Title: Discrimination of ADHD Subtypes Using Decision Tree on Behavioral, Neuropsychological and Neural Markers

Running title: Discrimination of ADHD Subtypes

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Abstract

Introduction: Attention Deficit/Hyperactivity Disorder (ADHD) is considered as a well-known neurodevelopmental disorder. Diagnosis and treatment of ADHD can often lead to a developmental trajectory toward positive results. The present study aimed to implement decision tree method to recognize children with and without ADHD, as well as ADHD subtypes.

Methods: In the present study, the subjects included 77 children with ADHD (subdivided into ADHD-I, N= 25; ADHD-H, N=14 and ADHD-C, N=22) and 43 typically developing children matched by IQ and age. Child Behavior Checklist (CBCL), Integrated Visual, and Auditory Test (IVA) and quantitative EEG during eye closed resting state were utilized to evaluate the level of behavioral, neuropsychology and electrophysiology respectively using a decision tree algorithm.

Results: Based on the results, excellent classification accuracy (100%) was obtained to discriminate children with ADHD from the control group. In addition, the ADHD subtypes including combined, inattention and hyperactive/impulsive subtypes were recognized from others with accuracy of 80.41%, 84.17% and 71.46%, respectively.

Conclusion: Our results showed that children with ADHD can be recognized from the healthy controls based on the neuropsychological data (sensory-motor parameters of IVA). In addition, subtypes of ADHD can also be distinguished from each other using behavioral, neuropsychiatric and electrophysiological parameters. The findings suggest decision tree method may present an efficient and accurate diagnostic tool for the clinicians.

Keywords: ADHD Subtypes, Behavior, Neuropsychology, Electrophysiology, Decision Tree
Highlights

• The Decision tree method may present an accurate diagnostic tool for the clinicians.

• Neuropsychological measures can better recognize the children with and without ADHD

• When the behavioral, neuropsychology and electrophysiology measures are integrated, they can better differentiate ADHD subtypes.

Plain Language Summary

ADHD is a neurodevelopmental disorder with high rate prevalence can drastically influence children’s life. However, diagnosis of ADHD is still a challenging issue and there is no single test available to be used as the 'gold standard' for diagnosis of ADHD. However, evidence has shown that simultaneously use of behavioral, neuropsychological and electrophysiological approaches can be useful in identifying this disorder and its subtypes. In this regard, classification algorithms such as decision trees, can be used for categorizing the related features. The results of this study showed that utility of decision tree in three levels of behavioral,
neuropsychology and electrophysiology can be detect ADHD and its subtypes with high accuracy.

1. Introduction

ADHD is regarded as a neurodevelopmental disorder which was considered as a disorder of childhood. According to American Psychiatric Association (American Psychiatric Association, 2013(DSM-V)), ADHD with the prevalence of 5% can drastically influence children’s achievements in school, their social interactions, and their life quality. The core symptoms of ADHD are inattention, hyperactivity and impulsivity. Moreover, it is a psychiatric disorder which starts in the childhood and continues until adulthood in about 50% of evaluated cases (Cheung et al., 2015; Franke et al., 2018). However, diagnosis of ADHD is still a challenging issue, which roots to its etiologies. It is the reason that there is no single test available to be used as the 'gold standard' for diagnosis of ADHD. Therefore, researchers such as Barkley (1997) believe that clinicians should be able to examine multiple sources of evidence and put them together for diagnostics purpose.

One of the most effective ways for understanding ADHD is behavioral rating. In this regard, both parents and teachers are often requested to complete behavioral
rating scales like the Child Behavior Checklist ((CBCL) Achenbach & Rescorla, 2001) to determine presence or absence of the ADHD symptoms. Zenglein et al. (2016) indicated the availability of four CBCL-derived subgroups related to ADHD. These subgroups are different based on their risk factors, along with the severity of psychopathological symptoms. Although behavioral rating can provide quantitative information on a wide range of behaviors, but parents and teachers are normally failed to make a distinction between the symptoms. On the other hand, there is a poor correlation between assessment results of the parents and the teachers. Moreover, they also do not have a proper understanding of the symptom (Snyder, Rugino, Hornig, & Stein, 2015).

