2020

Finding Brain Predictors Of Psychostimulant Medication Use In Adhd Using Machine Learning

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FINDING BRAIN PREDICTORS OF PSYCHOSTIMULANT MEDICATION USE IN
ADHD USING MACHINE LEARNING

A Thesis Presented

by

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to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Master of Science
Specializing in Pharmacology

August, 2020

Defense Date: July 24, 2020
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ABSTRACT

Psychostimulant medication is the first line of treatment for Attention deficit/hyperactivity disorder (ADHD). Despite the prevalence of ADHD, there is a lack of understanding of the underlying neurophysiological mechanisms of the disorder and its pharmacological treatments. Existing neuroimaging research shows some consistent structural differences in ADHD, but it can be difficult to discern what is relevant. Machine learning algorithms present a novel way of analyzing a large amount of data by making predictions based on pattern detection.

The present study applied an elastic-net logistic machine learning model to structural magnetic resonance imaging (sMRI) data from the Adolescent Brain Cognitive Development (ABCD) Study to predict ADHD diagnosis and psychostimulant medication use. Based on Matthews correlation coefficient and receiver operating characteristic curves, the model achieved modest success in classifying ADHD diagnosis and psychostimulant use amongst the whole sample regardless of the inclusion of covariates, along with psychostimulant use amongst males assigned at birth and ADHD-negative subjects. Classifying psychostimulant use was consistently more successful than classifying ADHD diagnosis. In line with existing ADHD research, important features for prediction included subregions in the frontal, temporal, and parietal lobes. Correlations between several subregional volumes and stimulant use had opposing directions in the ADHD-positive sample compared with other groups, implying an ADHD-dependent effect of medication. The finding that stimulant use is more detectable from sMRI data than ADHD urges further investigation of these commonly prescribed drugs and their relationship to the brain, especially in children and adolescents.

ACKNOWLEDGEMENTS

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CHAPTER 1: BACKGROUND

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most commonly diagnosed neuropsychiatric disorders among children and adolescents, affecting an estimated 7.2% of children under 18 worldwide (Thomas et al., 2015). The disorder is characterized in the DSM-5 (APA, 2013) by two primary symptom clusters: inattention symptoms such as distractibility, forgetfulness, or difficulty completing tasks, and hyperactive/impulsive symptoms, such as fidgeting or talking excessively. Diagnostic criteria are met if 6 or more symptoms (in one or both clusters) have been present for at least six months, with an onset of some symptoms prior to age 12, and current symptoms are developmentally inappropriate and cause functional impairment in at least 2 environments (eg. home and school). For full diagnostic criteria, see the Appendix.

Children affected by ADHD can experience a lot of difficulty as a result of the disorder impairing their ability to function in various environments. This interference has a negative impact on multiple aspects of kids' everyday lives, from schoolwork and learning to social interaction (Barbaresi et al., 2007; McGee et al., 2002; Mrug et al., 2001). This is understandably distressing for many children, and the fact that it happens during crucial development times means it can have long-term effects on mood and social adjustment, even if the disorder itself remits over time. Studies of the long-term outcomes of childhood ADHD have shown associations with lower social function, self-esteem and educational, occupational, and economic attainments in adulthood compared to controls, as well as, higher rates of antisocial personality disorders, substance use disorders, and psychiatric hospitalizations (Harpin et al., 2016; Hechtman et al., 2016; Klein et al.,

2012). It is clear that as a result of the disorder and associated symptoms, the quality of life for affected individuals is often reduced in both the short and long term.

Fortunately, there are a number of approved treatments for ADHD. Psychostimulant drugs, such as methylphenidate (MPH) and amphetamines (AMP) are the most common form of ADHD treatment (National Institute of Mental Health, 2016). These medications have consistently shown robust effects in improving attention and reducing hyperactivity in affected individuals (Wolraich et al., 2019). Pharmacological treatment is effective at reducing symptoms, and in combination with behavioral therapy shows substantial improvement in academic, family, and social functions (Pliszka, 2019). Treatment seems to reduce ADHD-related functional impairments in the long term as well. Treated ADHD groups show improvement in social and academic functioning compared to untreated ADHD groups even after 2 or more years of medication (Arnold et al., 2020; Harpin et al., 2016). More investigation is needed on the efficacy after decades or more, but overall stimulants are accepted as very effective in treating ADHD.

Knowledge regarding the pharmacology of psychostimulants has grown significantly since amphetamine was first discovered in 1910. All psychostimulants act by increasing availability of the catecholamine neurotransmitters dopamine (DA) and norepinephrine (NE) in corticostriatal systems (Heal et al., 2013). The mechanisms of action are many and vary between amphetamines and methylphenidate, but both subclasses have this same primary effect. For review, see Faraone (2018).

Amphetamines inhibit dopamine transporters (DATs) and norepinephrine transporters (NETs), reducing reuptake of these neurotransmitters and thus increasing the amounts present in the synapse. AMPs also inhibit vesicular monoamine transporter 2

(VMAT-2), a protein responsible for transporting monoamine neurotransmitters out of the synapse and into vesicles. This inhibition also increases free DA and NE in the cytosol, along with other monoamines such as serotonin (5-HT). Monoamine oxidase (MAO), which breaks down extracellular neurotransmitters in this family, is inhibited by amphetamines as well, further contributing to the increased availability of these substrates. Like amphetamines, methylphenidate increases cytosolic DA and NE by inhibiting their respective transporters. Additionally, it redistributes VMAT-2, leading to accumulation of DA in the synapse. There is also some evidence of MPH enhancing serotonergic activity by acting as an agonist at the 5-HT 1A receptor (Markowitz, Straughn, & Patrick, 2003).

Although stimulants are effective treatment for ADHD, it is not entire clear why their aforementioned mechanisms lead to the behavioral effects (Andersen, 2005). The DA system has many functions, including the mediation of voluntary movement and reward processes, while NE is known to modulate various cognitive processes including attention and working memory. It follows that dysregulation of these systems could lead to ADHD symptoms which are treated by increasing availability of these substrates.

Like most neurologically-based disorders, however, our knowledge of the underlying physiology of ADHD is lacking, so the exact role psychostimulants play in treating the disorder is not immediately evident. ADHD is generally thought to be a neurodevelopmental deficit in which maturation of the brain, particularly the prefrontal cortex, is delayed or abnormal, resulting in difficulties executing control processes. This is supported by a large body of research showing ADHD-related structural changes throughout the brain. However, the differences seen in ADHD vary widely across studies.

Most consistently across large studies, ADHD groups show reduced volumes compared to controls in the frontal cortex, caudate nucleus, cerebellum, and putamen, as well as reduced global cortical volume. (Frodl & Skokauskas, 2011; Hoogman et al., 2019; Nakao et al., 2011; Schweren et al., 2013). Various analyses have also found ADHD-related volume reduction in other areas, including the nucleus accumbens, temporal cortex, anterior cingulate cortex, hippocampus, amygdala, and globus pallidus (Frodl & Skokauskas, 2011; Hoogman et al., 2019). Differences are widespread and relatively inconsistent, but basal ganglia structures in particular are largely implicated. These structures rely on the dopaminergic system, which may relate to the efficacy of stimulant medication which enhances DA activity. Again, this area is crucial in reward processing and movement regulation—both functions disrupted in ADHD—supporting the idea that alterations in this area are related to the disorder.

It is unclear whether or not the clinical benefit of stimulant medication is related to these structural alterations. Some research implies a potential normalizing effect of medication in ADHD. Schweren et al. (2013) found that ADHD-related differences in the anterior cingulate cortex, pulvinar nucleus of the thalamus, posterior inferior cerebellum, and white matter were not seen in medicated ADHD groups. Other studies have also found that medication in ADHD is associated with structural volumes more similar to controls rather than untreated ADHD (Frodl & Skokauskas, 2011; Nakao et al., 2011). In one of the largest and more recent meta-analyses, however, no significant effect of stimulant medication on brain structure was found (Hoogman et al., 2017). These inconsistencies could be due to differences in study design—some stimulant-related alterations may be too localized to be detected by some methods of MRI analysis like

voxel-based morphometry (Frodl & Skokauskas, 2012). Nonetheless, a clear relationship of stimulants and brain structure is not established.

It is important to note as well that the efficacy of medication is not necessarily related to structural alterations. Psychostimulants exert their effects on neurotransmitter systems, so effects on brain structure may be secondary or even unrelated. Said neurotransmitter systems appear to play an important part in the disorder (Solanto, 2002). The efficacy of stimulants targeting DA and NE suggests dysregulation in these systems in particular, and current knowledge of the role of these substrates is in line with this idea. The frontostriatal-thalamic circuits are associated with motor initiation and inhibition and are heavily reliant on DA. Dopamine, along with NE, also plays an important role in reward and executive functions that regulate attention in the PFC (reviewed by Andersen, 2005). Although DA and NE are clearly important in the pathophysiology of ADHD, it is likely more complex. Several other pathways have been implicated in ADHD, including glutamate, serotonin, and acetylcholine (Faraone, 2018). These different systems interact with one another to regulate a multitude of functions, which may be why ADHD can present with different combinations of symptoms and comorbidities, or why individuals respond differently to medications. However, it is unclear if or how these hypothesized chemical deficits are related to structural alterations in the disorder.

Although significant differences between ADHD and healthy control brains are frequently found, they are so varied that it has been difficult to narrow these differences down into a defined neural signature of the disorder. The lack of concrete biological markers for ADHD means that diagnosis is a subjective process. Criteria are well-

defined, but diagnosis is often based on reports from teachers and parents—opinions that can be easily influenced by societal expectations and bias. For example, boys and children who are the youngest in their class are more frequently diagnosed (Holland & Sayal, 2019). This has raised concern that the disorder could often be misdiagnosed, leading to overmedication of non-affected individuals and lack of treatment for many affected individuals, especially girls.

