Neurotherapeutics (2012) 9:531–541
DOI 10.1007/s13311-012-0123-z

Preventive Interventions for ADHD: A Neurodevelopmental Perspective

Jeffrey M. Halperin · Anne-Claude V. Bédard · Jocelyn T. Curchack-Lichtin

Published online: 13 June 2012

Abstract It is proposed that the time is ripe for the development of secondary preventive interventions for attention-deficit/hyperactivity disorder (ADHD). By targeting preschool children, a developmental stage during which ADHD symptoms first become evident in most children with the disorder, many of the adverse long-term consequences that typify the trajectory of ADHD may be avoided. A dynamic/interactive model of the biological and environmental factors that contribute to the emergence and persistence of ADHD throughout the lifespan is proposed. Based on this model, it is argued that environmental influences and physical exercise can be used to enhance neural growth and development, which in turn should have an enduring and long-term impact on the trajectory of ADHD. Central to this notion are 2 hypotheses: 1) environmental influences can facilitate structural and functional brain development, and 2) changes in brain structure and function are directly related to ADHD severity over the course of development and the degree to which the disorder persists or remits with time. We present experimental and correlational data supporting the first hypothesis and longitudinal data in individuals with ADHD supporting the second. The case is made for initiating such an intervention during the preschool years, when the brain is likely to be more "plastic" and perhaps susceptible to lasting modifications, and before complicating factors, such as comorbid psychiatric disorders, academic failure, and poor social and family relationships emerge, making successful treatment more difficult. Finally, we review recent studies in young children with ADHD that might fall under the umbrella of secondary prevention.

Keywords ADHD · prevention · environmental enrichment · development · early intervention · preschool.

J. M. Halperin · J. T. Curchack-Lichtin
Department of Psychology,
Queens College of the City University of New York,
Flushing, New York 11367, USA

J. M. Halperin · A.-C. V. Bédard
Department of Psychiatry, Mount Sinai School of Medicine,
New York, New York 10029, USA

J. M. Halperin (✉) · J. T. Curchack-Lichtin
Neuropsychology Doctoral Program,
The Graduate Center of the City University of New York,
New York, New York 10016, USA
e-mail: jeffrey.halperin@qc.cuny.edu

Attention-deficit/hyperactivity disorder (ADHD) is an early emerging neurodevelopmental disorder that persists into adolescence and early adulthood for a substantial portion of afflicted individuals [1]. In addition to the "core symptoms" of inattention, impulsiveness, and hyperactivity that define the disorder, a substantial portion of individuals diagnosed with ADHD present with an array of neurocognitive deficits, psychiatric comorbidities, and social and emotional difficulties [2, 3]. As a result of persisting impairments across an array of behavioral domains, long-term outcome for many, if not most, children with ADHD is far from optimal [4].

There are several evidence-based pharmacological and psychosocial interventions that are effective for treating the core symptoms and, to a lesser extent, the associated features in youth with ADHD. Both stimulant [5] and nonstimulant [6] medications reduce the severity of core ADHD symptoms, as well as associated oppositional defiant behaviors. Similarly, parent- and school-based behavioral interventions have frequently [7], but not always [8], been reported to have a positive impact on an array of behavioral difficulties in children with ADHD. However, a minority of individuals with ADHD are effectively treated throughout the course of the disorder [9], and treatment gains tend to be short-lived, with limited, if any, long-term beneficial effects [10]. As such, even with "successful" treatment during childhood, the chronic and impairing course of ADHD throughout the lifespan continues to take a significant toll on the lives of patients, their families, and society. Thus, the development of novel interventions that provide enduring benefit could have a substantial impact in terms of cost and human suffering.

The development of new treatments for ADHD has predominantly focused on the school-age years (for more detail see Toplak et al. [11]), a time at which ADHD is most commonly diagnosed. Yet, compelling arguments have been made for the use of earlier interventions that might alter the trajectory of the disorder, and thus avoid many of the long-term negative consequences of ADHD [12–14]. Early intervention targets the child at a time when the brain is more "plastic" and perhaps more amenable to lasting "rewiring." Furthermore, early intervention can potentially be used during the beginning stages of ADHD, before complicating factors, such as comorbid psychiatric disorders, academic failure, poor social relationships, low self-esteem, and negative parent and family attitudes become barriers to successful treatment [12]. Through the identification of young, "at-risk" children, who may not meet full diagnostic criteria for ADHD, it may be possible to use developmentally sensitive preventive interventions that will not only alter the chronically impaired course of ADHD, but will prevent the onset of many of the social, emotional, and academic difficulties that impede successful treatment during later phases of development.

Primary, Secondary, and Tertiary Prevention

Preventive interventions are typically characterized as primary, secondary, or tertiary [15]. Primary preventions impede the emergence of a disorder or injury, and typically take the form of public health initiatives, such as the use of seatbelts in cars, inoculations for viral diseases, or promoting exercise and healthy diets for preventing obesity and cardiovascular disease. For ADHD and other neurodevelopmental disorders, primary prevention initiatives include programs that promote maternal health during pregnancy, such as warnings against alcohol and cigarette use, as well as initiatives to reduce environmental toxins, such as lead and mercury. These initiatives will not eradicate ADHD, but they may lower incidence rates.

Secondary preventive interventions detect the disorder at its earliest stages while it may be more treatable, slow its progression, and/or alter its trajectory to minimize later complications. Examples of secondary preventive interventions include early identification of potentially severe illness through the use of mammography, cardiac stress tests, and colonoscopy. Early detection, prior to the onset of serious (or in some cases any) symptomatology, leads to the implementation of an intervention designed to reduce (or eliminate) the likelihood of severe consequences in the future. Early intervention programs for "at-risk" children, such as Head Start, would fall into this category.

Finally, tertiary prevention uses treatment that is unlikely to be curative but will manage or limit complications after the disorder has manifested. Common examples are the use of insulin for diabetes, alcohol and drug abuse treatment programs, and, most relevant here, psychostimulants or parent training for individuals with ADHD.

