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International Journal of Psychophysiology 58 (2005) 81 – 93
INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY
www.elsevier.com/locate/ijpsycho

The neurophysiology of attention-deficit/hyperactivity disorder

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Received 23 September 2004; received in revised form 8 January 2005; accepted 27 January 2005
Available online 24 June 2005

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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doi:10.1016/j.ijpsycho.2005.03.011

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/

posterior delta relative power, and a third subtype with increased beta and decreased alpha relative power (Clarke et al., 2001b).

In addition, Clarke et al. (2002) have demonstrated that the QEEG pattern of AD/HD was not altered by the presence of co-morbid oppositional defiant disorder, which has implications for possible applications in clinical practice. A small independent subset of AD/HD children with excess beta activity that was more prone to temper tantrums and to be moody has also been identified. The beta excess was found primarily in the frontal regions and may be associated with frontal lobe self-regulation and inhibition control (Clarke et al., 2001b). In this subset, treatment with stimulant medications for 6 months showed a decrease in absolute beta activity and frontal total power, although these changes represented a reduction in power, rather than a normalization of the QEEG (Clarke et al., 2001b). An increased theta/beta power ratio derived from a single vertex recording has been recently used to classify children with AD/HD compared to normal controls (Monastra et al., 1999). This study conducted with 469 participants, 6–20 years of age, has indicated that the QEEG scanning procedure was reliable ($r = .96$), consistent with the Attention-Deficit Disorders Evaluation Scale and the Test of Variables of Attention, and differentiated participants with AD/HD from a non-clinical control group ($p < .001$). The sensitivity of this QEEG-derived index was 90%, with a specificity of 94% (Monastra et al., 2001). A review of this literature has recently been published (Barry et al., 2003).

The Neurometric QEEG technique, developed by John et al. (1977, 1988) compares the QEEG of individuals with a normal database (John et al., 1983, 1989). The neurometric method has been shown to be a sensitive indicator of cortical electrophysiological dysfunction in children and adults with neurological and psychiatric diseases (John et al., 1983, 1992; Prichep and John, 1992). Using this method, Chabot and Serfontein (1996) and Chabot et al. (1996), showed that 80% of 407 ADHD and U-ADD children–similar to AD/HDcom and AD/HDin children (respectively) but defined using DSM-III-R criteria (APA, 1987)–had a QEEG frequency abnormality, with 38.1% showing a theta excess, 28.0% an alpha excess, and 13.1% a beta excess. Further, a specificity of 88% and a sensitivity of 93.7% were obtained for the discrimination between 310 normal children and 407 children with ADHD or U-ADD (6–16 years old). Moreover, ADHD/U-ADD could be distinguished from children with LD with a sensitivity of 97% and a specificity of 84.2%. Further, within a sample of 344 ADHD and U-ADD and 245 LD children, a cluster analysis procedure identified five major QEEG profiles, and two of these clusters contained approximately 90% of the ADHD and U-ADD children (Chabot et al., 2001). Within these two subtypes, the first was characterized by alpha excess in both absolute and relative power while the second displayed theta excess. Note that these two clusters were also differentiated by differences in power asymmetry, coherence and mean frequency and as such are not directly comparable to the results of Clarke et al. (2001b). Note also that Chabot and Serfontein (1996) identified an alpha excess subtype not reported by Clarke et al. (2001b).

The heterogeneity found among this population of children has also been reported in a study by Gustafsson et al. (2000), combining a SPECT analysis with QEEG and clinical signs in AD/HD, where the findings suggest that there may be at least two functional disturbances in AD/HD. QEEG has also been found useful in the optimization of treatment response to stimulant medications (Prichep and John, 1990; McIntyre et al., 1981; Steinhausen et al., 1984) Within the AD/HD population, QEEG differences were found between those who showed a short-term (initial response to one dose) positive response to treatment with dexamphetamine or methylphenidate and those who did not benefit. Although the sensitivity and specificity levels of this discriminant function were modest (68.7% and 67.5%), the function was very accurate (84.8%) in classifying children who had shown a previous negative response to either dexamphetamine or methylphenidate. Pre-treatment QEEG and behavioral measures showed a sensitivity of 83% and a specificity of 88.2% in predicting long-term treatment response to both (Chabot et al., 1996, 1999). A review of QEEG research and critical issues involved in its clinical utilization has recently been published (Chabot et al., 2005).