With medication being the first-line treatment for the disorder, correct diagnosis should be a priority--especially in the case of psychostimulants which are already subject to a fair amount of controversy due to their side effects and potential for abuse (Pliszka, 2019). There are a few non-stimulant drugs (atomoxetine, guanfacine, and clonidine) approved for the disorder, but stimulants generally remain the first choice for therapy based on evidence of greater efficacy (Faraone, 2018).

Stimulants are generally well-tolerated at therapeutic doses, but they can potentially be accompanied by serious adverse effects. Cardiovascular side effects—most commonly increased heart rate and blood pressure--are frequently reported, probably due to stimulant effects on the adrenergic system. More intense adverse cardiovascular events including myocardial infarction or stroke sometimes also occur, although usually only in patients with a history of cardiac problems. This is especially important to consider in the case of ADHD, as the affected individuals are likely to require medication for multiple years throughout adolescence, and often further into life—ADHD is also present in adulthood for approximately 2.5-4.4% of people (Kessler et al., 2007; Simon et al., 2009). Despite the prevalence, effects of such long-term medication use have not been well studied. Additionally, stimulants are commonly used by people who do not have

ADHD, whether recreationally or due to misdiagnosis (Sansone & Sansone, 2007). Knowledge of the effects on non-ADHD individuals is very limited as this is difficult to study.

The body of research dedicated to ADHD and related drugs is so massive that it can be difficult to synthesize findings into meaningful conclusions. So many brain regions and systems seem to be related to the disorder that the ability to make concrete statements is compromised, and it may feel as though we are no closer to understanding the physiology than we were when it was first described in 1902 (CDC, 2018).

Machine learning is a novel method of data analysis that may help clarify our understanding of ADHD. These algorithms are designed to analyze large datasets and learn to make predictions based on detected patterns. Supervised classification models, in which pre-classified training data is presented to the model to teach it to identify groups, are of particular interest in medicine. In the machine learning process, data is split into a training set and a test set. The model is evaluated and tuned utilizing the training data, allowing for the final test to be performed on completely new data which helps prevent over-fitting—when the model is too sensitive to irrelevant features. Another useful step in guarding against model over-fitting is known as k-fold cross-validation of the training set, in which the data is further divided into a specified number of 'folds'. In evaluating the model, one fold is selected to be held out and the model is trained on the remaining folds. This process is be repeated multiple times with different folds held out, allowing the performance metrics to be averaged over several iterations, providing a better representation of metrics. It is even possible to repeat the entire k-fold process with different random splits. These methods ensure rigorous testing of the model while leaving

enough unseen data for the final test. The ability to efficiently and soundly analyze large amounts of data and expand this analysis to inference and prediction makes machine learning an invaluable tool in the future of scientific research. Machine learning has already shown promise by using medical images to successfully diagnose metastatic lymph nodes and classify different types of melanomas (Nichols, Chan, & Baker, 2019). Similar models can also be used to analyze neuroimaging data, and in fact have identified autism spectrum disorder based on structural MRI images (Bezgin, Lewis, & Evans, 2018).

The present study will apply a machine learning paradigm to behavioral and MR data from the Adolescent Brain Cognitive Development (ABCD) Study, a 10-year nationwide study of over eleven-thousand children aged 9 and 10 at baseline. ADHD diagnosis was assessed using the Kiddie-Schedule of Affective Disorders and Schizohprenia (KSADS; Kaufman, Birmaher, Brent, Ryan, & Rao, 2000). Scores for past and present ADHD symptoms and parent report of stimulant medication use will be used to classify the participants. Binary machine learning models will be utilized to address **two specific aims: 1. to predict ADHD diagnosis from structural MRI data, and 2. to predict stimulant use (regardless of diagnosis) using structural MRI data**. Successful models will be examined to identify the features that were most important for classification. This may provide valuable insight into neurobiological mechanisms of ADHD and advance understanding of how stimulants affect brain development in those with ADHD. Based on past MRI meta-analyses, we expect predictive features of ADHD to include volume of the cerebellum, frontal cortex, caudate nucleus, corpus callosum,

accumbens, amygdala, hippocampus, and/or putamen. (Hoogman et al., 2017; Schweren et al., 2013).

CHAPTER 2: METHODS

2.1. The ABCD Study

The ABCD Study (https://abcdstudy.org) aims to characterize development of the brain throughout the crucial window of adolescence and the relationships of many environmental factors to this process. With 21 sites across the United States and a total of 11,875 participants at baseline, it is the largest study of adolescent development and health to date. Beginning at ages 9 and 10, participants will be followed for ten years. Each year, a variety of behavioral, neurocognitive, and biospecimen data is collected from participants, and MRI scans are performed bi-annually beginning at baseline.

Although the large sample size inherently provides high statistical power, great care was taken during the recruitment phase to ensure the demographic distribution of the sample would be representative of the greater adolescent population. Recruitment for the study was done through schools nationwide, and the schools were selected using statistical software to ensure a stratified probability sample. The demographic distributions in the cohort were also monitored throughout the recruitment phase and recruitment strategies adjusted to achieve a distribution comparable to that of the greater United States (Garavan et al., 2018).

The present analysis utilizes only a small part of the data available from the ABCD Study. Thus, only relevant methodology will be discussed in detail here. For information on all ABCD Study protocol, see (https://abcdstudy.org/scientists/protocols/). All data was obtained from the Annual NDA Data Release 2.0.1 available at https://nda.nih.gov/abcd.

2.2. Magnetic Resonance Imaging (MRI)

All preprocessing and processing on MRI data from the ABCD Study was performed by the ABCD Data Analysis and Informatics Resource Center (DAIRC) prior to the data being released. For details on this process, see Hagler et al. (2019). The structural data used in the present investigation is contained in the sets "ABCD sMRI Part 1" and "ABCD sMRI Part 2", described as "sMRI morphometric and image intensity measures". Morphometric data is comprised of subcortical regional volume, cortical volume, cortical thickness, cortical area, and sulcal depth. Image intensity measures are gray and white matter intensity levels in both T1-weighted (T1w) and T2-weighted (T2w) scans, and cortical contrast (the normalized difference between gray and white matter intensity) in T1w and T2w scans. These measures are parcellated in two ways: by regions of interest (ROIs) in the Deskian/Killiany atlas, and by fuzzy cluster parcels based on genetic correlation of surface area, resulting in a total of 1196 sMRI variables. For a full list of included measures, see the ABCD Data Dictionary for these datasets (https://nda.nih.gov/data_structure.html?short_name=abcd_smrip101, https://nda.nih.gov/data_structure.html?short_name=abcd_smrip201).

2.3. Behavioral Assessments

A parent or guardian of each participant in the ABCD study completes the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), an established diagnostic semi-structured interview for mood and behavioral disorders in children and adolescents (Kaufman et al., 2000). Based on the parent-reported K-SADS scores, participants were classified into ADHD-positive or ADHD-negative groups. Participants receiving a binary

score of 1 (positive) in one or both of the present and past ADHD categories (items "ksads_14_853_p" and "ksads_14_854_p" respectively in the dataset "ABCD Parent Diagnostic Interview for DSM-5 Full") comprised the ADHD-positive group for this analysis.

2.4. Medication Inventory

Data on the medications the participants are using is collected as part of the ABCD Study. Parents/guardians were asked to provide any prescription and over-the-counter medications their children had used in the two weeks prior to the baseline visit. The medication inventory includes the name and dosage of the drug, as well as whether or not it is XR (extended release). If the medication had been used in the past 24 hours, it was recorded how long ago the medication was taken.

2.5. Data Processing and Cleaning

2.5.1. Medication Classification

Each prescription drug coded in the NDA 2.0.1 data release was classified into a broader drug group using the United States Pharmacopeia Drug Classification (USP-DC) 2019 (https://www.usp.org/health-quality-safety/usp-drug-classification-system). Each subject received scores for the number and class of neuropsychiatric drugs they were taking. Then, since ADHD medication is of particular interest, the number and distribution of ADHD medications for each participant was determined. For the machine learning analysis, participants were classified into stimulant-positive (exposed to any

stimulant medication in the past two weeks) or stimulant-negative (no reported current stimulant medication exposure) binary groups.

2.5.2. sMRI and Covariate Cleaning

For quality control, a number of subjects were dropped due to missing data. The number of missing variables for each variable, or column, was found as part of the data loading function in the machine learning toolbox, which returns a list of all columns with missing values and any strings which are present in multiple names of these columns. 249 columns containing the string 'smri_t2w.' had 617 missing variables, and 3 columns containing the string 'smri_vol_subcort.aseg_' had 112 missing values, so the data was re-loaded with any columns containing these strings removed. Then, since these categories comprised most of the missing data, subjects with any remaining missing data were removed, yielding 10440 subjects with 821 sMRI variables each. After overlap with the available ADHD and stimulant use data, 9074 subjects remained. In the analyses including covariates, 8713 subjects had available data.

2.5.3. Final Dataset

From the 11,875 subjects in the ABCD study, a final sample of 9074 passed all data cleaning and quality control steps. Figure 1 shows the loss of subjects at each step. Stimulant medication status and ADHD diagnosis for each subject were loaded as binary variables (0 = negative, 1 = positive). See Table 1 for distributions of race/ethnicity, sex assigned at birth, MRI scanner manufacturer, and pubertal development stage in these

subjects. See Figures 2 and 3 for distributions of interview age and highest guardian

education level.
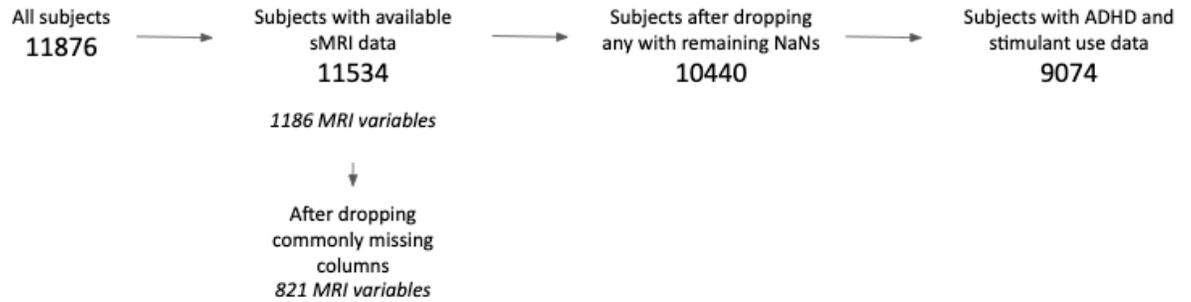
Figure 1. Number of subjects available throughout the data cleaning process

Table 1. Distribution of race, sex assigned at birth, MRI manufacturer, and pubertal development stage covariates among the ABCD subjects used in analysis.

