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Functional EEG connectivity is a neuromarker for adult attention deficit hyperactivity disorder symptoms

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HIGHLIGHTS

- EEG functional connectivity predicted attention deficit hyperactivity disorder (ADHD) symptoms in adults.
- EEG functional connectivity may be a neuromarker for adult ADHD.
- EEG connectivity did not reliably distinguish between ADHD, 1st degree relative and control groups.

ABSTRACT

Objective: Altered brain functional connectivity has been shown in youth with attention-deficit/hyperactivity disorder (ADHD). However, relatively little is known about functional connectivity in adult ADHD, and how it is linked with the heritability of ADHD.
Methods: We measured eyes-open and eyes-closed resting electroencephalography (EEG) from 38 adults with ADHD, 45 1st degree relatives of people with ADHD and 51 healthy controls. Functional connectivity among all scalp channels was calculated using a weighted phase lag index for delta, theta, alpha, beta and gamma frequency bands. A machine learning analysis using penalized linear regression was used to identify if connectivity features (10,080 connectivity pairs) could predict ADHD symptoms. Furthermore, we examined if EEG connectivity could accurately classify participants into ADHD, 1st degree relatives and/or control groups.
Results: Hyperactive symptoms were best predicted by eyes-open EEG connectivity in delta, beta and gamma bands. Inattentive symptoms were predicted by eyes-open EEG connectivity in delta, alpha and gamma bands, and eyes-closed EEG connectivity in delta and gamma bands. EEG connectivity features did not reliably classify participants into groups.
Conclusions: EEG connectivity may represent a neuromarker for ADHD symptoms.
Significance: EEG connectivity may help elucidate the neural basis of adult ADHD symptoms.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) affects 0.6–7.3% of adults worldwide and is highly heritable (Faraone et al., 2005; Larsson et al., 2014; Fayyad et al., 2017). ADHD is regarded as a neurodevelopmental disorder starting in childhood, although symptoms that continue into adulthood for the majority of individuals (Kessler et al., 2010; Kooij et al., 2010; American Psychiatric Association, 2013), and is characterized by symptoms such as hyperactivity, impulsivity, inattention or their combination. When compared to childhood ADHD, relatively little is known about the neurobiology of adult ADHD, particularly with respect

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to the organization of relevant brain networks. One way to elucidate the nature of these networks is to examine functional connectivity – statistical dependencies among brain areas – while the person is not engaged in any particular task (i.e., resting state). This functional connectivity can be measured with excellent temporal resolution, and in a range of frequency bands, using electroencephalography (EEG). EEG functional connectivity studies in childhood and adolescent ADHD have generally shown that children with ADHD have hyper-synchronized EEG compared to that of healthy controls (González et al., 2015).

There is a growing appreciation that ADHD may represent the extreme end of a continuum of symptoms (Casey et al., 2014), and furthermore that a focus on symptoms may be particularly useful for characterizing brain-behavior relationships. For example, there is some evidence for an association between EEG functional connectivity and the severity of ADHD symptoms. In children with ADHD, reduced frontal alpha coherence (Barry et al., 2011) was correlated with increased hyperactivity symptoms, and a more centralized alpha and beta band network topology associated with poorer attention symptoms (Janssen et al., 2017). Only one previous study examined adult ADHD (9 ADHD vs. 15 control participants; Barttfeld et al., 2014) and reported increased fronto-occipital functional connectivity in delta band in ADHD, which was associated with higher levels of hyperactivity, impulsivity and depressive symptoms.

Biological parents and siblings of individuals with ADHD are 2–8 times more likely to also display behavioral symptoms of ADHD relative to controls (Faraone et al., 2005; Larsson et al., 2014). Twin and family studies show that the heritability of self-rated ADHD symptoms is 30–40% in adults, but siblings and parents do not often present with symptoms at clinical levels (Brikell et al., 2015). Nevertheless, it is unclear if shared symptoms result from a common environment or the heritability of underlying neurobiological mechanisms. Insight might come from *mediational endophenotype research* that aims to identify neurobiological processes that mediate the relationship between genes and behavior (Hutchinson et al., 2013; Tye et al., 2014). Mediational endophenotypes are defined as subclinical quantitative markers of gene expression that are associated with the disorder, represent a trait and are found in unaffected relatives who carry the gene but do not manifest disease symptoms at clinical level (Kendler and Neale, 2010; Hutchinson et al., 2013). Electrophysiological measures are well-suited for mediational endophenotype research because these measures are highly heritable and associated with specific genetic variants (e.g., theta power heritability estimate of 0.77 (Castellanos and Tannock, 2002; Tye et al., 2011; McLoughlin et al., 2014). To the best of our knowledge, no study to date has investigated EEG resting state connectivity as a potential endophenotype for adult ADHD.

EEG connectivity is difficult to measure accurately. Previous studies of EEG connectivity in ADHD often calculated linear correlations between separate signals recorded on the scalp (González et al., 2015). Such approaches, however, are insensitive to non-linear correlations, are susceptible to volume conduction and conflate phase and amplitude correlations (Vinck et al., 2011). Volume conduction distributes the signal from one neural source across two or more EEG electrodes thus leading to spurious correlations (van Diessen et al., 2015). In addition, the effect of volume conduction occurs when there is zero-phase difference (or lag) between two signals (i.e., when there is no delay between signals). An advanced measure of connectivity that diminishes this effect is the *weighted phase lag index* (WPLI, Vinck et al., 2011). WPLI measures the phase difference between two signals; and attenuates the effect of volume conduction by weighting the phase differences close to the zero-phase lag with a lower value than other non-zero-phase lags. Thus, WPLI accurately and reliably quantifies how pairs of different scalp regions are functionally connected (Vinck et al., 2011; van Diessen et al., 2015). In addition, because WPLI is based on phase differences – and not on signal amplitude – it is insensitive to the disease specific spectral changes in amplitude that have been documented in ADHD (Snyder and Hall, 2006; Loo and Makeig, 2012), and which can confound connectivity estimates (van Diessen et al., 2015).

Machine learning is a powerful method for interrogating how highly complex scalp data (e.g., thousands of pair-wise connections across several power bands) may influence behavioral symptoms. With respect to ADHD and EEG, machine learning has primarily been used with EEG spectral power to create classification models that distinguish children with ADHD from neurotypical controls (Pulini et al., 2018), although few classification studies have used EEG connectivity patterns to this end (Ahmadlou and Adeli, 2010, 2011; Pereda et al., 2018). Ahmadlou and colleagues (Ahmadlou and Adeli, 2010, 2011) reported classification accuracies of 87.5% and 95.6% for a synchronization pattern in posterior-frontal connections in theta band and in temporal-frontal connection in delta band. Another study (Pereda et al., 2018) found approximately 95% classification accuracy for a functional connectivity pattern with 280 features. Previous studies used connectivity measures sensitive to volume conduction (i.e., synchronization likelihood measures; van Diessen et al., 2015). Furthermore, these studies included relatively small sample sizes (N = 24–54), which can lead to more variable accuracy estimates.

Machine learning in ADHD has also been biased by circular analyses (e.g., all data were included during feature-selection prior to model creation), and lack of out-of-sample validation. These methodological steps can lead to 'overfitting'; that is, the fit of the model is largely influenced by idiosyncrasies in data resulting in a model that does not generalize to new datasets (see Pulini et al., 2018, for a discussion of this issue with specific reference to ADHD). Overfitting is an issue relevant to EEG as the number of input variables often exceed the number of participants; for example, 64 EEG channels at delta, theta, alpha, beta and gamma frequency bands yields over 10,000 combinations of pairs and frequency bands. This issue can be diminished by applying special methods developed for machine learning with relatively large samples (i.e., penalized regression; Doyle et al., 2015; Gillan and Whelan, 2017; Yarkoni and Westfall, 2017). One such method is the 'Elastic Net' (Zou and Hastie, 2005), which accommodates multi-collinearity (i.e., correlation between independent variables in a regression model) and selects a subset of the most predictive variables (i.e., feature selection). Note that we use the term 'predict' to refer to out-of-sample validation (see Bzdok and Ioannidis, 2019; Rutledge et al., 2019; Yarkoni and Westfall, 2017).