2.3. The VARETA technique

In the last few years a new method for localizing electrical activity in the brain, called Variable Resolution Electromagnetic Tomography (VARETA), has been developed. This neuroimaging technique allows an estimation of the distribution of the electrical generators for each frequency band within the brain, by applying a mathematical inverse solution to the EEG data. The anatomical definitions of regional probability for source localization used in VARETA are derived from a Probabilistic Brain Atlas (PBA) developed at the Montreal Neurological Institute (Evans et al., 1993). Use of the PBA obviates the need for individual MRI scans, in exchange for sacrificing precise anatomical localization. Three-dimensional coordinates for the position of each scalp electrode, defined by the International 10/20 Electrode Placement System, have been published (Scherg and Von Cramon, 1985). These coordinates were used to project each electrode position onto the scalp of the average head, thus placing the proportional EEG electrode set into spatial registration with the proportional PBA. Based on this EEG-MRI head model, the problem of the 3-D sources of EEG may be specified in the frequency domain (Valdes-Sosa et al., 1992, 1996; Bosch-Bayard et al., 2001). Resting, eyes-closed EEGs from over 300 normal individuals constituted a normative database for 'neurometricizing' VARETA using narrow band spectral analysis from 0.39 to 19 Hz in increments of 0.39 Hz (John

et al., 1977, 1988). Using the resulting set of normal values for narrow band spectral power at each scalp electrode (Valdes-Sosa et al., 1990, 1992), the sources of power at each frequency were localized. Three-dimensional color-coded tomographic images can then be generated, with source generator distributions superimposed upon the trans-axial, coronal and sagittal slices of the PBA. In each case, the frequency at which the maximum significance was found is taken as the frequency of the main source. The VARETA method is a useful adjunct to the QEEG analysis. It may confirm the neurometric QEEG results and provide additional information about the localization of the abnormal sources of surface electrical activity. Nevertheless, VARETA, like other inverse methods, has some limitations: it represents only an approximate solution for source generators, identifying the most probable neuroanatomical generators.

Our preliminary VARETA results (Chabot et al., 2001) indicated that the neural substrates of AD/HD involve a number of different brain structures. Specific regional abnormalities were observed in the two major EEG-defined subtypes of the DSM-III-R ADHD and U-ADD children we identified. The most significant abnormalities were found at 11 Hz (alpha band) and at 5.4 Hz (theta band), respectively. The distribution of the neural generators in these two sets of VARETA images were localized within basal ganglia and right anterior cortical regions at 11 Hz, and in hippocampal, para-hippocampal and temporal cortical regions at 5.4 Hz. These results provide evidence suggesting that the alpha and theta generators are located in two different neural systems and that the involvement of one or another of these systems may determine the distinctive QEEG and VARETA features of these two EEG-defined AD/HD subtypes. Interestingly, a study combining SPECT and QEEG analysis (Gustafsson et al., 2000) reported similar findings. Indeed, it has been hypothesized that there may be at least two functional disturbances in AD/HD, one specific neurodevelopmentally determined disturbance of the frontal lobes, especially of the right hemisphere, related to behavior deviance, and another disturbance of the integration of the temporal lobes, the cerebellum and subcortical structures, related to motor planning and aspects of cognition.

3. Theta and alpha generators: a neurophysiological model of AD/HD

It has been proposed that theta and alpha activity are generated respectively in the septal–hippocampal circuit and in thalamo-cortical loops (Klemm, 1976; Steriade et al., 1990; Lopes Da Silva et al., 1980, 1990; Lopes Da Silva, 1996). Within the theta-generating septal–hippocampal pathway (see Fig. 1), the septal nucleus and the nucleus accumbens receive an inhibitory modulation through the

