Working Memory in ADHD: Prefrontal/Parietal Connections

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Abstract: Current theories of dopaminergic and noradrenergic mechanisms, which are thought to be of importance in the regulation of attention are reviewed. A biphasic model of dopaminergic function is described, in which tonic dopamine exerts a suppressive influence on subcortical dopamine systems by altering tonic/phasic dopaminergic relationships. Noradrenergic mechanisms are of importance in modulating sensory processing at the prefrontal cortical level. The work of Silberstein and colleagues utilizing Steady-State Visually Evoked Potential, during the course of an A-X Continuous Performance Task enables examination of the spatial distribution and dynamics of electrical brain activity during the task. The maintenance of activation in the interval between A and X provides a measure of working memory, thought to be related to prefrontal-parietal activation, which is facilitated by administration of methylphenidate to children with ADHD, suggesting that working memory may be a core deficiency in children with ADHD. While tonic dopamine activity in ventral striatum/accumbens gates inhibitory activity, dorsolateral prefrontal-parietal connections allow maintenance of working memory required for goal completion.

INTRODUCTION

The investigation of Attention Deficit Hyperactivity Disorder (ADHD) in children has made advances in neurophysiological and genetic areas over the last ten years, but despite these advances the biological mechanisms involved in disturbances of attention are still unclear. A recent important text edited by Solanto, Arnsten, and Castellanos [1] discusses the basic and clinical neuroscience of stimulant drugs and ADHD, and draws attention to dopaminergic and noradrenergic influences, thought to be of importance in the action of stimulant drugs. The present review, outlines current theories, reviews work by the present authors, who used the Continuous Performance Test, as well as suggesting possible drug targets.

DOPAMINE TRANSMITTERS

Levy [2] discussed the implications of clinical, animal and neuroanatomical studies of differential isomer and dosage effects of central nervous system stimulant medications for the dopamine theory of attention deficit disorder. Central to the theory were animal studies by Glowinski et al [3], which demonstrated that mesocortico-prefrontal DA neurons lacked autoreceptors and presynaptic receptors, unlike the basal ganglia where dopaminergic activity is controlled by autoreceptors. These differences were thought to explain differential effects of stimulant medications at low compared with high dose levels.

Castellanos [4] extended the above theory to suggest that neuronal signals which travel directly to the medial globus pallidus result in net amplification via thalamic excitatory fibers, which feedback to cortical output neurons, while an indirect pathway from the lateral globus pallidus and substantia nigra increased tonic cortical inhibition. Castellanos proposed that presynaptic effects might predominate in D2-rich subcortical regions, where presynaptic receptors are abundant, producing decreased synaptic dopamine and post-synaptic effects might predominate in D4-rich cortical regions, which lack presynaptic receptors, producing increased synaptic dopamine [5].

Swanson et al [6] reviewed current genetic studies of dopamine genes and ADHD. They point out that family, twin and adoption studies have documented a strong genetic basis for ADHD. Two candidate genes, the dopamine transporter (DAT) and dopamine receptor D4 (DRD4) were investigated. While these studies provide converging evidence for the association of dopamine genes and ADHD (three published studies of the DAT1 gene [7-9] and four of five published studies of the DRD4 7-repeat allele [10-14] found positive associations). A recent Swanson et al study [15] did not replicate the association of reaction time measures with the 7-repeat DRD4.allele. Swanson et al [6] point out that while both candidate dopamine genes (DAT1 and DRD4) have been reported to be associated with ADHD in different samples, the association has not been strong (i.e. a relative risk of about 1.5-2), suggesting that ADHD may have multiple causes. They postulate that the 7-R allele of the DRD4 gene may produce a receptor that is subsensitive to dopamine, while the I0-R allele of the DAT1 gene may be associated with a dopamine transporter, which is abnormally efficient at the re-uptake process.

Single photon emission computed tomography studies in adults have shown that methylphenidate lowers increased striatal DAT availability in adults suffering from ADHD.
Use of radioactive isotopes is not possible in children, as delayed response, delayed alternation and delayed match prefrontal cortex (PFC). They have shown beneficial effects on spatial working memory and attentional functions of the primates, which indicated the NE has an important influence on the locus coeruleus (LC).

Thought to be dysregulated in ADHD, possibly via deficits in normal attention and impulse control. Positron emission tomographic studies have shown that post-synaptic alpha 2A receptor stimulation inhibits irrelevant and distracting sensory processing through effects on pyramidal cells that project to (posterior) sensory association cortices. When a selective alpha, adrenergic agonist was infused into the PFC spatial working memory was impaired, suggesting an opposing role between alpha 1 and alpha 2 agonists.