In this study, we sought to identify the EEG connectivity parameters that (1) could predict ADHD symptoms, and (2) best classify adults into ADHD, 1st degree relative and unrelated, healthy control categories. To this end, we combined WPLI (to estimate functional connectivity) with a machine learning approach using penalized regression. As studies have shown the EEG connectivity findings to differ between eyes-open and eyes-closed conditions in children with ADHD (González et al., 2013; Alba et al., 2016), we included both conditions to investigate if either yielded better performance. We used the Elastic Net to interrogate the large amount of data and therefore avoid overfitting. Based on previous research (Ahmadlou and Adeli, 2010, 2011; Barry et al., 2011; Barttfeld et al., 2014; González et al., 2015; Janssen et al., 2017) we hypothesized that increased functional connectivity within frontal and between fronto-posterior electrodes would be best predictors for elevated ADHD symptoms, and that elevated functional connectivity in delta and theta band would be the best predictors for ADHD status.

2. Materials and methods

2.1. Participants

Thirty-eight people with an ADHD diagnosis, 45 1st degree relatives of people with ADHD (18 siblings, 27 parents) and 51 healthy controls were recruited from the general population, support groups and a secondary mental health care service (see Table 1 and Supplementary Method for participant information). Recruitment of ADHD/1st degree relative dyads was challenging and therefore we also recruited people with ADHD and 1st degree relatives of those with ADHD separately; our data contains 3 dyads. Participants received €40 euro plus any travel expenses. Ethical approval was obtained from the School of Psychology Research Ethics Committee of Trinity College Dublin, the Human Research Ethics Committee of University College Dublin and the Research Ethics Committee of St. Patrick's Mental Health Services, and the research was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all participants both in person prior to the testing session and online prior to completing the survey.

2.2. Procedure

Resting-state EEG was collected as part of a larger study on ADHD. Prior to in-laboratory data collection, participants completed a battery of online surveys, including demographic details and the Conners' Adult ADHD Rating Scale (CAARS, Conners et al., 1999). The CAARS has two types of summary scores: scores relating to four CAARS factor scores (i.e., Hyperactivity/Restlessness, Impulsiveness/Emotionality, Inattention/Memory and Self-concept), and two subscales measuring hyperactivity/impulsivity and inattention symptoms as outlined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM; American Psychiatric Association, 2000). These measures are highly correlated (Supplementary Table S1). We focused here on the CAARS factor scores but have repeated all analyses with the DSM scores in Supplementary Information (see Supplementary Fig. S2 and Supplementary Tables S7–S11). For ease of expression we hereafter refer to the CAARS factor scores simply as 'ADHD symptoms'. Participants taking methylphenidate (n = 14) or lisdexamfetamine (n = 3) abstained from medication for 36 hrs prior to EEG data collection. On the day of data collection, participants were screened for co-morbidities using a shortened version of the Structural Clinical Interview DSM-IV (SCID; including subsections screening for psychosis, mood disorders, dysthymia, bipolar disorder, suicidality, eating disorders and substance abuse). The measurement time in the day varied across participants. Full recruitment criteria and screening methods are described in Supplementary Method.

Participants were seated in a quiet, darkened room for the EEG testing that included a 3-minute eyes-open and 3-minute eyes-closed resting-state EEG. EEG data were recorded using the ActiveTwoBiosemi™ system from 70 electrodes (64 scalp electrodes, www.biosemi.com), organized according to the 10–5 system (Oostenveld and Praamstra, 2001) with a sampling rate of 512 Hz. The vertical and horizontal electro-oculograms were recorded bilaterally from approximately 2 cm below the eye and from the outer canthi, respectively. Two electrodes were placed on the mastoids. Participants were seated 1.05 m from a cathode ray tube computer monitor with screen resolution of 1024 × 768 pixels and at a refresh rate of 75 Hz. During the eyes-open condition, the participant was instructed to look at a cross in the middle of the computer screen for three minutes. In the eyes-closed condition, the participant was instructed to close their eyes and wait for the experimenter to tell them three minutes had passed.

2.3. Data analysis

2.3.1. EEG data pre-processing

We employed the same methods for EEG data pre-processing as reported in Kiiski et al. (2018, p. 6): "EEG data pre-processing employed the EEGLAB toolbox (Delorme and Makeig, 2004); http://sccn.ucsd.edu/eeglab) in conjunction with the FASTER plug-in (Fully Automated Statistical Thresholding for EEG artifact Rejection; Nolan et al., 2010), http://sourceforge.net/projects/faster). EEG data were bandpass filtered between 1 and 95 Hz, notch frequencies were set to 48–52 Hz. FASTER (Nolan et al., 2010) automatically identified artefactual (i.e., non-neural) independent components and removed them from the EEG data. The FASTER toolbox also removed epochs with large artefacts (e.g., muscle twitch) and interpolated channels with poor signal quality. Visual inspection of the EEG data was then performed in order to ensure that the data was of good quality and noisy data due to bad electrode contact and/or excessive motor activity was removed if necessary. All pre-processing parameters for FASTER for this study are included in the Supplementary Material (Supplementary material_FASTER processing.mat)". On average, 98% of the data length during eyes-closed was kept after the visual quality check (standard deviation-SD: 2.83%). During eyes-open, 97.32% (SD = 3.7%) was kept (see Supplementary Table S2 for group differences). EEG data were average referenced across all scalp electrodes (appropriate when using a high-density EEG array). The EEG data were then epoched into 5-s segments. Participants with fewer than 20 epochs, corresponding to less than 55.5% of the whole individual's data, were excluded from further analyses: 5 from the ADHD group, 1 from the 1st degree relative group, and 1 from the controls group during eyes-open condition; and 2 from the ADHD group, and 1 from the 1st degree relative group during eyes-closed condition. This resulted in 32 ADHD subjects, 44 1st degree relatives, and 48 controls to be included the eyes-open analysis, as well as in 35 ADHD, 45 1st degree relative and 51 control participants that were included in the eyes-closed analysis. With this sub-sample, the average number of epochs during eyes-closed condition in the ADHD group was 33.15 (SD = 3.55), 33.05 (SD = 2.95) in the 1st degree relative group, and 34.50 (SD = 2.17) in the control group. During eyes-open condition, the average number of epochs in the ADHD group was 32.19 (SD = 4.56), 32.02 in the 1st degree relative group (SD = 3.28), and 33.06 in the control group (SD = 3.71) (see Supplementary Table S2 for group statistics).

2.3.2. Connectivity analysis

EEG data were filtered in the delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (15–30 Hz), and gamma (30–45 Hz) bands using a Butterworth filter. The weighted phase lag index (WPLI) between all possible pairs from 64 channels was calculated (2,016 pairs). The WPLI measures the lead/lag (i.e., positive/negative) phase difference between two signals and weights the phase differences close to the zero-phase lag with a lower value to diminish the contribution of volume conduction (Vinck et al., 2011). The WPLI per frequency band was calculated per epoch and averaged across epochs.

We used penalized regression, in the form of the Elastic Net (Zou and Hastie, 2005). The Elastic Net performs well on neural data, relative to other types of machine, for a range of effect sizes and sample size (see Jollans et al., 2019), and has been utilized in recent EEG studies (Kiiski et al., 2018; O'Halloran et al., 2019; Rueda-Delgado et al., 2019). This approach was used to (1) fit linear regression models to the EEG connectivity data to predict ADHD symptoms, and (2) fit logistic regression models to the EEG connectivity data to classify participants into ADHD, 1st degree relative and/or control groups. We arranged the data into

Table 1
The full demographic details and the ADHD symptom profile of the participants.

