

Attention-deficit hyperactivity disorder (ADHD): an updated review of the essential facts

J. Tarver,^{*†} D. Daley^{*†} and K. Sayal^{*†}

^{*}Division of Psychiatry and Applied Psychology, University of Nottingham, Nottingham, UK, and

[†]Centre for ADHD and Neurodevelopmental Disorders Across the Lifespan (CANDAL), University of Nottingham, Nottingham, UK

Accepted for publication 6 March 2014

Abstract

Attention-deficit hyperactivity disorder (ADHD) is a complex disorder that can affect individuals across the lifespan. It is associated with substantial heterogeneity in terms of aetiology, clinical presentation and treatment outcome and is the subject of extensive research. Because of this, it can be difficult for clinicians to stay up to date with the most relevant findings and know how best to respond to parents' questions and concerns about the disorder and interventions. This is a narrative review that aims to summarize key findings from recent research into ADHD and its treatment that clinicians can share with families in order to increase their knowledge about ADHD and intervention options. ADHD develops as a result of complex interplay between interdependent genetic and non-genetic factors. The disorder is associated with substantial impairments in functioning and poor long-term outcomes. Pharmacological and non-pharmacological treatment options are available for symptom management and to improve function, but functioning outcomes often fail to normalize in children with ADHD. Despite extensive advances in understanding this complex disorder, it is clear that there is still a long way to go. In particular, we address the need for future non-pharmacological interventions to be more specifically targeted for ADHD symptoms and its commonly associated functioning deficits in order to ensure the best long-term outcomes for children with ADHD.

Keywords

ADHD, attention-deficit disorder, environmental influences, genetics, treatment

Correspondence:

David Daley, PhD,
Institute of Mental
Health, University of
Nottingham Innovation
Park, Triumph Road,
Nottingham NG7 2TU, UK
E-mail: david.daley@
nottingham.ac.uk

Background

Attention-deficit hyperactivity disorder (ADHD) is a developmental disorder characterized by developmentally inappropriate levels of hyperactivity, impulsivity and inattention (APA 2013). The American Psychiatric Association's (APA) Diagnostic and Statistical Manual (DSM-5) states that patients must have experienced a minimum of six symptoms of inattention (e.g. failing to sustain attention in tasks or play activities, not listening when being spoken to directly), or six symptoms of hyperactivity/impulsivity (e.g. talking excessively, fidgeting with hands or feet). The manual distinguishes between three subtypes of the disorder: predominantly hyperactive/impulsive type, predominantly inattentive type and combined type. In order to reach diagnosis according to the latest version of the DSM, symptoms must have onset before the age of 12 (rather

than an age 7 cut-off for symptom-related impairment in DSM-IV), be pervasive across settings (e.g. home and school) and associated with substantial impairment in functioning (APA 2013).

Prevalence and developmental course

ADHD is common, with worldwide prevalence estimated at approximately 5% (Polanczyk *et al.* 2007). Although originally seen as a disorder of childhood, the lifelong prevalence of ADHD is now widely acknowledged. Symptoms and neuro-psychological impairments associated with ADHD are evident in preschool children (Daley *et al.* 2009) and although symptoms may decline with age in some cases, ADHD symptoms and impairments can persist into adulthood (Geissler & Lesch 2011). Prevalence rates in adult community samples are

estimated at approximately 2.5% (Simon *et al.* 2009). It is likely that a substantial number of young people accessing services for ADHD will require transition into adult services (Taylor *et al.* 2010). Consequently, adult ADHD services are now developing in parts of the UK.

Aetiology

Despite being one of the most studied psychiatric disorders, the exact cause of ADHD is still unknown (Thapar *et al.* 2013). Potential risk factors can be considered in terms of biological and environmental factors (some of which we will discuss below) with emerging aetiological research focusing on potential interactions and correlations between inherited and non-inherited factors which may heighten risk for ADHD.

Genetics

With heritability estimates of around 0.7, ADHD is considered one of the most heritable psychiatric conditions (Faraone *et al.* 2005). However, no single genetic risk factor has yet been identified, making it likely that ADHD develops as a result of the interaction between multiple genetic risk variants, each of small effect (Thapar *et al.* 2013). Research has thus far focused on genes involved in dopaminergic transmission due to observed dopamine deficiency in children with ADHD (Spencer *et al.* 2005) and the therapeutic benefits provided by methylphenidate, a dopamine agonist. A meta-analysis of commonly studied candidate genes has revealed moderate associations between ADHD and variants of the dopamine transporter (DAT1), dopamine receptors (DRD4 and DRD5) and the serotonin transporter (5HTT) (Gizer *et al.* 2009). Genome-wide searches (GWAS) have yet to identify a single candidate gene through 'hypothesis-free' testing (Franke *et al.* 2009), although this is probably due to insufficient sample sizes to date (Thapar *et al.* 2013).

Brain structure

Neuroimaging techniques such as magnetic resonance imaging (MRI) have identified a number of morphological abnormalities in the brains of children with ADHD. While ADHD is associated with reduced global brain volume (Castellanos *et al.* 2002), specific regional abnormalities have also been identified, namely reduced grey matter in regions forming part of frontostriatal circuits (Nakao *et al.* 2011). In addition, atypical white matter volume in numerous neural tracts suggests impaired communication between some of these implicated

brain regions (Nagel *et al.* 2011). Other abnormalities identified include cortical thinning (Batty *et al.* 2010) and some suggest that cortical development may be delayed in children with ADHD, who reach peak levels of cortical thickness approximately 3 years later than typically developing controls (Shaw *et al.* 2007). The pathogenesis of ADHD is therefore likely to be the result of complex structural abnormalities involving a number of brain regions and connecting circuitry (Cortese 2012). At least some of these structural abnormalities are likely to have a genetic basis; as evidenced by structural abnormalities observed in unaffected siblings of children with ADHD (Durstun *et al.* 2004). However, associations between adverse institutional rearing and reduced cortical thickness are also apparent (McLaughlin *et al.* 2013), highlighting the role of environmental experience on brain development.

Pre-natal smoking

Maternal smoking during pregnancy has often been cited as a potential environmental risk factor for ADHD in offspring, with estimated pooled odds ratio of 2.39 (Langley *et al.* 2005). However, emerging evidence is beginning to suggest that this association may be the result of confounding genetic or environmental factors rather than the detrimental effects of maternal smoking on foetal brain development. For example, Langley and colleagues (2012) reported associations between both maternal *and* paternal smoking during pregnancy, with no statistical difference between the magnitudes of the associations. The association between paternal smoking and child ADHD also remained in families where mothers did not smoke during pregnancy. In addition, genetically sensitive designs of children conceived via assisted contraception allow comparison of mother-child dyads who are genetically unrelated with those genetically related (Thapar *et al.* 2013). Such study designs have revealed that maternal smoking during pregnancy was only related to ADHD symptoms in offspring who *were* genetically related to their mothers (Thapar *et al.* 2009). Despite this, the relatively small amount of mothers who smoke during pregnancy (or report smoking during pregnancy) has resulted in small sample sizes to date and the potential environmental risk of smoking during pregnancy cannot yet be categorically ruled out (Thapar *et al.* 2009).

