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The neurophysiology of attention-deficit/hyperactivity disorder

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Abstract

Recent reviews of the neurobiology of Attention-Deficit/Hyperactivity Disorder (AD/HD) have concluded that there is no single pathophysiological profile underlying this disorder. Certainly, dysfunctions in the frontal/subcortical pathways that control attention and motor behavior are implicated. However, no diagnostic criteria or behavioral/neuroimaging techniques allow a clear discrimination among subtypes within this disorder, especially when problems with learning are also considered. Two major Quantitative EEG (QEEG) subtypes have been found to characterize AD/HD. Here we review the major findings in the neurophysiology of AD/HD, focusing on QEEG, and briefly present our previous findings using a source localization technique called Variable Resolution Electromagnetic Tomography (VARETA). These two techniques represent a possible objective method to identify specific patterns corresponding to EEG-defined subtypes of AD/HD. We then propose a model representing the distribution of the neural generators in these two major AD/HD subtypes, localized within basal ganglia and right anterior cortical regions, and hippocampal, para-hippocampal and temporal cortical regions, respectively. A comprehensive review of neurochemical, genetic, neuroimaging, pharmacological and neuropsychological evidence in support of this model is then presented. These results indicate the value of the neurophysiological model of AD/HD and support the involvement of different neuroanatomical systems, particularly the dopaminergic pathways.

Keywords: Attention-Deficit/Hyperactivity Disorder; QEEG; Neuroanatomical model

1. Introduction

Attention-Deficit/Hyperactivity Disorder (AD/HD), with or without hyperactivity, still remains one of the most controversial issues in child psychiatry, especially in the endeavor to clarify the relationship between this disorder and Learning Disability (LD). The controversy begins with the operational definition of this pathology and, in general, with the terminology for classification and evaluation of children with behavioral and cognitive problems. Over time, the label for defining children who have in common some degree of inattentiveness, distractibility, impulsivity, hyperactivity, aggressiveness and learning problems has been changed repeatedly until the current definition, which distinguishes those who are predominantly inattentive (AD/HDin), or predominantly hyperactive–impulsive (AD/HDhyp), from a combined type (AD/HDcom), as a part of the same syndrome, but distinct from LD (American Psychiatric Association, 1987, 1994).

No current diagnostic criteria or technique allows a clear discrimination among and within these two neuropsychiatric entities, and there is considerable comorbidity between these two classes of disorders. Small sample sizes and restricted patient sampling procedures make it difficult to generalize research findings about possible pathophysiological substrates that might serve to define this population of children. Further, both are associated with an increased incidence of other psychiatric problems, such as anxiety, conduct, oppositional defiant, obsessive–compulsive or mood disorders (Biederman et al., 1991; Cantwell and Baker, 1991; Semrud-Clikeman et al., 1992; Bird et al.,

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1993; Pliszka, 2000). Finally, the broad nature of interventional strategies required for these disorders suggests that a heterogeneous population of children may be subsumed under the denominations of AD/HDin, AD/HDcom and LD (Semrud-Clikeman et al., 1992; Mann et al., 1992; Barkley, 1997a; Weinberg and Brumback, 1992). Due to the difficulty of classification, epidemiological data are widely different from study to study. The prevalence of AD/HD has been estimated around 5–10% among school-aged children (Rostain, 1991; Schachar, 1991; Taylor et al., 1991; Cantwell, 2004; Scahill and Schwab-Stone, 2000; Brown et al., 2001) and the prevalence of LD around 5% (Lyon, 1996). A review of epidemiological studies using standardized diagnostic criteria suggests that 3–6% of the school-aged population (elementary through high school) may suffer from AD/HD, although the percentage of US youth being treated for AD/HD is at the lower end of this prevalence range (Goldman et al., 1998).

