Published in final edited form as:
Neurosci Biobehav Rev. 2011 January ; 35(3): 621–634. doi:10.1016/j.neubiorev.2010.07.006.

The Influences of Environmental Enrichment, Cognitive Enhancement, and Physical Exercise on Brain Development: Can we Alter the Developmental Trajectory of ADHD?

Jeffrey M. Halperin[1,2] and **Dione M. Healey**[3]

[1]Department of Psychology, Queens College of the City University of New York, USA
[2]Department of Psychiatry, Mount Sinai School of Medicine, New York, USA [3]Department of Psychology, University of Otago, New Zealand

Abstract

Attention-deficit/Hyperactivity Disorder (ADHD) is characterized by a pervasive pattern of developmentally inappropriate inattentive, impulsive and hyperactive behaviors that typically begin during the preschool years and often persist into adulthood. The most effective and widely used treatments for ADHD are medication and behavior modification. These empirically-supported interventions are generally successful in reducing ADHD symptoms, but treatment effects are rarely maintained beyond the active intervention. Because ADHD is now generally thought of as a chronic disorder that is often present well into adolescence and early adulthood, the need for continued treatment throughout the lifetime is both costly and problematic for a number of logistical reasons. Therefore, it would be highly beneficial if treatments would have lasting effects that remain after the intervention is terminated. This review examines the burgeoning literature on the underlying neural determinants of ADHD along research demonstrating powerful influences of environmental factors on brain development and functioning. Based upon these largely distinct scientific literatures, we propose an approach that employs directed play and physical exercise to promote brain growth which, in turn, could lead to the development of potentially more enduring treatments for the disorder.

Keywords

ADHD; Neural Development; Neurocognitive functioning; Environmental enrichment; Exercise; Treatment

INTRODUCTION

Attention-deficit/Hyperactivity Disorder (ADHD) is a chronic, highly prevalent neurodevelopmental disorder which affects as many as 9% of school-age children (Pastor & Reuben, 2008). ADHD typically emerges during the preschool years, persists through adolescence and into adulthood for many afflicted individuals, and causes significant

functional disability throughout the lifespan (American Psychiatric Association Task Force on DSM-IV, 2000). Several effective empirically-validated psychopharmacologic and behavioral interventions for ADHD are currently available. These interventions have been shown to ameliorate the core symptoms of ADHD and to improve academic performance across a wide array of school-related measures. However, such gains are rarely maintained after the termination of treatment (Chronis, Pelham, Jr., Gnagy, Roberts, & Aronoff, 2003; Chronis et al., 2004; Jensen et al., 2007), and relatively few individuals with ADHD receive effective treatment throughout the full course of their disorder (Corkum, Rimer, & Schachar, 1999; Jensen et al., 2007; MTA Cooperative Group, 1999; MTA Cooperative Group, 2004; Perwien, Hall, Swensen, & Swindle, 2004; Sanchez, Crismon, Barner, Bettinger, & Wilson, 2005; Weiss, Gadow, & Wasdell, 2006; Molina et al., 2009). The need for continued treatment throughout the lifetime is both costly and problematic for a number of logistical reasons. Therefore, it would be highly beneficial if a treatment could be employed that would have lasting effects that remain after the active intervention is terminated.

Recent research has begun to elucidate the underlying neural (Casey et al., 1997; Castellanos, 2001; Makris et al., 2007; Schulz et al., 2004; Schulz, Newcorn, Fan, Tang, & Halperin, 2005a; Seidman, Valera, & Makris, 2005; Shaw et al., 2006; Shaw et al., 2007b; Shaw et al., 2007a) and neurocognitive (Sergeant, Oosterlaan, & van der Meere, 1999; van Mourik, Oosterlaan, & Sergeant, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) determinants of ADHD. Additionally, a distinct scientific literature, largely consisting of research with animals, indicates that an array of neurodevelopmental processes facilitate efficient neurotransmission and are highly responsive to environmental influences. The bringing together of these scientific literatures may provide valuable insights for the development of more enduring treatments for ADHD.

OVERVIEW OF EVIDENCE-BASED TREATMENTS FOR ADHD

Pharmacological interventions, most prominently stimulant medication, and behavioral interventions in the forms of parent training and contingency management in the classroom, are considered the best-supported treatments for ADHD. These interventions result in significant benefits for children with ADHD in multiple domains of functioning (Conners, 2002; Greenhill, Halperin, & Abikoff, 1999; Pelham, Jr., Wheeler, & Chronis, 1998; Pelham, Jr. & Fabiano, 2008; Spencer et al., 1996). For example, studies of behavioral parent training (BPT) for ADHD have demonstrated improvements in ADHD symptoms (Anastopoulos, Shelton, DuPaul, & Guevremont, 1993; Sonuga-Barke, Daley, Thompson, Laver-Bradbury, & Weeks, 2001; Cunningham, Bremner, & Boyle, 1995), as well as co-occurring oppositional problems and impairment in children (Erhardt & Baker, 1990; Pisterman et al., 1989; Pisterman et al., 1992). BPT also improves parental functioning (e.g., decreased stress, enhanced competence) (Anastopoulos et al., 1993; Pisterman et al., 1992; Sonuga-Barke et al., 2001). Moreover, behavior contingency management in the classroom yields improvements in teacher reports of children's functioning, observed behavior of children with ADHD in the classroom setting, as well as better academic productivity (Abramowitz, O'Leary, & Rosen, 1987; Fabiano et al., 2007; Pelham, Jr. et al., 1998; Hoffman & DuPaul, 2000). While data indicate that behavioral treatments are not, on the group level, as effective as carefully-monitored stimulant medication, the large Multimodal Treatment Study of ADHD (MTA Study) found that their pure behavioral treatment group improved to a similar degree as their community treated control group, the majority of whom received medication treatment from their provider outside of the study (MTA Cooperative Group, 1999).

Stimulant medication has been shown to improve functioning in children with ADHD, with studies demonstrating improvements in core symptoms of ADHD, compliance, aggression,

and academic productivity (Conners, 2002; Greenhill et al., 1999; Spencer et al., 1996). Effect-size calculations from both behavioral interventions and stimulant medication studies demonstrate that these interventions result in substantial improvements across domains of functioning (Conners, 2002; Pelham, Jr. et al., 2008). Collectively, compelling evidence indicates that behavioral interventions and stimulant medication improve the functioning of children with ADHD and, in some cases, have additional benefits for their families. However, noted below, are several limitations to these treatments which necessitate further investigation into alternative interventions for children with ADHD.

Key Limitations of Current Evidence-Based Interventions for ADHD

Although clearly efficacious, there are limitations to current evidence-based interventions. Stimulant medication is an easy intervention to implement, but many parents prefer not to use medication as a treatment for their child with ADHD (Pisecco, Huzinec, & Curtis, 2001; Power, Hess, & Bennett, 1995). Moreover, a substantial number of children experience notable side effects with stimulant medication (MTA Cooperative Group, 2004; Swanson et al., 2006; Swanson et al., 2007a; Wigal et al., 2006) that may prohibit continued use. In addition, recent concerns have been raised by the American Heart Association (American Heart Association, 2008) suggesting problematic interactive effects of stimulant medication with underlying cardiac conditions that may further limit the acceptability of stimulant medication for children with ADHD, or at least make it less palatable to parents. Behavioral interventions, in contrast, are more palatable but much more difficult to implement, generally quite costly, and may be less effective than stimulant medications (MTA Cooperative Group, 1999).

In addition, there are several limitations that both stimulant medication and behavioral interventions share in common. First, although both treatments are efficacious, the behavior of a significant number of children with ADHD is not normalized by the use of these interventions (Hoza et al., 2005; Swanson et al., 2001). Swanson and colleagues (Swanson et al., 2001) found that 32–64% of children continued to exhibit clinically significant levels of ADHD despite intensive stimulant medication and behavioral treatment regimens. Moreover, Hoza et al. (Hoza et al., 2005) found that despite intensive treatment over 14 months, children continued to have difficulties in peer relationships. Therefore, although children with ADHD may do significantly better with stimulant medication and/or behavioral interventions relative to baseline, they still appear deviant relative to their peers in key areas of functioning.

Furthermore, treatment effects rarely persist past the point of active dosing/ implementation (Chronis et al., 2003; Chronis et al., 2004). This suggests that implementation of behavioral interventions and stimulant medication temporarily suppresses behavioral difficulties and that these difficulties resurface when treatment is no longer active. As such, there are no apparent changes in the underlying deficits that produce the behavioral manifestations of ADHD.

In addition, although ADHD is considered a chronic condition that impacts functioning across multiple settings, which would thus require long-term treatment that impacts each affected setting, long-term adherence to both stimulant medication and behavioral interventions is often poor. For instance, there is considerable noncompliance with stimulant medication (MTA Cooperative Group, 2004; Corkum et al., 1999; Jensen et al., 2007; Perwien et al., 2004; Sanchez et al., 2005; Weiss et al., 2006). More than half of children prescribed stimulant medication stop receiving treatment within a school year (Sanchez et al., 2005), and most maintain good adherence for fewer than two months (Perwien et al., 2004). It has been estimated that fewer than 10% of children with ADHD persist with long-term medication treatment (Weiss et al., 2006). For behavioral interventions to be

implemented over the long-term, willingness among key adults (teachers and parents) to implement highly intensive interventions over long periods of time, with high levels of fidelity, is necessary but extremely challenging (Chronis et al., 2001; Witt, 1986).

Lastly, the collective evidence suggests that stimulant medication use has few, if any, long-term benefits for children with ADHD (Charles & Schain, 1981; Loe & Feldman, 2007; Molina et al., 2007; Paternite, Loney, Salisbury, & Whaley, 1999; Satterfield, Hoppe, & Schell, 1982; Swanson et al., 2007b; Weiss & Hechtman, 1993; Molina et al., 2009). This finding also applies to behavioral interventions (Molina et al., 2007; Pelham, Jr. et al., 2008). Thus, although acute benefits of stimulant medication and behavioral interventions are well-documented in the literature, the lack of normalization of functioning for many children following treatment, lack of generalization of treatment effects, difficulties in long-term adherence, and lack of clear improvement in long-term functioning following the use of these interventions are discouraging.

Given these findings, an alternative approach to ameliorating the difficulties of children with ADHD is indicted. The extensive literature indicating neurobiological deficits in ADHD, and the strong body of evidence regarding neural rehabilitation, suggests that research examining the impact of pharmacologic as well as environmental manipulations on neural growth, and lasting cognitive function, could provide a potentially fruitful avenue for novel treatment approaches for this highly impairing and oftentimes life-long disorder.

NEURAL SUBSTRATES OF ADHD

Neuroimaging Evidence

Neuroimaging studies suggest an important role for frontostriatal circuits along with a wide array of other cortical and subcortical brain regions in the pathophysiology of ADHD. Numerous structural MRI studies have reported smaller regions in the prefrontal cortex (PFC) of youth with ADHD (Castellanos et al., 1996; Castellanos et al., 2002a; Durston et al., 2004; Filipek et al., 1997; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990; Kates et al., 2002; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002; Sowell et al., 2003). Similarly, studies have found reduced caudate nucleus size (Filipek et al., 1997; Hynd et al., 1993), reduced volume in the globus pallidus (Castellanos et al., 1996); and reduced callosal area in ADHD (Baumgardner et al., 1996; Giedd et al., 1994; Hynd et al., 1991; Hill et al., 2003; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994).

Structural anomalies have also been reported in several brain regions outside of the frontal lobes and striatum. Studies have noted reduced volume in several parts of the cerebellum in ADHD (Castellanos et al., 2002a; Castellanos et al., 1996; Durston et al., 2004; Posner & Petersen, 1990) as well as posterior cortical anomalies (Durston et al., 2004; Filipek et al., 1997; Sowell et al., 2003). Additionally, several (Berquin et al., 1998; Castellanos et al., 1996; Castellanos, 2001; Castellanos et al., 2002a; Hill et al., 2003), but not all (Durston et al., 2004; Filipek et al., 1997; Hynd et al., 1990; Mostofsky et al., 2002), studies report reduced whole brain size in children with ADHD. A key review of the structural MRI literature (Seidman et al., 2005) found support for the notion that ADHD is associated with frontostriatal abnormalities. However, an increasing number of studies, demonstrating widespread neural abnormalities affecting other cortical regions and the cerebellum, were highlighted.

Recently, studies have begun to use MRI to examine differences in cortical thickness between individuals with and without ADHD. In a series of developmentally-sensitive longitudinal studies Shaw et al. (Shaw et al., 2006; Shaw et al., 2007a; Shaw et al., 2007b) reported that children with ADHD followed a similar sequential pattern of cortical

development, yet were delayed by as much as 2 – 3 years, depending upon the specific cortical region (Shaw et al., 2007a). These findings were interpreted as suggesting developmental delays rather than permanent anomalies in ADHD. Additional research from this group (Shaw et al., 2006) found links between cortical thickness and clinical outcome such that ADHD children with worse outcome had “fixed” thinning of the left medial PFC and those with better outcomes had right parietal normalization, which was suggested to represent compensatory cortical change. Similarly, McAlonan et al (McAlonan et al., 2009) reported an association between the magnitude of age-related growth in the anterior cingulate, striatum and medial temporal cortex, and improvements in neurocognitive measures of response inhibition in school-age children with ADHD. Further, better clinical outcome was linked to the presence of the DRD4-7-repeat allele (Shaw et al., 2007b), which was associated with thinner right orbitofrontal/inferior prefrontal and posterior parietal cortices. This thinning was most apparent in childhood and largely resolved in adolescence. Yet, these executive function networks which include the dorsolateral PFC, anterior cingulate cortex and inferior parietal lobe remain thinner in adults with ADHD (Makris et al., 2007). A recent review focusing on trajectories of brain development (Shaw, Gogtay, & Rapoport, 2010) suggests that remission in ADHD with age may be linked to a normalization of initial delays or deficits in brain networks, whereas ADHD persistence into adolescence may be associated with a lack of normalization and perhaps a more deviant trajectory of brain growth.

