

# Developmental phenotypes and causal pathways in attention deficit/hyperactivity disorder: potential targets for early intervention?

Edmund J.S. Sonuga-Barke<sup>1,2</sup> and Jeffrey M. Halperin<sup>3,4</sup>

<sup>1</sup>Developmental Brain-Behaviour Laboratory, University of Southampton, UK; <sup>2</sup>Department of Experimental Clinical and Health Psychology, Ghent University, Belgium; <sup>3</sup>Department of Psychology, Queens College, City University of New York, USA; <sup>4</sup>Department of Psychiatry, Mount Sinai School of Medicine, USA

Early intervention approaches have rarely been implemented for the prevention of attention deficit/hyperactivity disorder (ADHD). In this paper we explore whether such an approach may represent an important new direction for therapeutic innovation. We propose that such an approach is most likely to be of value when grounded in and informed by developmental models of the dynamic, complex and heterogeneous nature of the condition. First, we set out a rationale for early intervention grounded in the science of ADHD viewed through developmental models. Second, we re-examine the concept of disorder-onset from the perspective of developmental trajectories and phenotypes. Third, we examine potential causal pathways to ADHD with regard to originating risk, pathophysiological mediators, environmental moderators and developmental continuities. Finally, we explore the potential value of strategies for identifying young children at risk for ADHD, and implementing interventions in ways that can target these underlying pathogenic processes. The utility of such an approach represents an important area for future research but still requires 'proof of concept'. Therefore prior to widespread clinical implementation, far greater knowledge is required of (i) developmental pathways into ADHD, (ii) the value of identifying neuropsychological mediators of these pathways, and (iii) the extent to which targeting mediating mechanisms will improve treatment outcomes for children with ADHD. **Keywords:** Attention deficit/hyperactivity disorder, preschool, early intervention, translational, development, treatment, longitudinal studies.

Attention deficit/hyperactivity disorder (ADHD) is a chronic debilitating condition associated with significant costs to patients, families and society, and burden to social and health care services (Taylor & Sonuga-Barke, 2008). Although current treatments can often be implemented effectively (Banaschewski et al., 2006), there is still considerable unmet clinical need. **Clinical benefits from pharmacological interventions often dissipate over time (Jensen et al., 1999) and long-term effects remain uncertain (Jensen et al., 2007; Molina et al., 2009).** Compliance with stimulant medication is also quite poor (Corkum, Rimer, & Schachar, 1999; Perwien, Hall, Swensen, & Swindle, 2004; Sanchez, Crismon, Barner, Bettinger, & Wilson, 2005): fewer than 10% of children with ADHD persist with long-term medication treatment (Weiss, Gadow, & Wasdell, 2006). There are also side-effects, especially affecting sleep (Graham & Coghill, 2008), appetite (Karabekiroglu, Yazgan, & Dedeoglu, 2008) and growth (Swanson et al., 2007a). To complicate matters further, parents and clinicians often have reservations about using medication to control behaviour, especially in very young children (Berger, Dor, Nevo, & Goldzweig, 2008). Available behaviour modification strategies

are more complex and time consuming to implement, and typically less efficacious for core symptoms of ADHD (Antshel & Barkley, 2008), although valuable when targeted at complications of ADHD such as oppositional behaviour (Jones, Daley, Hutchings, Bywater, & Eames, 2008). Generalisation and maintenance of effects have rarely been shown for such treatments (McGoey, Eckert, & Paul, 2002; Barkley et al., 2000). Similar to medication, gains rarely persist long after active treatment is terminated (Chronis et al., 2004; Pelham & Fabiano, 2008).

Thus there remains a need for the development of new therapeutic approaches for ADHD that can produce **generalised long-lasting change**. In this paper we examine a potential role for early intervention in therapeutic innovation (Tamm et al., 2005). Our goal is not to provide a 'prescription for early intervention' in ADHD but rather to make a case for this as a rational approach to therapeutic innovation. In the process we review and synthesise diverse literatures from both within and outside the narrowly defined ADHD domain, and then propose a general framework to guide such an enterprise as well as some practical examples of instantiation. Initially we set out the scientific and clinical case for early intervention as a rational basis for treatment

Conflict of interest statement: No conflicts declared.

© 2009 The Authors

Journal compilation © 2009 Association for Child and Adolescent Mental Health.

Published by Blackwell Publishing, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main Street, Malden, MA 02148, USA

development in ADHD. Next we introduce the concept of early developmental phenotypes. We then describe how studying developmental phenotypes and their specific causes and mediating processes can help us identify potential targets for early intervention. This builds on our taxonomy of putative developmental pathways to account for the potential heterogeneity of the condition. Finally we explore possible ways to identify early risk for later ADHD and assess the value of different approaches to early intervention.

### **A: The early intervention proposition in ADHD – a translational framework for conceptualising therapeutic innovation?**

In this paper we explore the hypothesis that early intervention for ADHD which **targets underlying causal pathways** (Nigg, 2006) **can reduce the likelihood of disorder emerging, limit its persistence, and cut its associated long-term burden** (Tamm et al., 2005). We propose that: (i) rational treatment development involves identifying/targeting the causes of a condition; (ii) causes of ADHD should be cast, not as **static/fixed neuro-psycho-biologic deficits**, but rather in terms of underlying developmental processes (Taylor, 1999; Schmidt & Peterman, 2008); and (iii) targeting these processes early can bring about fundamental alterations in the pathogenesis of ADHD, and thus prevent the emergence, or moderate the course of, the disorder. Based on this logic early intervention for ADHD should, in principle, have preventative potential. Below we set out the logic behind this vision in more detail and highlight many of the very considerable barriers to bringing it to fruition.

#### *I: Toward therapeutic innovation in ADHD: Is there a need to embrace translational science?*

Therapeutic innovation can emerge from knowledge of the causes of the disorder which can be used to target treatments. The search for these targets is one element of translational science (Curry, 2008). The development of existing therapeutic approaches to ADHD has rarely been directly informed by knowledge of its psychopathophysiology (Beauchaine, Neuhaus, Brenner, & Gatke-Kopp, 2008). Rather, new treatments have emerged as a result of clinical insight and/or trial and error, or have been borrowed from other therapeutic domains.

As our knowledge-base relating to the causes of ADHD grows (Nigg, 2006) it becomes more feasible to ground the search for new treatments in translational science than it was in the past (Bellgrove, O'Connell, & Vance, 2008). Nevertheless, there have been few attempts to systematically implement such an approach in relation to ADHD (see Kerns, Eso, & Thomson, 1999; Klingberg et al., 2005; Shalev, Tsal,

& Mevorach, 2007). Innovations in drug treatments have been based primarily on an improved understanding of the psychopharmacology of existing treatments (e.g., the development of extended release formulations of methylphenidate – Volkow & Swanson, 2003; Swanson et al., 2003). In general, non-pharmacological approaches, typically adapted from generic models of intervention 'borrowed' from other clinical domains (Sonuga-Barke, Thompson, Abikoff, Klein, & Brotman, 2006), have rarely been developed with the goal of treating the 'causes' of ADHD. Relatedly, innovative use of attention training (Sohlberg & Mateer, 2001) and neurofeedback (Heinrich, Gevensleben, & Strehl, 2007) build on generic accounts of attention rather than on ADHD models (Lubar, 1997). Where ADHD models have guided therapeutic innovation, (e.g., working memory training; Klingberg et al., 2005) efficacy remains to be clearly established.

The failure of basic research into the underpinnings of ADHD to influence treatment development could have two causes. First, we may not have adequate models of the causes of ADHD. A second possibility is that though such models exist they cannot be implemented.

#### *II: The bio-medical model is a barrier to translational science in ADHD*

More than three decades of intense research into 'the causes' of ADHD have yielded a vast database relating ADHD to a range of genetic and environmental risk factors (Taylor & Sonuga-Barke, 2008) and neuro-psychological and -biological alterations (Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008). Nevertheless, a complete understanding of the condition remains a distant goal.

Data suggest that: (i) ADHD has a complex causal structure with different facets interacting in additive, synergistic and possibly antagonistic ways (Nigg, 2006); (ii) initiating neurobiological causes are remote from the disorder and operate as non-deterministic risk factors that are mediated and moderated by multiple factors (Taylor, 1999); (iii) effects of any one factor or set of related/interacting factors are likely to be small and operate in different ways in different children (Taylor & Sonuga-Barke, 2008; Swanson et al., 2007b). Such aetiological heterogeneity is increasingly apparent in the literature and suggests that different sub-groups of patients may 'follow' different pathways (Nigg, 2006). It is also evident in everyday clinical reality (Taylor et al., 2004) where treatments should be tailored to meet specific needs of individual patients (Leslie, Stallone, Weckerly, McDaniel, & Monn, 2006); (iv) ADHD is a lifespan developmental disorder; its roots can be traced back to the early stages of life and its clinical manifestations often persist into adolescence and adulthood (Vaughan, Wetzel, & Kratochvil, 2008; Schmidt & Peterman, 2008).

The challenges presented by this mix of factors is exacerbated by the fact that the science of ADHD remains (at least implicitly) wedded to the traditional **bio-medical model**, which does not provide a framework for modelling complex and developing systems (Sonuga-Barke, 1998). The search for core fixed deficits, which this model promotes, is deficient as a basis for ADHD research (Sonuga-Barke & Castellanos, 2005). **It cannot account for the way causal processes seem to interact in dynamic and non-linear ways producing diverse patterns of persistence and remission found in ADHD** (Halperin, Trampush, Miller, Marks, & Newcorn, 2008) and leading to the emergence of comorbidities (Mannuzza, Klein, Abikoff, & Moulton, 2004). **It takes us no further in understanding how different groups of individuals can display markedly different patterns of brain alterations and neurocognitive deficits and yet all still have ADHD** (Sonuga-Barke, 2005). Singh (2008) recently identified the bio-psycho-social model, in which ADHD is seen as caused by the interplay of genetic and environmental influences that occurs over development in underlying neurobiologic systems, as potentially the most useful framework for understanding ADHD.

### III: Modelling complexity and heterogeneity in ADHD by studying developmental processes

The bio-psycho-social model (Engel, 1977) provides a conceptual basis for research into the causes of psychiatric conditions such as ADHD (Fava & Sonino, 2008). It views mental health problems as emerging out of developmental pathways from risk to disorder, with the course determined by the interplay between genetic and environmental risk factors manifest in alterations to underlying neurobiological processes. Crucially it embodies a dynamic, rather than a static/fixed, conception of cause. From this perspective, ADHD cannot be understood simply in terms of structural and functional brain deficits (or their specific aetiological precursors). Rather it views ADHD in terms of the *processes of alteration*, and their associated determinants, that affect brain structure and function during development and that may be manifest as such deficits.

This developmental psychopathology perspective, well established for other conditions (Cicchetti & Toth, 2009), was first applied systematically to ADHD by Taylor (1999) and is increasingly embraced (Halperin & Schulz, 2006; Kieling, Goncalves, Tanock, & Castellanos, 2008; Sagvolden, Johansen, Aase, & Russell, 2005; Nigg, 2006; Sonuga-Barke, 2003, 2005; Swanson et al., 2007b). A recent synthesis of elements from these accounts (Sonuga-Barke, 2009) develops several important themes. First, the existence of a continuum of neurobiological risk in the population, neither exclusively genetic nor environmental in origin, but rather the product of an interplay between numerous individual risk

factors (Thapar, Langley, Asherson, & Gill, 2007). Second, psychopathophysiological mechanisms altered in ADHD mediate the developmental risk-disorder pathway (Sonuga-Barke, 2005). Third, the conditional nature of effects are complicated by both equi-finality (different originating risks leading to the same clinical outcome) and multi-finality (the same pattern of risk factors leading to different outcomes; Cicchetti & Blender, 2006). That is, outcomes are determined by the extent to which originating risk is moderated by later factors to alter the trajectory of development. Moderation may be protective (i.e., resilience; Rutter et al., 2007) – where for instance an at-risk child has a good outcome because of some secondary endogenous or exogenous resilience mechanism (e.g., personality, intelligence, supportive/constructive parenting). It could also have a negative character whereby children with few apparent risk factors go on to develop ADHD. Understanding these moderating influences is assumed to be vital to predicting the emergence of disorder, its persistence and offset, and the development of other outcomes associated with the disorder. Developmental heterogeneity is at the heart of this conception, with the goal of identifying the diversity of causal processes paramount.

### IV: Shifting the focus to early intervention and prevention

A developmental psychopathology perspective **shifts the search for treatment targets from fixed core deficits to multiple developmental processes that mediate the disorder**. This developmental conception of ‘cause’ distinguishes causal processes from developmental outcomes (i.e., the disorder), and gives particular priority to precursor states and processes as intervention targets. As such, **intervening early should be more successful than waiting until outcomes are established and then trying to reverse the pathogenic process**.

Nevertheless, despite the growing adoption of a developmental perspective on ADHD and the successful application of the principles of prevention science to other disorder (see Rapee, 2008 for a discussion), early intervention has been less frequently used for ADHD than other disorders (Shaw, Dishion, Supplee, Gardner, & Arnds, 2006). This reluctance may to a certain extent be shaped by a **deterministic notion of cause** that leads to the idea that ADHD is not amenable to the moderating effects of environmental and/or biological manipulations. Recent evidence regarding brain plasticity in developmental disorders may be seen to contradict this position (Dawson, 2008), and the conditional nature of risk-disorder pathways should temper such deterministic pessimism.

In keeping with this we postulate that early intervention that targets these processes could alter developmental trajectories and improve outcomes

over the long term (Miklowitz & Cicchetti, 2006). However, the veracity of this hypothesis remains an open empirical question; there is little or no evidence to date to support it. It is possible that early intervention may in the end not be an effective strategy in the case of ADHD, in terms of its ability to fundamentally redirect developmental pathways, and we may be over-estimating the degree to which developmental pathways can be actively mediated and moderated. Environmental correlates and/or neuropsychological alterations may simply be passive markers of pathways rather than actively determining their trajectory. We may also be overestimating the extent to which environmental experiences influence underlying neurobiological processes in ADHD, despite evidence for neural plasticity in the developing brain in response to environmental manipulations more generally (Neville, 2006; Luciana, 2003; but see Rapoport & Gogtay, 2008). Indeed, in general the impact of environmental factors on neurobiological outcomes is thought to be constrained by the influence of stabilising genetic processes such as canalisation (Hernandez-Lloreda & Colmenares, 2005). Even assuming that risk-disorder pathways in ADHD are amenable to influence, what is the case for intervening early in development? First, **brain plasticity appears greatest during early phases of development and therefore more susceptible to the influence of environmental experience** (for good or for bad; Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005; Vuksic, Rados, & Kostovic, 2008; Bischof, 2007) (but see canalisation above). Second, **early intervention can occur before strong behavioural habits are formed in the child exacerbating patterns of impairment**. Third, **early intervention may increase receptiveness of parents and families before negative attitudes that often accompany ADHD have hardened, making family-based interventions difficult**. Fourth, it can operate before the disorder has become complicated by the experience of school failure and associated low self-esteem.

