THE UNIVERSITY OF CHICAGO

Predicting attention deficit hyperactivity disorder symptoms in development with functional brain connectivity

By

Julia Pruin

June 2021

A paper submitted in partial fulfillment of the requirements for the
Master of Arts degree in the
Master of Arts Program in the Social Sciences

Faculty Advisor: Monica Rosenberg, PhD
Preceptor: Samantha Fan, PhD

Acknowledgements

Data used in the preparation of this thesis were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children age 9-10 and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators.

~

This work would not have been possible without the help of our quality control team for the ABCD fMRI data: Omid Kardan, Andrew J. Stier, Carlos Cardenas-Iniguez, Yuting Deng, Taylor Chamberlain, Wesley J. Meredith, Kathryn E. Schertz, Xihan Zhang, Jillian E. Bowman, Tanvi Lakhtakia, Lucy Tindel, Marc G. Berman, & Monica D. Rosenberg.

Abstract

Sustained attention is an important cognitive process that affects various other aspects of cognition. A common focus for the study of sustained attention is attention-deficit hyperactivity disorder among children. The Adolescent Brain Cognitive Development (ABCD) Study provides ADHD symptomology scores from the Child Behavior Checklist, as well as rest and *n*-back task fMRI data from children between the ages of 9 and 13. In the current study, a preexisting connectome-based predictive modeling (CPM) protocol is used to predict sustained attention abilities and changes in those abilities over a three-year time span. Additionally, a new predictive model is created to judge whether a protocol based on child brain data is more effective at estimating sustained attention scores that one trained on adult data. The attempt at applying a "publication-preregistered" model and developing a new one opens up a host of outstanding questions. Future longitudinal efforts of the ABCD study would afford more opportunities to study sustained attention with functional connectivity.

Introduction

Sustained attention is a crucial aspect of cognition. Defined as the ability to attend to a stimulus and maintain focus on it for a period of time (Sarter, Givens, and Bruno, 2001), sustained attention has been found to influence other cognitive processes such as perception (Ling and Carasco, 2006), working memory, and learning (Cowan, 1998). However, despite this importance, sustained attentional abilities can vary between individuals. For example, whereas some individuals are able to focus on a task at hand for long periods of time, others lose focus more easily due to mind wandering or external distraction. Rosenberg and colleagues (2016) found that individual sustained attention performance could be distinguished and predicted over time (Rosenberg et al, 2020), which was further corroborated by Wu et al., (2020). Moreover, sustained attention can be impaired in psychological disorders such as schizophrenia (Liu et al., 2002), bipolar disorder (Maalouf, et al., 2010), and autism (Chien, et al., 2015).

The hallmark disorder for studying sustained attention is attention deficit hyperactivity disorder (ADHD; Barkley, 1997). ADHD is a notoriously heterogenous disorder (Luo et al., 2019; Samea et al., 2019), existing on a spectrum of severity and symptoms, meaning that diagnosis based on generalized criteria from the DSM-V may not capture the full breadth of impairments within a single individual. Besides deficits to sustained attention, ADHD is also characterized by impulsivity and hyperactivity (APA, 2013), all three being signs of impaired executive function (Barkley, 1997). It is diagnosed in approximately five percent of children world-wide (Polanczyk et al., 2007) and is typically diagnosed through a battery of clinical interviews and behavioral measures (Sibley et al., 2012). In addition to the three main impairments that characterize ADHD, the disorder can have detrimental effects on the development of a child, including disordered temperament (Anckarsäter et al., 2006), deficits to working memory, and trouble making social connections (Kofler et al., 2011). Past neuroimaging studies of ADHD have identified several neuroanatomical changes that distinguish patients' brains from those of the neurotypical population. Individuals with ADHD show a reduced volume (Krain and Castellanos, 2006) and abnormal activation in the prefrontal cortex (Durston, 2003). There is often hypoactivation of the executive control network and ventral attention network (Cortese et al., 2012), and patients often follow a lower developmental track relative to their neurotypical peers (Castellanos et al., 2002). However, these findings were primarily found in studies that compared group-level differences, rather than in studies that considered symptom severity of an individual's unique symptom profile.

In recent years, functional connectivity measured with functional magnetic resonance imaging (fMRI) has been used to study individual differences in sustained attention ability, including among patients with ADHD. Functional connectivity refers to a correlation in the blood oxygenation level-dependent (BOLD) signal time courses of two distinct areas of the brain observed during scans (Rosenberg and Chun, 2020). These scans reveal networks of interacting brain regions that may not otherwise be fully understood with exploration of just one region of the brain in isolation. Functional brain connectivity networks are unique to an individual, like a fingerprint, lending themselves to the exploration of individual differences (Finn et al., 2015), and are stable over time (Horien et al., 2019). Different networks exist within a brain for different aspects of cognitive functioning, and even for different facets within some cognitive activities such as attention (Rosenberg, Finn, et al., 2017), including sustained attention networks (Rosenberg et al., 2016). Functional connectivity has also been used to predict individual differences in the ability to suppress distraction (Poole et al., 2016), adding credence to the idea that individual differences in functional connectivity are stable and unique. In the case of Wu and colleagues (2020), functional connectivity models can also predict performance on other measures of attention, such as the visual attentional blink task (Wu, et al., 2020).

Functional connectivity has proven to be a reliable and valid measure of sustained attention function in adults and a relatively small sample of children and adolescents, both with and without ADHD (for more details, see Rosenberg at al., 2016). Other work has found increased functional brain connectivity within the motor cortex (O'Halloran et al., 2018) and overall dysmaturation of functional connectivity networks in the brains of patients with ADHD (Kessler et al., 2016). Despite this initial evidence that functional connectivity patterns can capture ADHD symptoms, it remains an open question whether the same network that predicts sustained attention in adulthood will generalize to capture sustained attention function in a large-scale heterogeneous developmental sample with and without a variety of clinical diagnoses, including ADHD. Recent evidence suggests that functional networks are stable over the course of development from childhood to adulthood, indicated by the fact that the same functional connectivity model has been able to accurately predict sustained attention in both adults (the population it was trained on) and children (Rosenberg, 2016; Rosenberg, Casey, & Holmes, 2018). However, given the heterogenous nature of ADHD, it is uncertain whether the same model might accurately predict symptoms for the disorder, even if the model is valid in both neurotypical adult and adolescent populations. Furthermore, few studies to date have investigated whether functional connectivity is predictive of future behavior, in addition to current functioning. Some past studies have been able to use functional connectivity to predict improvements in symptoms of children with autism (Plitt et al. 2015) and dyslexia (Hoeft, 2011), but similar results have not been found in samples of patients with ADHD.

To address these matters, the current study will test three main questions. First, we will test whether an existing neuromarker of sustained attention generalizes to predict ADHD symptoms from functional connectivity in the Adolescent Brain Cognitive Development Study (ABCD) sample. Second, we will ask whether that same model can accurately predict *changes* in ADHD symptoms observed across a three-year timespan (age 9-10 to age 11-12). Third, we will build a new connectome-based model in the ABCD dataset to define a development-specific marker of ADHD symptoms, and, if it successfully predicts ADHD symptoms, ask whether it overlaps with functional connectivity networks previously implicated in the disorder.

General Methods

Participants

The data used for the current investigation was from the ABCD Study, a large-scale ongoing initiative to research development and health from childhood to late adolescence. Information is collected from twenty-one sites around the United States and coordinated by the National Institutes of Health (NIH). Data were accessed via the NIH Mental Health Data Archive (DOI 10.15154/1519007). The sample is heterogenous and transdiagnostic, consisting of 11,878 participants starting at the ages of 9-10 and continuing every year for ten years after that (data collection is currently in its fourth year). Data are collected on each participant’s physical and mental health, as well as their culture, environment, substance use, and neurocognition. Every other year, structural and functional magnetic resonance imaging (MRI) data are collected. The present study utilizes fMRI from the baseline data release and behavioral data from all three of the releases available so far.

For the purposes of this study, ADHD symptoms were operationalized as the ADHD subscale from the DSM-V Oriented scales of the Child Behavior Checklist (CBCL; Nakamura,

2009) which was completed by a parent. Although we were primarily interested in ADHD subscale *t*-scores as a continuous measure of ADHD symptom frequency and severity, we note that a *t*-score of 70 or higher on a scale of 50 to 90 was considered diagnosable. No child in the final sample had a CBCL ADHD subscale score above an 80. Only participants with all three years of CBCL data, as well as resting-state and *n*-back task fMRI data (see below for details), were included in subsequent analysis. In addition to using the original *t*-scores, the slope of the scores over the three years was also calculated for each subject as a measure of participants' changes in attention problems from age 9-10 to 11-12 years.

