Computers in Biology and Medicine 88 (2017) 93–99

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/compbiomed

Diagnosis of attention deficit hyperactivity disorder using imaging and signal processing techniques

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ARTICLE INFO

Keywords:
ADHD
Psychopathology
Dopamine
Pharmacological therapy
EEG
fMRI

ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) is the most common childhood psychiatric disorder that may continue through adolescence and adulthood. Hyperactivity, inattention and impulsivity are the key behavioral features observed in children with ADHD. ADHD is normally diagnosed only when a child continues to have symptoms of hyperactivity, impulsivity and inattention at a greater degree than the normal for six months or more. In recent years there has been significant research to diagnose ADHD in a quantitative way using medical imaging and signal processing techniques. This paper presents a review of recent research on diagnosis of ADHD using medical imaging and signal processing techniques. This research is especially valuable for early diagnosis of ADHD.

1. Introduction

Anomalous neural connectivity results in disrupted brain functionality leading to neuro-developmental disorders. Attention-Deficit Hyperactivity Disorder (ADHD), autism, mental retardation, cerebral palsy, conduct disorder, impairments in vision and hearing are some of the neuro-developmental disorders observed in children [1]. ADHD is one of the common neuro-developmental and psychiatric disorders observed during childhood that progresses into adulthood. It is associated with the functioning of the neurological system and brain [2].

According to National Institute of Mental Health (NIMH), the major symptoms of ADHD are inattention, difficulty in learning, restlessness, and impulsivity. Tendency to procrastinate, chronic lateness, irritability, mood swings, low self-esteem and sense of insecurity are some of the features observed in adults with ADHD. Around 70% of children with ADHD continue to have some amount of hyperactivity and impulsivity during their adolescence and adulthood [3]. Significant features of ADHD are summarized in Table 1.

According to the Centers for Disease Control and Prevention (CDC), 5.1 million children in the age group of 4–17 years have been diagnosed with ADHD. Mild ADHD can be diagnosed around 7 years, moderate ADHD around 6 years and severe ADHD is being diagnosed around 4 years of age. In the United States around 3.5 million children are on ADHD medication. It is found that male to female ratio with ADHD is approximately 2:1. Prevalence of ADHD depends on ethnic backgrounds. For example, in the U.S. 4.1 million Non-Hispanic children, 0.9 million African American children and 0.6 million Hispanic children are diagnosed with ADHD [7].

Statistics has shown that children with ADHD are on the rise. In 2003, the percentage of ADHD children was 7.3%; in 2009, the percentage rose to 9.5% and in 2011, the number of children with the diagnosis of ADHD was 11.0%. It is reported that on the average, the yearly percentage rise of ADHD children during the years 2003–2011 is 5% [8].

The Project to Learn about Youth- Mental Health (PLAY-MH) is an on-

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http://dx.doi.org/10.1016/j.compbiomed.2017.07.009
Received 5 May 2017; Received in revised form 21 June 2017; Accepted 6 July 2017

Table 1
Significant features observed in children with ADHD.

Authors	Symptoms	Characteristics
Anton et al. (2009) [4], Post et al. (2012) [5]	Inattentive behavior	● Difficulty in learning and concentration ● Poor handwriting ● Day dreaming ● Disturbed frame of mind
Anton et al. (2009), Aziz et al. (2012) [6]	Hyperactivity	● Highly restless ● Getting engaged into dangerous tasks ● Wriggle and writhe in their seats
Aziz et al. (2012), Post et al. (2012)	Impulsiveness	● Highly impatient ● Interrupting others ● Prowling

going research to define the psychopathology of ADHD. It is presumed that brain injuries, genetic, and environmental factors can also contribute to the ADHD pathogenesis. Fig. 1 shows the brain structures implicated in ADHD. The dorsal anterior midcingulate cortex (daMCC) is situated on the medial surfaces of the frontal lobes, referred as 24c'/32′ in humans. It acts inside the motor networks to improve the state of decision making and implementation [9]. It also maintains connectivity with attention, cognition, motor region including the dorsolateral prefrontal cortex (DLPFC), parietal cortex, striatum and premotor cortex [10].

With the advancement in technology and introduction of various analytical tools, research to identify the structure of the ADHD brain, its wave patterns and functional connectivity is on the rise. In recent years a number of researchers have used different neuro-imaging and signal processing approaches for the early detection of ADHD. This paper presents a review of recent research on diagnosis of ADHD using medical imaging and signal processing techniques such as Electroencephalography (EEG), Quantitative Electroencephalography (QEEG), magnetoencephalography (MEG), Magnetic Resonance Imaging (MRI), and functional MRI (fMRI) [11,12]. Summaries of probable risk factors and various medications for treatment of ADHD are also presented.