A key issue when implementing an early or preventive intervention for ADHD is which children get targeted. If the threshold is set too high, many 'at-risk' children will be missed. If set too low, many children will receive unnecessary treatment. Balancing the relative benefits and costs of missing some 'at-risk' children versus unnecessarily identifying and treating children rests largely upon the 'invasiveness' of the intervention, its cost, and its potential delivery system. If the intervention is 'invasive' (e.g., medication) or extremely costly (e.g., intensive individualised treatment), only those with clear evidence of elevated risk will likely participate, leaving many children who go on to develop ADHD without early intervention. Notwithstanding these factors, the early intervention approach to ADHD treatment still requires proof of concept; the hypothesis remains largely untested. Our expecta-

tion is that prevention approaches used for related disorders such as conduct disorder are likely to be unsuccessful because they do not target the underlying causal processes of ADHD. We believe that for ADHD, the identification of moderators of neurobiological processes may be an essential precursor to early intervention.

## **B: Considerations regarding the concept of disorder-onset from a developmental perspective**

From an early intervention perspective, a key outcome of interest is the *onset* of the disorder. However, if we define disorder-onset simply as the transition from no ADHD to ADHD on the assumption that there are clear boundaries, we come up against a number of problems.

### *I: Despite the practical value of categorical diagnosis, ADHD is more accurately characterised as a dimension*

A categorical diagnosis of ADHD with clear boundaries between the presence and absence of the syndrome facilitates clinical decision making (Sonuga-Barke, 1998). However, clinical pragmatics and scientific reality diverge because an underlying causal discontinuity between normality and the disorder state is very rare: mental disorder syndromes are seldom present in an all-or-nothing way (see Helzer, Kraemer, & Krueger, 2006). From a bio-psycho-social perspective, where multiple risk factors operate together to create a spectrum of disease liability, syndrome boundaries represent differences in degree rather than kind. While there are good conceptual reasons to think of ADHD in this way, there is also empirical evidence to back up this claim (Polderman et al., 2007; Lahey et al., 2008).

Taxonomic studies of ADHD provide unanimous support for the notion of ADHD as a pole of a continuum distributed throughout the population, rather than a qualitatively discrete category (Haslam et al., 2006; Frazier, Youngstrom, & Naugle, 2007). Furthermore, there is no difference in patterns of heritability in the extreme of the distribution (Gjone, Stevenson, & Sundet, 1996).

The developmental corollary of the continuum conceptualisation of ADHD is that syndrome onset represents a transition of degree rather than of kind. As with diagnostic thresholds, these developmental thresholds are inevitably arbitrary to some degree and rest on general cultural norms about behaviour and development (Timimi & Taylor, 2004; Leung et al., 1996) filtered through the expectations of individuals applying these standards (e.g., parents, patients, teachers, clinicians; Maniadaki, Sonuga-Barke, Kakouros, & Karaba, 2007; Sonuga-Barke, Minocha, Taylor, & Sandberg, 1993).

### II: ADHD expression fluctuates during development

There is also within-individual variation regarding the extent to which diagnostic criteria for the disorder are fulfilled at any given time (von Stauffenberg & Campbell, 2007). The categorical approach is deficient in capturing this dynamic nature of symptom expression (Lahey, Pelham, Loney, Lee, & Willcutt, 2005). Symptom levels and patterns fluctuate from day to day and year to year. Individuals around the diagnostic boundaries may meet criteria at one time but not at a second time, while at a third time they may once again fulfil criteria. For individuals at the diagnostic margins this presents a serious challenge to current diagnostic approaches – should we say they have a disorder at time 1, not at time 2 and then again at time 3? Further, it is almost impossible to determine whether fluctuations represent real changes in behaviour or varying standards imposed by those evaluating the child's behaviour (e.g., different teachers).

We suggest redefining and broadening the concept of disorder-onset by moving from a static clinical phenotype to a developmental one incorporating the notion of syndrome trajectory (Sonuga-Barke, 2009). Through this we attempt to capture 'growth' by depicting patterns of symptom increase, persistence, diminution and more general fluctuation across time. This will allow us to draw potentially important distinctions between 'early emerging' and 'late emerging' and 'persisting' and 'non-persisting' variations (Sonuga-Barke, Auerbach, Campbell, Daley, & Thompson, 2005). The degree to which diagnostic criteria are met at any one time will be placed in the context of a developmental trajectory, therefore providing the phenotypic anchor to characterise causal processes.

### III: The 'onset' of the syndrome may not correspond to the 'onset' of impairment

The third complication in defining disorder-onset as the developmental outcome of interest relates to the need for the presence of impairment (Healey, Miller, Castelli, Marks, & Halperin, 2008). It is unclear whether to focus on: (i) the disorder per se (i.e., symptoms plus impairment); (ii) impairment (even with insufficient symptoms); or (iii) the syndrome (i.e., a constellation of symptoms even if there is insufficient impairment for the diagnosis). From a scientific perspective the syndrome is probably most important in that it is the most direct and specific outcome of the causal processes. However, from a 'clinical' point of view, it is impairment that justifies intervention. Given our focus on early intervention, it is important that we understand the factors that determine the onset of impairment and their relationship to the underlying causes of the syndrome. However, the concept of impairment is in many ways more problematic than the concept of syndrome

(Gathje, Lewandowski, & Gordon, 2008; Coghill, Danckaerts, Sonuga-Barke, Sergeant, & European Guidelines Group, 2009). Impairment is also a continuum and there are difficulties inherent in defining its onset in categorical terms. Furthermore, the relationship between symptoms and impairment depends to a significant degree on the general cultural definition of what constitutes competence. Where expectations of performance/competence are highest impairment thresholds will be lowest. Our approach is to characterise impairment as a developmental complication of the syndrome, and then identify the factors *that create a context for success or failure in everyday activities*. In this sense, we can talk about a particular developmental phenotype with co-occurring impairment.

Box 1 outlines what we hypothesise to be key elements to conceptualising ADHD from a developmental perspective as described above. It is from these central tenets that our proposal for early intervention emerges.

## C: ADHD developmental phenotypes and early causal pathways

### I: Early-emerging developmental phenotypes of ADHD

There is an increased tendency for ADHD to be identified and diagnosed during the preschool years (Posner et al., 2007; Egger, Kondo, & Angold, 2006; Healey et al., 2008), although the vast majority of cases are identified in middle childhood. The existence of early- and later-emerging forms of ADHD highlights potential heterogeneity in ADHD developmental phenotypes. Furthermore, it raises questions about the nature and significance of early-emerging symptoms and related impairment and the extent to which these are equivalent to later-emerging forms. Are these early-emerging symptoms precursors of long-term difficulty, either through their persistence (homotypic continuity; Lahey, Pelham, Loney, Lee, and Willcutt, 2005) or their role as a precursor for other problems (i.e., heterotypic continuity; Lee, Lahey, Owens, &

#### Box 1: ADHD: A developmental Conceptualization

- A developmental conceptualisation posits-
  - ADHD as emerging from multiple underlying developmental processes; it is not a fixed/static disorder;
  - originating risk for ADHD as potentially being moderated by later factors to alter the trajectory during development;
  - ADHD as the product of a dynamic interplay between numerous individual risk factors:
- Aetiologically, physiologically and phenomenologically heterogeneous;
  - onset of ADHD as a transition of degree rather than of kind.
  - ADHD as having different developmental phenotypes (i.e., early v late emerging; persistent v fluctuating).

Hinshaw, 2008)? From a clinical perspective it is important to avoid over-pathologising early indicators of ADHD if it can be shown that they resolve with time (Smith & Corkum, 2007). On the other hand, we must not underestimate the clinical significance of early-appearing signs of elevated, but sub-diagnostic or non-impairing symptoms, which may represent early indicators of a full-blown disorder (Sonuga-Barke, Stevenson, Thompson, & Viney, 1997).

Early- and late-emerging forms of ADHD share many features. However, some researchers have adopted a more generic 'hard to manage' classification, collapsing ADHD and conduct problems in relation to preschool expressions (e.g., Campbell, Pierce, March, Ewing, & Szumowski, 1994). The evidence for such a combined category is no stronger in the early years than it is in the school-age years, as symptoms of ADHD (inattention, overactivity and impulsiveness) cluster together and are distinctive from, though overlapping with, symptoms of conduct problems (Fantuzzo et al., 2001; Gadow, Nolan, Sprafkin, & Schwartz, 2002; Sonuga-Barke et al., 1997; Pavuluri & Luk, 1998; Egger et al., 2006). Furthermore, patterns of association between these two domains seem similar in the preschool and the school-age periods (Harvey, Friedman-Weieneth, Goldstein, & Sherman, 2007). The distinction between hyperactive-impulsive and inattentive symptom domains is fairly robust in the preschool period (Hardy et al., 2007), with some suggestion that inattention symptoms are the better predictor of later psychopathology (Smidts & Oosterlaan, 2007). Three domains of impairment seem especially characteristic of early-emerging ADHD: developmental delay, deficient pre-academic skills, poor social skills and problems establishing and maintaining close relationships (Kern et al., 2007).

Longitudinal studies following up children from the preschool period suggest only moderate continuity, with early-emerging ADHD symptoms persisting in only a proportion of cases (Lavigne et al., 1998; Mathiesen & Sanson, 2000). Persistence of problems in clinically referred samples is common, but most children identified as having a disorder in preschool have improved considerably by school entry (Campbell et al., 1994; Lavigne et al., 1998; Marakovitz & Campbell, 1998). A more general pattern of problems may persist even in those children for whom ADHD itself diminishes over time (Lee et al., 2008). There is both moderate homotypic and heterotypic continuity. The possibility that early ADHD represents a risk for later conduct problems via parental responses to challenging behaviour and their potential to generate coercive cycles of parent-child interaction need also be considered (Chronis et al., 2007). Interestingly, environmental factors appear to operate differently for ADHD symptoms and aggression (Jester et al., 2005).

Early indicators of later ADHD, rooted in subtle variations in infant characteristics, include **neuro-**

**developmental immaturity, increased activity level, emotional dysregulation, over-responsivity to environmental stimulation, and lower cognitive functioning** (Auerbach et al., 2005; Carlson, Jacobvitz, & Sroufe, 1995; Degangi, Porges, Sickel, & Greenspan, 1993; Ebstein et al., 1998; Jacobvitz, & Sroufe, 1987; Morrell & Murray, 2003; Rende, 1993; Wolke, Rizzo, & Woods, 2002; Sanson, Smart, Prior, & Oberkland, 1993; Esser, Fischer, Wyschkon, Laucht, & Schmidt, 2007a). However, once again the predictive power of these markers is generally weak. As children enter the preschool period ADHD severity is a significant indicator of the early emergence and persistence of ADHD (Wahlstedt, Thorell, & Bohlin, 2008; Leblanc et al., 2008), which in some children may reflect a putative temperamental predisposition to problems of affect and cognitive regulation (Arseneault et al., 2003; Caspi, Henry, McGee, Moffitt, & Silva, 1995; Moffitt, 1993). The presence of oppositional and defiant behaviour is a predictor of the early emergence of impairment (Campbell et al., 1994; DuPaul, McGoey, Eckert, & VanBrakle, 2001; Keenan & Wakschlag, 2000; Speltz, McClellan, DeKlyen, & Jones, 1999). Early referral is most strongly predicted by defiance, tantrums, and aggression (Eyberg, Boggs, & Algina, 1995; Lavigne et al., 1998). Underlying neuropsychological impairment appears to be associated with continuity in ADHD rather than conduct problems (Brocki, Nyberg, Thorell, & Bohlin, 2007). Although the association between these two components is well established, much more research is required to tease apart the nature of their causal relationship (Jester et al., 2005).

Sonuga-Barke et al. (2005) suggested an illustrative developmental taxonomy as an aide to thinking about early developmental heterogeneity in ADHD. Four phenotypes were postulated. In type I (*Emergent oppositionality*) early sub-clinical preschool ADHD, indicating a relatively low level of risk in and of itself, represents a risk factor for later oppositional problems with this link being moderated by the presence of coercive and negative parenting. In type II (*Late onset ADHD*), varying levels of early emerging ADHD symptoms remain sub-clinical during the early years but emerge in a clinically significant form either because the levels of symptoms are moderated upwards over time by environmental or genetic factors (Jester et al., 2005; Chronis et al., 2007), or because a change in setting creates a context for impairment not present earlier (e.g., as a child's regulatory abilities are challenged by the demands of the classroom). Type III (*Preschool limited ADHD*) was hypothesised to be marked by moderate to high levels of early-emerging ADHD symptoms and associated impairment with the pathways to long-term disorder being interrupted by protective features in the child's social environment at home and/or school (such as proactive, firm, limit-setting at home, an appropriately structured classroom). Here the downward spiral into poor outcome may be

avoided. Type IV (*Early-onset chronic ADHD*) was hypothesised to be marked by severe preschool ADHD and perhaps a temperamentally-based difficulty in mood regulation marked by temper tantrums; problems interact to lead to early-onset, chronic combined ADHD and oppositionality. A persistence of problem behaviours in these two domains is accompanied by increasing cycles of coercion within the family and in turn the exacerbation of the problems themselves. This framework, although only suggestive, may provide a basis for exploring the configurations of associations and characteristics of the different patterns of emergence and persistence in ADHD developmental trajectories. The issue of whether such multiple developmental phenotypes should be regarded as discrete in any sense raises issues similar to those raised by the category vs. continuum debate more generally in relation to ADHD. In this sense the boundaries between early- and late-emerging symptoms and persisting and desisting phenotypes are likely to be no less fuzzy than those between disorder and no disorder, although there has been no direct empirical test of this as yet. To the extent that this is true, defining the specific boundaries between different developmental phenotypes within the broader ADHD domain will be no less arbitrary than for the ADHD diagnosis itself. However, drawing distinctions between different developmental phenotypes provides us with a potentially useful scientific and clinical heuristic. It is in this spirit that we promote a developmental typology to express ADHD heterogeneity.

## II: Putative causal underpinnings of early developmental phenotypes

There is currently little data of direct relevance to the issue of early, as opposed to late, emergence of ADHD; however, we will attempt to draw out the possible implications of data collected with older children for our understanding of early developmental phenotypes.

