



Is there any incremental benefit to conducting neuroimaging and neurocognitive assessments in the diagnosis of ADHD in young children? A machine learning investigation

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ABSTRACT

Given the negative trajectories of early behavior problems associated with ADHD, early diagnosis is considered critical to enable intervention and treatment. To this end, the current investigation employed machine learning to evaluate the relative predictive value of parent/teacher ratings, behavioral and neural measures of executive function (EF) in predicting ADHD in a sample consisting of 162 young children (ages 4–7, mean age 5.55, 82.6 % Hispanic/Latino). Among the target measures, teacher ratings of EF were the most predictive of ADHD. While a more extensive evaluation of neural measures, such as diffusion-weighted imaging, may provide more information as they relate to the underlying cognitive deficits associated with ADHD, the current study indicates that measures of cortical anatomy obtained in research studies, as well cognitive measures of EF often obtained in routine assessments, have little incremental value in differentiating typically developing children from those diagnosed with ADHD. It is important to note that the overlap between some of the EF questions in the BRIEF, and the ADHD symptoms could be enhancing this effect. Thus, future research evaluating the importance of such measures in predicting children's functional impairment in academic and social areas would provide additional insight into their contributing role in ADHD.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a developmental disorder, characterized by symptoms of inattention, hyperactivity and impulsive behavior (see Mahone and Denckla, 2017 for a historical overview). The National Resource Center on ADHD (NRC) currently indicates that fifteen million individuals have ADHD in America. ADHD has a worldwide prevalence of 7.2 % in children (Wolraich et al., 2019). Early identification and treatment of ADHD is considered critical due to the serious consequences of ADHD, including but not limited to academic/school and social difficulties (Hoza, 2007; Moffitt et al., 2002; Ros and Graziano, 2018; Shaw et al., 2003). Previous ADHD research implicates the important role of executive function (EF) processes (Barkley, 1997; Sergeant, 2000; Sonuga-Barke, 2002), with strong observed links between EF deficits and academic (Biederman et al., 2004; Blair and Razza, 2007; Clark et al., 2010) and social difficulties (Hill, 2004; Riggs et al., 2006). Machine learning techniques can leverage these important measures as a means to help identify 1) the most important predictors critical for successful classification of ADHD,

and 2) provide objective measures of the relative clinical utility of target predictors. To this end, the current study evaluated the predictive utility of EF measures in three categories, namely parent/teacher ratings of EF, behavioral performance in EF tasks, and neural measures of cortical thickness in brain regions that support EF in a sample of 162 children between ages 4–7 (mean age 5.5 years).

An important advantage of multivariate modeling approaches in cognitive and translational neuroscience research has been their ability to combine information from data in a distributed fashion. As opposed to traditional univariate approaches, where data (such as signal intensity from functional MRI) are averaged over a specific region of interest (ROI), and compared to the mean signal in another ROI to assess potential differences in magnitude of neural activation, multivariate approaches use data from distributed patterns of a neural measure (e.g., brain activity or anatomical properties of the brain), and apply computational models to the data that extend beyond conducting statistical analyses on averages [for reviews see (Davis and Poldrack, 2013; Haxby, 2012; Haxby et al., 2001; Norman et al., 2006; Yang et al., 2012)]. While computationally more challenging, this latter approach

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enables researchers to answer key questions regarding mental representations (e.g., what type of information is represented in different brain regions and at different stages of cognitive processing) in cognitive neuroscience research (Haxby et al., 2001; Kuhl et al., 2011; Liang et al., 2013; Norman et al., 2006; Öztekin and Badre, 2011; Polyn et al., 2005)], and provides unique opportunities for clinical diagnosis and prediction of disorder or symptom severity, as well as behavioral outcomes associated with specific disorders. Despite this promising potential for such computational, multivariate approaches to advance translational neuroscience, significant challenges and pitfalls have prevented the development of generalizable methods and approaches that can be applied in clinical settings [see (Arbabshirani et al., 2017; Kassraian-Fard et al., 2016; Varoquaux, 2018; Varoquaux et al., 2017; Woo et al., 2017)].

One commonly recognized obstacle is *small sample size*, which leads to overfitting. Overfitting refers to the modeling of noise in the data rather than the underlying pattern of interest, which results in good performance on the training data, but poor performance on previously unseen data. Accordingly, overfitting is a major obstacle in generating a valid predictive model that can produce generalizable results for clinical diagnosis, and which can be used across a variety of clinical settings (Arbabshirani et al., 2017; Foster et al., 2014; Kassraian-Fard et al., 2016; Pulini et al., 2019; Varoquaux, 2018; Varoquaux et al., 2017; Woo et al., 2017). Indeed, most neuroscience studies suffer from small sample sizes (Arbabshirani et al., 2017; Foster et al., 2014; Kassraian-Fard et al., 2016; Pulini et al., 2019; Varoquaux, 2018). Notably, the current investigation leveraged a data set with a larger sample size (162 participants) that provided a unique opportunity to leverage predictive modeling that utilized a machine learning approach.

Another salient pitfall centers around the selection of features in the model. Two important factors stand out with respect to this obstacle (Arbabshirani et al., 2017; Foster et al., 2014; Woo et al., 2017). The first is *unbiased feature selection*. In their critical review of predictive modeling approaches for clinical diagnosis, Arbabshirani et al. (Arbabshirani et al., 2017) and Woo et al. (Woo et al., 2017) point out that it is common for predictive modeling studies to use a group analysis over the whole dataset to select appropriate features for the classifier. This, however, constitutes “double dipping” and produces biased results. In our approach, our feature selection was performed *a priori*, based on the ADHD literature that highlights the importance of executive function for ADHD, and prior research on the neurobiology of executive function. The second obstacle is *the need for theoretical motivation for selection of features*. In addition to selecting features in an unbiased manner, several critique articles (Foster et al., 2014; Kassraian-Fard et al., 2016; Woo et al., 2017) have put forth the importance of theoretical relevance of the features in the model, especially in the context of clinical diagnosis. Accordingly, in the current investigation, we limited our features to those that are theoretically relevant, namely the cognitive and neurobiological measures of executive function.