The importance of **neuropsychological assessment** in evaluation of ADHD is based on the hypothesis that particular features of neuropsychological performance are related to the behavioral symptoms. These features are specified based on Diagnostic and Statistical Manual of Mental Disorders (Tinius) criteria (Kofler, Rapport, Bolden, Sarver, & Raiker, 2010). One the tools that can be used for measuring cognitive performance of the subjects is Continuous performance test (CPT). The CPTs are considered as neuropsychological tests which measures individual’s attention and impulsivity and can be implemented in clinical practices as a part of the diagnostic process. However, the utility of continuous performance test (CPT) as an assessment tools for diagnosis ADHD is still a challenging issue. Studies have
shown deficits in the CPT is not observed in all the ADHD children (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Trommer, Hoeppner, Lorber, & Armstrong, 1988). Therefore, the CPT has not been suggested for individual diagnosis purpose. Nevertheless, there are studies that demonstrate sensitivity and specificity of 94% for diagnosis of ADHD using the integrated visual and auditory test (IVA) as a CPT test (Tinius, 2003). Furthermore, CPT test is able to identify this disorder from typically developed individuals, from other types of disorders, differentiate between subtypes of ADHD and those ADHD who display comorbidity with other disorders (see review article Hall et al., 2015). In addition, meta-analyses of cognitive functions by neuropsychological tests have pointed to dysfunction of cortical–subcortical circuitry that are different in various cognitive domains (Riccio, Reynolds, Lowe, & Moore, 2002; Wang et al., 2013). For instance, disruption in Fronto-temporo-limbic circuits and the cerebellum are positively linked to sustained attention and executive control. These circuitries can be traced using various neuroimaging techniques (Wang et al., 2013).

Among them, **EEG** is a common tool to study on neurodevelopmental disorders. It is a useful, non-invasive technique, with excellent temporal resolution. EEG-based studies have reported an increase in slow waves mainly in theta and a decrease in fast waves, especially in beta in children with ADHD (Barry, Clarke, & Johnstone, 2003; Buyck & Wiersema, 2014; Kitsune et al., 2015). Monastra, Lubar, and Linden
implemented theta and beta power in order to identify the individuals with and without ADHD with 90% sensitivity and 94% specificity. The theta to Beta ratio (TBR) was approved by the Food and Drug Administration (FDA) in 2013 as a diagnostic aid marker for the ADHD. Nonetheless, there are still some opposite findings about validity of TBR as diagnosis marker as well (Arns, Conners, & Kraemer, 2013; Loo & Makeig, 2012).

The present study aimed to classify the children based on their behavioral, neuropsychological and electrophysiological data. In this regard, classification algorithms such as decision trees, discriminant analysis, rule-based methods, logistic regression, and neural networks can be used for categorizing the related features. Studies have shown capability of the decision trees to accurately handle a multi-class classification problem. (Liaw & Wiener, 2002). A decision tree is considered as a top-down structure of nodes with directed edges that commonly used in data mining studies. The feature data of an input set is divided into different branches based on their information gain. The tree is formed by assigning the feature with highest gain ratio as the root and the process is continued until either all classes are recognized or the stopping criteria is reached (Han, Pei, & Kamber, 2011). Data gathering, processing and analysis are described in the following sections.
2. Method

2-1. Sample and Procedure

In order to conduct the present study, a sample of 104 boys were evaluated using CBCL, IVA and EEG respectively. Accordingly, Subjects with age range of 7-12 years were divided into four groups including ADHD combined (n=22), inattentive (n=25), hyperactive/impulsive subtype (n=14), and 43 typically developing controls (TDC). Based on the results, as shown in Table 1, no significant differences were observed in age and IQ scores between the groups.

The children with ADHD were recruited from different Child Psychiatry Clinics in Tehran. The Persian version of the Structured Clinical Interview for DSM-V (SCID) was used for diagnostic assessment, which was conducted by a board certified child and adolescent psychiatrist and a senior clinical psychologist. The average SCID-scores of inattentive, hyperactive/impulsive and combined DSM-V symptoms for the whole ADHD group (n=61) were 7.0 (SD=1.3), 8.2 (SD=2.9) and 6.3 (SD=1.3), respectively. The TDC group included the children without any abnormality based on the DSM-V criteria, who were selected from two elementary schools in Tehran. All subject had normal intelligence scores by using Raven's Progressive Matrices (90-124), right-handed based on self-report, with a normal or corrected-to-normal vision/hearing. However, a history of problematic prenatal or neonatal periods, brain
damage, central nervous system diseases, convulsive disorders and sensorimotor deficits were considered as the exclusion criteria.