*Originating risk.* Identifying early risk factors for ADHD is complicated by the fact that ADHD, like other disorders, is probably the result of the interplay between genes and environment (e.g., gene-environment correlation and interaction), with effects operating in different ways in different individuals (i.e., aetiological heterogeneity). Although, highly heritable (Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2003; Thapar, Harrington, Ross, & McGuffin, 2000), ADHD is not a genetic disorder in a straightforward sense (Thapar, O'Donovan, & Owen, 2005; Asherson, Kuntsi, & Taylor, 2005). Evidence from candidate gene linkage and genome-wide association studies is consistent with the notion that many genes of small effect are implicated in ADHD (Faraone et al., 2005; Thapar et al., 2005; Arcos-Burgos et al., 2004; Hebebrand

et al., 2006; Lasky-Su et al., 2008). Pre- and perinatal environmental factors also appear to play an important role in the risk equation (Taylor & Rogers, 2005), with more or less compelling evidence relating to maternal smoking (Thapar et al., 2003), alcohol consumption (Vaurio, Riley, & Mattson, 2008), use of drugs of abuse (Linares et al., 2006), deficient diet (Gale et al., 2008) and exposure to stress during pregnancy (Rodriguez & Bohlin, 2005; O'Connor, Heron, Golding, & Glover, 2003). Low birth weight and perinatal complications may also be risk markers (Bhutta, Cleves, Casey, Craddock, & Anand, 2002; Ben Amor et al., 2005). Effects of individual factors are small and inconsistent. Mechanisms proposed to account for these effects include biological programming in response to the adverse uterine environment (Swanson et al., 2007b), subtle brain damage due to factors such as hypoxia (Halperin & Schulz, 2006; Lou, 1996) and the environmental moderation of genes' effects (Mill & Petronis, 2008). Exposure to prenatal risk exposure appears to be moderated by polymorphisms in dopamine genes (e.g., Kahn, Khoury, Nichols, & Lanphear, 2003; Brookes et al., 2006; Becker, El-Faddagh, Schmidt, Esser, & Laucht, 2008; Todd & Neuman, 2007). Gene-environment effects may not be limited to the prenatal physical environment, with recent evidence of risk genotypes (e.g., 5-HTT-LPR) interacting with social adversity to increase ADHD risk (Retz et al., 2008; Reif et al., 2007; Sonuga-Barke et al., 2008c).

**Environmental exposures may moderate gene expression – i.e., 'switch on' or 'switch off' a susceptibility gene (Mill & Petronis, 2008) – or a gene may alter risk-exposure patterns, or increase resilience to adverse events (Belsky, Fearon, & Bell, 2007).** Assessing the significance of genetic and environmental factors and their interaction is complicated by the inevitable co-variation of risks (gene-environment correlation) which have proved extremely challenging to tease apart (Taylor & Rogers, 2005)

*Psychopathophysiological mediators.* ADHD children's brains are smaller on average than their peers' (Castellanos et al., 2002), with differences emerging in the cerebellum, as well as several cortical and subcortical regions (Valera, Faraone, Murray, & Seidman, 2007; Ellison-Wright, Ellison-Wright, & Bullmore, 2008). Delays in maturation are apparent throughout the cortex during the school years (Shaw et al., 2006, 2007), and adults with ADHD appear to have differential cortical thinning in prefrontal regions (Makris et al., 2007). ADHD is also associated with altered catecholamine functioning (Oades et al., 2005; Pliszka, 2005; but see Gonon, 2009), with PET studies suggesting abnormal dopamine receptor functioning, although findings have not been consistent (Spencer et al., 2007; Volkow et al., 2007a, 2007b). Crucially, neural networks which underpin higher cognitive processes are modulated by DA and

NE branches, and medications which act on catecholamines improve functioning across several neuropsychological domains deficient in ADHD (e.g., Turner, Blackwell, Dowson, McLean, & Sahakian, 2005; Bush et al., 2008). The catecholamine hypothesis is further supported by genetic studies (Faraone et al., 2005) and by knock-out and lesion animal models (Arnsten & Li, 2005; Madras, Miller, & Fischman, 2005). Although this pattern of circumstantial evidence has convinced many of the causal role of catecholamine dysregulation, and dopamine deficits in particular (Swanson et al., 2007b), the possibility that neurochemical effects could be the marker of some more fundamental neurobiological effect needs to be born in mind (Madras, Miller, & Fischman, 2002), as must the complex way in which neurotransmitters interact (Olijslagers, Werkman, McCreary, Kruse, & Wadman, 2006).

Consistent with evidence of alterations to brain regions implicated in cognitive control, ADHD is often seen as an executive function disorder. It is associated with a range of neuropsychological deficits in EF domains (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005); and deficits linked to pre-frontal hypo-activation in the frontal cortex (Rubia et al., 1999; Durston et al., 2003; Fallgatter et al., 2005) and the neo-striatum (i.e., caudate and putamen; Rubia et al., 1999; Vaidya, Bunge, Dudukovic, & Zalecki, 2005). Reduced functional connectivity in key brain regions associated with EF has been observed (Castellanos et al., 2008). Understanding executive deficits in ADHD is complicated by the facts that: (i) effect sizes are moderate at best (Nigg et al., 2005); (ii) children with disorders other than ADHD show executive dysfunctions (Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2004); (iii) adequate performance on most executive function tasks are dependent upon more basic cognitive processes that have been shown to be deficient in ADHD (e.g., visual memory – Rhodes, Coghill, & Matthews, 2004; timing – Smith, Taylor, Rogers, Newman, & Rubia, 2002; basic attentional mechanisms – Booth, Carlson, & Tucker, 2007; motor coordination – Carte, Nigg, & Hinshaw, 1996).

ADHD performance seems also highly sensitive to changes in motivational context and the state of the individual (see below; Sergeant, 2005; Luman, Oosterlaan, & Sergeant, 2005; Sonuga-Barke, Wiersma, van der Meere, & Roeyers, in press). ADHD children show altered processing of motivational stimuli (e.g., rewards and punishments; Luman et al., 2005), especially when delayed (e.g., Marco et al., 2009), an effect explained in terms of altered reward signalling (Sagvolden et al., 2005; Tripp & Wickens, 2008) and/or an aversion to delay (Sonuga-Barke et al., 2008a). The brain circuits implicated here, although functionally and structurally distinct from executive circuits, are heavily modulated by dopamine and there is evidence for altered brain activations to rewards in ADHD (Scheres et al., 2006;

Ströhle et al., 2008; Plichta et al., 2009). ADHD patients may also suffer from state regulation deficits (Sergeant, 2005). ADHD appears psychopathophysiologically as well as aetiologically heterogeneous.

*Moderating environmental factors.* Central to our case for the power of early intervention in ADHD is that causal pathways are amenable to environmental manipulations. Evidence for this comes from a number of sources. Early institutional exposure (Rutter et al., 2007) is associated with increased rates of ADHD (Stevens et al., 2008; Sonuga-Barke & Rubia, 2008). Evidence also suggests that the family environment might determine the course and persistence of the condition. ADHD appears to elicit negative, intrusive and harsh parenting (Seipp & Johnston, 2005), while inappropriate parenting can exacerbate ADHD itself (e.g. Morrell & Murray, 2003). Belsky et al. (2007) found that reduced maternal sensitivity was associated with poorer attention later in childhood. Inappropriate parenting towards ADHD children in middle childhood is associated with the onset of comorbid conduct disorder (Taylor, Chadwick, Heptinstall, & Danckaerts, 1996) and depression (Ostrander & Herman, 2006).

The physical/chemical postnatal environment may also be important. Diet may play a more significant role than once thought (McCann et al., 2007). Evidence for a role for malnutrition and dietary deficiency is limited (Sonuga-Barke et al., 2008b; Konofal, Lecendreux, Arnulf, & Mouren, 2004), but fatty acid intake may play a role (Richardson & Montgomery, 2005). Low-level exposure to lead (Nigg et al., 2008) and to toxins, such as those contained in insecticides, has also been noted as possibly important (Mariussen & Fonnum, 2006). Early exposure to psychostimulants might also be associated with long-term adaptations and alterations to the brain (Grund, Lehman, Bock, Rothenberger, & Teuchert-Noodt, 2006), some of which may have therapeutic potential (Dommett, Henderson, Westewell, & Greenfield, 2008).

### *III: Developmental similarities and continuities in psychopathophysiology*

Early intervention targets are only of value if we can be confident of the similarity between, and the continuity of, causal factors across development. Given the paucity of relevant studies in early development we have only a fragmented picture of the neuropsychology and -biology associated with early developmental phenotypes. In general the neuropsychological data support the existence of (i) executive deficits and related cognitive problems (Seidman, 2006), and (ii) motivational and (iii) energetic abnormalities across different periods of the lifespan (Marco et al., 2009; Wiersma, van der Meere, Antrop, & Roeyers, 2006). Evidence in relation to these types of deficits in early-onset forms

comes from a number of sources (Thorell, 2007; Sonuga-Barke et al., 2003b; Marks et al., 2005; Berwid et al., 2005), and these could be investigated further as early treatment targets. However, owing to a dearth of neuropsychological longitudinal studies we know little regarding continuities between early and later deficits. Halperin et al. (2008) found that continuity between childhood and adolescent ADHD was associated with the presence of underlying deficits in cognitive efficiency and regulation combined with the failure to develop effective higher-order control. This finding is consistent with the notion that recovery from ADHD is associated with improvements in executive control functions (Halperin & Schulz, 2006). However, the direction of causation remains unclear – do improved executive functions yield a reduction in ADHD severity as posited by Halperin and Schulz (2006) or are executive impairments epiphenomenal and remit in concert with ADHD symptoms over development (Carr, Nigg, & Henderson, 2006)? Preliminary functional magnetic resonance imaging (fMRI) findings indicate that prefrontal activation in response to inhibition in adolescents with childhood ADHD corresponds to the persistence of symptoms (Schulz, Newcorn, Fan, Tang, & Halperin, 2005a; Schulz et al., 2005b). In studies of the transition from early to late manifestations of the disorder, early-appearing cognitive deficits predict disorder persistence (Wahlstedt et al., 2008; Von Stauffenberg and Campbell, 2007). There have been no studies of developmental continuity in motivational or energetic processes over this period to our knowledge.

#### *IV: Developmental heterogeneity: Do multiple causal pathways underpin the diversity of developmental phenotypes?*

Evidence for heterogeneity in the psychopathophysiology of ADHD, as well as in developmental phenotypes and clinical presentations, is growing. Consistent with this, pathophysiological subtypes – either at the level of etiological factors (Swanson et al., 2007b) or underlying neuropsychology (Sonuga-Barke, 2005; Nigg et al., 2005) – have been proposed. Sonuga-Barke et al. (2003a) studied executive deficits and motivational alterations (i.e., delay aversion) in a group of preschool children. Some children had executive dysfunction but no delay aversion while others had delay aversion but no executive dysfunction. Thorell (2007) also found that delay aversion and inhibitory control were distinctive components in a preschool sample and had different developmental outcomes. This, together with similar data from samples of older children (Solanto et al., 2001; Toplak, Jain, & Tannock, 2005) and animal models (Van den Bergh et al., 2006), raises the question of whether there are delay-averse and executive dysfunction subtypes of ADHD (Sonuga-Barke et al., 2008a).

These distinctions in individuals *suggest* differential development pathways – perhaps each with its own originating causes, mediating mechanisms and environmental moderators and perhaps each marked by a different developmental phenotype (pattern of emergence, persistence and outcome). However, testing whether such pathways are distinctive in terms of either disorder expression or underlying causes requires a new perspective on ADHD and a new programme of research. Crucially, we know almost nothing about the specificity of the relationship between different potential etiological factors, pathophysiological processes and phenotypic outcomes (but see Thorell, 2007). Further, cognitive and motivational factors inevitably interact throughout development (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006), a fact that clearly complicates the task of identifying markers of different cognitive and motivational pathways.

Heterogeneity in developmental pathways has critical implications for early intervention strategies. First, no one treatment target is likely to be relevant for every individual and different treatments addressing different deficits are likely to be differentially effective. Second, and following on from this, effective early intervention may rely on identifying which treatment targets and therefore which treatments are most relevant for a particular child.

Box 2 summarises our hypotheses linking causal pathways, developmental phenotypes and the belief that these factors are susceptible to environmental influences. Together these form the rationale for the putative affects of early intervention across the lifespan.

#### **D: Reflections on early identification and intervention as a basis for therapeutic innovation**

Above we have set out a rationale for the hypothesis that early intervention for ADHD can be effective if it

##### **Box 2:** Casual Pathways, Developmental Phenotypes, and Early intervention for ADHD

- The rationale for early intervention is that–
  - early developmental phenotypes of ADHD can be identified;
  - phenotypes evolve during development;
  - environmental variations have the potential to influence brain and behavioral development and phenotypic expression so that casual pathways to ADHD associated with phenotypic expression are amenable to environmental manipulations;
- Early Intervention that targets underlying casual pathways need to be developed to test if they can–
  - reduce the likelihood of disorder emerging;
  - alter developmental trajectories;
  - limit severity and/or persistence across the lifespan;
  - diminish long-term burden associated with ADHD.

targets early causal pathways to alter the underlying pathophysiology of the disorder and produce persistent and generalised change (cf. Dawson, 2008). To test this hypothesis we need first to be able to differentiate those youngsters who require intervention from those that don't, to carry out assessments to match children with the right intervention (given the range of developmental phenotypes and pathways), and then to develop interventions that can successfully target the underlying causes of the emerging disorder. Throughout this paper we have highlighted the lack of directly relevant empirical evidence and the need for additional research with regard to this approach; the early intervention approach for ADHD still requires proof of concept. The empirical study of early assessment and intervention in ADHD is therefore still in its infancy (cf. Kern et al., 2007). Early intervention studies have adopted standard pharmacological (Greenhill, Posner, Vaughan, & Kratochvil, 2008) and/or generic family-based models (Jones et al., 2008). These approaches have produced clinical improvements (Ghuman, Arnold, & Anthony, 2008), but the extent to which they 'correct' negative developmental trajectories, the gold-standard test of an effective early intervention strategy, is currently not known. Further, there have been few attempts to develop methods for identifying 'children at risk for ADHD' and no attempt to identify different developmental phenotypes. There has been little or no systematic assessment of feasibility, effectiveness or cost-effectiveness of broad-based early intervention strategies as has occurred for other conditions (Gill, Hyde, Shaw, Dishion, & Wilson, 2008). In this section we are therefore necessarily limited to reflecting on the *principles* that should govern early identification and intervention approaches in ADHD, while looking at how these principles can be put into *practice* more effectively.

### *I: Can we identify children who might benefit from early intervention?*

While we have data on early risk indicators, especially for persistence of early established disorder (Brocki et al., 2007), far more research is needed into the indicators of ADHD trajectories as well as their practical clinical value (Esser, Fischer, Wyschkon, Laucht, & Schmidt, 2007b). The task of early identification of individuals at risk is complicated by at least three factors: (i) the interactive way in which risks operate; (ii) the non-deterministic way in which these factors seem to be related to possible (endo)phenotypic indicators of risk; and (iii) the incomplete patterns of continuity from early phenotypic indicators to later disorder – i.e., only some young children showing initial symptoms and/or impairment go on to have later problems. Can we predict different patterns of emergence, persistence and remission of disorder?