Functional MRI tasks

Each child was meant to have two in-scanner *n*-back task runs and four resting-state runs from which the functional connectivity networks were then constructed. The *n*-back task assesses a child's working memory and emotional regulation processes. Participants are shown pictures of happy, fearful, and neutral faces, as well as place photographs as controls, and asked to recall whether the photo they are being presented was seen either immediately prior (0-back) or two photos ago (2-back), depending on the block. In each of the two approximately 5-minute task runs, 0-back and 2-back blocks were presented four times and children were scored based on the accuracy of their judgements (Cohen et al., 2016). The task is thought to tax sustained attention (in both the 0-back and 2-back task blocks) and working memory (during 2-back task blocks). Similarly, the four resting-state runs, lasting 5 minutes each, may have been another test of control and patience for young children (who were asked to remain awake and still during the scans), so both types of scans were included, to determine if one would be a better predictor of sustained attention than the other.

Functional MRI preprocessing

All of the BOLD fMRI data had previously been normalized to the MNI152 non-linear 6th generation template, undergone motion correction and bandpass filtering, and registered to the T1 weighted scan within subjects, before undergoing visual quality assurance. The data were used to generate functional connectivity matrices using the whole-brain parcellation scheme defined by Shen and colleagues (2013), consisting of 268 nodes (Shen et al., 2013), and Fisher *z*-transformed to stabilize variance.

After preprocessing, some children only had one available functional connectivity matrix and others had none at all. Participants with no usable functional connectivity data, as well as runs with missing data in any Shen atlas node and/or mean frame-to-frame displacement greater than 0.2 millimeters or maximum head displacement greater than 2 millimeters were excluded from analysis. The total subsample of viable participants with rest runs was 1724, 51% of which were female. The total number of participants with included *n*-back task runs was 874, of which 52% were female. In both groups, ages at the time of the first release and fMRI data collection ranged from 9 to 10.9 and ages at the time of release three ranged from 10.75 to 13.5. 716 participants were in both the rest and *n*-back task subsamples.

Study 1

Methods

In Study 1, we tested whether a pre-existing model of sustained attention generalized to predict ADHD symptoms in the ABCD sample. Connectome-based predictive modeling (CPM) is a data-driven protocol used to create models that are able to predict behavior based on functional brain imaging data (Shen et al., 2017). The model used for the purposes of the current study, a sustained attention CPM (saCPM), was developed by Rosenberg and colleagues (2016) and is applied with a freely available protocol (https://github.com/monicadrosenberg/Rosenberg_PNAS2020). The saCPM is comprised of a high-attention network and low-attention network mask, which are applied to functional connectivity matrices from new participants to determine how strongly they express the high-attention network and the low-attention network. The difference calculated between the network strengths is then fit to a predefined linear model that was originally trained on adult data (Rosenberg et al., 2016). The model is applied to novel functional connectivity matrices to predict sustained attention function. The model outputs are predicted behavioral values, which are then correlated with the observed ADHD *t*-scores from the ABCD dataset in order to determine how accurate the predictions were. In Study 1A, saCPM predictions were correlated with baseline ADHD *t*-scores (only from the first year of data collection). In Study 1B, saCPM predictions were correlated with the ADHD *t*-score slopes. The values predicted by the saCPM were *z*-scored to standardize them. In both cases, rest and *n*-back task functional connectivity matrices were analyzed separately.

Results

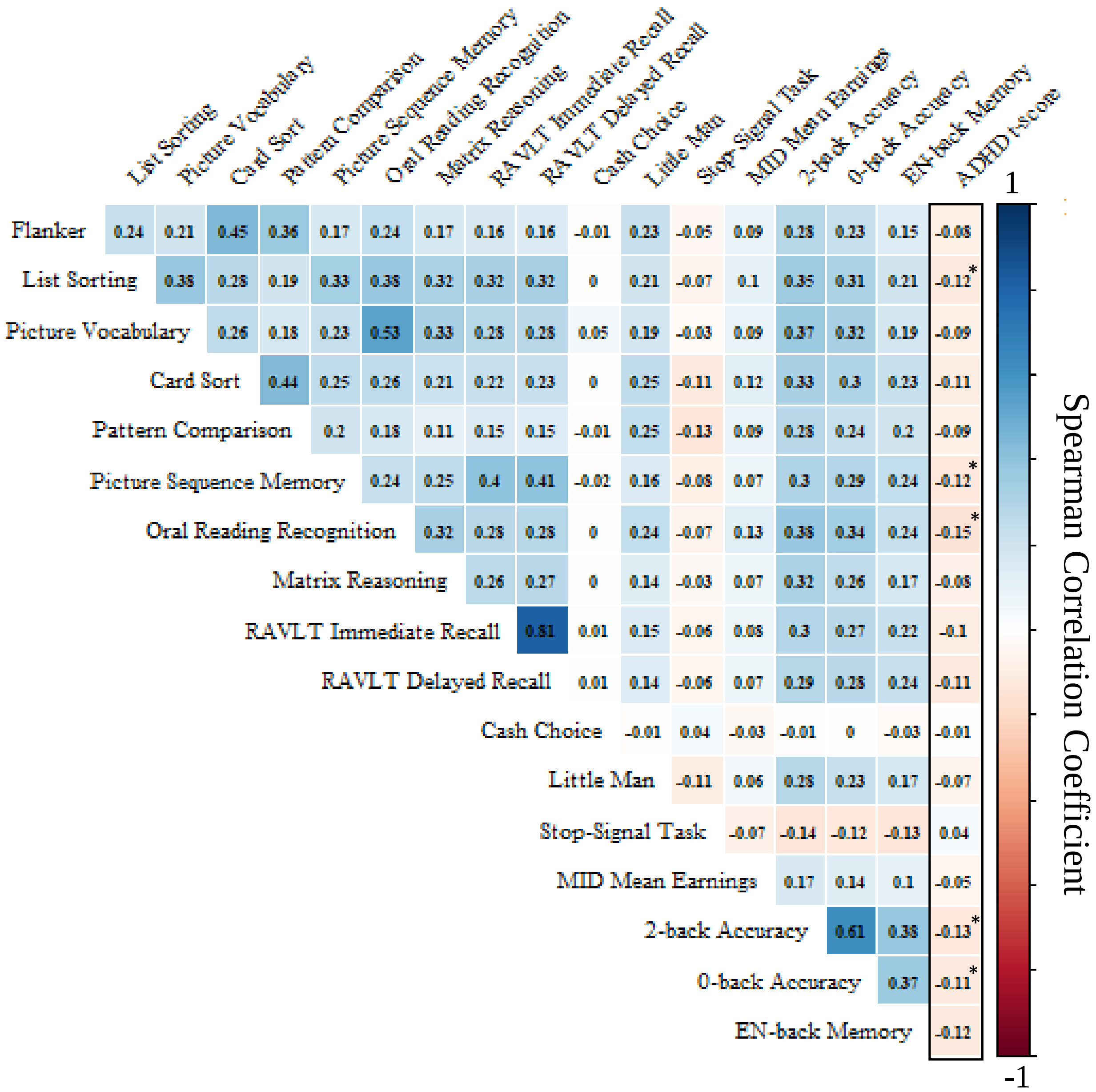
Relating ADHD symptoms to sociodemographic measures

Prior to analyses, we evaluated the relationship between baseline ADHD *t*-scores and measures that have been shown to affect prevalence and diagnosis rates of ADHD. These included race/ethnicity (Fairman, Peckham, & Sclar, 2020), sex (Arnold, 1996), socio-economic status (SES; Rieppi et al., 2002), and age (Schwandt & Wuppermann, 2016). SES was significantly related to ADHD *t*-scores (task group: $F = 4.94$, df = 9, $p < 0.01$; rest group: $F = 3.22$, df = 9, $p < 0.01$) for both the task and rest groups, such that lower SES was associated with higher ADHD scores (task: $r = -0.14$, $p < 0.01$; rest: $r = -0.1$, $p < 0.01$), which is consistent with previous literature

(Rieppi et al., 2002). On the other hand, age (task: $r = 0.018$, $p = 0.61$; rest: $r = 0.009$, $p = 0.7$), sex (task: $t = 1.46$, df = 789.54, $p = 0.144$; rest: $F = 2.858$, df = 1617.56, $p = 0.09$), and race/ethnicity (task: $F = 0.863$, df = 4, $p = 0.486$; rest: $F = 0.808$, df = 4, $p = 0.52$) were not significantly related to baseline ADHD symptomology. These analyses provide evidence that, should brain-based models predict ADHD symptoms, brain-behavior relationships are unlikely to be driven by age, sex, or race/ethnicity. Future works that use the ABCD sample should take into account additional confounding variables such as SES.