1.1. Current study

The ADHD Heterogeneity of Executive Function and Emotion Regulation Across Development (AHEAD) study aims to characterize the heterogeneity of well-established predictors of ADHD among young children (ages 4-to-7, mean age 5.5 years) across multiple levels of analysis. It thus uniquely provides multiple measures of executive function, which we focus in the current investigation, at both behavioral/cognitive and neural levels at an age-range where early diagnosis of ADHD is critically important. Notably, several research groups have previously applied machine learning to better characterize the heterogeneity of the behavioral profile in ADHD [for instance see (Karlunas et al., 2019; Qureshi et al., 2016)]. However, to date, none of the attempts have been adapted for clinical diagnosis in children with early diagnosis—i.e., in the pre-K age range during which initial contact with educators and clinicians typically occurs. Our AHEAD study provides a

unique data set with the potential for a significant contribution in this domain.

The AHEAD study is among the first to scan children with ADHD as young as 4–7 years. Indeed, only a few imaging studies have evaluated the neurobiology of ADHD in this young age range. Jacobson and colleagues (Jacobson et al., 2018) evaluated structural scans from 90 4–5 year-old preschoolers. They noted volume reductions in bilateral frontal, parietal and temporal cortices for children with ADHD compared to controls. Furthermore, specific subregions of the frontal cortex were significantly correlated with ADHD symptom severity. In another investigation, Rosch and colleagues (Rosch et al., 2018) evaluated subcortical volumes in 87 4–5 year-old preschoolers, and observed the largest reductions in the caudate, globus pallidus, and the thalamus for children with ADHD. The age range in majority of the other existing studies is usually 9 or older, with few studies also sampling an age range of 7 and above (Fair et al., 2012; Karlunas et al., 2014, 2019; Qureshi et al., 2017). Given that early diagnosis of ADHD is critical for informing treatment, the current investigation provides a unique opportunity to assess whether predicting ADHD from scans is feasible in this age range.

1.1.1. Executive function and ADHD

Importantly, previous research points to the critical role of executive function (EF) processes in ADHD (Barkley, 1997; Sergeant, 2000; Sonuga-Barke, 2002). Crucially, a strong relationship has been noted between EF deficits and academic (Biederman et al., 2004; Blair and Razza, 2007; Clark et al., 2010), as well as social difficulties (Hill, 2004; Riggs et al., 2006). With respect to the neurobiological markers that support EF, previous research notes the functional interactions among lateral frontal, inferior frontal/insular (Aron et al., 2004), medial frontal/anterior cingulate/pre-SMA (Aron et al., 2004; Bunge and Wright, 2007; Fedota et al., 2014; Miller and Cohen, 2001; Rushworth et al., 2005), lateral parietal (Corbetta and Shulman, 2002), and dorsal striatal (Morein-Zamir and Robbins, 2015) regions of the brain (Hart et al., 2014). Accordingly, our machine learning approach in this investigation focuses on the cognitive behavioral and neural measures of executive function, with the primary goal of assessing the utility of predicting ADHD diagnostic category from the target measures of executive function. Within this overarching goal, we pursued two aims: 1) to evaluate the predictive value of behavioral and neural correlates of executive function, and 2) to determine the relative importance of each measure in predicting ADHD diagnostic category. Given the implicated importance of executive function in ADHD, we hypothesized that our models would successfully predict ADHD diagnostic category.

2. Materials and methods

2.1. Participants and recruitment

Children and their caregivers were recruited from local schools and mental health agencies via brochures, radio and newspaper ads, and open houses/parent workshops. Legal guardians contacted the clinic and were directed to the study staff for screening questions to determine eligibility. For the ADHD sample, if the parent (1) endorsed clinically significant levels of ADHD symptoms (six or more symptoms of either Inattention or Hyperactivity/Impulsivity according to the DSM-5 OR a previous diagnosis of ADHD), (2) indicated that the child is currently displaying clinically significant academic, behavioral, or social impairments as measured by a score of 3 or higher on a seven-point impairment rating scale (Fabiano et al., 2006), and (3) were not taking any psychotropic medication, the parent and child were invited to participate in an assessment to determine study eligibility. For the typically developing sample, if the parent (1) endorsed less than 4 ADHD symptoms (across either Inattention or Hyperactivity/Impulsivity according to the DSM-5), (2) less than 4 Oppositional Defiant Disorder (ODD) symptoms, and (3) indicated no clinically significant impairment (score below 3 on the impairment rating scale), the parent and child were invited to

participate in an assessment to determine study eligibility. Participants were also required to be enrolled in school during the previous year, have an estimated IQ of 70 or higher, have no confirmed history of an Autism Spectrum Disorder, and be able to attend an 8-week summer treatment program (Graziano et al., 2014) prior to the start of the next school year (ADHD groups only). Due to the young age of the sample, only disruptive behavior disorders were extensively examined for diagnostic purposes.