In the prevention literature a distinction is drawn between primary, secondary and tertiary prevention. Primary prevention stops the development of the disease process before it occurs. Secondary prevention involves attempts to inhibit the progress from early signs to the development of the syndrome. Tertiary prevention reduces impairment in those already affected. The feasibility of each level of prevention depends on whether risk can be assessed effectively at different points across development. First, in relation to targeted primary intervention we need to consider indicators of originating risk (Esser et al., 2007a). Using genetic and pre-/peri-natal environmental risk markers, in principle, intervention can begin very early – perhaps even before phenotypic patterns emerge. However, given current knowledge about the predictive power of these risk markers, predicting developmental outcome on the basis of originating risks is currently not possible (Esser et al., 2007b). Therefore genetic or prenatal screening is not a viable basis for early targeting of interventions. It also raises ethical issues of a most serious nature (Yeh, Morley, & Hall, 2004). More fundamentally, given this and the synergistic way in which genetic and pre- and postnatal environmental risks interact in non-deterministic ways, it is unlikely that assessing risk for ADHD on the basis of genetic screening will ever be desirable or possible (Kerruish & Robertson, 2005).

Secondary intervention based on the identification of early phenotypic indicators may represent a more promising approach for early risk profiling. Key predictors appear to include putative temperamental hyperactivity (Wahlstedt et al., 2008), co-occurring problems in other domains (especially mood regulation; Esser et al., 2007a) and early underlying neuropsychological impairment (Brocki et al., 2007). Negative parenting may also portend persistence (Jester et al., 2005). The predictive value of these different markers may increase with age. Esser et al. (2007a) reported that measures of temperamental dysregulation were better predictors at 24 than 12 months. The overall risk associated with the diverse biological and environmental factors which these indicators mark has not been systematically quantified, nor has its practical value as a basis for early intervention been assessed.

As far as tertiary prevention is concerned, early-emerging, severe and impairing ADHD is a predictor of persistence at least into the school years. Lahey et al. (2004) found that up to 80% of children who met criteria for preschool ADHD with pervasive functional impairment continued to have problems as they entered the school years. However, in this case the 'full' disorder was to all intents and purposes already present and it could be argued that treatment would be justified on the basis of the presence of the disorder itself at that time, rather than in terms of what it predicted about the future.

The Lahey data also highlight the existence of children who do not show persistence despite exhibiting early-emerging and severe patterns (i.e., the diminishing pattern described by Sonuga-Barke et al., 2005). A key question therefore is whether this group can be identified. Currently, limited data preclude the ability to identify factors that moderate pathways to produce this early-emerging diminishing phenotype. However, if we could distinguish 'time limited' and persistent forms of early-emerging ADHD then one would be unlikely to employ as aggressive and comprehensive (and costly) an intervention approach for the former as for the latter group (Sonuga-Barke et al., 2005).

Even less is known of the factors that determine late- rather than early-emerging patterns. Again genetic factors may play a role but school entry may be an especially important provoking factor. Some children may be especially vulnerable to the impact of the transition from the home environment to the more rigorous demands of the classroom setting. The therapeutic value of managing the home-to-school transition for some children has not been studied.

For those children whose temperamentally driven hyperactivity is a risk for the development of conduct problems but not ADHD, markers of potential risk are likely to be as much in the negative interaction within the preschool family environment as they are to be characteristics of the child (Burke, Pardini, & Loeber, 2008; Degnan, Calkins, Keane, & Hill-Soderlund, 2008; Chronis et al., 2007). Here parent training packages may be especially fruitful. There is a growing literature suggesting that effective early identification and intervention strategies can target these sorts of children effectively (Gill et al., 2008).

Given the possible eventual clinical significance of sub-clinical problems manifested during the preschool years, effective early intervention strategies may need to include some element of universal screening. Screening assessment for ADHD is less developed than for other disorders (Hill, Lochman, Coie, Greenberg, & Conduct Problems Prevention Research Group, 2004). The heterogeneity of developmental phenotypes further complicates the already difficult task of identifying risk factors because screening tasks ideally should identify predictors of later disorder and distinguish between different trajectories of disorder emergence and persistence. Given this, it is possible that such screening will need to focus not only on symptoms but on intellectual delay, neuropsychological deficits and the family environment. Overall, targeted primary intervention is unlikely to be feasible. Furthermore, our current understanding of early markers of later disorder-onset and disorder persistence is insufficient to provide accurate targeting of secondary prevention. Tertiary intervention seems potentially more feasible but better models of early predictors of long-term impairment and burden are still required.

## *II: Can we develop effective early interventions that target the putative causal pathways underpinning ADHD developmental phenotypes?*

Evidence suggests a more limited efficacy of psychostimulants with preschoolers than older children (Kollins & Greenhill, 2006). The 'Preschool ADHD Treatment Study' (Greenhill et al., 2006) found that overall methylphenidate was superior to placebo and generally well tolerated. Positive effects were less consistent and more reduced in the presence of comorbidity (Ghuman et al., 2007) to a greater degree than is the case with older children. Side-effects and adverse events were common (Wigal et al., 2006) and a large proportion of patients failed to complete a 10-month continuation phase (Vitiello et al., 2007). Some evidence also exists for the value of non-stimulants with younger ADHD children (Kratovich et al., 2007). Crucially, there is no evidence that early medication either reduces the persistence of ADHD or mitigates the full onset of the disorder in sub-clinical cases. The role of medication in early intervention strategies remains to be defined.

Other considerations aside, medication is likely to remain a controversial option for preschoolers and early intervention is likely to rely on developing effective non-pharmacological interventions. There are a range of non-pharmacological options (including child-centred cognitive behavioural and cognitive approaches; Toplak, Connors, Shuster, Knezevic, & Parks, 2008) but psychosocial interventions delivered by parents and teachers are most commonly used. In particular, it has been argued that parent training packages based on generic social learning approaches (Forehand & McMahon, 1981), e.g., Parent-Child Interaction Therapy (Eyberg, Boggs, and Algina, 1995), the Incredible Years (Webster-Stratton, Reid, & Hammond, 2001) or Triple P (Bor, Sanders, & Markie-Dadds, 2002), when appropriately adapted for use with ADHD children, represent a useful treatment option. These approaches reduce levels of oppositionality, defiance and conduct problems in children and improve mental health in their parents (Serketich & Dumas, 1996), effects that generalise to the ADHD population (Hartman, Stage, & Webster-Stratton, 2003). Improvements seen at home do not necessarily generalise to other settings (Taylor & Biglan, 1998). In non-referred groups of preschoolers with hard-to-manage behaviour, generic parent training approaches may improve parent-rated attention problems (Bor et al., 2002; Strayhorn & Weidman, 1989; Jones et al., 2008). However, as in the case with older children (reviewed in Hinshaw, Klein, & Abikoff, 1998, 2002; McGoey et al., 2002), findings with preschoolers with severe ADHD symptoms are less convincing (Barkley et al., 2000; Pisterman et al., 1989, 1992). As with medication in preschoolers, nothing is known of whether parenting approaches can alter trajectories and improve outcomes over the longer term.

What can be done to optimise the impact of early non-pharmacological strategies? In this paper we have set out the hypothesis that therapeutic innovations that target the underlying causal processes are likely to be most effective. For instance, the failure of children to develop effective executive control has been proposed as a putative cause of ADHD (Nigg et al., 2005), at least for a sub-group of children, with measurable deficits being present by the age of 3 years (Brocki et al., 2007).

Computerised cognitive training can improve attentional control in neuropsychological rehabilitation (Michel & Mateer 2006; O'Connell et al., 2008). The case for its use to target alterations in developing neural systems is less clear. **However, a compelling case for such an approach was made by Rueda et al. (2005), based on the notion that developing attention circuitry was particularly amenable to experience between the ages of 3 and 7.** This is consistent with studies of dyslexia (Chenault, Thomson, Abbott, & Berninger, 2006), language impairment (Stevens et al., 2008) and school readiness (Diamond, Barnett, Thomas, & Munro, 2007). With regard to ADHD there are studies of working memory training in school-age children (Klingberg et al., 2005) as well as other forms of attention training focusing on a wider range of cognitive skills that may also have value (Toplak et al., 2008). Preliminary data indicate that training produces improvements in working memory and other cognitive domains, although evidence that these effects translate into changes in ADHD symptoms is less clear-cut (Klingberg et al., 2005). Studies with adults suggest that these effects are associated with increased prefrontal and parietal activation (Klingberg et al., 2005) and changes in dopamine function (McNab et al., 2009). This training approach has recently been implemented with younger children (Thorell, Lindqvist, Nutley, Bohlin, & Klingberg, 2009), although effects did not generalise to other executive functions. More research in these groups is required before such approaches can be recommended as treatment elements in an ADHD early intervention programme.

In the preschool years it may be more effective to embed cognitive enhancement within a general parent training approach. Such a delivery system may better match the needs of young ADHD children. For instance, in the New Forest Parenting Programme (NFPP), developed as a specialised psychological intervention for preschool children with ADHD (Sonuga-Barke et al., 2006), a cognitive element has been included to improve attentional control, working memory and general self-regulation. This relies on the primary caregiver to carry out activities and home work exercises intended to enhance certain regulatory skills and promote executive function development. By making the parent the agent of change and integrating training within everyday activity it was hoped that maintenance of

effects over time and generalisation across settings would be optimised. The parent becomes the promoter of psychological growth within the child. The approach is implemented using games requiring attention, concentration, turn-taking, working memory and delay of gratification. The parent is also encouraged to use real-world situations that call for the use of the regulatory skills being taught (i.e., teachable moments). This naturalistic behavioural teaching approach provides numerous opportunities for generalisation, a central concern and goal in the behavioural treatment of children with ADHD. A recent small-scale randomised controlled trial of this intervention implemented with 3- to 5-year-olds with ADHD reported large effects on core symptoms of ADHD (Thompson et al., 2009).

A related approach (**Training Executive, Attention and Motor Skills; TEAMS**), being developed by Halperin, Healey and collaborators (unpublished), similarly focuses on the development of a wide array of higher cognitive and motor skills in preschoolers with ADHD through the use of game-like activities that are presented to children in small group settings. As with NFPP, parents are used as facilitators of practice and generalisation.

The causal heterogeneity of ADHD means that different treatment targets are likely to be relevant for different children given that similar developmental phenotypes might be underpinned by different patterns of neuropsychological and/or family dysfunction. Given the heterogeneity at some future point in time there may be value in neuropsychological testing to identify different core deficits and help tailor treatments. However, first we need to establish a clearer picture of the neuropsychological underpinnings of different developmental phenotypes and then we need to develop easy to implement, valid and reliable indices of different aspects of neuropsychological impairment as they manifest in ADHD. Training approaches to target different deficits, similar to those employed for working memory, are feasible. For instance, Sonuga-Barke (2004) has argued that operant techniques of fading and shaping may be an especially good way of altering incentive structures and improving delay behaviour (Neef, Bicard, & Endo, 2001). However, until and unless such clearly defined developmental phenotypes are identified and differentially validated, a more broad-based approach that strives to enhance multiple potential 'causal' domains of functioning, as in NFPP and TEAMS, may represent a more optimal starting point for the development of novel prevention interventions. As outlined in Box 3, we propose several key elements that might form the basis or conceptual framework for the development of novel prevention intervention programmes that might mitigate the severity of ADHD across the lifespan.

Nevertheless, far more research is necessary to determine whether early intervention can be effec-

**Box 3:** Potentially Important Elements for Early Intervention

- In order to optimize their chances of success, our hypothesis is that early interventions should
  - be initiated prior to the onset of severe symptoms;
  - target underlying ‘casual’ pathways and developmental processes to prevent or moderate the course of the disorder and precursor states and pathological processes;
  - expand into the child’s ‘real life’ to facilitate generalization (e.g., teachable moments);
  - be developmentally appropriate and preferably intrinsically rewarding (i.e., fun) for preschoolers.

**Box 4:** Proposed Research Agenda for the Development Of Early Intervention for ADHD

- Identify early predictors of distinct ADHD trajectories (who needs early interventions?);
- Validate distinctions between candidate developmental phenotypes (e.g., are there distinct developmental trajectories relating to neuropsychological subtypes?);
- Determine whether neuropsychological deficits are mediators of ADHD trajectory;
- Identify moderators of neurobiological and neuro-behavioral processes;
- Determine whether improvement in specific neuropsychological/cognitive domains of weakness reduce ADHD severity;
- Determine the feasibility, effectiveness and cost-effectiveness of broad-based early intervention strategies.

tively implemented to alter the adverse course typically associated with ADHD across the lifespan. Box 4 outlines what we believe to be key issues that need to be clarified by future research. Such

research, in turn, will greatly facilitate the eventual development of effective prevention interventions for ADHD as we have conceptualised it.

In summary, we propose that early identification and intervention can be an effective basis for innovation for the treatment of ADHD if it can target the underlying causal mechanisms responsible for the disorder. Brain plasticity during early development and the moderated and mediated nature of ADHD outcomes highlight the potential of such an approach. However, more research is needed to characterise early developmental phenotypes of ADHD and their underlying causal processes to improve early identification of young children at risk, to identify treatment targets, and to develop new and innovative therapeutic approaches that have the potential to fundamentally alter developmental outcomes.

### Acknowledgements

We are extremely grateful to Professor Jim Swanson for helpful discussions of the issues raised in this paper over many years and for the constructive comments of the three reviewers.

### Correspondence to

Edmund J.S. Sonuga-Barke, Developmental Brain-Behaviour Laboratory, School of Psychology, University of Southampton, Southampton, SO17 1BJ, UK.

### Key points

- ADHD is increasingly recognised as a pathophysiologically complex and heterogeneous condition implicating multiple causal pathways.
- Developmental approaches are ultimately likely to provide the best way of characterizing and understanding these pathways.
- Such a perspective, when combined with increasing evidence for plasticity in brain structure and function, highlights the potential value of early intervention as a way of improving developmental trajectories in ADHD.
- Although pharmacological and psychological interventions in preschool can reduce ADHD symptoms and associated impairment, data to date do not suggest that they alter long term developmental pathways into the disorder.
- From a translational viewpoint, neuro-biological and -psychological mediators and environmental moderators of developmental pathways represent novel, putative early intervention treatment targets: Early detection and intervention models for ADHD need to target tailored treatments toward causal processes and developmental phenotypes.
- However, evidence from large scale longitudinal studies about the neuro-developmental bases of early ADHD phenotypes are a prerequisite for the successful implementation of this approach, and such data are currently lacking.

