Title: Evidence for Similar Structural Brain Anomalies in Youth and Adult Attention-Deficit/Hyperactivity Disorder: A Machine Learning Analysis

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Abstract:

ADHD affects 5% of children world-wide. Of these, two-thirds continue to have impairing symptoms of ADHD into adulthood. Although a large literature implicates structural brain differences in the pathophysiology of the disorder, it is not clear if adults with ADHD have similar neuroanatomical impairments as those seen in children with recent reports from the large ENIGMA-ADHD consortium finding structural abnormalities for children but not for adults. This paper uses deep learning neural network classification models to determine if there are neuroanatomical changes in the brains of children with ADHD that are also observed for adult ADHD, and vice versa. We found that structural MRI data can significantly separate ADHD from control participants for both children and adults. Consistent with the prior reports from ENIGMA-ADHD, prediction performance and effect sizes were better for the child than the adult samples. The model trained on adult samples significantly predicted ADHD in the child sample, suggesting that our model learned anatomical features that common to ADHD in childhood and adulthood. These results support the continuity of ADHD's pathophysiology from childhood to adulthood. In addition, our work demonstrates a novel use of neural network classification models to test hypotheses about developmental continuity.

Introduction

ADHD is a common disorder affecting 5% of children and 3% of adults [1]. It is associated with injuries [2], traffic accidents [3], increased health care utilization [4, 5], substance abuse [6, 7], criminality [8], unemployment [9], divorce [10], suicide [11, 12], AIDS risk behaviours [13] and premature mortality [14]. The cost of adult ADHD to society is between $77.5 and $115.9 billion each year [15].

After decades of work documenting ADHD's high heritability (76%) [16], we now know from a genome wide association study (GWAS) of over 50,000 samples that the common DNA variants associated with ADHD's significant polygenic risk are highly enriched for genes expressed in brain [17] and that many of these genes are expressed in pathways crucial for neurodevelopment [18]. A role for brain dysfunction in the aetiology of ADHD was suspected for some time by the mechanism of action of the medications that treat ADHD [19].

Because many structural magnetic resonance imaging (sMRI) studies had been published with conflicting results, the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) ADHD Working Group create a large collaborative data set with sufficient power to detect small effects. The ENIGMA-ADHD working group found small, statistically significant sub-cortical volumetric reductions [20], cortical thinning and reduced surface area [21] to be associated with ADHD in children but not adults. Using data from the Allen Brain Atlas, Hess et al. [22, 23] subsequently compared gene expression profiles between brain regions that were and were not implicated in the ENIGMA-ADHD subcortical analyses. Gene expression profiles for three pathways were significantly correlated with ADHD-associated volumetric reductions: apoptosis, oxidative stress, and autophagy. These results suggest that variability of structural brain anomalies in ADHD might be explained, in part, by the differential vulnerability of these regions to mechanisms mediating apoptosis, oxidative stress, and autophagy. Hess et al.'s findings also provide some validation of the ENIGMA-ADHD findings.

An intriguing finding from the ENIGMA-ADHD results was that all significant findings were for childhood ADHD. They found no significant findings for adult ADHD. We use the term childhood ADHD to refer to ADHD ascertained in childhood, understanding from our meta-analysis that two-thirds will persist into young adulthood and that persistence continues to decline with age [1]. We use the term adult ADHD to refer to childhood onset ADHD that has persisted into adulthood, which is how it is defined in DSM 5 and in the ENIGMA-ADHD sub-studies. The ENIGMA-ADHD results are partly consistent with longitudinal studies show decreases in ADHD vs. control differences in regional volumes and cortical thicknesses [24-26]. Those ADHD participants whose brains become more neurotypical were more likely than others to show remission of symptoms [27, 28]. But, although these longitudinal studies show reductions in case vs control differences, they also suggest that those difference should be evident to some degree in cases that persist into adulthood.

Although the expectation of finding substantial continuity between childhood and adult ADHD has been widely accepted [29-31] and recently confirmed by a large GWAS [32], this idea has been challenged [33]. Thus, given these prior data and the controversy about the continuity of ADHD into adulthood, we sought to test the idea that the ADHD-associated volumetric reductions seen in children with ADHD would be detected in adults with ADHD by applying machine learning algorithms. Given that symptoms and impairments persist into adulthood for most children with ADHD [1, 34], we hypothesized that ADHD-related brain structure differences in adults would be consistent with those observed in children.