Prematurity/low birthweight

Low birthweight (LBW) has also been linked to an increased risk for ADHD. Children born pre-term (<26 weeks and hence likely to be have LBW) are approximately four times more likely

to be diagnosed with ADHD, particularly the inattentive subtype (Johnson *et al.* 2010). In order to help decipher whether premature birth or small body size may explain this relationship, Heinonen and colleagues (2010) conducted a longitudinal case–control study controlling for the independent effects of LBW and premature birth. The authors found no association between being born pre-term and later clinical levels of ADHD symptoms. However, children born small for their gestational age were three times more likely to reach clinical cut-off criteria for ADHD compared with children with average birthweight for gestational age. The observed association between LBW and ADHD in MZ and DZ twins discordant for LBW helps to remove the influence of potential confounding genetic effects explaining this relationship (Hultman *et al.* 2007). However, the exact mechanism behind this relationship is unknown, although animal studies point to the effect of foetal growth restriction on brain development (Mallard *et al.* 1995).

Diet

Cross-sectional studies have observed nutritional deficiencies in children with ADHD relative to typically developing children. Among others, these include fatty acids (Stevens *et al.* 1995), zinc (Arnold *et al.* 2005) and iron (Cortese *et al.* 2012b). In addition, some studies report positive correlations between nutrition deficiency and ADHD symptom severity (Konofal *et al.* 2004; Arnold *et al.* 2005). However, there is insufficient evidence at this stage to implicate such deficiencies as a causal factor in ADHD (Thapar *et al.* 2013). Nutritional deficiencies are not a consistent observation, possibly because of methodological differences between studies (Cortese *et al.* 2012a). It is also unclear whether diet is the primary cause of nutritional deficiencies or whether the nutrients are metabolized differently in some children with ADHD (Burgess *et al.* 2000).

Despite this, many parents may report diet as a factor that exacerbates their child's ADHD symptoms (Daley 2006). Artificial food colourings have been found to increase hyperactivity in both typically developing children (McCann *et al.* 2007) and children already displaying high levels of hyperactivity, although with a relatively small effect size (0.28; Schab & Trinh 2004). Dietary intervention may therefore be a promising option to ameliorate symptoms in some children (Sonuga-Barke *et al.* 2013); we will return to discuss this later in the review.

Familial environment/parenting

Adverse familial environments and parenting practices are commonly observed in families of children with ADHD (Johnston

& Mash 2001; Hinshaw 2002; Seipp & Johnston 2005). However, the extent to which such parenting practices are casual factors in ADHD, or rather responsive to negative child behaviour remains unclear. Longitudinal evidence exploring the temporal relationship between parenting and ADHD is beginning to emerge but thus far has produced relatively mixed findings (Lifford *et al.* 2008; Keown 2012). It is most likely that the relationship between parenting and child behaviour is bi-directional, and parents respond to genetically determined negative child behaviour in a way that serves to maintain or exacerbate the child's behaviour (Johnston & Jassy 2007). Encouraging parents to engage in supportive and proactive parenting could therefore interrupt risk pathways (Sonuga-Barke *et al.* 2005). Additionally, parenting may also be an important factor contributing to other areas of functioning that are commonly suboptimal in ADHD, including oppositional behaviour and academic, social and cognitive functioning (Hughes & Ensor 2009; Deault 2010).

The high heritability rates of ADHD make it possible that a number of parents attending clinics may have ADHD themselves and their symptoms are likely to impact on their parenting skills. Parental ADHD is associated with the use of more adverse discipline practices and higher levels of family chaos (Johnston *et al.* 2012). Parental ADHD may only come to light when parents present to services with their children and consequently, they may require referral to specialist adult ADHD services (NICE 2008).

Early deprivation/neglect

While the influence of less than optimal parenting practices on ADHD remains unclear, there seems to be stronger evidence implicating severe early neglect as a risk factor for later ADHD type symptoms. Although not likely to be a common pathway to ADHD in the UK, cases of severe deprivation and neglect experienced by children raised in Romanian orphanages is associated with later inattention and over activity, despite subsequent adoption into UK families (Rutter *et al.* 2001).

Gene–environment interactions

It is generally accepted that complex disorders such as ADHD develop as the result of interplay between genetic and environmental factors (Rutter *et al.* 2006). Gene–environment interactions (GxE) offer a plausible explanation as to why some children show susceptibility to environmental risks while others are somewhat resilient (Wermter *et al.* 2010). Although still in their infancy, exploratory studies are beginning to identify

circumstances in which specific genetic variants and environmental factors interact to heighten risk of ADHD (Nigg *et al.* 2010). However, despite encouraging early findings, there is currently a lack of replication in GxE effects and heterogeneity among trials prevents pooled analysis of effects (Nigg *et al.* 2010). In addition, genes and environments can overlap in other ways (gene–environment correlations; rGE). For example, genes can determine the types of environment a person is exposed to (including the quality of parenting received), while environmental experience can also influence gene expression (Rutter *et al.* 2006). rGE may therefore manifest as GxE interactions and future research designs should control for the potential confounding influences of rGE (Wermter *et al.* 2010).

Co-morbidities and functional impairments

ADHD is often comorbid with a number of other psychiatric conditions and functional impairments which may become evident during clinical assessments. Parents may report more concern about such impairments than ADHD symptoms and these are therefore important factors to consider during treatment planning. While discussion of all possible presenting co-morbidities and functioning deficits is beyond the scope of this review, we touch upon some of the most common in the following section.

Neuropsychological functioning

A number of neuropsychological models of ADHD have attempted to explain the behavioural and cognitive manifestations of ADHD. These include deficits in executive function (EF) (Barkley 1997; Castellanos & Tannock 2002), delay aversion (Sonuga-Barke *et al.* 1992) and temporal processing deficits (Sonuga-Barke *et al.* 2010). EF is used to describe higher-order cognitive functions including inhibitory control and working memory. EF deficits have featured prominently in neuropsychological models of ADHD and are in keeping with the structural abnormalities observed in the frontal regions of the brain discussed above (Seidman 2006). Functional magnetic resonance imaging (fMRI) data also reveal hypo-activation in areas involved in EF in children with ADHD (Cortese *et al.* 2012c), who often perform poorly on tasks measuring aspects of EF (Willcutt *et al.* 2005). Behaviourally, EF deficits may manifest as forgetfulness and difficulty in planning and co-ordinating everyday tasks such as getting ready for school. However, distinct neuropsychological profiles are evident in children with ADHD and are demonstrated by differential performance on a number of tasks measuring neuropsychological

functioning (Coghill *et al.* 2013b). More recent models of ADHD have attempted to capture this heterogeneity by incorporating a number of pathways that may affect children differently (Sonuga-Barke 2002; Sonuga-Barke *et al.* 2010). Alternative theories include delay aversion, based upon evidence that children with ADHD display preference for smaller immediate rewards, rather than larger later ones (Sonuga-Barke *et al.* 1992) and temporal processing deficits which lead children to under-estimate passage of time (Toplak *et al.* 2006; Luman *et al.* 2008). This particular deficit may explain behaviours such as an inability to wait turn (Toplak & Tannock 2005).