Relating ADHD symptoms to measures of cognition

We next tested whether ADHD *t*-scores were related to other cognitive and attentional measures available in the ABCD Study to assess their validity (see Figure 1). In addition to both versions of the *n*-back task (0-back: $r = -0.11$, $p < 0.05$; 2-back: $r = -0.13$, $p < 0.05$), ADHD t-scores were also significantly correlated with the NIH Toolbox List Sorting Task ($r = -0.12$, $p < 0.05$), NIH Toolbox Picture Sequence Memory Task ($r = -0.12$, $p < 0.05$), and NIH Toolbox Oral Reading Recognition Task ($r = -0.15$, $p < 0.05$), demonstrating that individuals who perform better on these tasks show lower ADHD symptom scores. These tasks tax working memory, episodic memory, and reading abilities, respectively (Rosenberg, Martinez, et al., 2020).



	List Sorting	Picture Vocabulary	Card Sort	Pattern Comparison	Picture Sequence Memory	Oral Reading Recognition	Matrix Reasoning	RAVLT Immediate Recall	RAVLT Delayed Recall	Cash Choice	Little Man	Stop-Signal Task	MID Mean Earnings	2-back Accuracy	0-back Accuracy	EN-back Memory	ADHD t-score
Flanker	0.24	0.21	0.45	0.36	0.17	0.24	0.17	0.16	0.16	-0.01	0.23	-0.05	0.09	0.28	0.23	0.15	-0.08
List Sorting		0.38	0.28	0.19	0.33	0.38	0.32	0.32	0.32	0	0.21	-0.07	0.1	0.35	0.31	0.21	-0.12*
Picture Vocabulary			0.26	0.18	0.23	0.53	0.33	0.28	0.28	0.05	0.19	-0.03	0.09	0.37	0.32	0.19	-0.09
Card Sort				0.44	0.25	0.26	0.21	0.22	0.23	0	0.25	-0.11	0.12	0.33	0.3	0.23	-0.11
Pattern Comparison					0.2	0.18	0.11	0.15	0.15	-0.01	0.25	-0.13	0.09	0.28	0.24	0.2	-0.09
Picture Sequence Memory						0.24	0.25	0.4	0.41	-0.02	0.16	-0.08	0.07	0.3	0.29	0.24	-0.12*
Oral Reading Recognition							0.32	0.28	0.28	0	0.24	-0.07	0.13	0.38	0.34	0.24	-0.15*
Matrix Reasoning								0.26	0.27	0	0.14	-0.03	0.07	0.32	0.26	0.17	-0.08
RAVLT Immediate Recall									0.81	0.01	0.15	-0.06	0.08	0.3	0.27	0.22	-0.1
RAVLT Delayed Recall										0.01	0.14	-0.06	0.07	0.29	0.28	0.24	-0.11
Cash Choice											-0.01	0.04	-0.03	-0.01	0	-0.03	-0.01
Little Man												-0.11	0.06	0.28	0.23	0.17	-0.07
Stop-Signal Task													-0.07	-0.14	-0.12	-0.13	0.04
MID Mean Earnings														0.17	0.14	0.1	-0.05
2-back Accuracy															0.61	0.38	-0.13*
0-back Accuracy																0.37	-0.11*
EN-back Memory																	-0.12

Figure 1: Spearman correlations between all cognitive tasks and the CBCL ADHD subscale t-scores (far right column) for the entire sample of ABCD participants who had real values for all included measures. Correlations between the other cognitive task replicate previous findings (Rosenberg et al., 2020). Significant correlations (p < .05) are denoted with an asterisk.

Distribution of ADHD symptoms and changes in symptoms over time

The baseline and slopes of the CBCL ADHD subscale *t*-scores for both rest and task groups were plotted as a distribution to observe trends in the data (see Figures 2 and 3). As stated previously, there was a large amount of overlap between the groups, but there were enough distinct participants to justify separate groups and distributions. The modal baseline *t*-score is 50, with very few extreme values above the diagnosis threshold of 70, the maximum observed value being 80 (see Figure 2). The mean value of the rest group baseline scores was 52.4 with a standard deviation of 4.64 and median of 50. For the rest group, the mean score was 52, median was 50, and standard deviation was 4.43. The median and mode slopes of both groups were zero (see Figure 3). The rest group had a mean slope of 0.01, with a standard deviation of 0.16 and values ranging from -1.16 to 1.01. The mean slope of the task group was 0.012, standard deviation of 0.17, and values in a range from -1.61 to 0.95. When correlated, the baseline scores and slopes for both the task and rest groups showed a modest negative trend (task: $r = -0.37$, $p < 0.01$; rest: $r = -0.39$, $p < 0.01$), suggesting that children with the minimal baseline score of 50 were more likely to show an increase in score or show little change over time (see Figure 4). Conversely, children with more extreme scores were more likely to decrease their score as they got older.

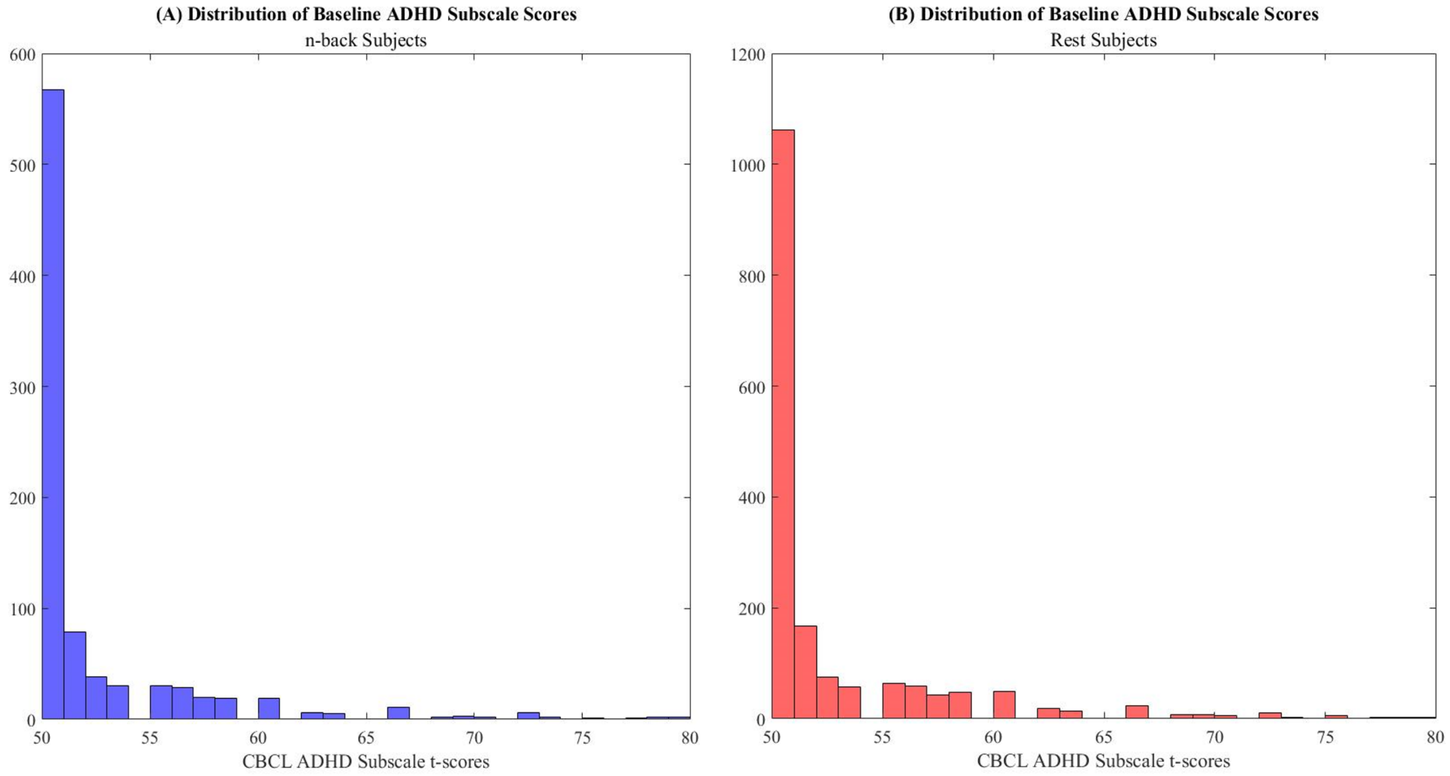


Figure 2: Distribution of CBCL ADHD subscale *t*-scores for the task and rest groups. Both samples have a clear mode score of 50.