Materials and Methods

MRI Samples

The current study was approved by all contributing members of the ENIGMA-ADHD Working Group, which provided T1-weighted structural MRI (sMRI) data from 4,183 subjects from 35 participating sites (by Aug 2019). Each participating site had approval from its local ethics committee to perform the study and to share de-identified, anonymized individual data. Images were processed using the consortium's standard segmentation algorithms in FreeSurfer (V5.1 and V5.3) [20]. 151 variables were used including 34 cortical surface area, 34 cortical thickness measurements and 7 subcortical regions from each hemisphere, and intracranial volume (ICV). Subjects missing more than 50% of variables were removed. Remaining missing values and outliers (outside of 1.5 times the interquartile range (iqr 1.5)) were replaced with imputed values

using multiple imputation with chained equations in STATA15. The final ML dataset consisted 4,042 subjects from 35 sites, among which 45.8% were non-ADHD controls (n=1,850, male to female ratio (m/f) = 1.42) and 54.2% ADHD participants (n=2,192, m/f=2.79). Ages ranged from four to 63 years old; 60.7% were children (age<18 years, n=2,454) and 39.3% were adults (age≥18 years, n= 1,588). ADHD diagnosis was significantly biased by sex ($X^2_{(1)}$ = 66.9, p<.0001), sites ($X^2_{(1)}$ = 146.73, p<.0001), age ($X^2_{(1)}$ =4.28, p=0.04).

To balance the confounding factors, we took the following steps. First, we randomly assigned samples to training (~70%), validation (~15%), and test (~15%) subsets within each diagnosis, sex, age subgroup (child vs adult) and site to ensure that the train/validation/test subsets have the same composition of these variables. 12 sites that provided only cases or only controls (total 203 subjects) were excluded during the initial train/validation/test split because their samples cannot provide an unbiased learning during the training and validation steps. These samples were added to the test set for final test evaluation. Supplementary Table 1 shows the sample splitting from each site. Next, we balanced the training set for the case and control groups within each sex, age and site subgroup by random oversampling of the under-represented diagnostic group, a procedure commonly used to deal with class imbalance. The resulting balanced training set is described in Table 1. The validation and test sets were not balanced by age, sex and site, however due to our sample splitting procedures, they contain the same demographic samples as the training set. In addition, the test set also contains samples from sites that had been excluded from the training set due to not having a site-specific control group.

Feature preprocessing

Principal factors factor analysis (PFFA) with varimax rotation on sMRI features on the training set identified 46 factors that explained >90% of the variance. Factor scores were computed for all subjects based on the training set PFFA. All input features were scaled based on the training set's minimum and maximum values.

Neural Network Framework

We implemented multilayer perceptron (MLP) neural network models using the Keras API (version 2.3.1) and the TensorFlow library (version 1.14.0). We used HyperOpt [35] to search the neural network hyperparameter spaces including numbers of layers, numbers of units and dropout rates in each layer, learning rate and batch normalization size. We also tested different activation functions and optimizers. We used binary cross entropy as the loss function. Early stopping was implemented to avoid overfitting. Best model architecture and hyperparameters were chosen based on the lowest total validation loss. Final test scores were obtained on the test set with ensemble learning approach [36]. All machine learning algorithms were written in Python 3.5.

Analysis Pipeline

Our analysis pipeline starts with two base models that used data from the corresponding age groups during the model training and validation phase and tested also on data from their corresponding age groups. The child model used only child samples during model training, validation and hyperparameter optimization, and tested on child test set. The adult model, similarly, was trained and validated on the adult samples and tested on the adult test set. We examined models using MRI features only, as well as those included age and sex information.

Next, we tested if the model trained and validated on the adult samples, the adult model, could be used to predict child ADHD, and vice versa. We hypothesized that if the ADHD vs. control sMRI differences seen in children are also present in adult ADHD brains, then the base models for each age group should be able to predict ADHD in the other age group. To create the largest test sets possible, we tested the child model on all the adult samples, and the adult model on all the child samples.

Model evaluation

The sigmoid function in the output layer of the neural network generates a continuous score that assesses the probability for each individual to be classified as ADHD. We name this continuous output the brain risk score.