Solanto, Arnsten and Castellanos [1] have edited an important text on Stimulant Drugs and ADHD. Solanto et al [26] reviewed the critical role of the prefrontal cortex (PFC) in regulating attention, inhibiting inappropriate or impulsive behaviours and using working memory to plan, organise and guide behaviour effectively. Research in rodents and monkeys indicates that both dopamine and norepinephrine have profound effects on the cognitive functioning of the PFC. Low levels of dopamine D1 and norepinephrine alpha-2 receptor stimulation are essential for PFC function, while very high levels of dopamine D1 and alpha-1 receptor stimulation impair PFC function. Beneficial effects of guanfacine ([α-2A adrenergic agonist) on cognitive performance, have been described by Arnsten [27] and Jakala et al [28].

Solanto et al [26] also discuss subcortical dysfunction at basal ganglia, cerebellar and locus coeruleus (LC) levels. The ventral striatum (nucleus accumbens) (as described by Grace) [19] plays a critical role in individuals with ADHD, where low tonic dopamine levels allow proportionately elevated phasic DA release.

Berridge [29] reviewed the role of the LC. Recordings from the LC in monkeys show that during alert waking the LC exhibits moderate baseline firing. In contrast, the phasic responses of the LC to target stimuli were most pronounced during an optimal alert state, and diminished during either drowsy or hyperaroused states. Solanto [25] suggests that the PFC may regulate appropriate phasic response of the LC.

Recent imaging studies [30] indicate that the cerebellum is activated during alert states, and cerebellar dysfunction may be involved in the hyperactivity observed in ADHD [31].

PREFRONTAL-PARIETAL INTERACTION

While the above hypotheses suggest important roles for both anterior (dopaminergic) and posterior (noradrenergic) attention systems in ADHD, there have been few, if any direct demonstrations of such reciprocal relationships in ADHD children. However, recent work reviewed below [32], utilizing the Continuous Performance Task, suggests prefrontal-parietal interactions in ADHD children.

Levy and Hobbes [33] described the use of an age-normalised, Continuous Performance Test (X version) which distinguished a group of 15 hyperkinetic children from 83 normal school children. Levy and Hobbes [34] utilised the CPT to examine the effect of methylphenidate on task performance after a prior treatment with haloperidol. Methylphenidate was shown to diminish attention deficits in...
a group of 12 boys, diagnosed with attention deficit disorder with hyperactivity, but when preceded by haloperidol, this effect was blocked in all the vigilance subtests. The findings were thought to imply a primarily dopaminergic action of methylphenidate in attention-disordered children.

Levy and Hobbes [35] utilized data from the 1988 study to examine the effect of methylphenidate over the course of the Continuous Performance Task (Blocks 1 and 2). They showed a significant drug vs time interaction over the course of the CPT. This effect was antagonised by haloperidol. The study was the first to show a significant effect of methylphenidate (and of haloperidol in opposite direction) during the second half of the CPT task. Methylphenidate was thought to allow increased activation over the course of the task.

Event Related Potential (ERP) studies of ADHD have also been used to examine activation processes in ADHD children. The most commonly examined component is the P300, that is a late positive wave with a latency of 300 to 800 ms [36]. The amplitude of the P300 is influenced by stimulus probability or relevance, and the latency is influenced by cognitive, perceptual or memory load [36]. It is thought to reflect allocation of attention and stimulus evaluation processes, as well as updating of internal representations and working memory [37]. Most studies in ADHD children have found the amplitude of the P300 to be reduced in children with ADHD [36-38].

Silberstein et al [32] and Farrow et al (in preparation) have utilized a Steady-State Visually Evoked Potential (SSVEP), which measures cortical electrical activity over the course of an A-X Continuous Performance Task (children are asked to press a button when they see an X proceeded by an A). The technique, also known as Steady-State Probe Topography (SSPT), enables examination of disturbances in the spatial distribution and dynamics of brain electrical activity. (Reductions in SSVEP amplitude have previously been associated with increased cortical activation [39,40]). The investigators found that compared to the mean amplitude during a reference task, control subjects demonstrated SSVEP amplitude reductions, during the A-X interval. Transient amplitude reductions occurred in frontal regions, while right parietal and occipital amplitude reductions were sustained throughout the 3.5 second A-X interval.