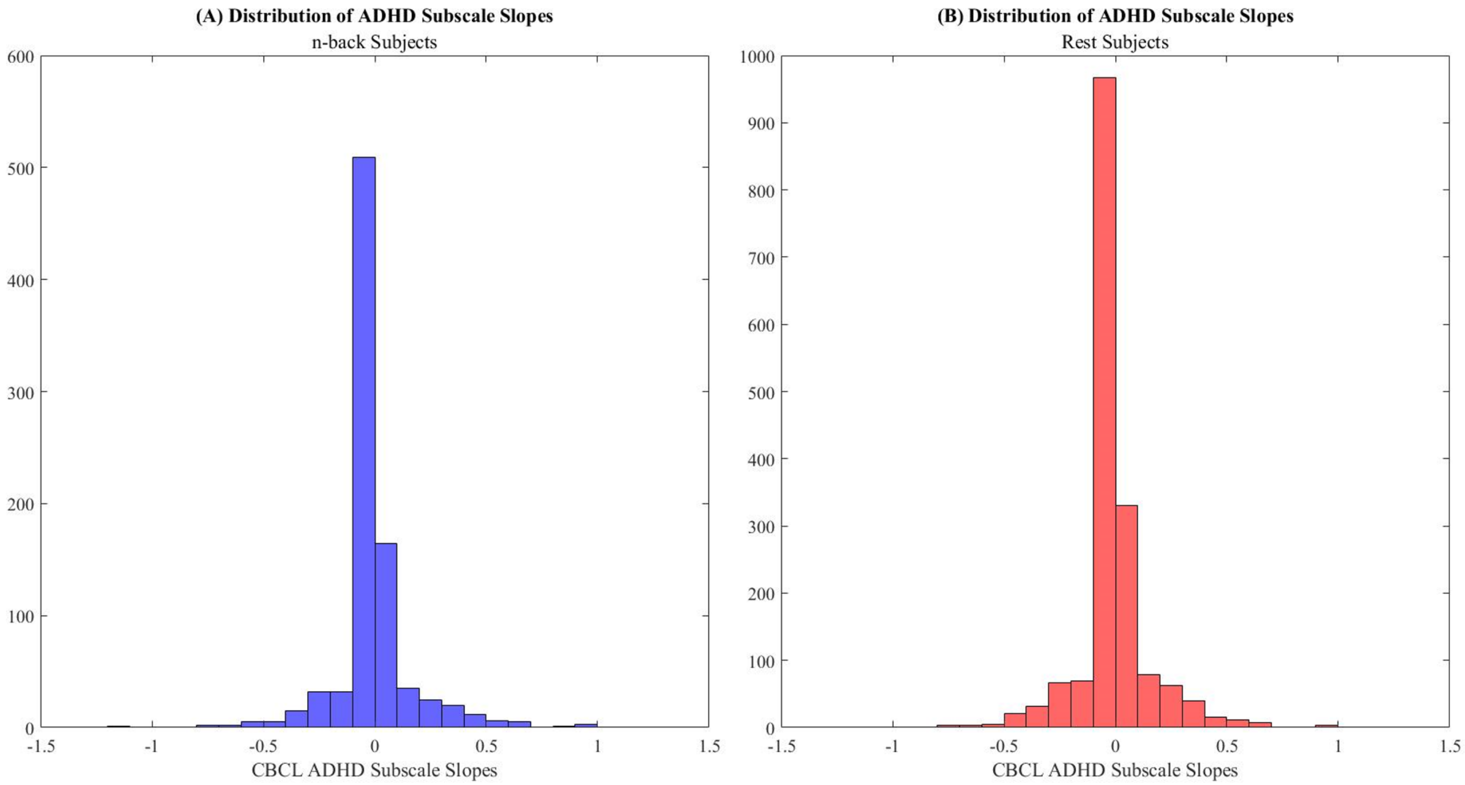


Figure 3: Distribution of ADHD subscale *t*-scores for both task and rest samples. The majority of slopes are centered around 0, indicating that most participants across both groups showed little change in attentional abilities.

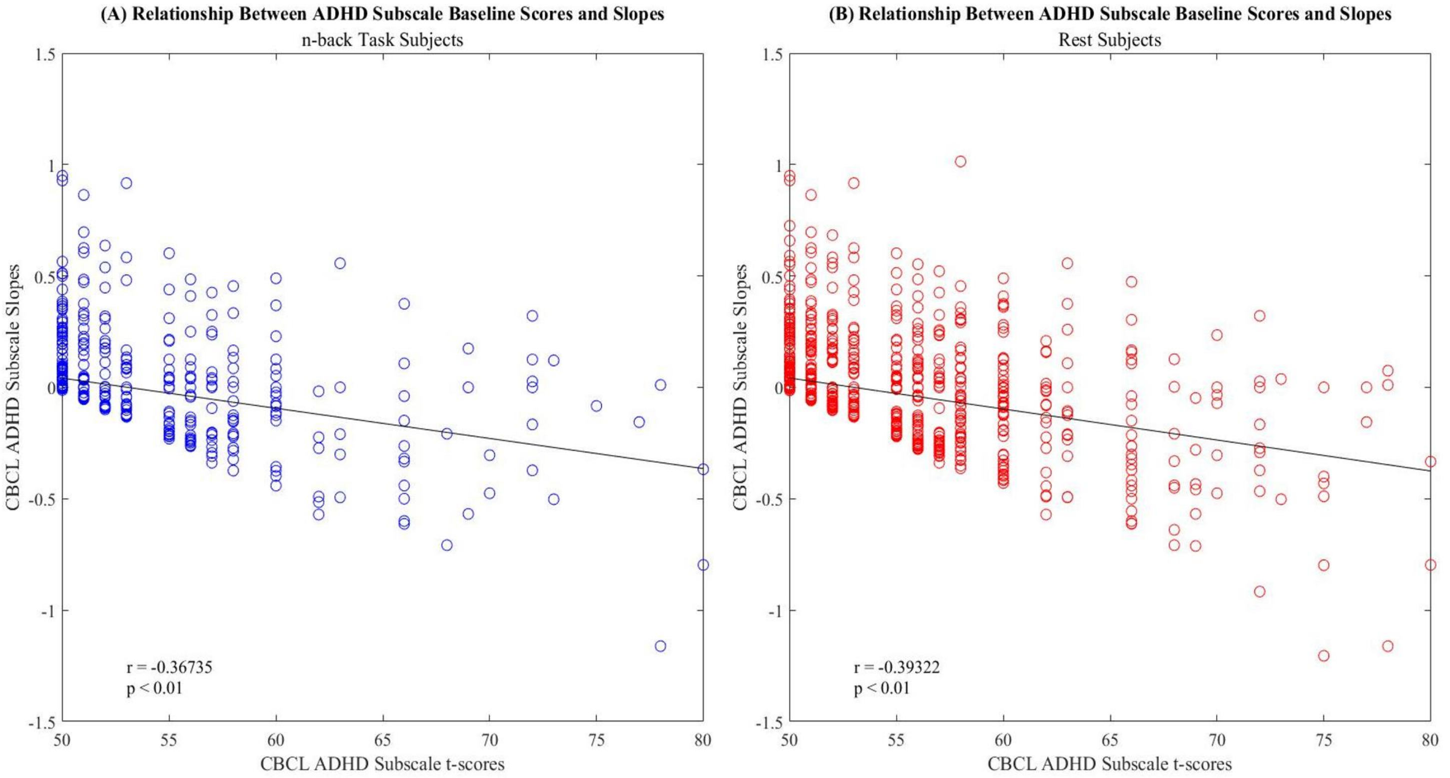


Figure 4: The correlation between ADHD *t*-scores and slopes calculated from all three time points of behavioral scores. Participants with higher baseline scores tend to show more change over time.

Connectome-based predictive modeling

In Study 1A, the saCPM analysis of baseline ADHD *t*-scores, both task and rest groups showed non-significant negative correlations between predicted and actual behavioral scores (task: *r* = -0.003, *p* = 0.93; rest: *r* = -0.007, *p* = 0.76; see Figure 5). Study 1B correlated the same saCPM model predictions to change in ADHD *t*-scores over time, operationalized as the slopes across the three years of data collection. Correlations between saCPM predictions and ADHD *t*-score slopes were not statistically significant (task: *r* = -0.06, *p* = 0.09; rest: *r* = 0.02, *p* = 0.44; see Figure 6).