Consistent with the structural MRI data, functional MRI (fMRI) studies provide compelling data indicating functional brain differences between individuals with ADHD and controls. These functional studies have linked neural anomalies to deficiencies in a wide array of neurocognitive processes including inhibitory control (Casey et al., 1997; Durston et al., 2003; Schulz et al., 2004; Schulz et al., 2005a; Tamm, Menon, Ringel, & Reiss, 2004; Vaidya et al., 1998), conflict resolution (Bush et al., 1999; Tamm et al., 2004), motor control (Rubia et al., 1999), timing (Durston et al., 2007), attention (Cao et al., 2008; Sonuga-Barke & Castellanos, 2007; Uddin et al., 2008a) and working memory (Valera, Faraone, Biederman, Poldrack, & Seidman, 2005). Although findings have not always been consistent, many studies have reported greater and more diffuse PFC and basal ganglia responses to increased cognitive demands in participants with ADHD. These findings are reminiscent of the immature brain function associated with susceptibility to interference in young children (Casey, Tottenham, & Fossella, 2002).

Recently, there has been an emerging shift in focus among neuroimaging studies from the examination of specific brain regions to an examination of networks or how specific regions are connected or interact (for review, see (Konrad & Eickhoff, 2010). This research, which is in its infancy and still has many methodological issues to tackle, has focused largely, on two proposed neural systems. The Default Mode Network (DFN), comprised of the precuneus, posterior cingulate cortex, the medial prefrontal cortex and portions of the parietal cortex (Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008), has been shown to be most active during rest, and to deactivate during active task engagement (Raichle et al., 2001). In contrast, a second network, which includes the dorsolateral prefrontal cortex, the intraparietal sulcus, and the supplementary motor area is more quiescent during rest and becomes activated during periods of task engagement. This latter system seems more linked to increased alertness and response preparation than to any specific cognitive process (Konrad et al., 2010). These two neural systems have been described as being ‘anti-correlated’ such that when the task positive fronto-parietal system turns-on in response to task demands, the DFN becomes less active, and when at rest the DFN is most active, and activity in the fronto-parietal system diminishes (Fox et al., 2005; Sonuga-Barke et al., 2007).

When comparing ADHD participants to controls, some data suggest, reduced functional activity and connectivity within the DFN during rest (Castellanos et al., 2008; Uddin et al., 2008b), but others report an overactive DFN during quiescence (Tian et al., 2006; Tian et al., 2008). Sonuga-Barke & Castellanos (Sonuga-Barke et al., 2007) have hypothesized that, among those with ADHD, the DFN does not adequately deactivate during task engagement, which in turn interferes with the neural circuits that underlie the ability to efficiently engage in active tasks. According to this hypothesis, the interference results in frequent errors and lapses in attention, as evidenced by the frequently reported increased reaction time variability associated with ADHD (Castellanos & Tannock, 2002b; Kuntsi, Oosterlaan, & Stevenson, 2001; Russell et al., 2006). Notably, psychostimulant treatment has been found to improve DFN suppression during active task engagement in youth with ADHD (Peterson et al., 2009), as well as to decrease reaction time variability (Spencer et al., 2009).

Finally, recent research has also examined connectivity during active task engagement. Two studies (Rubia et al., 2010; Vloet et al., 2010) have reported decreased functional connectivity during active task performance in children with ADHD, which may in part be normalized by treatment with stimulant medication (Rubia et al., 2009). However, in adults with ADHD a more complicated pattern of regional increases and decreases in functional connectivity has been reported (Wolf et al., 2009).

Thus, when taken together, neuroimaging studies provide compelling evidence for neurodevelopmental differences between individuals with and without ADHD that span a wide array of brain regions and neural circuits.

Neuropsychological Findings

Consistent with the neuroimaging data, neuropsychological data provide clear evidence that children with ADHD have impairments in a wide array of neurocognitive domains. Much of the literature has focused on executive functions (EFs) which are mediated by circuits involving the PFC. Studies most consistently find deficits in inhibitory control (Barkley, 1997; Casey et al., 1997; Durston et al., 2003), regulation of attention (Pennington, Groisser, & Welsh, 1993; Swanson et al., 1991; Halperin et al., 1993; Johnson et al., 2008), working memory (Castellanos et al., 2002b; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005), planning (Pennington et al., 1993; Barkley, 1997), and shifting sets (Seidman et al., 1995; Reader, Harris, Schuerholz, & Denckla, 1994; Hall, Halperin, Schwartz, & Newcorn, 1997). Willcutt et al's. (Willcutt et al., 2005) meta-analysis of 83 studies (total N = 6,703), which focused on 13 EF tasks, clearly indicated that groups of children with ADHD perform more poorly than controls on many EF measures, with effect sizes generally in the medium range (.46 - .69). However, because of the relatively modest effect sizes, it was concluded that EF weaknesses are "neither necessary nor sufficient to cause all cases of ADHD." Nonetheless, EF deficits likely contribute to the functional impairments that are present in many children with ADHD.

Despite the common conceptualization of ADHD as a disorder of EFs (Barkley, 1997), children with ADHD also differ from controls on a broad range of non-EF functions such as motor coordination (Blondis, 1999; Carte, Nigg, & Hinshaw, 1996; Kadesjo, Kadesjo, Hagglof, & Gillberg, 2001; Sheppard, Bradshaw, Georgiou, Bradshaw, & Lee, 2000; Steger et al., 2001), perception (Garcia-Sanchez, Estevez-Gonzalez, Suarez-Romero, & Junque, 1997; Mangeot et al., 2001), language (Beitchman, Tuckett, & Batth, 1987; Beitchman et al., 1996; Carte et al., 1996; Humphries, Koltun, Malone, & Roberts, 1994; Purvis & Tannock, 1997; Tirosh & Cohen, 1998), visuomotor integration (Raggio, 1999), and learning and memory (Felton, Wood, Brown, Campbell, & Harter, 1987). Meta-analyses (Frazier, Demaree, & Youngstrom, 2004; van Mourik et al., 2005; Willcutt et al., 2005) indicate an array of executive and non-executive function deficits in children with ADHD. Furthermore,

increased variability in reaction time (RT) is among the most consistently reported deficits in children with ADHD (Castellanos et al., 2002b; Russell et al., 2006; Spencer et al., 2009). Additional presumably "non-executive" parameters have been shown to differentiate ADHD from non-ADHD children, including signal detectability (*d*') and response bias (lnβ) variables from continuous performance tests (CPTs; (Losier, McGrath, & Klein, 1996). Kuntsi and colleagues (Kuntsi et al., 2001) reported that RT variability discriminated ADHD children from controls better than measures of inhibition and working memory, and Epstein and colleagues (Epstein et al., 2003) reported variability in *d*', lnβ, and RT to be strongly associated across multiple ADHD symptom domains. A recent study (Rommelse et al., 2007) reported that after controlling for "lower order" cognitive processes, there was little evidence for primary EF deficits in children with ADHD. As such, some have hypothesized that the EF deficits frequently observed in children with ADHD may be due to deficiencies in largely subcortical, regulatory systems, rather than cortical EF circuitry per se (Douglas, 1999; Halperin & Schulz, 2006; Rommelse et al., 2007; Sergeant et al., 1999; Sonuga-Barke et al., 2007).

In addition to more broadly assessing neurocognitive deficits in individuals with ADHD, several studies have focused more specifically on the three distributed neural networks hypothesized to underlie attention (Posner et al., 1990). One meta-analysis of 14 studies found little or no evidence for any visuospatial attention deficits in ADHD, including those functions typically attributed to the anterior or executive attention system (Huang-Pollock & Nigg, 2003). However, more recently, Johnson et al. (Johnson et al., 2008) reported evidence for impaired alerting and conflict resolution in youth with ADHD as measured using the Attention Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002). As posited by Posner and colleagues, the alerting network is driven largely by noradrenergic input from the locus coeruleus to the frontal and parietal lobes, whereas conflict resolution is more closely linked to a dopaminergic system involving the basal ganglia, anterior cingulate and the dorsolateral prefrontal cortex (Posner et al., 1990; Posner, Sheese, Odludas, & Tang, 2006).

From this review of the neuropsychological and neuroimaging studies, we can see that the findings do not support simple models that posit that ADHD is due to dysfunction of a few isolated brain regions, including the PFC. Rather, individuals with ADHD differ from controls on measures derived from multiple brain regions and across a wide array of neurocognitive domains. Further, studies examining cortical thickness provide compelling evidence that careful examination of developmental trajectories may be key to uncovering the neural substrates of ADHD, and that clinical outcomes might be linked to cortical development and compensatory mechanisms that develop throughout childhood.

NEURODEVELOPMENTAL PERSPECTIVES ON ADHD

Throughout the past decade investigators have increasingly embraced the notion that ADHD is best viewed within the context of a developmental trajectory rather than that of a static medical condition (Halperin et al., 2006; Sagvolden, Johansen, Aase, & Russell, 2005; Sonuga-Barke & Halperin, 2009; Taylor, 1999), and notably, that this developmental trajectory may be different for boys and girls (Mahone & Wodka, 2008). It is through this developmental perspective that one is most likely to identify the mediators and moderators of the diverse outcomes characteristic of youth with ADHD. Compelling data support an array of hypotheses that posit executive (Pennington & Ozonoff, 1996), motivational (Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Sonuga-Barke, Williams, Hall, & Saxton, 1996), inhibitory control (Barkley, 1997), cognitive-energetic (Sergeant et al., 1999) and reward-related (Sagvolden et al., 2005) deficits as being central to the etiology of ADHD. More recently, it has been proposed that there may be multiple causal pathways that

contribute to the *emergence of ADHD* in early childhood (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2002). However, little consideration has been afforded to *pathways out of ADHD* or the mechanisms by which the severity of the disorder diminishes over time, which could serve as the conceptual basis for the development of novel, perhaps enduring, interventions.

In an attempt to explain the commonly observed diminution in ADHD symptoms across the lifespan, Halperin and colleagues (Halperin et al., 2006; Halperin, Marks, & Schulz, 2008) have posited distinct neurocognitive mechanisms for the etiology of and relative recovery from ADHD. Specifically, they hypothesized that ADHD is caused by non-cortical neural dysfunction that is present early in ontogeny and remains relatively static throughout life. In this regard, the disorder is never really "cured" or "out-grown." Nonetheless, they posited that the reduction of symptoms oftentimes seen over development are at least partially accounted for by the degree to which prefrontally-mediated EFs and other higher cortical functions, which emerge throughout childhood and adolescence, can compensate for these more primary and enduring subcortical deficits.

As such, the PFC and other cortical regions may be involved in the reduction in severity of symptoms and impairment from ADHD rather than the etiology of the disorder. The efficiency of later cortical developmental processes may determine the extent to which an individual can compensate for or have a diminution of ADHD symptoms. This hypothesis is consistent with data suggesting that trajectories of cortical development throughout middle childhood might be closely linked to ADHD outcomes (Shaw et al., 2006; Shaw et al., 2007b), and that lower reaction time variability is associated with increased activation of the prefrontal circuit (prefrontal cortex and caudate) in children with ADHD (Suskauer et al., 2008). This latter finding was interpreted as prefrontal compensation for a more primary motor deficiency. In addition, fMRI findings indicate that PFC activation in response to inhibition in adolescents with childhood ADHD corresponds to the persistence of symptoms, such that those who are less symptomatic appear more like never-ADHD controls (Schulz et al., 2005b; Schulz et al., 2005a). Finally, longitudinal data (Halperin, Trampush, Miller, Marks, & Newcorn, 2008) examining neurocognitive functioning in adults who had ADHD in childhood, indicate that only those in whom ADHD has persisted differ from controls on measures of EFs such as working memory, sustained attention and inhibitory control.

This hypothesized developmentally-related compensation for earlier deficits may also be related to changes in functional connectivity in the brain that occurs over development. For example, Dosenbach et al. (Dosenbach et al., 2007) described two distinct "top-down" functional control networks in adults; a frontoparietal network involved in adaptive online task control and a cinguloopercular network involved in more stable set control. When compared across groups of children, adolescents and adults, a clear pattern of developmentally-related differences emerged such that short-range connections associated with these networks decreased whereas long-range connections increased across development (Fair et al., 2007). These findings suggest greater segregation between networks as well as improved integration within networks with increased age. It is possible that these developmental processes that support the maturation of this dual-network control system play a critical role in the hypothesized compensation for earlier deficits in youth with ADHD. Notably, this pattern of developmental decreases in local connectivity and increases in long-range connectivity does not appear limited to these specific neural systems. Rather, it appears to be a more general developmental principle that operates throughout the brain (Fair et al., 2009; Supekar, Musen, & Menon, 2009).

Finally, it has been hypothesized that the persistence of ADHD into adulthood, or the relative diminution of symptoms across the lifespan, is genetically mediated (Faraone,

2004). Supporting this hypothesis, Kuntsi et al. (Kuntsi, Rijsdijk, Ronald, Asherson, & Plomin, 2005) found in a longitudinal study of 4,000 twin pairs that symptom stability in ADHD from early-to-mid childhood was primarily due to shared genetic influences. Further, at the molecular level, children with ADHD who had at least one copy of the DRD4 7-repeat allele had a distinct trajectory of cortical development characterized by normalized cortical thinning, were less likely to maintain a diagnosis of ADHD at follow-up, had higher IQs, and exhibited better global functioning than children with ADHD without a DRD4 7-repeat allele; despite no differences in ADHD symptoms at baseline. This is consistent with findings of Swanson et al. (Swanson et al., 2000) who reported that the presence of the DRD4 7-repeat allele in children with ADHD was associated with fewer neuropsychological deficits. Additionally, the presence/absence of the 7-repeat allele may also underlie a key gene x environment interaction in relation to ADHD, its trajectory, and potential treatment response. As compared to children without the DRD4 7-repeat allele, the behavior of those with a 7-repeat allele was found to be more sensitive to the quality of parenting received (Sheese, Voelker, Rothbart, & Posner, 2007) and to have a better treatment response to a psychosocial parenting intervention (Bakermans-Kranenburg, van Ijzendoorn, Pijlman, Mesman, & Juffer, 2008). These data suggest that there may be genetic differences in the degree to which both the environment and delivered treatments influence developmental trajectories in children.