	A [a]	*R*	*C*		
	N / %			*Omnibus test*	*Posthoc*[x]
Total N	38	45	51		
Sex (% male)	50	22.2	43.1	$\chi^2(2) = 7.64^*$	
Ethnicity (% Caucasians)	94.7	95.6	88.2	$\chi^2(2) = 2.23$ *ns.*	
	Mean (SD)				
Age (years)	27.1 (10.4)	38.0 (14.2)	29.9 (11.6)	$F(2,133) = 9.25^‡$	R > A & C
Education (years) [b]	16.8 (4.2)	15.9 (2.5)	17.3 (2.6)	$F(2,130) = 2.39$ *ns.*	
Estimated IQ - age corrected [c]	113.1 (10.5)	111.0 (9.1)	114.0 (6.8)	$F(2,105) = 1.13$ *ns.*	
Fatigue baseline (0–100%) [d]	33.1 (20.7)	22.9 (19.5)	23.5 (16.9)	$\chi^2(2) = 6.80^*$	A > R & C
Sleepiness baseline (0–100%) [d]	37.3 (23.8)	20.9 (21.3)	25.8 (20.7)	$\chi^2(2) = 8.50^*$	A > R
Fatigue testing [e]	9.2 (22.2)	22.6 (24.5)	22.6 (19.6)	$F(2,115) = 4.13^*$	R & C > A
Sleepiness testing [e]	3.8 (25.2)	24.9 (26.7)	17.2 (27.3)	$F(2,115) = 5.59^†$	R > A
CAARS T scores [f]					
- DSM4 Hyperactivity/Impulsivity	73.2 (14.0)	54.7 (14.1)	48.9 (11.2)	$F = 39.85^‡$	A > R & C
- DSM4 Inattention	84.2 (7.3)	60.5 (15.9)	53.2 (12.1)	$F = 70.38^‡$	A > R > C
- DSM4 total symptoms	82.9 (8.6)	59.2 (16.2)	52.0 (12.5)	$F = 64.58^‡$	A > R > C
- Hyperactivity/Restlessness	66.8 (11.1)	53.9 (9.8)	47.8 (8.5)	$F = 42.52^‡$	A > R > C
- Impulsiveness/Emotionality	69.3 (11.6)	55.9 (13.4)	46.5 (7.8)	$F = 46.86^‡$	A > R > C
- Inattention/Memory	78.8 (8.2)	59.0 (13.0)	50.6 (8.5)	$F = 86.11^‡$	A > R > C
- Self concept	66.2 (10.7)	58.3 (13.7)	51.3 (8.8)	$F = 19.48^‡$	A > R > C
- ADHD index	75.8 (7.8)	59.2 (14.1)	48.9 (7.3)	$F = 75.91^‡$	A > R > C
	N / %				
Occupation[g]				$\chi^2(12) = 18.96$ *ns.*	
- % students	60.5	29.5	52.0		
- % unemployed/homemaker	10.5	15.9	4.0		
- % unskilled	2.6	2.3	2.0		
- % semi-skilled	5.3	6.8	10.0		
- % skilled, clerical/sales	5.3	13.6	8.0		
- % semi-professional/managerial/technical	2.6	20.5	6.0		
- % professional	13.2	11.4	18.0		
Monthly income [h]				$\chi^2(12) = 18.37^*$	
- % Less than €900	75.7	33.3	53.1		
- % €900-€1350	2.7	13.3	16.3		
- % €1350-€1800	5.4	11.1	8.2		
- % €1800-€2250	8.1	11.1	6.1		
- % €2250-€2700	5.4	13.3	6.1		
- % More than €2700	2.7	17.8	10.2		

Note. $^*p < 0.05$, $^†p < 0.01$, $^‡p < 0.001$, *ns* = not significant. A = ADHD participants, R = 1st degree relatives of people with ADHD, C = healthy controls, Edu yrs = years of education, SES = socio-economic status, Estimated IQ - age corrected = IQ estimated based on National Adult Reading Test (NART; Nelson and Willison, 1991) and corrected for age for participants aged 55–69 years (see Willshire et al., 1991; Strauss and Spreen, 1998 for details), Fatigue baseline = level of fatigue experienced before testing estimated using continuous Visual Analogue Scale with the score on the line converted into a percentage (0–100%), Fatigue testing = % of fatigue after testing subtracted from % of fatigue before testing, Sleepiness baseline = level of sleepiness experienced before testing estimated using continuous Visual Analogue Scale with the score on the line converted into a percentage (0–100%), Sleepiness testing = % of sleepiness after testing subtracted from % of sleepiness before testing, CAARS T scores = CAARS raw score corrected for age and sex (for each subscale). Occupation categories based on Crawford (1992) and Callahan and Eyberg (2010) with the addition of students included as their own category.

[a] 9 ADHD participants had a self-reported co-morbid psychiatric and/or neurological condition; 1 case of depression, 3 cases of anxiety, 1 case of Mild Asperger's syndrome, 3 cases of dyslexia, 1 case of dyscalculia.
[b] data missing from 2 ADHD and 1 1st degree relative participants.
[c] no data for 8 ADHD, 6 1st degree relative and 14 control participants due to English not being Native language or missing data.
[d] data missing from 3 ADHD and 4 1st degree relative and 7 control participants.
[e] data missing from 7 ADHD and 4 1st degree relative and 7 control participants.
[f] df = (2,133) for all CAARS T score subscale group comparisons.
[g] data missing from 1 1st degree relative and 1 control participant.
[h] data missing from 1 ADHD and 2 control participants.
[x] Bonferroni-test, $p < 0.05$.

a matrix with the number of subjects as rows (126 for eyes-closed and 124 for eyes-open condition), and the connectivity pairs for each frequency band as the columns (i.e., 10,080 pairs). Sex and age were added as covariates.

We used a nested cross-validation procedure to identify the best hyperparameters of the Elastic Net model. The Elastic Net hyperparameters consist of a complexity penalty and a weighting parameter between lasso and ridge regression. The nested cross-validation consisted of four steps. First, participants were randomly partitioned into mainfolds and subfolds. A mainfold consisted of a training set (90% of all participants) and a testing set (10% of all participants). Training sets were further partitioned, at random, into sub-folds. Sub-folds consisted of a training subset (90% of training set participants) and a testing subset (10% of training set participants). Ten subfolds were generated within each mainfold and, overall, 10 mainfolds were generated.

Second, at the subfold level, an Elastic Net model was fit on a training subset using a range of hyperparameters. When fitting linear regression models (to predict ADHD symptoms) the range for the two hyperparameters was set to 0.01 to 1 in 15 linearly-spaced bins (i.e., a search grid of 225 parameter-pair values). The best hyperparameter combination, per subfold, was defined as the one with the lowest mean-squared error (MSE) between the predicted value and the measured value of that test subset. When fitting logistic regression models (to classify participants) the range was set to 0.01 to 10 for the complexity hyperparameter.

The best hyperparameter combination, per subfold, was defined as the one with the lowest logistic loss of the predicted probability compared to the real group assignment. The logistic loss penalizes heavily predicted probabilities that are far from the real group assignment, and softly predicted probabilities that are less far from the real group assignment.

Third, the mode of the selected complexity hyperparameter and the median of the weighting hyperparameter across subfolds was selected per mainfold. With these parameters, a new model was fit on the training set and tested on the test set of that mainfold.

Four, the above procedure was repeated for each mainfold. The predictions of each mainfold were then pooled to calculate the final performance measures. For the linear regression models, the final performance measures were the cross-validated Pearson's r (i.e., the correlation between the out-of-sample predicted symptom score and the actual symptom score) and MSE. For the logistic regression/classification models, the final performance measure was the area under the curve (AUC).

The above procedure (i.e., Steps 1–4) was performed 100 times, whereby the participants were randomly assigned to mainfolds. To further test the performance of the model, we applied the above procedure using random-label permuted data, with each participant randomly assigned the score/group of another participant (i.e., null model). To evaluate the effect of covariates (age and sex) in the models, we ran all this procedure using EEG data only and compared the results to the models that included the EEG data and covariates.

The performance measures of the 100 repetitions of the original models were compared to the performance measures of the null models using a *t*-test to evaluate if the model prediction was more probable than chance. For the *linear regression* models, eight models were fitted to four ADHD symptoms (Hyperactivity/Restlessness, Impulsiveness/Emotionality, Inattention/Memory and Self-concept) for eyes-open and eyes-closed data; and four models were fit to the DSM scales (2 DSM dimensions for both eyes-open and eyes-closed). The original model was deemed to be successful if both the Pearson's r was statistically significantly higher and MSE was statistically significantly lower than the respective measures of the null models, with a Bonferroni corrected p value of 0.05/12 = 0.0042. For the *logistic/classification* models, AUC of the 100 repetitions of the null models were compared to the AUC of the original models with a Wilcoxon test. In total six models were fitted to classify the participants into ADHD, 1st degree relative and/or control categories (i.e., eyes-open and eyes-closed; ADHD vs. control, ADHD vs. 1st degree relative and 1st degree relative vs. control models). Models were considered successful if the AUC was significantly higher than the values obtained from the null models, with a significance threshold of 0.05/6 = 0.00833.

To aid interpretation, the surviving connectivity pairs were further separated into *short* (less than 10.43 cm), *medium* (between 10.43 cm and 15.4 cm) and *long* (over 15.4 cm) length connections based on the 33th and 66th percentile of the distribution of all possible pair Euclidian distances.