Emotional functioning

Emotional dysfunction is also a common feature of ADHD. Many parents report that their child displays low levels of emotional control and high negative emotionality (high levels of anger, frustration) (Anastopoulos *et al.* 2011). They may also display impairments during emotion recognition tasks (Da Fonseca *et al.* 2009; Sjowall *et al.* 2013). As with neuropsychological functioning, emotion functioning deficits in ADHD are heterogeneous. For example, analysis of autonomic activity during emotion suppression and induction tasks reveal differential patterns of arousal in children with ADHD according to the levels of pro-social behaviour that they display (Musser *et al.* 2013). There is a need for increased understanding of the role of emotional processing in children with ADHD (Martel 2009) and possible inclusion of emotion regulation into future neuropsychological models. This follows evidence that some children show deficits in emotion functioning yet remain unimpaired on measures of neuropsychological functioning including executive function and delay aversion (Sjowall *et al.* 2013). In addition, emotional regulation is a key factor in predicting later adverse life events including school exclusions and difficulties with family relationships highlighting the importance of targeting emotional functioning in interventions (Barkley & Fischer 2010).

Social/peer functioning

Children with ADHD often display impaired social performance and are more likely to be nominated by their peers as someone they would least like to be friends with (Hinshaw & Melnick 1995; Hoza *et al.* 2005). The behavioural manifestations associated with ADHD are likely to affect social performance, resulting in children appearing as less attractive playmates (Hoza 2007). For example, children with ADHD combined type are more aggressive and intrusive during social

interactions, whereas primarily inattentive children may appear withdrawn and display poorer memory of interactions (Mikami *et al.* 2007).

Academic functioning

Academic underachievement is a common feature of children with ADHD and is evident from pre-school (DuPaul *et al.* 2001) through to adolescence (Frazier *et al.* 2007). ADHD is associated with poorer grades and lower scores on standardized tests of academic ability (Barry *et al.* 2002; Loe & Feldman 2007). It has been suggested that symptoms of inattention and EF deficits may play a larger role in academic functioning deficits compared with symptoms of hyperactivity or comorbid disruptive behaviour (Daley & Birchwood 2010). Children with ADHD are more likely to require specialist academic support, repeat a school year or leave school with little or no qualifications (Barkley *et al.* 2006). The ability of interventions to target academic functioning is therefore paramount in order to ensure the best long-term outcomes for children with ADHD.

Disruptive behaviour disorders

ADHD is highly comorbid with disruptive behaviour disorders including oppositional defiant disorder (ODD) and conduct disorder (CD); as many as 50% of children also display CD or ODD (Biederman *et al.* 1991; Faraone *et al.* 2002). Early intervention may be key with children displaying early signs of hyperactivity and disruptive behaviour, given the added complexity and more adverse long-term outcomes associated with comorbid behavioural problems (Connor *et al.* 2010). In addition, evidence suggests that children with ADHD and established behaviour problems tend to be more resistant to treatment (Villodas *et al.* 2012).

Mood and anxiety disorders

Mood disorders (e.g. major depressive disorder, dysthymia and bipolar disorder) and anxiety disorders (e.g. separation anxiety, generalized anxiety disorder, panic disorder) are also commonly observed in children with ADHD. In a clinically referred sample of 381 school age children with ADHD, 50% also had a mood disorder, while 33% displayed anxiety disorders (Wilens *et al.* 2002). Treatment with stimulant medication may reduce the risk of later development of mood and anxiety disorders (Biederman *et al.* 2009). There is also evidence suggesting that children displaying comorbid internalizing symptoms or

anxiety show preferential response to behavioural interventions (Jensen *et al.* 2001; van den Hoofdakker *et al.* 2007).

Tic disorders

Children with ADHD may also present with comorbid tic disorders or Tourette syndrome (TS). It is estimated that 60–70% of children with TS will also meet diagnostic criteria for ADHD (Swain *et al.* 2007). The presence of tics can complicate treatment planning because of concerns that pharmacological treatment can exacerbate tic symptoms. However, there is evidence that treatment with methylphenidate and atomoxetine can be effective treatments for ADHD symptoms without worsening tic symptoms (Bloch *et al.* 2009). Treatment of ADHD symptoms is important given the adverse consequences associated with comorbid ADHD symptoms in children with TS (Debes *et al.* 2010).

Substance misuse

ADHD is also associated with later problems with substance misuse. Approximately one in four patients with substance dependence will also have ADHD (van Emmerik-van Oortmerssen *et al.* 2012). It is unclear at this stage to what extent this association is accounted for by comorbid CD. While it is likely that children with comorbid CD are at heightened risk for later substance misuse (Lee *et al.* 2011), the independent effect of ADHD symptoms on later substance misuse is also evident (Szobot *et al.* 2007). Meta-analytical evidence suggests that treatment with pharmacotherapy is associated with a 1.9-fold reduction in risk for later substance misuse, compared with children who did not receive treatment with pharmacotherapy (Wilens *et al.* 2003)

Motor co-ordination

Poor motor co-ordination affects some children with ADHD, particularly boys (Cole *et al.* 2008). Motor deficits may manifest as involuntary movements that occur in the presence of voluntary movements, possibly because of inhibitory control deficits (Mostofsky *et al.* 2003), or poor rhythm or timing in movements (Cole *et al.* 2008). Difficulties in motor co-ordination can result in clumsiness, perhaps explaining the high rates of injury in children with ADHD (Rowe *et al.* 2004) and poor handwriting (Brossard-Racine *et al.* 2011) and performance in sports (Harvey *et al.* 2009).

Treatment

Although there is currently no cure for ADHD, pharmacological and non-pharmacological treatment options are available for symptom management and to improve function. Pharmacological treatments include both stimulant and non-stimulant options, while recommended non-pharmacological treatments include behavioural parenting interventions and child psychological therapy.

Pharmacotherapy

Pharmacotherapy has proven efficacy for short-term improvement in ADHD symptoms and is consequently recommended as part of a multimodal treatment approach for school age children displaying moderate to severe levels of impairment (NICE 2008). The stimulant methylphenidate is the most commonly prescribed medication for ADHD (Buitelaar & Medori 2010) and works by increasing extracellular levels of dopamine by blocking its reuptake into the presynaptic neuron. Lisdexamphetamine dimesylate (LDX), is an alternative long-acting stimulant option licensed for treatment in the UK after proven efficacy and tolerability in clinical trials (Coghill *et al.* 2013a). LDX could be considered when little clinical benefit is observed from the maximum tolerable doses of methylphenidate. Atomoxetine offers an alternative non-stimulant option and works by increasing extracellular levels of noradrenaline. Generally, head to head trials suggest that methylphenidate is more efficacious than atomoxetine, particularly long-acting formulations (Hanwella *et al.* 2011). Atomoxetine is therefore recommended for children who are unresponsive to methylphenidate, experience intolerable side-effects or when clinicians have concerns about inappropriate use of stimulants.

