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Electroencephalography as a clinical tool for diagnosing and monitoring attention deficit hyperactivity disorder: a cross-sectional study

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ABSTRACT

Objectives: The aim of this study was to develop and test, for the first time, a multivariate diagnostic classifier of attention deficit hyperactivity disorder (ADHD) based on EEG coherence measures and chronological age.

Setting: The participants were recruited in two specialised centres and three schools in Reykjavik.

Participants: The data are from a large cross-sectional cohort of 310 patients with ADHD and 351 controls, covering an age range from 5.8 to 14 years. ADHD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria using the K-SADS-PL semistructured interview. Participants in the control group were reported to be free of any mental or developmental disorders by their parents and had a score of less than 1.5 SDs above the age-appropriate norm on the ADHD Rating Scale-IV. Other than moderate or severe intellectual disability, no additional exclusion criteria were applied in order that the cohort reflected the typical cross section of patients with ADHD.

Results: Diagnostic classifiers were developed using statistical pattern recognition for the entire age range and for specific age ranges and were tested using cross-validation and by application to a separate cohort of recordings not used in the development process. The age-specific classification approach was more accurate (76% accuracy in the independent test cohort; 81% cross-validation accuracy) than the age-independent version (76%; 73%). Chronological age was found to be an important classification feature.

Conclusions: The novel application of EEG-based classification methods presented here can offer significant benefit to the clinician by improving both the accuracy of initial diagnosis and ongoing monitoring of children and adolescents with ADHD. The most accurate possible diagnosis at a single point in time can be obtained by the age-specific classifiers, but the age-independent classifiers are also useful as they enable longitudinal monitoring of brain function.

Strengths and limitations of this study

- For the first time, a multivariate diagnostic classifier of attention deficit hyperactivity disorder (ADHD) has been developed, based on EEG coherence measures and chronological age, using data from 630 recordings.
- In addition to cross-validation, a cohort of completely independent EEG recordings that were not used in training the classifiers was used for testing.
- The underlying population and EEG equipment were quite tightly controlled, as the participants in the study were all recruited in Iceland and the EEG recordings were all made with similar hardware and software.
- The patient group is cross-sectional, which can be considered not only as a limitation but also as a strength of the study, because it reflects the realities of clinical practice. This patient group is highly heterogenic by nature, and hence a clinical diagnostic method developed for the general clinical population using this group is likely to be more widely applicable and have greater clinical utility.

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neuropsychiatric disorder among school-age children with an estimated worldwide prevalence of 5.9–7.1%.[1] Clinical diagnosis currently relies on the assessment of behavioural patterns and characteristics, using questionnaires and information provided by close observers of the child's behaviour.[2] A lack of confidence in diagnosis, which is inherently subjective as it is limited to interviews, review of patient history and rating scales, has been demonstrated to be one of the barriers to effective treatment.[3] In addition, the diagnostic process consists of many elements and can

therefore be time-consuming and expensive. However, despite the clear need for development of an objective and independent diagnostic test for ADHD, such a tool remains elusive. Although the underlying differences in the central nervous system (CNS) in children with ADHD have been widely studied, the findings from neurobiological research have not so far been translated into diagnostic methods suitable for use in clinical practice.

EEG measures electrical signals at the scalp which are generated by synaptic activity in the cerebral cortex, which is driven by the underlying brain network and neurotransmitter systems and hence also sensitive to subcortical function.[4] The technique has a long history of providing functional information on the CNS, including in children with behavioural problems. The first EEG recordings in humans were made by Hans Berger in about 1928, and 10 years later the first EEG study on children with behavioural problems was presented. EEG recordings of 77 children with behavioural problems and 289 controls showed EEG abnormalities in 73% and severe EEG abnormalities in 59% of behaviourally disordered children.[5]

Neurobiologically, symptoms of ADHD have been associated with alterations in dopaminergic and noradrenergic function. One of the common treatments, the stimulant methylphenidate, which has been found to be effective in increasing attention and concentration in children diagnosed with ADHD, acts by blocking the dopamine and norepinephrine transporters in the brain and thereby increasing the level of dopamine and norepinephrine in the prefrontal cortex.[6 7] EEG has been shown to provide an indirect measure of the levels of these neurotransmitters as the signals reflect chemical activity at the synapses of the neurons.[8–10]

