REVIEW

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The role of working memory impairment in ADHD – new therapeutic indications

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Abstract: Many individuals affected with Attention Deficit Hyperactivity disorder (ADHD) are faced with a constellation of symptoms and few therapeutic options. Although most of the drugs currently available for treatment are effective to some degree and target the inattention component, they lack the specificity needed to treat cognitive symptoms. Many patients complain of memory deficits as part their inability to cope with daily activities. We review here some concepts of working memory impairment in ADHD, and attempt to apply it to new therapeutic strategies that might prove valuable for treatment. Rivastigmine, a slowly reversible inhibitor of acetylcholinesterase and butyrylcholinesterase, could alleviate the cognitive symptoms of impaired attention (possibly improving working memory function) of patients with ADHD through their action on the prefrontal cholinergic system. Rivastigmine is currently used to improve cholinergic neurotransmission and cognitive function in Alzheimer's disease (AD). Our discussion is aimed at broadening the spectrum of clinical diagnosis that could potentially benefit from it.

Key words: ADHD, Working Memory, Acetylcholinesterase Inhibitors, Rivastigmine

INTRODUCTION

Adult patients with ADHD struggle with inattention. They are easily distracted and have trouble paying attention and staying organized. They also have symptoms of hyperactivity and impulsivity, such as restlessness, fidgeting, inability to slow down, and lack of inhibition during social interaction. While ADHD was initially considered a childhood problem, it is now very clear that this neuropsychiatric disorder often continues into adulthood.

New therapeutic strategies are needed to cope with the enormous economic impact of this condition. The prevalence of ADHD varies from 2.0%-6.3% [1] and up to 18% in some studies [2]. In a population-based cohort followed from birth through 19 years, the cumulative incidence of ADHD was 16.0% using the most liberal definition, whereas the most restrictive estimate was 7.4% [3]. Prevalence for ADHD in adults is approximately 5%, or at least 11 millions of adults in the United States [4], and according to the National Comorbidity Survey Replication, 4.4% of adults in the US have ADHD [5]. More recent studies indicate that the persistence of symptoms of childhood ADHD into adulthood may be as high as 66-75%, and that between 1%-6% of the general adult population have appreciable evidence of ADHD [6, 7].

A diagnosis of ADHD should be considered in adults who have lifelong problems with inattention, disorganization and executive function, cognitive restlessness, vocational and academic underachievement, based on their intelligence and education, substance abuse, stability in relationships (e.g. multiple divorces), or who consistently engage in thrill-seeking and risky behaviors [6-11].

Health System impact is reflected also on the increased likelihood to sustain severe injuries in ADHD [12], significantly increasing the cost of medical care in multiple care delivery settings [13, 14].

The economic impact goes beyond the health care system since individuals with ADHD often find themselves impaired in several aspects of daily life: academic/employment under achievement, driving difficulties, increased risk for smoking, alcoholism, illicit drug abuse, impaired social relationships (e.g. higher rates of divorce) with associated economic impact on society [15].

Clinical Manisfestations of ADHD

The core symptoms of ADHD disorder are developmentally inappropriate and maladaptive degrees of inattention, hyperactivity, and impulsivity, resulting in clinically significant impairment in social, academic, or occupational functioning.

Symptoms usually begin before 7 years of age and persist for at least 6 months in 2 or more settings (home, school, or play). The criteria for age of onset of symptoms have been questioned. Although hyperactivity is usually noted before the age of 7, inattentiveness that impairs function may not [15]. Table 1 shows DSM-IV criteria for the clinical diagnosis of ADHD.

However, not all DSM-IV symptoms are equally discriminative or equally predictive of impairment. Recent evidence using an algorithm based on ROC analysis improved clinical diagnostic performance in ADHD.

ADHD associated symptoms not essential to the diagnosis include fine neuromotor abnormalities, gross neuromotor abnormalities, clumsiness, tics, learning problems, speech and language delays, sleep disorders, enuresis, encopresis, immaturity, disorganization, poor peer interactions, oppositionality, emotional distress, and antisocial behaviors. They may be more troubling than the hyperactivity or inattention, and may be the motivation for seeking assistance.

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Table 1 DSM-IV criteria for the clinical diagnosis of ADHD.