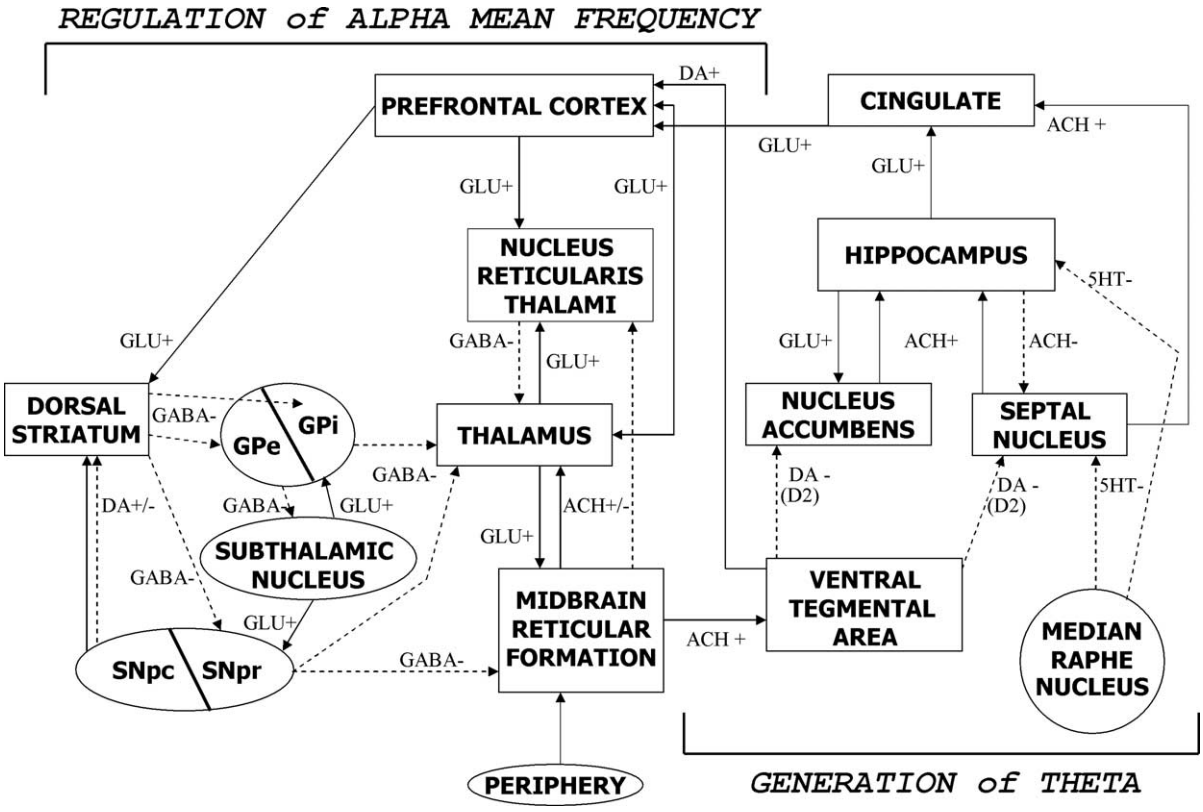

Fig. 1. Neurophysiological model of the regulation of the alpha and theta frequency bands. Full arrows indicate excitation; dashed arrows indicate inhibition. "GPe" and "GPi" refer (respectively) to the external and internal portions of the globus pallidus; "SNpc" and "SNpr" refer (respectively) to the substantia nigra pars compacta and substantia nigra pars reticulata.

dopamine (DA)ergic innervation from the ventral tegmental area, via D2 receptors (DeBoer and Abercrombie, 1996; Icarashi et al., 1997). Furthermore, the septal nucleus and the hippocampus are negatively modulated from the median raphe nucleus through a serotoninergic (5HT) input (Vertes and Kocsic, 1997). A blockade or a lesion of the median raphe nucleus results in the continuous presence of theta (Maru et al., 1979). From the septal nucleus and nucleus accumbens, acetylcholine (ACH)ergic efferents modulate the hippocampus and the cingulate cortex in a positive fashion. On the other hand, the hippocampus can slow the septal nucleus via acetylcholinergic neurons. Thus, a lesion at the level of the hippocampal–septal projection can cause over-activation of the circuit, resulting in an increase of theta activity (John, 1967; Anchel and Lindsley, 1984). Alternatively, an over-stimulation of this system might be secondary to disinhibition from negative dopaminergic regulation. This might occur when the DA levels at the synaptic cleft are low, possibly arising from a decrease of DA production and/or release from the ventral tegmental area, or an increase of the D2-autoreceptor efficacy of the mesolimbic neurons. A dysfunction of the mesolimbic system has been suggested to be the substrate of altered reinforcement mechanisms that might contribute to the behavioral problems of AD/HD (Russell et al., 1995). Therefore, the septo-hippocampal pathway can be considered as a monitoring system, whereas the nucleus accumbens, together with the caudate, represent the motor programming system. Finally, the prefrontal cortex may coordinate the activity of these two systems (Gray et al., 1991).