### References

- Antshel, K.M., & Barkley, R. (2008). Psychosocial interventions in attention deficit hyperactivity disorder. *Child and Adolescent Psychiatric Clinics of North America*, 17, 421–437.
- Arcos-Burgos, M., Castellanos, F.X., Pineda, D., Lopera, F., Palacio, J.D., Palacio, L.G., et al. (2004).

- Attention-deficit/hyperactivity disorder in a population isolate: Linkage to loci at 4q13.2, 5q33.3, 11q22, and 17p11. *American Journal of Human Genetics*, 75, 998–1014.
- Arnsten, A.F.T., & Li, B.M. (2005). Neurobiology of executive functions: Catecholamine influences on prefrontal cortical functions. *Biological Psychiatry*, 57, 1377–1384.
- Arseneault, L., Moffitt, T.E., Caspi, A., Taylor, A., Rijdsdijk, F.V., Jaffee, S.R., et al. (2003). Strong genetic effects on cross-situational antisocial behaviour among 5-year-old children according to mothers, teachers, examiners-observers and twins' self reports. *Journal of Child Psychology and Psychiatry*, 44, 832–848.
- Asherson, P., Kuntsi, J., & Taylor, E. (2005). Unraveling the complexity of attention-deficit hyperactivity disorder: A behavioural genomic approach. *British Journal of Psychiatry*, 187, 103–105.
- Auerbach, J.G., Landau, R., Berger, A., Arbelle, S., Faroy, M., & Karplus, M. (2005). Neonatal behavior of infants at familial risk for ADHD. *Infant Behavior and Development*, 28, 220–224.
- Banaschewski, T., Coghill, D., Santosh, P., Zuddas, A., Asherson, P., Buitelaar, J., et al. (2006). Long-acting medications for the hyperkinetic disorders – a systematic review and European treatment guideline. *European Child and Adolescent Psychiatry*, 15, 476–495.
- Barkley, R.A., Shelton, T.L., Crosswait, C., Moorehouse, M., Fletcher, K., Barrett, S., et al. (2000). Multi-method psycho-educational intervention for preschool children with disruptive behavior: Preliminary results at post-treatment. *Journal of Child Psychology and Psychiatry*, 41, 319–332.
- Beauchaine, T.P., Neuhaus, E., Brenner, S.L., & Gatke-Kopp, L. (2008). Ten good reasons to consider biological processes in prevention and intervention research. *Development and Psychopathology*, 20, 745–774.
- Becker, K., El-Faddagh, M., Schmidt, M.H., Esser, G., & Laucht, M. (2008). Interaction of dopamine transporter genotype with prenatal smoke exposure on ADHD symptoms. *Journal of Pediatrics*, 152, 263–269.
- Bellgrove, M.A., O'Connell, R.G., & Vance, A. (2008). Genetics of cognitive deficits in ADHD: Clues for novel treatment methods. *Expert Review of Neurotherapeutics*, 8, 553–561.
- Belsky, J., Fearon, R.M.P., & Bell, B. (2007). Parenting, attention and externalizing problems: Testing mediation longitudinally, repeatedly and reciprocally. *Journal of Child Psychology and Psychiatry*, 48, 1233–1242.
- Ben Amor, L., Grizenko, N., Schwartz, G., Lageix, P., Baron, C., Ter-Stepanian, M., et al. (2005). Perinatal complications in children with attention-deficit hyperactivity disorder and their unaffected siblings. *Journal of Psychiatry and Neuroscience*, 30, 120–126.
- Berger, I., Dor, T., Nevo, Y., & Goldzweig, G. (2008). Attitudes toward attention-deficit hyperactivity disorder (ADHD) treatment: Parents' and children's perspectives. *Journal of Child Neurology*, 23, 1036–1042.
- Berwid, O.G., Kera, E.A.C., Marks, D.J., Santra, A., Bender, H.A., & Halperin, J.M. (2005). Sustained attention and response inhibition in young children at risk for attention deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry*, 46, 1219–1229.
- Bhutta, A.T., Cleves, M.A., Casey, P.H., Craddock, M.M., & Anand, K.J.S. (2002). Cognitive and behavioral outcomes of school-aged children who were born preterm – a meta-analysis. *Journal of the American Medical Association*, 288, 728–737.
- Bischof, H.J. (2007). Behavioral and neuronal aspects of developmental sensitive periods. *Neuroreport*, 18, 461–465.
- Booth, J.E., Carlson, C.L., & Tucker, D.M. (2007). Performance on a neurocognitive measure of alerting differentiates ADHD combined and inattentive subtypes: A preliminary report. *Archives of Clinical Neuropsychology*, 22, 423–432.
- Bor, W., Sanders, M.R., & Markie-Dadds, C. (2002). The effects of the Triple P-Positive Parenting Program on preschool children with co-occurring disruptive behavior and attentional/hyperactive difficulties. *Journal of Abnormal Child Psychology*, 30, 571–587.
- Brocki, K.C., Nyberg, L., Thorell, L.B., & Bohlin, G. (2007). Early concurrent and longitudinal symptoms of ADHD and ODD: Relations to different types of inhibitory control and working memory. *Journal of Child Psychology and Psychiatry*, 48, 1033–1041.
- Brookes, K.J., Mill, J., Guindalini, C., Curran, S., Xu, X.H., Knight, J., et al. (2006). A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. *Archives of General Psychiatry*, 63, 74–81.
- Burke, J.D., Pardini, D.A., & Loeber, R. (2008). Reciprocal relationships between parenting behavior and disruptive psychopathology from childhood through adolescence. *Journal of Abnormal Child Psychology*, 36, 679–692.
- Bush, G., Spencer, T.J., Holmes, J., Shin, L.M., Valera, E.M., Seidman, L.J., et al. (2008). Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Archives of General Psychiatry*, 65, 102–114.
- Campbell, S.B., Pierce, E.W., March, C.L., Ewing, L.J., & Szumowski, E.K. (1994). Hard-to-manage preschool boys – symptomatic behavior across contexts and time. *Child Development*, 65, 836–851.
- Carlson, E.A., Jacobvitz, D.J., & Sroufe, L.A. (1995). A developmental investigation of inattentiveness and hyperactivity. *Child Development*, 66, 37–54.
- Carr, L.A., Nigg, J.T., & Henderson, J.M. (2006). Attentional versus motor inhibition in adults with attention deficit hyperactivity disorder. *Neuropsychology*, 20, 430–441.
- Carte, E., Nigg, J., & Hinshaw, S. (1996). Neuropsychological functioning, motor speed, and language processing in boys with and without ADHD. *Journal of Abnormal Child Psychology*, 24, 481–498.
- Caspi, A., Henry, B., McGee, R.O., Moffitt, T.E., & Silva, P.A. (1995). Temperamental origins of child and adolescent behavior problems – from age 3 to age 15. *Child Development*, 66, 55–68.
- Castellanos, F.X., Lee, P.P., Sharp, W., Jeffries, N.O., Greenstein, D.K., Clasen, L.S., et al. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/

- hyperactivity disorder. *Journal of the American Medical Association*, 288, 1740–1748.
- Castellanos, F.X., Margulies, D.S., Kelly, C., Uddin, L.Q., Ghaffari, M., Kirsch, A., et al. (2008). Cingulate-precuneus interactions: A new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 63, 332–337.
- Castellanos, F.X., Sonuga-Barke, E.J.S., Milham, M.P., & Tannock, R. (2006). Characterizing cognition in ADHD: Beyond executive dysfunction. *Trends in Cognitive Sciences*, 10, 117–123.
- Chenault, B., Thomson, J., Abbott, R.D., & Berninger, V.W. (2006). Effects of prior attention training on child dyslexics' response to composition instruction. *Developmental Neuropsychology*, 29, 243–260.
- Chronis, A.M., Fabiano, G.A., Onyango, A.N., Pelham, W.E., Lopez-Williams, A., Chacko, A., et al. (2004). An Evaluation of the summer treatment program for children with attention-deficit/hyperactivity disorder using a treatment withdrawal design. *Behaviour Therapy*, 35, 561–585.
- Chronis, A.M., Lahey, B.B., Pelham, W.E., Williams, S.H., Bauman, B.L., Kipp, H., et al. (2007). Maternal depression and early positive parenting predict future conduct problems in young children with attention-deficit/hyperactivity disorder. *Developmental Psychology*, 43, 70–82.
- Cicchetti, D., & Blender, J.A. (2006). A multiple-levels-of-analysis perspective on resilience – implications for the developing brain, neural plasticity, and preventive interventions. In B.M. Lester, A.S. Masten, & B. M&cEwen (Eds.), *Resilience in children* (pp. 248–258). Annals of the New York Academy of Sciences, vol. 1094. New York: New York Academy of Sciences.
- Cicchetti, D., & Toth, S.L. (2009). The past achievements and future promises of developmental psychopathology: The coming of age of a discipline. *Journal of Child Psychology and Psychiatry*, 50, 16–25.
- Coghill, D., Danckaerts, M., Sonuga-Barke, E., Sergeant, J., & European Guidelines Group (2009). Practitioner Review: Quality of life in child mental health – conceptual challenges and practical choices. *Journal of Child Psychology and Psychiatry*.
- Corkum, P., Rimer, P., & Schachar, R. (1999). Parental knowledge of attention-deficit hyperactivity disorder and opinions of treatment options: Impact on enrolment and adherence to a 12-month treatment trial. *The Canadian Journal of Psychiatry*, 44, 1043–1048.
- Curry, S.H. (2008). Translational science: Past, present, and future. *Biotechniques*, 44, II–VIII.
- Dawson, G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Development and Psychopathology*, 20, 775–803.
- Degangi, G., Porges, S., Sickel, R., & Greenspan, S. (1993). Four year follow-up of a sample of regulatory disordered infants. *Infant Mental Health Journal*, 14, 330–343.
- Degnan, K.A., Calkins, S.D., Keane, S.P., & Hill-Soderlund, A.L. (2008). Profiles of disruptive behaviour across early childhood: Contributions of frustration, physiological regulation, and maternal behaviour. *Child Development*, 79, 1357–1376.
- Diamond, A., Barnett, W.S., Thomas, J., & Munro, S. (2007). The early years – preschool program improves cognitive control. *Science*, 318, 1387–1388.
- Dommett, E.J., Henderson, E.L., Westewell, M.S., & Greenfield, S.A. (2008). Methylphenidate amplifies long-term plasticity in the hippocampus via noradrenergic mechanisms. *Learning and Memory*, 15, 580–586.
- DuPaul, G.J., McGoey, K.E., Eckert, T.L., & VanBrakle, J. (2001). Preschool children with attention-deficit/hyperactivity disorder: Impairments in behavioral, social, and school functioning. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40, 508–515.
- Durston, S., Tottenham, N.T., Thomas, K.M., Davidson, M.C., Eigsti, I.M., Yang, Y.H., et al. (2003). Differential patterns of striatal activation in young children with and without ADHD. *Biological Psychiatry*, 53, 871–878.
- Ebstein, R., Levine, J., Geller, V., Auerbach, J., Gritsenko, I., & Belmaker, R. (1998). Dopamine D4 receptor and serotonin transporter promoter in the determination of neonatal temperament. *Molecular Psychiatry*, 3, 238–246.
- Egger, H.L., Kondo, D., & Angold, A. (2006). The epidemiology and diagnostic issues in preschool attention-deficit/hyperactivity disorder – a review. *Infants and Young Children*, 19, 109–122.
- Ellison-Wright, I., Ellison-Wright, Z., & Bullmore, E. (2008). Structural brain change in attention deficit hyperactivity disorder identified by meta-analysis. *BMC Psychiatry*, 8, 51.
- Engel, G. (1977). The need for a new medical model: A challenge for biomedicine. *Science*, 196, 129–136.
- Esser, G., Fischer, S., Wyschkon, A., Laucht, M., & Schmidt, M.H. (2007a). Predictors of hyperkinetic disorder – early recognition in childhood. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*, 35, 127–136.
- Esser, G., Fischer, S., Wyschkon, A., Laucht, M., & Schmidt, M.H. (2007b). Precursors of hyperactive disorders: Potential early diagnosis in infants? *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*, 35, 179–1488.
- Eyberg, S.M., Boggs, S.R., & Algina, J. (1995). Parent-child interaction therapy – a psychosocial model for the treatment of young-children with conduct problem behaviors and their families. *Psychopharmacology Bulletin*, 31, 83–91.
- Fallgatter, A.J., Ehlis, A.C., Rosler, M., Strik, W.K., Blocher, D., & Herrmann, M.J. (2005). Diminished prefrontal brain function in adults with psychopathology in childhood related to attention deficit hyperactivity disorder. *Psychiatry Research-Neuroimaging*, 138, 157–169.
- Fantuzzo, J., Grim, S., Mordell, M., McDermott, P., Miller, L., & Coolahan, K. (2001). A multivariate analysis of the revised Conners' Teacher Rating Scale with low-income, urban preschool children. *Journal of Abnormal Child Psychology*, 29, 141–152.
- Faraone, S.V., Perlis, R.H., Doyle, A.E., Smoller, J.W., Goralnick, J.J., Holmgren, M.A., et al. (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 57, 1313–1323.