Using the brain risk scores, we calculated Cohen's *d* effect sizes for child and adult test sets. We computed receiver operating characteristic (ROC) curves and used the area under the ROC curve (AUC) as our primary measure of accuracy. The AUC and its confidence intervals were calculated in Stata 15 using the empirical method and compared with nonparametric approach by DeLong et al. [37]. We also computed precision-recall (PR) curves and reported the area under the PR curves, as well as the Brier loss for the final models as measures of accuracy and goodness of fit.

Results

Figure 1A Top portion shows the test set AUCs (as dots) and their 95% confidence intervals (as horizontal lines) for the base models using only MRI factors. The model trained and validated on child data predicted child ADHD with a significant AUC 0.64 (95%CI 0.58-0.70). In contrast, the model trained and validated on adult data resulted in a marginally significant AUC (0.56, 95%CI 0.49- 0.62, p= 0.057). The difference between the two base models' AUCs was also marginally significant ($X^2_{(1)}$ = 3.4, p= 0.065). The areas under the precision-recall curve (AUPRC) were higher for the adult model (AUPRC = 0.74) than the child model (AUPRC= 0.68). Using the model predicted brain risk scores, we calculated the Cohen's *d* effect sizes in the test set to be 0.47 for child samples (95%CI: 0.27 - 0.68) and 0.15 (-0.08 - 0.39) for the adult samples.

After adding age and sex as predictors, the adult model (Figure 1B Top) increased the AUC to 0.62 (95%CI 0.56 - 0.69). The AUPRC for the adult model also slightly increased (to 0.79. Adding age and sex as predictors to the child model did not affect either the AUC, nor the AUPRC. The Cohen's *d* effect sizes in the test set were 0.48 for children (95%CI: 0.27-0.69) and 0.39 (0.15-0.63) adults. All above models had similarly small Brier scores (0.25).

It is worth noting that, because the training samples had been balanced for age and sex, these variables are not predictive of ADHD for either the child and adult test sets. To verify this, linear regression using only age and sex and their interactions to predict ADHD in the child and adult samples resulted in non-significant AUCs (child AUC 0.51, 95%CI: 0.45-0.57; adult AUC 0.46, 95%CI: 0.39-0.53).

Tests of Hypotheses

For models using only MRI features, neither the adult, nor child models were successful at predicting ADHD in the other age group (Figure 1A Bottom). However, the adult model that used both MRI features and age and sex was able to predict the child samples significantly (AUC = 0.60, 95%CI: 0.58-0.62, Figure 1B Bottom). In contrast, the child model did not significantly predict ADHD when applied to the adult samples (AUC = 0.52, 95%CI: 0.49, 0.55, Figure 1B Bottom).

Discussion

Consistent with previous ENIGMA ADHD findings [20, 38], we found that the ability of structural MRI data to discriminate people with and without ADHD is much stronger for children than adults, which is consistent with a broader literature showing that ADHD-associated structural brain differences diminish with age [24-28]. While the ENIGMA ADHD study did not find any significant differences between ADHD and control subjects for adults, our adult model did achieve a significant AUC 0.62 (95%CI 0.56-0.69) and a high area under the PR curve (AUPRC=0.79). Consistent with the ENIGMA findings, our model-predicted brain risk scores had a larger effect size for the children than adults in both the models using MRI features and those with age and sex added. Notably, our effect sizes were two times greater than the largest of those individual regions reported in prior ENIGMA ADHD studies for both children (Cohen's *d* = -0.21) and adults (Cohen's *d* =-.16)[20, 38].

Although the results from the child and adult base models indicate that sMRI data are not sufficiently predictive to be useful in clinical practice, they provide three crucial pieces of evidence that will be useful in future attempts at predictive modeling. First, our results are the first to confirm in the largest possible adult ADHD MRI sample available, that adults with ADHD differ significantly from adults without ADHD on sMRI features.

Second, the improvements we found by adding age and sex to the adult model indicate that these demographic variables must moderate the predictive ability of sMRI features. We believe that these demographics moderate the sMRI effects because our regression models show that the demographic variables on their own have no predictive utility (which was fixed in advance by balancing the case and control training samples by age and sex). Third, we have shown that machine learning methods dramatically increase the ADHD vs. Control effect size compared with the univariate ENIGMA analyses.

