencies. An important follow-up for this data is to observe which of these adolescents develop an AUD to see whether white matter integrity truly influences predisposition. Another potential weakness to this study is the lack of concrete AUD diagnosis data for the parents of our subjects. We only have self-

reported data available, so there may have been large variations in severity of alcohol use problems between the subjects' family histories.

Overall, the finding of lower FA values near the anterior insula in adolescents with a family history of alcohol use disorders provides insight into the underlying neural mechanisms that contribute to increased risk for alcohol use disorders in this population. In addition, the finding that SES is a moderating variable for this relationship is important for determining the balance between environmental and genetic factors. Since the current consensus is that there are a multitude of factors contributing to AUD predisposition, it is important to emphasize that while there was a significant relationship between family history and white matter integrity for a specific section of the AIns-NAcc tract, it is not the only factor to consider and may also not be a contributor at all when it comes to future AUD development. However, it does allow us to conclude that there could be a significant relationship between family history and genetic white matter integrity for the first 25% of the AIns-NAcc tract in general, whether it should contribute to AUD development or not.

References

- Acheson, A., Wijtenburg, S. A., Rowland, L. M., Winkler, A. M., Gaston, F., Mathias, C. W., Fox, P. T., Lovallo, W. R., Wright, S. N., Hong, L. E., Dougherty, D. M., & Kochunov, P. (2014). Assessment of whole brain white matter integrity in youths and young adults with a family history of substance-use disorders. *Human brain mapping*, 35(11), 5401–5413. <https://doi.org/10.1002/hbm.22559>
- Amark, C. (1951). A study in alcoholism; clinical, social-psychiatric and genetic investigations. *Acta psychiatrica et neurologica Scandinavica. Supplementum*, 70, 1-283.
- Begleiter, H., & Porjesz, B. (1999, July). What is inherited in the predisposition toward alcoholism? A proposed model. *Alcoholism: Clinical and Experimental Research*. <https://doi.org/10.1111/j.1530-0277.1999.tb04269.x>
- Chiang, M.-C., McMahon, K. L., de Zubicaray, G. I., Martin, N. G., Hickie, I., Toga, A. W., Wright, M. J., & Thompson, P. M. (2011). Genetics of white matter development: A DTI study of 705 twins and their siblings aged 12 to 29. *NeuroImage*, 54(3), 2308–2317. <https://doi.org/10.1016/j.neuroimage.2010.10.015>
- Chung, T., & Clark, D. B. (2014). Insula white matter volume linked to binge drinking frequency through enhancement motives in treated adolescents. *Alcoholism, clinical and experimental research*, 38(7), 1932–1940. <https://doi.org/10.1111/acer.12461>
- Cloninger, C. R. (1983). Genetic and environmental factors in the development of alcoholism. *Journal of Psychiatric Treatment & Evaluation*.
- Cloninger, C. R., Bohman, M., & Sigvardsson, S. (1981). Inheritance of alcohol abuse: Cross-fostering analysis of adopted men. *Archives of general psychiatry*, 38(8), 861-868.
- Colich, N. L., Rosen, M. L., Williams, E. S., & McLaughlin, K. A. (2020). Biological aging in childhood and adolescence following experiences of threat and deprivation: A systematic review and meta-analysis. *Psychological bulletin*, 146(9), 721.
- Cservenka, A. (2016, January 1). Neurobiological phenotypes associated with a family history of alcoholism. *Drug and Alcohol Dependence*. Elsevier Ireland Ltd. <https://doi.org/10.1016/j.drugalcdep.2015.10.021>
- Destrieux, C., Fischl, B., Dale, A., and Halgren, E. (2010). Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *NeuroImage*, 53(1), 1–15.
- Fischl, B. (2012). FreeSurfer. *Neuroimage*, 62(2), 774-781.
- Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., and Dale,