During intake, ADHD diagnosis (and comorbid disruptive behavior disorders) was assessed through a combination of parent structured interview (Computerized-Diagnostic Interview Schedule for Children (Shaffer et al., 2000) and parent and teacher ratings of symptoms and impairment (Disruptive Behavior Disorders Rating Scale, Impairment Rating Scale (Fabiano et al., 2006) as is recommended practice (Pelham et al., 2005). Specifically, the DBD rating scales and diagnostic interview were combined using an “or rule,” which identifies the presence of a symptom if endorsed by either informant while clinically significant problems at home and school were defined by at least a “3” on a “0 to 6” impairment rating scale (Bird et al., 1992; Sibley et al., 2016). Individuals administering the DISC were clinical graduate students (masters and doctoral level) who were trained and supervised by a licensed psychologist (3rd author). Dual Ph.D. level clinician review was used to determine diagnosis. Of relevance to the current study, the BRIEF rating scale (parent and teacher) was not used for any diagnostic purposes. The final sample included 162 children (87 with ADHD, and 75 healthy developing controls). Among the participants with ADHD, 61 (70 %) had a comorbid ODD or Conduct Disorder (CD) diagnosis. Parental consent and assent was obtained in accordance with the Office of Research Integrity at Florida International University.

2.2. Measures of executive function (EF)

2.2.1. Parent/teacher ratings of EF

We utilized the Emergent Metacognition Index (MCI) *t*-score from the Behavior Rating Inventory of Executive Function (BRIEF, BRIEF-P, (Isquith et al., 2004)) for our measure of parent and teacher ratings of executive function. The MCI is thought to reflect the ability to maintain information and/or activities in working memory, as well as to plan and organize problem-solving approaches. In the BRIEF Preschool, The MCI is composed of the Working Memory and Plan/Organize scales. In the BRIEF Child, the MCI is composed of the Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor scales. In our sample, BRIEF-P was completed for 115 of our participants (ages 4–5; Chronbach’s alpha for MCI .976 for BRIEF-P Teacher and .970 for BRIEF-P Parent), and BRIEF Child was completed for 47 of our participants (ages 6–7; Chronbach’s alpha for MCI .724 for Teacher and .978 for Parent).

2.2.2. Behavioral/cognitive measures of EF

Our dataset allowed us to evaluate performance in three tasks that measure executive function:

i). *The Flanker Task*. The Flanker Task of Inhibitory Control and Attention is part of the EF assessments utilized in the NIH Toolbox-Cognition battery (<http://www.nihtoolbox.org>). This task measures the participant’s responses under conditions where the surrounding stimuli and target are either congruent or incongruent. We used the Uncorrected Standardized Score as our dependent measure for this task.

ii). *The Dimensional Change Card Sorting Task (DCCS)*. The DCCS is also part of the Cognition battery of the NIH Toolbox. Participants sort objects by color or shape.

Both the Flanker and DCCS tasks have been validated with children as young as age 3 (Zelazo et al., 2013). The Uncorrected Standardized Score was used as the dependent measure.

iii). *Head-Toes-Knees-Shoulders (HTKS) Task*. HTKS (Cameron Ponitz et al., 2008) is a brief and widely-used task with young children ages 4–7 that assesses multiple aspects of EF. This task implements pairings of

behavioral rules: “touch your head” and “touch your toes”, “touch your shoulders” and “touch your knees”. The children first respond naturally, and then are asked to switch the rules by responding in the opposite manner. Graziano and colleagues (Graziano et al., 2015) have previously established the ecological validity of this task in young children with ADHD. Participants’ total score on the task was used as the dependent measure.

2.2.3. Neurobiological measures

All imaging was performed using a research-dedicated 3 T Siemens MAGNETOM Prisma MRI scanner (V11C) with a 32-channel coil located on the university campus. Children first completed a preparatory phase using realistic mock scanner in the room across the hall from the magnet. Here they were trained to stay still, and were also acclimated to the enclosed space of the magnet, the back projection visual presentation system, and to the scanner noises (in this case, presented with headphones). When they were properly trained and acclimated, they were moved to the magnet. In the magnet, during the structural scans, children watched a child-friendly movie of their choice. Ear protection was used, and sound was presented through MRI compatible headphones.

Structural MRI scans were collected using a 3D T1-weighted sequence (axial; 1 × 1 × 1 mm, 7 min 14 s) with prospective motion correction (Siemens vNAV; Tisdall et al., 2012), according to the Adolescent Brain and Cognitive Development (ABCD) protocol (Hagler et al., 2019). To provide a semi-automated parcellation of the cerebral cortices and volume of subcortical structures, we constructed two-dimensional surface renderings of each participant’s brain using FreeSurfer (Dale et al., 1999; Fischl and Dale, 2000). We computed cortical thickness and subcortical volume as part of the standard FreeSurfer reconstruction pipeline (Rohde et al., 2004), as this has been shown to have high correspondence to histological measurements (Yeh et al., 2010).

2.3. Quality control of magnetic resonance imaging scans

Movement artifacts in T1-weighted MRI scans are common, especially in pediatric populations in this age range, and especially in children with ADHD. Fortunately, FreeSurfer is robust to movement-related artifacts and, except in extreme cases, is able to accurately identify intensity differences between white matter and grey matter inherent in the T1-weighted image. In some cases, however, manual intervention is necessary. In this manual intervention, each individual MRI scan is inspected, and in cases where the program does not adequately identify the appropriate regional boundaries, manual edits are employed. We also visually rated each T1-weighted image on a seven-point scale ranging from “Poor = 1” to “Excellent = 4”, with allowances for half-points (e.g., 3.5). Scans for both groups were generally rated “Very Good” to “Excellent”, with an average of 3.61 for the ADHD group, and 3.54 for the typical control group. There were no significant group differences for the quality of the scans, $t(145.46) = -0.72, p = 0.47$.