Many EEG studies carried out during the past two decades show differences in brain activity in children diagnosed with ADHD compared to controls. The majority of these studies rely on power-spectral analysis of individual channels and frequencies; the most commonly reported differences are increased power in the θ band (4–7 Hz) and decreased power in the β band (13–30 Hz) in frontal areas. These results show, in principle, that EEG measures are capable of discriminating between patients with ADHD and controls. However, there is a lack of methodological standardisation and the studies vary in the age range of the participants included, the number and position of EEG channels used, the recording conditions (eye state and use of a task) and the analysis methods.[11–14] Overall, this body of literature provides good evidence for electrophysiological differences at the group level which are clinically relevant, but the methods are not in general accessible for widespread diagnostic use in the clinic, due to the reliance on subjective interpretation.

Recent research on the underlying neurobiological basis of ADHD has focused increasingly on neuronal connectivity and synchronisation between brain areas.[15] Studies using functional MRI have found atypical connectivity in the resting-state brain network of individuals with ADHD.[16 17] Similarly, studies measuring the coherence between different EEG channels in children diagnosed with ADHD and the effect of stimulant medication have reported significant differences between the groups as well as between good and poor responders to medication.[14 18 19]

The methods available to analyse EEG have improved greatly in recent years with advancements in signal processing techniques and statistical methods. In particular, multivariate statistical approaches enable the inclusion of a wide range of the available EEG measures into a single classifier, avoiding the need to concentrate on individual channels and frequency bands and potentially improving the accuracy and robustness of EEG-based diagnosis. Magee *et al*[20] used a combination of factor, cluster and regression analysis to develop a diagnostic classifier for a homogeneous group of patients with ADHD based on EEG power measures across all frequency bands and channels, obtaining an overall classification sensitivity of 89.0% and a specificity of 79.6%. Poil *et al*[21] classified ADHD adults versus controls with 67% sensitivity and 83% accuracy with support vector machine classification. Such a multivariate statistical approach can be further extended to include multiple EEG features, including coherence measures.[22 23] These are particularly relevant in ADHD as EEG coherence reflects the connectivity and synchronisation of different brain areas, thus providing potential measures of the underlying dysfunction. Further, as EEG features change significantly with age, particularly in children,[24 25] chronological age can be included as a feature in the analysis, to account for natural brain development. The aim of this study was to develop and test a multivariate diagnostic classifier of ADHD based on EEG coherence measures and chronological age, using data from a large cross-sectional cohort of patients with ADHD and controls covering a broad age range.

METHODS

Participants

Six hundred and sixty-one children and adolescents were recruited into this study: 310 participants diagnosed with ADHD and a control group of 351 participants not diagnosed with ADHD. The age range was 5.8–14 years, the average age being 9.6 years for the ADHD group and 9.5 years for the control group. The male:female ratio was 3:1 for the ADHD group and 1:1 for the control group. The participants in the ADHD group were recruited in two specialised centres in Reykjavik, Iceland: the Department of Child and Adolescent Psychiatry at Landspitali University Hospital and the Health Care Centre for Developmental Disorders. The participants in the control group were recruited in three schools in Reykjavik, selected for reasons of convenience.

The individuals in the ADHD group were diagnosed according to Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV)[2] using the K-SADS-PL semistructured interview,[26–28] performed by experienced clinicians. There are three subtypes of ADHD and, in this study, 33% of the participants in the ADHD group were predominantly inattentive, 2% were predominantly hyperactive/impulsive, and 65% were of the combined subtype. The mean score on the ADHD Rating Scale-IV for the ADHD group is 2.84 SD above the age-appropriate norm.

As we wanted to include a wide range of participants typical of the broad spectrum of patients with ADHD typically presenting in the clinic, no exclusions relating to medication status were applied. Therefore, the ADHD group included the following three participants: medication-naïve patients (N=150 recordings), patients receiving treatment at the time of the recording (N=100 recordings), and patients on medication (N=65) but not actually receiving treatment at the time of the recording.