3. Results

3.1. Resting-state EEG connectivity predicting ADHD symptoms

Results from the machine learning analysis when predicting ADHD symptoms are displayed in Table 2 and in Supplementary Table S3. Connectivity patterns within each frequency range (i.e., the delta, theta, alpha, beta and gamma) that best predict different ADHD symptoms (i.e., hyperactivity/restlessness, inattention/memory and self-concept symptoms) are described below. Findings are reported separately for the eyes-open and eyes-closed condition. Figs. 1–3 illustrate the best predictors of ADHD symptoms (i.e., connectivity pairs with a selection frequency higher than 50%).

3.1.1. Eyes-open

3.1.1.1. Hyperactivity/Restlessness subscale. The cross-validated *r* was 0.35 and significantly better than the null models ($t(198) = 22.23$, $p = 6.7e{-}56$). Delta band predictors of hyperactivity/restlessness symptoms consisted of increased connectivity in inter-hemispheric frontal and right-lateralized medium length connections, and in inter-hemispheric long connections over central electrodes; there was decreased connectivity in right-lateralized short, medium and long connections (Fig. 1, left; Table 3). Theta band predictors primarily consisted of decreased connectivity in medium length connections between fronto-central electrodes. Alpha band predictors included increased connectivity in right-lateralized connections and decreased connectivity in inter-hemispheric connections across centro-parietal electrodes. Beta band predictors consisted of increased connectivity in frontal short and in multiple inter-hemispheric connections between central

Table 2
Machine learning analysis results showing mean cross-validated *r* for predicting ADHD symptoms in the original models, and whether they performed better than the null models.

		Factor scores			
		Hyperactivity/Restlessness	Impulsiveness/ Emotionality	Inattention/Memory	Self-concept
Eyes-open					
Mean original (SD)	MSE	126.5 (6.84)	270.4 (13.18)	245.4 (13.57)	170.1 (9.9)
	r	0.35 (0.05)	−0.12 (0.05)	0.17 (0.06)	0.14 (0.06)
Mean null (SD)	MSE	178.4 (24.93)	250.47 (29.59)	298.2 (41.53)	202.5 (26.43)
	r	−0.011 (0.15)	−0.006 (0.13)	−0.02 (0.14)	−0.026 (0.14)
t-test with 198 df (p value)	MSE	−20.06 (1.4e−49)*	6.15 (4.15e−9)	−12.1 (1.3e−25)*	−11.47 (1.1e−23)*
	r	22.23 (6.7e−56)*	−8.17 (3.7e−14)	12.6 (3.4e−27)*	10.6 (2.9e−21)*
Eyes-closed					
Mean original (SD)	MSE	245.02 (12.64)	250.9 (12.38)	249.3 (14.1)	232.01 (11.54)
	r	0.232 (0.05)	−0.01 (0.05)	0.176 (0.06)	−0.18 (0.05)
Mean null (SD)	MSE	199.8 (28.01)	255.8 (32.67)	300.2 (36.92)	207.1 (25.57)
	r	−0.02 (0.15)	−0.011 (0.13)	0.004 (0.13)	−0.011
t-test with 198 df (p value)	MSE	15.7 (1.3e−33)	−1.4 (0.16)	−12.9 (5.3e−28)*	8.87 (4.4e−16)
	r	−13.96 (2.7e−31)	4.4e−2 (0.97)	11.99 (2.9e−25)*	−12.18 (7.6e−26)

Note: MSE = mean squared error; r = Pearson's r; SD = standard deviation; df = degrees of freedom.
* denotes original model to have statistically significantly higher *r* and MSE compared to null model (with a Bonferroni corrected *p* value of 0.05/12 = 0.0042).

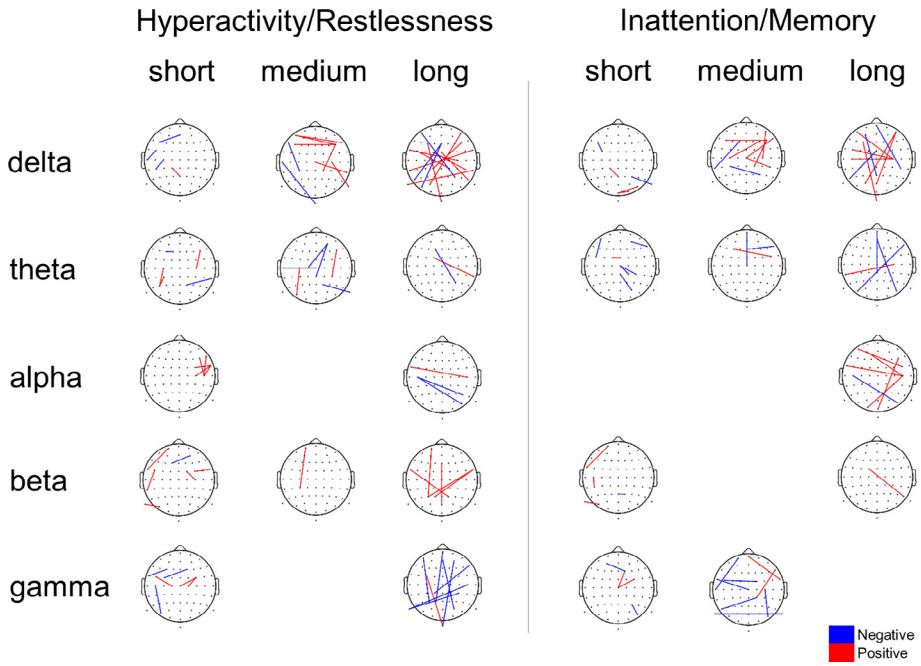

Fig. 1. Topographical plots with connectivity pairs with a selection frequency higher than 50% for the eyes-open condition predicting hyperactivity and inattention symptoms. Blue indicates a negative association between the connectivity and the ADHD symptoms. Red indicates a positive association between the connectivity and the ADHD symptoms. Left, the Hyperactivity/Restlessness symptoms; Right, the Inattention/Memory symptoms.

electrodes. Gamma predictors consisted of decreased connectivity in left-lateralized short connections and in long connections between fronto-parietal, and inter-hemispheric, electrodes.

3.1.1.2. Inattention/Memory subscale. The cross-validated r was 0.17 and significantly higher than the null models ($t(198) = 12.6$, $p = 3.4e{-}27$). Delta band predictors of inattention/memory symptoms consisted of increased connectivity in parietal short, fronto-central medium and in long connections between fronto-parietal and inter-hemispheric electrodes, and of decreased connectivity in medium-long connections between central electrodes (Fig. 1, right; Table 4). Theta band predictors included decreased connectivity in parietal short, frontal short-medium and long connections between frontal and parietal electrodes. Alpha band predictors consisted of increased connectivity in inter-hemispheric connections between frontal and centro-parietal electrodes. Beta band predictors were sparse. Gamma band predictors consisted of decreased connectivity in inter-hemispheric frontal short-medium and parietal medium connection.

3.1.1.3. Self-concept subscale. The cross-validated r was 0.14 and significantly higher than the null models ($t(198) = 10.6$, $p = 2.9e{-}21$). Delta band predictors included increased connectivity in right-lateralized short, and medium-long connections between inter-hemispheric, fronto-central electrodes, and decreased connectivity in long connections between frontal and centro-parietal electrodes (Fig. 2; Table 5). Theta band predictors included decreased connectivity in long connections between inter-hemispheric, and frontal and centroparietal electrodes. Alpha band predictors consisted of increased connectivity in frontal short and inter-hemispheric long connections over central midline electrodes, and decreased connectivity in long connections between inter-hemispheric parietal electrodes. Beta band predictors included increased connectivity in right-frontal short and inter-hemispheric, long connections between central midline electrodes, and decreased connectivity in short and long connections between

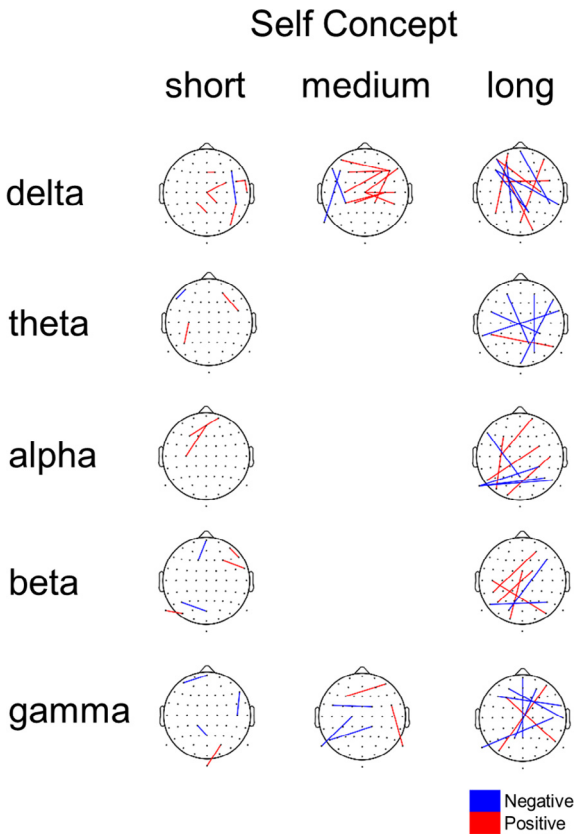

Fig. 2. Topographical plots with connectivity pairs with a selection frequency higher than 50% for eyes-open condition predicting Self-concept subscale scores. Blue indicates a negative association between the connectivity and the ADHD symptoms. Red indicates a positive association between the connectivity and the ADHD symptoms.