Race/Ethnicity	Count	Frequency (%)
White	4831	53.3
Black	1259	13.9
Hispanic/Latino	1845	20.4
Asian	200	2.2
Other	924	10.2

Sex Assigned at Birth	Count	Frequency (%)
Female	4501	49.6
Male	4568	50.4

MRI Scanner

Manufacturer	Count	Frequency (%)

GE Medical Systems	2126	24.4
Philips Medical Systems	1111	12.7
SIEMENS	5494	62.3

Pubertal

Development Stage	Count	Frequency (%)
1	4502	51.6
2	2054	23.5
3	2042	23.4
4	127	1.5
5	6	0.001
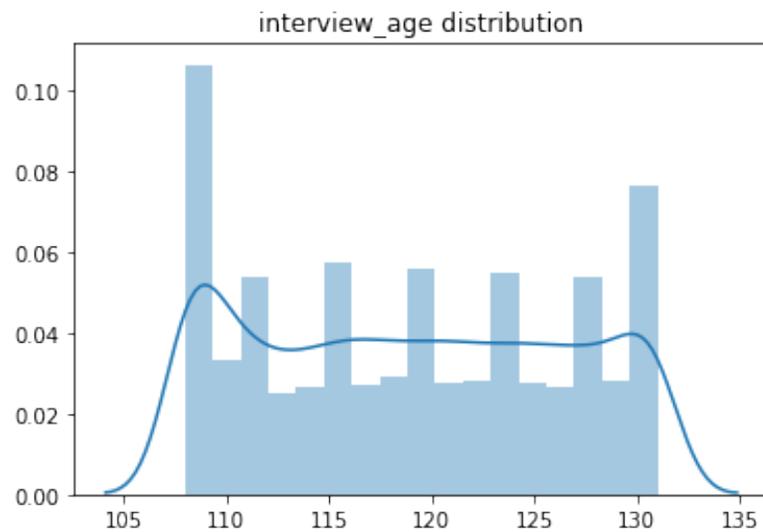
Figure 2. Distribution of age (in months) at the time of interview among the ABCD subjects used in analysis.

Note. Age in months by frequency. Mean = 119, standard deviation = 7.46

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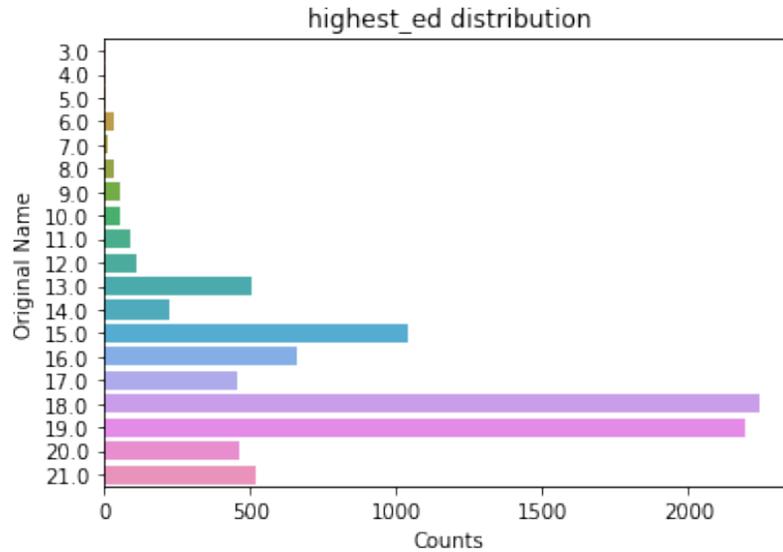
Figure 3. Distribution of highest guardian's education among the ABCD subjects used in analysis.
Note. Names of categorical variables are: 0 = Never attended/Kindergarten only; 1 = 1st grade; 2 = 2nd grade; 3 = 3rd grade; 4 = 4th grade; 5 = 5th grade; 6 = 6th grade; 7 = 7th grade; 8 = 8th grade; 9 = 9th grade; 10 = 10th grade; 11 = 11th grade; 12 = 12th grade; 13 = High school graduate; 14 = GED or equivalent; 15 = Some college; 16 = Associate degree: Occupational; 17 = Associate degree: Academic Program; 18 = Bachelor's degree; 19 = Master's degree; 20 = Professional School degree; 21 = Doctoral degree

A stratifying validation strategy was implemented. This creates groups stratified by ADHD diagnosis and stimulant medication status and ensures that the distribution of these groups is preserved whenever the data is split, such as into the train and test datasets or into folds. Figure 4 shows the distribution of these stratified variables.

adhd_diagnosis	stim_use	Counts
0	0	8162
0	1	261
1	0	473
1	1	178

Figure 4. Groups stratified by ADHD diagnosis and stimulant medication status. *Note.* A value of 0 represents a negative case and a value of 1 represents a positive case of each variable.

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2.6. Machine Learning Framework

ABCD_ML (https://github.com/sahahn/ABCD_ML), a Python-based machine learning toolbox incorporating Scikit-learn software (Pedregosa et al., 2011), was used to analyze the data. For all models, a test set containing 20% of the data was set aside so that models were ultimately tested on their ability to classify on data that was not used during the training process. The test/train split is randomized for each individual analysis but always preserves the distribution of the stratified groups. As discussed previously, a separate testing set helps to guard against over-fitting. An over-fitted model relies on relationships that may be present in the training dataset, but do not hold in general. Testing the model on completely unseen data that is known to have the same distribution better reflects how well the model would perform in the real world. Table 5 shows the sizes of the train and test datasets for each model.

In the evaluation phase, several types of models (decision tree, svm classifier, ridge logistic, and elastic net logistic) were tested on the training data. Descriptions of these models can be found in the Scikit-learn user guide (https://scikit-learn.org/stable/supervised_learning.html). For all models, we used a k-fold cross-validation strategy with 3 splits (folds) and 2 repeats. This combination of parameters is a good balance between statistical variance and required computing power, as more folds or splits would require more power.

2.6.1. Machine Learning Model Evaluation

For each model, a Matthews correlation coefficient (MCC) and the macro receiver operating characteristic area under the curve (ROC AUC) were calculated. The Matthews

correlation coefficient (MCC) is one of the best standalone measures of the quality of a binary classifier (Chicco & Jurman, 2020). It is the only metric which accounts for all possible outcomes in a confusion matrix (true positive, false positive, true negative, and false negative). Furthermore, it is sensitive to the relative size of the positive and negative classes, so it remains an excellent metric even in cases where one class is much larger than the other, such as in our models where the non-ADHD and stimulant-negative classes are much larger than their positive counterparts. The ROC AUC is also used to evaluate a model's predictive quality. In the context of binary classification, the ROC curve plots the false positive rate by the true positive rate. The area under this curve is essentially a measure of the classifier's probability of making a correct prediction. A value of 0 represents only wrong predictions, while a value of 1 represents only correct predictions.

2.6.2. Analyses For Specific Aims

Aim 1 was to predict ADHD diagnosis from structural MRI data, and Aim 2 was to predict stimulant use (regardless of diagnosis) using structural MRI data. Therefore the analytic methods were identical for both sets of analyses.

For predicting ADHD diagnosis, an elastic net logistic model showed the most success in the evaluation phase of the whole sample, so this model framework was chosen for use in all analyses. Given the known influence of demographics on ADHD diagnoses, a model with covariates (in the context of machine learning, additional features in the predictive model) was analyzed. The following covariates were used: race/ethnicity, sex assigned at birth, pubertal development stage, and highest education

level of a parent/guardian. It was found that all models using these covariates relied heavily on sex assigned at birth as a predictive feature more than any neuroimaging features. Thus, to investigate the potential contribution of sex to classification without obscuring the predictive power of neuroimaging data, covariates were removed and separate models were run on three different samples: The whole sample, subjects assigned female at birth, and subjects assigned male at birth. All three of these were analyzed with two models: one to predict ADHD diagnosis, and one to predict stimulant use.

To further investigate the relationship of stimulant medication to the brain structure and ADHD, four additional models were evaluated and tested: predicting stimulant use in both ADHD-positive and ADHD-negative groups and predicting ADHD diagnosis in both a stimulant-positive and stimulant-negative groups.

To determine if results were statistically significant (ie. not likely to be spurious), the p-value for each ROC AUC was calculated using the formula described by Mason & Graham (2002). Models were considered significant at a p value < 0.05. Models that were statistically significant were examined for feature importance. The top 10 features--those with the largest (in the positive or negative direction) average beta weight--are presented for the 6 significant analyses.

2.6.3. Sample Characteristics

Tables 2-4 show the distributions of the dependent variables (ADHD status and stimulant medication status) of the groups tested in each analysis.