Comorbid disorders are common in ADHD and, again, were not excluded in order that the patients recruited would be typical of the normal range seen in clinic. The only exclusion criterion applied was moderate or severe intellectual disability. In our ADHD group, 60% of the participants had at least one comorbid disorder and 22% had two or more. The most common comorbid disorders were oppositional defiant disorder (N=92), autism spectrum disorder (N=41), anxiety disorders (N=28) and tics (N=25). These types and frequencies are comparable to the comorbidities presented in the study of Patel.[29] The parents of the participants in both groups provided information on their history of head injuries, migraine, epilepsy, tics and sleep disturbances but none of these were applied as exclusion criteria.

The children and adolescents in the control group were reported to be free of any mental or developmental problems by their parents. Additionally, they all had a score of less than 1.5 SDs above the age-appropriate norm on the ADHD Rating Scale-IV (mean score −0.31 SD from norm) (table 1).[30–32]

The parents or other caregivers of all participants provided written informed consent prior to participation.

EEG data acquisition

The EEGs were recorded using NicoletOne EEG Systems from Natus. Recordings were made at a sampling rate of 512 Hz for 3 min with eyes closed at rest. Participants were seated in a chair and were alerted if they moved too much or if their EEG showed signs of drowsiness. The amplifier had a band pass from 0.5 to 70 Hz, with a 50 Hz notch filter. The electrodes were placed on the scalp according to the international 10–20 system using 17 electrodes: Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, O1 and O2, all referenced to Fpz. The impedance was kept below 5 kΩ for all electrodes. Eye movements were monitored for horizontal and vertical movements by measurement of the electrooculogram. The recordings were re-referenced to an average montage prior to subsequent data analysis, which was carried out in the Matlab environment from MathWorks. According to the protocol, the recording was to be repeated if a technical problem occurred. As a result, no participants were excluded due to bad quality EEG.

In total, 351 recordings were obtained from control participants (one per participant). Of the 351 recordings obtained from the 310 patients with ADHD, 100 were recordings from patients on medication (methylphenidate N=76, atomoxetine N=22, methylphenidate and atomoxetine N=2) and 251 were recordings from patients on no treatment. 41 of the patients had their EEG recorded twice, once while not on treatment and again at a different time while on treatment.

The recordings were divided into two separate cohorts. The first ‘training’ cohort, consisting of 315 ADHD and 315 control recordings, was used to train the diagnostic classifier. The second ‘test’ cohort, consisting

Table 1 Details of the ADHD participants assigned to the training cohort and the test cohort, including gender, number of comorbidities and ADHD subgroups, and if they were medicated at the time of the recording (two visits means there is one recording from the subject on medication and 48 h of free medication)

	Training group	Percentage	Test group	Percentage
Total participants	274	100	36	100
Male	212	76	26	72
Female	62	24	10	28
No comorbidity	109	38	11	31
1+ comorbidity	165	62	20	56
2+ comorbidity	61	22	5	14
ADHD IA	89	34	13	36
ADHD COM	180	64	22	61
ADHD H/I	5	2	1	3
Medicated	59	33	10	28
Non-medicated	174	67	26	72
2 visits	41	13	0	0

ADHD, attention deficit hyperactivity disorder.

Table 2 Details of the EEG recordings assigned to the training cohort and the division into four age groups

Training set Age group	ADHD Minimum age	ADHD Maximum age	N	Control Minimum age	Control Maximum age	N
1	5.9	8.3	90	5.8	7.8	90
2	8.4	9.9	90	7.8	10.0	90
3	10.0	12.0	90	10.1	12.3	90
4	12.1	13.8	45	12.3	14.0	45
1–4	5.9	13.8	315	5.8	14.0	315

ADHD, attention deficit hyperactivity disorder.
These data were used to train classifiers for ADHD vs controls.

of 36 ADHD and 36 control recordings, was not involved in the training process and was used solely for independent testing of the classifiers obtained.

In both cases, the cohorts were subdivided into four separate age ranges to enable investigation of the utility of age-specific classifiers. In addition, the training cohort was divided into three equal age-independent subcohorts consisting of 105 ADHD and 105 control recordings apiece, each with a similar age distribution covering the entire range, by dividing each of the age groups into three equal parts, to enable investigation of the variability of age-independent classifiers trained on different data sets. Details of the cohorts and age-specific subgroups are provided in tables 2 and 3.