Inattention has been defined as the presence of 6 of the following 9 characteristics:
(1) Often fails to pay close attention to details, or makes careless mistakes in schoolwork, work, or other activities.
(2) Often has difficulty sustaining attention in tasks or play activities.
(3) Often does not seem to listen when spoken to directly.
(4) Often does not follow through on instructions, and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions).
(5) Often has difficulty organizing tasks and activities.
(6) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (schoolwork or homework).
(7) Often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools).
(8) Is often easily distracted by extraneous stimuli.
(9) Is often forgetful in daily activities.
Hyperactivity-impulsivity is defined by the presence of 6 of 9 behaviors, 6 of which relate to hyperactivity and 3 to impulsivity.
(1) Often fidgets with hands or feet or squirms in seat.
(2) Often leaves seat in classroom or in other situations in which remaining seated is expected.
(3) Often runs about or climbs excessively in inappropriate situations (in adolescents or adults, this may be limited to subjective feelings of restlessness).
(4) Often has difficulty playing or engaging in leisure activities quietly.
(5) Is often „on the go" or often acts as if „driven by a motor."
(6) Often talks excessively.
(7) Often blurts out answers before questions have been completed.
(8) Often has difficulty waiting for his/her turn.
(9) Often interrupts or intrudes on others (butts into conversations or games).
Four attention deficit hyperactivity syndromes have been defined in DSM-IV, depending on combination of symptoms.

Prefrontal Cortex as a Neural Substrate for Attention

Brain imaging, electrical stimulation, and neurophysiological studies have all implicated the prefrontal cortex in the top-down control of attention. Feedback from the prefrontal cortex has been proposed to bias activity in the visual cortex in favor of attended stimuli over irrelevant distracters. The prefrontal cortex plays an important role in attentional processes due in part to its contribution through working memory, as discussed below.

In humans, as demonstrated by a recent fMRI study, complex mental operations rely on a distributed cortical network (parasagittal, left parietal and left dorsolateral prefrontal cortices) involving attention, executive function and short term mnemonic processes [16]. Humans are able to target information stored in the working memory and use it to guide attention during object search. Moreover, working memory and attentional processes could be functionally separated in a behavioral task involving shifting attention during visual search tasks when the identity of the visual target was stable across time [17]. Attention processes maintain feature binding in short-term memory in humans [18] and in nonhuman primates, the prefrontal cortex plays a critical role in the ability to flexibly reallocate attention in a top-down approach on the basis of changing task demands: macaques with lesions in the lateral prefrontal cortex depict attentional deficits independent of oculomotor control [19].

The lateral prefrontal cortex is also critically involved in broad aspects of executive behavioral control and strategic behavioral planning. The implementation of behavioral rules and in setting multiple behavioral goals has recently been documented in both human and nonhuman primates. Novel findings of neuronal activity have specified how neurons in this area take part in selective attention for action, and in selecting an intended action [20].

Involvement of Prefrontal Cortex in ADHD

The prefrontal cortex also plays an important role in certain memory processes. Working memory, the type of memory subserved by prefrontal cortex, is often affected in individuals with ADHD, and correlate well with prefrontal cortical inefficiency [21]. Adults with prefrontal lesions have little difficulty learning new information, but perform poorly in tasks requiring recall of previously learned information when internally generated strategies are employed [22]. Patients with prefrontal lesions also do not use effectively organizational strategies when initially encoding information, and have difficulty filtering out irrelevant information during retrieval. Impairments in working memory is characteristic of ADHD patients [23, 24], although this symptom is not specifically identified in DSM-IV criteria. Patients often describe difficulty 'keeping in mind' itemized information, such as remembering telephone numbers for short periods of time. They also have more difficulty solving arithmetic problems, attributable to working memory deficits [25, 26].