- Fava, G.A., & Sonino, N. (2008). The biopsychosocial model thirty years later. *Psychotherapy and Psychosomatics*, 77, 1–2.
- Forehand, R.L., & McMahon, R.J. (1981). *Helping the noncompliant child: A clinician's guide to parent training*. New York: The Guilford Press.
- Frazier, T.W., Youngstrom, E.A., & Naugle, R.I. (2007). The latent structure of attention-deficit/hyperactivity disorder in a clinic-referred sample. *Neuropsychology*, 21, 45–64.
- Gadow, K.D., Nolan, E.E., Sprafkin, J., & Schwartz, J. (2002). Tics and psychiatric comorbidity in children and adolescents. *Developmental Medicine and Child Neurology*, 44, 330–338.
- Gale, C.R., Robinson, S.M., Godfrey, K.M., Law, C.M., Schlotz, W., & O'Callaghan, F.J. (2008). Oily fish intake during pregnancy – association with lower hyperactivity but not with higher full-scale IQ in offspring. *Journal of Child Psychology and Psychiatry*, 49, 1061–1068.
- Gathje, R.A., Lewandowski, L.J., & Gordon, M. (2008). The role of impairment in the diagnosis of ADHD. *Journal of Attention Disorders*, 11, 529–537.
- Geurts, H.M., Verté, S., Oosterlaan, J., Roeyers, H., & Sergeant, J.A. (2004). How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? *Journal of Child Psychology and Psychiatry*, 45, 836–854.
- Ghuman, J.K., Arnold, L.E., & Anthony, B.J. (2008). Psychopharmacological and other treatments in preschool children with attention-deficit/hyperactivity disorder: Current evidence and practice. *Journal of Child and Adolescent Psychopharmacology*, 18, 413–447.
- Ghuman, J.K., Riddle, M.A., Vitiello, B., Greenhill, L.L., Chuang, S.Z., Wigal, S.B., et al. (2007). Comorbidity moderates response to methylphenidate in the Preschoolers with Attention-deficit/hyperactivity disorder Treatment Study (PATS). *Journal of Child and Adolescent Psychopharmacology*, 17, 563–579.
- Gill, A., Hyde, L.W., Shaw, D.S., Dishion, T.J., & Wilson, M.N. (2008). The family check-up in early childhood: A case study of intervention process and change. *Journal of Clinical Child and Adolescent Psychology*, 37, 893–904.
- Gjone, H., Stevenson, J., & Sundet, J.M. (1996). Genetic influence on parent-reported attention-related problems in a Norwegian general population twin sample. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35, 588–596.
- Gonon, F. (2009). The dopaminergic hypothesis of attention-deficit/hyperactivity disorder needs re-examining. *Trends in Neuroscience*, 32, 2–8.
- Graham, J., & Coghill, D. (2008). Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder – epidemiology, prevention and management. *CNS Drugs*, 22, 213–237.
- Greenhill, L., Kollins, S., Abikoff, H., McCracken, J., Riddle, M., Swanson, J., et al. (2006). Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45, 1284–1293.
- Greenhill, L.L., Posner, K., Vaughan, B.S., & Kratochvil, C.J. (2008). Attention deficit hyperactivity disorder in preschool children. *Child and Adolescent Psychiatry Clinics of North America*, 17, 347–366.
- Grund, T., Lehman, K., Bock, N., Rothenberger, A., & Teuchert-Noodt, G. (2006). Influence of methylphenidate on brain development – an update of recent animal experiments. *Behavioral Brain Functions*, 2, 2.
- Halperin, J.M., & Schulz, K.P. (2006). Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. *Psychological Bulletin*, 132, 560–581.
- Halperin, J.M., Trampush, J.W., Miller, C.J., Marks, D.J., & Newcorn, J.H. (2008). Neuropsychological outcome in adolescents/young adults with childhood ADHD: Profiles of persisters, remitters and controls. *Journal of Child Psychology and Psychiatry*, 49, 958–966.
- Hardy, K.K., Kollins, S.H., Murray, D.W., Riddle, M.A., Greenhill, L., Cunningham, C., et al. (2007). Factor structure of parent- and teacher-rated attention-deficit/hyperactivity disorder symptoms in the Preschoolers with Attention-deficit/hyperactivity disorder Treatment Study (PATS). *Journal of Child and Adolescent Psychopharmacology*, 17, 621–633.
- Hartman, R.R., Stage, S.A., & Webster-Stratton, C. (2003). A growth curve analysis of parent training outcomes: Examining the influence of child risk factors (inattention, impulsivity, and hyperactivity problems), parental and family risk factors. *Journal of Child Psychology and Psychiatry*, 44, 388–398.
- Harvey, E.A., Friedman-Weieneth, J.L., Goldstein, L.H., & Sherman, A.H. (2007). Examining subtypes of behavior problems among 3-year-old children, part I: Investigating validity of subtypes and biological risk-factors. *Journal of Abnormal Child Psychology*, 35, 97–110.
- Haslam, N., Williams, B., Prior, M., Haslam, R., Graetz, B., & Sawyer, M. (2006). The latent structure of attention-deficit/hyperactivity disorder: A taxometric analysis. *Australian and New Zealand Journal of Psychiatry*, 40, 639–647.
- Healey, D.M., Miller, C.J., Castelli, K.L., Marks, D.J., & Halperin, J.M. (2008). The impact of impairment criteria on the rates of ADHD diagnoses in preschoolers. *Journal of Abnormal Child Psychology*, 36, 771–778.
- Hebebrand, J., Dempfle, A., Saar, K., Thiele, H., Herpertz-Dahlmann, B., Linder, M., et al. (2006). A genome-wide scan for attention-deficit/hyperactivity disorder in 155 German sib-pairs. *Molecular Psychiatry*, 11, 196–205.
- Heinrich, H., Gevensleben, H., & Strehl, U. (2007). Neurofeedback – train your brain to train behaviour. *Journal of Child Psychology and Psychiatry*, 48, 3–16.
- Helzer, J.E., Kraemer, H.C., & Krueger, R.F. (2006). The feasibility and need for dimensional psychiatric diagnoses. *Psychological Medicine*, 36, 1671–1680.
- Hernandez-Lloreda, M.V., & Colmenares, F. (2005). Regularities and diversity in developmental pathways: Mother-infant relationships in hamadryas baboons. *Developmental Psychobiology*, 47, 297–317.
- Hill, L.G., Lochman, J.E., Coie, J.D., Greenberg, M.T., & Conduct Problems Prevention Research Group (2004). Effectiveness of early screening for externalizing problems: Issues of screening accuracy and utility. *Journal of Consulting and Clinical Psychology*, 72, 809–820.

- Hinshaw, S.P., Klein, R.G., & Abikoff, H. (1998). Childhood attention-deficit hyperactivity disorder: Nonpharmacologic and combination approaches. In P.E. Nathan, & J.M. Gorman, (Eds.), *A guide to treatments that work* (pp. 27–41). New York: Oxford University Press.
- Hinshaw, S.P., Klein, R.G., & Abikoff, H. (2002). Childhood attention-deficit hyperactivity disorder: Nonpharmacologic treatments and their combination with medication. In P.E. Nathan, & J.M. Gorman (Eds.), *A Guide to Treatments that Work* (2nd edn, pp. 1–23). New York: Oxford University Press.
- Jacobvitz, D., & Sroufe, A. (1987). The early caregiver-child relationship and attention deficit disorder with hyperactivity in kindergarten: A prospective study. *Child Development*, *58*, 1496–1504.
- Jensen, P.S., Arnold, L.E., Richters, J.E., Severe, J.B., Vereen, D., Vitiello, B., et al. (1999). A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *56*, 1073–1086.
- Jensen, P.S., Arnold, L.E., Swanson, J.M., Vitiello, B., Abikoff, H.B., Greenhill, L.L., et al. (2007). 3-year follow-up of the NIMH MTA study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*, 989–1002.
- Jester, J.M., Nigg, J.T., Adams, K., Fitzgerald, H.E., Puttler, L.I., Wong, M.M., & Zucker, R.A. (2005). Inattention/hyperactivity and aggression from early childhood to adolescence: Heterogeneity of trajectories and differential influence of family environment characteristics. *Development and Psychopathology*, *17*, 99–125.
- Jones, K., Daley, D., Hutchings, J., Bywater, T., & Eames, C. (2008). Efficacy of the Incredible Years Programme as an early intervention for children with conduct problems and ADHD: Long-term follow-up. *Child: Care, Health and Development*, *34*, 380–390.
- Kahn, R.S., Khoury, J., Nichols, W.C., & Lanphear, B.P. (2003). Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviours. *Journal of Pediatrics*, *143*, 104–110.
- Karabekiroglu, K., Yazgan, Y.M., & Dedeoglu, C. (2008). Can we predict short-term side effects of methylphenidate immediate-release? *International Journal of Psychiatry in Clinical Practice*, *12*, 48–54.
- Keenan, K., & Wakschlag, L.S. (2000). More than the terrible twos: The nature and severity of behavior problems in clinic-referred preschool children. *Journal of Abnormal Child Psychology*, *28*, 33–46.
- Kern, L., DuPaul, G.J., Volpe, R.J., Sokol, N.G., Lutz, J.G., Arbolino, L.A., et al. (2007). Multisetting assessment-based intervention for young children at risk for attention deficit hyperactivity disorder: Initial effects on academic and behavioral functioning. *School Psychology Review*, *36*, 237–255.
- Kerns, K., Eso, K., & Thomson, J. (1999). Investigation of a direct intervention for improving attention in young children with ADHD. *Developmental Neuropsychology*, *16*, 273–295.
- Kerruish, N.J., & Robertson, S.P. (2005). Newborn screening: New developments, new dilemmas. *Journal of Medical Ethics*, *31*, 393–398.
- Kieling, C., Goncalves, R.R.F., Tannock, R., & Castellanos, F.X. (2008). Neurobiology of attention deficit hyperactivity disorder. *Child and Adolescent Psychiatric Clinics of North America*, *17*, 285–307.
- Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlstrom, K., et al. (2005). Computerized training of working memory in children with ADHD – a randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, *44*, 177–186.
- Kollins, S.H., & Greenhill, L. (2006). Evidence base for the use of stimulant medication in preschool children with ADHD. *Infants and Young Children*, *19*, 132–141.
- Konofal, E., Lecendreux, M., Arnulf, I., & Mouren, M.C. (2004). Iron deficiency in children with attention-deficit/hyperactivity disorder. *Archives of Pediatrics and Adolescent Medicine*, *158*, 1113–1115.
- Kratochvil, C.J., Vaughan, B.S., Mayfield-Jorgensen, M.L., March, J.S., Kollins, S.H., Murray, D.W., et al. (2007). A pilot study of atomoxetine in young children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, *17*, 175–185.
- Lahey, B.B., Pelham, W.E., Loney, J., Kipp, H., Erhardt, A., Lee, S.S., et al. (2004). Three-year predictive validity of DSM-IV attention deficit hyperactivity disorder in children diagnosed at 4–6 years of age. *American Journal of Psychiatry*, *161*, 2014–2020.
- Lahey, B.B., Pelham, W.E., Loney, J., Lee, S.S., & Willcutt, E. (2005). Instability of DSM-IV subtypes of ADHD from preschool through elementary school. *Archives of General Psychiatry*, *62*, 896–902.
- Lahey, B.B., Rathouz, P.J., Van Hulle, C., Urbano, R.C., Krueger, R.F., Applegate, B., et al. (2008). Testing structural models of DSM-IV symptoms of common forms of child and adolescent psychopathology. *Journal of Abnormal Child Psychology*, *36*, 187–206.
- Lasky-Su, J., Anney, R., Neale, B.M., Franke, B., Zhou, K., Maller, J.B., et al. (2008). Genome-wide association scan of attention deficit hyperactivity disorder. *American Journal of Medical Genetics Part B: Neuro-psychiatric Genetics*, Epub ahead of print.
- Lavigne, J.V., Arend, R., Rosenbaum, D., Binns, H.J., Christoffel, K.K., & Gibbons, R.D. (1998). Psychiatric disorders with onset in the preschool years: I. Stability of diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry*, *37*, 1246–1254.
- Leblanc, N., Boivin, M., Dionne, G., Brendgen, M., Vitaro, F., Tremblay, R.E., & Perusse, D. (2008). The development of hyperactive-impulsive behaviors during the preschool years: The predictive validity of parental assessments. *Journal of Abnormal Child Psychology*, *36*, 977–987.
- Lee, S.S., Lahey, B.B., Owens, E.B., & Hinshaw, S.P. (2008). Few preschool boys and girls with ADHD are well-adjusted during adolescence. *Journal of Abnormal Child Psychology*, *36*, 373–383.
- Leslie, L.K., Stallone, K.A., Weckerly, J., McDaniel, A.L., & Monn, A. (2006). Implementing ADHD guidelines in primary care: Does one size fit all? *Journal of Health Care for the Poor and Underserved*, *17*, 302–327.
- Leung, P.W., Luk, S.L., Ho, T.P., Taylor, E., Mak, F.L., & BaconShone, J. (1996). The diagnosis and prevalence

- of hyperactivity in Chinese schoolboys. *British Journal of Psychiatry*, 168, 486–496.
- Linares, T.J., Singer, L.T., Kirchner, H.L., Short, E.J., Min, M.O., Hussey, P., et al. (2006). Mental health outcomes of cocaine-exposed children at 6 years of age. *Journal of Pediatric Psychology*, 31, 85–97.
- Lou, H.C. (1996). Etiology and pathogenesis of attention-deficit hyperactivity disorder (ADHD): Significance of prematurity and perinatal hypoxic-haemodynamic encephalopathy. *Acta Paediatrica*, 85, 1266–1271.
- Lubar, J.F. (1997). Neocortical dynamics: Implications for understanding the role of neurofeedback and related techniques for the enhancement of attention. *Applied Psychophysiology and Biofeedback*, 22, 111–126.
- Luciana, M. (2003). Cognitive development in children born preterm: Implications for theories of brain plasticity following early injury. *Development and Psychopathology*, 15, 1017–1047.
- Luman, M., Oosterlaan, J., & Sergeant, J.A. (2005). The impact of reinforcement contingencies on AD/HD: A review and theoretical appraisal. *Clinical Psychology Review*, 25, 183–213.
- Madras, B. K., Miller, G. M., & Fischman, A.J. (2005). The dopamine transporter and attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 57, 1397–1409.
- Madras, B.K., Miller, G.M., & Fischman, A.J. (2002). The dopamine transporter: Relevance to attention deficit hyperactivity disorder (ADHD). *Behavioural Brain Research*, 130, 57–63.
- Makris, N., Biederman, J., Valera, E.M., Bush, G., Kaiser, J., Kennedy, D.N., et al. (2007). Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. *Cerebral Cortex*, 17, 1364–1375.
- Maniadaki, K., Sonuga-Barke, E., Kakouros, E., & Karaba, R. (2007). Parental beliefs about the nature of ADHD behaviours and their relationship to referral intentions in preschool children. *Child Care Health and Development*, 33, 188–195.
- Mannuzza, S., Klein, R.G., Abikoff, H., & Moulton, J.L. (2004). Significance of childhood conduct problems to later development of conduct disorder among children with ADHD: A prospective follow-up study. *Journal of Abnormal Child Psychology*, 32, 565–573.
- Marakovitz, S.E., & Campbell, S.B. (1998). Inattention, impulsivity and hyperactivity from preschool to school age: Performance of hard-to-manage boys on laboratory measures. *Journal of Child Psychology and Psychiatry*, 39, 841–851.
- Marco, R., Miranda, A., Schlotz, W., Melia, A., Mulligan, A., Müller, U., et al. (2009). Delay and reward choice in ADHD: An experimental test of the role of delay aversion. *Neuropsychology*, 23, 367–380.
- Mariussen, E., & Fønnum, F. (2006). Neurochemical targets and behavioral effects of organohalogen compounds: An update. *Critical Reviews in Toxicology*, 36, 253–289.
- Marks, D.J., Berwid, O.G., Santra, A., Kera, E.C., Cryulnik, S.E., & Halperin, J.M. (2005). Neuropsychological correlates of ADHD symptoms in preschoolers. *Neuropsychology*, 19, 446–455.
- Mathiesen, K.S., & Sanson, A. (2000). Dimensions of early childhood behavior problems: Stability and predictors of change from 18 to 30 months. *Journal of Abnormal Child Psychology*, 28, 15–31.
- McCann, D., Barrett, A., Cooper, A., Crumpler, D., Dalen, L., Grimshaw, K., et al. (2007). Food additives and hyperactive behaviour in 3 and 8/9 year old children in the community. *Lancet*, 370, 1560–1567.
- McGoey, K.E., Eckert, T.L., & Paul, G.J. (2002). Early intervention for preschool-age children with ADHD: A literature review. *Journal of Emotional and Behavioral Disorders*, 10, 14–28.
- McNab, F., Varrone, A., Farde, L., Jucaite, A., Bystritsky, P., Forssberg, H., et al. (2009). Changes in cortical dopamine D1 receptor binding associated with cognitive training. *Science*, 323, 800–802.
- Michel, J.A., & Mateer, C.A. (2006). Attention rehabilitation following stroke and traumatic brain injury. A review. *Europa Medicophysica*, 42, 59–67.
- Miklowitz, D.J., & Cicchetti, D. (2006). Toward a life span developmental psychopathology perspective on bipolar disorder. *Development and Psychopathology*, 18, 935–938.
- Mill, J., & Petronis, A. (2008). Pre- and peri-natal environmental risks for attention-deficit hyperactivity disorder (ADHD): The potential role of epigenetic processes in mediating susceptibility. *Journal of Child Psychology and Psychiatry*, 49, 1020–1030.
- Moffitt, T.E. (1993). The neuropsychology of conduct disorder. *Development and Psychopathology*, 5, 135–151.
- Molina, B.S.G., Hinshaw, S.P., Swanson, J.M., Arnold, L. E., Vitiello, B., Jensen, P.S., Epstein, J.N., Hoza, B., Hechtman, L., Abikoff, H.B., Elliott, G.R., Greenhill, L.L., Newcorn, J.H., Wells, K.C., Wigal, T., Gibbons, R.D., Hur, K., Houck, P.R., & the MTA Cooperative Group. (2009). 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*, 48, 484–500.
- Morrell, J., & Murray, L. (2003). Parenting and the development of conduct disorder and hyperactive symptoms in childhood: A prospective longitudinal study from 2 months to 8 years. *Journal of Child Psychology and Psychiatry*, 44, 489–508.
- Neef, N.A., Bicard, D.F., & Endo, S. (2001). Assessment of impulsivity and the development of self-control in students with attention deficit hyperactivity disorder. *Journal of Applied Behavior Analysis*, 34, 397–408.
- Neville, H.J. (2006). Different profiles of plasticity within human cognition. In Y. Munakata, & M.H. Johnson, (Eds.), *Processes of change in brain and cognitive development: Attention and Performance XXI* (pp. 287–314). Oxford: Oxford University Press.
- Nigg, J.T. (2006). What causes ADHD? Toward a multi-path model for understanding what goes wrong and why (p. 422). New York: The Guilford Press.
- Nigg, J.T., Knottnerus, G.M., Martel, M.M., Nikolas, M., Cavanagh, K., Karmaus, W., & Rappley, M.D. (2008). Low blood lead levels associated with clinically diagnosed attention-deficit/hyperactivity disorder and mediated by weak cognitive control. *Biological Psychiatry*, 63, 325–331.