Signal processing and statistical analysis

The coherence between 12 different electrode pairs (6 intrahemispheric and 6 interhemispheric), for each of the 16 different spectral features, was extracted from the EEG recordings, giving a total of 192 coherence measures. Details of the spectral features and electrode pairs used are given in table 4; note that only coherence measures (ie, not absolute or relative powers) were used in the construction of the classifiers. In addition, the chronological age of the subject was used as a feature in the data analysis. The reliability of the EEG features used in this study has already been investigated.[23 33] An automatic artefact removal scheme is applied by a robust fit of each feature.

The spirit of the feature extraction is to capture the relevant degrees of freedom in the multivariate signal. In order to capture the connectivity degrees of freedom, the choice was to consider the autocorrelation function between electrodes in the average montage. The spectral features related to connectivity were then estimated from that. In practice, this is done by considering the autocorrelation function for 2 s segments and evaluating the spectrum for each segment. The segments considered are all segments within the selected recording with a 1sec overlap. A Bartlet window is applied to each segment. The analysis results in a spectrum for each segment. This ensemble is then used in order to estimate a representative spectrum by applying robust fitting over all spectra. In that way, incidental artefacts are avoided. This evaluation was repeated for five consecutive 36 s intervals of the recording. The outcomes for the intervals were then averaged and applied. The classical qEEG spectral features for each channel are obtained in a similar manner, again in the average montage.

The data are analysed applying a statistical pattern recognition (SPR) technique, based on support vector machines, which is used to construct a classifier from two groups of qEEGs, for example, qEEGs from groups A and B.[10] When an EEG is classified, the classifier returns an index, the A–B index, with a value between 0 and 1. If the A–B index is close to 0, the EEG is indistinguishable from the EEGs in group A, and if the A–B index is close to 1, the EEG is indistinguishable from the EEGs in group B. Each classifier relies on a set of 20 features out of the 193 available features. Twenty features were chosen because there is experience in using that number of features from an earlier work where the size of groups is comparable.[23] Even though it is possible that some of those features are redundant, a usable set of features has been obtained. For each classifier

Table 3 Details of the EEG recordings assigned to the test cohort and the division into four age groups

Test set Age Group	ADHD Min age	ADHD Max age	N	Control Min age	Control Max age	N
1	6.5	8.2	8	6.3	7.3	10
2	8.4	9.8	9	7.8	9.8	8
3	10.4	12.0	6	10.2	12.2	11
4	12.2	14.0	13	12.3	13.6	7
1–4	6.5	14.0	36	6.3	13.6	36

These data were used for independent testing of the classifiers obtained.
ADHD, attention deficit hyperactivity disorder.

Table 4 Coherence features extracted from the EEG for the statistical pattern classifiers

Spectral feature	Description
1	Power in the δ frequency band (0.5–3.5 Hz)
2	Power in the θ frequency band (3.5–7.5 Hz)
3	Power in the α_1 frequency band (7.5–9.5 Hz)
4	Power in the α_2 frequency band (9.5–12.5 Hz)
5	Power in the β_1 frequency band (12.5–17.5 Hz)
6	Power in the β_2 frequency band (17.5–25 Hz)
7	Power in the γ frequency band (25–40 Hz)
8	Relative power in the δ frequency band
9	Relative power in the θ frequency band
10	Relative power in the α_1 frequency band
11	Relative power in the α_2 frequency band
12	Relative power in the β_1 frequency band
13	Relative power in the β_2 frequency band
14	Relative power in the γ frequency band
15	Total power of the EEG power spectrum (0.5–40 Hz)
16	Peak α frequency
Electrode pairs for which the coherences were evaluated for each spectral feature:	
	Far intrahemispheric
1–6	F3/O1, F4/O2, F3/P3, F4/P4, C3/O1, C4/O2
	Far interhemispheric
7–12	F3/F4, T3/T4, C3/C4, T5/T6, P3/P4, O1/O2

construction, there are therefore 8×10^{26} distinct possibilities. A genetic algorithm[34] was applied to select the features used in the construction of the classifier for each pair of groups. The target value of the genetic evolution of classifiers was the area under the curve (AUC) of the corresponding receiver operating characteristic (ROC) curve. The AUC represents the quality of the classifier; if AUC=0.5, the classification is random, and if AUC=1, then the classification is perfect. The objective was not to find the best classifier in each case, which is a near impossible task, but rather to find a classifier with clinically acceptable qualities.