Thus, from a developmental perspective, interventions that promote neural growth, functional connectivity, and lasting cognitive facilitation could potentially provide a fruitful avenue for novel treatment approaches for this highly impairing oftentimes life-long disorder. Further, it is possible, that some children may be more or less genetically susceptible to respond to such interventions. As described below, accumulating evidence clearly indicates that early brain development is highly susceptible to environmental influences.

NEURAL DEVELOPMENT

Human central nervous system development proceeds in a systematic manner that begins before conception and continues at least into early adulthood. Nevertheless, brain development is non-linear, and progresses in a localized and region-specific manner that coincides with functional maturation (Huttenlocher & Dabholkar, 1997; Keshavan, Anderson, & Pettegrew, 1994). Of particular relevance are the relatively late and protracted development of the basal ganglia and cerebral cortex, including the PFC, and the motor and higher cortical functions that they mediate (Asato, Terwilliger, Woo, & Luna, 2010; Barkovich, 2005; Barnea-Goraly et al., 2005; Benes, 1989; Chelune, Ferguson, Koon, & Disckey, 1986; Giedd et al., 1996; Giedd et al., 1999; Gogtay et al., 2004; Goldman, 1971; Goldman & Galkin, 1978; Huttenlocher & de Court, 1987; Huttenlocher, 1990; Huttenlocher et al., 1997; Hynd et al., 1993; Keshavan et al., 1994; McKay, Halperin, Schwartz, & Sharma, 1994; Mrzljak, Uylings, van Eden, & Judas, 1990; Passler, Isaac, & Hynd, 1985; Welsh, Pennington, & Groisser, 1991; Yakovlev & Lecours, 1967).

The human brain develops primarily in utero and is approximately 80% of adult size by the age of 2 years (Giedd et al., 1999; Kretschmann, Kammradt, Krauthausen, Sauer, & Wingert, 1986). The process of myelination also begins in utero and proceeds rapidly up to age 2 years (Brody, Kinney, Kloman, & Gilles, 1987; Kinney, Brody, Kloman, & Gilles, 1988), but continues well into adolescence and early adulthood (Asato et al., 2010). The first two years of life are also a period of rapid synapse formation that occurs at varying times and rates in different brain regions, reaching maximum density at age 3 months in the auditory cortex and at age 15 months in the PFC, and resulting in an overproduction of synapses (Huttenlocher et al., 1987; Huttenlocher et al., 1997). Synaptogenesis is followed

by a plateau phase extending over several years, during which neurons begin to form complex dendritic trees (Mrzljak et al., 1990). These two processes seem to account for the increase in cortical gray matter in childhood found in MRI studies (Giedd et al., 1996; Giedd et al., 1999; Gogtay et al., 2004; Shaw et al., 2006; Shaw et al., 2007a).

Subsequent brain development, beginning at about 5 years of age, is marked as much by cortical organization and refinement as by neuronal growth. Cortical gray matter continues to thicken during the school-age years with about half of the cortical regions attaining peak thickness by the median age of 7.5 years (Shaw et al., 2007a), and cortical thickness peaking at around 10.2 to 12.8 years in the parietal cortex and around 11.0 to 12.1 years in the frontal lobe (Giedd et al., 1996; Giedd et al., 1999; Gogtay et al., 2004). Throughout this period the experience-dependent pruning of inefficient synapses in the cortex is also taking place (Giedd et al., 1996; Giedd et al., 1999; Gogtay et al., 2004; Huttenlocher et al., 1987; Huttenlocher et al., 1997). Synaptic pruning progresses in a region-specific manner and eventually reduces synaptic density to 60% of maximum (Huttenlocher et al., 1987; Huttenlocher et al., 1997), although it is mostly after puberty that the developmental process of cortical thinning occurs. These processes all facilitate efficient neural transmission and are necessary for the functional maturation of the brain. As in humans, this plateau phase of cortical thickness lasts through puberty in monkeys and is thought to be indicative of the need for consistent and high synaptic density during the formative years when learning and experiences are most intense (Bourgeois, Goldman-Rakic, & Rakic, 1994). While much of neural development is likely to be genetically programmed, considerable data indicate that variability in development across the lifespan is at least in part related to one's experiences.

Environmental Influences on Neurodevelopment

The notion that life experiences and one's environment can influence both cognitive and neural development was first clearly articulated in 1949 by Hebb (Hebb, 1949), who postulated that synapses are strengthened when presynaptic fibers repeatedly participate in activating the postsynaptic neuron. Subsequently, Hubel and Wiesel's (Hubel & Wiesel, 1970; Wiesel & Hubel, 1965) classic experiments demonstrated environmental influences on neural plasticity and neurodevelopment in the visual system in cats. In the 1960s Rosensweig and colleagues (Rosenzweig, Krech, Bennett, & Diamond, 1962; Rosenzweig, 1966; Rosenzweig & Bennett, 1969; Rosenzweig, Love, & Bennet, 1968) systematically began to examine the influence of environmental manipulations on brain weight, cortical thickness and the structure of dendrites, as well as on cognitive functioning. In the 1970s, Greenough et al. (Greenough, Volkmar, & Juraska, 1973b; Greenough & Volkmar, 1973a; Greenough, West, & DeVoogd, 1978) expanded this work to include the effects of environmental enhancements on a range of parameters of brain function including dendritic branching, spine density, synaptogenesis, angiogenesis, and gliogenesis.

Since these early seminal studies, an abundant scientific literature, primarily, but not exclusively, in non-human species, has examined the impact of environmental influences on molecular and cellular aspects of neural development as well as on an array of behavioral and cognitive functions. The precise environmental manipulations required to best facilitate specific aspects of neural development, the critical periods in development when they are optimally applied, and the duration necessary for such interventions have remained somewhat elusive. However, there is no longer doubt that brain development is highly responsive to increased levels of physical activity/exercise as well as environmental enrichment. While a full review of this extensive literature is beyond the scope of this paper, a brief overview is warranted. A plethora of studies in rodents have shown that environmental enrichment increases neuronal size, dendritic branching and spine number, synaptic density and overall neurotransmission in the neocortex (Diamond, Krech, & Rosenzweig, 1964; Diamond, 1967; Globus, Rosenzweig, Bennett, & Diamond, 1973;

Green & Greenough, 1986; Greenough et al., 1973b; Greenough et al., 1973a; Greenough et al., 1978; Leggio et al., 2005; Rosenzweig & Bennett, 1996). Environmental enrichments also enhance neurogenesis (Kempermann, Kuhn, & Gage, 1998; Nilsson, Perfilieva, Johansson, Orwar, & Eriksson, 1999), long-term potentiation (LTP; Duffy, Craddock, Abel, & Nguyen, 2001), neurotrophin levels (Ickes et al., 2000; Pham, Soderstrom, Winblad, & Mohammed, 1999; Pham, Winblad, Granholm, & Mohammed, 2002), dendritic spine growth and branching (Faherty, Kerley, & Smeyne, 2003; Green, Greenough, & Schlumpf, 1983; Rampon et al., 2000), synaptophysin levels (Frick & Fernandez, 2003; Nithianantharajah, Levis, & Murphy, 2004), and nerve growth factor mRNA and CREB gene expression (Torasdotter, Metsis, Henriksson, Winblad, & Mohammed, 1996; Torasdotter, Metsis, Henriksson, Winblad, & Mohammed, 1998; Williams et al., 2001) in the dentate gyrus of the hippocampus. Consistent with the effects of environmental enrichment on neurodevelopment, numerous studies have shown that it significantly improves performance on an array of spatial and nonspatial memory tasks in rats (Leggio et al., 2005; Nilsson et al., 1999) and mice (Kempermann, Kuhn, & Gage, 1997; Williams et al., 2001).

Evidence for the impact of environmental enrichment in humans is far more limited and centers largely on the concept of ‘cognitive reserve’ as related to the emergence of Alzheimer’s disease. Epidemiologic data provide a compelling link between increased participation in intellectual and social activities in daily life and a slower cognitive decline in the elderly (Scarmeas & Stern, 2004). Furthermore, cognitive exercises show promise as effective interventions for slowing the trajectory of cognitive and functional decline that is associated with dementia (Gates & Valenzuela, 2010).

In addition to environmental enhancements, physical exercise, most commonly in the form of wheel running in rodents, has also been shown to enhance neural growth and development, as well as associated behavioral and cognitive functions. Physical exercise increases levels of synaptic proteins (Vaynman, Ying, Yin, & Gomez-Pinilla, 2006), glutamate receptors (Farmer et al., 2004) and the availability of brain-derived neurotrophic factor (BDNF) (Berchtold, Chinn, Chou, Kesslak, & Cotman, 2005) and insulin-like growth factor-1 (Trejo, Carro, & Torres-Aleman, 2001), all of which can enhance neural plasticity. Specifically, treadmill exercises in rats increase cell proliferation via insulin-like growth factor-1 (Trejo et al., 2001) and cell proliferation and survival in the dentate gyrus (van Praag, Kempermann, & Gage, 1999b). These neural changes in response to physical exercise are accompanied by behavioral changes such that physical exercise enhances spatial learning (Fordyce & Farrar, 1991; Fordyce & Wehner, 1993) and passive avoidance memory (Samorajski et al., 1985).

Physical exercise has also been reported to increase BDNF levels (Ferris, Williams, & Shen, 2007; Gold et al., 2003; Rasmussen et al., 2009; Seifert et al., 2010; Strohle et al., 2010; Tang, Chu, Hui, Helmeste, & Law, 2008; Zoladz et al., 2008), enhance cognitive performance (Baker et al., 2010; Ferris et al., 2007; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001), and to promote brain health (Colcombe et al., 2003) in human adults. One study that examined BDNF levels in children with ADHD reported that as compared to controls, those with ADHD had increased levels of BDNF, and that BDNF levels correlated with neuropsychological performance as indicated by number of errors on a continuous performance test (Shim et al., 2008). However, BDNF change in response to exercise was not assessed.

Exercise and environmental enhancements also have been shown to have a positive effect on outcome in several animal models of neurodevelopmental disorders. Wheel running from an early age delays the onset of motor deficits in knock-out mouse models of Huntington’s

disease (van Dellen, Cordery, Spires, Blakemore, & Hannan, 2008), and complex motor training in rats enhances synaptogenesis in the motor cortex and motor coordination following lesions of the sensorimotor cortex (Jones, Chu, Grande, & Gregory, 1999). Perhaps more relevant to the current thesis, chronic exercise blunted the developmental rise of blood pressure while increasing glutamic acid decarboxylase mRNA in the caudal hypothalamus in spontaneously hypertensive rats, which are commonly used as an animal model for ADHD (Little, Kramer, Beatty, & Waldrop, 2001). Finally, rat pups born from alcohol-intoxicated mothers have been shown to have diminished c-Fos activity in the hippocampus along with an array of neurobehavioral deficits. Postnatal treadmill exercise not only enhances c-Fos activity in the hippocampus (Sim et al., 2008), but exercise and various forms of environmental enrichment reduce the severity of behavioral deficits associated with maternal alcohol intoxication (Hannigan, O'Leary-Moore, & Berman, 2007). Thus, at least in animals, interventions involving environmental enrichment and physical exercise can yield lasting positive effects on behavioral anomalies due to both genetic and environmental etiologies.

Most rodent studies focusing on environmental enrichments employ a combination of social (e.g., multiple animals in a cage), cognitive (e.g., toys, tunnels) and motor (e.g., running wheels) stimuli. As such, it is difficult to determine the extent to which any one of these contributes to the positive outcome. Data suggest that both exercise and environmental enhancement contribute to positive neurodevelopmental outcomes, although not necessarily in an identical manner. Some evidence suggests that exercise affects the brain similarly to environmental enrichment, with changes including enhanced hippocampal LTP (Kim et al., 2004) and neurogenesis (van Praag, Christie, Sejnowski, & Gage, 1999a; van Praag et al., 1999b), as well as increased hippocampal and neocortical neurotrophin mRNA expression (Neeper, Gomez-Pinilla, Choi, & Cotman, 1995; Neeper, Gomez-Pinilla, Choi, & Cotman, 1996). Other studies suggest that individual elements may have different effects on neural plasticity and development. Manipulations involving problem solving and coordination increase synapse formation in the cerebellar cortex (Kleim, Vij, Ballard, & Greenough, 1997; Kleim et al., 1998), whereas repetitive physical exercise increases cerebellar blood vessel density (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990). Exercise has also been found to improve spatial memory and preserve cognitive function in aging rats (Anderson et al., 2000; Fordyce et al., 1991) and mice (Anderson et al., 2000; Fordyce et al., 1993; van Praag et al., 1999a). Nevertheless, some data (Faherty et al., 2003) suggest that environmental enhancements are more effective for facilitating neural changes than exercise alone, while others (Lambert, Fernandez, & Frick, 2005) suggest that exercise, but not cognitive stimulation improves spatial memory.

Thus, preclinical data indicate that environmental enhancement and exercise have positive morphological, chemical and cognitive effects on the brain across the lifespan. Much of the human literature, with moderate success, has focused on the latter end of the developmental spectrum, with the aim of addressing cognitive declines characteristic of the elderly. These data suggest that cognitive and social stimulation, as well as physical exercise, may delay the onset of dementia and other neurodegenerative diseases (Scarmeas & Stern, 2004; Ravaglia et al., 2008; Kramer & Erickson, 2007; Arkin, 2007; Rolland et al., 2007). Furthermore, in adults, cognitive training increases cortical brain activity (Olesen, Westerberg, & Klingberg, 2004) and alters dopamine D1 receptor binding in both the prefrontal and parietal cortices (McNab et al., 2009).