For the above-stated reasons, it would be of great importance to find a biological marker that could help physicians in making a differential diagnosis and selecting a treatment for children with learning and attention problems. A National Institute of Mental Health Committee has identified Quantitative Electroencephalography (QEEG) as a possible objective method to identify functional measures of child and adolescent psychopathology (Jensen et al., 1993). Compared with other methods of functional neuroimaging (PET, SPECT, fMRI), QEEG is easier to perform, less expensive, non-invasive and safer (Kuperman et al., 1990). In addition to QEEG, a new source localization method called Variable Resolution Electromagnetic Tomography (VARETA; Valdes-Sosa et al., 1996; Bosch-Bayard et al., 2001) provides a virtual MRI representation of the EEG generators within the brain. Such localization might yield further insight into the underlying pathophysiology of AD/HD.

In this paper, we summarize the major findings of neurobiological studies on AD/HD, highlighting convergent points of view about pathophysiological substrates. Consistent with these investigations, we describe our results using the VARETA method in an exploratory fashion in the two main EEG-defined subtypes of AD/HD children obtained with a QEEG analysis. We also examine the clinical role of these techniques in the evaluation of AD/HD brain dysfunction. According to our findings, we propose a neurophysiological model for AD/HD that substantially involves the dopaminergic pathways.

2. Neurophysiological studies

2.1. EEG studies

A wide literature of EEG research on AD/HD has been inconclusive in documenting the prevalence and the nature of any hypothetical neurophysiological dysfunction in these children (Stevens et al., 1968; Shetty, 1971; Blume, 1982; Andriola, 1983; Kellaway, 1990). In the last decade, some studies using conventional EEG have reported abnormal findings ranging from 30% to 60% in children with AD/HD (Small, 1993), while others reported a proportion of only 1 of 11 (Phillips et al., 1993). Thus, routine conventional EEG screening may be of limited value in childhood behavioral and cognitive problems without clinical evidence of a neurological disorder. However, a preliminary report of EEG changes associated with a double-blind, placebo-controlled administration of methylphenidate among children with AD/HD suggests that there may be different electrophysiological correlates to methylphenidate medication among those who are medication responders or non-responders (Loo et al., 1999).

2.2. QEEG studies

The possible clinical uses of QEEG have been reviewed by Hughes and John (1999). QEEG appears to have much to offer in relation to evaluation, diagnosis and treatment selection, as well as the monitoring of medication effects, by differentiating specific subtypes within the heterogeneous group of AD/HD. It may also help to identify neurophysiological mechanisms responsible for the development of this disorder (Prichep and John, 1990; Suffin and Emory, 1995; Kuperman et al., 1996; Chabot and Serfontein, 1996; Chabot et al., 1996, 1999, 2001). The most common finding in QEEG studies has been increased low-frequency activity, predominantly theta. Differences at low frequencies have been reported in both absolute and relative power between AD/HD children and control groups, particularly evident in the frontal and central regions (Mann et al., 1992; Montagu, 1975; Lubar et al., 1985; Lubar, 1991; Matsuura et al., 1993; Lazzaro et al., 1998). Generalized theta excess has been found in AD/HD children in both the resting state and during cognitive activity (DeFrance et al., 1996). This generalized theta excess has been reported to be accompanied by deficits in alpha and beta, with a greater degree of abnormality in AD/HDcom than in AD/HDin children (Clarke et al., 1998). With increasing age, the EEG of an AD/HDin group was found to change at a similar rate to the changes found in a normal group, with the differences (greater in males) in power levels remaining constant. In the AD/HDcom group, the power was found to change at a greater rate than in the AD/HDin group, with power levels of the two AD/HD groups becoming similar with age. These results are supportive of a two-component model of AD/HD, with the hyperactive/impulsive component maturing with age and the inattentive component remaining more stable (Clarke et al., 2001a). Further, this group of authors identified three EEG-based AD/HD subtypes based upon the cluster analyses of a sample of 184 AD/HD boys. These included a subset with increased theta and decreased delta and beta relative power, a second with increased theta and decreased alpha relative power with increased central/