2.4. Machine learning approach

2.4.1. Features

Following the strong link between ADHD and executive function observed in prior research, our features constitute parent/teacher ratings of executive function (the Emergent Metacognition Composite score from BRIEF), performance in the three tasks that measure executive function (Flanker task, Dimensional Card Sorting task, HTKS task), and cortical thickness measures in the subregions of the frontal (superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus- pars opercularis, inferior frontal gyrus- pars triangularis, inferior frontal gyrus- pars orbitalis, insula, anterior cingulate, middle-anterior cingulate, middle-posterior cingulate, rectus) and parietal (superior parietal lobule, intraparietal and transverse parietal sulci, angular gyrus, supramarginal gyrus, and precuneus) cortices in both hemispheres (see Supplementary

Figs. 1–3). In addition to these target cortical thickness measures, we further conducted exploratory follow-up analyses on cortical volume in these regions (Supplementary Fig. 3), as well as subcortical volume in the cerebellum, caudate, putamen, hippocampus and the amygdala (Supplementary Fig. 4). Finally, we also evaluated two demographic features, namely age and child sex.

2.4.2. Model construction and assessment

We employed the *scikit-learn* (<https://scikit-learn.org/stable/>) open source machine learning platform for constructing our models. In order to evaluate feature importance from classifier coefficients, we adapted a Support Vector Machine classifier with a linear kernel. For model validation, we leveraged the built-in cross-validation function of the *scikit-learn* library. In this approach, the data is split into training and test sets. This is repeated five times, using different portions of the data as training and test. Specifically, in each iteration, the classifier is tested on a portion of the data set that it did not see during training, following the recommended approach in the field (e.g., Varoquaux, 2018; Varoquaux et al., 2017). Performance was then evaluated with the commonly employed accuracy scores, as well as precision, recall, and area under the receiver operator characteristic curve (ROC AUC) metrics. Following the recommended practice in the field, our primary assessment of statistical significance employed permutation tests (Combrisson and Jerbi, 2015; Noirhomme et al., 2014; Pereira et al., 2009). 5000 permutations were employed for each evaluated model. Along with permutation tests, we also report two baseline accuracy levels (see Table 1) as additional benchmark comparisons, namely the baseline for ADHD in our current sample, and the baseline for ADHD in the population. Our dataset consists of 87 participants with ADHD, and 75 typically developing (TD) children. Accordingly, the baseline for the present data set is .537. The population baseline, derived from the pooled worldwide prevalence of ADHD among children (Wolraich et al., 2019) is .072. In addition to Support Machine Vector classifiers, we also report performance metrics from two additional classifiers, namely Naïve Bayes and Random Forest Classifiers (see Supplementary Table 1).

3. Results

Below we assess our target measures and their predictive utility for ADHD classification. Our analytic plan follows a two-step approach to determine model performance and relative predictive utility of our target features: 1) *Feature Elimination*. To this end, we ran multiple models and compared the performance metrics across the models. This approach pursued four categories of models, i) a model including the demographics features (age and sex), ii) a model including the parent/teacher ratings of EF (Emergent Metacognition Composite t-score from BRIEF), iii) a model including the behavioral/cognitive measures of EF (including scores from HTKS, Flanker and Dimensional Card Sorting tasks), and iv) neural models assessing cortical thickness measures in our target regions for EF. 2) *Feature Importance Rankings*. Within each model, we were able to further assess the relative importance of our features for predicting diagnostic category. We utilized the coefficients of our linear SVM classifier as an index for the relative importance across our features

Table 1
Model performance metrics across the four sets of target features.

Models	Performance Metric					Model Evaluation		
	Accuracy	Precision	Recall	F ₁	ROC-AUC	PT	CSB	PPB
1. Demog.	.574	.585	.736	.651	.624	$p < .047$.537	.072
2. P/T Rat.	.926	.940	.919	.929	.982	$p < .001$.537	.072
3. EF Tasks	.667	.709	.644	.674	.738	$p < .001$.537	.072
4. Neural	.612	.640	.646	.641	.624	$p < .016$.537	.072

PT = Permutation Tests.

CSB = Baseline for ADHD in the current study.

PPB = Baseline for prevalence of ADHD in the population.

within each model.

3.1. Predicting ADHD diagnostic category

For each model, a Support Vector Machine classifier with a linear kernel was trained to distinguish the two diagnostic categories (ADHD diagnosis absent, ADHD diagnosis present) using the target features. We scaled our features using the *MinMaxScaler* function built in the *sci-kit* machine learning library. To evaluate the performance of our models, we conducted cross validation across five indices (k-folds). Adapting five-folds follows the recommendation of Varoquaux and colleagues (Varoquaux, 2018; Varoquaux et al., 2017), whose work suggested random splits with 20 % data yield the best cross validation results in machine learning applications in neuroscience research. In machine learning research, performance of classifiers is usually reported as the F₁ score, which is the harmonic mean of precision and recall. For better interpretability, we report performance here in terms of accuracy with respect to the ADHD class, but include F₁ scores in the tables.

To evaluate feature importance rankings, we leveraged the magnitude of classifier coefficients across the target features in the model. Weights obtained from the resultant classifier coefficients of linear SVM classifiers can be utilized to infer feature importance rankings within the assessed model. Thus, the average classifier coefficients across the five cross-validation indices provided an index for the feature importance rankings for each model evaluated. Fig. 1 illustrates the feature importance rankings and classifier performance across the four sets of models, described in more detail below.