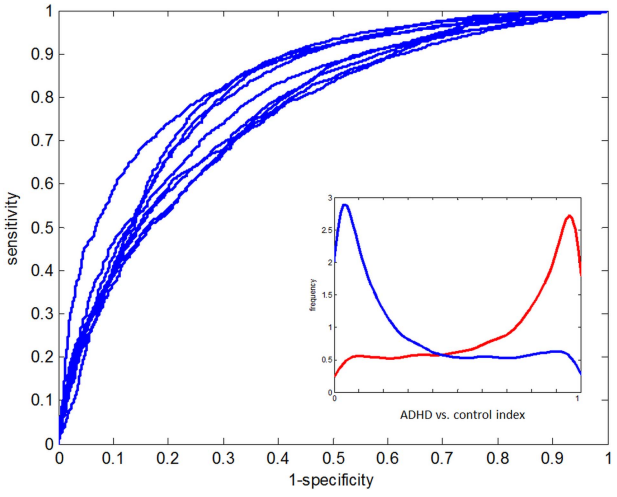

Figure 1 Receiver operating characteristic (ROC) curves corresponding to the nine age-independent classifiers for attention deficit hyperactivity disorder (ADHD) participants and control participants in the age range 6–14 years. The inset shows the separation of the ADHD group (red) from the control group (blue) in the classifiers as evaluated by 10-fold cross-validation. The ROC statistics are listed in table 5.

Statistical properties of the classifiers, including the AUC, accuracy, sensitivity and specificity, were estimated using 10-fold cross validation.[23] The SDs of those are estimated using the bootstrap approach.[35] The classifiers are categorised by the AUC value: excellent (AUC ≥0.90), good (0.9 >AUC ≥0.8), and fair (0.8 >AUC ≥0.7).

To obtain a non-biased evaluation of the importance of the chronological age it was given equal weight to the EEG features. Thus, whether or not it was included in the best set of features was determined solely by the random processes of the evolutionary algorithm.

Two approaches to the classifier construction were investigated in this study. First, age-independent classifiers were constructed, using data from participants distributed evenly over the entire age range; and second, age-specific classifiers were generated for each age group independently.

Age-independent classifiers

Nine ADHD versus control classifiers were constructed from all possible pairs of the three control and ADHD subcohorts of the training cohort, each having a similar age distribution across the entire range and containing 105 recordings. This approach is more robust than generating a single classifier for a single large data set and also enables the variability of the classification system to be estimated. This methodology is based on our experience from our previous work.[23] The point is to avoid imbalances in group sizes and increase robustness. Also, the time it takes to calculate the AUC for thousands of classifiers is relatively short (days) for group sizes of around 100.

Age-specific classifiers

Separate ADHD vs. control classifiers were constructed for each of the four age groups in the training cohort (see table 2). Thus, the classifiers for age groups 1–3 were constructed using data from 180 recordings, 90 from the ADHD group and 90 from the control group. The classifier for age group 4 was based on data from 90 recordings, 45 from the ADHD group and 45 from the control group.

Finally, to provide an independent assessment of the accuracy of the classifiers generated, the recordings from the test cohort (see table 3), which were not used in the training of the classifiers, were evaluated. The classification of an individual results in an ADHD versus control index, which ranges from 0 to 1. If the index is below 0.50, the individual is classified as a control but ADHD otherwise.

Table 5 The ROC curve statistics for the nine age-independent ADHD versus control classifiers

Classifier: nr	AUC	Tp	Fn	Tn	Fp	Accuracy	Age (Y/N)	AUC category
1	0.82	0.80	0.20	0.72	0.28	0.76	Y	Good
2	0.80	0.78	0.22	0.67	0.33	0.72	Y	Good
3	0.82	0.85	0.15	0.66	0.34	0.75	Y	Good
4	0.85	0.78	0.22	0.76	0.24	0.77	Y	Good
5	0.76	0.75	0.25	0.64	0.36	0.70	N	Fair
6	0.81	0.78	0.22	0.72	0.28	0.75	Y	Good
7	0.77	0.62	0.38	0.78	0.22	0.70	Y	Fair
8	0.75	0.73	0.27	0.65	0.35	0.69	Y	Fair
9	0.77	0.79	0.21	0.62	0.38	0.70	Y	Fair
Mean (SD)	0.79(0.03)	0.76(0.06)	0.24(0.06)	0.69(0.06)	0.31(0.06)	0.73(0.03)		

The Age column indicates whether not the chronological age is one of the features in the corresponding classifier (Y: yes; N: no).
ADHD, attention deficit hyperactivity disorder; Fn, false negatives; Fp, false positives; ROC, receiver operating characteristic; Tn, true negatives; Tp, true positives.