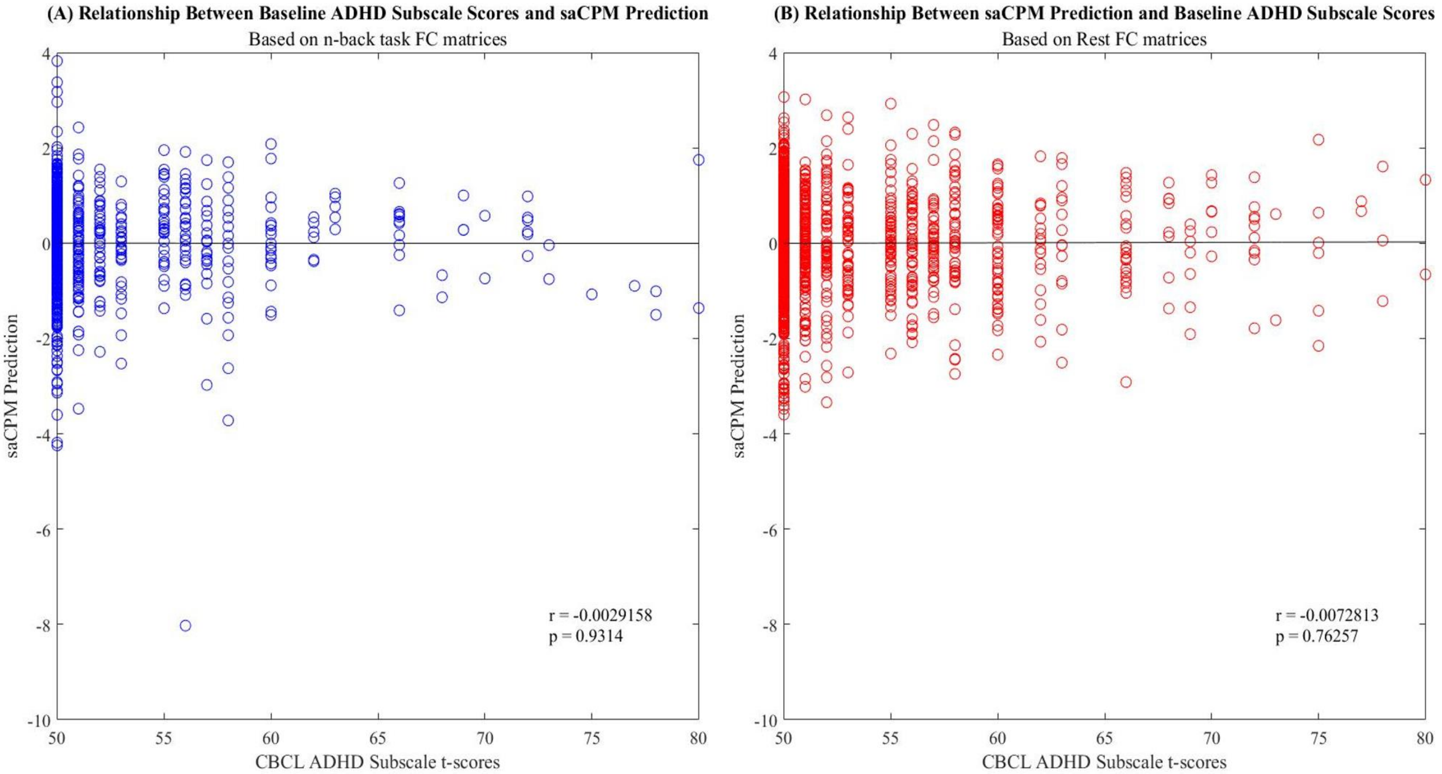


Figure 5: The correlation between baseline ADHD *t*-scores and predicated behavioral values produced from the saCPM.

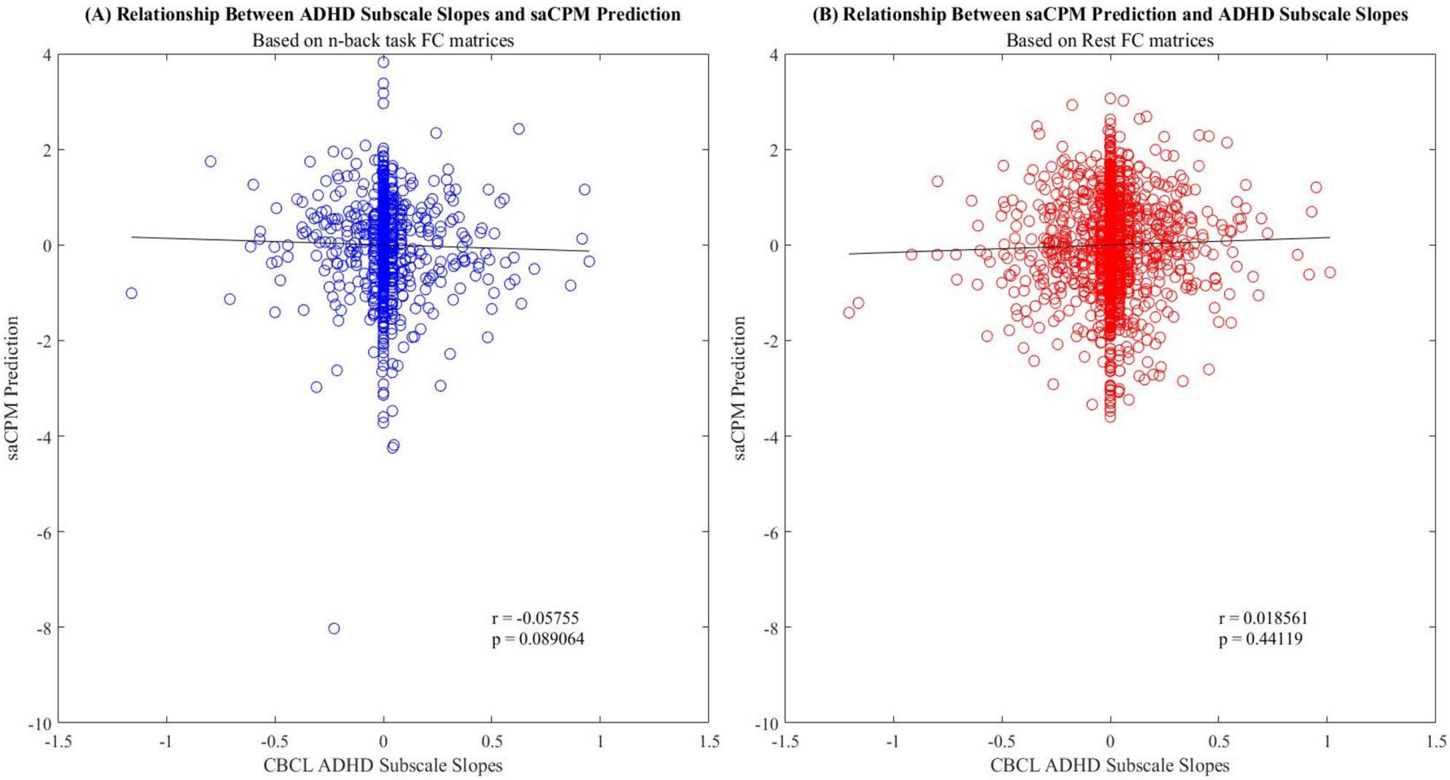


Figure 6: The correlation between the ADHD slopes and behavioral values predicted by the saCPM for both the task and rest samples.

Study 2

Methods

In Study 2, we asked whether a new model, built in the ABCD dataset, would be better suited to predict ADHD symptoms in a developmental sample, rather than applying a pre-existing adult model. The open-source CPM protocol used (Finn et al., 2017; Shen et al., 2015; https://github.com/YaleMRRC/CPM) trains a new model based on the ABCD functional connectivity matrices and behavioral data by correlating the edges of each participant's functional connectivity matrix with the baseline ADHD *t*-scores (see Figure 7). Within a *k*-fold cross-validation loop, the most statistically significant correlations are extracted, summed, and fit to a new linear model. The new model is tested by correlating the predicted and observed scores, similarly to the comparisons from Study 1. For the purposes of this study, ten folds were performed and a significance threshold of 0.01 was used for feature selection. As with the first study, analyses were performed on rest and *n*-back task data separately.

In the process of conducting this analysis it was also discovered that, due to the nature of the way the model building protocol was originally coded, the sample size must be divisible by the number of folds specified (in this case, ten). Otherwise, remaining behavioral values will automatically be assigned the predicted value of zero. To avoid this, the sample sizes of both groups were rounded down to the nearest number divisible by ten: 1720 for the rest sample and 870 for the task sample.

An exploratory analysis trained and tested CPMs using data only from individuals with scores higher than 50, given that the majority of participants (task: 570/870 = 65%; rest: 1060/1720 = 61%) had the lowest possible ADHD *t*-score (i.e., 50).