- Nigg, J.T., Willcutt, E.G., Doyle, A.E., & Sonuga-Barke, E.J.S. (2005). Causal heterogeneity in attention-deficit/hyperactivity disorder: Do we need neuropsychologically impaired subtypes? *Biological Psychiatry*, *57*, 1224–1230.
- O'Connell, R.G., Bellgrove, M.A., Dockree, P.M., Lau, A., Fitzgerald, M., & Roberson, I.H. (2008). Self-alert training: Volitional modulation of autonomic arousal improves sustained attention. *Neuropsychologia*, *46*, 1379–1390.
- O'Connor, T.G., Heron, J., Golding, J., & Glover, V. (2003). Maternal antenatal anxiety and behavioural/emotional problems in children: A test of a programming hypothesis. *Journal of Child Psychology and Psychiatry*, *44*, 1025–1036.
- Oades, R.D., Sadile, A.G., Sagvolden, T., Viggiano, D., Zuddas, A., Devoto, P., et al. (2005). The control of responsiveness in ADHD by catecholamines: Evidence for dopaminergic, noradrenergic and interactive roles. *Developmental Science*, *8*, 122–131.
- Olijslagers, J.E., Werkman, T.R., McCreary, A.C., Kruse, C.G., & Wadman, W.J. (2006). Modulation of midbrain dopamine neurotransmission by serotonin, a versatile interaction between neurotransmitters and significance for antipsychotic drug action. *Current Neuropharmacology*, *4*, 59–68.
- Ostrander, R., & Herman, K.C. (2006). Potential cognitive, parenting, and developmental mediators of the relationship between ADHD and depression. *Journal of Consulting and Clinical Psychology*, *74*, 89–98.
- Pavuluri, M.N., & Luk, S.L. (1998). Recognition and classification of psychopathology in preschool children. *Australian and New Zealand Journal of Psychiatry*, *32*, 642–649.
- Pelham, W.E. Jr, & Fabiano, G.A. (2008). Evidence-based psychosocial treatments for attention-deficit/hyperactivity disorder. *Journal of Clinical Child and Adolescent Psychology*, *37*, 184–214.
- Perwien, A., Hall, J., Swensen, A., & Swindle, R. (2004). Stimulant treatment patterns and compliance in children and adults with newly treated attention-deficit/hyperactivity disorder. *Journal of Managed Care Pharmacy*, *10*, 122–129.
- Pisterman, S., Firestone, P., McGrath, P., Goodman, J.T., Webster, I., Mallory, R., & Goffin, B. (1992). The role of parent training in treatment of preschoolers with ADHD. *American Journal of Orthopsychiatry*, *62*, 397–408.
- Pisterman, S., McGrath, P., Firestone, P., Goodman, J.T., Webster, I., & Mallory, R. (1989). Outcome of parent-mediated treatment of preschoolers with attention deficit disorder with hyperactivity. *Journal of Consulting and Clinical Psychology*, *57*, 628–635.
- Plichta, M.M., Vasic, N., Wolf, R.C., Lesch, K.P., Brummer, D., Jacob, C., et al. (2009). Neural hypo-responsiveness and hyper-responsiveness during immediate and delayed reward processing in adult attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *65*, 7–14.
- Pliszka, S.R. (2005). The neuropsychopharmacology of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *57*, 1385–1390.
- Polderman, T.J.C., Derks, E.M., Hudziak, J.J., Verhulst, F.C., Posthuma, D., & Boomsma, D.I. (2007). Across the continuum of attention skills: A twin study of the SWAN ADHD rating scales. *Journal of Child Psychology and Psychiatry*, *48*, 1080–1087.
- Posner, K., Melvin, G.A., Murray, D.W., Gugga, S.S., Fisher, P., Skrobala, A., et al. (2007). Clinical presentation of attention-deficit/hyperactivity disorder in preschool children: The Preschoolers with Attention-deficit/hyperactivity Treatment Study (PATS). *Journal of Child and Adolescent Psychopharmacology*, *17*, 547–562.
- Rapee, R.M. (2008). Prevention of mental disorders: Promises, limitations, and barriers. *Cognitive and Behavioral Practice*, *15*, 47–52.
- Rapoport, J.L., & Gogtay, N. (2008). Brain neuroplasticity in healthy, hyperactive and psychotic children: Insights from neuroimaging. *Neuropsychopharmacology*, *33*, 181–197.
- Reif, A., Rosler, M., Freitag, C.M., Schneider, M., Eujen, A., Kissling, C., et al. (2007). Nature and nurture predispose to violent behavior: Serotonergic genes and adverse childhood environment. *Neuropsychopharmacology*, *32*, 2375–2383.
- Rende, R.D. (1993). Longitudinal relation between temperament traits and behavioral syndromes in middle childhood. *Journal of the American Academy of Child and Adolescent Psychiatry*, *32*, 287–290.
- Retz, W.G., Freitag, C.M., Retz-Junginger, P., Wenzler, D., Schneider, M., Kissling, C., et al. (2008). A functional serotonin transporter promoter gene polymorphism increases ADHD symptoms in delinquents: Interaction with adverse childhood environment. *Psychiatry Research*, *158*, 123–131.
- Rhodes, S.M., Coghill, D.R., & Matthews, K. (2004). Methylphenidate restores visual memory, but not working memory function in attention deficit-hyperkinetic disorder. *Psychopharmacology*, *175*, 319–330.
- Richardson, A.J., & Montgomery, P. (2005). The Oxford-Durham study: A randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics*, *115*, 1360–1366.
- Rietveld, M.J.H., Hudziak, J.J., Bartels, M., van Beijsterveldt, C.E.M., & Boomsma, D.I. (2003). Heritability of attention problems in children: I. Cross-sectional results from a study of twins, age 3–12 years. *American Journal of Medical Genetics Part B—Neuropsychiatric Genetics*, *117B*, 102–113.
- Rodriguez, A., & Bohlin, G. (2005). Are maternal smoking and stress during pregnancy related to ADHD symptoms in children? *Journal of Child Psychology and Psychiatry*, *46*, 246–254.
- Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S.C.R., Simmons, A., et al. (1999). Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: A study with functional MRI. *American Journal of Psychiatry*, *156*, 891–896.
- Rueda, M.R., Rothbart, M.K., McCandliss, B.D., Saccomanno, L., & Posner, M.I. (2005). Training, maturation, and genetic influences on the development of executive attention. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 14931–14936.
- Rutter, M., Beckett, C., Castle, J., Colvert, E., Kreppner, J., Mehta, M., et al. (2007). Effects of profound early institutional deprivation: An overview of findings from a UK longitudinal study of Romanian adoptees. *European Journal of Developmental Psychology*, *4*, 332–350.

- Sagvolden, T., Johansen, E.B., Aase, H., & Russell, V.A. (2005). A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behavioral and Brain Science*, *28*, 397–419.
- Sanchez, R.J., Crismon, M.L., Barner, J.C., Bettinger, T., & Wilson, J.P. (2005). Assessment of adherence measures with different stimulants among children and adolescents. *Pharmacotherapy*, *25*, 909–917.
- Sanson, A., Smart, D., Prior, M., & Oberklaid, F. (1993). Precursors of hyperactivity and aggression. *Journal of the American Academy of Child and Adolescent Psychiatry*, *32*, 1207–1216.
- Scheres, A., Dijkstra, M., Ainslie, E., Balkan, J., Reynolds, B., Sonuga-Barke, E., et al. (2006). Temporal and probabilistic discounting of rewards in children and adolescents: Effects of age and ADHD symptoms. *Neuropsychologia*, *44*, 2092–2103.
- Schmidt, S., & Peterman, F. (2008). Developmental psychopathology of ADHD. *Zeitschrift für Psychiatrie Psychologie und Psychotherapie*, *56*, 265–274.
- Schulz, K.P., Newcorn, J.H., Fan, J., Tang, C.Y., & Halperin, J.M. (2005a). Brain activation gradients in ventrolateral prefrontal cortex related to persistence of ADHD in adolescent boys. *Journal of the American Academy of Child and Adolescent Psychiatry*, *44*, 47–54.
- Schulz, K.P., Tang, C.Y., Fan, J., Marks, D.J., Newcorn, J.H., Cheung, A.M., et al. (2005b). Differential prefrontal cortex activation during inhibitory control in adolescents with and without childhood attention-deficit/hyperactivity disorder. *Neuropsychology*, *19*, 390–402.
- Seidman, L.J. (2006). Neuropsychological functioning in people with ADHD across the lifespan. *Clinical Psychology Review*, *26*, 466–485.
- Seipp, C.M., & Johnston, C. (2005). Mother–son interactions in families of boys with attention-deficit/hyperactivity disorder with and without oppositional behavior. *Journal of Abnormal Child Psychology*, *33*, 87–98.
- Sergeant, J.A. (2005). Modeling attention-deficit/hyperactivity disorder: A critical appraisal of the cognitive-energetic model. *Biological Psychiatry*, *57*, 1248–1255.
- Serketich, W.J., & Dumas, J.E. (1996). The effectiveness of behavioral parent training to modify antisocial behavior in children: A meta-analysis. *Behavior Therapy*, *27*, 171–186.
- Shalev, L., Tsal, Y., & Mevorach, C. (2007). Computerized progressive attentional training (CPAT) program: Effective direct intervention for children with ADHD. *Child Neuropsychology*, *13*, 382–388.
- Shaw, D.S., Dishion, T.J., Supplee, L., Gardner, F., & Arnds, K. (2006). Randomized trial of a family-centered approach to the prevention of early conduct problems: 2-year effects of the family check-up in early childhood. *Journal of Consulting and Clinical Psychology*, *74*, 1–9.
- Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J.P., Greenstein, D., et al. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Science*, *104*, 19649–19654.
- Singh, I. (2008). Science and society: Beyond polemics: Science and ethics of ADHD. *Nature Reviews Neuroscience*, *9*, 957–964.
- Smidts, D.P., & Oosterlaan, J. (2007). How common are symptoms of ADHD in typically developing preschoolers? A study on prevalence rates and prenatal/demographic risk factors. *Cortex*, *43*, 710–711.
- Smith, A., Taylor, E., Rogers, J.W., Newman, S., & Rubia, K. (2002). Evidence for a pure time perception deficit in children with ADHD. *Journal of Child Psychology and Psychiatry*, *43*, 529–542.
- Smith, K.G., & Corkum, P. (2007). Systematic review of measures used to diagnose attention-deficit/hyperactivity disorder in research on preschool children. *Topics in Early Childhood Special Education*, *27*, 164–173.
- Sohlberg, M.M., & Mateer, C.A. (2001). Improving attention and managing attentional problems: Adapting rehabilitation techniques to adults with ADHD. In J. Wasserstein, L. Wolf, & F.F. LeFever (Eds.), *Adult attention deficit disorder: Brain mechanisms and life outcomes* (pp. 359–375). Annals of the New York Academy of Sciences, Vol. 931. New York: New York Academy of Sciences.
- Solanto, M.V., Abikoff, H., Sonuga-Barke, E., Schachar, R., Logan, G.D., Wigal, T., et al. (2001). The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: A supplement to the NIMH multimodal treatment study of AD/HD. *Journal of Abnormal Child Psychology*, *29*, 215–228.
- Sonuga-Barke, E., Beckett, C., Kreppner, J., Castle, J., Colvert, E., Stevens, S., et al. (2008b). Is sub-nutrition necessary for a poor outcome following early institutional deprivation? *Developmental Medicine and Child Neurology*, *50*, 664–671.
- Sonuga-Barke, E.J. (2003). The dual pathway model of AD/HD: An elaboration of neuro-developmental characteristics. *Neuroscience and Biobehavioural Reviews*, *27*, 593–604.
- Sonuga-Barke, E.J. (2005). Causal models of attention-deficit/hyperactivity disorder: From common simple deficits to multiple developmental pathways. *Biological Psychiatry*, *57*, 1231–1238.
- Sonuga-Barke, E.J., Sergeant, J., Nigg, J., & Willcutt, E. (2008a). Executive dysfunction and delay aversion in ADHD: Nosological and diagnostic implications. *Child and Adolescent Psychiatric Clinics of North America*, *17*, 367–384.
- Sonuga-Barke, E.J.S. (1998). Categorical model in child psychopathology: A conceptual and empirical analysis. *Journal of Child Psychology and Psychiatry*, *9*, 115–133.
- Sonuga-Barke, E.J.S. (2004). On the reorganisation of incentive structure to promote delay tolerance: A therapeutic possibility for AD/HD? *Neural Plasticity: Special Issue: Clinical, Experimental and Modeling Studies in ADHD*, *11*, 23–28.
- Sonuga-Barke, E.J.S. (2009). Attention deficit/hyperactivity disorder: Towards a development synthesis. In P. Zelazo, (Ed.), *Oxford handbook of developmental psychology*. New York: Oxford University Press.
- Sonuga-Barke, E.J.S., Auerbach, J., Campbell, S.B., Daley, D., & Thompson, M. (2005). Varieties of preschool hyperactivity: Multiple pathways from risk to disorder. *Developmental Science*, *8*, 141–150.
- Sonuga-Barke, E.J.S., & Castellanos, F.X. (2005). A common core dysfunction in attention-deficit/hyperactivity disorder: A scientific red herring? *Behavioral and Brain Sciences*, *28*, 443–444.