The Aims of this Article

We believe, as has been suggested elsewhere [12–14], that the time is ripe for the development of secondary preventive interventions for ADHD. By specifically targeting preschool children, it is not only possible, but perhaps likely, that many of the adverse long-term consequences that typify the trajectory of ADHD can be avoided. In making this argument, we will first present a dynamic/interactive model of the biological and environmental factors that contribute to the emergence of ADHD in early childhood and to its persistence throughout life. From this model, logical targets for interventions that may yield sustainable therapeutic change emerge. In particular, we will argue that environmental enrichment, primarily in the form of neurocognitive enhancement and physical exercise, can be used to enhance neural development, which, in turn, will have an enduring impact on the trajectory of ADHD. Central to this notion are 2 hypotheses: 1) changes in brain structure and function over the course of development are directly related to ADHD severity and the degree to which the disorder persists or remits with time; and 2) neurocognitive enrichment and physical exercise can facilitate structural and functional brain development. We will review longitudinal, experimental, and correlational data that support these hypotheses. Next, we will make the case for why it is preferable to start such interventions during the preschool years. Finally, we will review recent studies in young children with ADHD that might fall under the umbrella of secondary prevention.

A Dynamic/Interactive Model of the Emergence and Persistence of ADHD

Research into the causes of ADHD has demonstrated evidence for what is probably a dynamic interplay among genes, prenatal environment, and postnatal environment. With this in mind, ADHD has been conceptualized through an epigenetic model, in which these 3 factors interact to influence the developmental trajectory of the brain [16].

Genetic Determinants

There is no question that genes play an important role in the emergence and persistence of the disorder. Twin studies suggest a heritability index estimate of 0.76 [17]. Although the precise genes that lead to increased risk for ADHD have remained elusive, among the many genetic markers studied, DAT1, DRD4, DRD5, 5HTT, DBH, ADRA2A, TPH2, MAOA, and SNAP25 were recently identified as having the most empirical support [18]. Further data suggest that the trajectory of ADHD across the lifespan or the degree to which symptoms persist or decline is genetically mediated [19, 20]. For example, using a longitudinal twin cohort, Kuntsi et al. [20] reported that symptom stability was primarily due to shared genetic influences. Children with ADHD who had at least one copy of the DRD4 7-repeat allele exhibited normalized cortical thinning over development, higher IQ scores, better global functioning, and were less likely to maintain their ADHD diagnosis at follow-up compared with children with ADHD without a DRD4 7-repeat allele. Importantly, those with and without a DRD4 7-repeat allele did not differ in ADHD symptoms at baseline.

In addition, some genes may alter children's response to interactions with environmental factors to affect ADHD [16]. For example, children with the DRD4 7-repeat allele, as compared to those without the 7-repeat allele, were found to be more sensitive to the quality of parenting received [21] and to have a superior response to a parenting intervention [22], suggesting genetic differences in the degree to which environmental factors influence developmental trajectories in children with ADHD. Similarly, variations in the dopamine transporter gene (DAT1) and the serotonin transporter gene (5HTT) have been reported to moderate the sensitivity of children with ADHD to maternal positive emotional expression [23]. Most recently [24], variations in DAT1 were reported to moderate the response of children with ADHD to behavioral parent training such that those with no or only one DAT1 10-repeat allele had a more positive response.

Yet, the degree to which one's genetic make-up directly influences sensitivity to environmental factors and/or environmental influences result in epigenetic alterations in gene function remains unknown. For example, several studies have shown that aspects of early parenting behavior and rearing in rodents have lasting effects on the behavior of the offspring, and that these behavioral alterations are mediated by changes in gene expression that result from environmental factors (for more detail see Meaney [25]). These epigenetic alterations to gene expression can result in adverse consequences for the offspring, such as those resulting from increased maternal stress [26], or in positive consequences, such as those resulting from improved caregiving to the neonate [27]. Although the data in humans are far more limited, 1 postmortem study has linked altered epigenetic regulation of hippocampal glucocorticoid receptor expression specifically with early child abuse [28]. Notably, environmentally-induced epigenetic changes to gene expression appear to be reversible through environmental enrichment [29].

Prenatal Environment

Beyond genes, exposure to certain factors in the prenatal environment increases risk for ADHD. For instance, maternal use of tobacco, alcohol, caffeine, and certain psychotropic medication during pregnancy may increase risk of ADHD in offspring [16, 30]. Poor maternal nutrition (e.g., obesity, low iron, and fatty acids) [31, 32], maternal stress during pregnancy [33], maternal gestational diabetes [34], and exposure to chemicals and heavy metals have also been implicated [16, 30]. As only some children with these exposures go on to develop ADHD, it is possible that genes influence sensitivity to at least some adverse prenatal environmental factors.

Neural Factors

These complex interactions of genetic and environmental factors, which differ across individuals, directly impact brain development (for more detail see Kieling et al. [35]). ADHD has been purported to involve disruption within a diverse set of brain regions, including most prominently frontostriatal circuitry and the cerebellum [36, 37]. Recently, considerable attention has been paid to disruptions within the default mode network [38].

These disruptions to brain development are purported to underlie the wide array of neurocognitive deficits commonly seen in children with ADHD. Meta-analyses [39–43] indicate a wide range of executive and nonexecutive function deficits in children with ADHD. From a developmental perspective, ADHD has been hypothesized [44], with some supporting data [45, 46], to be associated with early appearing and lasting subcortical dysfunction, whereas recovery throughout development is associated with improvements in executive control functions.