A number of adverse side-effects may be reported with pharmacological treatment. Some of the most common include loss of appetite and sleep problems. Generally, such side-effects are manageable and tolerable, particularly if the desired treatment outcomes are evident (Cortese *et al.* 2013). Adherence to drug treatment can also be problematic but may be improved with longer lasting drug formulations which do not require multiple doses to be taken throughout the day (Adler & Nierenberg 2010). It is of note that despite their widely acknowledged short-term efficacy, the long-term effectiveness of pharmacological treatment for ADHD remains in doubt and functioning outcomes often fail to normalize (Nijmeijer *et al.* 2008; Langberg & Becker 2012). Therefore, although medication may improve academic productivity and behaviour in the classroom (Prasad *et al.* 2012), it is important for clinicians to be realistic

with parents during treatment planning about the ability of medication to normalize functioning outcomes such as academic performance (Antshel *et al.* 2011).

Non-pharmacological treatment options

A number of non-pharmacological treatment options are available as intervention options for ADHD. Although they may offer less control over symptoms, it is important for clinicians to be aware of and have access to non-pharmacological options for a number of reasons. Firstly, while questions regarding their safety and efficacy in very young children remain, medication is not currently recommended for preschool children (Daley *et al.* 2009). In addition, some parents may feel uncomfortable or have ethical concerns about modifying their child's behaviour with drug treatment. Finally, adverse side-effects may prevent their use. Behavioural parenting interventions, social skills training and cognitive behavioural therapy are recommended as treatment options in the UK (NICE 2008).

Parenting interventions

Behavioural parenting interventions are recommended as first line treatment options for the treatment of ADHD in childhood (NICE 2008). Recommended interventions are based on social learning principles and include strategies for parents aimed at increasing the frequency of adaptive child behaviours while reducing the occurrence of non-compliant or disruptive behaviour. Their efficacy as treatments for ADHD symptoms has been previously supported by meta-analyses (Fabiano *et al.* 2009). However, concern has been raised as to whether recommended parenting interventions are sufficiently targeting ADHD symptoms, following evidence that effect sizes for behavioural interventions (including parenting interventions) drop to near zero when analysing data from informants who are probably blind to treatment allocation (Sonuga-Barke *et al.* 2013).

There is a need for future clinical trials of non-pharmacological interventions in ADHD to include blinded measures to ensure their efficacy as treatments for core ADHD symptoms. It is probable that parental report of symptoms following parenting interventions is prone to bias after the investment of time that parents spend in delivering the intervention. However, it is important to remember that parenting interventions should be seen as components of treatment targeting a wide range of outcomes and may provide additional benefit for child and parental well-being beyond ADHD symptom

reduction (Sonuga-Barke *et al.* 2006). During treatment planning, clinicians should consider factors known to lead to poorer treatment outcomes from parenting interventions. These include broad co-morbidity in children, parental ADHD symptoms, parenting efficacy and parental depressive symptoms (Sonuga-Barke *et al.* 2002; Owens *et al.* 2003; van den Hoofdakker *et al.* 2010).

Classroom-based interventions

Similar to parenting interventions, classroom-based interventions usually include behavioural strategies for the teacher and promote the use of token economy or contingency-based programmes to improve problematic classroom behaviour. Classroom-based interventions can also include components aimed at improving academic performance, for example shortening task length according to the child's attention span (DuPaul *et al.* 2011). A number of randomized controlled trials have reported beneficial effects of classroom-based interventions on child behaviour (Chronis *et al.* 2006). Although, as with parenting interventions, there is a need for their efficacy to be confirmed with observations from blinded informants (Sonuga-Barke *et al.* 2013). If classroom interventions are being utilized, integration between home and school is vital to ensure consistency in behavioural approach (Raggi & Chronis 2006). The use of daily report cards can promote communication between home and school by encouraging parental reinforcement at home for behaviour observed during the school day (DuPaul *et al.* 2011).

Child psychological therapy

Psychological treatment for children with ADHD can include sessions covering social skills training, anger management and problem solving. Although such approaches are recommended for some children with ADHD (NICE 2008), the evidence supporting their efficacy is limited at this stage (Toplak *et al.* 2008; Storebo *et al.* 2011). The Incredible Years (IY) programme offers a child training programme that when used in adjunct to the IY parenting programme, is associated with improvement in ADHD symptoms and defiant child behaviour in pre-school children (Webster-Stratton *et al.* 2011). In addition, treatment effects were maintained 12 months post intervention (Webster-Stratton *et al.* 2013). It is possible that psychological treatment may be more efficacious when implemented as part of a multimodal approach during the pre-school years, although this is a matter awaiting future research.

Diet

Above, we referred to a series of recently published meta-analyses of non-pharmacological interventions for the treatment of ADHD. Sonuga-Barke and colleagues (2013) reported that effect sizes for all interventions dropped to non-significance in analyses of outcomes from probably blinded assessors, with the exception of two dietary interventions (free fatty acid supplementation and restricted food colouring). This could therefore be taken as evidence that dietary interventions offer the most promise for the future of non-pharmacological interventions for ADHD. However, NICE guidelines do not currently recommend the use of dietary interventions. Meta-analyses have shown that restricted food colouring diets and omega-3 supplementation are effective in reducing ADHD symptoms, yet effect sizes are small and study inclusion is often restricted to families where parents have reported an adverse link between food and their child's behaviour (Bloch & Qawasmi 2011; Nigg *et al.* 2012). The methodological quality of some dietary intervention studies has also been questioned (Nigg *et al.* 2012). Restrictive diets are likely to be difficult and expensive for parents to implement, particularly in families facing other psychosocial adversities. Where parents report a link between food and drink consumption and their child's behaviour, they should be encouraged to keep a food diary and clinicians should consider possible referral to a dietician where necessary (NICE 2008).

Discussion and summary

ADHD is a heterogeneous disorder; aetiological factors, clinical presentation and response to treatment are likely to vary greatly between individuals. For that reason, it can be very difficult for clinicians to answer parents' questions and advise them about ADHD in their child. Despite huge developments in ADHD research over the past 10 years or so, it is clear that there is still a long way to go before we fully understand risk factors for the disorder and the best treatment approaches. However, in this review, we have briefly summarized some of the key research findings that may be useful for clinicians when addressing queries from parents.

We have discussed some of the commonly cited factors that have been associated with heightened risk of ADHD diagnosis or symptoms. GxE offer substantial promise for the future understanding of ADHD aetiology (Wermter *et al.* 2010) and genetic research is striving to identify specific interactions between gene variants and environmental risk factors that heighten risk for ADHD. Identifying environmental risk factors that may heighten

risk for disorder in those with genetic vulnerability is paramount given that they are likely to be more amenable to intervention; we are probably a long way from genetic research holding any clinical impact (Thapar *et al.* 2013).

