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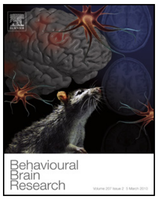

Research report

Stop and look! Evidence for a bias towards virtual navigation response strategies in children with ADHD symptoms

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HIGHLIGHTS

- Participants with ADHD symptoms less likely to reach trials to criteria on spatial navigation task.
- ADHD symptoms improved performance on the probe trial during spatial navigation task.
- Children with ADHD symptoms rely on caudate dependent response learning strategies.
- Repetition and reward strategies likely most effective for children exhibiting ADHD symptoms.

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ABSTRACT

Studies in children show that the development of spatial competence emerges between seven and eight years of age. Multiple memory systems (hippocampus-dependent spatial and caudate nucleus-dependent response learning) are involved in parallel processing of information during navigation. As a hippocampus-dependent spatial strategy also relies on frontoparietal executive control and working memory networks that are impaired in ADHD, we predicted that children will be more likely to adopt a response strategy as they exhibit ADHD symptoms. We tested 285 healthy children on a virtual radial-arm maze paradigm in order to test this hypothesis. We found that children displaying at least one ADHD symptom were more likely to have a perfect performance on a probe trial, which suggests that they did not rely on environmental landmarks. Children with ADHD symptoms may primarily rely on caudate nucleus-dependent response learning strategies at the expense of hippocampus-dependent spatial strategies. Repetition and reward based learning strategies, which are hallmarks of response learning, may be most effective in children exhibiting ADHD symptoms.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is caused by the complex interplay of genetic and environmental risk factors. It is behaviorally characterized by the presence of inattention, hyperactivity, and impulsivity. Some ADHD symptoms are often found in most healthy children, but it is only when the number of symptoms is above a clinical threshold, and when there is functional impairment, that a diagnosis is made. Although ADHD is a clinical category, genetic, brain imaging, neuropsychological and clinical studies suggest that ADHD is the extreme and impairing end of a continuous quantitative trait [49]. This categorical definition fails to capture the whole variation in the normal population in terms of symptoms. Therefore we took the approach of assessing ADHD as a discrete variable in an epidemiological sample of twins, with a range going from 0 up to 18 symptoms.

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Functional imaging studies have related ADHD to hypoactivation in the frontoparietal executive control network, putamen, and ventral attention network [46]. Structural imaging studies detected reduced volumes in basal ganglia regions like the right globus pallidus, as well as the right putamen and caudate nucleus regions of the striatum. These findings are consistent with the classical model of ADHD as a disorder of deficient frontostriatal circuitry [53,54]. However, other brain regions such as the hippocampus [36] have also been implicated, perhaps as a result of other primary deficits.

There is evidence for a view of the cognitive deficits in ADHD that includes the frontal cortex. The frontal view suggests that executive dysfunction gives rise to the behavioral symptoms of ADHD [2], a claim which is supported by the observation that many of the deficits associated with ADHD are similar to those that follow damage to the frontostriatal circuitry. For example, like patients with damage to the frontal cortex, people with ADHD have been shown to have impairments with set shifting, response inhibition, working memory, and planning [26,40,41,43,45]. Recent studies have consistently correlated changes in prefrontal activity with striatal functioning during performance on tasks known to be affected in ADHD [3,11].

Persistent working memory deficits have also been demonstrated in children and adults with ADHD [48,1], especially when the tasks placed a high demand on central executive function (temporary storage, maintenance, and manipulation of information). A recent study has demonstrated that ADHD interfered with performance in a demanding conditional associative learning task [16] which utilized a method of learning dependent upon the frontostriatal network [20,25,35,16]. These results argue that deficits in a demanding, but not simple, conditional associative learning task are indicative of maladaptive prefrontal strategies during encoding, rather than of a primary functional deficit in the striatum.

In some studies, ADHD has been shown to produce deficits in memory tasks that are thought to depend on regions beyond the frontostriatal network. For example, children with ADHD showed impairments in a paired-associative learning task [8,12], which required learning to associate an arbitrary pair of words. This kind of associative learning is thought to rely on the medial temporal lobe (MTL) [14]). The MTL is a region not typically implicated in ADHD, as demonstrated in a number of studies showing preserved performance in MTL-dependent tasks [41]. Several authors have suggested that prefrontal dysfunction also causes deficits in more difficult paired-associative tasks [8]. Explicitly providing a learning strategy to children with ADHD increased performance in free recall memory tasks, which strongly suggests that the capability to form new memories is intact in ADHD, and that ineffectual contributions of the prefrontal cortex to the various memory systems are the cause of memory problems [9].