The results from our hypothesis testing provide further information that is useful in understanding the continuity of child and adult ADHD. Consistent with our hypothesis, the adult model, trained only on adult samples, significantly predicted ADHD in the child samples. This suggests that the adult model was able to learn combinations of structural features that are relevant for discriminating the structural MRI scans from children with and without ADHD. This implies that some of ADHD's sMRI pathophysiology that is relevant for persistent cases is also relevant in childhood (only some of which will be persistent into adulthood). This conclusion must, however, be considered equivocal because the child model did not successfully predict ADHD in the adult samples. To resolve this issue, future studies will need to find a way to better discriminate sMRI features associated with the onset of ADHD and those associated with the persistence of ADHD.

Our work should be interpreted in the context of several limitations. First, because we combined data across many sites, we inherit all the limitations of the original studies. Heterogeneity of methods across studies may have added noise to the combined data set that made it difficult to discriminate the data from people with and without ADHD. Second, we only used structural imaging data. Incorporating other imaging modalities might provide clearer results and conclusions. Third, we used pre-defined structures from ENIGMA standard image processing pipeline as features. It is possible that other methods such as one using 3D images as input features, in a convolutional neural network would uncover useful features leading to increased classification accuracy. However, the 3D images are not available. Finally, our use of neural networks makes it difficult to clarify the importance of each brain region in the model's algorithm.

Despite these limitations, we have shown that a neural network approach is able to detect case-control sMIR differences in adults with ADHD that could not be detected with standard analyses. We have also provided some evidence for the continuity of sMRI findings from childhood into adulthood.

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List of Tables:

Table 1. Training set sample characteristics after balancing for age and sex
Supplementary Table 1. Sample subsets from each site.

Figure Legends

Figure 1 Area Under the Receiver Operating Characteristic Curve for the Test Results. Area under the receiver operating characteristic curve (AUC) accuracy statistics for the held-out test results were plotted (as dots) with their 95% confidence intervals (as horizontal lines). The vertical line at an AUC of 0.5 indicates a chance level of diagnostic accuracy. If the 95%CI does not overlap with the 0.5 vertical line, it indicates significant predictive accuracy.

A. AUC comparison of the models using only MRI features. **B.** AUC comparison of the models using MRI features plus age and sex. In both **A** and **B**, **Top** portion shows the base models, where models were trained and validated in child or adult samples and tested on their corresponding age groups; **Bottom** portion tests the hypotheses that if model trained/validated on child samples can also predict adult ADHD and vice versa. Note that test sample consists of combined training, validation and test sets from the other age group because they are not used in the model optimization and training.