Consistent with the diversity of cognitive deficits often seen in children with ADHD, longitudinal neuroimaging studies by Shaw et al. [47, 48] found that cortical maturation of children with ADHD was delayed throughout most of the cerebral cortex by as much as 2 to 3 years, most prominently in prefrontal regions. Moreover, children with better outcomes demonstrated normalization within right parietal cortex, whereas those with poorer outcomes showed "fixed" thinning of left medial prefrontal cortex [47]. In addition, cortical thinning that continued into adulthood in the dorsolateral prefrontal cortex, anterior cingulate, and inferior parietal lobe, as well as progressive volume loss in the cerebellum, were linked to the persistence of ADHD symptoms [49]. Most recently [50], in a 33-year follow-up study, ADHD probands were found to have significantly thinner cortices in the dorsal attentional network and limbic areas than adults with no history of ADHD. In addition, gray matter was significantly decreased in probands in several subcortical brain regions. Notably, relative to those with persistent ADHD, remitters (those with childhood ADHD who no longer had ADHD at follow-up) tended to have thicker cortices in several regions, leading the authors to suggest that diagnostic remission may result from compensatory maturation of prefrontal, cerebellar, and thalamic circuitry.

Similar to structural neuroimaging data, functional magnetic resonance imaging data indicate that brain activation elicited by an inhibitory control task closely parallels the degree of persistence of ADHD symptoms in adolescents with childhood ADHD, with remitters, as compared to persisters, more closely resembling their peers who never had ADHD [51]. Furthermore, neuropsychological performance of adolescents and young adults with improving ADHD trajectories diverges from persisters and more closely approaches their peers who never had ADHD across an array of "effortful" tasks (e.g., working memory, inhibitory control, sustained attention) [45, 46]. Finally, in a longitudinal sample of preschool children, preliminary analyses indicate that over a three-year period variation over time in neuropsychological function parallels changes in symptom severity and that behavioral improvements in "at-risk" preschoolers are preceded by changes in neurocognitive function [52]. Thus, the limited data available are consistent with the hypothesis that normalization of brain anomalies and/or enhanced cortical development are associated with disorder remission, whereas lack of normal maturation may be associated with persistence of ADHD throughout development [13, 44, 48–50, 52].

"Setting the Stage" for ADHD

Thus, compelling data indicate that complex interactions among genes and the prenatal environment influence early brain development, which in turn predisposes an individual to ADHD. We propose that by the time of birth, or very shortly thereafter, the stage is set for the expression of some form of the ADHD phenotype [44], but the manner in which that phenotype is manifested is influenced, to a substantial degree, by an array of environmental factors that affect postnatal neural and behavioral development. Although postnatal factors affect the development of all children, more vulnerable children with a predisposition toward ADHD may be particularly sensitive to adverse environmental conditions, but their developmental course can also be positively affected by enhanced environmental conditions.

As depicted in Fig. 1, we posit that genes and the prenatal environment interact bi-directionally, so that genes influence the prenatal environment and the environment, via epigenetic mechanisms, influences gene functions. Together, these serve to shape the brain of the newborn. After birth, postnatal environmental factors continue to influence neural development, both directly as well as potentially indirectly, via the insertion of epigenetic genetic marks (e.g., DNA methylation) (for more detail see Caldji et al. [53]). Thus, not only do environmental influences moderate the relationship between brain structure/function and ADHD severity, but aspects of the postnatal environment have a direct impact on brain growth and development. ADHD-related behaviors perpetuate these interactions, in that the behaviors emitted by children with ADHD often elicit negative responses from those around them [54].

Postnatal Environmental Influences on Neural and Behavioral Development

Although the quality of parenting is unlikely to be a primary cause of ADHD, it is among several postnatal environmental risk factors that may influence severity and/or impairment. These include poor parenting, home discord, low socioeconomic status, institutionalized care, and exposure to violence and trauma [16]. Some studies suggest that young children who watch a lot of television are at increased risk for attentional problems later on [55, 56]. In contrast to these risk factors, less has been written about positive influences that might protect children from the adverse long-term trajectory that is typically associated with the disorder. Perhaps, by systematically targeting postnatal environmental

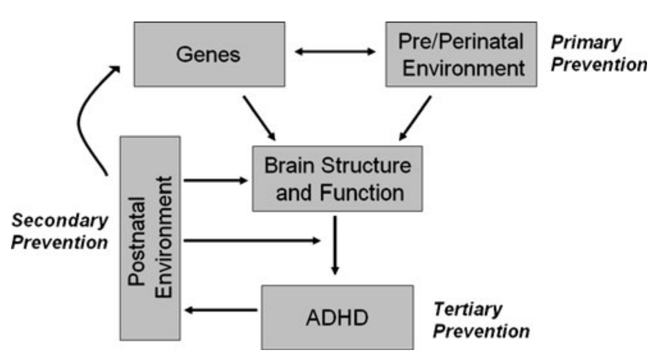

Fig. 1 A dynamic/interactive model of the emergence and persistence of attention-deficit/hyperactivity disorder (ADHD), along with loci for preventative interventions

influences, enduring effects on the emergence and trajectory of ADHD can be achieved [12–14].

The Influence of Environmental Enrichment and Exercise on Brain Growth

A wealth of research has demonstrated the powerful effects of physical exercise and cognitive enrichment in nonhuman species, and similar findings are rapidly emerging from research with humans. These studies have been the focus of several recent reviews [57, 58], and thus are discussed only briefly here.

Physical Exercise

As reviewed elsewhere [59, 60], physical exercise has been shown to increase levels of brain-derived neurotrophic factor, levels of synaptic proteins, glutamate receptors, and the availability of insulin-like growth factor, all of which contribute to cell proliferation and neural plasticity. Notably, exercise-induced neural changes in rodents are accompanied by behavioral changes, such as enhanced spatial learning and memory. Importantly, the greatest cell proliferation in response to exercise occurs early in development [61], suggesting that exercise interventions may be particularly effective during early childhood. Nevertheless, the beneficial effects of exercise are not limited to early childhood. Physical exercise has consistently been reported to increase brain-derived neurotrophic factor levels, enhance cognitive performance, and promote brain health in human adults.

Aerobic fitness in typically-developing children predicts differences in brain function, as detected with event-related potentials and functional magnetic resonance imaging, as well as improved cognitive abilities [62]. Although most studies of exercise in children have focused on typically-developing youth, the areas of cognition that were found to be improved mainly included those related to executive functioning and the activation of prefrontal cortex, and thus are highly relevant to ADHD. While some attention has been paid to the impact of acute physical activity on ADHD symptoms [63], and investigators have pointed out the theoretical potential of chronic physical exercise in ADHD [64, 65], randomized controlled trials of physical exercise as a treatment for ADHD have yet to be published.