Although early childhood is the period of greatest neural plasticity, and the most prominent cell proliferation in response to exercise has been shown to occur at younger ages in rats (Kim et al., 2004), far less research has been conducted with children. Two studies have examined exercise regimes in children with ADHD; one reporting a blunted catecholamine

response (Wigal et al., 2003) and the other showing changes in eye blink responses and reductions in motor impersistence that was specific to boys (Tantillo, Kesick, Hynd, & Dishman, 2002). However, neither study examined clinical response nor brain-related changes following exercise. With regard to cognitive enhancement, Rueda et al. (Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005) showed that attention training in preschool children yielded changes in executive functioning and parallel alterations in event related responses (ERPs) reflecting patterns typical of older individuals. Thus, literature in children is sparse, but the extensive body of animal research suggests that environmental enrichment and early brain rehabilitation could play a key role in the treatment, and possibly even the amelioration, of ADHD symptomatology through improving the core neural deficits associated with the disorder.

COGNITIVE TRAINING PARADIGMS IN CHILDREN WITH ADHD

In recent years there has been a growing interest in neurocognitive intervention approaches to treating childhood ADHD with the ultimate aim of developing more lasting treatments for the disorder (Toplak, Connors, Shuster, Knezevic, & Parks, 2008). The majority of these approaches have targeted either attention or working memory (Karatekin, 2006; Kerns, Eso, & Thomson, 1999; Klingberg, Forssberg, & Westerberg, 2002; Klingberg et al., 2005; O'Connell, Bellgrove, Dockree, & Robertson, 2006; Rapport et al., 1996; Shalev, Tsal, & Mevorach, 2007). The basic premise of these approaches is that deficits in the targeted cognitive domain are causally related to ADHD symptoms and that remediation of these deficits will lead to lasting improvements. Collectively these studies have shown that cognitive interventions for children with ADHD improve working memory, inhibition, attention, and nonverbal reasoning ability, and may reduce behavioral symptoms of ADHD as reported by parents and/or teachers (Kerns et al., 1999; Klingberg et al., 2005; Shalev et al., 2007).

Several studies have evaluated the effects of cues to improve attention in children with ADHD (Karatekin, 2006; O'Connell et al., 2006; Rapport et al., 1996). Karatekin (Karatekin, 2006) showed that adolescents with ADHD had deficits in accuracy and reaction time during antisaccade tasks relative to typically developing adolescents, but improved with the implementation of visual and auditory cognitive scaffolds. O'Connell et al. (O'Connell et al., 2006) reported that although alerting cues improved short-term sustained attention in children with ADHD, they did not improve sustained attention throughout the experimental task. Finally, Rapport et al. (Rapport et al., 1996) compared methylphenidate to an attentional training intervention in two girls with ADHD and found that both improved performance on a continuous performance task and on the Matching Unfamiliar Figures Test. However, these cognitive effects were not maintained during withdrawal of these interventions, and neither was the short-term impact of methylphenidate and the attention training system on observed behavior.

Other studies have focused on improving attention in children with ADHD through more intensive, targeted attention-focused training programs. Kerns et al. (Kerns et al., 1999) evaluated the program Pay Attention!, which uses a set of visual and auditory activities designed to train different levels of attention, including sustained, selective, alternating, and divided attention. Results indicated improvements on several neurocognitive and academic achievement measures compared to controls. However, only minimal changes in ADHD behavioral symptoms were reported by teachers, and parents reported no changes. More recently, a computerized progressive attentional training (CPAT) program was evaluated in 20 children with ADHD (Shalev et al., 2007) and showed improved performance on nonstandardized academic tests (i.e., reading comprehension, speed of copying) as well as parent-reported inattentive symptoms at home.

In addition to attention-based interventions, the Cogmed Working Memory Training Program (Cogmed) has demonstrated efficacy for enhancing working memory and reducing behavioral symptoms of ADHD (Klingberg et al., 2002; Klingberg et al., 2005). In two studies involving children with ADHD, Cogmed was compared to an identical computer program that implemented low difficulty working memory tasks unadjusted to meet the working memory levels of the child. In a multisite clinical trial (Klingberg et al., 2005), beneficial effects of Cogmed were reported in school-aged children with ADHD. Significant intervention effects were found on measures of visual (Span board) and verbal (Digit Span from the WISC-III) working memory, nonverbal complex reasoning (Raven's Progressive Matrices), and response inhibition (Stroop task), compared to the low-level working memory computer task. Notably, results from this study also found maintenance of treatment gains on several outcomes at 3-month follow-up. However, treatment effects were found on parent but not teacher ratings of children's ADHD behavior and oppositionality.

The studies discussed above have generally focused on the ecological validity of the intervention, as related to behavioral changes, but few have assessed the important question of neural plasticity or brain changes as a function of cognitive training. To our knowledge only one such study has been conducted with children. Rueda et al. 2005 showed that a brief 5-day attention training intervention with preschool children resulted in changes in executive functioning as well as in changes in event related responses (ERPs) that seemed to parallel normal developmental brain responses. Specifically, trained 4-year-old children generated a pattern of ERPs that were similar to typically-developing 6-year-olds, and trained 6-year-olds' ERP patterns became more adult-like. Similarly, in adults, cognitive training, specifically in the form of the Cogmed working memory system, has been shown to increase brain activity in parietal and frontal regions linked to working memory (Olesen et al. 2004) and, importantly, to alter dopamine D1 receptor binding in both the prefrontal and parietal cortices (McNab et al.2009), suggesting a potential mechanism of action.

Thus, some progress has been made in developing non-pharmacologic interventions to ameliorate underlying cognitive dysfunctions in children with ADHD, and importantly, preliminary data suggest that such interventions have the potential to modify brain function. Notably, however, these approaches focus on specific cognitive domains (i.e., attention and working memory), primarily involve intensive computer-based interventions, and have reported some difficulties with compliance and/or retention (e.g., only 18/27 children completed Klingberg et al's (2005) treatment study). The focus on a specific cognitive domain is problematic because ADHD is a heterogeneous disorder, with most children experiencing impairments in multiple cognitive domains and only a portion have deficits in any single domain (Nigg et al., 2005). Therefore, the narrow focus may limit effectiveness across a wide range of children with the disorder.

Additionally, while the use of computers can provide well-controlled and highly sophisticated interventions with built-in scaffolding of difficulty, generalizability to the real world might be a concern. Most children with ADHD experience considerable difficulties in the social realm; and it is unclear whether improvements on computer tasks will generalize to the outside world in which they must function.

Finally, many of the current training paradigms require intensive effort over extended periods of time on a daily basis. For example, Cogmed requires 40 minutes a day, 5 days per week for 5 consecutive weeks. Reported difficulties in retention rates for such interventions indicate that these approaches may be unpalatable to children and families (Klingberg et al., 2005).

Cognitive Enhancement in the Child's Social Milieu

Although not directly targeting children with ADHD, Diamond et al. (Diamond, Barnett, Thomas, & Munro, 2007) evaluated "Tools of the Mind" (Tools), a comprehensive evidence-based preschool curriculum targeting EF development which is delivered within a social context as opposed to relying on computer administration. This intervention is relevant to ADHD given the noted difficulties that many children with ADHD have with EFs (Doyle, 2006; Willcutt et al., 2005) and the notion that improved EF over development should reduce the severity of ADHD symptoms and impairments (Halperin and Schulz, 2006). Tools is based on Luria's (Luria, 1966) and Vygotsky's (Vygotsky, 1978) work on higher mental functions and operates on the premise that a comprehensive system of activities undertaken within the context of a social environment promotes EF development. In Tools, techniques for supporting, training, and challenging EFs are interwoven within classroom activities. For example, while children are learning language skills or math, they also receive training in executive skill development. Teachers are taught how to implement and support the use of these activities throughout the preschool day. In a sample of preschool children from low-income urban preschools, Tools was compared to the school district's existing literacy program, which focused on similar academic content to that of Tools but did not address EF development (Diamond et al., 2007). Results of this randomized trial demonstrated that preschool children in Tools-based classrooms significantly improved performance on experimental measures of inhibitory control, working memory, and cognitive flexibility. Behavioral changes were not assessed in this study.

Although the Tools program is a preventive intervention that has been used successfully in a high-risk population rather than in children with ADHD per se, it has design aspects that are appealing to cognitive-based interventions for children with ADHD. First, the intervention is focused on the early childhood period - a time when executive and other higher cortical functions are emerging developmentally. This may be preferable to a remediation approach of teaching skills to children well past the point when these skills have typically developed (Tremblay, 2006). Second, key adult figures within the lives of these children (i.e., teachers) implement this intervention within the setting that these children live and learn (i.e., school), intensifying the dose of intervention that a child receives. Moreover, the intervention is seamlessly integrated within the school context and relies on activities that children find to be enjoyable and that teachers can readily support - making the intervention more likely to be sustained.

FUTURE DIRECTIONS FOR NEUROCOGNITIVELY-BASED TREATMENTS OF ADHD

As described above, an important step forward would be to consider more ecologically valid and easily generalizable delivery mechanisms for these types of interventions. Diamond et al.'s (Diamond et al., 2007) work sets the scene for this as their intervention was integrated into the everyday school program. While this is an ideal platform for intervention, it is unlikely to be possible to have all school programs adapted; and even if it were, it would be very difficult for teachers to individualize the program to children's specific needs. Therefore the field would be well-served by trying to design ecologically valid home-based interventions to complement what is available to date.

One way to do this would be to administer the intervention in the form of "play" (ranging from quiet play to that involving physical exercise) within the family. Most studies examining the role of play in development have focused on its role in the development of social skills and interpersonal development. As children move from early "parallel play"

into social interactive play, they learn to "read" others' intentions, take turns, regulate their emotions and behavior, and engage in the give-and-take of interpersonal relations. It is within this social context that many of the higher-order executive functions, that may be uniquely human, are most likely to develop and flourish (Diamond et al., 2007; Luria, 1966; Vygotsky, 1978). Although research is limited, juvenile play has been posited to play a role in facilitating neural development. Similar to the effects physical exercise on brain functioning in humans (Gold et al. 2003; Ferris, Williams & Shen, 2007; Rasmussen et al. 2009; Seifert et al. 2010; Strohle et al. 2010; Tang et al. 2008; Zoladz et al. 2008), Gordon, Burke, Akil, Watson, & Panksepp (2003) reported that play increases BDNF, a key modulator of neuronal development and plasticity, in the amygdala and dorsolateral PFC of juvenile rats. Similarly, juvenile play in rats stimulates c-Fos gene expression in a number of brain areas (Gordon, Kollack-Walker, Akil, & Panksepp, 2002). Finally, "chronic play therapy" reduced right frontal lesion-induced hyperactivity in juvenile rats, and enhanced access to rough-and-tumble play in normal animals improved performance on indices of behavioral inhibition (Panksepp, Burgdorf, Turner, & Gordon, 2003). Based on these and similar findings, Panksepp and colleagues (Panksepp, 2007; Panksepp et al., 2003) have speculated that the impulsive and hyperactive behaviors characteristic of ADHD may reflect overactive playful urges in some children and that enhanced access to play may have therapeutic benefits. However, data supporting or refuting this speculation are sparse.

Thus the creative use of *directed play*, which incorporates cognitive challenges and physical exercise, may have the potential to serve as a vehicle for treatment of children with ADHD. In particular, the intrinsic rewarding qualities of play (i.e., it's fun) makes it an ideal delivery system for treatment of children with ADHD, who are known to be highly responsive to continuously rewarding contingencies; yet highly resistant to more effortful and less rewarding (i.e., less fun) tasks. In addition, physically and cognitively demanding play within a social context can be used to mold and develop social skills and, when structured in the appropriate manner, can potentially enhance cognitive and behavioral development, and neural growth. Importantly, we do not propose that this approach to intervention would necessarily target or remediate the core neural pathology that causes ADHD. Rather, it would facilitate development and growth of a wide array of cortical regions and their associated functions, which in turn, would allow for the implementation of compensatory mechanisms that have the potential to improve functioning in individuals with the disorder.

There are numerous common children's games, activities and exercises that would be easy for families to play together and involve the use of wide ranging brain areas, targeting the diffuse neurocognitive deficits that have been associated with ADHD. For example, the game "S]imon-says" involves inhibitory control, "my grandmother went to the market" involves working memory, and "hopscotch" involves physical exercise and requires motor control. We hypothesize that an intervention that focuses on encouraging parents to play these games in a structured and incremental manner with their children, and encouraging children to play these games with siblings and friends, on a daily basis, if complied with, would have an impact on both neural development and behavioral regulation. As compared to other more effortful and less palatable interventions, compliance may be less of a problem with such an intervention. Also, unlike other neurocognitive training programs that continue for a fixed period of time, at which point training ends, in this case, the goal would be for the wide ranging play activities to continue long after the termination of the active intervention. While in the short-term it is unlikely that such an intervention would generate effect sizes comparable to medications, the goal is to impact the long-term trajectory of the disorder. As such, extended follow-up periods will be required to make comparisons to well-validated treatments (i.e., stimulant medication; behavior modification).

In addition, beyond directed play and exercises with parents, it is possible that engaging children in sports, nature (Kuo & Taylor, 2004), and other group-based cognitively and physically challenging activities may provide an avenue for neural and cognitive growth that would serve to facilitate the diminution of ADHD severity across development. Such activities could be provided in schools (Diamond et al., 2007), after school programs, or in summer camps, although it would be important that the activities continue over an extended period of time.

Although many questions remain regarding the clinical utility these cognitive and exercise-related interventions for children with ADHD, there are several clear directions for future work in this area that, ultimately, will allow us to determine the usefulness of this treatment modality within the context of well-established interventions for children with ADHD.