Table 2. Distribution of ADHD status and stimulant use status for all subjects in each sample. *Note.* **In cases where a variable was constant (eg. in the ADHD-negative sample), distributions are not shown.**

Sample	*N (*total)	ADHD status distribution (0,1)	Stimulant status distribution (0,1)
Whole	9074	8423, 651	8635, 439
Whole (with covars)	8713	8103, 628	8315, 416
Assigned female at birth	4501	4281, 220	4383, 118
Assigned male at birth	4568	4137, 431	4247, 321
ADHD-positive	2035	--	1508, 527
ADHD-negative	8999	--	8704, 295
Stimulant-positive	503	296, 207	--
Stimulant-negative	9487	8955, 532	--

Table 3. Distribution of ADHD status and stimulant use status for the training set in each sample. *Note.* **In cases where a variable was constant (eg. in the ADHD-negative sample), distributions are not shown.**

Sample	*N (*training subjects)	ADHD status distribution (0,1)	Stimulant status distribution (0,1)
Whole	7259	6739, 520	6908, 351
Whole (with covars)	6984	6482, 502	6651, 333
Assigned female at birth	3600	3424, 176	3505, 95
Assigned male at birth	3654	3309, 345	3397, 257
ADHD-positive	1628	--	1206, 422
ADHD-negative	7199	--	6963, 236

Stimulant-positive	402	237, 165	--
Stimulant-negative	7589	7163, 426	--

Table 4. Distribution of ADHD status and stimulant use status for the test set in each sample. *Note.* **In cases where a variable was constant (eg. in the ADHD-negative sample), distributions are not shown.**

Sample	N (test subjects)	ADHD status distribution (0,1)	Stimulant status distribution (0,1)
Whole	1815	1684, 131	1727, 88
Whole (with covars)	1747	1621, 126	1664, 83
Assigned female at birth	901	857, 44	878, 23
Assigned male at birth	914	828, 86	850, 64
ADHD-positive	407	--	302, 105
ADHD-negative	1800	--	1741, 59
Stimulant-positive	101	59, 42	--
Stimulant-negative	1898	1792, 106	--

CHAPTER 3: RESULTS

3.1. Model Testing

3.1.1. Metrics

Table 5. Metrics obtained from the testing phase of the elastic net ADHD diagnosis classifier in each group. *Note.* **Plots for significant ROC AUC curves can be found in the specified figures. The feature importances for models with significant ROC curves can be found in the specified figures.**

***p* < .05.**

Sample	All (with covars)	All (without covars)	Males	females	Stim-pos	Stim-neg
Matthews Correlation Coefficient	0.008176	0.013582	0.034584	0.001769	0.0116051	-0.012500
Macro ROC AUC (Fig. 5)	0.554728 (Fig. 5a)	0.552633 (Fig. 5b)	0.519159	0.516017	0.529056	0.505807
ROC AUC p-value	0.0202*	0.0222*	0.2706	0.3555	0.3099	0.3434
Feat Importances	Fig. 6	Fig. 7	NA	NA	NA	NA

Table 6. Metrics obtained from the testing phase of the elastic net stimulant use classifier in each group. *Note.* **Plots for significant ROC AUC curves can be found in the specified figures. The feature importances for models with significant ROC curves can be found in the specified figures.**

*p < .05. **p < .01. ***p < .001*

Sample:	All (with covars)	All (without covars)	Males	females	ADHD-pos	ADHD-neg
Matthews Correlation Coefficient	0.035022	0.007727	0.066780	0.040118	0.036059	-0.015081
Macro ROC AUC (Fig. 5)	0.651254 (Fig. 5c)	0.594758 (Fig. 5d)	0.611444 (Fig. 5e)	0.483581	0.573195 (Fig. 5f)	0.533816
ROC AUC p-value	1.6012e-06***	0.0013**	8.7480e-04***	0.3896	0.0127*	0.1882
Feat Importances	Fig. 8	Fig. 9	Fig. 10	NA	Fig. 11	NA

3.1.2. ROC Curves

a

ROC: ADHD Diagnosis in whole sample (no covars)

b

ROC: ADHD Diagnosis in whole sample (with covars)

c

ROC: Stimulant Use in whole sample (with covars)

d

ROC: Stimulant Use in whole sample (no covars)

e

ROC: Stimulant Use in males

f

ROC: Stimulant Use in ADHD-positive subjects
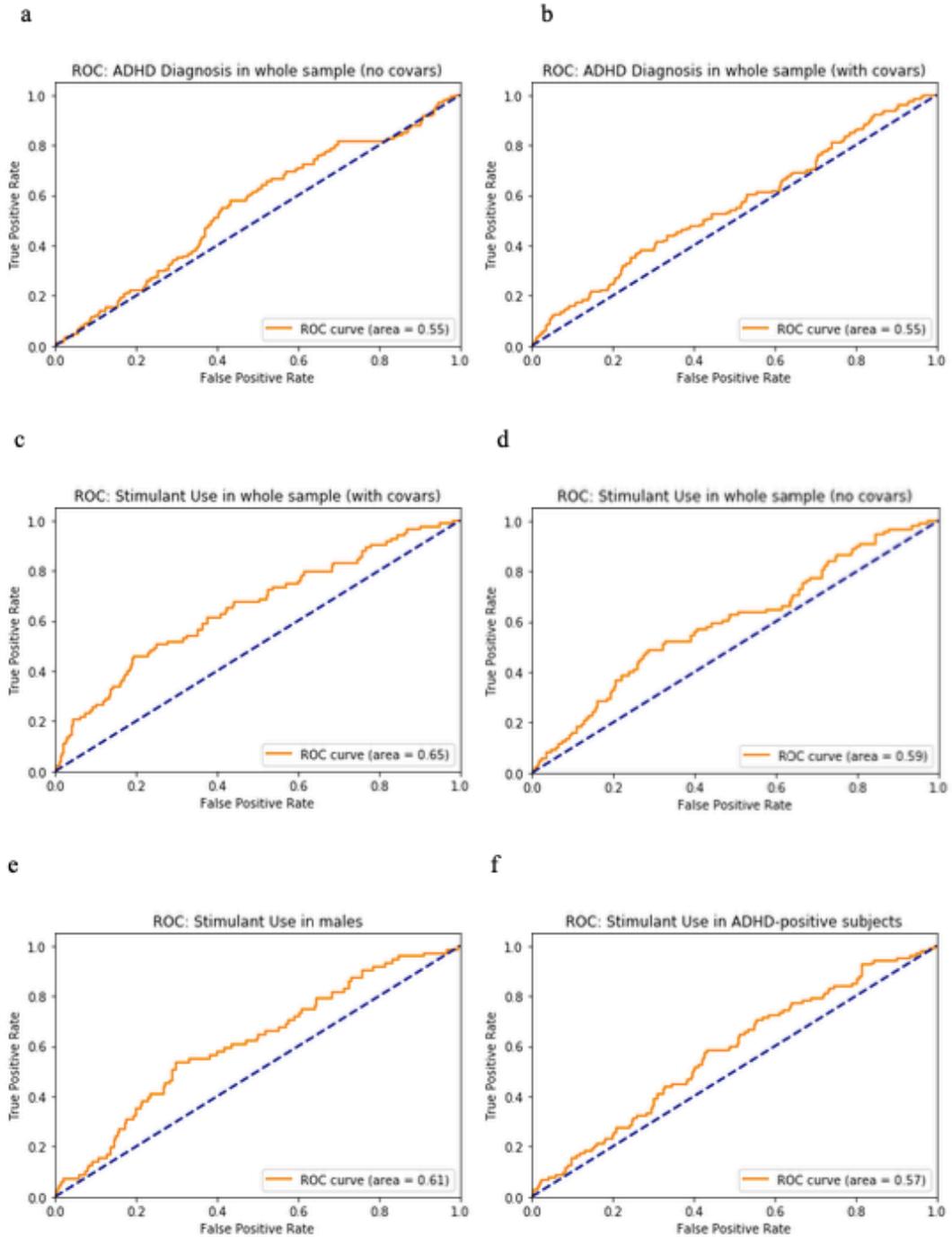
Figure 5. ROC curves for all models with a significant (p < 0.05) ROC AUC score