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Tables

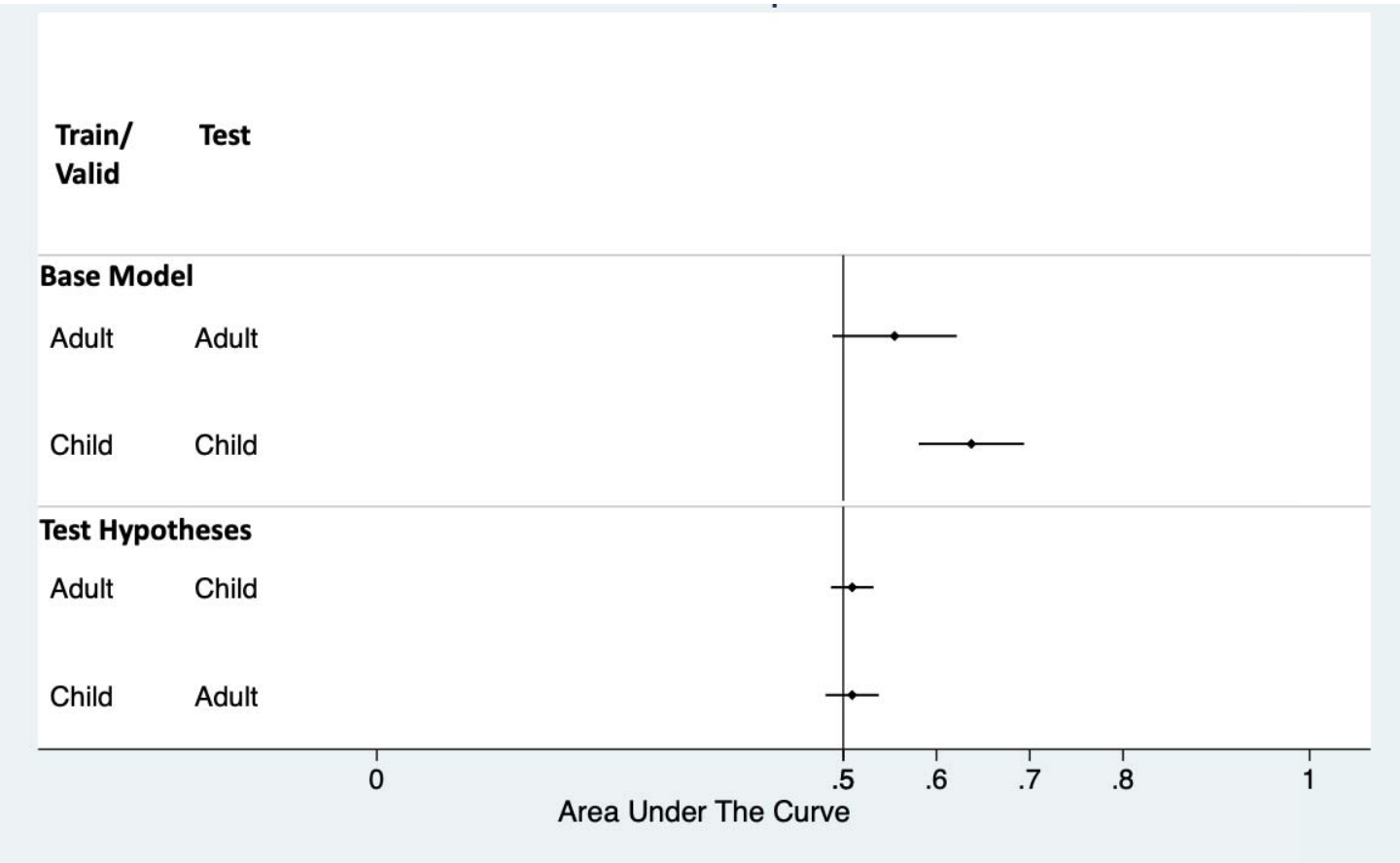
Table 1. Training set sample characteristics after balancing for age and sex

Diagnosis		Child (Age <18)		Adult (Age ≥18)	
		Female	Male	Female	Male
Control	N of Subjects	352	714	224	373
	Mean Age	11.3	11.6	31.9	28.1
	SD of Age	2.9	2.9	11.5	9.4
ADHD	N of Subjects	352	714	224	373
	Mean Age	11.0	11.8	32.2	28.8
	SD of Age	2.6	2.7	10.6	9.4