Mean and standard deviation of groups based on age and intelligence

<table>
<thead>
<tr>
<th>Measure</th>
<th>TDC</th>
<th>ADHD-I</th>
<th>ADHD-H</th>
<th>ADHD-C</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>43</td>
<td>25</td>
<td>14</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>9.3 (1.4)</td>
<td>8.7 (1.2)</td>
<td>9.4 (1.7)</td>
<td>9.1 (.99)</td>
<td>2.03</td>
<td>0.11</td>
</tr>
<tr>
<td>IQ</td>
<td>102.9 (10.9)</td>
<td>103.5 (10.12)</td>
<td>107.5 (9.27)</td>
<td>103.1 (11.02)</td>
<td>0.1</td>
<td>0/95</td>
</tr>
</tbody>
</table>

2-2. Measures

2-2-1. Behavioral Rating

All of the subjects were evaluated by using the Child Behavior Checklist (CBCL, 1) after it was answered by their parents. The CBCL ver.6-18 is a standardized form which is filled out by parents for explaining their children’s behavioral and emotional symptoms. The questionnaire includes 118 items which can rate a child behavior during the last six months. The six DSM-oriented scales were used for the purpose of this study. The validity and reliability of the test could be found at http://www.aseba.org/.
2-2-2. Neuropsychological test

In order to evaluate inattention and impulsivity in both visual and auditory modalities, the Integrated Visual and Auditory (IVA) test (Sandford & Turner, 2000) is considered as a kind of Continuous Performance Test (CPT). This test provides the possibility of evaluating the commission errors (i.e., impulsivity and response inhibition, reflected in IVA “Prudence” scores), omission errors (i.e., inattention, reflected in “Vigilance” scores) and mean reaction time (Speed”). Furthermore, the IVA is able to differentiate different types of the ADHD including predominantly inattentive, predominantly hyperactive-impulsive, and combined (Sanford & Turner, 1995).

2-2-3. Neurophysiology

EEG data was registered by using a 19-electrode Mitsar amplifier (www.mitsar-medical.com) with sampling rate of 250 Hz. Electrodes were placed on the scalp by using a standard 10-20 montage (Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, O1, O2). In addition, the average of ears channels was utilized as the reference and FPz as the ground electrode and the electrode impedances were kept below 5 kΩ.

After recording, a self-written program using Matlab (https://www.mathworks.com) and EEGLab functions (https://sccn.ucsd.edu/eeglab/) were implemented to process the data. Standard preprocessing consisted of a band-pass filtering (1-40 Hz),
segmenting the data into epochs of 1 second duration, automatic rejection of disrupted channels conducted by using probability, spectrum and kurtosis criteria. Interpolating the rejected channels by averaging its spherical neighbors, eliminating unreliable epochs, and resorting to the mean of all the channels. In the next procedure, Fast Fourier Transform (FFT) was implemented for transforming the preprocessed EEG data into the frequency domain, and accordingly the absolute power and relative power of the data was computed in Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), and Beta (13-30Hz) frequency bands. Finally, the power ratio was evaluated for the theta/beta frequency band.

2-3. Classification paradigm

In the present study, a decision-tree method was used to classify the four above-mentioned groups using their behavioral, neuropsychological and neurophysiological data. In order to perform the classification using decision tree paradigm, first, a ‘training’ set of input parameters is utilized based on behavioral, neuropsychological and neurophysiological data of the subjects. Then, a decision tree structure is formed based of the information gain of each input parameters. The extracted model was used as a predictive decision support model for the data of new subjects. A decision-tree has a flowchart-like upside-down tree structure (Han, Pei, & Kamber, 2011), in which data parameter with the highest information gain among
all the parameters is placed as root of tree (e.g., sensory-motor parameter of IVA). Subsequently, other nodes are created and the tree branches expand. The nodes indicate the best capable parameter to separate the subjects. Expansion of the tree structure stops where all the classes are recognized or the maximum level of expansion is reached. After constructing the model, the decision-tree structure schematically demonstrates several features and conditions that are used to categorize all the subjects into their appropriate classes. Interpretation of the tree is based on the rules that can be used for identification of a class of subjects.