3.1.1. Model 1: demographics

The demographics model included two features, child age and sex. Across the five cross-validation indices, this model yielded an average accuracy of .574 ($p < .047$), with child sex yielding classifier coefficients of higher magnitude than age (see Fig. 1). Higher coefficients for child sex presumably arise from the disproportionate sex distribution across the two groups, with boys more represented in the ADHD group (74 %) compared to the TD group (61 %).

3.1.2. Model 2: parent and teacher ratings of executive function

Our second model included the Emergent Metacognition Index t-scores from the BRIEF parent and BRIEF teacher ratings. This model achieved an average accuracy score of .926 ($p < .001$), with the teacher ratings yielding higher classifier coefficients compared to parent ratings (Fig. 1).

3.1.3. Model 3: behavioral/cognitive measures of executive function

Our EF tasks included the DCCS, the Flanker task, and the Head-toes Knees-Shoulder Task (HTKS). This model leveraged the behavioral performance across the three tasks in order to distinguish ADHD diagnostic category. The model achieved an average accuracy score of .667 ($p < .001$), with the HTKS and Flanker tasks yielding classifier coefficients of greater magnitude than the DCCS task.

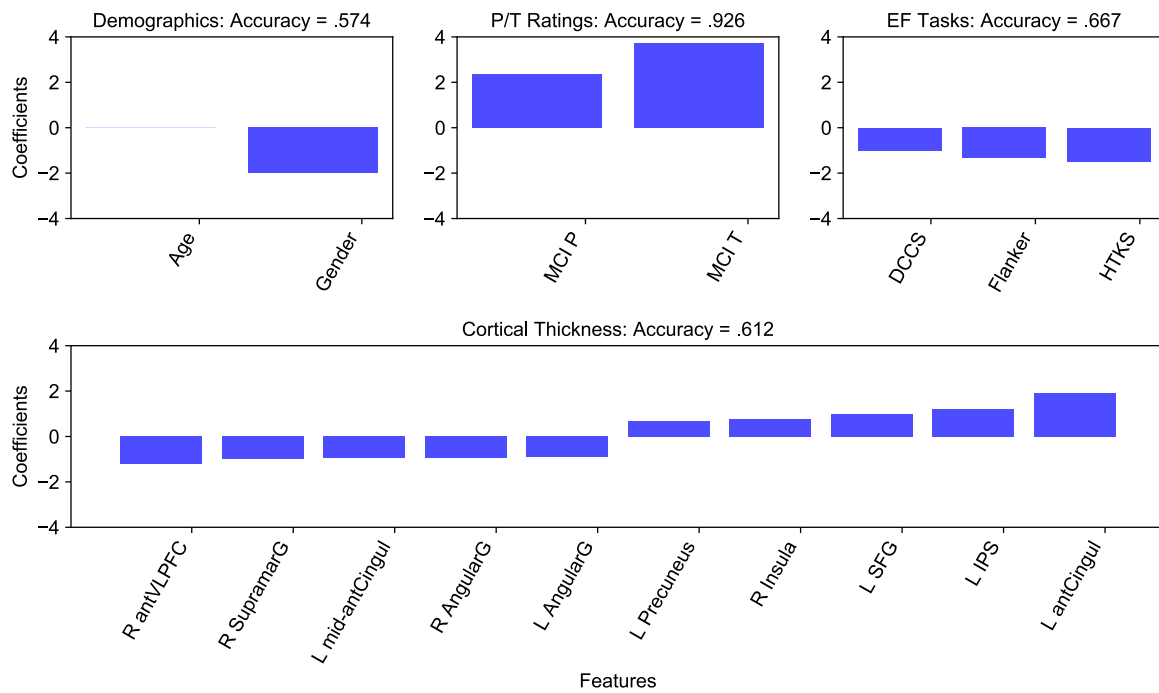


Fig. 1. Accuracy and feature importance rankings from the four sets of models (1-demographics, 2-parent/teacher ratings of EF as measured by the Meta Cognition Index of the BRIEF assessment, 3- EF tasks, Dimensional Card Sorting, Flanker, and Head-Toes-Knees-Shoulders tasks, 4- Neural Measures, namely cortical thickness measures (the top 10 most important regions are shown).

3.1.4. Model 4: neural measures of cortical thickness

Our next set of models explored our neural measures of cortical thickness in target regions that support executive function. We first ran a model including cortical thickness measures in both hemispheres of the brain. Fig. 1 depicts classifier performance (average accuracy .612, $p < .016$), and coefficients for the top 10 features in this model. We next ran two models that contained features from the left and right hemispheres respectively. The model assessing cortical thickness measures from the left hemisphere yielded an average accuracy of .612 ($p < .01$), while the model evaluating cortical thickness measures from the right hemisphere achieved an accuracy of .50 ($p > .64$). Accordingly, our current investigation points to the more pronounced importance of the left hemisphere in predicting diagnostic category. In the left hemisphere, the regions yielding the top three classifier coefficients were the anterior cingulate, the intraparietal and transverse parietal sulci, and the superior frontal gyrus (Fig. 1).

3.1.5. Model 5: full model

Among the four sets of models evaluated, our analyses implicate the BRIEF Emergent Metacognition ratings (with teacher ratings ranking higher than the parent ratings in predicting diagnostic category) to be the most important sets of features. This model achieved .926 accuracy. We next evaluated whether the classifier's performance could be further improved by including additional features from our target measures. This full model included the demographics, the parent/teacher ratings of MCI, cognitive measures of EF, and cortical thickness in the left anterior cingulate, the left intraparietal transverse parietal sulci and the left superior frontal gyrus. Across the five cross-validation indices, this full model achieved an average accuracy of .944 ($p < .001$). Table 1 summarizes the performance metrics across the models.