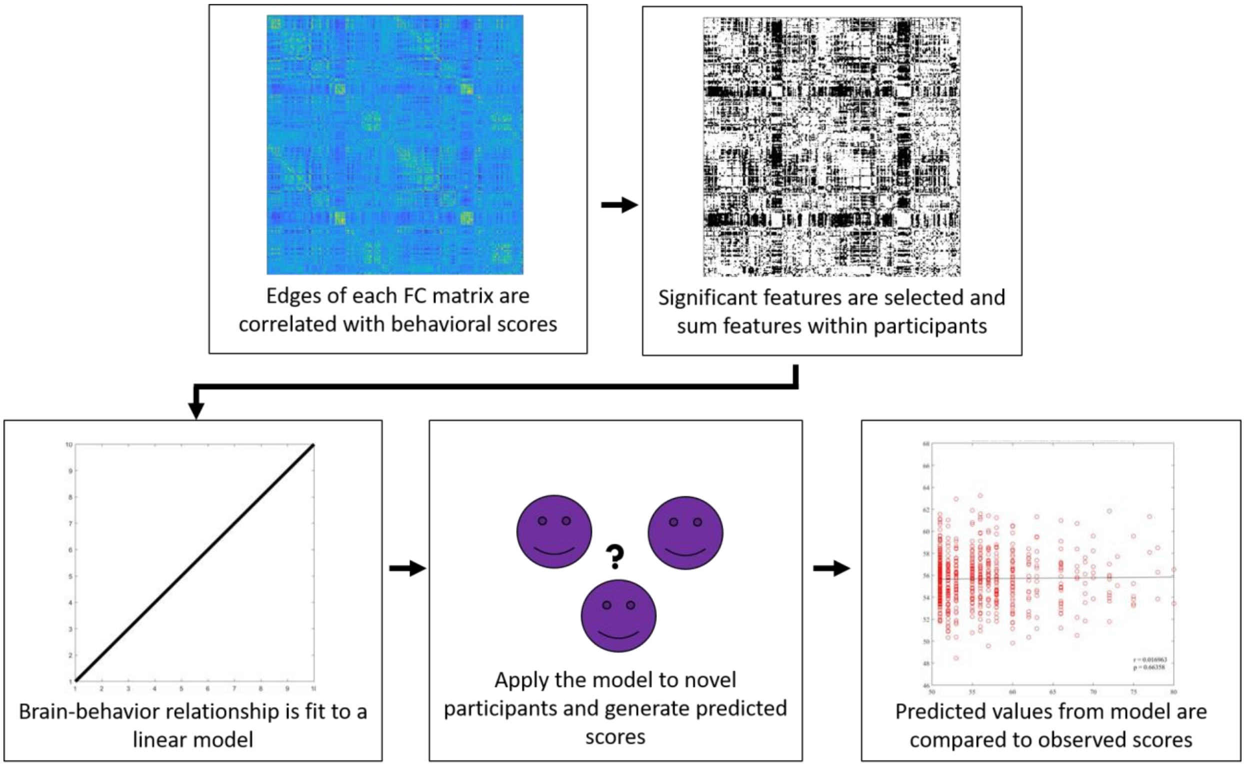


Figure 7: The basic steps of a CPM protocol are shown above. For each participant, the edges of the functional connectivity matrix are correlated with ADHD t-scores, significant features are selected, summed, and fit to a linear model with the other participant values. The predicted values are then correlated with observed values from the sample (Finn et al., 2017; Shen et al., 2015).

Results

In Study 2A we built a new predictive sustained attention model for the ABCD sample, which was originally overwhelmed by a high number of behavioral scores of 50. With the vast majority of behavioral scores being the same, the CPM protocol predicted that *all* behavioral values for the sample should be 50, regardless of the observed value. As such, both the rest and task correlations between predicted and observed values were not significant (task: $r = 0.056$, $p = 0.178$; rest: $r = 0.025$, $p = 0.29$).

In an exploratory analysis (Study 2B), we built a new model only including participants with a baseline ADHD subscale *t*-score above 50. Models built in this sample also did not significantly predict behavior (Figure 8). The task group ($n = 300$) showed a significant *negative* correlation between real and predicted values ($r = -0.14$, $p = 0.015$). This was an unexpected result likely due to noise, as it was expected that those with higher observed symptomology *t*-scores would have higher predicted scores under the newly constructed model. Instead, we see that participants with higher ADHD scores were associated with lower predicted scores. The rest group ($n = 660$) still showed little to no relationship between predicted and observed ADHD *t*-scores and was not significant ($r = 0.04$, $p = 0.26$).

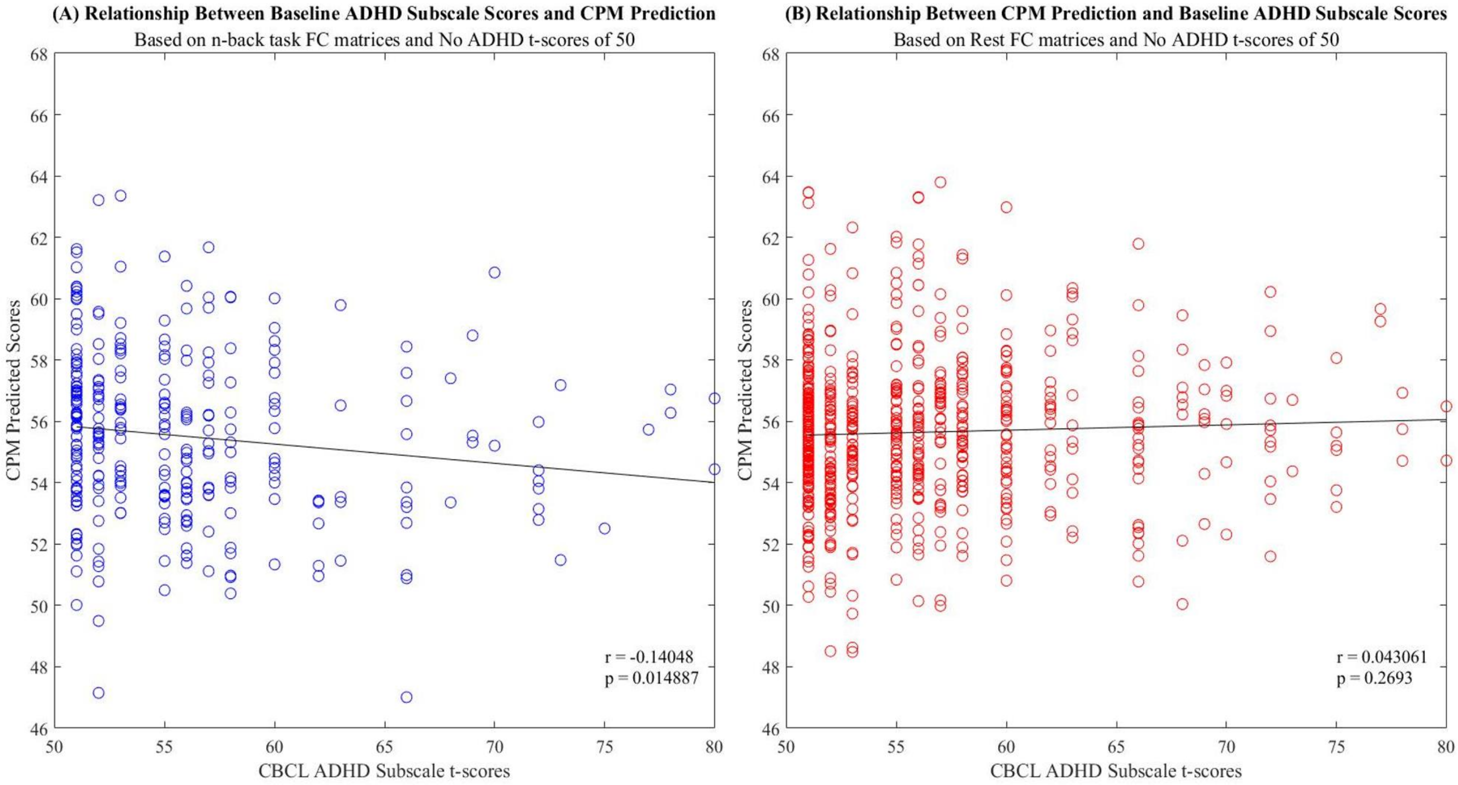


Figure 8: The correlation between baseline ADHD *t*-scores and predicted scores from the newly constructed model, only including baseline scores over 50.

General Discussion

Across two studies, we utilized data from the ABCD Study to investigate the relationship between functional connectivity and ADHD symptomology in children between the ages of 9 and 14. In Study 1, a preexisting neuromarker of sustained attention for adults was used to predict behavioral scores based on functional connectivity matrices from both rest and *n*-back in-scanner tasks, as well as changes in those behavioral scores over the three-year time period currently covered by ABCD. In Study 2, a new model was built based on the same behavioral and brain data to explore whether a model created from adolescent information might have more predictive power. Our results showed that the saCPM from adults did not significantly predict baseline *t-scores* nor the change in scores over time, operationalized as the slope between the three timepoints. A new model developed from *n*-back functional connectivity matrices also did not accurately predict behavior (predictions were significantly negative although the effect size was small, suggesting that the result was driven by noise).