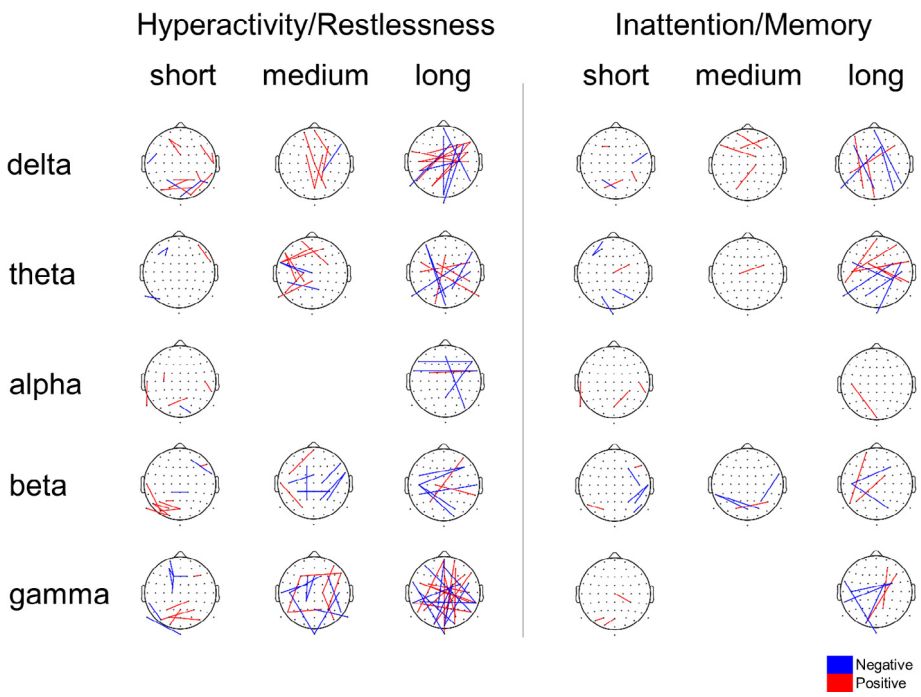

Fig. 3. Topographical plots with connectivity pairs with a selection frequency higher than 50% for eyes-closed condition predicting hyperactivity and inattention symptoms. Blue indicates a negative association between the connectivity and the ADHD symptoms. Red indicates a positive association between the connectivity and the ADHD symptoms. Left, the Hyperactivity/Restlessness symptoms; Right, the Inattention/Memory symptoms.

Table 3
Best predictors (i.e., features that were selected more than 80% of the iterations) in the eyes-open Hyperactivity/Restlessness model. Predictors are ordered in descending order according to the selection frequency.

Frequency band	Pair	Type	Side	Distance (cm)	% Selection frequency	Beta value
delta						
	CP1 & Pz	intra	left	5.32	100	1.555
	P9 & TP8	inter		17.42	100	1.237
	F7 & CP3	intra	left	11.72	94.4	−0.525
	PO7 & Fz	intra	left	17.92	87.7	−0.442
	F6 & CP2	intra	right	12.20	87.2	0.442
	PO3 & AF8	inter		19.76	86	0.500
	TP7 & FT8	inter		19.99	85	0.402
	F5 & F6	inter		14.58	82.2	0.376
theta						
	FC1 & TP8	inter		17.33	93.8	0.564
	C1 & AF4	inter		13.45	92.4	−0.513
	F6 & C4	intra	right	7.69	84.6	0.422
	CP3 & P5	intra	left	4.75	82.7	0.442
	T7 & Cz	intra	left	14.39	81.4	−0.349
	F6 & CP4	intra	right	10.66	81.3	0.398
alpha						
	C5 & PO8	inter		17.67	99.9	−1.353
	FT8 & FC4	intra	right	7.33	95	0.732
	FT8 & C4	intra	right	8.25	94.9	0.654
	FT7 & C6	inter		19.49	80.1	0.339
beta						
	F1 & AF4	inter		8.01	99.6	−0.966
	P3 & FT8	inter		18.67	93.9	0.671
	P9 & PO7	intra	left	4.98	93.7	0.632
	Fp1 & CP3	intra	left	15.20	82.6	0.364
gamma						
	P9 & C6	inter		19.16	92	−0.494
	C5 & PO7	intra	left	9.63	89.6	−0.472
	FC5 & FC2	inter		13.73	87.1	−0.528
	Afz & PO4	intra	right	18.52	83	−0.378

Table 4
Best predictors (i.e., features that were selected more than 80% of the iterations) in the eyes-open Inattention/Memory model. Predictors are ordered in descending order according to the selection frequency.

Frequency band	Pair	Type	Side	Distance (cm)	% Selection frequency	Beta value
delta						
	CP1 & Pz	intra	left	5.32	100	1.667
	P7 & FCz	intra	left	15.88	99.9	−1.636
	PO3 & AF8	inter		19.76	99.5	1.532
	F8 & Cz	intra	right	14.39	96	0.912
	F3 & Iz	intra	left	19.09	95.9	0.823
	AF7 & C4	inter		17.01	85.7	0.525
	Oz & PO8	intra	right	6.18	85.3	0.547
	FC5 & C4	inter		16.88	83.1	0.528
	C3 & F4	inter		14.45	81	0.490
theta						
	Afz & PO8	intra	right	18.80	96.2	−1.022
	FC1 & FCz	intra	left	3.82	95.8	1.049
	AF7 & FC5	intra	left	6.54	90	−0.780
alpha						
	C5 & PO8	inter		17.67	89.7	−0.698
	FT7 & C6	inter		19.49	80.8	0.469
beta						
	Pz & P2	intra	right	2.92	99.7	−1.513
	P9 & PO7	intra	left	4.98	97.5	1.068
	F1 & TP7	intra	left	13.92	91.1	−0.694
	Fp1 & FT7	intra	left	9.07	84.6	0.502
gamma						
	P9 & C6	inter		19.16	100	−1.680
	FT7 & Cz	intra	left	14.39	96	−1.258
	FC4 & Cz	intra	right	8.45	95.6	1.036
	FC5 & FC2	inter		13.73	91.1	−0.694
	F5 & POz	intra	left	17.31	81.9	−0.488

Table 5
Best predictors (i.e., features that were selected more than 80% of the iterations) in the eyes-open Self-concept model. Predictors are ordered in descending order according to the selection frequency.