Acknowledgments

The authors wish to acknowledge the many hours of discussions with Drs. David Marks, Anil Chacko, Anne-Claude Bedard, and Ms. Jocelyn Curchack, Each of these individuals enhanced our thinking regarding the development of enduring treatments for children with ADHD. We also wish to acknowledge the assistance of Professor Neil McNaughton, who read an early draft of this manuscript and provided invaluable feedback. This work was supported in part by grants # R21MH085898 and R01 MH068286 from the National Institute of Mental Health.

Reference List

Abramowitz AJ, O'Leary SG, Rosen LA. Reducing off-task behavior in the classroom: a comparison of encouragement and reprimands. Journal of Abnormal Child Psychology 1987;15:153–163. [PubMed: 3611515]

American Heart Association. American Academy of Pediatrics/American Heart Association clarification of statement on cardiovascular evaluation and monitoring of children and adolescents with heart disease receiving medications for ADHD. 2008 Internet Communication.

American Psychiatric Association.Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders : DSM-IV-TR. Washington, D.C: American Psychiatric Association; 2000.

Anastopoulos AD, Shelton TL, DuPaul GJ, Guevremont DC. Parent training for attention-deficit hyperactivity disorder: its impact on parent functioning. Journal of Abnormal Child Psychology 1993;21:581–596. [PubMed: 8294653]

Anderson BJ, Rapp DN, Baek DH, McCloskey DP, Coburn-Litvak PS, Robinson JK. Exercise influences spatial learning in the radial arm maze. Physiol Behav 2000;70:425–429. [PubMed: 11110995]

Arkin S. Language-enriched exercise plus socialization slows cognitive decline in Alzheimer's disease. Am.J.Alzheimers.Dis.Other Demen 2007;22:62–77. [PubMed: 17534004]

Asato MR, Terwilliger R, Woo J, Luna B. White Matter Development in Adolescence: A DTI Study. Cereb.Cortex. 2010

Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch.Neurol 2010;67:71–79. [PubMed: 20065132]

Bakermans-Kranenburg MJ, van Ijzendoorn MH, Pijlman FT, Mesman J, Juffer F. Experimental evidence for differential susceptibility: dopamine D4 receptor polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. Dev.Psychol 2008;44:293–300. [PubMed: 18194028]

Barkley RA. Behavioral inhibition, sustained attention, and executive function: Constructing a unified theory of ADHD. Psychological Bulletin 1997;121:65–94. [PubMed: 9000892]

Barkovich AJ. Magnetic resonance techniques in the assessment of myelin and myelination. J Inherit.Metab Dis 2005;28:311–343. [PubMed: 15868466]

Barnea-Goraly N, Menon V, Eckert M, Tamm L, Bammer R, Karchemskiy A, et al. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. Cereb Cortex 2005;15:1848–1854. [PubMed: 15758200]

Baumgardner TL, Singer HS, Denckla MB, Rubin MA, Abrams MT, Colli MJ, et al. Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder. Neurology 1996;47:477–482. [PubMed: 8757024]

Beitchman J, Tuckett M, Batth S. Language delay and hyperactivity in preschoolers: evidence for a distinct group of hyperactives. Can J Psychiatry 1987;33:77.

Beitchman JH, Brownlie EB, Inglis A, Wild J, Ferguson B, Schachter D, et al. Seven-year follow-up of speech/language impaired and control children: psychiatric outcome. J Child Psychol Psychiatry 1996;37:961–970. [PubMed: 9119943]

Benes FM. Myelination of cortical-hippocampal relays during late adolescence. Schizophr.Bull 1989;15:585–593. [PubMed: 2623440]

Berchtold NC, Chinn G, Chou M, Kesslak JP, Cotman CW. Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. Neuroscience 2005;133:853–861. [PubMed: 15896913]

Berquin P, Giedd J, Jacobsen L, Hamburger S, Krain A, Rapoport J, et al. Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. Neurology 1998;50:1087–1093. [PubMed: 9566399]

Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proc Natl Acad Sci U S A 1990;87:5568–5572. [PubMed: 1695380]

Blondis T. Motor disorders and attention-deficit/hyperactivity disorder. Pediatr Clin North Am 1999;46:899–913. [PubMed: 10570695]

Bourgeois JP, Goldman-Rakic PS, Rakic P. Synaptogenesis in the prefrontal cortex of rhesus monkeys. Cereb.Cortex 1994;4:78–96. [PubMed: 8180493]

Brody BA, Kinney HC, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. J Neuropathol.Exp Neurol 1987;46:283–301. [PubMed: 3559630]

Bush G, Frazier JA, Rauch SL, Seidman LJ, Whalen PJ, Jenike MA, et al. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting stroop. Biological Psychiatry 1999;45:1542–1552. [PubMed: 10376114]

Cao Q, Zang Y, Zhu C, Cao X, Sun L, Zhou X, et al. Alerting deficits in children with attention deficit/hyperactivity disorder: Event-related fMRI evidence. Brain Res. 2008

Carte E, Nigg J, Hinshaw S. Neuropsychological functioning, motor speed, and language processing in boys with and without ADHD. J Abnormal Child Psychol 1996;24:481–498.

Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB, et al. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 1997;36:374–383. [PubMed: 9055518]

Casey BJ, Tottenham N, Fossella J. Clinical, imaging, lesion, and genetic approaches toward a model of cognitive control. Dev.Psychobiol 2002;40:237–254. [PubMed: 11891636]

Castellanos FX. Neural substrates of attention-deficit hyperactivity disorder. Advances in Neurobiology 2001;85:197–206.

Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Archives of General Psychiatry 1996;53:607–616. [PubMed: 8660127]

Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 2002a;288:1740–1748. [PubMed: 12365958]

Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghaffari M, Kirsch A, et al. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biological Psychiatry 2008;63:332–337. [PubMed: 17888409]

Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat.Rev.Neurosci 2002b;3:617–628. [PubMed: 12154363]

Charles L, Schain R. A four-year follow-up study of the effects of methylphenidate on the behavior and academic achievement of hyperactive children. Journal of Abnormal Child Psychology 1981;9:495–505. [PubMed: 7328229]

Chelune GJ, Ferguson W, Koon R, Disckey TO. Frontal lobe dysinhibition in attention-deficit disorder. Child Psychiatry and Human Development 1986;16:221–234. [PubMed: 3743175]

Chronis AM, Fabiano GA, Gnagy EM, Wymbs BT, Maclean IB, Pelham WE. Comprehensive, sustained behavioral and pharmacological treatment for attention-deficit/hyperactivity disorder: A case study. Behaviour Therapy 2001;8:346–359.

Chronis AM, Fabiano GA, Onyango AN, Pelham WE, Lopez-Williams A, Chacko A, et al. An Evaluation of the summer treatment program for children with attention-deficit/hyperactivity disorder using a treatment withdrawal design. Behaviour Therapy 2004;35:561–585.

Chronis AM, Pelham WE Jr, Gnagy EM, Roberts JE, Aronoff HR. The impact of late-afternoon stimulant dosing for children with ADHD on parent and parent-child domains. J.Clin.Child Adolesc.Psychol 2003;32:118–126. [PubMed: 12573937]

Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E, et al. Aerobic fitness reduces brain tissue loss in aging humans. J.Gerontol.A Biol.Sci.Med.Sci 2003;58:176–180. [PubMed: 12586857]

Conners CK. Forty years of methylphenidate treatment in Attention-Deficit/ Hyperactivity Disorder. J.Atten.Disord 2002;6 Suppl 1:S17–S30. [PubMed: 12685516]

Corkum P, Rimer P, Schachar R. Parental knowledge of attention-deficit hyperactivity disorder and opinions of treatment options: impact on enrollment and adherence to a 12-month treatment trial. Can.J.Psychiatry 1999;44:1043–1048. [PubMed: 10637684]

Cunningham CE, Bremner R, Boyle M. Large group community-based parenting programs for families of preschoolers at risk for disruptive behaviour disorders: utilization, cost effectiveness, and outcome. J.Child Psychol.Psychiatry 1995;36:1141–1159. [PubMed: 8847377]

Diamond A, Barnett WS, Thomas J, Munro S. Preschool program improves cognitive control. Science 2007;318:1387–1388. [PubMed: 18048670]

Diamond MC. Extensive cortical depth measurements and neuron size increases in the cortex of environmentally enriched rats. J Comp Neurol 1967;131:357–364.

Diamond MC, Krech D, Rosenzweig MR. The effects of an enriched environment on the histology of the rat cerebral cortex. J Comp Neurol 1964;123:111–120. [PubMed: 14199261]

Dosenbach NU, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RA, et al. Distinct brain networks for adaptive and stable task control in humans. Proc.Natl.Acad.Sci.U.S.A 2007;104:11073–11078. [PubMed: 17576922]

Douglas, VI. Cognitive control processes in Attention-Deficit/Hyperactivity Disorder. In: Quay, HC.; Hogan, AE., editors. Handbook of disruptive behavior disorders. 1999 ed.. New York, NY: Kluwer Academic / Plenum Publishers; 1999. p. 105-138.

Doyle AE. Executive functions in attention-deficit/hyperactivity disorder. J.Clin.Psychiatry 2006;67 Suppl 8:21–26. [PubMed: 16961426]

Duffy SN, Craddock KJ, Abel T, Nguyen PV. Environmental enrichment modifies the PKA-dependence of hippocampal LTP and improves hippocampus-dependent memory. Learn.Mem 2001;8:26–34. [PubMed: 11160761]

Durston S, Davidson MC, Mulder MJ, Spicer JA, Galvan A, Tottenham N, et al. Neural and behavioral correlates of expectancy violations in attention-deficit hyperactivity disorder. J.Child Psychol.Psychiatry 2007;48:881–889. [PubMed: 17714373]

Durston S, Hulshoff Pol HE, Schnack HG, Buitelaar JK, Steenhuis MP, Minderaa RB, et al. Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. J Am Acad Child Adolesc.Psychiatry 2004;43:332–340. [PubMed: 15076267]

Durston S, Tottenham NT, Thomas KM, Davidson MC, Eigsti IM, Yang Y, et al. Differential patterns of striatal activation in young children with and without ADHD. Biological Psychiatry 2003;53:871–878. [PubMed: 12742674]

Epstein JN, Erkanli A, Conners CK, Klaric J, Costello JE, Angold A. Relations between Continuous Performance Test performance measures and ADHD behaviors. Journal of Abnormal Child Psychology 2003;31:543–554. [PubMed: 14561061]

Erhardt D, Baker BL. The effects of behavioral parent training on families with young hyperactive children. J.Behav.Ther.Exp.Psychiatry 1990;21:121–132. [PubMed: 2273073]

Fabiano GA, Pelham WE, Gnagy EM, Burrows-Maclean L, Coles EL, Chacko A, et al. The single and combined effects of multiple intensities of behavior modification and methylphenidate for children with ADHD in a classroom setting. School Psychology Review 2007;36:195–216.

Faherty CJ, Kerley D, Smeyne RJ. A Golgi-Cox morphological analysis of neuronal changes induced by environmental enrichment. Brain Res Dev Brain Res 2003;141:55–61.

Fair DA, Cohen AL, Power JD, Dosenbach NU, Church JA, Miezin FM, et al. Functional brain networks develop from a "local to distributed" organization. PLoS.Comput.Biol 2009;5:e1000381. [PubMed: 19412534]

Fair DA, Dosenbach NU, Church JA, Cohen AL, Brahmbhatt S, Miezin FM, et al. Development of distinct control networks through segregation and integration. Proc.Natl.Acad.Sci.U.S.A 2007;104:13507–13512. [PubMed: 17679691]

Fan J, McCandliss BD, Sommer T, Raz A, Posner MI. Testing the efficiency and independence of attentional networks. J.Cogn Neurosci 2002;14:340–347. [PubMed: 11970796]

Faraone SV. Genetics of adult attention-deficit/hyperactivity disorder. Psychiatr.Clin.North Am 2004;27:303–321. [PubMed: 15063999]

Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. Neuroscience 2004;124:71–79. [PubMed: 14960340]

Felton RH, Wood FB, Brown IS, Campbell SK, Harter MR. Separate verbal memory and naming deficits in attention deficit disorder and reading disability. Brain and Language 1987;31:171–184. [PubMed: 3580837]

Ferris LT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. Med.Sci.Sports Exerc 2007;39:728–734. [PubMed: 17414812]

Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology 1997;48:589–601. [PubMed: 9065532]

Fordyce DE, Farrar RP. Physical activity effects on hippocampal and parietal cortical cholinergic function and spatial learning in F344 rats. Behav Brain Res 1991;43:115–123. [PubMed: 1867753]

Fordyce DE, Wehner JM. Physical activity enhances spatial learning performance with an associated alteration in hippocampal protein kinase C activity in C57BL/6 and DBA/2 mice. Brain Res 1993;619:111–119. [PubMed: 8374769]

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc.Natl.Acad.Sci.U.S.A 2005;102:9673–9678. [PubMed: 15976020]

Frazier TW, Demaree HA, Youngstrom EA. Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. Neuropsychology 2004;18:543–555. [PubMed: 15291732]

Frick KM, Fernandez SM. Enrichment enhances spatial memory and increases synaptophysin levels in aged female mice. Neurobiol Aging 2003;24:615–626. [PubMed: 12714119]

Garcia-Sanchez C, Estevez-Gonzalez A, Suarez-Romero E, Junque C. Right hemisphere dysfunction in subjects with attention-deficit disorder with and without hyperactivity. J Child Neurol 1997;12:107–115. [PubMed: 9075020]

Gates N, Valenzuela M. Cognitive exercise and its role in cognitive function in older adults. Curr.Psychiatry Rep 2010;12:20–27. [PubMed: 20425306]

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat.Neurosci 1999;2:861–863. [PubMed: 10491603]

Giedd JN, Castellanos FX, Casey BJ, Kozuch P, King AC, Hamburger SD, et al. Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. American Journal of Psychiatry 1994;151:665–669. [PubMed: 8166306]

Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, et al. Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cereb Cortex 1996;6:551–560. [PubMed: 8670681]