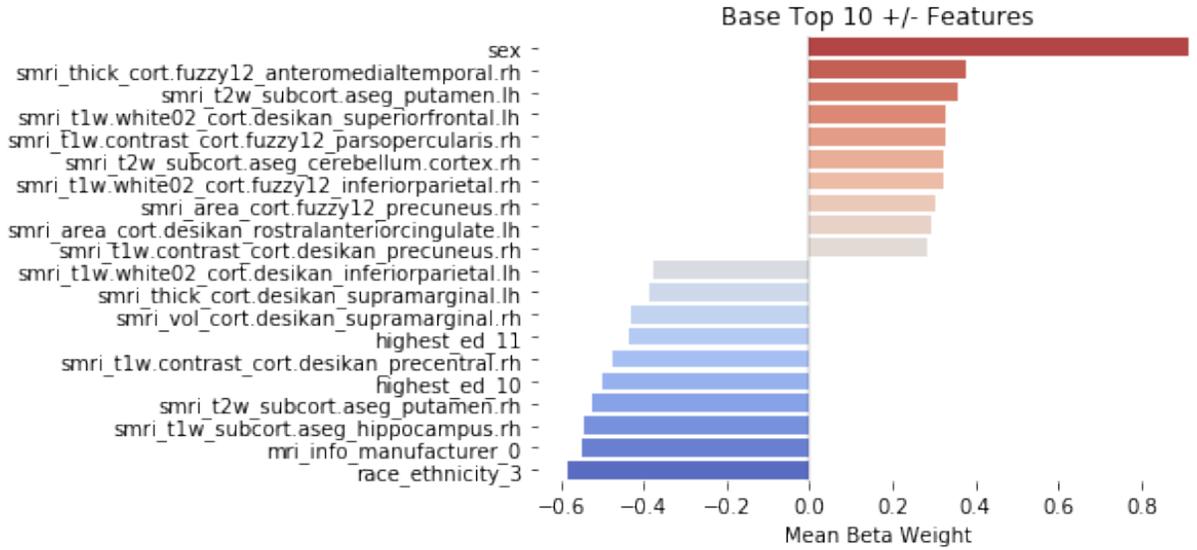### 3.1.3. Feature Importances

Figure 6. Feature Importances for predicting ADHD diagnosis in whole sample (with covariates).
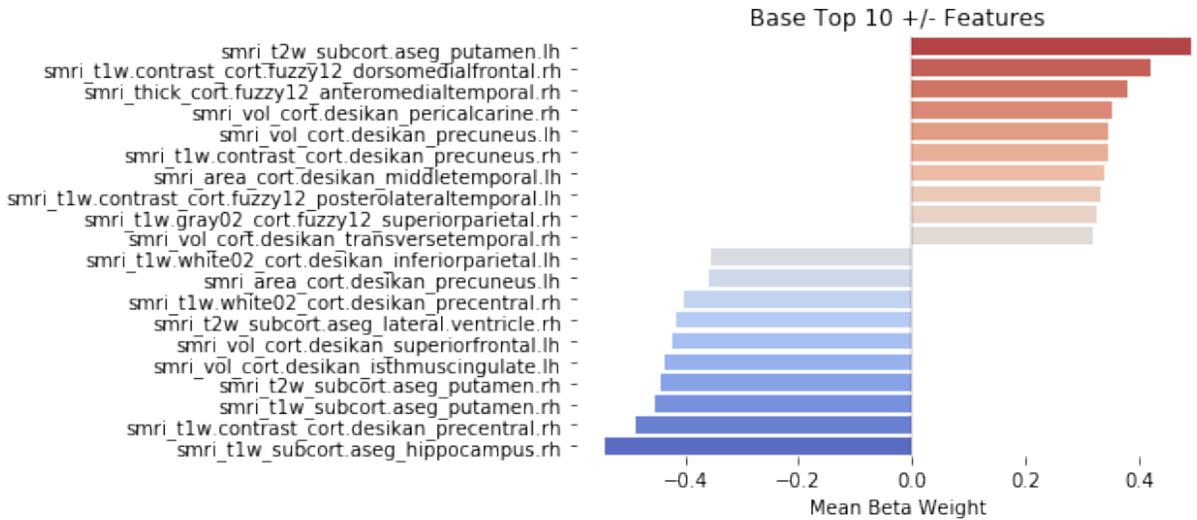

Figure 7. Feature Importances for predicting ADHD diagnosis in whole sample (no covariates).
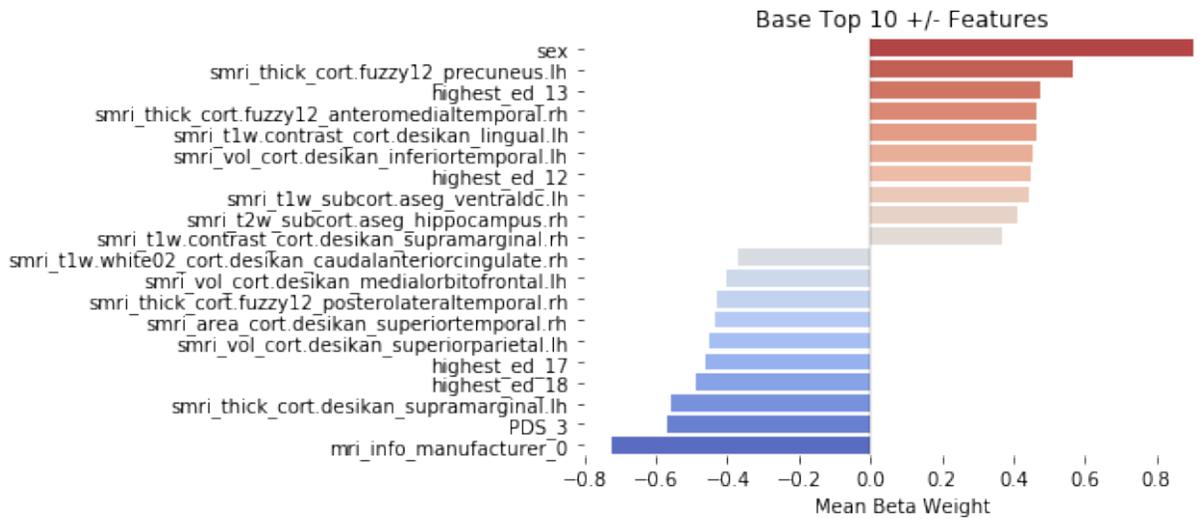
Figure 8. Feature Importances for predicting stimulant use in whole sample (with covariates).
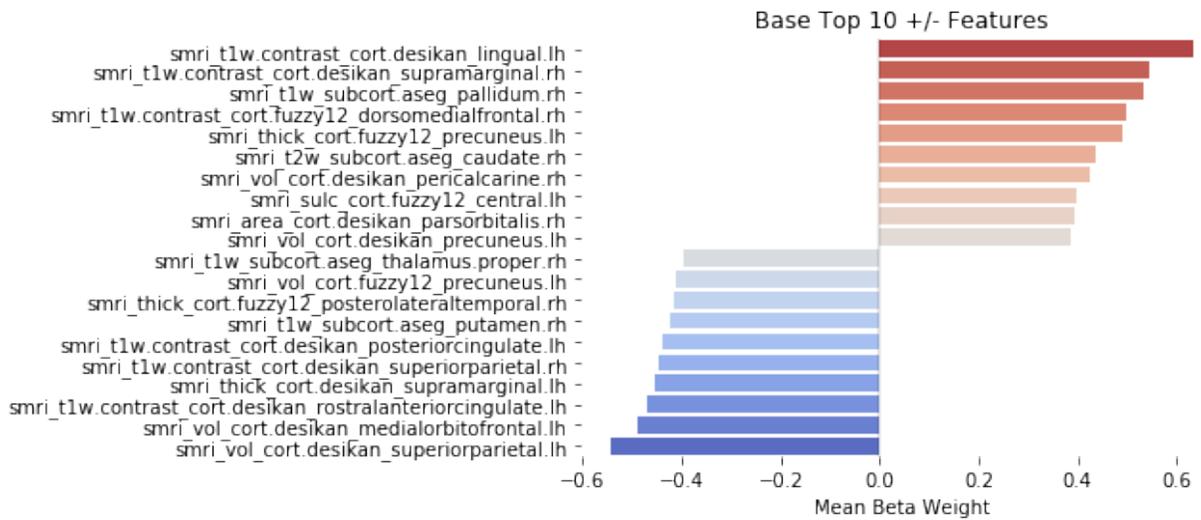

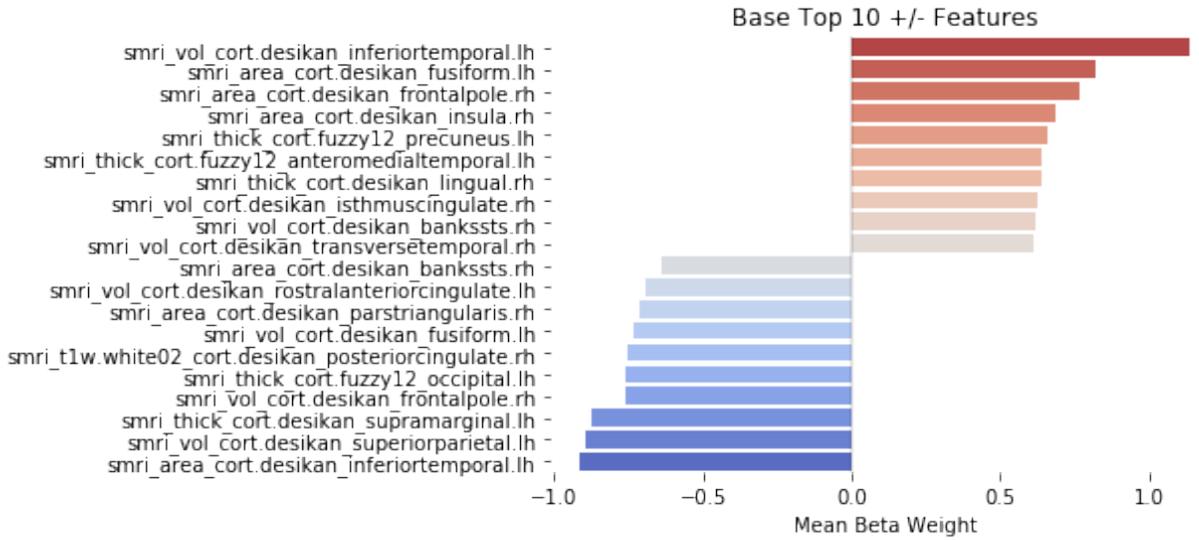**Figure 9. Feature Importances for predicting stimulant use in whole sample (without covariates).**

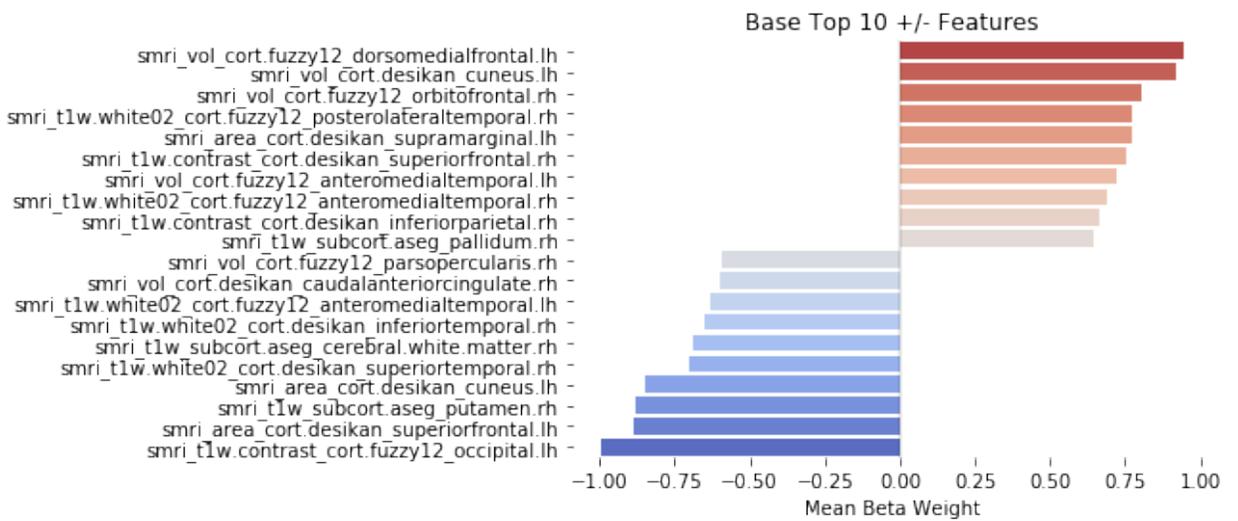**Figure 10. Feature Importances for predicting stimulant use in assigned-male-at-birth.**

Figure 11. Feature Importances for predicting stimulant use in ADHD-positive subjects.