Frequency band	Pair	Type	Side	Distance (cm)	% Selection frequency	Beta value
delta						
	POz & AF8	intra	right	18.80	97.5	0.805
	F5 & P2	inter		17.28	96.4	−0.695
	F8 & Cz	intra	right	14.39	94.6	0.735
	CP1 & Pz	intra	left	5.32	94.3	0.620
	C3 & F4	inter		14.45	93.8	0.678
	Cz & CP6	intra	right	11.76	93.4	0.661
	FC3 & FC6	inter		16.00	90.7	0.464
	CP1 & C4	inter		11.67	88.9	0.499
	FT8 & T8	intra	right	3.13	86.8	0.445
	AF7 & P2	inter		18.79	84.8	−0.431
	F3 & O2	inter		19.11	82.2	0.388
	CP6 & PO8	intra	right	6.54	81.4	0.377
	F7 & CP3	intra	left	11.72	81.4	−0.417
theta						
	AF4 & FC6	intra	right	7.17	96.5	0.781
	AF7 & F7	intra	left	3.13	87.2	−0.473
	AF4 & PO4	intra	right	17.42	87.1	−0.461
	FC5 & CP4	inter		17.46	83.7	−0.424
	FC3 & CP4	inter		15.32	83.4	−0.375
alpha						
	F1 & F3	intra	left	2.97	87.4	−0.517
	F7 & Pz	intra	left	17.01	86.2	−0.455
	C3 & Fp2	inter		15.79	85.1	0.468
beta						
	P9 & CPz	intra	left	15.37	100	−1.437
	C5 & PO8	inter		17.67	94.7	0.707
	F4 & FT8	intra	right	7.64	84.4	0.390
	P5 & FC2	inter		16.07	82.4	0.430
gamma						
	Pz & Fpz	midline		18.67	98.9	−1.131
	P9 & C6	inter		19.16	97.9	−0.722
	Iz & PO4	intra	right	8.09	93.9	0.633
	FC6 & P10	intra	right	11.50	93.9	0.629
	PO7 & AF8	inter		19.99	87.7	0.485
	P1 & AF4	inter		17.65	85.7	−0.575

frontal and parietal electrodes. Gamma band predictors consisted of increased connectivity in medium-long connections between frontal and central electrodes, and of decreased connectivity in short-to-long connections between fronto-central and centro-parietal electrodes.

The Impulsiveness/Emotionality subscale did not have a cross-validated *r* higher than the null models.

3.1.2. Eyes-closed

3.1.2.1. Inattention/Memory subscale. The cross-validated *r* was 0.18 and was significantly higher than the null models ($t(198) = 11.99$, $p = 2.9e{-}25$). Delta band predictors included increased connectivity in frontal medium and long connections between centro-parietal electrodes, and decreased connectivity in long connections spanning between frontal and parietal electrodes (Fig. 3, left; Table 6). Theta band predictors consisted of increased connectivity in inter-hemispheric long connections between fronto-central electrodes, and decreased connectivity in short and long connections between centro-parietal electrodes. Alpha band predictors were very few. Beta band predictors included decreased connectivity in right-lateralized short connections and in medium-long connections between centro-parietal electrodes. Gamma band predictors consisted of increased connectivity in short and long connections between central and parietal electrodes, and decreased connectivity in long connections between central and parietal electrodes.

No other eyes-closed models reached significance.

To estimate the effect of covariates age and sex had on the results, the analyses were repeated without age and sex in the models estimated. Similar measures were obtained when EEG data only was used for prediction (Supplementary Table S3), which indicates that the results are not due to the inclusion of the covariates age and sex.

3.2. Classification analysis with resting-state EEG connectivity

Wilcoxon tests showed that the AUC in original models were significantly higher than the AUC in null models for all contrasts and conditions (ADHD vs. 1st degree relatives, ADHD vs. controls, 1st degree relatives vs. controls during eyes-open and eyes-closed; see Table 7).

We further inspected the classification accuracy of the models with Receiver Operating Characteristic (ROC) curves for the original and null models (Supplementary Fig. S1). Bootstrapped confidence intervals overlapped in most of the models. This indicates that, although the averaged AUC was higher in original compared to null models, the original models did not perform well. This was further confirmed with the recall measure (true positive rate) which was either significantly better (higher) in null models or not different from null models (Table 7). After the same threshold of the correlation models (selection frequency higher than 50%) was applied, only three models had predictors that survived this threshold: ADHD vs. 1st degree relatives during eyes-open (24 predictors), ADHD vs. 1st degree relatives during eyes-closed (12 predictors), and 1st degree relatives vs. controls during eyes-closed (1 predictor).

3.2.1. Eyes-open

ADHD vs. 1st degree relative classification model, the best predictors for ADHD status included increased connectivity in short alpha and in medium connections in delta between centro-parietal electrodes. The best predictors for 1st degree relatives control status were sparse (see Fig. 4 and Supplementary Table S4).

3.2.2. Eyes-closed

In the ADHD vs. 1st degree relatives group classification model, the best predictors for ADHD status included increased connectivity in short-medium theta connections. In the 1st degree relative vs. control classification model only 1 predictor in the delta band survived the threshold (see Fig. 5 and Supplementary Table S5).

To estimate the effect of covariates age and sex had on the classification performance, the analyses were repeated without age and sex in the models estimated. Similar results were found when using the EEG data only for the models (Supplementary Table S6), which indicates that the predictive power of the models does not depend on the inclusion of covariates.

Table 6
Best predictors (i.e., features that were selected more than 80% of the iterations) in the eyes-closed Inattention/Memory model. Predictors are ordered in descending order according to the selection frequency.

Frequency band	Pair	Type	Side	Distance (cm)	% Selection frequency	Beta value
delta						
	CP5 & F6	inter		18.89	97.5	1.257
	CP4 & P6	intra	right	4.75	96.8	1.006
	P9 & F2	inter		19.29	95.1	−0.915
	P3 & POz	intra	left	6.20	88.4	−0.623
	F2 & PO8	intra	right	16.90	81.4	−0.528
theta						
	AF3 & F5	intra	left	4.01	97.1	−1.091
	FC1 & TP8	inter		17.33	91.9	0.724
	TP7 & Fpz	intra	left	16.17	82.5	0.554
	C5 & AF8	inter		17.67	80.8	0.553
alpha						
	CP1 & Fp2	inter		17.33	92.2	−0.793
beta						
	TP7 & POz	intra	left	12.03	100	−2.367
	P7 & PO3	intra	left	5.82	99.9	1.832
	Fp1 & P7	intra	left	16.17	93.9	0.850
	F6 & F8	intra	right	3.08	92.1	0.717
	C5 & PO4	inter		16.00	91.9	−0.807
	C5 & F4	inter		16.31	80.4	−0.538
gamma						
	C5 & FC4	inter		16.74	99.8	−1.532
	PO7 & PO3	intra	left	3.65	99.7	1.295
	AF3 & C1	intra	left	10.84	94.4	−0.992
	FT7 & Iz	intra	left	15.91	93.7	−0.853

Table 7
Prediction accuracy (AUC, F score, APR, Recall and Specificity) of classification models using eyes-open or eyes-closed resting-state EEG.

		Eyes-open			Eyes-closed		
		ADHD vs Relatives	ADHD vs Controls	Controls vs Relatives	ADHD vs Relatives	ADHD vs Controls	Controls vs Relatives
AUC	mean original (SD)	0.578 (0.043)	0.575 (0.055)	0.548 (0.059)	0.669 (0.050)	0.603 (0.057)	0.617 (0.067)
	mean null (SD)	0.472 (0.070)	0.479 (0.052)	0.471 (0.054)	0.471 (0.063)	0.467 (0.063)	0.476 (0.048)
	Z (p value)	9.58 (9.5e−22)*	9.73 (2.28e−22)*	8.1 (5.29 e−16)*	11.94 (7.35e−33)*	10.73 (7.34e−27)*	11.27 (1.82e−29)*
F score	Mean original (SD)	0.308 (0.008)	0.293 (0.007)	0.325 (0.003)	0.330 (0.012)	0.29 (0.006)	0.318 (0.005)
	mean null (SD)	0.299 (0.006)	0.288 (0.005)	0.325 (0.002)	0.312 (0.004)	0.29 (0.006)	0.315 (0.003)
	Z (p value)	8.87 (7.5e−19)*	7.25 (4.3e−13)*	0.15 (0.88)	11.11 (1.06e−28)*	5.28 (1.3e−7)*	6.23 (3.45e−10)*
APR	Mean original (SD)	0.446 (0.033)	0.399 (0.042)	0.421 (0.064)	0.561 (0.052)	0.408 (0.061)	0.485 (0.063)
	mean null (SD)	0.386 (0.066)	0.355 (0.069)	0.441 (0.052)	0.412 (0.052)	0.337 (0.082)	0.384 (0.095)
	Z (pvalue)	7.99 (1.36e−15)*	5.36 (8.34e−8)*	−1.67 (0.0096)	11.41 (3.75e−30)*	6.67 (2.53e−11)*	9.38 (6.82e−21)*
Recall	mean original (SD)	70.13 (25.23)	73.16 (32.13)	70 (39.6)	69.12 (21.15)	61.35 (37.32)	49 (30.16)
	mean null (SD)	74.09 (33.76)	61.66 (40.81)	60.20 (40.91)	67.82 (38.79)	78.12 (34.51)	71.45 (38.43)
	Z (p value)	−3.09 (2.02e−3)*	0.03 (0.98)	0.71 (0.48)	−2.91 (3.6e−3)*	−4.88 (1.1e−6)*	−4.56 (5e−6)*
Specificity	mean original (SD)	46.41 (24.99)	37.08 (33.41)	33.33 (40.06)	57.79 (21.04)	47.86 (37.95)	63.1 (30.74)
	mean null (SD)	32.07 (36.67)	42.83 (42.6)	44.06 (42.72)	37.48 (40.60)	25.94 (37.19)	31.74 (39.81)
	Z (p value)	4.37 (1.26e−5)*	1.11 (0.27)	−0.6 (0.55)	3.97 (7.12e−5)*	5.91 (3.5e−9)*	5.53 (3.2e−8)*

Note. ADHD vs Controls = a classification model for ADHD and control participants, ADHD vs Relatives = a classification model for ADHD and 1st degree relative participants, Controls vs Relatives = a classification model for 1st degree relative and control participants; AUC = area under the curve statistic, APR = area under precision recall curve, SD = standard deviation,
* denotes original model to have statistically significantly higher test statistic compared to null model ($p < 0.00833$).