Environmental Enrichment

Similar to physical exercise, environmental and cognitive enrichment have been shown to influence both brain structure and function. As reviewed elsewhere [13], environmental enrichment increases neuronal size, neurotrophin levels, synaptophysin levels, dendritic branching and spine number, synaptic density, neocortical neurotransmission, and neurogenesis and nerve growth factor mRNA and CREB gene expression in the hippocampus in rodents. These changes have been associated with improved performance on various spatial and nonspatial memory tasks. In humans, epidemiological data indicate an association between increased participation in social and intellectual activities in daily life and a slower rate of cognitive decline in the elderly [66]; cognitive exercise may also be an effective intervention for slowing the trajectory of cognitive and functional decline associated with dementia [67].

Attention and cognitive training programs in school-age children with ADHD have reported both functional [68] and structural [69] brain changes, and several of these programs have reported cognitive improvements on measures of response inhibition, sustained attention, working memory, executive function, and academic performance, in addition to ADHD symptoms [70–72]. Studies of similar training paradigms for attention, memory, and executive function in typically developing preschool children (including at-risk children) have reported improvements in inhibitory control, working memory, cognitive flexibility, academic performance, IQ, and event-related potential amplitude in frontal and frontoparietal areas [73–76].

In summary, there is ample evidence that cognitive enrichment and physical exercise can have positive effects on the brain and cognition. In view of data indicating that variation in ADHD severity across the lifespan is linked to variation in neural [47, 49, 51] and cognitive [45, 46] development, it seems likely that a program of cognitive and/or physical exercise could be implemented to enhance brain function, and in turn yield lasting positive effects on the trajectory of ADHD. If implemented early on, such a program could prevent many of the more severe consequences of a lifetime with ADHD.

Rationale for Early Intervention

We outline, as follows, a prevention-based approach for ADHD built on early detection and intervention. The goal is to reduce the likelihood of the emergence and/or persistence of ADHD from its earliest manifestations by facilitating brain growth to alter its adverse long-term trajectory. As reviewed elsewhere [12], there are several key reasons to believe that early interventions during the prodromal stages of ADHD may be more effective than treatments after outcomes are established and barriers to successful treatment are in place.

Early Childhood is a Critical Period for Brain Development and Neural Plasticity

The human brain reaches approximately 80 % of adult size by 2 years of age [77] and changes minimally in size after age 5 [78]. Myelination begins *in utero* and proceeds rapidly through the age of 2 years [79]. Furthermore, the first 2 years of life are a period of rapid synapse formation, which results in an overproduction of synapses [80], followed by a plateau phase extending over several years, during which neurons begin to form complex dendritic trees [81]. These 2 processes seem to account for the increase in cortical gray matter in childhood found in magnetic resonance imaging studies [47, 82, 83]. Subsequently, brain development is characterized largely by cortical organization and refinement relative to neuronal growth. Designing interventions that facilitate development of highly malleable learning-dependent brain networks have been proposed [13], with early childhood as a "window of opportunity" for intervention when brains are believed to be more "plastic" and children may be most amenable to learning new skills [84]. Nevertheless, the notion that the young brain is more plastic is not firmly grounded in data, and the likelihood of recovery from brain damage clearly varies depending on a number of factors, including the nature and extent of the injury, as well as the timing of the post-lesion evaluation [85]. Yet, promoting brain growth to prevent the onset of or facilitate recovery from a condition such as ADHD may not be the same as recovering from a head injury or brain lesion. Thus, much of the human literature sheds limited light on this issue. Animal research provides some evidence for greater impact of environmental enrichment at earlier ages [61, 86], but the extent to which this translates to humans is unknown.

Early Intervention Precedes the Onset of Many Comorbid Conditions

ADHD is associated with high rates of comorbid psychiatric conditions that are themselves associated with unique impairments (separate from or synergistic with ADHD) and that often require separate treatments. Most conditions that frequently co-occur with ADHD, including tic disorders, depression, anxiety disorders, obsessive compulsive disorder, bipolar disorder, conduct and substance use disorders, and personality disorders, emerge after the onset of ADHD [87, 88]. High rates of these later-emerging comorbid disorders suggest that ADHD might be a risk factor for them. Ideally, prevention-based early interventions should take place at an age by which early signs of ADHD can be detected, but prior to the time that chronic and impairing comorbidities take hold [12]. In this way, perhaps, not only would ADHD be of lesser severity, but the emergence of these highly impairing comorbid disorders might be prevented.

Early Intervention May Result In the Diminution of Later Impairment

If effective interventions can be established early, then complications associated with academic failure, poor social relationships, low self-esteem, and negative parent and family attitudes can potentially be avoided [14]. Childhood behavioral problems are associated with substantial delays in motor, language, play, school, and social skills, even prior to entry into kindergarten [89]. Early interventions that take place prior to the development of engrained behavioral patterns in the child may improve parents' receptiveness to treatment and avoid the development of negative ADHD-related parent-child difficulties.

Early Interventions in ADHD Have Shown Persisting Efficacy

Unlike treatment of ADHD during the school-age years, some preschool interventions provide preliminary evidence of persisting benefits beyond the termination of active treatment. *The Incredible Years* [90] and *Triple P* [91], both parent-focused interventions for preschoolers, have yielded behavioral improvements that persist beyond the end of treatment, although in general, they have a greater impact on disruptive behaviors than ADHD symptoms per se. Sonuga-Barke et al. [92] found significant reductions in ADHD symptoms in preschoolers after parent training that persisted for 15 weeks post-treatment. More recently, in a randomized controlled trial using their *Revised New Forest Parenting Programme (NFPP)*, which focuses on self-regulation and the quality of mother–child interactions, this same group found large effect sizes for improving ADHD symptoms that persisted for 9 weeks post-treatment [93].