In contrast, ADHD subjects demonstrated much smaller frontal amplitude reductions and increased parieto-occipital amplitude (ie less activation) suggesting they failed to increase cortical activation according to task demands. The largest group differences occurred at the disappearance of the A, when controls showed extensive activation, particularly in the parieto-occipital region, while ADHD subjects showed reduced activation in the parieto-occipital region. The disappearance of the A also coincided with large latency reductions in controls at frontal and temporal sites, while in ADHD subjects there were latency increases.

A further study (Farrow et al, in preparation) examined changes in SSVEP following methylphenidate administration in 60 boys with ADHD (mean age 10 years 1 month), recently diagnosed according to DSM-IV criteria (Diagnostic and Statistical Manual of the American Psychiatric Association – 4th edition). SSVEP amplitude and latency during the A-X interval, before methylphenidate, and 90 minutes after administration of 0.3 mg/kg of methylphenidate was examined. After methylphenidate, there was increased activation predominantly in frontal and occipital regions, and reduced parieto-occipital latency, at the disappearance of A, in the A-X interval. The most sustained and significant changes occurred in the right parietal region. There were also transient reductions in frontal latency, particularly after the disappearance of the A. The results are thought to suggest that right prefrontal and right parietal processes, which are involved in performance of the CPT-AX task in healthy control children, are deficient in ADHD children, and are enhanced by methylphenidate in ADHD children. In particular, these processes may be involved in the maintenance of activation in the interval between A and X, allowing a ‘working’ retention of the parameters necessary for correct task performance.

Goldman-Rakic [21,41] described the role of the primate pre-frontal cortex in spatial cognition, from the point of view of connectivity with major neurological centers. The pre-frontal cortex in primate studies was found to be integral to delayed response tasks, which required behaviour to be guided by representations of discrimination stimuli, rather than those stimuli. Thus, the work of Goldman-Rakic in primates and the above SSVEP findings suggest that prefrontal-parietal reverberating reciprocal circuits maintain the visuo-spatial representation required for delayed response and for CPT performance. The activation of cortical circuits is maintained by subcortical tone acting directly and indirectly [3, 42]. Gray et al [42] elaborated a model describing intercorrelations between basal ganglia and accumbens, which monitor switching from one step to the next of a motor program.

Goldman-Rakic et al [43] have described the anatomical overlap of different monoaminergic receptors in the same cortical strata, suggesting that there may be families of receptors linked by localization on common targets. This would provide the anatomical basis for subcortical influences on prefrontal/parietal systems. On the other hand, the complimentary laminar distribution of D_{1} vs D_{2}, 5-HT_{1}, vs 5-HT_{3} and alpha vs beta adrenergic receptors, raises the possibility that different subtypes within a given class, may have distinctive actions in the cortex, by virtue of their localisation on different cells, or possibly on different portions of the same cell. For example, Wilson et al [44] have shown that the prefrontal cortex is segregated into object and spatial domains with separate connections.

Denny and Rapport [45] have described a model, which postis that working memory plays a pivotal role in the organisation of behaviour. Organised responding is functionally dependant on the capacity of working memory to (a) generate and maintain representations of input stimuli (b) search memory traces for matches and (c) access and maintain representations of behavioural responses appropriate to input stimuli. Failure of working memory leads not only to disorganised behaviour but also motivates children to redirect their attention to other stimuli in the environment (stimulation seeking), giving rise to frequent
rapid shifts in activity. Working memory is viewed as a causal cognitive process that is the direct consequence of one or more neurobiological substrates.

The present review suggests that prefrontal-parietal activation is an important component of working memory in CPT tasks, shown to be impaired in ADHD children, and suggests that CPT models should be useful in the investigation of drug targets for ADHD. While the inhibitory role of prefrontal/striatal circuits have been described by Castellanos [4] and others, the importance of prefrontal/parietal pathways for working memory has not been emphasised (see Castellanos [46, pp 244] for path diagram). While the inhibitory role of prefrontal/striatal circuits have been described by Castellanos and others, the importance of prefrontal/parietal pathways for working memory has not been emphasised. Thus, while the tonic dopaminergic activity within the ventral striatum/accumbens described by Grace [20] gates the inhibitory activity of the prefrontal cortex, the dorsolateral prefrontal/parietal connections allow maintenance of working memory required for goal completion.

**ABBREVIATIONS**

ADHD = Attention Deficit Hyperactivity Disorder

DA = Dopamine

DAT = Dopamine transporter

DRD4 = Dopamine 4 receptor gene

NE = Noradrenaline

LC = Locus coeruleus

CPT = Continuous Performance Task

ERP = Event Related Potential

SSVEP = Steady State Visually Evoked Potential

SSPT = Steady State Probe Tomography

**REFERENCES**


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