The thalamus seems to be the main structure involved in the generation of alpha activity (Steinhausen et al., 1984; Toumskoy and Maiorchik, 1969; Thatcher and John, 1977; Isachev et al., 1999). Thalamic neurons have the unique ability to shift between the oscillatory and tonic firing modes. In this way, the traffic of stimuli to the cortex from the exterior world via the thalamus is regulated. The alert behavioral state is characterized by desynchronized EEG. This is caused by tonic firing of thalamo-cortical neurons. Oscillatory neural behavior within thalamo-cortical circuits relies on the intrinsic ability of a group of thalamic neurons within the nucleus reticularis thalami to impose their oscillatory behavior on thalamo-cortical circuitry (Steriade et al., 1990, 1993; Steriade and Llinas, 1988). In addition to this intrinsic thalamo-cortical activity, a fundamental role is played by neurotransmitter systems that project upon and within the thalamo-cortical structures. The thalamic relay nuclei represents an interface between inhibitory inputs via γ-aminobutyric acid (GABA) from the nucleus reticularis thalami, which continuously modulates the ascending flow of thalamo-cortical impulses and excitatory inputs via ACH from the midbrain reticular formation. The midbrain reticular formation is itself an interface between incoming stimuli from the peripheral sensory receptors and a dopaminergic mediated striato-nigral regulation (Vaccarino et al., 1985; Petrovicky, 1988). In addition, nucleus reticularis thalami neurons receive excitatory glutamate (GLU)ergic inputs from the cortex (lamina VI) and from the thalamic relay nuclei, but also inhibitory acetylcholinergic afferents from the midbrain reticular formation (Scheibel et al., 1973). Reciprocal excitation exists between the cortex and thalamus, and there is also reciprocal inhibition among the nucleus reticularis thalami neurons (GABAergic interneurons) (Asanuma, 1989; McCormick and Huguenard, 1992; Bal and McCormick, 1993; Raos and Bentivoglio, 1993). Further, the striatal structures have been hypothesized to exert an inhibitory function on the thalamus and, thus, on the sensory input to the cerebral cortex, as well as on arousal. Basal ganglia relay stations and thalamo-cortical circuitry (Alexander et al., 1986, 1990) participate in a cortical–striatal–thalamic–cortical circuit. In this system, the dorsal striatum sends efferents, received from the cortex, to the thalamus through the globus pallidus internal and external portions (GPi, GPe) and substantia nigra pars reticulata (SNpr) via direct excitatory and indirect inhibitory pathways. The thalamus in turn feeds back to the cortex, and substantia nigra pars reticulata modulates the midbrain reticular formation. This circuit (cortico-striatal–thalamic–cortical network), which receives afferents also from the noradrenergic brainstem nuclei, is believed to serve as the anatomic substrate for many executive functions and for regulation of behavioral responses (arousal). Its involvement in animal models of AD/HD has been extensively demonstrated (Papa et al., 1998).

Release of DA from terminals of the nigro-striatal projection, which arises from the substantia nigra pars compacta (SNpc), appears to facilitate transmission over the direct pathway via activation of D1 receptors and to inhibit transmission over the indirect pathway via activation of D2 receptors. Thus, the overall effect of DA released at the dorsal striatum appears to be a reduction of basal ganglia output, with disinhibition of globus pallidus leading to increased activity of thalamocortical neurons and a facilitation of movement. Dysregulation in this complex system might be responsible for either an increase or decrease of alpha activity. Hyperactivation of thalamus, reflected by alpha excess, might be due either to an inadequate inhibitory tone of the basal ganglia neurons via the indirect pathway or to an excessive activation via the direct pathway, secondary to an increase of DA levels (Hallett, 1993; Saint-Cyr et al., 1995). Thus, relative overactivity of the DA nigro-striatal circuit might be the pathophysiological mechanism involved in the symptom of hyperactivity in children with AD/HD (Castellanos, 1997).