Although we hypothesized that functional connectivity observed during the *n*-back task may outperform rest for predicting ADHD symptoms in development because the *n*-back task (and the 0-back version specifically) has previously been shown to tax sustained attention (Karatekin, Marcus, & Couperus, 2007), the results of Study 1 and Study 2 did not support this hypothesis. The analyses based on rest functional connectivity matrices were not significant and while the task-based analyses were significant in Study 2B, it was unable to accurately predict ADHD *t-scores.* While collecting rest data might be a test of self-control for a young child, it is not incredibly engaging for the participant and may not strongly activate the attention networks in the brain. The *n*-back task does not appear to be a pure measure of sustained attention, perhaps due to its combined scores between the 0-back and 2-back versions, which tax working memory in addition to sustained attention (Rosenberg, Martinez, et al., 2020).

The current study faced limitations that could have led to the observed null results. First, much of the variance in ADHD *t*-scores in the sample was removed when the fMRI data underwent visual quality control and filtering for frame displacement. Children who struggled with attention may also have been less likely to stay still and focus during the scan sessions and may therefore have been removed from the sample before analysis. This limited both the number of higher ADHD symptomology scores and low attention network strength in the sample and may have inherently biased the analysis towards children with fewer deficits in attention. The overwhelming number of minimum behavioral scores would also be likely to confound the analysis, as seen in Study 2A. We hypothesize that similar results would have been presented, had a model been constructed with slopes as well, given the large number of participants that saw little to no change in ADHD symptomology scores over the three time points. The small number of time points could have also posed a problem for analyses, therefore limiting the range of growth that could potentially be experienced by a child in the ten years the ABCD Study plans to cover. This limitation would necessitate waiting several more years until more data is released. Overall, the null results of the current study may be due to the higher amount of noise typical of clinical measures (Weyandt, Swentosky, & Gudmundsdottir, 2013) and the natural heterogeneity of ADHD as a disorder.

Our preliminary analyses found that the CBCL ADHD subscale *t*-scores were significantly correlated with several cognitive measures available in the ABCD Study, including the 0-back and 2-back tasks, the NIH Toolbox List Sorting Task, NIH Toolbox Picture Sequence Memory Task and NIH Toolbox Oral Reading Recognition Task. This was consistent with our hypothesis that the ADHD *t*-scores were a valid measure of cognitive abilities in the sample. Despite these relationships, however, it is possible that ADHD *t*-scores are optimized to capture differences between individuals with and without ADHD diagnoses, rather than more fine-grained individual differences in sustained attention function.

In addition to these relationships, we observed numerical trends in the behavioral data (albeit nonsignificant) that were consistent with prior hypotheses, such that children with higher ADHD subscale scores are more likely to experience a lessening of symptoms as time went on. This is consistent with some previous work in the literature which found that ADHD symptom reduction was associated with biological maturity (Gustafsson et al., 2010). However, that work was with younger children (ages 7-9) and prior work found no significant relationship between age and ADHD symptom improvement (Gustafsson et al, 2008). Another possible explanation for the decrease in ADHD symptoms is the potential overdiagnosis of ADHD in children, a sentiment which is becoming increasingly common among the general public (Sciutto & Eisenberg, 2007). Existing literature suggests that children who are younger relative to their grade-level peers are more likely to be diagnosed with ADHD, meaning that the children might just appear to be immature and impulsive when they are simply being compared to older students (Evans, Morrill, & Parente, 2010). These same children are also more likely to be medicated in what researchers postulate as an attempt to increase classroom productivity (Schwandt & Wupperman, 2016). Again, this could lend credence to a general growing maturity in the sample, which naturally decreases attention and executive control deficits.

We outline several future directions, in light of the fact that more data from the ABCD Study are still to be released in the coming years. First, it remains possible that the in-scanner tasks or behavioral measures used in the current work could have simply not been sufficiently taxing to sustained attention abilities in order to magnify behaviorally relevant individual differences in functional connectivity. Future work should explore some of the many other task and survey data collected by the ABCD Study as predictors of sustained attention. For example, the Stop-Signal Task (SST; Logan, 1994) is an in-scanner task that has been shown to tax attention and inhibitory control (O'Halloran et al., 2018), which would also be conducive to the purposes of the current study. However, in the first release of ABCD, there were several design issues with the in-scanner SST that made it unreliable in subsequent analyses (Bisset et al., 2021). Should these issues be corrected in future releases, the SST could become a viable tool in conducting future sustained attention research. As stated previously, ADHD is a very heterogenous disorder that may not make it a strong enough proxy for sustained attention. Future studies might benefit from using more general clinical attention measures, rather than a specific diagnostic label. Additionally, a behavioral measure that could be helpful in this endeavor is the Attention subscale (Achenbach & Rescorla, 2001) from the original subscales of the CBCL. Should future research include subjects with ADHD symptomology, it may be advantageous to use a sample made up of participants that have been officially diagnosed with ADHD. Such a sample could provide more detailed records about the treatment plan they are following and any medication they are taking that might attenuate sustained attention impairment. These are factors that were not taken into account in the current study but could potentially lead to drastic changes in ADHD symptomology and sustained attention abilities over time. As more tasks and measures are added to the ABCD dataset and more years of data are released to the scientific community, further investigation of the relationships discussed in this paper could prove invaluable in understanding the development of attentional networks and abilities in childhood and throughout adolescence.

In summary, models based on functional connectivity patterns from the ABCD Study were unable to accurately predict ADHD symptomology scores, neither with the predefined saCPM nor with a newly developed connectome-based predictive model. As data collection for the ABCD Study continues, future work can test whether adult-defined models better predict behavioral scores as the participants get older and develop patterns of structural and functional brain organization more similar to those of adults. More broadly, as functional connectivity becomes a more widely used method in the field of cognitive neuroscience, CPM and other similar methods may become useful tools in the diagnosis of disorders that impair sustained attention, including ADHD, and predicting how those disorders can change over time.

References

Achenbach, T. M., & Rescorla, L. A. (2001). Manual for ASEBA School Age Forms & Profiles. Burlington, VT: University of Vermont Research Center for Children, Youth and Families.

American Psychiatric Association. (2013). Neurodevelopmental Disorders. In *Diagnostic and statistical manual of mental disorders* (5th ed.). doi: 10.1176/appi.books.9780890425596.744053

Anckarsäter, H., Stahlberg, O., Larson, T., Hakansson, C., Jutblad, S. B., Niklasson, L., ... & Rastam, M. (2006). The impact of ADHD and autism spectrum disorders on temperament, character, and personality development. *American Journal of Psychiatry*, *163*(7), 1239-1244.

Arnold, L. E. (1996). Sex differences in ADHD: Conference summary. Journal of abnormal child psychology, 24(5), 555-569.

Barkley, R.A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin, 121*, 65–94.

Bisset, P.G., Hagen, M.P., Jones, H.M., Poldrack, R.A. (2021). Design issues and solutions for stop-signal data from the Adolescent Brain Cognitive Development (ABCD) study. *eLife, 10*:e60185.

Castellanos, F.X., Lee, P.P., Sharp, W., et al. (2002). Developmental Trajectories of Brain Volume Abnormalities in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. *JAMA, 288*(14), 1740–1748.

Chien, Y. L., Gau, S. S., Shang, C. Y., Chiu, Y. N., Tsai, W. C., & Wu, Y. Y. (2015). Visual Memory and Sustained Attention Impairment in Youths with Autism Spectrum Disorders. *Psychological medicine, 45*(11), 2263.

Cohen, A.O., Conley, M.I., Dellarco, D.V., Casey, B.J. (2016). The impact of emotional cues on short-term and long-term memory during adolescence. Society for Neuroscience, San Diego, CA.

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M.P., & Castellanos, F.X. (1998). Toward Systems Neuroscience of ADHD: A meta-analysis of 55 fMRI studies. *American Journal of Psychiatry 2012, 169*(10), 1038-1055.

Cowan, N. (1998). *Attention and Memory: An integrated framework*. Oxford University Press.

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,* 184-195.

Evans, W.N., Morrill, M.S., Parente, S.T. (2010). Measuring inappropriate medical diagnosis and treatment in survey data: The case of ADHD among school-age children. *Journal of Health Economics, 29*(5), 657-673.

Fairman, K. A., Peckham, A. M., & Sclar, D. A. (2020). Diagnosis and Treatment of ADHD in the United States: Update by Gender and Race. Journal of Attention Disorders, 24(1), 10–19.

Finn, E.S., Shen, X., Scheinost, D., Rosenberg, M.D., Huang, J., Chun, M.M., Papademetris, X., Constable, R.T. (2015). Functional Connectome Fingerprinting: Identifying individuals using patterns of brain connectivity. *Nature Neuroscience*, *18*(11), 1664-1671.

Gustafsson, P., Thernlund, G., Besjakov, J., Karlsson, M., Ericsson, I. and Svedin, C. (2008), ADHD symptoms and maturity – a study in primary school children. Acta Pædiatrica, 97: 233-238.

Gustafsson, P., Holmström, E., Besjakov, J. and Karlsson, M. (2010), ADHD symptoms and maturity – a follow-up study in school children. Acta Pædiatrica, 99: 1536-1539.