Globus A, Rosenzweig MR, Bennett EL, Diamond MC. Effects of differential experience on dendritic spine counts in rat cerebral cortex. J Comp Physiol Psychol 1973;82:175–181. [PubMed: 4571892]

Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proc.Natl.Acad.Sci.U.S.A 2004;101:8174–8179. [PubMed: 15148381]

Gold SM, Schulz KH, Hartmann S, Mladek M, Lang UE, Hellweg R, et al. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. J.Neuroimmunol 2003;138:99–105. [PubMed: 12742659]

Goldman PS. Functional development of the prefrontal cortex in early life and the problem of neuronal plasticity. Exp.Neurol 1971;32:366–387. [PubMed: 4999861]

Goldman PS, Galkin TW. Prenatal removal of frontal association cortex in the fetal rhesus monkey: anatomical and functional consequences in postnatal life. Brain Res 1978;152:451–485. [PubMed: 99206]

Gordon NS, Burke S, Akil H, Watson SJ, Panksepp J. Socially-induced brain 'fertilization': play promotes brain derived neurotrophic factor transcription in the amygdala and dorsolateral frontal cortex in juvenile rats. Neurosci.Lett 2003;341:17–20. [PubMed: 12676333]

Gordon NS, Kollack-Walker S, Akil H, Panksepp J. Expression of c-fos gene activation during rough and tumble play in juvenile rats. Brain Res.Bull 2002;57:651–659. [PubMed: 11927369]

Green EJ, Greenough WT. Altered synaptic transmission in dentate gyrus of rats reared in complex environments: evidence from hippocampal slices maintained in vitro. J Neurophysiol 1986;55:739–750. [PubMed: 3009728]

Green EJ, Greenough WT, Schlumpf BE. Effects of complex or isolated environments on cortical dendrites of middle-aged rats. Brain Res 1983;264:233–240. [PubMed: 6850295]

Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. Journal of the American Academy of Child and Adolescent Psychiatry 1999;38:503–512. [PubMed: 10230181]

Greenough WT, Volkmar FR. Pattern of dendritic branching in occipital cortex of rats reared in complex environments. Exp Neurol 1973a;40:491–504. [PubMed: 4730268]

Greenough WT, Volkmar FR, Juraska JM. Effects of rearing complexity on dendritic branching in frontolateral and temporal cortex of the rat. Exp Neurol 1973b;41:371–378. [PubMed: 4126876]

Greenough WT, West RW, DeVoogd TJ. Subsynaptic plate perforations: changes with age and experience in the rat. Science 1978;202:1096–1098. [PubMed: 715459]

Hall S, Halperin JM, Schwartz S, Newcorn J. Behavioral and executive functions in children with attention-deficit hyperactivity disorder and reading disability. Journal of Attention Disorders 1997;1:235–247.

Halperin, JM.; Marks, DJ.; Schulz, KP. Neuropsychological Perspectives of ADHD. In: Morgan, JE.; Ricker, JH., editors. Handbook of Clinical Neuropsychology. Swets and Zeitlinger; 2008. p. 333-345.

Halperin JM, Newcorn JH, Matier K, Sharma V, McKay KE, Schwartz S. Discriminant validity of attention-deficit hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 1993;32:1038–1043. [PubMed: 8407749]

Halperin JM, Schulz KP. Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. Psychol Bull 2006;132:560–581. [PubMed: 16822167]

Halperin JM, Trampush JT, Miller CJ, Marks DJ, Newcorn JH. Neuropsychological Outcome in Adolescents/Young Adults with Childhood ADHD: Profiles of Persisters, Remitters and Controls. Journal of Child Psychology and Psychiatry 2008;49:958–966. [PubMed: 18573145]

Hannigan JH, O'Leary-Moore SK, Berman RF. Postnatal environmental or experiential amelioration of neurobehavioral effects of perinatal alcohol exposure in rats 6. Neurosci Biobehav Rev 2007;31:202–211. [PubMed: 16911827]

Hebb, DO. New York: Wiley; 1949. The organization of behavior: a neuropsychological theory; p. 335

Hill DE, Yeo RA, Campbell RA, Hart B, Vigil J, Brooks W. Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. Neuropsychology 2003;17:496–506. [PubMed: 12959515]

Hoffman JB, DuPaul GJ. Psychoeducational interventions for children and adolescents with attention-deficit/hyperactivity disorder. Child Adolesc.Psychiatr.Clin.N.Am 2000;9:647–661. ix. [PubMed: 10944660]

Hoza B, Gerdes AC, Mrug S, Hinshaw SP, Bukowski WM, Gold JA, et al. Peer-assessed outcomes in the multimodal treatment study of children with attention deficit hyperactivity disorder. J.Clin.Child Adolesc.Psychol 2005;34:74–86. [PubMed: 15677282]

Huang-Pollock CL, Nigg JT. Searching for the attention deficit in attention deficit hyperactivity disorder: the case of visuospatial orienting. Clin.Psychol.Rev 2003;23:801–830. [PubMed: 14529699]

Hubel DH, Wiesel TN. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. J Physiol 1970;206:419–436. [PubMed: 5498493]

Humphries T, Koltun H, Malone M, Roberts W. Teacher-identified oral language difficulties among boys with attention problems. J Dev Behav Pediatr 1994;1994:2–92.

Huttenlocher PR. Morphometric study of human cerebral cortex development. Neuropsychologia 1990;28:517–527. [PubMed: 2203993]

Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J.Comp Neurol 1997;387:167–178. [PubMed: 9336221]

Huttenlocher PR, de Court. The development of synapses in striate cortex of man. Hum.Neurobiol 1987;6:1–9. [PubMed: 3583840]

Hynd GW, Hern KL, Novey ES, Eliopulos D, Marshall R, Gonzalez JJ, et al. Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. Journal of Child Neurology 1993;8:339–347. [PubMed: 8228029]

Hynd GW, Semrud-Clikeman M, Lorys AR, Novey ES, Eliopulos D. Brain morphology in developmental dyslexia and atention deficit disorder/hyperactivity. Archives of Neurology 1990;47:919–926. [PubMed: 2375699]

Hynd GW, Semrud-Clikeman M, Lorys AR, Novey ES, Eliopulos D, Lyytinen H. Corpus callosum morphology in attention deficit-hyperactivity disorder: morphometric analysis of MRI. J Learn.Disabil 1991;24:141–146. [PubMed: 2026955]

Ickes BR, Pham TM, Sanders LA, Albeck DS, Mohammed AH, Granholm AC. Long-term environmental enrichment leads to regional increases in neurotrophin levels in rat brain. Exp Neurol 2000;164:45–52. [PubMed: 10877914]

Jensen PS, Arnold LE, Swanson JM, Vitiello B, Abikoff HB, Greenhill LL, et al. 3-year follow-up of the NIMH MTA study. J Am Acad Child Adolesc Psychiatry 2007;46:989–1002. [PubMed: 17667478]

Johnson KA, Robertson IH, Barry E, Mulligan A, Daibhis A, Daly M, et al. Impaired conflict resolution and alerting in children with ADHD: evidence from the Attention Network Task (ANT). J.Child Psychol.Psychiatry 2008;49:1339–1347. [PubMed: 19120713]

Jones TA, Chu CJ, Grande LA, Gregory AD. Motor skills training enhances lesion-induced structural plasticity in the motor cortex of adult rats. J Neurosci 1999;19:10153–10163. [PubMed: 10559423]

Kadesjo C, Kadesjo B, Hagglof B, Gillberg C. ADHD in Swedish 3- to 7-year-old children. Journal of the American Academy of Child and Adolescent Psychiatry 2001;40:1021–1028. [PubMed: 11556625]

Karatekin C. Improving antisaccade performance in adolescents with attention-deficit/hyperactivity disorder (ADHD). Exp.Brain Res 2006;174:324–341. [PubMed: 16639499]

Kates WR, Frederikse M, Mostofsky SH, Folley BS, Cooper K, Mazur-Hopkins P, et al. MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. Psychiatry Research 2002;116:63–81. [PubMed: 12426035]

Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. Nature 1997;386:493–495. [PubMed: 9087407]

Kempermann G, Kuhn HG, Gage FH. Experience-induced neurogenesis in the senescent dentate gyrus. J Neurosci 1998;18:3206–3212. [PubMed: 9547229]

Kerns K, Eso K, Thomson J. Investigation of a direct intervention for improving attention in young children with ADHD. Developemental Neuropsychology 1999;16:273–295.

Keshavan MS, Anderson S, Pettegrew JW. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. J.Psychiatr.Res 1994;28:239–265. [PubMed: 7932285]

Kim YP, Kim H, Shin MS, Chang HK, Jang MH, Shin MC, et al. Age-dependence of the effect of treadmill exercise on cell proliferation in the dentate gyrus of rats. Neurosci Lett 2004;355:152–154. [PubMed: 14729257]

Kinney HC, Brody BA, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants. J Neuropathol.Exp Neurol 1988;47:217–234. [PubMed: 3367155]

Kleim JA, Swain RA, Armstrong KA, Napper RM, Jones TA, Greenough WT. Selective synaptic plasticity within the cerebellar cortex following complex motor skill learning. Neurobiol Learn Mem 1998;69:274–289. [PubMed: 9707490]

Kleim JA, Vij K, Ballard DH, Greenough WT. Learning-dependent synaptic modifications in the cerebellar cortex of the adult rat persist for at least four weeks. J Neurosci 1997;17:717–721. [PubMed: 8987793]

Klingberg T, Fernell E, Olesen PJ, Johnson M, Gustafsson P, Dahlstrom K, et al. Computerized training of working memory in children with ADHD--a randomized, controlled trial. Journal of the American Academy of Child and Adolescent Psychiatry 2005;44:177–186. [PubMed: 15689731]

Klingberg T, Forssberg H, Westerberg H. Training of working memory in children with ADHD. J.Clin.Exp.Neuropsychol 2002;24:781–791. [PubMed: 12424652]

Konrad K, Eickhoff SB. Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. Hum.Brain Mapp 2010;31:904–916. [PubMed: 20496381]

Kramer AF, Erickson KI. Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. Trends Cogn Sci 2007;11:342–348. [PubMed: 17629545]

Kretschmann HJ, Kammradt G, Krauthausen I, Sauer B, Wingert F. Brain growth in man. Bibl.Anat 1986:1–26. [PubMed: 3707509]

Kuntsi J, Oosterlaan J, Stevenson J. Psychological mechanisms in hyperactivity: I. Response inhibition deficit, working memory impairment, delay aversion, or something else? J.Child Psychol.Psychiatry 2001;42:199–210. [PubMed: 11280416]

Kuntsi J, Rijsdijk F, Ronald A, Asherson P, Plomin R. Genetic influences on the stability of attention-deficit/hyperactivity disorder symptoms from early to middle childhood. Biological Psychiatry 2005;57:647–654. [PubMed: 15780852]

Kuo FE, Taylor AF. A potential natural treatment for attention-deficit/hyperactivity disorder: evidence from a national study. Am.J.Public Health 2004;94:1580–1586. [PubMed: 15333318]

Lambert TJ, Fernandez SM, Frick KM. Different types of environmental enrichment have discrepant effects on spatial memory and synaptophysin levels in female mice. Neurobiol Learn Mem 2005;83:206–216. [PubMed: 15820856]

Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch.Neurol 2001;58:498–504. [PubMed: 11255456]

Leggio MG, Mandolesi L, Federico F, Spirito F, Ricci B, Gelfo F, et al. Environmental enrichment promotes improved spatial abilities and enhanced dendritic growth in the rat. Behav Brain Res 2005;163:78–90. [PubMed: 15913801]

Little HR, Kramer JM, Beatty JA, Waldrop TG. Chronic exercise increases GAD gene expression in the caudal hypothalamus of spontaneously hypertensive rats. Brain Res Mol Brain Res 2001;95:48–54. [PubMed: 11687276]

Loe IM, Feldman HM. Academic and educational outcomes of children with ADHD. J.Pediatr.Psychol 2007;32:643–654. [PubMed: 17569716]

Losier BJ, McGrath PJ, Klein RM. Error patterns on the continuous performance test in non-medicated and medicated samples of children with and without ADHD: a meta-analytic review. J.Child Psychol.Psychiatry 1996;37:971–987. [PubMed: 9119944]

Luria, A. The Higher Cortical Functions in Man. New York: 1966.

Lyoo IK, Noam GG, Lee CK, Lee HK, Kennedy BP, Renshaw PF. The corpus callosum and lateral ventricles in children with attention-deficit hyperactivity disorder: a brain magnetic resonance imaging study. Biological Psychiatry 1996;40:1060–1063. [PubMed: 8915567]

Mahone EM, Wodka EL. The neurobiological profile of girls with ADHD. Dev.Disabil.Res.Rev 2008;14:276–284. [PubMed: 19072756]

Makris N, Biederman J, Valera EM, Bush G, Kaiser J, Kennedy DN, et al. Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. Cereb.Cortex 2007;17:1364–1375. [PubMed: 16920883]

Mangeot S, Miller L, McIntosh D, McGrath-Clarke J, Simon J, Hagerman R, et al. Sensory modulation dysfunction in children with attention-deficit-hyperactivity disorder. Dev Med Child Neurol 2001;43:399–406. [PubMed: 11409829]

Martinussen R, Hayden J, Hogg-Johnson S, Tannock R. A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 2005;44:377–384. [PubMed: 15782085]

McAlonan GM, Cheung V, Chua SE, Oosterlaan J, Hung SF, Tang CP, et al. Age-related grey matter volume correlates of response inhibition and shifting in attention-deficit hyperactivity disorder. Br.J.Psychiatry 2009;194:123–129. [PubMed: 19182173]

McKay KE, Halperin JM, Schwartz ST, Sharma V. Developmental analysis of three aspects of information processing: Sustained attention, selective attention, and response organization. Developmental Neuropsychology 1994;10:121–132.