The Barkley model [4, 25] of ADHD predicts concomitant deficits in working memory and in the development of a sense of time as a consequence of poor behavioral inhibition. Reduced lateral prefrontal activation in adult patients with attention-deficit/hyperactivity disorder during a working memory task (n-back paradigm) has been recently reported using near-infrared spectroscopy [27]. Moreover, in a recent Chinese study using a resting-state fMRI based classifier, increased activity of both the prefrontal cortex and anterior cingulate cortex was found in ADHD [28]. In addition, familial vulnerability to attention-deficit/hyperactivity disorder has been reported to be related to atypical prefrontal activity during cognitive control tasks (stimulus sensitive). The same study also found deficits in the cerebellum associated with cognitive control (time sensitive) in ADHD patients using functional neuroimaging [29] and independently replicated by Valera et al [30]. In another fMRI study, a decreased activation in the ventral prefrontal cortex of ADHD subjects and their affected relatives was shown to be associated with poor inhibitory control, and proposed as a neuroimaging tool indicator to identify intermediate phenotypes in studies investigating gene effects in ADHD [31]. In addition, response inhibition deficits have been observed in ADHD patients even when the executive function demands of tasks are minimal [32].

Altered electroencephalogram performance in ADHD regarding time estimation parameters as indicators of working memory performance has also been reported and proposed as an electrophysiological tool for diagnosis and follow up of ADHD patients [33]. An increased interhemispheric theta and beta coherence, as well as an excessive beta power on EEG profile, has been recently found in ADHD underlying brain dysfunction in the frontal lobes [34]. Aberrant neural oscillatory activity in cortical-striatal-thalamo-cortical circuits has been recently postulated in ADHD, and compensatory systems within the prefrontal cortex have been suggested as modulating the misguided striatal and thalamocortical oscillations [35].

Disease States and the Prefrontal Cortex Cholinergic System

ADHD: Functional and morphological studies in Attention Deficit Hyperactivity Disorder affected individuals suggest a prefrontal cortex dysfunction. This cortical region is regulated by subcortical systems, including noradrenergic, dopaminergic, cholinergic, serotonergic, and histaminergic pathways. A wealth of data in humans and in animal models demonstrates dopamine [36, 37] and noradrenergic [38-40] regulation as the base of current ADHD therapeutic strategies. The current view, based the behavioral disturbances of ADHD as the result of an imbalance between NE and DA systems in the prefrontal cortex, with inhibitory DA activity being decreased and NE activity increased relative to non-ADHD subjects.

AD: Modulation of the cholinergic neurotransmitter system results in changes in memory performance, including working memory, in animals and in patients with Alzheimer disease. Using PET in *healthy individuals* during performance of a working memory task, a continuous infusion of physostigmine, an acetylcholinesterase inhibitor, improved working memory efficiency, as indicated by faster reaction times, and correlated well with a reduced working memory task-related activity in anterior and posterior regions of right midfrontal gyrus, a region shown previously to be associated with working memory [41]. These results suggest that enhancement of cholinergic function can improve processing efficiency, and thus reduce the effort required to perform a working memory task, and that activation of the right prefrontal cortex is associated with task effort. In a more recent study, Furey et al [42] documented the relationship between the behavioral effects of cholinergically-induced improvements in working memory performance on task-induced neural activity in multiple cortical regions associated with early processing (medial occipital visual cortex), and regions associated with attention, memory encoding, and memory maintenance (right frontal cortex, left temporal cortex, left anterior cingulate, and left hippocampus). The involvement of the cholinergic system in the prefrontal cortex has also been postulated as one modulated by experience in animal models of aging [43], and in human studies using PET in the elderly during a working memory task [44]. In agreement with this, both catecholaminergic and cholinergic systems are known to mutually interact in the prefrontal cortex and have been shown to influence executive cognitive functions, such as „resistance to interference" and „attentional switching", as well as mnemonic encoding and retrieval processes, through the interaction with the temporal lobes. Although no full-scale clinical trials on the effects of pharmacological agents on verbal perseveration have been conducted to date, existing preclinical trials suggest that both presynaptic and postsynaptic dopaminergic agents can reduce perseverative response by increasing inhibitory control processes. Cholinesterase inhibitors and other cholinergic agents have been shown to reduce perseverative responding by reducing verbal intrusions [45]. Also, choline acetyltransferase activity in the prefrontal cortex has been found to be reduced in late stages of Alzheimer's disease [46], suggesting increased severity of clinical progression toward dementia. The effects of acetylcholinesterase inhibitors on the cerebral cholinergic neuronal system in the prefrontal cortex have also been investigated in nonhuman primate models combining PET and microdialysis. In the referred study, by using an oculomotor delayed response task, aged monkeys showed impaired working memory performance compared to young monkeys, and the impaired performance was partly improved by the administration of donepezil [47, 48]. At the molecular level, long-lasting alternative splicing of neuronal acetylcholinesterase pre-mRNA occurs during neuronal development and following stress in the prefrontal cortex, possibly altering synaptic properties in this brain region [30], and the loss of frontal cortical nAchRs (specifically alpha7 and alpha4beta2 nAchR subtypes) are correlated to a decline in both working and reference memory function in Alzheimer's disease [49].