In the case of the age-independent classifiers, each test cohort recording was classified nine times, once for each classifier, and the overall result for the subject was then obtained using the average of the nine ADHD indices.

RESULTS

Training and validation of the classifiers

Age-independent classifiers

Nine age-independent classifiers were constructed, one for each pair of ADHD and control subcohorts in the training cohort. The resulting classifiers are presented in figure 1 by their corresponding ROC curves. The 10-fold cross-validation statistics and the corresponding category for each classifier are shown in table 5. Five classifiers are good and four classifiers are fair. Overall, the system of nine classifiers is on the borderline of good to fair with AUC=0.79±0.03.

The inset in figure 1 shows how well the ADHD and control groups are separated in this system, based on 10-fold cross-validation. There is some overlap, which is to be expected, but the groups have been separated successfully.

In table 5, it is indicated whether chronological age was one of the features used in the classifier. In eight out of the nine classifiers, age has been selected as a feature by the evolutionary algorithm.

Age-specific classifiers

Four age-specific classifiers were constructed, one for each age group (table 6). The resulting classifiers are presented in figure 2 by their corresponding ROC curves. The 10-fold cross-validation statistics and the corresponding category for each classifier is shown in table 6. Three classifiers are good and one is excellent. Overall, the system of four classifiers is on the borderline of excellent to good with AUC=0.88±0.04.

Chronological age was selected as a feature by the evolutionary algorithm for the two youngest age groups, see table 6, but not for the two older age groups.

Classification of test cohort

Both systems, the age-independent classifiers and the age-specific classifiers, were used to classify independent data from the test cohort of 71 recordings, with the results shown in tables 7 and 8.

The results are in agreement with the ROC statistics of both systems obtained during training and validation. The overall accuracy of the age-independent system when applied to the test cohort is 76%, compared to the ROC accuracy from cross-validation of 73%±3% obtained during validation. In the case of the age-specific system, the overall test cohort accuracy is 76%, compared to the corresponding ROC accuracy of 81%±4%.

Table 6 The ROC curve statistics for the four age-specific ADHD versus control classifiers

Classifier: age group	AUC	Tp	Fn	Tn	Fp	Accuracy	Age (Y/N)	AUC category
1	0.85	0.85	0.15	0.70	0.30	0.78	Y	Good
2	0.87	0.87	0.13	0.74	0.26	0.80	Y	Good
3	0.84	0.78	0.22	0.78	0.22	0.78	N	Good
4	0.94	0.87	0.13	0.88	0.12	0.87	N	Excellent
Mean (SD)	0.88 (0.04)	0.84 (0.04)	0.16 (0.04)	0.77 (0.08)	0.23 (0.08)	0.81 (0.04)		

The AUC shows good to excellent accuracy.
The Age column indicates whether or not the chronological age is one of the features in the corresponding classifier (Y: yes; N: no)
ADHD, attention deficit hyperactivity disorder; AUC, area under the curve; Fn, false negatives; Fp, false positives; ROC, receiver operating characteristic; Tn, true negatives; Tp, true positives.