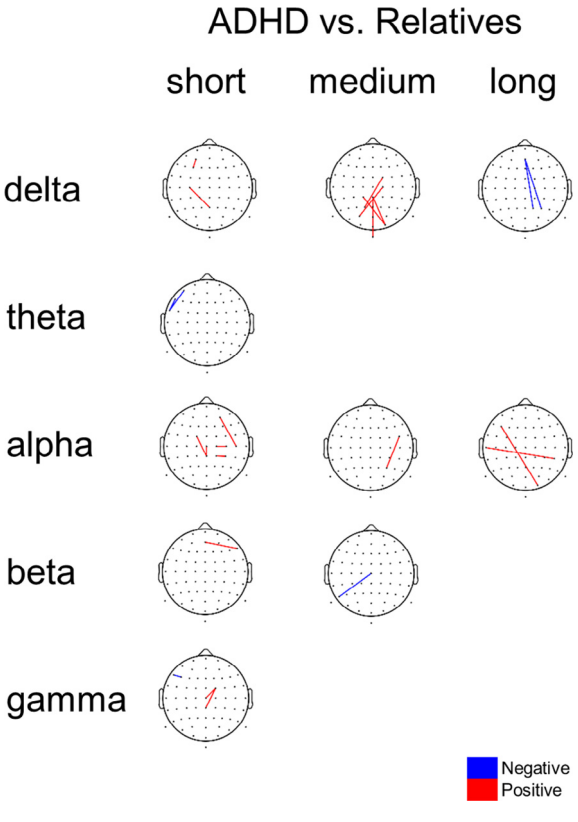

Fig. 4. Topographical plots with connectivity pairs with a selection frequency higher than 50% in the ADHD vs. 1st degree relative classification models for eyes-open condition. Red indicates a positive weight assigned to the connectivity, i.e., a higher weight towards the group ADHD. Blue indicates a negative weight assigned to the connectivity, i.e., a higher weight towards the group 1st degree relative.

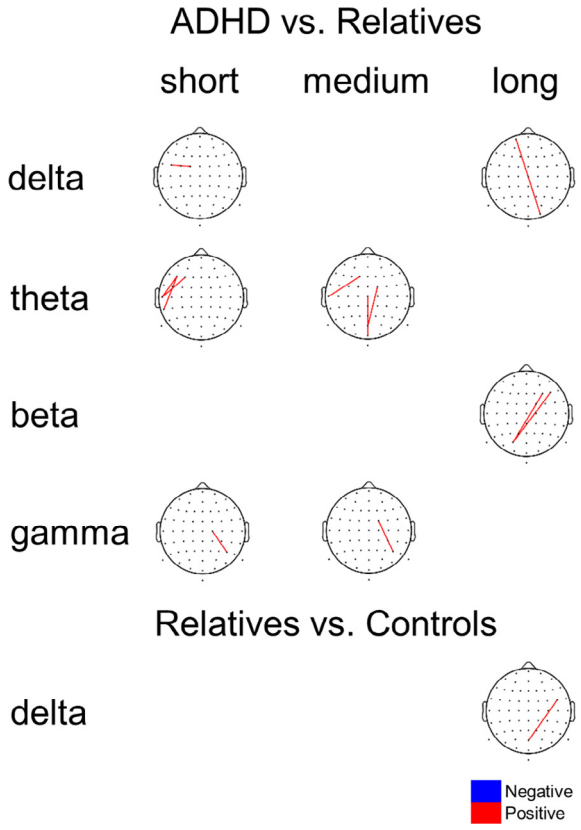

Fig. 5. Topographical plots with connectivity pairs with a selection frequency higher than 50% in the models contrasting ADHD vs. 1st degree relatives (top) and 1st degree relatives vs. controls (bottom) for eyes-closed condition. Blue indicates a negative weight assigned to the connectivity, i.e., a higher weight towards the first group in the contrast. Red indicates a positive weight assigned to the connectivity, i.e., a higher weight towards the second group in the contrast.

4. Discussion

Our understanding and capacity to recognize adult ADHD will be enhanced by identifying specific neuromarkers for symptoms and/or diagnosis-status. These neuromarkers could be beneficial complementary and objective tools to assist ADHD nosology. In this context, we combined a sophisticated measure of EEG functional connectivity (WPLI) with machine learning (Elastic Net penalized regression). Findings indicated that EEG connectivity best characterizes ADHD symptoms on a continuum, rather than as clinical categories, and that EEG functional connectivity in eyes-open condition may serve as a neuromarker for ADHD symp-

toms. Specifically, functional connectivity patterns during eyes-open EEG predicted heightened hyperactive, impulsive and inattentive symptoms (cross-validated r ranged from 0.14 to 0.35). Also, functional connectivity patterns during eyes-closed EEG predicted increased inattention symptoms (cross-validated r ranged from 0.18 to 0.23). However, EEG connectivity did not reliably classify participants into ADHD, 1st degree relative and control groups. Although the classification models fitted the data better than the random models (AUCs ranged from 0.55 to 0.67, $p < 0.008$), results were variable (as indicated by bootstrapped confidence intervals and recall measure) and had few predictors surviving a relatively low selection threshold.

This study revealed that patterns of EEG functional connectivity, after controlling for age and sex, could predict the increased level of hyperactive/impulsive and inattentive/memory symptoms across all participants, not just those with a diagnosis with ADHD. This is consistent with reports of increased EEG functional connectivity to be increased in delta in adult ADHD (Barttfeld et al., 2014) and in a range of frequency bands in childhood ADHD (González et al., 2015) when compared to controls. This study also suggests that EEG functional connectivity is not predictive of diagnostic-status (i.e., ADHD or control). This outcome stands in contrast to previous reports that EEG functional connectivity can successfully classify children into ADHD and control groups (Ahmadlou and Adeli, 2010, 2011; Pereda et al., 2018).

Taken together, our findings are consistent with a dimensional psychiatry framework (Casey et al., 2013, 2014), including the Research Domain Criteria (RDoC; Cuthbert and Insel, 2013). From this perspective, psychiatric conditions represent the extreme end of a continuum. Integrating behavioral symptoms to neurobiology – here, EEG functional connectivity – is also a goal of dimensional psychiatry. Although ADHD symptom severity was associated with EEG connectivity in previous research, these studies (Barry et al., 2011; Barttfeld et al., 2014; Janssen et al., 2017) included only ADHD participants and conducted correlational, rather than predictive (i.e., out-of-sample validation) analyses (Bzdok and Ioannidis, 2019; Rutledge et al., 2019 Yarkoni and Westfall, 2017).

With respect to inattentive symptoms, Barry and colleagues (Barry et al., 2011), reported that left-lateralized coherences of delta, alpha, beta and gamma, and a smaller frontal interhemispheric coherence in alpha, correlated negatively with inattentive and total number of ADHD symptoms (using a coherence analysis with 5-mins eyes-closed condition). Another study (Janssen et al., 2017) also reported a negative correlation that showed a more centralized EEG source functional network in alpha and beta bands to be associated with poorer attention skills. Our results were somewhat overlapping: we found that elevated inattention symptoms were best predicted by increased eyes-open EEG connectivity in delta and alpha, plus decreased eyes-open EEG connectivity in delta and gamma, and by decreased eyes-closed EEG connectivity in delta and gamma. In contrast to previous findings, we found connectivity in theta band predicted the severity of inattention symptoms, which included increased eyes-closed EEG connectivity in long connections between frontal and central electrodes, decreased eyes-open connectivity in long connections between frontal and parietal electrodes, and decreased eyes-closed connectivity in long connections between central and parietal electrodes.