3. Results

Comparison of four classes of the subjects based on behavioral, cognitive and their neural markers using decision tree algorithm guided us to the results presented at Figure1. It should be noted that all the features were used as input parameters of the decision tree, and the nodes were selected based on their information gain scores. Table 2 also presents the interpretation of the results presented in Figure1. Each rule explain how we could discriminate a class of subjects while the most important features and their score criteria are also presented.

Table 2. Rule sets for decision tree to classify four class of subjects including typical, ADHD-Combined, ADHD-Inattentive, and ADHD-Hyperactive

<table>
<thead>
<tr>
<th>Path</th>
<th>Explanation of the Rule</th>
</tr>
</thead>
</table>

13
1 If Sensory Motor < 54 then class “Typical”
2 If Sensory Motor ≥ 54 and Mood Effective Disorder ≥ 89 then class “Inattentive”
3 If Sensory Motor ≥ 54 and Mood Effective Disorder < 89 and Visual Prudence ≥ 82.5 and power ration $(\delta/\gamma)_{Fp1} \leq 3.78$ then class “Hyperactive”
4 If Sensory Motor ≥ 54 and Mood Effective Disorder < 89 and Visual Prudence ≥ 82.5 and Absolute power $\beta_{Fp1} < 4.1$ then class “Combined”
5 If Sensory Motor ≥ 54 and Mood Effective Disorder < 89 and Visual Prudence ≥ 82.5 and power ration $(\delta/\gamma)_{Fp1} > 3.78$ then class “Inattentive”
6 If Sensory Motor ≥ 54 and Mood Effective Disorder < 89 and Visual Prudence < 82.5 and Absolute power $\beta_{Fp1} < 4.1$ then class “Inattentive”
Fig 1. Decision tree structure resulting from our dataset. Class labels were determined by typical (1), Combined (2), Inattentive (3), and Hyperactive (4). Beta_Fp1 demonstrates the absolute power in β- band for Fp1 location, while Fp1-delta VS gamma indicates the δ to γ power ratio for Fp1 location.

The accuracy of decision tree classifier for discrimination of the four classes of the subjects was 84.01% based on the test data in a one-leave-out manner, where one sample was left out from each group for evaluating the classifier in each step during the data partitioning the data.

Table 3. Performance of decision tree classifier to identify 4 different classes of subjects including typical, ADHD-Combined, ADHD-Inattentive, and ADHD-Hyperactive with one-leave-out validation

<table>
<thead>
<tr>
<th>Class of subjects</th>
<th>Classification accuracy (±std)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical</td>
<td>100 (±0.00)</td>
<td>0</td>
</tr>
<tr>
<td>Combined</td>
<td>80.41 (±9.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inattentive</td>
<td>84.17 (±4.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperactive</td>
<td>71.46 (±8.95)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

A graphical representation of the results are presented in Figure 2, 3. As presented in Figure1, the sensory motor visual as a cognitive score could discriminate the typical group from others with 100 percent accuracy. Then, Figure 2 presents that adding mood effect disorder as a behavioral feature could help to discriminate inattentive subjects with high accuracy, while they do not enable us to differentiate between combined and hyperactive subjects. Figure3 also show that adding neurophysiological features (delta/gamma ratio at channel FP1) with visual
prudence quotient is also helpful to discriminate hyperactive subject with a high accuracy rate. These results indicate that behavioral, cognitive and neurophysiological features have different level of importance for discrimination of specific subtype of ADHD.

Fig 2. Decision rules to discriminate typical subjects from ADHD groups based on the neuropsychological measures (sensory-motor score in IVA)
Fig 3. Representation of $\delta/\gamma$ ratio at Fp1 location for separating different types of ADHD