Alternatively, decreased activity in the cortex–thalamic glutamatergic neurons (i.e., hypoactivation of the prefrontal cortex) could result in a thalamic disinhibition from the nucleus reticularis thalami control, with a subsequent alpha excess. Such hypoactivation of the prefrontal cortex might be secondary to low DA levels. Thus, low mesocortical DA levels represent another possible biological substrate of AD/

HD. Compatible with this idea, Heilman et al. (1991) proposed that children with AD/HD have a right-sided frontal–striatal dysfunction due to impairment of the mesocortical DA system. Robbins et al. (Robbins, 2000; Christakou et al., 2001; Dias et al., 1996) have shown that disruption of the mesocortical dopaminergic innervation can result in a difficulty in maintaining attention and in poor control of impulses. Finally, a lack of inhibitory autoreceptors of the mesocortical dopaminergic system, producing decreased synaptic DA, has been hypothesized (Castellanos, 1997).

In summary, although a noradrenergic dysfunction may also play a role, it is conceivable that imbalances in the dopaminergic system, such as hyperactivity of the nigro-striatal pathway and/or hypoactivation of the mesolimbic and/or mesocortical pathways, are the pathophysiological substrate of AD/HD. These hypotheses are in line with the dopaminergic theory of AD/HD (Levy, 1991), which restates the concept of Minimal Brain Dysfunction Syndrome (Wender, 1971) in terms of a disorder of polysynaptic dopaminergic circuits between prefrontal and striate centers. Satterfield and Dawson (1971) earlier suggested that weak frontal cortical inhibitory control over limbic functions might lead to AD/HD. The VARETA results presented above (Chabot et al., 2001) suggest that there might be an involvement of the main dopaminergic systems, as evidenced by the fact that the alpha and theta neural generators are linked to all these systems. Subsequent sections of this article summarize research from multidisciplinary sources that support these conclusions.

4. Studies of the DA system and AD/HD

4.1. Animal studies

Work in primates suggests that mesocortical DA is involved in direct gating of selective excitatory synaptic inputs to prefrontal neurons during cognition (Sawagushi and Goldman-Rakic, 1994; Williams and Goldman-Rakic, 1995). The fronto-striatal regions have rich interconnections, particularly between the caudate and orbito-frontal and dorso-lateral cortices (Alexander et al., 1986; Goldman-Rakic, 1987). A lesion of these interconnections would explain deficits in the arousal-motor regulatory systems (Iversen, 1977; VerFallie and Heilman, 1987). More specifically, frontal catecholamine depletion would cause an increase in distractibility (disruption of top–down attentional processing) while caudate DA loss would not disrupt the ability to acquire and shift an attentional set (Crofts et al., 2001). In a similar fashion, different studies on a rat model of AD/HD have shown an altered dopaminergic function in different brain regions, such as prefrontal cortex, nucleus accumbens and caudate-putamen (Russell et al., 1995; Papa et al., 1998). Furthermore, the altered distribution of D1 and D2 receptors revealed a modulatory influence of DA receptors in the cross-talk within the anterior forebrain. The differential distribution and regulation of DA receptor subtypes following administration of a DA reuptake blocker, as well as the different regional cross-talk in the target sites of nigro-striatal and mesolimbic DA systems, lends some support to the DA hypothesis of AD/HD in children (Carey et al., 1998). Interestingly, in the rat neocortex, it has been possible to discriminate dissociable effects of mediofrontal, cingulate, dorsolateral and parietal cortex on visual attentional function, suggesting the presence of parallel distributed neural systems accounting for different attentional performances (Muir et al., 1996). In addition, it has been demonstrated that poorly performing rats, with a deficit in selective attention accompanied by impulsivity, exhibited metabolic dysfunction in the cingulate and prefrontal cortices, suggesting that the neural network of attention in rats is remarkably analogous to that described in primates (Barbelivien et al., 2001). It has been shown that selective lesions of the nucleus accumbens core induce persistent impulsive choice and locomotor hyperactivity in rats. In contrast, damage to two of its afferents, the anterior cingulate cortex and medial prefrontal cortex, had no effect on this capacity. Moreover, attentional deficits were not evident in such animals. Thus, dysfunction of the nucleus accumbens core may be a key element in the neuropathology of impulsivity (Cardinal et al., 2001).