In this review we also referred to some of the functional impairments and co-morbidities that commonly occur in children with ADHD. It is vital that clinicians are aware of these factors during treatment planning and assessment. Such impairments are likely to leave children at risk for poorer outcomes in adulthood such as unemployment and difficult social relationships (Barkley *et al.* 2006). However, a major focus for future research should be on the development of interventions that target some of the functional impairments in children with ADHD. Even long-term treatment with medication is currently unable to normalize functioning outcomes such as social functioning and academic performance (Nijmeijer *et al.* 2008; Langberg & Becker 2012).

The efficacy of non-pharmacological interventions for core ADHD symptoms is currently receiving a lot of attention following the findings from the aforementioned meta-analyses reported by Sonuga-Barke and colleagues (2013). Such findings may lead some to question whether non-pharmacological interventions for ADHD are currently targeting ADHD symptoms sufficiently. There is now growing interest in the development of interventions that target some of the neuropsychological impairments thought to underlie ADHD (Halperin & Healey 2011; Halperin *et al.* 2012). However, at this stage it remains unclear whether improving cognitive deficits will result in subsequent improvement in ADHD symptoms. For example, some evidence suggests that improvement in neuropsychological functioning after treatment with pharmacotherapy is only modestly related to symptomatic improvement (Coghill *et al.* 2007). However, alternative longitudinal research has revealed that improvement in neuropsychological functioning over time is associated with attenuated ADHD symptoms (Rajendran *et al.* 2013). From a neurodevelopmental perspective, it is argued that such interventions should be implemented during the pre-school years in order to interrupt risk pathways (Sonuga-Barke & Halperin 2010). While the efficacy of preventative interventions are important and ongoing avenues for research into non-pharmacological interventions in ADHD, non-pharmacological interventions that are currently recommended should not be seen as redundant interventions following the Sonuga-Barke and colleagues (2013) findings. They are likely to offer therapeutic benefits to parent and child reaching beyond ADHD symptoms (Sonuga-Barke *et al.* 2006) and offer a suitable alternative intervention when treatment with pharmacotherapy is not appropriate or sufficient.

Key messages

- ADHD is a prevalent and heterogeneous disorder with both inherited and non-inherited factors playing a role in its complex aetiology.
- ADHD is associated with substantial impairment in numerous areas of functioning including social and peer functioning, academic attainment and emotional and cognitive functioning which are important to consider during treatment planning.
- Treatment options currently include pharmacological and non-pharmacological interventions which have varying degrees of evidence for their efficacy.
- Pharmacotherapy may be unable to normalize functioning. Development of interventions that successfully target functioning deficits is vital to improve the long-term outcomes of children with ADHD.

Conflict of interests

Professor Daley has served as a speaker or adviser for or received funding or travel support from Eli Lilly, Janssen-Cilag, UCB and Shire. Professor Daley has also been involved in the development, implementation and evaluation of the New Forest Parenting Programme for children with ADHD and has received royalties from sales of a New Forest Parent Training self-help book.

Acknowledgements

JT and KS are partially funded by the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for Nottinghamshire, Derbyshire, Lincolnshire and JT is partly funded by the Institute of Mental Health at the University of Nottingham.

References

- Adler, L. D. & Nierenberg, A. A. (2010) Review of medication adherence in children and adults with ADHD. *Postgraduate Medicine*, 122, 184–191.
- Anastopoulos, A. D., Smith, T. F., Garrett, M. E., Morrissey-Kane, E., Schatz, N. K., Sommer, J. L., Kollins, S. H. & Ashley-Koch, A. (2011) Self-regulation of emotion, functional impairment, and comorbidity among children with AD/HD. *Journal of Attention Disorders*, 15, 583–592.
- Antshel, K. M., Hargrave, T. M., Simonescu, M., Kaul, P., Hendricks, K. & Faraone, S. V. (2011) Advances in understanding and treating ADHD. *BMC Medicine*, 9, 72.

- APA (2013) *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Publishing, Arlington, VA, USA.
- Arnold, L. E., Bozzolo, H., Hollway, J., Cook, A., Disilvestro, R. A., Bozzolo, D. R., Crowl, L., Ramadan, Y. & Williams, C. (2005) Serum zinc correlates with parent- and teacher-rated inattention in children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, **15**, 628–636.
- Barkley, R. A. (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin*, **121**, 65.
- Barkley, R. A. & Fischer, M. (2010) The unique contribution of emotional impulsiveness to impairment in major life activities in hyperactive children as adults. *Journal of the American Academy of Child and Adolescent Psychiatry*, **49**, 503–513.
- Barkley, R. A., Fischer, M., Smallish, L. & Fletcher, K. (2006) Young adult outcome of hyperactive children: adaptive functioning in major life activities. *Journal of the American Academy of Child and Adolescent Psychiatry*, **45**, 192–202.
- Barry, T. D., Lyman, R. D. & Klinger, L. G. (2002) Academic underachievement and Attention-Deficit/Hyperactivity Disorder: the negative impact of symptom severity on school performance. *Journal of School Psychology*, **40**, 259–283.
- Batty, M. J., Liddle, E. B., Pitiot, A., Toro, R., Groom, M. J., Scerif, G., Liotti, M., Liddle, P. F., Paus, T. & Hollis, C. (2010) Cortical gray matter in attention-deficit/hyperactivity disorder: a structural magnetic resonance imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry*, **49**, 229–238.
- Biederman, J., Newcorn, J. & Sprich, S. (1991) Comorbidity of attention deficit hyperactivity disorder. *American Journal of Psychiatry*, **148**, 546–557.
- Biederman, J., Monuteaux, M. C., Spencer, T., Wilens, T. E. & Faraone, S. V. (2009) Do stimulants protect against psychiatric disorders in youth with ADHD? A 10-year follow-up study. *Pediatrics*, **124**, 71–78.
- Bloch, M. H. & Qawasmi, A. (2011) Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: systematic review and meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*, **50**, 991–1000.
- Bloch, M. H., Panza, K. E., Landeros-Weisenberger, A. & Leckman, J. F. (2009) Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, **48**, 884–893.
- Brossard-Racine, M., Majnemer, A., Shevell, M., Snider, L. & Belanger, S. A. (2011) Handwriting capacity in children newly diagnosed with Attention Deficit Hyperactivity Disorder. *Research in Developmental Disabilities*, **32**, 2927–2934.
- Buitelaar, J. & Medori, R. (2010) Treating attention-deficit/hyperactivity disorder beyond symptom control alone in children and adolescents: a review of the potential benefits of long-acting stimulants. *European Child and Adolescent Psychiatry*, **19**, 325–340.
- Burgess, J. R., Stevens, L., Zhang, W. & Peck, L. (2000) Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. *The American Journal of Clinical Nutrition*, **71**, 327S–330S.
- Castellanos, F. X. & Tannock, R. (2002) Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nature Reviews. Neuroscience*, **3**, 617–628.
- Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N. O., Greenstein, D. K., Clasen, L. S., Blumenthal, J. D., James, R. S., Ebens, C. L. & Walter, J. M. (2002) Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA: The Journal of the American Medical Association*, **288**, 1740–1748.
- Chronis, A. M., Jones, H. A. & Raggi, V. L. (2006) Evidence-based psychosocial treatments for children and adolescents with attention-deficit/hyperactivity disorder. *Clinical Psychology Review*, **26**, 486–502.
- Coghill, D., Banaschewski, T., Lecendreux, M., Soutullo, C., Johnson, M., Zuddas, A., Anderson, C., Civil, R., Higgins, N., Lyne, A. & Squires, L. (2013a) European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. *European Neuropsychopharmacology*, **23**, 1208–1218.
- Coghill, D., Seth, S. & Matthews, K. (2013b) A comprehensive assessment of memory, delay aversion, timing, inhibition, decision making and variability in attention deficit hyperactivity disorder: advancing beyond the three-pathway models. *Psychological Medicine*, available on CJO2013. doi:10.1017/S0033291713002547
- Coghill, D. R., Rhodes, S. M. & Matthews, K. (2007) The neuropsychological effects of chronic methylphenidate on drug-naïve boys with attention-deficit/hyperactivity disorder. *Biological Psychiatry*, **62**, 954–962.
- Cole, W., Mostofsky, S., Larson, J. G., Denckla, M. & Mahone, E. (2008) Age-related changes in motor subtle signs among girls and boys with ADHD. *Neurology*, **71**, 1514–1520.
- Connor, D. F., Steeber, J. & McBurnett, K. (2010) A review of attention-deficit/hyperactivity disorder complicated by symptoms of oppositional defiant disorder or conduct disorder. *Journal of Developmental and Behavioral Pediatrics*, **31**, 427–440.
- Cortese, S. (2012) The neurobiology and genetics of Attention-Deficit/Hyperactivity Disorder (ADHD): what every clinician should know. *European Journal of Paediatric Neurology*, **16**, 422–433.
- Cortese, S., Angriman, M., Lecendreux, M. & Konofal, E. (2012a) Iron and attention deficit/hyperactivity disorder: what is the empirical evidence so far? A systematic review of the literature. *Expert Review of Neurotherapeutics*, **12**, 1227–1240.
- Cortese, S., Azoulay, R., Castellanos, F. X., Chalard, F., Lecendreux, M., Chechin, D., Delorme, R., Sebag, G., Sbarbati, A. & Mouren, M.-C. (2012b) Brain iron levels in attention-deficit/hyperactivity disorder: a pilot MRI study. *World Journal of Biological Psychiatry*, **13**, 223–231.
- Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P. & Castellanos, F. X. (2012c) Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *American Journal of Psychiatry*, **169**, 1038–1055.