Hoeft, F., McCandliss B.D., Black, J.M., Gantman, A., Zakerani, N., Hulme, C., Lyytinen, H., Whitfield-Gabrieli, S., Glover, G.H., Reiss, A.L., & Gabrieli, J.D. (2011). Neural systems predicting long-term outcome in dyslexia. *Proceedings of the National Academy of the Sciences USA, 108,* 361–366.

Horien, C., Shen, X., Scheinost, D., Constable, R.T. (2019). The individual functional connectome is unique and stable over months to years. *NeuroImage, 189*, 676-687.

Karatekin, C., Marcus, D.J. and Couperus, J.W. (2007), Regulation of cognitive resources during sustained attention and working memory in 10-year-olds and adults. *Psychophysiology, 44*. 128-144.

Kessler, D., Angstadt, M., & Sripada, C. (2016). Growth Charting of Brain Connectivity Networks and the Identification of Attention Impairment in Youth. *JAMA Psychiatry, 73*(5), 481–489.

Kofler, M. J., Rapport, M. D., Bolden, J., Sarver, D. E., Raiker, J. S., & Alderson, R. M. (2011). Working memory deficits and social problems in children with ADHD. *Journal of abnormal child psychology*, *39*(6), 805-817.

Krain, A. L., & Castellanos, F. X. (2006). Brain development and ADHD. *Clinical psychology review*, *26*(4), 433-444.

Ling, S., Carrasco, M. (2006). When Sustained Attention Impairs Perception. *Nature Neuroscience, 9*, 1243–1245. https://doi.org/10.1038/nn1761

Liu, S. K., Chiu, C. H., Chang, C. J., Hwang, T. J., Hwu, H. G., & Chen, W. J. (2002). Deficits in sustained attention in schizophrenia and affective disorders: stable versus state-dependent markers. *American Journal of Psychiatry*, *159*(6), 975-982.

Logan, G.D. (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In D. Dagenbach & T. H. Carr (Eds), Inhibitory processes in attention, memory, and language: 189-239. San Diego: Academic Press.

Luo, Y., Weibman, D., Halperin, J. M., & Li, X. (2019). A Review of Heterogeneity in Attention Deficit/Hyperactivity Disorder (ADHD). *Frontiers in Human Neuroscience*, *13*, 42.

Maalouf, F.T., Klein, C., Clark, L., Sahakian, B.J., LaBarbara, E.J., Versace, A., Hassel, S., Almeida, J.C., Phillips, M.L. (2010). Impaired Sustained Attention and Executive Dysfunction: Bipolar disorder versus depression-specific markers of affective disorders, *Neuropsychologia*, *48*(6), 1862-1868.

Makris, N., Biederman, J., Valera, E. M., Bush, G., Kaiser, J., Kennedy, D. N., ... & Seidman, L. J. (2007). Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. *Cerebral cortex*, *17*(6), 1364-1375.

Nakamura, B.J., Ebesutani, C., Bernstein, A. et al. (2009). A Psychometric Analysis of the Child Behavior Checklist DSM-Oriented Scales. *Journal of Psychopathology and Behavioral Assessment*, *31*, 178–189. https://doi.org/10.1007/s10862-008-9119-8

O'Halloran, L. Cao, Z., Ruddy, K., Jollans, L., Albaugh, M.D., Aleni, A., et al. (2018). Neural Circuitry Underlying Sustained Attention in Healthy Adolescents and in ADHD Symptomatology. *Neuroimage, 169*, 395-406.

Plitt, M., Barnes, K. A., Wallace, G. L., Kenworthy, L. & Martin, A. (2015). Resting State Functional Connectivity Predicts Longitudinal Change in Autistic Traits and Adaptive

Functioning in Autism. *Proceedings of the National Academy of the Sciences USA, 112,* E6699–E6706

Polanczyk G., de Lima M.S., Horta B.L., et al (2007). The Worldwide Prevalence of ADHD: A systematic review and metaregression analysis. *American Journal of Psychiatry, 164*(6), 942–948.

Poole, V. N., Robinson, M. E., Singleton, O., DeGutis, J., Milberg, W. P., McGlinchey, R. E., ... & Esterman, M. (2016). Intrinsic functional connectivity predicts individual differences in distractibility. *Neuropsychologia*, *86*, 176-182.

Rieppi, R., Greenhill, L. L., Ford, R. E., Chuang, S., Wu, M., Davies, M., ... & Wigal, T. (2002). Socioeconomic status as a moderator of ADHD treatment outcomes. Journal of the American Academy of Child & Adolescent Psychiatry, 41(3), 269-277.

Rosenberg MD, Finn ES, Scheinost D, Papademetris X, Shen X, Constable RT, Chun MM. (2015). Resting-state brain connectivity predicts ADHD symptom severity in individual children. *Organization for Human Brain Mapping*, Honolulu, HI.

Rosenberg, M.D., Finn, E.S., Scheinost, D., Papademetris, X., Shen, X., Constable, R.T., & Chun, M.M. (2016). A Neuromarker Of Sustained Attention from Whole-Brain Functional Connectivity. *Nature Neuroscience*, *19*(1), 165-171.

Rosenberg, M.D., Finn, E.S., Scheinost, D., Constable, R.T., & Chun, M.M. (2017). Characterizing Attention with Predictive Network Models. *Trends in Cognitive Neurosciences, 21*(4), 290-302.

Rosenberg, M.D., Casey, B.J., & Holmes, A.J. (2018). Prediction Complements Explanation in Understanding the Developing Brain. *Nature Communications, 9*(589).

Rosenberg, M. D. & Chun, M. M. (2020). Network models of attention and working memory. In M. Gazzaniga & D. Poeppel (Eds.), *The Cognitive Neurosciences VI*. MIT Press.

Rosenberg, M. D., Martinez, S. A., Rapuano, K. M., Conley, M. I., Cohen, A. O., Cornejo, M. D., ... & Casey, B. J. (2020). Behavioral and neural signatures of working memory in childhood. Journal of Neuroscience, 40(26), 5090-5104.

Rosenberg, M.D., Scheinost, D., Greene, A.S., Avery, E.W., Kwon, Y.H., Finn, E.S., Ramani, R., Qiu, M., Constable, R.T., & Chun, M.M. (2020). Functional connectivity Predicts Changes in Attention Observed Across Minutes, Days, and Months. *Proceedings of the National Academy of the Sciences, 117*(7), 3797-3807.

Samea, F., Soluki, S., Nejati, V., Zarei, M., Cortese, S., Eickhoff, S.B., Tahmasian, M., Eickhoff C.R. (2019). Brain alterations in children/adolescents with ADHD revisited: A neuroimaging meta-analysis of 96 structural and functional studies. *Neuroscience & Biobehavioral Reviews, 100*, 1-8.

Sarter, M., Givens, B., and Bruno, J.P. (2001). The Cognitive Neuroscience of Sustained Attention: Where top-down meets bottom-up, *Brain Research Reviews, 35*(2), 146-160.

Sciutto, M.J., Eisenberg, M. (2007). Evaluating the Evidence for and Against the Overdiagnosis of ADHD. *Journal of Attention Disorders, 11*(2), 106-113.

Schwandt, H., Wuppermann, A. (2016). The youngest get the pill: ADHD misdiagnosis in Germany, its regional correlates and international comparison. *Labour Economics, 43*, 72-86.

Shen, X., Tokoglu, F., Papademetris, X., Constable, R.T. (2013) Groupwise Whole-Brain Parcellation From Resting-State fMRI Data for Network Node Identification. *Neuroimage, 15*(82), 403-15.

Shen X., Finn E.S., Scheinost D., Rosenberg M.D., Chun M.M., Papademetris X., Constable R.T. (2017). Using Connectome-based Predictive Modeling to Predict Individual Behavior from Brain Connectivity. *Nature Protocols, 12*(3), 506.

Sibley, M. H., Pelham, W. E., Jr., Molina, B. S. G., Gnagy, E. M., Waschbusch, D. A., Garefino, A. C., Kuriyan, A. B., Babinski, D. E., & Karch, K. M. (2012). Diagnosing ADHD in Adolescence. *Journal of Consulting and Clinical Psychology*, *80*(1), 139–150.

Weyandt, L., Swentosky, A., & Gudmundsdottir B.G. (2013). Neuroimaging and ADHD: fMRI, PET, DTI Findings, and Methodological Limitations. *Developmental Neuropsychology*, *38*(4), 211-225.

Wu, E.X., Liaw, G.J., Goh, R.Z., Chia, T.T., Chee, A.M., Obana, T., Rosenberg, M.D., Thomas Yeo, B.T., Asplund, C. L. (2020). Overlapping Attentional Networks Yield Divergent Behavioral Predictions Across Tasks: Neuromarkers for diffuse and focused attention? *Neuroimage, 209.*