4.2. Genetic studies

Consistent results from molecular genetic studies point strongly to the possible link between two specific genes, the DA transporter (SLC3A6) and the DA receptor 4 (DRD4), and AD/HD. Giros et al. (1996) showed that disrupting the SLC6A3 gene leads to a hyper-dopaminergic phenotype that includes spontaneous hyperlocomotion. This is consistent with the idea that abnormalities in the SLC6A3 gene could be a risk factor for AD/HD (Bannon et al., 1995; Cook et al., 1995; Gill et al., 1997; Gainetdinov et al., 1999). Studies of the DRD4 (LaHoste et al., 1996; Smalley et al., 1998; Swanson et al., 1998; Muglia et al., 2000) revealed that the seven-repeat allele of DRD4, which mediates blunted responses to DA, is expressed with higher rates in AD/HD children compared to controls and is associated with novelty-seeking behavior. There is no question that AD/HD is a polygenic disorder. It manifests as a wide spectrum of oftentimes varying symptoms, and it is doubtful that any one gene accounts for them all. Therefore, it is plausible that allelic variants in several different genes could characterize the disorder (DiMaio et al., 2003).

4.3. Neuroimaging studies

Many researchers (Lou et al., 1984, 1989; Hynd et al., 1990, 1991, 1993; Giedd et al., 1994; Castellanos et al., 1994, 1996, 2003; Amen and Carmichael, 1997; Casey et al., 1997; Filipek et al., 1997; Vaidya et al., 1998; Rubia et

al., 1999) have provided evidence of an involvement of the frontal or prefrontal brain regions and the caudate nucleus (dysfunction in networks associated with the frontal lobes, particularly the fronto-striatal system) in the pathogenesis of AD/HD in children. The majority of these papers reported a right side involvement. In a PET study, Zametkin et al. (1990) reported lower glucose metabolism in premotor and superior prefrontal cortex and in the right side of the cingulate, hippocampus, thalamus and caudate. Other structural neuroimaging studies have reported abnormalities in the globus pallidus (Singer et al., 2004; Aylward et al., 1996). In fMRI studies during the Stroop task, Bush et al. (1999) found activation of the fronto-striatal-insular circuit in AD/HD adults, different from normal subjects who showed activation of the anterior cingulate.

4.4. Pharmacological studies

The beneficial effects on AD/HD symptoms of stimulants that mimic catecholamines, in particular DA metabolism, lend strong support to the role of monoamine neurotransmitters in this disorder (Zametkin and Borcherding, 1989). Furthermore, the differential responsiveness of some AD/HD children to methylphenidate and to dexamphetamine suggests that several different neural systems might be involved in the pathogenesis of AD/HD. These data suggest that even if one stimulant is not helpful therapeutically, another might be useful. Indeed, although these two agents produce similar behavioral effects and both are DA releasers (Wallech, 1974; Chiueh and Moore, 1975; Moore, 1977), they have distinct mechanisms of action (Lawson-Wendling et al., 1981; Seiden, 1993; Segal, 1993; Sulzer et al., 1993; Pifl et al., 1995; Sonders et al., 1997) and specific target brain regions (Lawson-Wendling et al., 1981; Kehr et al., 1977; Pearl and Seiden, 1979; Lyness et al., 1980; Lin et al., 1996). Methylphenidate differs from dexamphetamine in that it exerts its central stimulant effects by releasing DA from a reserpine-sensitive storage pool (blocking the vesicular monoamine transporter important to DA re-uptake), while dexamphetamine releases DA from two DA storages (vesicular and cytoplasmic, the latter by blocking the plasmalemmal DA transporter). Besides, the two agents have regionally selective effects: dexamphetamine produces a dose-related increase of DA accumulation in the striatum, but not in other cerebral areas; methylphenidate exerts the same action at the hippocampal level and depresses the rate of DA accumulation in all other cerebral regions. Even more suggestive, many researchers have reported evidence of a specific dexamphetamine action on the striato-nigral-midbrain reticular formation system (Petrovicky, 1988; Sirkin and Teitelbaum, 1983; Poli and Palermo-Neto, 1985, 1986; Ryan et al., 1987; Dimpfel et al., 1988), which is integrated within the pathways leading to the alpha and theta pacemakers. Lin et al. (1996) have carried out a study to replicate the reports about the different specific brain targets for dexamphetamine and methylphenidate. The authors found that, even though both substances activate the whole brain, the first has a specificity for the caudate nucleus (dorsal striatum), while the second is more active in the medio-frontal cortex (which contains the cingulate gyrus). These sites are part of the two different systems that have been hypothesized to be the alpha and theta generators.