CHAPTER 4: DISCUSSION

In this analysis, the Matthews correlation coefficient and area under the receiver operating characteristic curve were obtained for all models. Although similar in their purpose, both metrics are helpful in interpreting a model. The MCC shows the strength of correlation between the true values and the model's predictions, while the ROC AUC represents a model's success over varying discrimination thresholds with the area under this curve representing the overall probability of correct classification. The shape of the ROC curve itself can also provide insight into the model's success (Mandrekar, 2010). An ideal model would have a steep incline at the beginning, indicating a high true positive rate and a low false positive rate. Comparing the ROC curve to a perfectly random curve (an AUC of 0.5) is a useful way to visualize this.

Based on these metrics, the results indicate that both ADHD diagnosis and stimulant use were overall difficult to predict using the structural MRI data. For ADHD diagnosis, running the model on the whole sample (both with and without covariates) produced a significant ROC AUC score, indicating a better than random prediction, however the MCCs are still quite small, although slightly higher for the analysis without covariates. This is reflected in the ROC curves—without covariates, there is a portion of middle thresholds with a much higher ratio of true positives to false positives, but at high and low thresholds it is close to random. Meanwhile, with covariates the curve is more consistent across all thresholds but generally closer to random. Overall they are similar in quality regardless of the inclusion of covariates, even though multiple covariates were among the top important features (Fig. 6) when included. These covariates, then, do not seem to be better predicting factors of ADHD than the neuroimaging features. It is

somewhat surprising, given the large feature importance for sex assigned at birth in the covariate analysis, that neither the male or female samples produced significant ADHD classifiers. This may be due to the smaller sample size of the subsets, compared to the larger whole sample for which results were significant.

Interestingly, The model was generally better at classifying stimulant use. Metrics were higher than those of the ADHD classifier in both whole-sample analyses. The stimulant use classifier produced a significant ROC AUC for male subjects, which did not achieve a significant value from the ADHD classifier. The classifier ROC AUC was also significant for ADHD-positive, but not ADHD-negative, subjects. The highest ROC AUC of any model was found for the stimulant use classifier which included covariates. The feature importances (Fig. 8) show different levels of highest guardian education as strong predictors. This is not entirely surprising as this demographic is tied to variables such as household income which could affect access to healthcare or the likelihood of receiving a prescription. Although this model had the highest ROC AUC, the MCC of 0.035 is indicative of poor performance—unlike the ROC AUC, the MCC accounts for the quality of negative classifications as well as positive, so this model may have many false negatives. Without covariates, it is slightly worse at predicting stimulant use, but the ROC AUC is still significant. The metrics in the ADHD-positive subset are very similar to those of the whole sample without covariates.

Based on the results of the ADHD classifiers, it seems that ADHD-positive subjects do not differ widely from the greater sample in their neuroimaging features, so it follows that they would be equivalent in their predictive power of stimulant use. However, the classifier was not only insignificant in the ADHD-negative subset, it

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produced a negative correlation coefficient. The fact that the same classifier was so much better at predicting stimulant use in the ADHD-positive sample than in an ADHD-negative one could indicate that stimulants affect those with ADHD differently than those without the disorder—a concept that has been proposed before but is not well-investigated (Lakhan & Kirchgessner, 2012; Moll et al., 2003; Repantis et al., 2010).

Of further note, the stimulant use classifier produced the highest MCC for the assigned-male-at-birth subset. At 0.067, although a relatively small value, it is nearly double the next highest MCC of 0.036 (the stimulant classifier in ADHD-positive subjects). This, taken into account with the significant ROC AUC score of 0.61, makes it by far the most successful classifier in this study. In contrast, the classifier did very poorly on the female subset, despite it being about the same size as the male subset. This may be because the female stimulant-positive group is very small, but it could also be indicative of a sex-related difference in response to medication, but like many possible sex-related differences in pharmacotherapy, this idea is not well-studied.

In addition to comparing the metrics of the machine learning model in the various groups, we can also examine which features were most important in the classifications. Although none of the models were reliable enough to be considered a diagnostic tool, valuable insight can still be gained from these feature importance values.

Many brain areas have been implicated in ADHD in previous neuroimaging research. The most consistent ADHD-related structural changes are seen in the cerebellum, frontal cortex, caudate nucleus, corpus callosum, accumbens, amygdala, hippocampus, and putamen. Promisingly, the putamen, frontal cortex, hippocampus, and caudate nucleus all appear as important features, some for more than one analysis.

Other areas found with important features were the temporal lobe, parietal lobe, right lateral ventricle, cingulate cortex, pallidum, central sulcus, ventral diencephalon, thalamus, insula, and occipital lobe. These findings support various literature linking abnormalities in many of these areas to ADHD (Durston, 2003; Fernández-Jaén et al., 2014; Hall et al., 2015; Hoogman et al., 2019; Schweren, 2013; Seidman, 2005). The success of the machine learning model is supported by ADHD research implicating many of the same brain regions. Although the predictive power of the morphology of these regions was relatively small in this paradigm, the consistency of implicated regions across different methods of analysis is strong evidence of their involvement in ADHD and related medication.

It is also informative to compare which features were useful in different classifiers and samples to better understand how these brain areas relate to ADHD and stimulant medication. Generally speaking, the beta weight of a feature can be interpreted as how much change in the target variable—in this case, the classifying value of 0 or 1—is attributed to the predictor variable. A positive beta weight indicates to what extent a higher value of the predictor variable is associated with a higher target variable, while a negative beta weight indicates the extent a lower value of the predictor is associated with a higher target value. We will discuss and compare the most important features for each classifier, along with possible interpretations of these differences.

A number of areas were relevant in both ADHD and stimulant use classification: the putamen, dorsomedial and superior frontal lobe, posterolateral and transverse temporal lobe, inferior parietal lobe, and pericalcarine cortex and precuneus in the parietal lobe.

A number of important features were intensity measures. Although the images were normalized, the intensity can still be affected by BOLD signal, but to a much greater extent movement in the scanner (Fair et al., 2013). There are many intensity measures present as important features across analyses, which may be an indicator that it is not the brain area that is relevant, but rather the level of movement of subjects. For ADHD predictions, there are intensity measures from the superiorfrontal cortex, precentral gyrus, posterolateral-, anteromedial-, inferior- and superior- temporal cortex, inferior and superior parietal cortex, hippocampus, pallidum, putamen, and right lateral ventricle. Notably, there are many intensity measures in the ADHD classifiers, but only a few in the stimulant use classifiers. If this is indeed representative of a participant moving more than average even after data normalization and cleaning, it would not be surprising if this kind of metric is among the best predictors of an ADHD diagnosis, since children with the disorder are liable to have difficulty remaining still for an MRI scan, particularly those not taking stimulants.

Several contrast measures in the frontal, temporal, parietal, cingulate, and occipital cortices also showed importance in predicting both ADHD diagnosis and stimulant use. These beta weights for contrast values were positive except in the cingulate cortex, where they were negative. Thus for most areas a larger contrast was associated with a higher probability of ADHD and stimulant use. Meanwhile, in the cingulate cortex, lower contrast is associated with higher probability of stimulant use. There is no immediately obvious pattern to these findings, and despite the fact that cortical contrast is not commonly examined in the context of ADHD, it has been shown to be increased in other neuropsychological disorders such as bipolar disorder and schizophrenia

(Jørgensen, 2016). Grey/white cortical contrast may be an indirect measure of cortical myelination levels, for which abnormalities have sometimes been linked to ADHD (Lesch, 2019).

In addition to intensity and contrast measures, many volumetric, area, and thickness measures were important features. These can be primarily split into four regions: frontal, temporal, parietal, and occipital. There are some consistencies in these regions' relationships across models, and some distinct differences. Generally, areas in the frontal lobe had lower volumes and areas associated with higher probability of ADHD diagnosis and stimulant medication use in the whole sample. In males, only the right frontal pole was among the important frontal features from this area, with a smaller area being associated with higher probability of stimulant use. In the ADHD-positive subset, however, higher volumes of frontal areas were associated with stimulant use. A similar pattern is seen with temporal regions—smaller volumes are associated with ADHD in the whole sample and with stimulant use in males, but larger volumes are associated with stimulant use in the ADHD-positive group. The parietal and occipital regions are more mixed, with some subregions showing positive associations for both classifiers and some negative. Only a few specific subregions appeared in more than one classifier's feature importance list; The right pericalcarine cortex had higher volumes associated with ADHD and stimulant use in the whole sample, and the left superior parietal cortex had smaller volumes associated with stimulant use in the whole sample and males.