We found that increased eyes-open EEG connectivity in medium-long central and inter-hemispheric delta and in long connections between inter-hemispheric and frontal and parietal electrodes in beta, and decreased eyes-open EEG connectivity in connections between frontal and parietal electrodes in delta and in long connections between frontal and parietal electrodes in gamma, best predicted elevated hyperactive symptoms. Although they did not specify connectivity in specific bands, the only other study that has investigated the EEG connectivity in adult ADHD (N = 9) (Barttfeld et al., 2014) reported a positive correlation between connectivity over frontal and central areas and levels of hyperactivity, impulsivity and depressive symptoms. In addition, we observed altered connectivity in connections between frontal and parieto/occipital electrodes. Similar network patterns have also been observed in other neuropsychiatric conditions, such as autism, schizophrenia and bipolar disorder (Baez et al., 2013; Barttfeld et al., 2014).

In addition, we found alpha band connectivity was not a particularly strong predictor, relative to other frequency bands, suggesting that alpha synchronization is not strongly associated with the ADHD symptom severity in adults, unlike results previously observed in children (Barry et al., 2011). Differences between previous findings and those reported here are likely due to several factors, in particular the age of participants and the different methods used to measure EEG connectivity. Negative correlations between EEG connectivity and ADHD symptoms in children may reflect compensatory mechanisms (Barry et al., 2011) or signal cortical immaturity in children (Fair et al., 2010; Janssen et al., 2017). In adults, where brain maturation is largely complete, it follows that the brain-behavior relationship cannot be based on neuromaturation *per se*.

To our knowledge, this study is the first to investigate EEG resting state connectivity as a potential mediational endophenotype for adult ADHD. Adult ADHD is one of the most heritable psychiatric disorders (heritability estimates based on cross-informant-ratings ranging from 70-80%; (Faraone et al., 2005; Larsson et al., 2014; Brikell et al., 2015). Mediational endophenotypes are subclinical quantitative markers of gene expression: they should be associated with the disease and should be overrepresented in unaffected relatives compared to unrelated controls. A mediational endophenotype may be useful for genetic research, as it should be closer to the gene than the ADHD symptoms themselves. Although the findings from the machine learning analysis reveals patterns of functional connectivity highly associated and predictive of the ADHD symptoms, there were no reliable between-group differences between controls and 1st degree relatives (AUC values of 0.548 and 0.617 for eyes-open and closed, respectively). Although quantitative EEG has long been posited as a potential mediational endophenotype (Castellanos and Tannock, 2002), it is possible that either different EEG measures (e.g., power) are or additional neurobiological measures are needed (e.g., MRI) to improve classification performance. It is also likely that, in machine learning terms, the 'label noise' of psychiatric diagnoses places an upper limit on the performance accuracy of classifiers that use biological information. That is, the testing instrument (e.g., CAARS) does not have perfect reliability and therefore category membership does not have distinct boundaries. However, other studies have found eyes-closed functional connectivity to accurately distinguish children with ADHD from controls: Ahmadlou and Adeli (2010, 2011) reported 87.5% and 95.6% accuracy rate for eyes-closed synchronization pattern in posterior-frontal connections in theta band and in temporal-frontal connection in delta band, and González et al. (2013) observed 74% accuracy rate for eyes-closed beta coherence and generalized synchronization between inter-hemispheric regions.

This study is one of the few resting-state connectivity studies on ADHD to use both eyes-open and eyes-closed conditions (González et al., 2013; Alba et al., 2016). Our results show that eyes-closed connectivity was worse at predicting ADHD symptom severity in comparison to eyes-open connectivity. Connectivity features that best predicted inattention symptoms (i.e., CAARS factor Inattention/Memory subscale) were for the most part similar across eyes-open and eyes-closed conditions. However, the eyes-closed condition also included increased connectivity in long,

inter-hemispheric connections between fronto-central electrodes in theta, and decreased eyes-closed connectivity in inter-hemispheric long connections in gamma. However, only the connectivity patterns during eyes-open EEG (and not eyes-closed EEG) reliably predicted hyperactivity symptoms (i.e., CAARS factor Hyperactivity/Restlessness subscale). The differences in functional connectivity between eyes-open and eyes-closed conditions are likely to be related to states of vigilance and arousal. For example, effective connectivity has been shown to increase in eyes-open condition but only for well-rested participants and not after sleep deprivation (Piantoni et al., 2013). The eyes-open and eyes-closed conditions also present with different arousal levels as skin conductance level has been shown to be greater during eyes-open relative to eyes-closed condition (Barry et al., 2007; Hüfner et al., 2009). In fact, people with ADHD tend to have lower arousal levels compared to controls (Barry et al., 2009; Clarke et al., 2013), and this hypoarousal of the central nervous system is one of the most reported theories explaining the altered EEG spectral power observed in ADHD (Barry et al., 2003,2009; Hobbs et al., 2007; Lansbergen et al., 2011; Woltering et al., 2012; Clarke et al., 2013). Importantly, the eyes-open connectivity pairs best predicting elevated hyperactivity symptoms (measured with both CAARS factor Hyperactivity/Restlessness and CAARS DSM Hyperactivity/Impulsivity subscale scores), or increased inattention symptoms (measured with CAARS factor Inattention/Memory and CAARS DSM Inattention subscale scores) overlapped considerably (Supplementary Fig. S3, Supplementary Table S11).

This study had several strengths. First, relatively large adult samples of participants with ADHD, 1st degree relatives and unaffected controls underwent high-density resting-state EEG (total N = 134). We included equal numbers of male and females with adult ADHD, which is more representative of the adult ADHD population: previous studies were either male only (Liu et al., 2014; Alba et al., 2016) or included fewer than 30% female (Ahmadlou and Adeli, 2010, 2011; Barry et al., 2011; Barttfeld et al., 2014; Janssen et al., 2017). The ADHD and control groups were sex-balanced and did not differ in age, education or IQ, and the analyses involving 1st degree relatives were corrected for age and sex effects as they were slightly older and included more women. We repeated the analyses with age- and sex-matched groups and found similar results. The participants were carefully screened for co-morbidities prior to testing to ensure they met the inclusion criteria. A strength of this study is that a majority (55%) of ADHD participants were medication-naïve, and those on medication completed a 36-hour washout prior the testing session. It is therefore unlikely that the increased alpha and gamma connectivity were a direct consequence of medication. It is also worth noting that we examined alpha and gamma *connectivity*, not amplitude. We employed an advanced method of weighted phase lag index (WPLI, (Vinck et al., 2011) that can measure functional connectivity without being confounded by volume conduction and spurious correlations. Furthermore, we used a sophisticated machine learning approach with penalized regression and out-of-sample validation to estimate prediction accuracies, thus avoiding many of the pitfalls associated with ADHD classification models (Pulini et al., 2018).

Our study did have some limitations: we did not have sufficient 1st degree relatives to investigate siblings and parents separately, which would have been desirable with respect to age matching. Despite a vigorous recruitment strategy, we could only recruit 3 ADHD-1st degree relative dyads, and it is possible that those who declined to participate (either probands or relatives) had higher ADHD symptoms. Furthermore, as we conducted a sensor-level analysis the localization of the alterations in functional connectivity and the functional significance of these findings is restricted and needs further research, by, for example, conducting EEG source analysis together with WPLI. In addition, as demonstrated by Jollans et al. (2019), prediction accuracy varies as a function of machine learning algorithm. It is possible that alternative methods applied to the same data could yield a different set of predictors. Although we used a simple machine learning approach (penalized regression), the interpretation of machine learning outputs remains a challenge (see Jollans and Whelan, 2016; Woo et al., 2017 for a discussion).

In conclusion, we revealed functional connectivity patterns predicting ADHD symptoms that may represent as neuromarkers for ADHD symptom severity. Taken together, these patterns of functional connectivity in these networks seen in adults may shed light into uncovering the neural and genetic basis of adult ADHD and of its symptoms.

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Disclosures

The authors had no conflicts of interest. The study sponsors had no involvement in the collection, analysis and interpretation of data and in the writing of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.08.010.

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