Thus, we propose that the AD/HD syndrome represents a heterogeneous group of children that could be subdivided into at least two different subtypes, each of which might be the result of a dysfunction of a specific neural system, as supported by the above pharmacological evidence.

5. Studies of the attention system

5.1. Neuropsychological studies

It has been proposed that the attention system is essentially localized in the right hemisphere, where it is distributed in three functional subsystems: (1) An executive network, dedicated to executive and control functions, is located mostly in the anterior cingulate cortex and basal ganglia; (2) An orienting/shifting (selective) attention network, hypothesized to disengage and orient/engage attention to new stimuli, localized in both superior parietal lobules, thalamus and midbrain; (3) A vigilance network, responsible for the maintenance of the alert state, localized in the right frontal lobe, especially the superior region of Brodmann's area 6 (Posner and Petersen, 1990; Baron, 1995; Posner and Raichle, 1996; Heslenfeld et al., 1997). More schematically, the attention system might be subdivided into two parts: the anterior system including striatal/cingulate/prefrontal cortex, the posterior system referring to the right superior parietal, inferior temporal cortex, superior colliculus and pulvinar, receiving dense noradrenergic innervation from the locus coeruleus (Pliszka et al., 1996; Himelstein et al., 2000). According to Pliszka et al. (1996), inability of noradrenaline to prime the posterior system could account for attentional problems, while loss of DA's ability to gate inputs to the anterior system might be linked to deficits in the executive function in AD/HD children. The noradrenergic dysfunction might have particular relevance given the advent of recent non-stimulant noradrenergic specific medications in AD/HD. The pattern of neuropsychological deficits shown by children with AD/HD suggests relatively specific problems in inhibitory control of attention selection (Williams et al., 2000) that might underlie the impulsivity of pervasively hyperactive children (Schachar and Logan, 1990). This cognitive deficit implicates brain areas including basal ganglia (involved in response execution) and ventro-lateral prefrontal cortical areas in AD/HD, thus providing evidence for disruption of fronto-striatal functional loops (important for inhibitory functions). Niedermeyer and Naidu (1998a,b) hypothesized a neurophysiological model of AD/HD. They emphasize the role of the frontal lobe as the inhibitor of

excessive motor activity. In light of this concept, a dysfunction in the frontal-motor cortex connection might underlie this disorder. A "lazy" frontal lobe would result in a disinhibition of motor activity as well as disturbed attention. Barkley (1997b) proposed a unitary theory of AD/HD that involves a deficit in behavioral inhibition of four executive neuropsychological functions: working memory, self-regulation of affect–motivation–arousal, internalization of speech and reconstruction (behavioral analysis and synthesis). Barkley has suggested that the inattentive subtype (AD/HDin) may represent a separate distinct disorder, with more problems with selective attention, sluggishness and memory retrieval, as well as problems with math, language and reading.

5.2. Neurophysiological studies

Neurophysiological studies focused on the attention processes and their localization in the brain have shown that the main structures involved in attention functions are the septo-hippocampal acetylcholinergic circuit (the theta system), which provides mechanisms for information processing and selective attention (Klemm, 1976; Baxter et al., 1997; Vinogradova et al., 1995, 1999) and which, together with the prefrontal cortex, would be involved in general attention and expectancy processes (Demiralp et al., 1994). Pharmacological manipulations of the septal cholinergic component of the theta rhythm, either by blocking muscarinic receptors (with scopolamine) or by increasing endogenous acetylcholine levels (by physostigmine), disturb information processing by the hippocampal neurons. The theta rhythm, thus, has been regarded as a selective filter, providing for processing and registration of information and simultaneously protecting it from the interference of other stimuli (Vinogradova et al., 1995, 1999). Lesions at the hippocampal level or of the septal–hippocampal projection reduce attention to conditioned stimuli (Baxter et al., 1997). One possible correlate of such action might be an effect on the amplitude of the theta rhythm. In fact, removal of the acetylcholinergic hippocampal input decreases the theta amplitude (Lee et al., 1994). It is not surprising that nicotinic cholinergic dysregulation could play an important role in the pathophysiology of AD/HD, considering that nicotinic activation enhances dopaminergic and noradrenergic neurotransmission.