In addition, several novel and innovative early interventions designed to improve behavioral control in young children with ADHD by enhancing neurocognitive functioning are currently being developed [94–96]. As previously described, children with ADHD often present with a wide array of neurocognitive impairments that are closely linked to neural dysfunction. As such, development of therapeutic modalities that directly address identified neurocognitive deficiencies may yield benefits that persist after formal treatment discontinuation, and in this way, more formidably impact the trajectories of youth with ADHD. These interventions all share several features in common, including using games or game-like activities as the drivers of neurocognitive development, the use of parents for delivering the treatment at high frequency at home, and the promotion of positive parent–child relationships through playing together.

Training Executive, Attention and Motor Skills (TEAMS) [96], a program developed for 4- and 5-year-old children with ADHD, uses games designed to target an array of neurocognitive skills (e.g., inhibition, sustained attention, memory, planning, and visuospatial and motor skills) frequently impaired in the disorder. This intervention involves 5 weekly, concurrently-held, child and parent groups. Children are introduced to and play the games during their group sessions. Parents are also taught the games and how to scaffold their difficulty levels. Parent sessions focus on how to incorporate the games into their busy lives on a daily basis, techniques for keeping the games fun and engaging, and how to tailor and modify the games to match the interest and ability level of the child. An open pilot study reported significant improvements of medium to large effect sizes in parent and teacher-rated ADHD symptoms that persisted at 3 months post-treatment [96].

Enhancing Neurocognitive Growth with the Aid of Games and Exercise (ENGAGE) is an early intervention for 3- and 4-year-old children with difficulties in self-control. Like TEAMS, it involves parents and children playing prescribed games on a daily basis for a 5-week period. ENGAGE targets 3 areas of self-control that are deficient in children with ADHD: 1) behavior, 2) cognition, and 3) emotion. A preliminary open trial showed improvements in parent-rated hyperactivity that was maintained throughout a 12-month follow-up period. In addition, significant improvements from pre- to post-treatment were found on tests of working memory and sensorimotor control [94].

Finally, Executive Training of Attention and Metacognition (ETAM) targets executive function deficits in 3- to 7-year-old children with ADHD through the use of behaviorally-based skills training and practice, along with training in metacognitive strategies. ETAM is an eight-week intervention with weekly concurrent child and parent groups, during which children practice game-like activities that promote executive function and self-regulation, and parents and their children develop a language to talk about attentional control (i.e., eyes looking, ears listening, brain thinking, body still) which serves as the metacognitive framework of the program. The activities, which are practiced at home with parents, focus on an array of executive functions. An open clinical trial of ETAM reported significant pre- to post-treatment improvements with moderate to large effect sizes on several measures of executive functions and on parent ratings of ADHD symptoms [95].

These new emerging interventions all target ADHD early in development, thereby improving the potential for affecting the developmental trajectory of the disorder. Importantly, they all incorporate therapeutic activities into daily life, improving their palatability to preschoolers and perhaps also their generalizability. While further study using more rigorous designs is necessary, collectively, these findings raise the possibility that interventions administered during the preschool years may yield lasting positive effects. Although the mechanisms by which these early interventions exert their positive influence remains unknown, we speculate that behavioral improvement is likely a result of the cognitive and physical exercises promoting brain growth

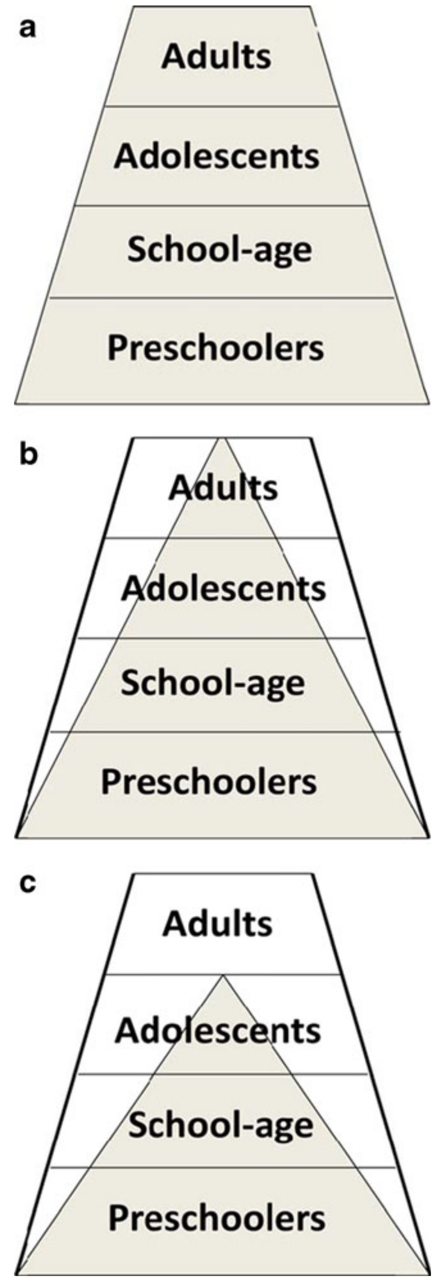

Fig. 2 Depiction of the developmental course of attention-deficit/hyperactivity disorder (ADHD) symptoms across the lifespan of children and the potential impact of early intervention on long-term symptom trajectories. The shaded area reflects the number of individuals with clinically significant symptoms at different ages. Narrowing of the shaded area reflects the diminution in prevalence and/or symptom severity with increasing age: (**a**) No intervention. (**b**) A small impact of intervention during early childhood substantially reduces long-term burden of the disorder. (**c**) A somewhat larger impact of intervention during early childhood may have dramatic effects on the long-term burden of the disorder

in combination with the delivery by parents improving parent–child relations.