Taken together, this regional data does imply that structural differences are associated with ADHD, but as in prior literature, these differences are widespread and

varied enough that even with a large sample size and powerful computing tools it is difficult to truly define them. Two implications of the patterns are especially interesting: First, that machine learning models are significantly more successful at identifying exposure to stimulant medication than at identifying ADHD, and second, that the associations found to identify stimulant use were in opposing directions in the ADHD-positive sample compared to the whole sample and other groups. If ADHD itself does not have concrete neurological markers, it could be concerning to some that medication does seem to have a noticeable impact on brain structure. Stimulant medication has long been controversial despite its therapeutic value due to its potential for abuse and misuse, along with the side effects that can be associated with it. This may be an indicator that prescriptions should be handled with more care as there is a great deal we do not know about the effects of these drugs on the brain, especially in the long term. On the contrary, psychostimulants are an effective treatment for the disorder, and may have differing effects depending on the ADHD state. The fact that stimulant medication was associated with increased volume in several areas in the ADHD-positive group, but with decreased volume in other samples could be interpreted as support for this idea. Although the volume of these areas in medicated ADHD individuals may not be significantly different from those in the greater population, they displayed detectable differences from non-medicated ADHD individuals. This is somewhat supportive of the proposed "normalizing" effect of medication on ADHD, but the relationship must be more complex considering the association with stimulant use was inverted for other samples. Furthermore, if stimulant medication did indeed have a normalizing effect on the brain, we would expect to see ADHD more easily detectable, and stimulant exposure less so—

the opposite of what was found. Since a number of participants taking stimulant medication did not meet ADHD criteria, however, our results do not necessarily dispute this theory. Rather, it seems more likely that stimulants affect individuals differently, possibly dependent to some level on whether or not they have ADHD.

4.1. Limitations

Although the sheer number of subjects and the care that goes into maintaining the integrity of data in the ABCD Study mitigate many common concerns, the present analysis is not without its limitations. Behavioral data used was reported by the parents of subjects so naturally it is subject to any biases the adult participants may have. Utilizing the parent-reported mental health data (rather than the child-reported counterpart) for ADHD scoring was meant to minimize this risk, as parent reports of ADHD symptoms have been shown to be reliable estimates of diagnosis (Visser et al., 2013). The collection of medication information on this scale can also be difficult. In the medication inventory instrument, dosage and most recent use of the medication is collected, but enough of this data was missing or unreliable that we elected only to use the type of medication in the present analysis. Another limitation Is that only current (the past two weeks) medication use was collected, therefore it is not known for how long participants had been taking medication, or what participants' past exposure to stimulants was. Some participants placed in the stimulant-negative group may have taken stimulants before, while some in the stimulant-positive group may have only started medication recently.

Another important consideration is the covariates. When included, the covariates did not significantly improve ADHD classification, but they did improve stimulant use

classification. As mentioned previously, it is not surprising that sociocultural factors would be associated with stimulant medication exposure. A higher value of the sex-assigned-at-birth variable was always strongly associated with ADHD and stimulant use. This variable is binary, where 0 = female, 1 = male, so males were significantly more likely to be positive in both classifications. Again, this is not surprising, as our sample showed ADHD to be somewhat more common in males, and this prevalence combined with cultural factors means males are more likely to receive medication. The only covariate which appeared in the feature importance lists that is of concern is the MRI manufacturer. The preprocessing done on the data should minimize the effect of external factors like this on imaging data, but this is not an uncommon problem. Since only one level of this variable appeared, and overall the covariates did not have a large effect on the model's success, it is not of great concern, but in future research, statistical measures could be implemented to control for the MRI manufacturer.

As mentioned in the discussion, subject movement during the scan may be one of the best categories of predictive features in classifying ADHD. This may be due to the nature of the disorder, or possibly that the structural data collected on these subjects is generally of low quality due to this movement. Either way, it is indicative of the limits of using MRI to study a disorder involving hyperactivity. Future analyses may want to include a quantitative measure of movement during the scan to directly account for this possibility.

4.2. Conclusions/Future Directions

Machine learning is a relatively novel tool in the context of neuropsychiatric disorders. Thus, there is no precedent for what to expect from an analysis like this one. Based on the body of research involving MRI data, we were able to make some predictions about individual features that may be important in the classification. All prior research, however, has been with the purpose of identifying significant ADHD-related differences in brain structure, rather than the present goal of identifying ADHD and medication use based on these differences. A test of whether or not any structural differences are strong and/or consistent enough to create a successful classification system has not previously been done. The models were successful at a low level at predicting ADHD diagnosis in a large sample, and slightly more successful at predicting stimulant medication use in the same large sample, as well as smaller subsets of assigned-male-at-birth subjects and ADHD-positive subjects. The important features from significantly successful models were in line with existing research regarding brain regions implicated in ADHD, which in the world of observational research is tightly intertwined with stimulant medication. Correlations between several subregional volumes and stimulant use had opposing directions in the ADHD-positive sample compared with other groups, implying an ADHD-dependent effect of medication.

The finding that stimulant use is more detectable from sMRI data than ADHD urges the further investigation of these commonly prescribed drugs and their relationship to the brain, especially in adolescents. Most research does not contain non-ADHD subjects who also take stimulant medication, as inducing this experimentally would be unethical—but in the ABCD sample and likely the greater population there are many

people who are already in this category, which is concerning in and of itself. Since the ABCD study is ongoing, however, future research will be able to examine the longitudinal ADHD and medication status on these same participants, which will provide much-needed knowledge regarding how these factors affect young people over time. It may also be beneficial to attempt a similar type of machine learning paradigm on other types of data to attempt to find better predictors. Functional MRI variables could be more strongly related to ADHD, but it would also be interesting to examine the predictive value of behavioral or cultural factors.

REFERENCES

American Psychiatric Association. (2013). Neurodevelopmental Disorders. In *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi-org/10.1176/appi.books.9780890425596.dsm01

Andersen, S. L. (2005). Stimulants and the developing brain. *Trends in Pharmacological Sciences*, *26*(5), 237–243. https://doi.org/10.1016/j.tips.2005.03.009

Arnold, L. E., Hodgkins, P., Kahle, J., Madhoo, M., & Kewley, G. (2020). Long-Term Outcomes of ADHD: Academic Achievement and Performance. *Journal of Attention Disorders*, *24*(1), 73–85. https://doi.org/10.1177/1087054714566076

Barbaresi, W. J., Katusic, S. K., Colligan, R. C., Weaver, A. L., & Jacobsen, S. J. (2007). Long-Term School Outcomes for Children with Attention-Deficit/Hyperactivity Disorder: A Population-Based Perspective. *Journal of Developmental & Behavioral Pediatrics*, *28*(4), 265–273. https://doi.org/10.1097/DBP.0b013e31811ff87d

Bezgin, G., Lewis, J. D., & Evans, A. C. (2018). Developmental changes of cortical white–gray contrast as predictors of autism diagnosis and severity. *Translational Psychiatry*, *8*. https://doi.org/10.1038/s41398-018-0296-2

CDC. (2018, September 28). ADHD Throughout the Years | CDC. Retrieved February 12, 2020, from https://www.cdc.gov/ncbddd/adhd/timeline.html

Chicco, D., & Jurman, G. (2020). The advantages of the Matthews correlation coefficient (MCC) over F1 score and accuracy in binary classification evaluation. *BMC Genomics*, *21*(1), 6. https://doi.org/10.1186/s12864-019-6413-7

Durston, S. (2003). A review of the biological bases of ADHD: What have we learned from imaging studies? *Mental Retardation and Developmental Disabilities Research Reviews*, *9*(3), 184–195. https://doi.org/10.1002/mrdd.10079

Fair, D., Nigg, J. T., Iyer, S., Bathula, D., Mills, K. L., Dosenbach, N. U., Schlaggar, B. L., Mennes, M., Gutman, D., Bangaru, S., Buitelaar, J. K., Dickstein, D. P., Di Martino, A., Kennedy, D. N., Kelly, C., Luna, B., Schweitzer, J. B., Velanova, K., Wang, Y.-F., … Milham, M. P. (2013). Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. *Frontiers in Systems Neuroscience*, *6*. https://doi.org/10.3389/fnsys.2012.00080

Faraone, S. V. (2018). The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and

other psychiatric comorbidities. *Neuroscience & Biobehavioral Reviews*, *87*, 255–270. https://doi.org/10.1016/j.neubiorev.2018.02.001

Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine*, *36*(2), 159–165. https://doi.org/10.1017/S003329170500471X

Fernández-Jaén, A., López-Martín, S., Albert, J., Fernández-Mayoralas, D. M., Fernández-Perrone, A. L., Tapia, D. Q., & Calleja-Pérez, B. (2014). Cortical thinning of temporal pole and orbitofrontal cortex in medication-naïve children and adolescents with ADHD. *Psychiatry Research: Neuroimaging*, *224*(1), 8–13. https://doi.org/10.1016/j.pscychresns.2014.07.004

Frodl, T., & Skokauskas, N. (2012). Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. *Acta Psychiatrica Scandinavica*, *125*(2), 114–126. https://doi.org/10.1111/j.1600-0447.2011.01786.x

Garavan, H., Bartsch, H., Conway, K., Decastro, A., Goldstein, R. Z., Heeringa, S., Jernigan, T., Potter, A., Thompson, W., & Zahs, D. (2018). Recruiting the ABCD sample: Design considerations and procedures. *Developmental Cognitive Neuroscience*, *32*, 16–22. https://doi.org/10.1016/j.dcn.2018.04.004

Hagler, D. J., Hatton, S., Cornejo, M. D., Makowski, C., Fair, D. A., Dick, A. S., Sutherland, M. T., Casey, B. J., Barch, D. M., Harms, M. P., Watts, R., Bjork, J. M., Garavan, H. P., Hilmer, L., Pung, C. J., Sicat, C. S., Kuperman, J., Bartsch, H., Xue, F., … Dale, A. M. (2019). Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. *NeuroImage*, *202*, 116091. https://doi.org/10.1016/j.neuroimage.2019.116091