4. Discussion

A large body of research has focused on the use of data-driven techniques to classify clinical diagnostics data accurately. Our main aim in this study was to evaluate the utility of decision tree algorithm in three levels of behavioral, neuropsychological and electrophysiological data; and use it for classification of a population of typically developed, and 3 subtype of ADHD children. Based on the results, decision tree showed a qualification to classify the above-mentioned groups with an accuracy of 84.01%. Specifically, the sensory motor score in IVA test could perfectly discriminate typical individuals from the ADHD groups (100% accuracy). In
addition, the mood effective disorder as a CBCL parameter accompanying with the visual prudence in IVA test, and beta in Fp1 region and delta/gamma ratio in Fp1 region as EEG parameters showed a nearly perfect classified ADHD-C from other groups with 80.41% accuracy. Also, the mood effective disorder along with visual prudence and delta/gamma ratio in Fp1 classified ADHD inattentive group with accuracy of 84.17%. Finally, the mood effective disorder along with visual prudence and delta/gamma ratio in Fp1 distinguished ADHD hyperactive from other groups with accuracy of 71.46%. To the best of our knowledge, this is the first study which represented such a perfect diagnostic classification for the ADHD subtypes. This classification method is a highly reliable and accurate approach and has been confirmed for clinical diagnosis. Based on the results, sensory-motor parameter could recognize the children with and without ADHD, and accordingly it can identify ADHD subtypes better when behavioral and electrophysiological and other neuropsychological variables were added. Thus, the result is a highly sensitive and specific when the measures are integrated, compared to the cases in which each measure is used alone for classifying the ADHD subtypes.

Interestingly, the cutoff score of 54 for sensory motor parameter implemented in decision tree was only at the 56 percentile of standardized samples which is considered as the average range of the samples. This fact proposes that such as cutoff alone does not present a clinical impairment. However, when the sensory motor
score is implied in combination with other measures could enhance accuracy of diagnostic likelihood. Thus, this method can help the clinicians to design accurate, and economical rational diagnostics. In this context, the study has pinpointed the sensory–motor deficits which are observed in the ADHD individuals such as concerns with motor sequence learning (Adi-Japha, Fox, & Karni, 2011), motor response to stimuli (Gorman Bozorgpour, Klorman, & Gift, 2013), fine motor skills, articulation (Iwanaga, Ozawa, Kawasaki, & Tsuchida, 2006).

Previous studies such as Finch, Davis, and Dean (2015) have also reported that sensory motor can identify the children with ADHD with the accuracy of 95%. Assessment of sensory and motor deficits is considered as a main element of the neuropsychological assessments because sensory–motor deficits can be related to dysfunctions in the central nervous system. In general, a sensory–motor deficit represents an underlying neurological etiology that may lead to some behavioral changes in children. Such behavioral changes have been reported in previous studies. For instance, Davis, Pass, Finch, Dean, and Woodcock (2009) indicated a positive relationship between the sensory–motor functioning, and academic achievement as well as cognitive processing in children with ADHD.

On the other hand, previous studies using machine learning techniques have also demonstrated ability of the automatic algorithms to categorize children with and without ADHD by utilizing the behavioral, and the neuropsychological measures.
Various classification algorithms have been used. For instance, Bledsoe et al. (2016) classified healthy controls and ADHD combined individuals using their behavioral symptoms and neuropsychological performances. Using the decision tree algorithm, they could reach to 100% accuracy. In addition, Cohen (2013) also showed that the decision tree can classify autistic individuals and ADHD subjects from healthy individuals based on their behavioral profiles with an accuracy rates of 94% and 87%, respectively. Another interesting study by Santos, Bastos, Andrade, Revoredo, and Mattos (2011) implemented naive Bayes and decision tree algorithms to classify the data obtained for ADHD children while playing a computer game. The naive Bayes algorithm could produce 68% sensitivity and 67% specificity. Nevertheless, the decision tree algorithm was only able to produce 55% of sensitivity and specificity. Although, sensitivity of the algorithm was less or equal to 0.22 to discriminate the ADHD subtypes. As compared to previous studies, results of current study showed that EEG features could cover the heterogeneity of ADHD subtypes and make the more distinguishable.

Despite the high accuracy rate of classification of ADHD subtypes and healthy controls, this study suffer from some limitations. For instance sample size of the subject should be enhanced and measurement of other neuropsychological tests must also be included before generalizing the results to other populations. Moreover, it is
proposed to include ADHD comorbid disorders such as oppositional defiant and conduct disorder in the future studies.

**Ethical Considerations**

**Compliance with ethical guidelines**

Subjects were assessed on the basis of informed consent signed by the parents, and the research protocol approved by the Iran University of Medical Sciences Ethics Committee.

**Conflicts of interest**

The authors state that there are no actual or potential conflicts of interest.

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Reference