The Potential Promise of Preventive Interventions for ADHD

The goal for the proposed approach of secondary preventive interventions is to reduce the likelihood of the emergence of ADHD and to slow its escalation in severity or persistence from its earliest manifestations by facilitating brain growth and development. This, in turn, should minimize many long-term complications typical of ADHD. Central to successful implementation of this approach is the notion that early identification is possible. While undoubtedly some children will be missed, for the most part, irrespective of whether the child meets full diagnostic criteria for ADHD, symptoms of hyperactivity and impulsivity are evident during the preschool years in most children who go on to develop the disorder. With increased rates of attendance at daycare and preschool over the past 2 decades [97], early identification of "at-risk" preschoolers should be easier than ever.

The fact that at-risk children who will not develop ADHD might also be identified and treated requires these interventions to be noninvasive, relatively low in cost, readily accessible, and easy to implement. Widespread use of preventive interventions targeting at-risk children would not only need to remain relatively risk-free, but, to the extent that it is possible, they should also be helpful to all children irrespective of at-risk status. In this regard, engaging in challenging and cognitively stimulating games should be enjoyable and growth-promoting, even in typically-developing children. With regard to cost, accessibility, and ease of implementation, several emerging programs [94–96] use a group-based approach that is overseen by a professional, but can be delivered largely by paraprofessionals and/or trained students, thus substantially lowering costs. In addition, the clinical setting might not be ideal for administering these interventions, which often require large playrooms for child groups. Rather, schools and community centers might be better suited, making the intervention accessible to large numbers of individuals. As for ease of implementation, it will be critical that these programs be highly palatable both to parents and children (and perhaps teachers) in a manner that will engage them in the intervention in an ongoing and meaningful way.

Early interventions for children at high risk for developing an array of difficulties other than ADHD have received attention over the past few decades. Such programs as Perry Preschool and the Abecedarian Project, as well as Head Start, have been shown to help shift the oftentimes poor trajectories associated with residence in high-poverty communities [98]. These relatively brief early intervention programs have been shown to alter educational, occupational, and criminal outcomes for vulnerable youth. As depicted in Fig. 2a to c, small changes to the trajectory of ADHD during the preschool years have the potential to yield very substantial benefits across the lifetime of a child. Figure 2a depicts the developmental course of ADHD, with decreasing prevalence and symptom severity associated with later phases in development. As shown in Fig. 2b and c, relatively modest changes in early childhood have the potential for substantial impact over the lifespan.

In summary, ADHD is a neurodevelopmental disorder, the symptoms of which often emerge during the preschool years. Substantial animal and human research has provided evidence that environmental stimulation and exercise can impact the developing brain. Early childhood is a critical period for brain development, and early intervention may be crucial for addressing an array of neurodevelopmental disorders, including ADHD. Intervention at an early age, by which ADHD can be detected, but prior to the emergence of many of the more chronic and impairing comorbidities and associated features that result in poor long-term outcome, may also be critical to altering the common course of lifelong impairment. Although correlational in nature, there is evidence to suggest that maturation of the brain and related improvements in neuropsychological functioning may translate into reduced ADHD symptom severity and impairment. Importantly, recent data from clinical trials demonstrate preliminary evidence that intervening early in ADHD can have persisting efficacy beyond the termination of active treatment. Longer term follow-up data from randomized controlled trials, in combination with neuroimaging pre- and post-treatment, will be a critical test of whether the interventions are in fact capable of altering the brain and truly shifting the course of the disorder.

Acknowledgments This work was supported by grants (R21/R33 MH085898 and R01 MH68286) from the National Institute of Mental Health to Jeffrey Halperin, and by a Canadian Institutes of Health Research Fellowship Award to Anne-Claude Bédard. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Mental Health, the National Institutes of Health, or the Canadian Institutes of Health Research. None of the authors have any real or perceived conflicts of interest.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. (Text revision). Washington, D.C. 2000.
2. Garcia CR, Bau CH, Silva KL, et al. The burdened life of adults with ADHD: Impairment beyond comorbidity. Eur Psychiatry 2010. doi:10.1016/j.eurpsy.2010.08.002