- Cortese, S., Holtmann, M., Banaschewski, T., Buitelaar, J., Coghill, D., Danckaerts, M., Dittmann, R. W., Graham, J., Taylor, E. & Sergeant, J. (2013) Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *Journal of Child Psychology and Psychiatry*, *54*, 227–246.
- Da Fonseca, D., Seguíer, V., Santos, A., Poinso, F. & Deruelle, C. (2009) Emotion understanding in children with ADHD. *Child Psychiatry and Human Development*, *40*, 111–121.
- Daley, D. (2006) Attention deficit hyperactivity disorder: a review of the essential facts. *Child: Care, Health and Development*, *32*, 193–204.
- Daley, D. & Birchwood, J. (2010) ADHD and academic performance: why does ADHD impact on academic performance and what can be done to support ADHD children in the classroom? *Child: Care, Health and Development*, *36*, 455–464.
- Daley, D., Jones, K., Hutchings, J. & Thompson, M. (2009) Attention deficit hyperactivity disorder in pre-school children: current findings, recommended interventions and future directions. *Child: Care, Health and Development*, *35*, 754–766.
- Deault, L. (2010) A systematic review of parenting in relation to the development of comorbidities and functional impairments in children with attention-deficit/hyperactivity disorder (ADHD). *Child Psychiatry and Human Development*, *41*, 168–192.
- Debes, N., Hjalgrim, H. & Skov, L. (2010) The presence of attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder worsen psychosocial and educational problems in Tourette syndrome. *Journal of Child Neurology*, *25*, 171–181.
- 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.
- DuPaul, G. J., Weyandt, L. L. & Janusis, G. M. (2011) ADHD in the classroom: effective intervention strategies. *Theory into Practice*, *50*, 35–42.
- Durston, S., Hulshoff Pol, H. E., Schnack, H. G., Buitelaar, J. K., Steenhuis, M. P., Minderaa, R. B., Kahn, R. S. & Van Engeland, H. (2004) Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. *Journal of the American Academy of Child and Adolescent Psychiatry*, *43*, 332–340.
- van Emmerik-van Oortmerssen, K., Van De Glind, G., Van Den Brink, W., Smit, F., Crunelle, C. L., Swets, M. & Schoevers, R. A. (2012) Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: a meta-analysis and meta-regression analysis. *Drug and Alcohol Dependence*, *122*, 11–19.
- Fabiano, G. A., Pelham, W. E., Coles, E. K., Gnagy, E. M., Chronis-Tuscano, A. & O'Connor, B. C. (2009) A meta-analysis of behavioral treatments for attention-deficit/hyperactivity disorder. *Clinical Psychology Review*, *29*, 129–140.
- Faraone, S. V., Biederman, J. & Monuteaux, M. C. (2002) Further evidence for the diagnostic continuity between child and adolescent ADHD. *Journal of Attention Disorders*, *6*, 5–13.
- Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A. & Sklar, P. (2005) Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *57*, 1313–1323.
- Franke, B., Neale, B. M. & Faraone, S. V. (2009) Genome-wide association studies in ADHD. *Human Genetics*, *126*, 13–50.
- Frazier, T. W., Youngstrom, E. A., Glutting, J. J. & Watkins, M. W. (2007) ADHD and achievement meta-analysis of the child, adolescent, and adult literatures and a concomitant study with college students. *Journal of Learning Disabilities*, *40*, 49–65.
- Geissler, J. & Lesch, K.-P. (2011) A lifetime of attention-deficit/hyperactivity disorder: diagnostic challenges, treatment and neurobiological mechanisms. *Expert Review of Neurotherapeutics*, *11*, 1467–1484.
- Gizer, I. R., Ficks, C. & Waldman, I. D. (2009) Candidate gene studies of ADHD: a meta-analytic review. *Human Genetics*, *126*, 51–90.
- Halperin, J. M. & Healey, D. M. (2011) The influences of environmental enrichment, cognitive enhancement, and physical exercise on brain development: can we alter the developmental trajectory of ADHD? *Neuroscience and Biobehavioral Reviews*, *35*, 621–634.
- Halperin, J. M., Marks, D. J., Bedard, A. C., Chacko, A., Curchack, J. T., Yoon, C. A. & Healey, D. M. (2012) Training executive, attention, and motor skills: a proof-of-concept study in preschool children with ADHD. *Journal of Attention Disorders*, doi: 10.1177/1087054711435681.
- Hanwella, R., Senanayake, M. & De Silva, V. (2011) Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. *BMC Psychiatry*, *11*, 176.
- Harvey, W. J., Reid, G., Bloom, G. A., Staples, K., Grizenko, N., Mbekou, V., Ter-Stepanian, M. & Joober, R. (2009) Physical activity experiences of boys with and without ADHD. *Adapted Physical Activity Quarterly*, *26*, 131–150.
- Heinonen, K., Räikkönen, K., Pesonen, A.-K., Andersson, S., Kajantie, E., Eriksson, J., Wolke, D. & Lano, A. (2010) Behavioural symptoms of attention deficit/hyperactivity disorder in preterm and term children born small and appropriate for gestational age: a longitudinal study. *BMC Pediatrics*, *10*, 91.
- Hinshaw, S. P. (2002) Preadolescent girls with attention-deficit/hyperactivity disorder: I. Background characteristics, comorbidity, cognitive and social functioning, and parenting practices. *Journal of Consulting and Clinical Psychology*, *70*, 1086–1098.
- Hinshaw, S. P. & Melnick, S. M. (1995) Peer relationships in boys with attention-deficit hyperactivity disorder with and without comorbid aggression. *Development and Psychopathology*, *7*, 627–647.
- van den Hoofdakker, B. J., Van Der Veen-Mulders, L., Sytema, S., Emmelkamp, P. M., Minderaa, R. B. & Nauta, M. H. (2007) Effectiveness of behavioral parent training for children with