In summary, our computational modeling approach implicates the Emergent Metacognition scores from the BRIEF assessment to be the most important target measure. More specifically, the teacher ratings were identified to be the most important feature. In our current set of findings, the two BRIEF ratings alone achieved an accuracy of .926. Adding additional features that included demographics, performance in

EF tasks and neural measures of cortical thickness in regions identified to be important in predicting ADHD diagnostic category increased the classifier's performance to .944. Thus, when considering different types of variables (e.g., demographics, parent/teacher ratings of EF, behavioral measures of EF, and neural measures of cortical thickness in regions that support EF) and their relative importance for classification of diagnostic category, our current set of analyses point to the critical importance of teacher ratings of executive function for classification of ADHD diagnostic category.

3.1.5.1. Additional analyses exploring cortical and subcortical volume.

While cortical thickness measures cannot be obtained for subcortical regions, gray matter volume measures allow assessing cortical and subcortical regions conjointly. Accordingly, we ran two separate models to evaluate the performance of gray matter volume in the cortical regions assessed in the above section, and the subcortical regions. The model that included volume in the cortical regions yielded an accuracy of .487 ($p > .663$). The model that included volume in the subcortical regions reached a higher accuracy of .524 ($p > .505$). While both models did not reach statistical significance, the subcortical regions yielding higher performance certainly warrants further investigation into the importance of subcortical neural measures. To further evaluate this possibility, we employed recursive feature elimination (using the built-in RFE function in sci-kit learn library in Python) on the entire set of features including gray matter volume in all cortical and subcortical regions assessed in our study. This feature selection approach allowed us to identify the most informative ten regions for predicting diagnostic category. Importantly, the classifier identified both cortical and subcortical regions including the right mid-VLPFC, the right amygdala, the left precuneus, the right caudate, the left intraparietal and transverse parietal sulci, the left insula, the left cerebellum, the right hippocampus, the right angular gyrus, and the left mid-anterior cingulate. When the classifier was run on the selected regions, it reached an accuracy of .587. Permutation tests indicated this performance to be significantly higher than chance ($p < .031$). The selected regions are consistent with previous research investigating cortical and subcortical volume measures in

this young age range, in implicating the left prefrontal cortex (Jacobson et al., 2018), the caudate (Hoogman et al., 2020; Rosch et al., 2018), as well as the hippocampus and the amygdala (Hoogman et al., 2020).

3.1.6. Controlling for scan quality, cerebellar and intracranial volume

We next ran an additional model assessing the diagnostic utility of scan quality, and overall differences across the two groups on cerebellar and intracranial volume. This model achieved .499 accuracy. Permutation tests further indicated that these variables did not reliably differentiate the two groups above chance ($p > .96$). To further ensure that scan quality is not contributing to the discrimination assessed by our machine learning models, we replicated our analyses excluding 7 participants (3 ADHD, 4 TD) with poorest scan quality (participants whose scans received a scan quality rating of 2). This additional analysis yielded very similar results replicating our original findings with respect to our target features. Specifically, the BRIEF model achieved an accuracy of .935 ($p < .001$), the executive function tasks achieved an accuracy of .652 ($p < .001$), and the cortical thickness model achieved an accuracy of .619 ($p < .011$). Models for cortical (accuracy = .523, $p > .39$) and subcortical volume (accuracy = .516, $p > .71$) remained statistically unreliable. Replicating our results above, the model assessing volume measures containing the selected features yielded higher performance and was significantly more successful than chance (accuracy = .639, $p < .003$). The only change observed was the control model including the demographics variables of child age and sex. This model achieved an average accuracy of .542 and our permutation tests indicated that this performance was not statistically significant in differentiating ADHD from TD participants ($p > .46$).

3.2. High comorbid ODD/CD in the ADHD sample

Recall that our ADHD sample has high (70 %) comorbid ODD/CD. As such, one concern that could potentially limit the implications of our results is that the high prevalence of ODD/CD might have contributed to the differentiation of diagnostic category in our models. Unfortunately, due to the low sample size of participants with only ADHD diagnosis ($n = 26$), it was not methodologically feasible/sound to run our models to distinguish the 3 diagnostic categories (i.e. 1- ADHD diagnosis absent, 2- only ADHD diagnosis present, and 3- ADHD + ODD/CD diagnosis present). To assess the potential impact/change in the performance of our models reported above, we repeated our analyses by excluding the 26 participants with only an ADHD diagnosis. Thus, we trained our classifiers to distinguish ADHD diagnostic category across our typically developing sample and children with ADHD + ODD/CD diagnosis. This set of models yielded similar results [accuracy = .918, $p < .001$ for parent/teacher ratings of EF, accuracy = .711, $p < .001$ for cognitive EF tasks, accuracy = .607, $p < .045$ for the neural measures of cortical thickness], except for the demographics model [accuracy = .511 $p > .85$] which was no longer significant.

We once again acknowledge that the most ideal approach to eliminate this potential confound would be to run models trained to distinguish the three diagnostic categories. Unfortunately, in our current data set, this was not possible due to the low number of participants in the ADHD-only category. Future work utilizing larger samples will be fundamental in thoroughly addressing comorbid ODD/CD within the ADHD sample.

4. Discussion

Given the negative trajectories of early behavior problems associated with ADHD, as well as its high public health cost, early diagnosis of ADHD is critical to enable early intervention and treatment. The current investigation aimed to evaluate the feasibility of predictive modeling using cognitive, behavioral and neurobiological measures of executive function for categorical classification of ADHD in young children. Notably, the current set of findings are the first to employ this approach

in Pre-K children. The AHEAD study is among the first to scan children with ADHD as young as 4–7 years (mean age 5.5 years) with a good sample size ($n > 160$). Given that early diagnosis of ADHD is critical, the current study provides a unique opportunity to assess whether predicting ADHD from scans is feasible in this age range.