3. Anastopoulos AD, Smith TF, Garrett ME, et al. Self-Regulation of emotion, functional impairment, and comorbidity among children with AD/HD. J Atten Disord 2011;15:583–592.
4. Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult outcome of hyperactive children: adaptive functioning in major life activities. J Am Acad Child Adolesc Psychiatry 2006;45:192–202.
5. Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. J Am Acad Child Adolesc Psychiatry 1999;38:503–512.
6. Wood JG, Crager JL, Delap CM, Heiskell KD. Beyond methylphenidate: nonstimulant medications for youth with ADHD. J Atten Disord 2007;11:341–350.
7. Pelham W, Fabiano G. Evidence-based psychosocial treatments for attention-deficit/hyperactivity disorder. J Clin Child Psychol 2008;37:184–214.
8. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 1999;56:1073–1086.
9. 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.
10. Molina BS, Hinshaw SP, Swanson JM, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 2009;48:484–500.
11. 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.
12. Sonuga-Barke EJ, Halperin JM. Developmental phenotypes and causal pathways in attention deficit/hyperactivity disorder: potential targets for early intervention? J Child Psychol Psychiatry 2010;51:368–389.
13. Halperin JM, Healey DM. The influences of environmental enrichment, cognitive enhancement, and physical exercise on brain development: can we alter the developmental trajectory of ADHD? Neurosci Biobehav Rev 2011;35:621–634.
14. Sonuga-Barke EJ, Koerting J, Smith E, McCann DC, Thompson M. Early detection and intervention for attention-deficit/hyperactivity disorder. Expert Rev Neurother 2011;11:557–563.
15. Caplan G, Grunebaum H. Perspectives on primary prevention. Arch Gen Psychiatry 1967;17:331–346.
16. Nigg J, Nikolas M, Burt SA. Measured gene-by-environment interaction in relation to attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2010;49:863–873.
17. Faraone SV, Perlis RH, Doyle AE, et al. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:1313–1323.
18. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. Hum Genet 2009;126:51–90.
19. Faraone SV. Genetics of adult attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2004;27:303–321.
20. 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. Biol Psychiatry 2005;57:647–654.
21. 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.
22. Bakermans-Kranenburg MJ, Van IMH, 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.
23. Sonuga-Barke EJ, Oades RD, Psychogiou L, et al. Dopamine and serotonin transporter genotypes moderate sensitivity to maternal expressed emotion: the case of conduct and emotional problems in attention deficit/hyperactivity disorder. J Child Psychol Psychiatry 2009;50:1052–1063.
24. van den Hoofdakker BJ, Nauta MH, Dijck-Brouwer DA, et al. Dopamine transporter gene moderates response to behavioral parent training in children with ADHD: a pilot study. Dev Psychol 2012;48:567–574.
25. Meaney MJ. Epigenetics and the biological definition of gene x environment interactions. Child Dev 2010;81:41–79.
26. Gudsnuk KM, Champagne FA. Epigenetic effects of early developmental experiences. Clin Perinatol 2011;38:703–717.
27. Branchi I, Karpova NN, D'Andrea I, Castren E, Alleva E. Epigenetic modifications induced by early enrichment are associated with changes in timing of induction of BDNF expression. Neurosci Lett 2011;495:168–172.
28. McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009;12:342–348.
29. Bredy TW, Zhang TY, Grant RJ, Diorio J, Meaney MJ. Peripubertal environmental enrichment reverses the effects of maternal care on hippocampal development and glutamate receptor subunit expression. Eur J Neurosci 2004;20:1355–1362.
30. Linnet KM, Dalsgaard S, Obel C, et al. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. Am J Psychiatry 2003;160:1028–1040.
31. Schlotz W, Jones A, Phillips DI, Gale CR, Robinson SM, Godfrey KM. Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. J Child Psychol Psychiatry 2010;51:594–602.
32. Rodriguez A. Maternal pre-pregnancy obesity and risk for inattention and negative emotionality in children. J Child Psychol Psychiatry 2010;51:134–143.
33. Martini J, Knappe S, Beesdo-Baum K, Lieb R, Wittchen HU. Anxiety disorders before birth and self-perceived distress during pregnancy: associations with maternal depression and obstetric, neonatal and early childhood outcomes. Early Hum Dev 2010;86:305–310.
34. Nomura Y, Marks DJ, Grossman B, et al. Exposure to gestational diabetes mellitus and low socioeconomic status: effects on neurocognitive development and risk of attention-deficit/hyperactivity disorder in offspring. Arch Pediatr Adolesc Med 2012;166(4):337–343. doi:10.1001/archpediatrics.2011.784
35. Kieling C, Goncalves RR, Tannock R, Castellanos FX. Neurobiology of attention deficit hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 2008;17:285–307.
36. Seidman LJ, Valera EM, Makris N. Structural brain imaging of attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:1263–1272.
37. Castellanos FX, Giedd JN, Marsh WL, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch Gen Psychiatry 1996;53:607–616.
38. Sonuga-Barke EJ, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neurosci Biobehav Rev 2007;31:977–986.
39. 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. Biol Psychiatry 2005;57:1336–1346.
40. Martinussen R, Hayden J, Hogg-Johnson S, Tannock R. A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2005;44:377–384.
41. Alderson RM, Rapport MD, Kofler MJ. Attention-deficit/hyperactivity disorder and behavioral inhibition: a meta-analytic review of