- ADHD in routine clinical practice: a randomized controlled study. *Journal of the American Academy of Child and Adolescent Psychiatry*, **46**, 1263–1271.
- van den Hoofdakker, B. J., Nauta, M. H., Van Der Veen-Mulders, L., Sytma, S., Emmelkamp, P. M. G., Minderaa, R. B. & Hoekstra, P. J. (2010) Behavioral parent training as an adjunct to routine care in children with attention-deficit/hyperactivity disorder: moderators of treatment response. *Journal of Pediatric Psychology*, **35**, 317–326.
- Hoza, B. (2007) Peer functioning in children with ADHD. *Journal of Pediatric Psychology*, **32**, 655–663.
- Hoza, B., Gerdes, A. C., Mrug, S., Hinshaw, S. P., Bukowski, W. M., Gold, J. A., Arnold, L. E., Abikoff, H. B., Conners, C. K. & Elliott, G. R. (2005) Peer-assessed outcomes in the multimodal treatment study of children with attention deficit hyperactivity disorder. *Journal of Clinical Child and Adolescent Psychology*, **34**, 74–86.
- Hughes, C. & Ensor, R. A. (2009) How do families help or hinder the emergence of early executive function? *New Directions for Child and Adolescent Development*, **2009**, 35–50.
- Hultman, C. M., Torráng, A., Tuvblad, C., Cnattingius, S., Larsson, J.-O. & Lichtenstein, P. (2007) Birth weight and attention-deficit/hyperactivity symptoms in childhood and early adolescence: a prospective Swedish twin study. *Journal of the American Academy of Child and Adolescent Psychiatry*, **46**, 370–377.
- Jensen, P. S., Hinshaw, S. P., Kraemer, H. C., Lenora, N., Newcorn, J. H., Abikoff, H. B., March, J. S., Arnold, L. E., Cantwell, D. P., Conners, C. K., Elliott, G. R., Greenhill, L. L., Hechtman, L., Hoza, B., Pelham, W. E., Severe, J. B., Swanson, J. M., Wells, K. C., Wigal, T. & Vitiello, B. (2001) ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. *Journal of the American Academy of Child and Adolescent Psychiatry*, **40**, 147–158.
- Johnson, S., Hollis, C., Kochhar, P., Hennessy, E., Wolke, D. & Marlow, N. (2010) Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. *Journal of the American Academy of Child and Adolescent Psychiatry*, **49**, 453–463.e451.
- Johnston, C. & Jassy, J. S. (2007) Attention-deficit/hyperactivity disorder and oppositional/conduct problems: links to parent-child interactions. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, **16**, 74.
- Johnston, C. & Mash, E. J. (2001) Families of children with attention-deficit/hyperactivity disorder: review and recommendations for future research. *Clinical Child and Family Psychology Review*, **4**, 183–207.
- Johnston, C., Mash, E. J., Miller, N. & Ninowski, J. E. (2012) Parenting in adults with attention-deficit/hyperactivity disorder (ADHD). *Clinical Psychology Review*, **32**, 215–228.
- Keown, L. J. (2012) Predictors of boys' ADHD symptoms from early to middle childhood: the role of father-child and mother-child interactions. *Journal of Abnormal Child Psychology*, **40**, 569–581.
- 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.
- Langberg, J. M. & Becker, S. P. (2012) Does long-term medication use improve the academic outcomes of youth with attention-deficit/hyperactivity disorder? *Clinical Child and Family Psychology Review*, **15**, 215–233.
- Langley, K., Rice, F., Van Den Bree, M. B. & Thapar, A. (2005) Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review. *Minerva Pediatrica*, **57**, 359–371.
- Langley, K., Heron, J., Smith, G. D. & Thapar, A. (2012) Maternal and paternal smoking during pregnancy and risk of ADHD symptoms in offspring: testing for intrauterine effects. *American Journal of Epidemiology*, **176**, 261–268.
- Lee, S. S., Humphreys, K. L., Flory, K., Liu, R. & Glass, K. (2011) Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. *Clinical Psychology Review*, **31**, 328–341.
- Lifford, K. J., Harold, G. T. & Thapar, A. (2008) Parent-child relationships and ADHD symptoms: a longitudinal analysis. *Journal of Abnormal Child Psychology*, **36**, 285–296.
- Loe, I. M. & Feldman, H. M. (2007) Academic and educational outcomes of children with ADHD. *Journal of Pediatric Psychology*, **32**, 643–654.
- Luman, M., Oosterlaan, J. & Sergeant, J. A. (2008) Modulation of response timing in ADHD, effects of reinforcement valence and magnitude. *Journal of Abnormal Child Psychology*, **36**, 445–456.
- Mallard, E., Waldvogel, H., Williams, C., Faull, R. & Gluckman, P. (1995) Repeated asphyxia causes loss of striatal projection neurons in the fetal sheep brain. *Neuroscience*, **65**, 827–836.
- Martel, M. M. (2009) Research Review: a new perspective on attention-deficit/hyperactivity disorder: emotion dysregulation and trait models. *Journal of Child Psychology and Psychiatry*, **50**, 1042–1051.
- McCann, D., Barrett, A., Cooper, A., Crumpler, D., Dalen, L., Grimshaw, K., Kitchin, E., Lok, K., Porteous, L. & Prince, E. (2007) Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *The Lancet*, **370**, 1560–1567.
- McLaughlin, K. A., Sheridan, M. A., Winter, W., Fox, N. A., Zeanah, C. H. & Nelson, C. A. (2013) Widespread reductions in cortical thickness following severe early-life deprivation: a neurodevelopmental pathway to attention-deficit/hyperactivity disorder. *Biological Psychiatry*, pii: S0006-3223(13)00769-5. doi: 10.1016/j.biopsych.2013.08.016.
- Mikami, A. Y., Huang-Pollock, C. L., Pfiffner, L. J., McBurnett, K. & Hangai, D. (2007) Social skills differences among attention-deficit/hyperactivity disorder types in a chat room assessment task. *Journal of Abnormal Child Psychology*, **35**, 509–521.
- Mostofsky, S. H., Newschaffer, C. J. & Denckla, M. B. (2003) Overflow movements predict impaired response inhibition in children with ADHD. *Perceptual and Motor Skills*, **97**, 1315–1331.
- Musser, E. D., Galloway-Long, H. S., Frick, P. J. & Nigg, J. T. (2013) Emotion regulation and heterogeneity in attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, **52**, 163–171.e162.