McNab F, Varrone A, Farde L, Jucaite A, Bystritsky P, Forssberg H, et al. Changes in cortical dopamine D1 receptor binding associated with cognitive training. Science 2009;323:800–802. [PubMed: 19197069]

Molina BS, Flory K, Hinshaw SP, Greiner AR, Arnold LE, Swanson JM, et al. Delinquent behavior and emerging substance use in the MTA at 36 months: prevalence, course, and treatment effects. Journal of the American Academy of Child and Adolescent Psychiatry 2007;46:1028–1040. [PubMed: 17667481]

Molina BS, Hinshaw SP, Swanson JM, Arnold LE, Vitiello B, Jensen PS, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. Journal of the American Academy of Child and Adolescent Psychiatry 2009;48:484–500. [PubMed: 19318991]

Mostofsky SH, Cooper KL, Kates WR, Denckla MB, Kaufmann WE. Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. Biological Psychiatry 2002;52:785–794. [PubMed: 12372650]

Mrzljak L, Uylings HB, van Eden CG, Judas M. Neuronal development in human prefrontal cortex in prenatal and postnatal stages. Prog Brain Res 1990;85:185–222. [PubMed: 2094894]

MTA Cooperative Group. 14-Month randomized clinical trial of treatment strategies for attention deficit hyperactivity disorder. Archives of General Psychiatry 1999;56:1073–1086. [PubMed: 10591283]

MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. Pediatrics 2004;113:754–761. [PubMed: 15060224]

Neeper SA, Gomez-Pinilla F, Choi J, Cotman C. Exercise and brain neurotrophins. Nature 1995;373:109. [PubMed: 7816089]

Neeper SA, Gomez-Pinilla F, Choi J, Cotman CW. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. Brain Res 1996;726:49–56. [PubMed: 8836544]

Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke EJ. Causal heterogeneity in Attention-Deficit/Hyperactivity Disorder: Do we need neuropsychologically impaired subtypes? Biological Psychiatry 2005;57:1224–1230. [PubMed: 15949992]

Nilsson M, Perfilieva E, Johansson U, Orwar O, Eriksson PS. Enriched environment increases neurogenesis in the adult rat dentate gyrus and improves spatial memory. J Neurobiol 1999;39:569–578. [PubMed: 10380078]

Nithianantharajah J, Levis H, Murphy M. Environmental enrichment results in cortical and subcortical changes in levels of synaptophysin and PSD-95 proteins. Neurobiol Learn Mem 2004;81:200–210. [PubMed: 15082021]

O'Connell RG, Bellgrove MA, Dockree PM, Robertson IH. Cognitive remediation in ADHD: effects of periodic non-contingent alerts on sustained attention to response. Neuropsychol.Rehabil 2006;16:653–665. [PubMed: 17127571]

Olesen PJ, Westerberg H, Klingberg T. Increased prefrontal and parietal activity after training of working memory. Nat.Neurosci 2004;7:75–79. [PubMed: 14699419]

Panksepp J. Can PLAY Diminish ADHD and Facilitate the Construction of the Social Brain? J.Can.Acad.Child Adolesc.Psychiatry 2007;16:57–66. [PubMed: 18392153]

Panksepp J, Burgdorf J, Turner C, Gordon N. Modeling ADHD-type arousal with unilateral frontal cortex damage in rats and beneficial effects of play therapy. Brain Cogn 2003;52:97–105. [PubMed: 12812809]

Passler MA, Isaac W, Hynd GW. Neuropsychological development of behavior attributed to frontal lobe functioning in children. Developmental Neuropsychology 1985;1:349–370.

Pastor PN, Reuben CA. Diagnosed attention deficit hyperactivity disorder and learning disability: United States, 2004–2006. Vital Health Stat 2008;10:1–14.

Paternite CE, Loney J, Salisbury H, Whaley MA. Childhood inattention-overactivity, aggression, and stimulant medication history as predictors of young adult outcomes. J.Child Adolesc.Psychopharmacol 1999;9:169–184. [PubMed: 10521010]

Pelham WE Jr, Fabiano GA. Evidence-based psychosocial treatments for attention-deficit/hyperactivity disorder. J.Clin.Child Adolesc.Psychol 2008;37:184–214. [PubMed: 18444058]

Pelham WE Jr, Wheeler T, Chronis A. Empirically supported psychosocial treatments for attention deficit hyperactivity disorder. J.Clin.Child Psychol 1998;27:190–205. [PubMed: 9648036]

Pennington BF, Groisser D, Welsh MC. Contrasting cognitive deficits in attention deficit hyperactivity disorder versus reading disability. Developmental Psychology 1993;29:511–523.

Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. J.Child Psychol.Psychiatry 1996;37:51–87. [PubMed: 8655658]

Perwien A, Hall J, Swensen A, Swindle R. Stimulant treatment patterns and compliance in children and adults with newly treated attention-deficit/hyperactivity disorder. J.Manag.Care Pharm 2004;10:122–129. [PubMed: 15032561]

Peterson BS, Potenza MN, Wang Z, Zhu H, Martin A, Marsh R, et al. An FMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. American Journal of Psychiatry 2009;166:1286–1294. [PubMed: 19755575]

Pham TM, Soderstrom S, Winblad B, Mohammed AH. Effects of environmental enrichment on cognitive function and hippocampal NGF in the non-handled rats. Behav Brain Res 1999;103:63–70. [PubMed: 10475165]

Pham TM, Winblad B, Granholm AC, Mohammed AH. Environmental influences on brain neurotrophins in rats. Pharmacol Biochem.Behav 2002;73:167–175. [PubMed: 12076736]

Pisecco S, Huzinec C, Curtis D. The effect of child characteristics on teachers' acceptability of classroom-based behavioral strategies and psychostimulant medication for the treatment of ADHD. J.Clin.Child Psychol 2001;30:413–421. [PubMed: 11501257]

Pisterman S, Firestone P, McGrath P, Goodman JT, Webster I, Mallory R, et al. The role of parent training in treatment of preschoolers with ADDH. Am.J.Orthopsychiatry 1992;62:397–408. [PubMed: 1497105]

Pisterman S, McGrath P, Firestone P, Goodman JT, Webster I, Mallory R. Outcome of parent-mediated treatment of preschoolers with attention deficit disorder with hyperactivity. J.Consult Clin.Psychol 1989;57:628–635. [PubMed: 2794183]

Posner MI, Petersen SE. The attention system of the human brain. Annual Review of Neuroscience 1990;13:25–42.

Posner MI, Sheese BE, Odludas Y, Tang Y. Analyzing and shaping human attentional networks. Neural Netw 2006;19:1422–1429. [PubMed: 17059879]

Power TJ, Hess LE, Bennett DS. The acceptability of interventions for attention-deficit hyperactivity disorder among elementary and middle school teachers. J.Dev.Behav.Pediatr 1995;16:238–243. [PubMed: 7593658]

Purvis KL, Tannock R. Language abilities in children with attention deficit hyperactivity disorders, reading disabilities, and normal controls. Journal of Abnormal Child Psychology 1997;25:133–144. [PubMed: 9109030]

Raggio D. Visuomotor perception in children with attention deficit hyperactivity disorder-combined type. Percept Mot Skills 1999;88:448–450. [PubMed: 10483637]

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc.Natl.Acad.Sci.U.S.A 2001;98:676–682. [PubMed: 11209064]

Rampon C, Tang YP, Goodhouse J, Shimizu E, Kyin M, Tsien JZ. Enrichment induces structural changes and recovery from nonspatial memory deficits in CA1 NMDAR1-knockout mice. Nat Neurosci 2000;3:238–244. [PubMed: 10700255]

Rapport MD, Loo S, Isaacs P, Goya S, Denney C, Scanlan S. Methylphenidate and attentional training. Comparative effects on behavior and neurocognitive performance in twin girls with attention-deficit/hyperactivity disorder. Behav.Modif 1996;20:428–430. [PubMed: 8875814]

Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Exp.Physiol 2009;94:1062–1069. [PubMed: 19666694]

Ravaglia G, Forti P, Lucicesare A, Pisacane N, Rietti E, Bianchin M, et al. Physical activity and dementia risk in the elderly: findings from a prospective Italian study. Neurology 2008;70:1786–1794. [PubMed: 18094335]

Reader MJ, Harris EL, Schuerholz LJ, Denckla MB. Attention deficit hyperactivity disorder and executive dysfunction. Developmental Neuropsychology 1994;10:493–512.

Rolland Y, Pillard F, Klapouszczak A, Reynish E, Thomas D, Andrieu S, et al. Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. J.Am.Geriatr.Soc 2007;55:158–165. [PubMed: 17302650]

Rommelse NN, Altink ME, De Sonneville LM, Buschgens CJ, Buitelaar J, Oosterlaan J, et al. Are motor inhibition and cognitive flexibility dead ends in ADHD? Journal of Abnormal Child Psychology 2007;35:957–967. [PubMed: 17503173]

Rosenzweig MR. Environmental complexity, cerebral change, and behavior. Am Psychol 1966;21:321–332. [PubMed: 5910063]

Rosenzweig MR, Bennett EL. Effects of differential environments on brain weights and enzyme activities in gerbils, rats, and mice. Dev Psychobiol 1969;2:87–95. [PubMed: 5407659]

Rosenzweig MR, Bennett EL. Psychobiology of plasticity: effects of training and experience on brain and behavior. Behav Brain Res 1996;78:57–65. [PubMed: 8793038]

Rosenzweig MR, Krech D, Bennett EL, Diamond MC. Effects of environmental complexity and training on brain chemistry and anatomy: a replication and extension. J Comp Physiol Psychol 1962;55:429–437. [PubMed: 14494091]

Rosenzweig MR, Love W, Bennet E. Effects of a few hours a day of enriched experience on brain chemistry and brain weights. Physiol Behav 1968;3:819–825.

Rubia K, Cubillo A, Smith AB, Woolley J, Heyman I, Brammer MJ. Disorder-specific dysfunction in right inferior prefrontal cortex during two inhibition tasks in boys with attention-deficit hyperactivity disorder compared to boys with obsessive-compulsive disorder. Hum.Brain Mapp 2010;31:287–299. [PubMed: 19777552]

Rubia K, Halari R, Cubillo A, Mohammad AM, Brammer M, Taylor E. Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in

medication-naive children with ADHD during a rewarded continuous performance task. Neuropharmacology 2009;57:640–652. [PubMed: 19715709]

Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SCR, Simmons A, et al. Hypofrontality in attention-deficit/hyperactivity disorder during higher-order motor control: a study with functional MRI. American Journal of Psychiatry 1999;156:891–896. [PubMed: 10360128]

Rueda MR, Rothbart MK, McCandliss BD, Saccomanno L, Posner MI. Training, maturation, and genetic influences on the development of executive attention. Proc.Natl.Acad.Sci.U.S.A 2005;102:14931–14936. [PubMed: 16192352]

Russell VA, Oades RD, Tannock R, Killeen PR, Auerbach JG, Johansen EB, et al. Response variability in Attention-Deficit/Hyperactivity Disorder: a neuronal and glial energetics hypothesis. Behav.Brain Funct 2006;2:30. [PubMed: 16925830]

Sagvolden T, Johansen EB, Aase H, Russell VA. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. Behav.Brain Sci 2005;28:397–419. [PubMed: 16209748]

Samorajski T, Delaney C, Durham L, Ordy JM, Johnson JA, Dunlap WP. Effect of exercise on longevity, body weight, locomotor performance, and passive-avoidance memory of C57BL/6J mice. Neurobiol Aging 1985;6:17–24. [PubMed: 4000382]

Sanchez RJ, Crismon ML, Barner JC, Bettinger T, Wilson JP. Assessment of adherence measures with different stimulants among children and adolescents. Pharmacotherapy 2005;25:909–917. [PubMed: 16006269]

Satterfield JH, Hoppe CM, Schell AM. A prospective study of delinquency in 110 adolescent boys with attention deficit disorder and 88 normal adolescent boys. Am J Psychiatry 1982;139:795–798. [PubMed: 7081495]

Scarmeas N, Stern Y. Cognitive reserve: implications for diagnosis and prevention of Alzheimer's disease. Curr.Neurol.Neurosci.Rep 2004;4:374–380. [PubMed: 15324603]

Schilbach L, Eickhoff SB, Rotarska-Jagiela A, Fink GR, Vogeley K. Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. Conscious.Cogn 2008;17:457–467. [PubMed: 18434197]

Schulz KP, Fan J, Tang CY, Newcorn JH, Buchsbaum MS, Cheung AM, et al. Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: an event-related FMRI study. Am J Psychiatry 2004;161:1650–1657. [PubMed: 15337656]

Schulz KP, Newcorn JH, Fan J, Tang CY, Halperin JM. Brain activation gradients in ventrolateral prefrontal cortex related to persistence of ADHD in adolescence. Journal of the American Academy of Child and Adolescent Psychiatry 2005a;44:47–54. [PubMed: 15608543]

Schulz KP, Tang CY, Fan J, Marks DJ, Cheung AM, Newcorn JH, et al. Differential prefrontal cortex activation during inhibitory control in adolescents with and without childhood ADHD. Neuropsychology 2005b;19:390–402. [PubMed: 15910125]

Seidman LJ, Biederman J, Faraone SV, Milberger S, Norman D, Seiverd K, et al. Effects of family history and comorbidity on the neuropsychological performance of children with ADHD: preliminary findings. Journal of the American Academy of Child and Adolescent Psychiatry 1995;34:1015–1024. [PubMed: 7665440]

Seidman LJ, Valera EM, Makris N. Structural brain imaging of attention-deficit/hyperactivity disorder. Biological Psychiatry 2005;57:1263–1272. [PubMed: 15949998]

Seifert T, Brassard P, Wissenberg M, Rasmussen P, Nordby P, Stallknecht B, et al. Endurance training enhances BDNF release from the human brain. Am.J.Physiol Regul.Integr.Comp Physiol 2010;298:R372–R377. [PubMed: 19923361]

Semrud-Clikeman M, Filipek PA, Biederman J, Steingard R, Kennedy D, Renshaw P, et al. Attention-deficit hyperactivity disorder: Magnetic resonance imaging morphometric analysis of the corpus callosum. Journal of the American Academy of Child and Adolescent Psychiatry 1994;33:875–881. [PubMed: 8083145]

Sergeant, JA.; Oosterlaan, J.; van der Meere, J. Information processing and energetic factors in Attention-Deficit/Hyperactivity Disorder. In: Quay, HC.; Hogan, AE., editors. Handbook of disruptive behavior disorders. New York, NY: Kluwer Academic / Plenum Publishers; 1999. p. 75-104.