- Sonuga-Barke, E.J.S., Dalen, L., & Remington, R.E.R. (2003b). Do delay aversion and inhibitory deficits make distinct contributions to pre-school AD/HD? *Journal of the American Academy of Child and Adolescent Psychiatry*, 42, 1335–1342.
- Sonuga-Barke, E.J.S., Daley, D., Thompson, M., & Swanson, J. (2003a). Preschool ADHD: Exploring uncertainties in diagnostic validity and utility, and treatment efficacy and safety. *Expert Reviews in Neurotherapeutics*, 3, 465–476.
- Sonuga-Barke, E.J.S., Lasky-Su, J., Neale, B.M., Oades, R., Chen, W., Franke, B., et al. (2008c). Does parental expressed emotion moderate genetic effects in ADHD? An exploration using a genome wide association scan. *American Journal of Medical Genetics*, 147B, 1359–1368.
- Sonuga-Barke, E.J.S., Minocha, K., Taylor, E., & Sandberg, S. (1993). Inter-ethnic bias in teachers' ratings of childhood hyperactivity. *British Journal of Developmental Psychology*, 11, 187–200.
- Sonuga-Barke, E.J.S., & Rubia, K. (2008). Inattentive and overactive children with histories of profound institutional deprivation compared to standard ADHD cases: A brief report. *Child Care Health and Development*, 34, 596–602.
- Sonuga-Barke, E.J.S., Stevenson, J., Thompson, M., & Viney, D. (1997). Patterns of behaviour problems among pre-school children. *Psychological Medicine*, 7, 909–918.
- Sonuga-Barke, E.J.S., Thompson, M., Abikoff, H., Klein, R., & Brotman, L.M. (2006). Non-pharmacological interventions for preschool ADHD: The case for specialized parent training. *Infants and Young Children*, 19, 142–153.
- Sonuga-Barke, E.J.S., Wiersema, J.R., van der Meere, J.J., & Roeyers, H. (in press). Context dependent-dynamic models of attention deficit/hyperactivity disorder: Differentiating common and unique elements of the state regulation deficit and delay aversion models. *Neuropsychology Review*.
- Speltz, M., McClellan, J., DeKlyen, M., & Jones, K. (1999). Preschool boys with oppositional defiant disorder: Clinical presentation and diagnostic change. *Journal of the American Academy of Child and Adolescent Psychiatry*, 38, 838–845.
- Spencer, T.J., Biederman, J., Madras, B.K., Dougherty, D.D., Bonab, A.A., Livni, E., et al. (2007). Further evidence of dopamine transporter dysregulation in ADHD: A controlled PET imaging study using altropine. *Biological Psychiatry*, 62, 1059–61.
- Stevens, S.E., Sonuga-Barke, E.J.S., Kreppner, J.M., Beckett, C., Castle, J., Colvert, E., et al. (2008). Inattention/overactivity following early severe institutional deprivation: Presentation and associations in early adolescence. *Journal of Abnormal Child Psychology*, 36, 385–398.
- Strayhorn, J.M., & Weidman, C.S. (1989). Reduction of attention deficit and internalizing symptoms in pre-schoolers through parent-child interaction training. *Journal of the American Academy of Child and Adolescent Psychiatry*, 28, 888–896.
- Ströhle, A., Stoy, M., Wrase, J., Schwarzer, S., Schlagenhauf, F., Huss, M., et al. (2008). Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. *Neuroimage*, 39, 966–972.
- Swanson, J., Gupta, S., Lam, A., Shoulson, I., Lerner, M., Modi, N., et al. (2003). Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder proof-of-concept and proof-of-product studies. *Archives of General Psychiatry*, 60, 204–211.
- Swanson, J.M., Elliott, G.R., Greenhill, L.L., Wigal, T., Arnold, L.E., Vitiello, B., et al. (2007a). Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46, 1015–1027.
- Swanson, J.M., Kinsbourne, M., Nigg, J., Lanphear, B., Stefanatos, G.A., Volkow, N., et al. (2007b). Etiologic subtypes of attention-deficit/hyperactivity disorder: Brain imaging, molecular genetic and environmental factors and the dopamine hypothesis. *Neuropsychology Review*, 17, 39–59.
- Tamm, L., Swanson, J.M., Lerner, M.A., Childress, C., Patterson, B., Lakes, K., et al. (2005). Intervention for preschoolers at risk for attention-deficit/hyperactivity disorder (ADHD): Service before diagnosis. *Clinical Neuroscience Research*, 5, 247–253.
- Taylor, E. (1999). Developmental neuropsychopathology of attention deficit and impulsiveness. *Development and Psychopathology*, 11, 607–628.
- Taylor, E., Chadwick, O., Heptinstall, E., & Danckaerts, M. (1996). Hyperactivity and conduct problems as risk factors for adolescent development. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35, 1213–1226.
- Taylor, E., Dopfner, M., Sergeant, J., Asherson, P., Banaschewski, T., Buitelaar, J., et al. (2004). European clinical guidelines for hyperkinetic disorder – first upgrade. *European Child and Adolescent Psychiatry*, 13, 17–130.
- Taylor, E., & Rogers, J.W. (2005). Practitioner Review: Early adversity and developmental disorders. *Journal of Child Psychology and Psychiatry*, 46, 451–467.
- Taylor, E.A., & Sonuga-Barke, E.J.S. (2008). Disorders of attention and activity. In M. Rutter, D. Bishop, D. Pine, S. Scott, J.S. Stevenson, E.A. Taylor, & A. Thapar, (Eds.), *Rutter's child and adolescent psychiatry* (pp. 521–542). Oxford: Wiley-Blackwell.
- Taylor, T.K., & Biglan, A. (1998). Behavioral family interventions for improving child-rearing: A review of the literature for clinicians and policy makers. *Clinical Child and Family Psychology Review*, 1, 41–60.
- Thapar, A., Fowler, T., Rice, F., Scourfield, J., van den Bree, M., Thomas, H., et al. (2003). Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. *American Journal of Psychiatry*, 160, 1985–1989.
- Thapar, A., Harrington, R., Ross, K., & McGuffin, P. (2000). Does the definition of ADHD affect heritability? *Journal of the American Academy of Child and Adolescent Psychiatry*, 39, 1528–1536.
- Thapar, A., Langley, K., Asherson, P., & Gill, M. (2007). Gene-environment interplay in attention-deficit hyperactivity disorder and the importance of a developmental perspective. *British Journal of Psychiatry*, 190, 1–3.
- Thapar, A., O'Donovan, M., & Owen, M.J. (2005). The genetics of attention deficit hyperactivity disorder. *Human Molecular Genetics*, 14, R275–R282.
- Thompson, M.J.J., Laver-Bradbury, C., Ayres, M., Le Poidevin, E., Mead, S., Dodds, C., et al. (2009).

- A small-scale randomised controlled trial of the revised New Forest Package for Preschoolers with Attention Deficit Hyperactivity Disorder. *European Child and Adolescent Psychiatry*, online first.
- Thorell, L.B. (2007). Do delay aversion and executive function deficits make distinct contributions to the functional impact of ADHD symptoms? A study of early academic skill deficits. *Journal of Child Psychology and Psychiatry*, 48, 1061–1070.
- Thorell, L.B., Lindqvist, S., Nutley, S.B., Bohlin, G., & Klingberg, T. (2009). Training and transfer effects of executive functions in preschool children. *Developmental Science*, 12, 106–113.
- Timimi, S., & Taylor, E. (2004). ADHD is best understood as a cultural construct. *British Journal of Psychiatry*, 184, 8–9.
- Todd, R.D., & Neuman, R.J. (2007). Rapid publication – gene–environment interactions in the development of combined type ADHD: Evidence for a synapse-based model. *American Journal of Medical Genetics Part B–Neuropsychiatric Genetics*, 144b, 971–975.
- Toplak, M.E., Connors, L., Shuster, J., Knezevic, B., & Parks, S. (2008). Review of cognitive, cognitive-behavioral, and neural-based interventions for attention-deficit/hyperactivity disorder (ADHD). *Clinical Psychology Review*, 28, 801–823.
- Toplak, M.E., Jain, U., & Tannock, R. (2005). Executive and motivational processes in adolescents with attention-deficit-hyperactivity disorder (ADHD). *Behavioral and Brain Functions*, 1, 8.
- Tripp, G., & Wickens, J. R. (2008). Dopamine transfer deficit: A neurobiological theory of altered reinforcement mechanisms in ADHD. *Journal of Child Psychology and Psychiatry*, 49, 691–704.
- Turner, D.C., Blackwell, A.D., Dowson, J.H., McLean, A., & Sahakian, B.J. (2005). Neurocognitive effects of methylphenidate in adult attention-deficit/hyperactivity disorder. *Psychopharmacology*, 178, 286–295.
- Vaidya, C.J., Bunge, S.A., Dudukovic, N.M., & Zalecki, C.A. (2005). Altered neural substrates of cognitive control in childhood ADHD: Evidence from functional magnetic resonance imaging. *American Journal of Psychiatry*, 162, 1605–1613.
- Valera, E.M., Faraone, S.V., Murray, K.E., & Seidman, L.J. (2007). Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 61, 1361–1369.
- Van den Bergh, F., Spronk, M., Ferreira, L., Bloemarts, E., Groenink, L., Olivier, B., et al. (2006). Relationship of delay aversion and response inhibition to extinction learning, aggression, and sexual behaviour. *Behavioural Brain Research*, 175, 75–81.
- Vaughan, B.S., Wetzell, M.W., & Kratochvil, C.J. (2008). Beyond the ‘typical’ patient: Treating attention-deficit/hyperactivity disorder in preschoolers and adults. *International Review of Psychiatry*, 20, 143–149.
- Vaurio, L., Riley, E.R., & Mattson, S.N. (2008). Differences in executive functioning in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. *Journal of the International Neuropsychological Society*, 14, 119–129.
- Vitiello, B., Abikoff, H.B., Chuang, S.Z., Kollins, S.H., McCracken, J.T., Riddle, M.A., et al. (2007). Effectiveness of methylphenidate in the 10-month continuation phase of the Preschoolers with ADHD Treatment Study (PATS). *Journal of Child and Adolescent Psychopharmacology*, 17, 593–603.
- Volkow, N.D., & Swanson, J.M. (2003). Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. *American Journal of Psychiatry*, 160, 1909–1918.
- Volkow, N.D., Wang, G.J., Newcorn, J., Fowler, J.S., Telang, F., Solanto, M.V., et al. (2007b). Brain dopamine transporter levels in treatment and drug naïve adults with ADHD. *Neuroimage*, 34, 1182–90.
- Volkow, N.D., Wang, G.J., Newcorn, J., Telang, F., Solanto, M.V., Fowler, J.S., et al. (2007a). Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 64, 932–940.
- Von Stauffenberg, C., & Campbell, S.B. (2007). Predicting the early developmental course of symptoms of attention deficit hyperactivity disorder. *Journal of Applied Developmental Psychology*, 28, 536–552.
- Vuksic, M., Rados, M., & Kostovic, I. (2008). Structural basis of development plasticity in the corticostriatal system. *Collegium Antropologicum*, 32, 155–159.
- Wahlstedt, C., Thorell, L.B., & Bohlin, G. (2008). ADHD symptoms and executive function impairment: Early predictors of later behavioral problems. *Developmental Neuropsychology*, 33, 160–178.
- Webster-Stratton, C., Reid, M.J., & Hammond, M. (2001). Preventing conduct problems, promoting social competence: A parent and teacher training partnership in Head Start. *Journal of Clinical Child Psychology*, 30, 283–302.
- Weiss, M.D., Gadow, K., & Wasdell, M.B. (2006). Effectiveness outcomes in attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry*, 67, 38–45.
- Wiersema, R., van der Meere, J., Antrop, I., & Roeyers, H. (2006). State regulation in adult ADHD: An event-related potential study. *Journal of Clinical and Experimental Neuropsychology*, 28, 1113–1126.
- Wigal, T., Grenhill, L., Chuang, S., McGough, J., Vitiello, B., Skrobala, A., et al. (2006). Safety and tolerability of methylphenidate in preschool children with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45, 1294–1302.
- Willcutt, E.G., Doyle, A.E., Nigg, J.T., Faraone, S.V., & Pennington, B.F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. *Biological Psychiatry*, 57, 1336–1346.
- Willcutt, E.G., Sonuga-Barke, E.J.S., Nigg, J.T., & Sergeant, J.A. (2008). Recent developments in neuropsychological models of childhood psychiatric disorders. In T. Banaschewski, & L.A. Rohde (Eds.), *Biological child psychiatry. Recent trends and developments*. Advances in Biological Psychiatry (vol. 24). Basel: Karger.
- Wolke, D., Rizzo, P., & Woods, S. (2002). Persistent infant crying and hyperactivity problems in middle childhood. *Pediatrics*, 109, 1054–1060.
- Yeh, M., Morley, K.I., & Hall, W.D. (2004). The policy and ethical implications of genetic research on attention deficit hyperactivity disorder. *Australian and New Zealand Journal of Psychiatry*, 38, 10–19.