- A.M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, 33, 341-355.
- Herting, M. M., Schwartz, D., Mitchell, S. H., & Nagel, B. J. (2010). Delay discounting behavior and white matter microstructure abnormalities in youth with a family history of alcoholism. *Alcoholism: Clinical and Experimental Research*, 34(9), 1590-1602.
- Jacob, T., Waterman, B., Heath, A., True, W., Bucholz, K. K., Haber, R., ... & Fu, Q. (2003). Genetic and environmental effects on offspring alcoholism: New insights using an offspring-of-twins design. *Archives of general psychiatry*, 60(12), 1265-1272.
- Lovallo, W. R., Cohoon, A. J., Acheson, A., Sorocco, K. H., & Vincent, A. S. (2019). Blunted stress reactivity reveals vulnerability to early life adversity in young adults with a family history of alcoholism. *Addiction*, 114(5), 798-806.
- Lu, L., Yang, W., Zhao, D., Wen, X., Liu, J., Liu, J., & Yuan, K. (2023). Brain recovery of the NAc fibers and prediction of craving changes in person with heroin addiction: A longitudinal study. *Drug and Alcohol Dependence*, 243, 109749.
- Manuweera, T., Kisner, M. A., Almira, E., & Momenan, R. (2022). Alcohol use disorder-associated structural and functional characteristics of the insula. *Journal of Neuroscience Research*, 100, 2077– 2089. <https://doi.org/10.1002/jnr.25113>
- Merikangas, K. (1990). The genetic epidemiology of alcoholism. *Psychological Medicine*, 20(1), 11-22. doi:10.1017/S0033291700013192
- Morales, A. M., Jones, S. A., Harman, G., Patching-Bunch, J., & Nagel, B. J. (2020). Associations between nucleus accumbens structural connectivity, brain function, and initiation of binge drinking. *Addiction biology*, 25(3), e12767. <https://doi.org/10.1111/adb.12767>
- Namkung, H., Kim, S. H., & Sawa, A. (2017). The Insula: An Underestimated Brain Area in Clinical Neuroscience, Psychiatry, and Neurology. *Trends in neurosciences*, 40(4), 200–207. <https://doi.org/10.1016/j.tins.2017.02.002>
- Naqvi, N. H., Rudrauf, D., Damasio, H., & Bechara, A. (2007). Damage to the insula disrupts addiction to cigarette smoking. *Science*, 315(5811), 531-534.
- Oscar-Berman, M., & Marinkovic, K. (2003). Alcoholism and the brain: an overview. *Alcohol research & health*, 27(2), 125.
- Rose, R. J. (1998). A developmental behavior-genetic perspective on alcoholism risk. *Alcohol health and research world*, 22(2), 131–143.

- Salgado, S., & Kaplitt, M. G. (2015). The nucleus accumbens: A comprehensive review. *Stereotactic and Functional Neurosurgery*. S. Karger AG. <https://doi.org/10.1159/000368279>
- Schuckit, M. A., Smith, T. L., Paulus, M. P., Tapert, S. F., Simmons, A. N., Tolentino, N. J., & Shafir, A. (2016). The ability of functional magnetic resonance imaging to predict heavy drinking and alcohol problems 5 years later. *Alcoholism: Clinical and Experimental Research*, 40(1), 206–213. <https://doi.org/10.1111/acer.12935>
- Serafini, R. A., Pryce, K. D., & Zachariou, V. (2020). The Mesolimbic Dopamine System in Chronic Pain and Associated Affective Comorbidities. *Biological psychiatry*, 87(1), 64–73. <https://doi.org/10.1016/j.biopsych.2019.10.018>
- Sher KJ, Grekin ER, Williams NA (2004): The development of alcohol use disorders. *Annu Rev Clin Psychol* 22, 1–22.
- Squeglia, L., Jacobus, J., Brumback, T., Meloy, M., & Tapert, S. (2014). White matter integrity in alcohol-naïve youth with a family history of alcohol use disorders. *Psychological Medicine*, 44(13), 2775–2786. doi:10.1017/S0033291714000609
- Ursache, A., Noble, K. G., & Pediatric Imaging, Neurocognition and Genetics Study. (2016). Socioeconomic status, white matter, and executive function in children. *Brain and behavior*, 6(10), e00531.
- Veer, I. M., Jetzschmann, P., Garbusow, M., Nebe, S., Frank, R., Kuitunen-Paul, S., ... & Walter, H. (2019). Nucleus accumbens connectivity at rest is associated with alcohol consumption in young male adults. *European Neuropsychopharmacology*, 29(12), 1476–1485.
- Waters, A. B., Sawyer, K. S., & Gansler, D. A. (2020). White matter connectometry among individuals with self-reported family history of drug and alcohol use disorders. *Drug and Alcohol dependence*, 206, 107710.
- Zimmermann, P., Wittchen, H. U., Höfler, M., Pfister, H., Kessler, R. C., & Lieb, R. (2003). Primary anxiety disorders and the development of subsequent alcohol use disorders: a 4-year community study of adolescents and young adults. *Psychological medicine*, 33(7), 1211–1222.