Schizophrenia: Despite the limited experimental evidence for abnormal cholinergic neurotransmission in psychiatric disorders, increased understanding of the role of acetylcholine in the human brain and its relationship to other neurotransmitter systems has led to a rapidly growing interest in the cholinergic system in schizophrenia [50]. Impairments in attentional functions represent a core aspect of the cognitive symptoms of schizophrenia. Attentional performance has been demonstrated to depend on the integrity and activity of cortical cholinergic inputs. In a recent study, impaired prefrontal acetylcholine release measured during the performance of an attentional task in a pharmacological animal model of schizophrenia, have suggested loss of cognitive control associated with cholinergic dysregulation [51].

Acetylcholine and other neurochemical systems in Working Memory

The prefrontal cortex innervated by the monoamines, dopamine (DA), noradrenaline (NA), and serotonin, as well as acetylcholine, has a marked influence on prefrontal working memory processes. However, their differential contribution to prefrontal functioning is less well understood. Some evidence supports the hypothesis that these neurochemical systems recruit distinct fronto-executive operations via a synergistic interaction with the PFC. Thus depletion of prefrontal serotonin selectively disrupts reversal learning, but not attentional set formation or set shifting. In contrast, depletion of prefrontal DA disrupts set formation, but not reversal of learning. NA depletion on the other hand specifically impairs set-shifting, whereas its effects on reversal learning remain unclear. Finally, depletion of prefrontal acetylcholine has no effect on either set formation or set shifting, but impairs serial reversal learning [52]. Different nicotinic acetylcholine receptor subtypes appear to modulate dopamine release from the striatum and prefrontal cortex [53]. Also, selective blockade of D_3 receptors in the prefrontal cortex facilitates frontocortical cholinergic transmission, and improves social memory in rats [54].

Evidence for acetylcholinesterase inhibition (ACHEI) improving working memory, attention, and memory

Evidence for the effect of rivastigmine on cortical AChE activity is found in the literature, with emphasis on the role of frontal AChE inhibition to explain clinical improvement in behavioral and attentional symptoms of AD [55, 56]. To date, some clinical trials have used add-on therapy with acetylcholinesterase inhibitors in schizophrenia as cognitive enhancers [57, 58]. However, many studies have been negative or inconclusive.

Studies have reported beneficial effects of cholinergic enhancers, e.g., rivastigmine, on memory in schizophrenia [59], while others have not [60]. These discrepancies are possibly related to the lack of specificity of the tests used. Guillem et al [61] have recently investigated the effect of rivastigmine on memory in schizophrenia using event-related potentials (ERPs). The results showed a trend for a benefit of rivastigmine on memory. ERP analysis revealed that rivastigmine affects the amplitudes of two components elicited within 150-300 ms over posterior (reduced N2b) and frontal sites (enhanced P2a). It also enhanced the magnitude of the memory (old/new) effect on two later components over posterior (N400) and frontal sites (F-N400). Together, these results suggest that rivastigmine improves selective attention by enhancing interference inhibition processes (P2a), and lowering the reactivity to incoming stimulus (N2b). It also improves the integration of information with knowledge (N400) and with its context (F-N400).

To the best of our knowledge, the therapeutic efficacy of rivastigmine in ADHD has not yet been evaluated. However, there are reports of improvement in attentional deficits in AD [62] and in dementia of Lewy bodies [63].

CONCLUSIONS

New studies are needed to address the physiopathology of working memory deficits in ADHD. Recent evidence from both animal and human studies reveals a possible role of working memory impairment in global cognitive function of ADHD. Although it is impossible to know *a priori* whether Acetyl cholinesterase inhibitors (AChEI) may increase functional performance in patients affected with ADHD, scientific evidence is rapidly accumulating to account for prefrontal cortex deficits in this group of patients.

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