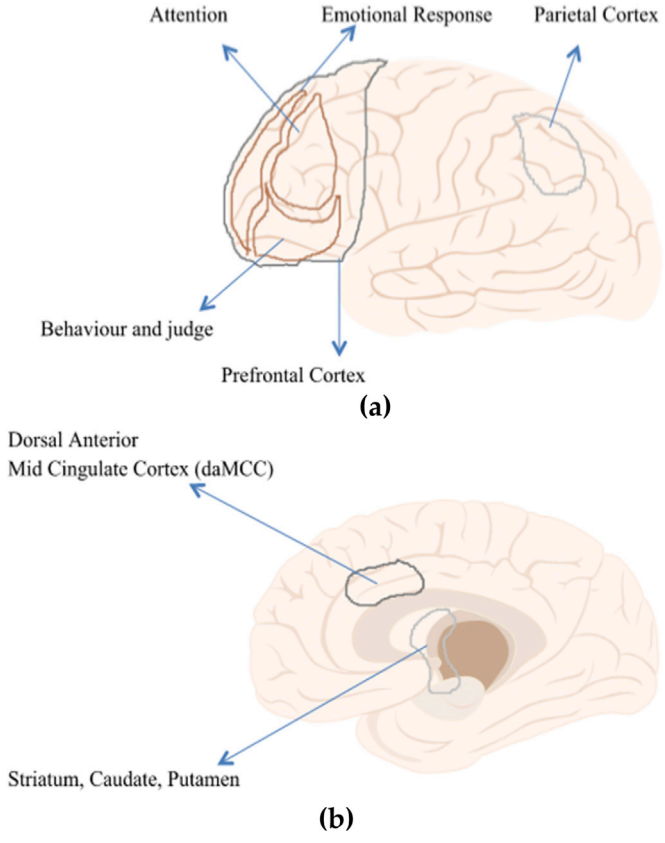

Fig. 1. Brain structures implicated in ADHD: a) the lateral prefrontal cortex, b) medial prefrontal cortex.

2. Risk factors

There are multiple factors that are presumed to cause ADHD. Some of the causative factors of ADHD are genetic, insufficient nutrition, environmental conditions and unexpected head injuries [13]. ADHD is a polygenic disorder due to additive effect of genes affecting serotonin, dopamine, gamma amino-butyric acid (GABA) and other neurotransmitters. Genetic and chromosomal studies are based on linkage and meta-analysis [14]. As an example fine mapping and genome linkage has revealed a linkage between chromosome bands 16p13, genes of serotonergic and dopaminergic system, containing DRD4, SLC6A3 and DBH and ADHD [15].

Copy number variants (CNVs) of genomic DNA in ADHD are studied during the genome-wide association studies [16]. CNVs linked with ADHD arise in the areas of genome connected with autism and schizophrenia. Genome-wide association studies are based on genetic variants in different individuals to check the association of variant and trait of the disorder [17].

The CNVs correspond to a large number of genome that is deleted, duplicated and inverted on certain chromosomes. Chromosomal microdeletions and microduplications lead to fragments of CNVs [18]. The DNA samples are sequenced and end sequences are delineated to genome of human reference, producing data related to mapping and type of structural variants [19]. In paired-end read mapping, paired reads are obtained from one DNA molecule showing corresponding conflicts in the mapping and permit the perception of insertions, deletions and inversion. The split-read mapping helps in detecting the occurrences in which part of a single read align are discontinuous to the reference genome [20]. Fig. 2 shows CNVs of genomic DNA in normal and ADHD.

ADHD is a complex disorder with polygenetic characteristics where multiple gene combinations contribute to the disorder. The presence of thinner brain tissue due to a genetic variation is visible in the ADHD brain and is reported to be associated with inattention in ADHD children [15]. Imbalance in food nutrients such as deficiency of essential fatty acids [21], sugars [22], high glycemic level in the blood can lead to the disconnected nerve fiber networks [23]. Complications in nerve fiber connectivity can result in brain dysfunction leading to inattention and hyperactivity. At least one study has shown artificial coloring and food dyes may contribute to development of ADHD [24].

A few studies have also reported that exposure to high lead concentration [25], fluorinated water [26], alcohol consumption [27] and smoking can also lead to the development of ADHD. Also, researchers have shown prefrontal viral infections, maternal anemia, lower serum level of iron and iodine, preeclampsia and trauma to the abdomen during pregnancy may be associated with ADHD [15,28]. Perinatal risk factors such as low birth weight, breech delivery, prematurity as well as postnatal viral infections, i.e., rubella, varicella, and measles may increase the risk of developing ADHD [29]. Further, encephalitis, head injury in early childhood, and endocrine disorders may be linked to ADHD.

3. Diagnosis of ADHD using brain imaging techniques

The strong desire to identify relevant bio-markers has brought together scientists from multiple disciplines to introduce novel analytical methods for the diagnosis. Different signal and image processing modalities have been used such as EEG [30–37], MRI [38,39], MEG [40], fMRI [41,42], single photon emission computed tomography (SPECT) [43], Positron Emission Tomography (PET), Diffusion Tensor Imaging (DTI) [44,45] and quantitative electroencephalography (QEEG) data [46]. Entropies have been applied to MEG data to differentiate normal and ADHD brains [47].

Hart et al. (2013) [48] performed a meta-analysis for inhibition and