Shalev L, Tsal Y, Mevorach C. Computerized progressive attentional training (CPAT) program: effective direct intervention for children with ADHD. Child Neuropsychol 2007;13:382–388. [PubMed: 17564853]

Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc.Natl.Acad.Sci.U.S.A 2007a;104:19649–19654. [PubMed: 18024590]

Shaw P, Gogtay N, Rapoport J. Childhood psychiatric disorders as anomalies in neurodevelopmental trajectories. Hum.Brain Mapp 2010;31:917–925. [PubMed: 20496382]

Shaw P, Gornick M, Lerch J, Addington A, Seal J, Greenstein D, et al. Polymorphisms of the dopamine D4 receptor, clinical outcome, and cortical structure in attention-deficit/hyperactivity disorder. Archives of General Psychiatry 2007b;64:921–931. [PubMed: 17679637]

Shaw P, Lerch J, Greenstein D, Sharp W, Clasen L, Evans A, et al. Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. Archives of General Psychiatry 2006;63:540–549. [PubMed: 16651511]

Sheese BE, Voelker PM, Rothbart MK, Posner MI. Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. Dev.Psychopathol 2007;19:1039–1046. [PubMed: 17931433]

Sheppard D, Bradshaw J, Georgiou N, Bradshaw J, Lee P. Movement sequencing in children with Tourette's syndrome and attention deficit hyperactivity disorder. Mov Disord 2000;15:1184–1193. [PubMed: 11104203]

Shim SH, Hwangbo Y, Kwon YJ, Jeong HY, Lee BH, Lee HJ, et al. Increased levels of plasma brain-derived neurotrophic factor (BDNF) in children with attention deficit-hyperactivity disorder (ADHD). Prog.Neuropsychopharmacol.Biol.Psychiatry 2008;32:1824–1828. [PubMed: 18760321]

Sim YJ, Kim H, Shin MS, Chang HK, Shin MC, Ko IG, et al. Effect of postnatal treadmill exercise on c-Fos expression in the hippocampus of rat pups born from the alcohol-intoxicated mothers. Brain Dev 2008;30:118–125. [PubMed: 17723286]

Sonuga-Barke EJ. Psychological heterogeneity in AD/HD--a dual pathway model of behaviour and cognition. Behav.Brain Res 2002;130:29–36. [PubMed: 11864715]

Sonuga-Barke EJ, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. Neuroscience & Biobehavioral Reviews. 2007

Sonuga-Barke EJ, Daley D, Thompson M, Laver-Bradbury C, Weeks A. Parent-based therapies for preschool attention-deficit/hyperactivity disorder: a randomized, controlled trial with a community sample. Journal of the American Academy of Child and Adolescent Psychiatry 2001;40:402–408. [PubMed: 11314565]

Sonuga-Barke EJ, Halperin JM. Developmental phenotypes and causal pathways in attention deficit/hyperactivity disorder: potential targets for early intervention? J.Child Psychol.Psychiatry. 2009

Sonuga-Barke EJ, Taylor E, Sembi S, Smith J. Hyperactivity and delay aversion--I. The effect of delay on choice. J.Child Psychol.Psychiatry 1992;33:387–398. [PubMed: 1564081]

Sonuga-Barke EJ, Williams E, Hall M, Saxton T. Hyperactivity and delay aversion. III: The effect on cognitive style of imposing delay after errors. J.Child Psychol.Psychiatry 1996;37:189–194. [PubMed: 8682898]

Sowell ER, Thompson PM, Welcome SE, Henkenius AL, Toga AW, Peterson BS. Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. Lancet 2003;362:1699–1707. [PubMed: 14643117]

Spencer SV, Hawk LW Jr, Richards JB, Shiels K, Pelham WE Jr, Waxmonsky JG. Stimulant treatment reduces lapses in attention among children with ADHD: the effects of methylphenidate on intra-individual response time distributions. Journal of Abnormal Child Psychology 2009;37:805–816. [PubMed: 19291387]

Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. Journal of the American Academy of Child and Adolescent Psychiatry 1996;35:409–432. [PubMed: 8919704]

Steger J, Imhof K, Coutts E, Gundelfinger R, Steinhausen H, Brandeis D. Attentional and neuromotor deficits in ADHD. Dev Med Child Neurol 2001;43:172–179. [PubMed: 11263687]

Strohle A, Stoy M, Graetz B, Scheel M, Wittmann A, Gallinat J, et al. Acute exercise ameliorates reduced brain-derived neurotrophic factor in patients with panic disorder. Psychoneuroendocrinology 2010;35:364–368. [PubMed: 19682803]

Supekar K, Musen M, Menon V. Development of large-scale functional brain networks in children. PLoS.Biol 2009;7:e1000157. [PubMed: 19621066]

Suskauer SJ, Simmonds DJ, Caffo BS, Denckla MB, Pekar JJ, Mostofsky SH. fMRI of Intrasubject Variability in ADHD: Anomalous Premotor Activity With Prefrontal Compensation. Journal of the American Academy of Child and Adolescent Psychiatry. 2008

Swanson J, Greenhill L, Wigal T, Kollins S, Stehli A, Davies M, et al. Stimulant-related reductions of growth rates in the PATS. J Am Acad Child Adolesc Psychiatry 2006;45:1304–1313. [PubMed: 17023868]

Swanson J, Oosterlaan J, Murias M, Schuck S, Flodman P, Spence MA, et al. Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention. Proc.Natl.Acad.Sci.U.S.A 2000;97:4754–4759. [PubMed: 10781080]

Swanson JM, Elliott GR, Greenhill LL, Wigal T, Arnold LE, Vitiello B, et al. Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. J Am Acad Child Adolesc Psychiatry 2007a;46:1015–1027. [PubMed: 17667480]

Swanson JM, Hinshaw SP, Arnold LE, Gibbons RD, Marcus S, Hur K, et al. Secondary evaluations of MTA 36-month outcomes: propensity score and growth mixture model analyses. Journal of the American Academy of Child and Adolescent Psychiatry 2007b;46:1003–1014. [PubMed: 17667479]

Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, et al. Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. Journal of the American Academy of Child and Adolescent Psychiatry 2001;40:168–179. [PubMed: 11211365]

Swanson JM, Posner MI, Potkin S, Bonforte S, Youpa D, Fiore C, et al. Activating tasks for the study of visual-spatial attention in ADHD children: A cognitive anatomic approach. Journal of Child Neurology 1991;6:S119–S127. [PubMed: 2002210]

Tamm L, Menon V, Ringel J, Reiss AL. Event-related FMRI evidence of frontotemporal involvement in abberant response inhibition and task switching in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2004;43:1430–1440. [PubMed: 15502603]

Tang SW, Chu E, Hui T, Helmeste D, Law C. Influence of exercise on serum brain-derived neurotrophic factor concentrations in healthy human subjects. Neurosci.Lett 2008;431:62–65. [PubMed: 18068900]

Tantillo M, Kesick CM, Hynd GW, Dishman RK. The effects of exercise on children with attention-deficit hyperactivity disorder. Med.Sci.Sports Exerc 2002;34:203–212. [PubMed: 11828226]

Taylor E. Developmental neuropsychopathology of attention deficit and impulsiveness. Dev.Psychopathol 1999;11:607–628. [PubMed: 10532627]

Tian L, Jiang T, Liang M, Zang Y, He Y, Sui M, et al. Enhanced resting-state brain activities in ADHD patients: a fMRI study. Brain Dev 2008;30:342–348. [PubMed: 18060712]

Tian L, Jiang T, Wang Y, Zang Y, He Y, Liang M, et al. Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci.Lett 2006;400:39–43. [PubMed: 16510242]

Tirosh E, Cohen A. Language deficit with attention-deficit disorder: a prevalent comorbidity. J Child Neurol 1998;13:493–497. [PubMed: 9796755]

Toplak ME, Connors L, Shuster J, Knezevic B, Parks S. Review of cognitive, cognitive-behavioral, and neural-based interventions for Attention-Deficit/Hyperactivity Disorder (ADHD). Clin.Psychol.Rev 2008;28:801–823. [PubMed: 18061324]

Torasdotter M, Metsis M, Henriksson BG, Winblad B, Mohammed AH. Expression of neurotrophin-3 mRNA in the rat visual cortex and hippocampus is influenced by environmental conditions. Neurosci Lett 1996;218:107–110. [PubMed: 8945739]

Torasdotter M, Metsis M, Henriksson BG, Winblad B, Mohammed AH. Environmental enrichment results in higher levels of nerve growth factor mRNA in the rat visual cortex and hippocampus. Behav Brain Res 1998;93:83–90. [PubMed: 9659990]

Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J Neurosci 2001;21:1628–1634. [PubMed: 11222653]

Tremblay RE. Prevention of youth violence: why not start at the beginning? Journal of Abnormal Child Psychology 2006;34:481–487. [PubMed: 16865544]

Uddin LQ, Kelly AM, Biswal BB, Margulies DS, Shehzad Z, Shaw D, et al. Network homogeneity reveals decreased integrity of default-mode network in ADHD. J.Neurosci.Methods 2008a; 169:249–254. [PubMed: 18190970]

Uddin LQ, Kelly AM, Biswal BB, Margulies DS, Shehzad Z, Shaw D, et al. Network homogeneity reveals decreased integrity of default-mode network in ADHD. J.Neurosci.Methods 2008b; 169:249–254. [PubMed: 18190970]

Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, et al. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. Proc.Natl.Acad.Sci.U.S.A 1998;95:14494–14499. [PubMed: 9826728]

Valera EM, Faraone SV, Biederman J, Poldrack RA, Seidman LJ. Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:439–447. [PubMed: 15737657]

van Dellen A, Cordery PM, Spires TL, Blakemore C, Hannan AJ. Wheel running from a juvenile age delays onset of specific motor deficits but does not alter protein aggregate density in a mouse model of Huntington's disease. BMC.Neurosci 2008;9:34. [PubMed: 18380890]

van Mourik R, Oosterlaan J, Sergeant JA. The Stroop revisited: a meta-analysis of interference control in AD/HD. J Child Psychol Psychiatry 2005;46:150–165. [PubMed: 15679524]

van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci U S A 1999a;96:13427–13431. [PubMed: 10557337]

van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 1999b;2:266–270. [PubMed: 10195220]

Vaynman SS, Ying Z, Yin D, Gomez-Pinilla F. Exercise differentially regulates synaptic proteins associated to the function of BDNF. Brain Res 2006;1070:124–130. [PubMed: 16413508]

Vloet TD, Gilsbach S, Neufang S, Fink GR, Herpertz-Dahlmann B, Konrad K. Neural mechanisms of interference control and time discrimination in attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 2010;49:356–367. [PubMed: 20410728]

Vygotsky, L. Mind in Society: The Development of Higher Psychological Processes. Cambridge: Harvard University Press; 1978.

Weiss, G.; Hechtman, LT. Hyperactive children grown up. Guilford Press; 1993.

Weiss MD, Gadow K, Wasdell MB. Effectiveness outcomes in attention-deficit/hyperactivity disorder. J.Clin.Psychiatry 2006;67 Suppl 8:38–45. [PubMed: 16961429]

Welsh MC, Pennington BF, Groisser BB. A normative-developmental study of executive function: A window on prefrontal function in children. Developmental Neuropsychology 1991;7:131–149.

Wiesel TN, Hubel DH. Extent of recovery from the effects of visual deprivation in kittens. J Neurophysiol 1965;28:1060–1072. [PubMed: 5883732]

Wigal SB, Nemet D, Swanson JM, Regino R, Trampush J, Ziegler MG, et al. Catecholamine response to exercise in children with attention deficit hyperactivity disorder. Pediatr.Res 2003;53:756–761. [PubMed: 12621106]

Wigal T, Greenhill L, Chuang S, McGough J, Vitiello B, Skrobala A, et al. Safety and tolerability of methylphenidate in preschool children with ADHD. J Am Acad Child Adolesc Psychiatry 2006;45:1294–1303. [PubMed: 17028508]

Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biological Psychiatry 2005;57:1336–1346. [PubMed: 15950006]

Williams BM, Luo Y, Ward C, Redd K, Gibson R, Kuczaj SA, et al. Environmental enrichment: effects on spatial memory and hippocampal CREB immunoreactivity. Physiol Behav 2001;73:649–658. [PubMed: 11495671]

Witt JC. Teachers' resistance to the use of school-based interventions. Journal of School Psychology 1986:37–44.

Wolf RC, Plichta MM, Sambataro F, Fallgatter AJ, Jacob C, Lesch KP, et al. Regional brain activation changes and abnormal functional connectivity of the ventrolateral prefrontal cortex during working memory processing in adults with attention-deficit/hyperactivity disorder. Hum.Brain Mapp 2009;30:2252–2266. [PubMed: 19107748]

Yakovlev, PI.; Lecours, AR. The myelogenetic cycles of regional maturation of the brain. In: Minkowski, A., editor. Regional Development of the Brain in Early Life. New York: Basil Blackwell Publisher; 1967. p. 3-70.

Zoladz JA, Pilc A, Majerczak J, Grandys M, Zapart-Bukowska J, Duda K. Endurance training increases plasma brain-derived neurotrophic factor concentration in young healthy men. J.Physiol Pharmacol 2008;59 Suppl 7:119–132. [PubMed: 19258661]