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

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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 (Corkurum, 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, & Waadell, 2006). There are also side-effects, especially affecting sleep (Graham & Coghill, 2008), appetite (Karabekiroglu, Yagzan, & 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 ADHD that can produce generalised long-lasting change. In this paper we examine a potential role for early intervention in ADHD that can produce generalised long-lasting change.
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 nonlinear 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, Tannock, & 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 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, Saccamanno, & 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 expectation 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 biopsychosocial 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 Staffenburg & 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 fulfill 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:
- Aetiological, 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).
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 (Funtuzzo 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-Weinehen, 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 neurological immaturity, increased activity level, emotional dysregulation, over-responsivity to environmental stimulation, and lower cognitive functioning (Auerbach et al., 2005; Carlson, Jacobvitz, & Sroufe, 1995; Degangi, Forges, SickeI, & 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, Wyachkon, 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 temperamentally 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, Cradock, & 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, Easer, & 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-HTR-LPR) interacting with social adversity to increase ADHD risk (Reif et al., 2008; Reif et al., 2007; Sonuga-Barke et al., 2008b). 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., 2007b, 2007a). 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 (Arnstén & 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, McCrerey, Kruse, & Wadmam, 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, & Zalezcki, 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, Vertie, 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, Wiersema, 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 & Wikens, 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; Konoval, 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 & Fonnun, 2006). Early exposure to psychostimulants might also be associated with long-term adaptations and alterations to the brain (Grund, Lehman, Bock, Rothenberger, & Teuchert-Noord, 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; Wiersema, 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 energetical 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

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**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.

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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 patterns 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 (Veh, 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 (Kratochvil 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, & 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; McGoy 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 pre-frontal 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.

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.

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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.

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