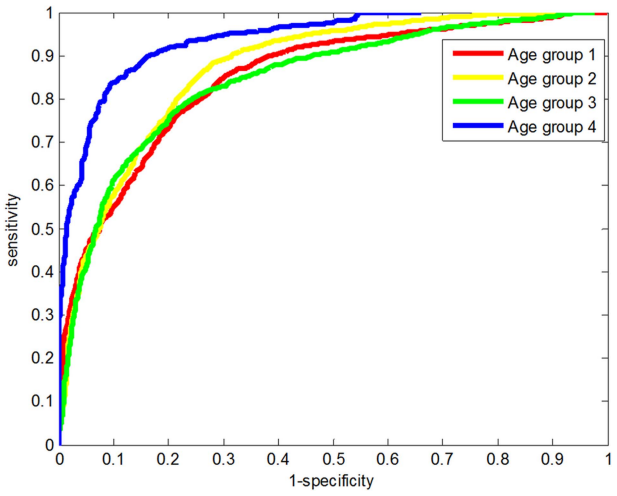

Figure 2 Receiver operating characteristic (ROC) curves corresponding to the four age-specific classifiers for attention deficit hyperactivity disorder (ADHD) participants and control participants. The age groups are defined in table 2. The corresponding ROC statistics are listed in table 6.

Identifying the most relevant EEG coherences

The optimal set of 20 features resulting from an evolutionary search does not necessarily contain only good features, in terms of separating the two training cohorts. Therefore, it is more sensible to select a few thousand of the classifiers generated by the evolutionary algorithm and identify those features that appear most often as the most relevant ones. Using this approach, the most relevant EEG coherence features are interhemispheric coherences in the central region of the brain. More specifically, these are all T3/T4 and C3/C4 coherences, except for the coherences in the α_2 band. The ADHD group shows elevated coherence values in the total power and all frequency bands except the α_2 band when compared to the control group. This is in accordance with a previous study by Barry *et al*[25] who reported an increase in the same interhemispheric EEG coherence values in the θ frequency band for the ADHD group when compared to controls. Furthermore, the results do not overlap with the main results of Duffy and Als[36] presenting the main EEG coherence features in autism spectrum disorder that are different from controls.

Table 7 Test data classified using the nine age-independent classifiers

Age group	Tp	Fn	Tn	Fp	Accuracy
1	0.70	0.30	0.88	0.12	0.79
2	0.63	0.37	0.67	0.33	0.65
3	0.73	0.27	0.83	0.17	0.78
4	0.86	0.14	0.77	0.23	0.82

Overall accuracy is 76%. The SD is 0.2 for all numbers in the table.
Fn, false negatives; Fp, false positives; Tn, true negatives; Tp, true positives.

Table 8 Test data classified using the four age-specific classifiers

Age group	Tp	Fn	Tn	Fp	Accuracy
1	0.70	0.30	0.75	0.25	0.73
2	0.75	0.25	0.67	0.33	0.71
3	0.64	0.36	0.83	0.17	0.74
4	0.71	0.29	1.00	0.00	0.86

The overall accuracy is 76%. The SD is 0.2 for all numbers in the table.
Fn, false negatives; Fp, false positives; Tn, true negatives; Tp, true positives.

Effects of comorbidity, ADHD subtype, medication, gender and severity of symptoms

In a cross-sectional cohort of ADHD individuals, more than half of them have a single comorbidity and a substantial portion has two comorbidities. In order to compare the ADHD individuals with no comorbidity with the ADHD individuals who have one or more comorbidities, the ADHD versus control indices were compared using ROC curve statistics. The results are shown in table 9. The two groups are indistinguishable in the training cohort.

The other corresponding subgroups were compared in the same manner and the results shown in table 9. In none of the comparisons do the two subgroups differ with respect to the ADHD versus control index (AUC<0.6).

The ADHD versus control index does not correlate with the severity of symptoms in the ADHD group in the training set, measured with the ADHD Rating Scale. The correlation coefficient is 0.033.

The training cohort can thus be considered to be independent of those factors. There are no effects on the classifiers due to comorbidity, ADHD subtype, medication, gender or severity of symptoms.

DISCUSSION

The results of the current study show differences in the EEG coherence of children and adolescents diagnosed with ADHD and healthy controls across a broad age range. Analysis of these recordings has produced classifiers based on features that separate the groups of patients with ADHD and controls. Although the statistical pattern analysis of EEG coherences has previously been used successfully for autism and Alzheimer's disease,[23 36] to the best of our knowledge this is the first time it has been demonstrated in patients with ADHD.

In addition to cross-validation, a cohort of completely independent EEG recordings that were not used in training the classifiers was used for testing. Using independent data to validate classification algorithms is the gold standard approach to assessing their validity.