the stop-signal paradigm. J Abnorm Child Psychol 2007;35:745–758.
42. 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.
43. Frazier TW, Demaree HA, Youngstrom EA. Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. Neuropsychology 2004;18:543–555.
44. 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.
45. Halperin JM, Trampush JW, Miller CJ, Marks DJ, Newcorn JH. Neuropsychological outcome in adolescents/young adults with childhood ADHD: profiles of persisters, remitters and controls. J Child Psychol Psychiatry 2008;49:958–966.
46. Bedard AC, Trampush JW, Newcorn JH, Halperin JM. Perceptual and motor inhibition in adolescents/young adults with childhood-diagnosed ADHD. Neuropsychology 2010;24:424–434.
47. Shaw P, Lerch J, Greenstein D, et al. Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2006;63:540–549.
48. Shaw P, Gogtay N, Rapoport J. Childhood psychiatric disorders as anomalies in neurodevelopmental trajectories. Hum Brain Mapp 2010;31:917–925.
49. Makris N, Biederman J, Valera EM, et al. Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. Cereb Cortex 2007;17:1364–1375.
50. Proal E, Reiss PT, Klein RG, et al. Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. Arch Gen Psychiatry 2011;68:1122–1134.
51. Schulz KP, Newcorn JH, Fan J, Tang CY, Halperin JM. Brain activation gradients in ventrolateral prefrontal cortex related to persistence of ADHD in adolescent boys. J Am Acad Child Adolesc Psychiatry 2005;44:47–54.
52. Halperin JM. The neurodevelopment of ADHD — longitudinal studies. The 22nd Annual EUNETHYDIS Meeting: The next 10 years; September 29–October 2, 2011; Budapest, Hungary.
53. Caldji C, Hellstrom IC, Zhang TY, Diorio J, Meaney MJ. Environmental regulation of the neural epigenome. FEBS Lett 2011;585:2049–2058.
54. Barkley RA, Cunningham CE. The effects of methylphenidate on the mother-child interactions of hyperactive children. Arch Gen Psychiatry 1979;36:201–208.
55. Swing EL, Gentile DA, Anderson CA, Walsh DA. Television and video game exposure and the development of attention problems. Pediatrics 2010;126:214–221.
56. Christakis DA, Zimmerman FJ, DiGiuseppe DL, McCarty CA. Early television exposure and subsequent attentional problems in children. Pediatrics 2004;113:708–713.
57. Voss MW, Nagamatsu LS, Liu-Ambrose T, Kramer AF. Exercise, brain, and cognition across the life span. J Appl Physiol 2011;111:1505–1513.
58. Ratey JJ, Loehr JE. The positive impact of physical activity on cognition during adulthood: a review of underlying mechanisms, evidence and recommendations. Rev Neurosci 2011;22:171–185.
59. Lojovich JM. The relationship between aerobic exercise and cognition: is movement medicinal? J Head Trauma Rehabil 2010;25:184–192.
60. Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity — exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. Sports Med 2010;40:765–801.
61. Kim YP, Kim H, Shin MS, 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.
62. Chaddock L, Erickson KI, Prakash RS, et al. A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. Brain Res 2010;1358:172–183.
63. Medina JA, Netto TL, Muszkat M, et al. Exercise impact on sustained attention of ADHD children, methylphenidate effects. Atten Defic Hyperact Disord 2010;2:49–58.
64. Archer T, Kostrzewa RM. Physical exercise alleviates ADHD symptoms: regional deficits and development trajectory. Neurotox Res 2012;21:195–209.
65. Gapin J, Etnier JL. The relationship between physical activity and executive function performance in children with attention-deficit hyperactivity disorder. J Sport Exerc Psychol 2010;32:753–763.
66. Scarmeas N, Stern Y. Cognitive reserve: implications for diagnosis and prevention of Alzheimer's disease. Curr Neurol Neurosci Rep 2004;4:374–380.
67. Gates N, Valenzuela M. Cognitive exercise and its role in cognitive function in older adults. Curr Psychiatry Rep 2010;12:20–27.
68. Hoekzema E, Carmona S, Tremols V, et al. Enhanced neural activity in frontal and cerebellar circuits after cognitive training in children with attention-deficit/hyperactivity disorder. Hum Brain Mapp 2010;31:1942–1950.
69. Hoekzema E, Carmona S, Ramos-Quiroga JA, et al. Training-induced neuroanatomical plasticity in ADHD: a tensor-based morphometric study. Hum Brain Mapp 2011;32:1741–1749.
70. Klingberg T, Fernell E, Olesen PJ, et al. Computerized training of working memory in children with ADHD — a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry 2005;44:177–186.
71. 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.
72. Kerns KA, Eso K, Thompson J. Investigation of a direct intervention for improving attention in young children with ADHD. Developmental Neuropsychology 1999;16:273–295.
73. Diamond A, Barnett WS, Thomas J, Munro S. Preschool program improves cognitive control. Science 2007;318:1387–1388.
74. 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.
75. Thorell LB, Lindqvist S, Bergman Nutley S, Bohlin G, Klingberg T. Training and transfer effects of executive functions in preschool children. Dev Sci 2009;12:106–113.
76. Bergman Nutley S, Soderqvist S, Bryde S, Thorell LB, Humphreys K, Klingberg T. Gains in fluid intelligence after training non-verbal reasoning in 4-year-old children: a controlled, randomized study. Dev Sci 2011;14:591–601.
77. Giedd JN, Blumenthal J, Jeffries NO, al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci 1999;2:861–863.
78. Bryck RL, Fisher PA. Training the brain: Practical applications of neural plasticity from the intersection of cognitive neuroscience, developmental psychology, and prevention science. Am Psychol 2012;67(2):87–100. doi:10.1037/a0024657
79. 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.
80. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 1997;387:167–178.
81. 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.
82. Shaw P, Eckstrand K, Sharp W, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A 2007;104:19649–19654.

83. Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci U S A 2004;101:8174–8179.
84. Andersen SL, Navalta CP. Annual Research Review: New frontiers in developmental neuropharmacology: can long-term therapeutic effects of drugs be optimized through carefully timed early intervention? J Child Psychol Psychiatry 2011;52:476–503.
85. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. Brain 2011;134(Pt 8):2197–221.
86. Kolb B, Coie J, Wishaw I. Is there an optimal age and anatomical sequelae of anatomical bilateral motor cortex lesions in rats on postnatal days 1, 10, and in adulthood. Brain Res 2000;882:62–74.
87. Taurines R, Schmitt J, Renner T, Conner AC, Warnke A, Romanos M. Developmental comorbidity in attention-deficit/hyperactivity disorder. Atten Defic Hyperact Disord 2010;2:267–289.
88. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593–602.
89. Montes G, Lotyczewski BS, Halterman JS, Hightower AD. School readiness among children with behavior problems at entrance into kindergarten: results from a US national study. Eur J Pediatr 2012;171(3):541–548. doi:10.1007/s00431-011-1605-4
90. Jones K, Daley D, Hutchings J, Bywater T, Eames C. Efficacy of the Incredible Years Programme as an early intervention for children with conduct problems and ADHD: long-term follow-up. Child Care Health Dev 2008;34:380–390.
91. Bor W, Sanders MR, Markie-Dadds C. The effects of the Triple P-Positive Parenting Program on preschool children with co-occurring disruptive behavior and attentional/hyperactive difficulties. J Abnorm Child Psychol 2002;30:571–587.
92. 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. J Am Acad Child Adolesc Psychiatry 2001;40:402–408.
93. Thompson MJ, Laver-Bradbury C, Ayres M, et al. A small-scale randomized controlled trial of the revised new forest parenting programme for preschoolers with attention deficit hyperactivity disorder. Eur Child Adolesc Psychiatry 2009; 18:605–616.
94. Healey DM, Halperin JM. Enhancing neurocognitive growth with the aid of games and exercise (ENGAGE): a novel early-intervention fostering the development of preschoolers' self-control. 2012;(under review).
95. Tamm L, Nakonezny PA, Hughes CW. An open trial of a meta-cognitive executive function training for young children with ADHD. J Atten Disord 2012;(in press).
96. Halperin JM, Marks DJ, Bedard AC, et al. Training executive, attention, and motor skills: a proof-of-concept study in preschool children with ADHD. J Atten Disord 2012. doi:10.1177/1087054711435681
97. West J, Wright D, Hausken EG. Child care and early education program participation of infants, toddlers, and preschoolers. National Center for Education Statistics [serial on the Internet] 1995. http://nces.ed.gov/pubsearch/pubsinfo.asp?pubid=95824.
98. Center on the Developing Child at Harvard University. A science-based framework for Early Childhood Policy: Using evidence to improve outcomes in learning, behavior, and health for vulnerable children. 2007 [cited February 23, 2007]. http://developingchild.harvard.edu/index.php/resources/reports_and_working_papers/policy_framework/.