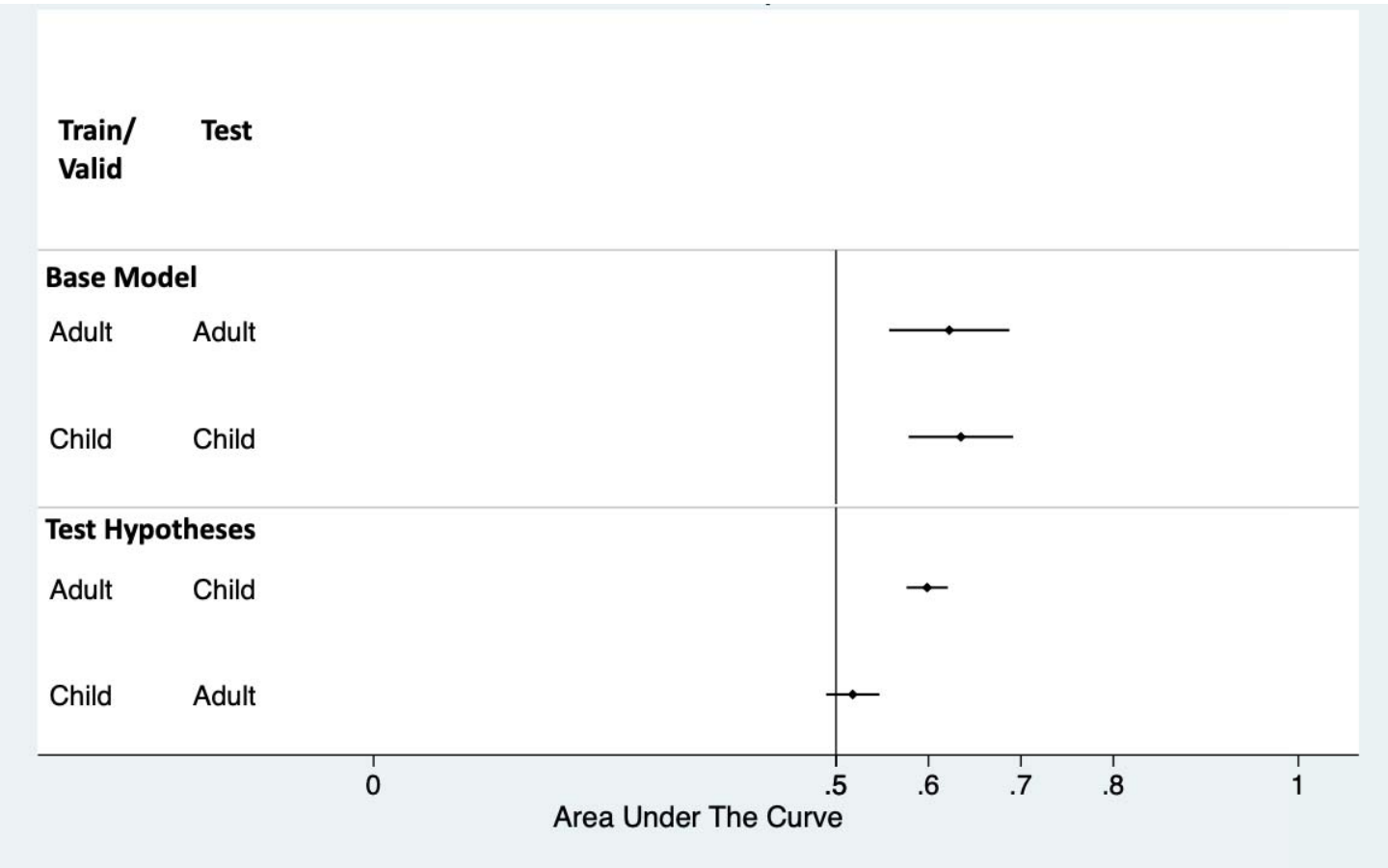
*Note: SD, standard deviation; N, total numbers.

Figure 1. Area Under the Receiver Operating Characteristic Curve for the Test Results

A. MRI Features Only



B. MRI Features plus Age and Sex



Supplementary Table 1. Total sample and train/validation/test splits from each site					
Sites	**Training**	**Validation**	**Test**	**Excluded**	**Total**
ACPU	46	11	9	1	67
ADHD_WUE	75	18	14	0	107
ADHD-DUB1	56	14	10	0	80
ADHD-DUB2	0	0	0	20	20
ADHD-Mattos	0	0	0	31	31
ADHD200_KKI	61	14	10	0	85
ADHD200_NYU	158	36	31	3	228
ADHD200_OHSU	61	16	12	0	89
ADHD200_Peking	139	31	27	0	197
ADHDKonrad	100	24	20	1	145
ADHD_Rubia1	45	11	9	6	71
ADHD_Russia	0	0	0	10	10
Barcelona	51	12	10	0	73
Bergen_SVG	35	10	6	0	51
Bergen_adultADHD	55	15	11	0	81
CAPS_UZH	41	9	5	0	55
DAT_london	38	11	7	0	56
Dundee	32	8	4	1	45
EPOD	0	0	0	92	92
Hartford_Olin	125	31	25	0	181
IMpACT_NL	188	42	38	0	268
MGH_ADHD	100	24	20	0	144
MTA	91	21	17	0	129
NICAP	102	24	20	0	146
NIH	282	63	59	9	413
NYU_ADHD	56	14	10	0	80
NeuroImage_ADAM	118	29	21	0	168
NeuroImage_NIJM	120	30	22	0	172
OHSU2018	161	36	32	0	229
SAOPAULO	92	22	18	1	133
Sussex	40	11	7	0	58
Tuebingen	0	0	0	28	28
UAB-ADHD	138	34	26	0	198
UCHZ	54	16	8	0	78
ZI-CAPS	24	7	3	0	34
Total	2,684	644	511	203	4,042