The relation between thalamus and attention has also been investigated by several authors. The participation of the limbic thalamus, the centrolateral nucleus and the nucleus reticularisc thalami, along with other subcortical (midbrain reticularis formation, basal ganglia) and cortical structures (cingulate, frontal eye fields, post-parietal cortex) has been highlighted as a part of the cortico-limbic-reticular network for attention functions (Brunia, 1993; Morecraft et al., 1993; Asarnow et al., 1994; Cohen et al., 1994; Fitzgibbon, 1994; Kuljis, 1994; Steckler et al., 1994; Andreasen et al., 1994, 1995; de Carvalho and Roitman, 1995; Lawrence and Sahakian, 1995; Newman, 1995; Raos et al., 1995; Steriade, 1995; Lekwuwa and Barnes, 1996; Brown and Marsden, 1998).

6. Conclusions

The diagnostic category AD/HD, as defined by APA, seems not to fit with the real heterogeneity of the symptoms exhibited in AD/HD and must be explained by multiple specific causes. Even though the intent of DSM-IV is to provide hierarchically organized categories of mental disorders that aid clinicians in differential diagnosis, certain criteria are too restrictive. In regard to AD/HD and LD, these are considered two mutually exclusive and non-overlapping entities. By this definition, a child cannot simultaneously meet criteria for AD/HD and LD. It is clear that AD/HD is a heterogeneous disorder. Therefore, it cannot be conceptualized as only one disease entity with a very narrow phenotype and a distinct etiology. Rather, it is believed to constitute a spectrum of disorders that subsume different subtypes of a larger population of children with attention and learning problems. To date, AD/HD is diagnosed solely on the basis of patterns of observable behavior. It has been difficult to identify specific biochemical or neurophysiological tests that may contribute to more accurate diagnosis. Identifying a biological measure that could aid in this distinction would help to refine diagnostic criteria and may provide more specific diagnostic tests for AD/HD and LD.

QEEG may prove to be the most clinically relevant imaging technique for use in children with attention and learning problems. Indeed, it can play an important role in the evaluation and treatment selection of AD/HD. Compared to other methods of functional neuroimaging (SPECT, PET, fMRI), QEEG has the advantage that it is non-invasive, easier to perform and safer, as well as less expensive. The clinical applications of this technique in diagnosing AD/HD may also provide information about the underlying physiological processes. By combining individual abnormal QEEG features together, the neurometric method can create multivariate discriminant functions that have a sensitivity, specificity and accuracy level much higher than univariate features alone. In addition to its diagnostic usefulness, an initial neurometric QEEG screening may aid in treatment selection (Chabot et al., 1999, 2001). Finally, the emergence of EEG biofeedback treatment techniques offers a direct application of QEEG for determining QEEG biofeedback treatment parameters and may offer effective treatment that is not medication oriented (Lubar, 1991).

The QEEG results can then be confirmed by VARETA analysis of the raw data. Thus, Neurometric QEEG analysis together with the VARETA technique could be useful not only in recognizing the different subtypes and in predicting the treatment response of AD/HD children, but also by helping us to better understand the biological basis of this disorder. Our findings involving the localization of QEEG

frequency abnormality mainly to the right frontal/basal ganglia and hippocampal/temporal regions are in agreement with current neuroanatomical theories of attention processes. The different QEEG/VARETA subtypes may reflect parallel distributed neural systems involved in attentional performance.

Altogether, we believe that our findings justify not only the clinical utilization of QEEG in the initial screening and treatment evaluation stages of AD/HD and LD children (Prichep and John, 1990; Chabot and Serfontein, 1996; Chabot et al., 1996, 1999), but also can aid in the detection of organicity as the cause of brain dysfunction in children presenting with learning and attention problems (Chabot et al., 2001). Finally, QEEG-based models may help explain the pathophysiology of these disorders.

Acknowledgements

The authors thank Dr. P. Valdes-Sosa and Dr. J. Bosch-Bayard for valuable contribution with the VARETA method.

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