Results from our machine learning models indicated that the full model including features from all sets of target features yielded a .944 performance in predicting diagnostic category. Crucially, most of this high performance is accounted by the parent/teacher BRIEF Emergent Metacognition Index scores, which alone achieved a performance of .926. These findings implicate the critical importance of this measure in predicting diagnostic category, and this has implications for clinical diagnosis. Thus, the current set of results suggest that the rating scales are enough to distinguish the presence or absence of ADHD, and that more expensive and extensive behavioral and neural testing might not be necessary. In particular, our models identified the teacher ratings to be most diagnostic in predicting diagnostic category, further suggesting that the functional impairments pertaining to executive function processes experienced in school can be clearly differentiated among children with ADHD from their typically developing peers. A recent study (Dekker et al., 2017) evaluated the relationship between parent/teacher ratings of executive function in BRIEF, executive function performance measures obtained from the Amsterdam Neuropsychological Tasks (ANT) and academic outcome measures. Notably, cognitive performance in the tasks, and teacher ratings of working memory and shifting were predictive of differences in spelling, while parent ratings were not. Our findings are consistent with this recent literature implicating a more important role of teacher ratings for executive function outcomes.

It is important to emphasize that from one perspective, it is not surprising that parent-teacher ratings on one assessment (i.e., BRIEF) are good at predicting diagnostic category that is itself predicated, in part, on parent-teacher ratings on another assessment (e.g., DBD rating scale). Notably, the teacher ratings were the strongest predictor. Thus, for simple categorical diagnosis, collection of additional measures does not provide substantial improvement in the detection of ADHD. This is important because this study addresses some of the critical questions raised by the American Academy of Pediatrics Subcommittee on Children and Adolescents with ADHD. In their recent Clinical Practice Guideline (Wolraich et al., 2019, p. 3) asked 1) what is the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among children younger than 7 years of age?; 2) what is the comparative diagnostic accuracy of EEG, imaging, or executive function approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals aged 7 to their 18th birthday?; 3) are there more formal neuropsychological, imaging, or genetic tests that improve the diagnostic process? (Wolraich et al., 2019). Our results map on to the committee's recommendations for young children in terms of the reliance on parent and teacher ratings scales for aiding clinicians in the diagnosis of ADHD. Thus, while data from our study shows that neurocognitive and imaging measures are not incrementally useful for simply detecting the presence or absence of ADHD, more research is needed to determine their utility as it relates to predicting more functional outcomes (e.g., academic/social impairments) as well as comorbid conditions. Furthermore, the implicated neurobiology might still provide important insight into a better understanding of the heterogeneity of ADHD, and individual variability in treatment response.

In addition to assessing the utility of the target measures in predicting ADHD diagnostic category, the classifier coefficients in our models allowed us to further rank our target features in their relative importance for predicting ADHD diagnostic category. Among the executive functions measured, performance in the HTKS task yielded the highest coefficient in our current investigation, and the Flanker task was identified as more diagnostic than the DCCS. With respect to the neural measures, regions of the left hemisphere were more diagnostic compared to the regions in the right hemisphere of the brain. Among our

target regions important for executive function, the top regions identified were the left anterior cingulate, the left superior frontal gyrus and the left intraparietal and transverse parietal sulci.

Subparts of the cingulate cortex, including the anterior and middle-posterior cingulate cortex have been previously implicated in ADHD research (Rubia, 2018). This region has been previously associated with cognitive and impulse control, and a decreased connectivity between the anterior cingulate and the posterior parietal cortex in ADHD has been observed in prior research [see Vogt (2019) for a review]. Given its implication in executive function and previous ADHD research, it is not surprising that our classifier indicated this region as one of the top predictors among the cortical thickness measures evaluated in our study.

The intraparietal sulcus is a very significant contributor to working memory (Chein et al., 2003; Cowan, 2016; Cowan et al., 2011; Öztekin et al., 2009; Smith and Jonides, 1998; Xu and Chun, 2006), and working memory deficits have been commonly observed in previous ADHD research (Hammer et al., 2015; Karalunas et al., 2017; Palladino and Ferrari, 2013; Raiker et al., 2019, 2012). Notably, this region has been previously implicated for its importance in supporting focus of attention during WM operations in healthy adults (Cowan et al., 2011; Öztekin et al., 2009). Given the widely-established deficits in working memory with ADHD, future research would benefit from a deeper investigation of the specific role of this region in potentially modulating ADHD related effects in working memory function.

The superior frontal gyrus (SFG), located at the superior part of the prefrontal cortex is anteromedially connected to the anterior and mid-cingulate. The dorsolateral portion of the SFG is connected with the dorsolateral and ventrolateral prefrontal cortex, and the posterior portion of the SFG is part of the motor control network (Li et al., 2013). Therefore, it has connections to significant regions that modulate motor, cognitive control and executive function. In addition, it is part of a relatively recently identified fiber pathway, the frontal aslant tract (FAT). Recent work from our group (Dick et al., 2019; Garic et al., 2019) has implicated FAT to be an important potential moderator for ADHD related deficits in executive function. Our modeling results implicate SFG as a potential diagnostic region. Unfortunately, our current parcellation did not allow us to independently evaluate the subregions of SFG. We thus note that future research would benefit from a more focused assessment of this region.