To date, no study has examined the interplay between learning dependent on the hippocampus versus that of the caudate nucleus part of the striatum in relation to ADHD. This is of particular interest because both systems interact with the prefrontal cortex, and a person's ability to utilize one system (i.e. caudate nucleus-dependent learning) over another in the same dual-solution task could provide valuable insight in the way in which information is encoded in children with ADHD. Therefore we have determined the type of learning strategy (hippocampus- and caudate nucleus-dependent) as a function of ADHD symptoms in an epidemiological sample [7]. In such a sample, ADHD symptoms are likely to be few, and above clinical threshold for a handful of children [37].

Navigation tasks are particularly well suited for investigating the role of memory systems during learning. It is well known that the striatum (which includes the caudate nucleus) is involved in stimulus-response learning in humans [5,18] and rodents [29,33,34,44]. Through repetition and habit formation, learning a series of stimulus-response associations allows for successful navigation along well-known routes [17]. On the other hand, the hippocampus is needed to form an abstract cognitive representation of space [5,18,31,34]. Cognitive mapping is a cognitively demanding mental feat. Forming a spatial representation of one's environment requires the association of space-defining stimuli in a reference frame that is independent of the viewer [31].

Previously, we have developed a virtual reality, human analogue of the radial arm maze, the 4-on-8 virtual maze (4/8VM), which can be completed using either cognitive mapping spatial strategy or a response strategy. Using this task, we have shown that approximately 50% of healthy adults spontaneously adopt a spatial strategy, with the other 50% using response a strategy [18]. We have also shown that spatial learners possess more grey matter in the hippocampus than response learners [5] and that they exhibit significantly greater fMRI activity in the hippocampus than response learners while navigating on the 4/8VM [18]. Response learners, on the other hand, were found to have activity in the caudate nucleus of the striatum [18]. Finally, we showed that the size of the hippocampus and caudate nucleus were negatively correlated [4,5], a finding that adds to the growing literature that describes the fact that either one of these two structures is used at a given time, possibly in a competitive manner [30,34].

Studies in children show that the development of spatial competence emerges between seven and eight years of age [22,32]. Two studies [6,24] have addressed the question of which memory system is preferentially active in children when faced with a task that can be solved using either the hippocampus- or the caudate nucleus-dependent learning. In Leplow et al.' study (2003), all the children over the age of 10 years old used a hippocampus dependent spatial strategy. The current investigation used our 4/8VM paradigm adapted for children [6]. Consistent with the study by [24], we also found that 8-year old children were more likely to spontaneously adopt a hippocampus-dependent strategy in the 4/8VM. However, response learning requires the association of body movements with a single position in the environment, while cognitive mapping requires learning the relationships between many items in the environment and a change of reference from body-centered to world-centered. Hippocampus-dependent spatial strategy thus requires complex initial encoding and effortful retrieval that depend on frontoparietal executive control and working memory networks. As ADHD is primarily related to deficits in these circuits, we predicted that children would be more likely to adopt a response strategy as they exhibit more ADHD symptoms.

2. Methods

2.1. Participants

From an initial sample of 299 eight year olds from the Quebec Newborn Twin Study [7], 285 children tested on the 4/8VM. Children were categorized as having used a hippocampus-dependent spatial strategy or a caudate nucleus-dependent response strategy based on verbal reports administered after the 4/8VM. Of the 285 children, 267 provided verbal reports and we were able to assess spontaneous strategy in 234 children in total. Among the remaining 234 children tested on the same version of the task (maximum of 8 errors before termination of a trial), 22 participants were excluded due to nausea, ($N = 5$)failure to cooperate, ($N = 8$) experimental error in administering the task, and ($N = 2$) failure to complete the task within the allotted time. The final sample used for analysis ($N = 223$) consisted of 115 boys and 108 girls and the average age for boys and girls combined was 8.43 ± 0.11 years old. Participants were screened for the presence of ADHD symptoms. Analysis of twin differences is beyond the scope of the current study, as is a detailed analysis of sex differences.