The age-specific classification approach is more accurate (76% accuracy in the independent test cohort and ROC accuracy of 81%±4%) than the age-independent version (76% accuracy in the independent test cohort and ROC accuracy of 73%±3%). In eight out of the nine

Table 9 ROC curve statistics for the separation of various subgroups in the cross-sectional ADHD cohort and the control cohort

	AUC	Accuracy	Sensitivity	Specificity
ADHD w/wo comorbidity*	0.54	0.56	0.73	0.39
ADHD COM versus ADHD IA	0.52	0.53	0.43	0.64
ADHD on/off medication†	0.51	0.53	0.47	0.60
ADHD girls versus boys	0.59	0.57	0.47	0.68
Control girls versus boys	0.53	0.55	0.72	0.38

*w/wo: with vs without.†On/off: on vs off.
ADHD, attention deficit hyperactivity disorder; ROC, receiver operating characteristic.

age-independent classifiers, and in age-specific classifiers for the younger two of the four age ranges, the evolutionary algorithm selected chronological age as one of the key features. In addition, the accuracy was highest for the oldest age group in all cases. These results reflect the high importance of age, which is to be expected since the brain matures significantly in the critical age range that we have studied (6–13 years), particularly at the younger end, resulting in significant changes in their EEG.[37 38] According to Shaw *et al*[39], the cortical development of children with ADHD is lagging behind those not diagnosed with ADHD. As the oldest age group is close to entering puberty, it is possible that a larger part of the participants in the control group has already moved to puberty than in the ADHD group. As children reach puberty, they experience hormonal and physical changes, and this might be one of the factors that explains the high accuracy in the oldest age group.

Despite the higher diagnostic accuracy of the age-specific classifiers, the age-independent classifiers have a particular potential application in monitoring brain function over time. If chronological age is removed, the other features remain the same as the age of the subject increases, thus enabling longitudinal measurements.

These results support those of previous published studies showing differences in various EEG coherence features of children diagnosed with ADHD compared to controls.[18 20]By using the coherence features, which represent the synchronisation between brain areas, and combining all the measures into a single classifier, we obtain more robust results than by analysing individual coherences between brain regions separately. In addition, our findings are consistent with the increasingly compelling results linking ADHD to deficits in brain connectivity.[7 40 41]

The patient group is highly heterogeneous, which can be considered not only as a limitation but also as a strength of the study, because it reflects the realities of clinical practice. The included participants were diagnosed with different subtypes of ADHD and had a range of comorbidities. Some of them were on treatment, some were not receiving treatment at the time of the recording and others were medication naïve. This patient group is highly heterogenic by nature, and hence a clinical diagnostic method developed for the general clinical population is likely to be more widely applicable and have greater clinical utility.

The participants in the study were all recruited in Iceland and the EEG recordings were all made with similar hardware and software. Hence, both the underlying population and EEG equipment were quite tightly controlled. To widen the validity, it would be interesting to test the classifiers with different EEG equipment and with a sample from different populations. Subsequently, the database could be extended to EEG recordings from children with autism spectrum disorder, anxiety, oppositional defiant disorder and other relevant disorders. Such a database would enable the building of a series of classifiers which would pave the way for differential EEG-based diagnosis of psychiatric disorders in children.

In conclusion, this study demonstrates that an EEG-based method using classification algorithms can bring a new perspective to the diagnosis of ADHD in children and adolescents. There is a need for such a system to provide not only the most accurate possible diagnosis at a single point in time, but also to enable the monitoring of brain function longitudinally. These requirements can be met through the age-specific and age-independent classifiers, respectively. Clinically, the diagnosis of ADHD is based on several sources of information, including standardised interviews, rating scales, developmental and medical history. No single source of information can be expected to have 100% accuracy, so a clinical decision must be based on several sources, sometimes providing conflicting information. The EEG classification serves as an additional source of information and has proved to be a helpful addition for the authors who have used it in their clinical work. The novel application of EEG-based classification methods presented here can offer significant benefit to the clinician by improving the accuracy of initial diagnosis and ongoing monitoring of children and adolescents with ADHD.

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NB contributed to the study design and quality control. GHJ managed the quality control, conducted the analysis and contributed to the study design, interpretation and the writing of the manuscript. KJ had the idea for the overall strategy of the research and managed the data analysis, and contributed to the interpretation and writing of the manuscript. All authors revised and approved the final manuscript.

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