Our study has a primary theoretical focus on executive function, given the importance of EF in ADHD. Accordingly, our analytical approach entailed focusing on regions that have been previously implicated in executive function processes, as opposed to adapting a feature-selection approach. However, it is conceivable that EF related effects might not predominantly emerge in this young age range, and that the early onset of ADHD in this age range might be more associated with subcortical regions (see Halperin and Schulz, 2006). While our primary focus was EF in this study, given the scarceness of literature on the neurobiology of ADHD on very young children, we believe it is important to provide an exploratory evaluation of how performance in the cortical EF regions compares to candidate subcortical regions (e.g., Hoogman et al., 2020) in this young age range. As such, we further conducted exploratory analyses on cortical volume in the target regions, as well as additional subcortical regions including the caudate, the putamen, the cerebellum, the amygdala and the hippocampus regions. In light of these additional exploratory follow-up analysis, we note that future research adapting a more data-driven approach that focuses on the whole brain might provide additional insight into a better understanding of the underlying neurobiology of ADHD in this young age range, and how it might change across development. While computationally more expensive, such approaches might bear the potential to better capture the heterogeneity of ADHD, the underlying trajectory of its neurobiology across development, and in doing so better inform theories of ADHD and cognitive development.

4.1. Directions for future research

The current set of findings were among the first in exploring the utility of predictive modeling for ADHD classification in the young age-range of 4–7 years. Our analyses evaluated structural brain measures. Whether the inclusion of more structural, and diffusion-weighted-imaging (DWI) measures yields better clinical utility is a question for further research to examine. However, to date, no predictive modeling approach has evaluated DWI measures for classification of ADHD. Notably, most computational modeling and machine learning approaches in the existing literature have focused on functional MRI data (most commonly functional connectivity analysis of resting state data). Accordingly, a major criticism has been the issue of transportability (Foster et al., 2014; Woo et al., 2017), and that the findings do not have the potential to generalize to or be easily applied in clinical settings. As such, the inclusion of DWI measures could potentially fill this important gap in the literature. Finally, network-based indicators of structure in addition to brain function might provide additional insight into the classification of ADHD and the heterogeneity of its neurobiology.

Acknowledging that neuroimaging may yield only minimal clinical utility with respect to categorical classification of ADHD, there are still reasons to continue to pursue research within this domain. First, a comprehensive modeling approach should be able to identify which neural measures are more diagnostic, and how they compare to non-neural measures, such as behavioral assessments of theoretically important constructs for ADHD, such as executive function. Second, the ability to derive the most diagnostic neural measures for ADHD classification can facilitate researchers to further investigate the direct link between these regions and the specificity of their functional outcomes are with respect to ADHD-related impacts on the corresponding cognitive constructs. Complementary efforts that utilize and combine predictive modeling approaches with further assessments of the implicated regions/neural measures in how they modulate ADHD-related functional outcomes can facilitate unique ways to define and understand this disorder, and may foster development of novel approaches to the classification and treatment of ADHD. Third, data driven approaches that seek to identify the most important set of neural measures can help clarify the distinct neurobiology of ADHD across development, and provide valuable insight for theories of ADHD and neurodevelopment.

4.2. Conclusion

The AHEAD study is among the first to provide executive function measures for young children with ADHD (ages 4–7) at multiple levels of analysis. Providing a large sample size with complementary measures for both cognitive/behavioral and neural measures of executive function, the AHEAD study enabled the first assessment of the feasibility of predictive modeling and machine learning approaches in diagnosis of ADHD in Pre-K children. Our results suggest the critical importance of teacher ratings of executive function in predicting ADHD diagnostic category. Our models further allowed ranking of the importance of our target behavioral and neural measures of executive function. Among the three executive function tasks evaluated, feature importance rankings implicated performance in the HTKS to be the most diagnostic executive function measure. While teacher ratings of EF are more cost effective and provided a strong prediction of diagnostic status, we once again emphasize the partial measurement overlap in the EF items assessed in the BRIEF questionnaire and those present in the DSM-5 criteria for ADHD. Thus, it will be important for future work to not only focus on the utility of neural, neurocognitive, and behavioral measures of EF as it relates to diagnostic classification, but most importantly how they may predict children's functional impairment in areas such as academic and social functioning.

Data availability statement

MRI imaging, physiologic, and behavioral data associated with the collected samples will be deposited on the NIMH Data Archive (<http://rdc.nimh.nih.gov/>). Additional data documentation and de-identified data will be deposited for sharing along with these data, which includes demographics and diagnosis, consistent with applicable laws and regulations. Submitted MRI data will conform to the Brain Imaging Data Standards (BIDS) structure (<http://bids.neuroimaging.io/>). Publication of data will occur during the project, if appropriate, and at the end of the project, consistent with normal scientific practices. Research data will be made available after the main findings from the final dataset have been accepted for publication. Users will be provided with the data under a data sharing agreement which specifies that 1) the data will be used only for research purposes; 2) data will be stored confidentially and securely, and 3) data will be destroyed after the analyses are complete. We agree to deposit data into NIMH Data Archive repository as soon as possible, but no later than within one year of the completion of the funded project period for the parent award or upon acceptance of the data for publication, or public disclosure of a submitted patent application, whichever is earlier.

We agree that data will be deposited and made available through NIMH Data Archive, and that these data will be shared with investigators working under an institution with a Federal Wide Assurance (FWA) and could be used for secondary study purposes. As we will be using the NIMH Data Archive, this repository has policies and procedures in place that will provide data access to qualified researchers, fully consistent with NIH data sharing policies and applicable laws and regulations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.dcn.2021.100966>.

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