Hall, M. G., Alhassoon, O. M., Stern, M. J., Wollman, S. C., Kimmel, C. L., Perez-Figueroa, A., & Radua, J. (2015). Gray matter abnormalities in cocaine versus methamphetamine-dependent patients: A neuroimaging meta-analysis. *The American Journal of Drug and Alcohol Abuse*, *41*(4), 290–299. https://doi.org/10.3109/00952990.2015.1044607

Heal, D. J., Smith, S. L., Gosden, J., & Nutt, D. J. (2013). Amphetamine, past and present – a pharmacological and clinical perspective. *Journal of Psychopharmacology (Oxford, England)*, *27*(6), 479–496. https://doi.org/10.1177/0269881113482532

Hechtman, L., Swanson, J. M., Sibley, M. H., Stehli, A., Owens, E. B., Mitchell, J. T., Arnold, L. E., Molina, B. S. G., Hinshaw, S. P., Jensen, P. S., Abikoff, H. B., Perez Algorta, G., Howard, A. L., Hoza, B., Etcovitch, J., Houssais, S., Lakes, K. D., Nichols, J. Q., & MTA Cooperative Group. (2016). Functional Adult Outcomes 16 Years After Childhood Diagnosis of Attention-Deficit/Hyperactivity

Disorder: MTA Results. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(11), 945-952.e2. https://doi.org/10.1016/j.jaac.2016.07.774

Harpin, V., Mazzone, L., Raynaud, J. P., Kahle, J., & Hodgkins, P. (2016). Long-Term Outcomes of ADHD: A Systematic Review of Self-Esteem and Social Function. *Journal of Attention Disorders*, *20*(4), 295–305. https://doi.org/10.1177/1087054713486516

Holland, J., & Sayal, K. (2019). Relative age and ADHD symptoms, diagnosis and medication: a systematic review. *European Child & Adolescent Psychiatry*, *28*(11), 1417–1429. https://doi.org/10.1007/s00787-018-1229-6

Hoogman, M., Bralten, J., Hibar, D. P., Mennes, M., Zwiers, M. P., Schweren, L., … Franke, B. (2017). Subcortical brain volume differences of participants with ADHD across the lifespan: an ENIGMA collaboration. *The Lancet. Psychiatry*, *4*(4), 310–319. https://doi.org/10.1016/S2215-0366(17)30049-4

Jørgensen, K. N., Nerland, S., Norbom, L. B., Doan, N. T., Nesvåg, R., Mørch-Johnsen, L., Haukvik, U. K., Melle, I., Andreassen, O. A., Westlye, L. T., & Agartz, I. (2016). Increased MRI-based cortical grey/white-matter contrast in sensory and motor regions in schizophrenia and bipolar disorder. *Psychological Medicine*, *46*(9), 1971–1985. https://doi.org/10.1017/S0033291716000593

Kaufman, J., Birmaher, B., Brent, D. A., Ryan, N. D., & Rao, U. (2000). K-SADS-PL. *Journal of the American Academy of Child & Adolescent Psychiatry*, *39*(10), 1208. https://doi.org/10.1097/00004583-200010000-00002

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., … Zaslavsky, A. M. (2006). The Prevalence and Correlates of Adult ADHD in the United States: Results From the National Comorbidity Survey Replication. American Journal of Psychiatry, 163(4), 716–723. https://doi.org/10.1176/ajp.2006.163.4.716

Klein, R. G., Mannuzza, S., Ramos Olazagasti, M. A., Roizen Belsky, E., Hutchison, J. A., Lashua-Shriftman, E., & Castellanos, F. X. (2012). Clinical and Functional Outcome of Childhood ADHD 33 Years Later. *Archives of General Psychiatry*, *69*(12), 1295–1303. https://doi.org/10.1001/archgenpsychiatry.2012.271

Lakhan, S. E., & Kirchgessner, A. (2012). Prescription stimulants in individuals with and without attention deficit hyperactivity disorder: Misuse, cognitive impact, and adverse effects. *Brain and Behavior*, *2*(5), 661–677. https://doi.org/10.1002/brb3.78

Lesch, K.-P. (2019). Editorial: Can dysregulated myelination be linked to ADHD pathogenesis and persistence? *Journal of Child Psychology and Psychiatry*, *60*(3), 229–231. https://doi.org/10.1111/jcpp.13031

Mandrekar, J. N. (2010). Receiver Operating Characteristic Curve in Diagnostic Test Assessment. *Journal of Thoracic Oncology*, *5*(9), 1315–1316. https://doi.org/10.1097/JTO.0b013e3181ec173d

Markowitz, J. S., Straughn, A. B., & Patrick, K. S. (2003). Advances in the Pharmacotherapy of Attention-Deficit-Hyperactivity Disorder: Focus on Methylphenidate Formulations. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *23*(10), 1281–1299. https://doi.org/10.1592/phco.23.12.1281.32697

Mason, S. J., & Graham, N. E. (2002). Areas beneath the relative operating characteristics (ROC) and relative operating levels (ROL) curves: Statistical significance and interpretation. *Quarterly Journal of the Royal Meteorological Society*, *128*(584), 2145–2166. https://doi.org/10.1256/003590002320603584

McGee, R., Prior, M., Williams, S., Smart, D., & Sanson, A. (2002). The long-term significance of teacher-rated hyperactivity and reading ability in childhood: Findings from two longitudinal studies. *Journal of Child Psychology and Psychiatry*, *43*(8), 1004–1017. https://doi.org/10.1111/1469-7610.00228

Moll, G. H., Heinrich, H., & Rothenberger, A. (2003). Methylphenidate and intracortical excitability: Opposite effects in healthy subjects and attention-deficit hyperactivity disorder. *Acta Psychiatrica Scandinavica*, *107*(1), 69–72. https://doi.org/10.1034/j.1600-0447.2003.02114.x

Mrug, S., Hoza, B., & Gerdes, A. C. (2001). Children with Attention-Defecit/Hyperactivity Disorder: Peer Relationships and Peer-Oriented Interventions. *New Directions for Child and Adolescent Development*, *2001*(91), 51–78. https://doi.org/10.1002/cd.5

National Institute of Mental Health (2016). *Mental Health Medications*. Retrieved March 20, 2015, from https://www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml#part_149861

Nichols, J. A., Chan, H. W. H., & Baker, M. A. B. (2019). Machine learning: applications of artificial intelligence to imaging and diagnosis. *Biophysical Reviews*, *11*(1), 111–118. https://doi.org/10.1007/s12551-018-0449-9

Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., Blondel, M., Prettenhofer, P., Weiss, R., Dubourg, V., Vanderplas, J., Passos, A., Cournapeau, D., Brucher, M., Perrot, M., & Duchesnay, É. (2011). Scikit-learn:

Machine Learning in Python. *Journal of Machine Learning Research*, *12*(85), 2825–2830.

Pliszka, S. R. (2019). Is There Long-Term Benefit From Stimulant Treatment for ADHD? *American Journal of Psychiatry*, *176*(9), 685–686. https://doi.org/10.1176/appi.ajp.2019.19070681

Repantis, D., Schlattmann, P., Laisney, O., & Heuser, I. (2010). Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. *Pharmacological Research*, *62*(3), 187–206. https://doi.org/10.1016/j.phrs.2010.04.002

Sansone, R. A., & Sansone, L. A. (2007). Prescription Psychostimulant Abuse. *Psychiatry (Edgmont)*, *4*(9), 18–19.

Schweren, L. J. S., de Zeeuw, P., & Durston, S. (2013). MR imaging of the effects of methylphenidate on brain structure and function in Attention-Deficit/Hyperactivity Disorder. *European Neuropsychopharmacology*, *23*(10), 1151–1164. https://doi.org/10.1016/j.euroneuro.2012.10.014

Seidman, L. J., Valera, E. M., & Makris, N. (2005). Structural Brain Imaging of Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, *57*(11), 1263–1272. https://doi.org/10.1016/j.biopsych.2004.11.019

Solanto, M. V. (2002). Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. *Behavioural Brain Research*, *130*(1), 65–71. https://doi.org/10.1016/S0166-4328(01)00431-4

Thomas, R., Sanders, S., Doust, J., Beller, E., & Glasziou, P. (2015). Prevalence of Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. *Pediatrics*, *135*(4), e994–e1001. https://doi.org/10.1542/peds.2014-3482

Visser, S. N., Danielson, M. L., Bitsko, R. H., Perou, R., & Blumberg, S. J. (2013). Convergent Validity of Parent-Reported Attention-Deficit/Hyperactivity Disorder Diagnosis: A Cross-Study Comparison. *JAMA Pediatrics*, *167*(7), 674–675. https://doi.org/10.1001/jamapediatrics.2013.2364

Wolraich, M. L., Hagan, J. F., Allan, C., Chan, E., Davison, D., Earls, M., … SUBCOMMITTEE ON CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVE DISORDER. (2019). Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Pediatrics*, *144*(4). https://doi.org/10.1542/peds.2019-2528

APPENDIX

ADHD Diagnostic Criteria from DSM-V (APA, 2013)

    A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

        1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

            ▪ **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

            a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).

            b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).

            c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).

            d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).

            e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).

            f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).

            g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).

            h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).

            i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

        2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

- **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
    a. Often fidgets with or taps hands or feet or squirms in seat.
    b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
    c. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
    d. Often unable to play or engage in leisure activities quietly.
    e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
    f. Often talks excessively.
    g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
    h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
    i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).
B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:
- **314.01 (F90.2) Combined presentation:** If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.
- **314.00 (F90.0) Predominantly inattentive presentation:** If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.
- **314.01 (F90.1) Predominantly hyperactive/impulsive presentation:** If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:

- **In partial remission:** When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

- **Mild:** Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.
- **Moderate:** Symptoms or functional impairment between "mild" and "severe" are present.
- **Severe:** Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.