- Nagel, B. J., Bathula, D., Herting, M., Schmitt, C., Kroenke, C. D., Fair, D. & Nigg, J. T. (2011) Altered white matter microstructure in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, **50**, 283–292.
- Nakao, T., Radua, J., Rubia, K. & Mataix-Cols, D. (2011) Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. *American Journal of Psychiatry*, **168**, 1154–1163.
- Nigg, J., Nikolas, M. M. & Burt, S. A. (2010) Measured gene by environment interaction in relation to Attention-Deficit/Hyperactivity Disorder (ADHD). *Journal of the American Academy of Child and Adolescent Psychiatry*, **49**, 863.
- Nigg, J. T., Lewis, K., Edinger, T. & Falk, M. (2012) Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives. *Journal of the American Academy of Child and Adolescent Psychiatry*, **51**, 86–97.e88.
- Nijmeijer, J. S., Minderaa, R. B., Buitelaar, J. K., Mulligan, A., Hartman, C. A. & Hoekstra, P. J. (2008) Attention-deficit/hyperactivity disorder and social dysfunctioning. *Clinical Psychology Review*, **28**, 692–708.
- NICE (2008) *Diagnosis and management of ADHD in children, young people and adults (National Clinical Practice Number 72)*. The British Psychological Society and the Royal College of Psychiatrists, London.
- Owens, E. B., Hinshaw, S. P., Kraemer, H. C., Arnold, L. E., Abikoff, H. B., Cantwell, D. P., Conners, C. K., Elliott, G., Greenhill, L. L., Hechtman, L., Hoza, B., Jensen, P. S., March, J. S., Newcorn, J. H., Pelham, W. E., Severe, J. B., Swanson, J. M., Vitiello, B., Wells, K. C. & Wigal, T. (2003) Which treatment for whom for ADHD? Moderators of treatment response in the MTA. *Journal of Consulting and Clinical Psychology*, **71**, 540–552.
- Polanczyk, G., De Lima, M., Horta, B., Biederman, J. & Rohde, L. (2007) The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *American Journal of Psychiatry*, **164**, 942–948.
- Prasad, V., Brogan, E., Mulvaney, C., Grainge, M., Stanton, W. & Sayal, K. (2012) How effective are drug treatments for children with ADHD at improving on-task behaviour and academic achievement in the school classroom? A systematic review and meta-analysis. *European Child and Adolescent Psychiatry*, **22**, 203–216.
- Raggi, V. L. & Chronis, A. M. (2006) Interventions to address the academic impairment of children and adolescents with ADHD. *Clinical Child and Family Psychology Review*, **9**, 85–111.
- Rajendran, K., Trampush, J. W., Rindskopf, D., Marks, D. J., O'Neill, S. & Halperin, J. M. (2013) Association between variation in neuropsychological development and trajectory of ADHD severity in early childhood. *American Journal of Psychiatry*, **170**, 1205–1211.
- Rowe, R., Maughan, B. & Goodman, R. (2004) Childhood psychiatric disorder and unintentional injury: findings from a national cohort study. *Journal of Pediatric Psychology*, **29**, 119–130.
- Rutter, M., Moffitt, T. E. & Caspi, A. (2006) Gene–environment interplay and psychopathology: multiple varieties but real effects. *Journal of Child Psychology and Psychiatry*, **47**, 226–261.
- Rutter, M. L., Kreppner, J. M. & O'Connor, T. G. (2001) Specificity and heterogeneity in children's responses to profound institutional privation. *The British Journal of Psychiatry*, **179**, 97–103.
- Schab, D. W. & Trinh, N. H. (2004) Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *Journal of Developmental and Behavioral Pediatrics*, **25**, 423–434.
- 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.
- Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J., Greenstein, D., Clasen, L., Evans, A., Giedd, J. & Rapoport, J. (2007) Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences*, **104**, 19649–19654.
- Simon, V., Czobor, P., Bálint, S., Mészáros, Á. & Bitter, I. (2009) Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *The British Journal of Psychiatry*, **194**, 204–211.
- Sjowall, D., Roth, L., Lindqvist, S. & Thorell, L. B. (2013) Multiple deficits in ADHD: executive dysfunction, delay aversion, reaction time variability, and emotional deficits. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, **54**, 619–627.
- Sonuga-Barke, E. (2002) Psychological heterogeneity in AD/HD: a dual pathway model of behaviour and cognition. *Behavioural Brain Research*, **130**, 29–36.
- Sonuga-Barke, E. & Halperin, J. M. (2010) Developmental phenotypes and causal pathways in attention deficit/hyperactivity disorder: potential targets for early intervention? *Journal of Child Psychology and Psychiatry*, **51**, 368–389.
- Sonuga-Barke, E., Taylor, E., Sembi, S. & Smith, J. (1992) Hyperactivity and delay aversion – I. The effect of delay on choice. *Journal of Child Psychology and Psychiatry*, **33**, 387–398.
- Sonuga-Barke, E., Daley, D. & Thompson, M. (2002) Does maternal ADHD reduce the effectiveness of parent training for preschool children's ADHD? *Journal of the American Academy of Child and Adolescent Psychiatry*, **41**, 696–702.
- Sonuga-Barke, E., Auerbach, J., Campbell, S., Daley, D. & Thompson, M. (2005) Varieties of preschool hyperactivity: multiple pathways from risk to disorder. *Developmental Science*, **8**, 141–150.
- Sonuga-Barke, E., Thompson, M., Abikoff, H., Klein, R. & Brotman, L. M. (2006) Nonpharmacological interventions for preschoolers with ADHD – The case for specialized parent training. *Infants and Young Children*, **19**, 142–153.
- Sonuga-Barke, E., Bitsakou, P. & Thompson, M. (2010) Beyond the dual pathway model: evidence for the dissociation of timing, inhibitory, and delay-related impairments in attention-deficit/

- hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, **49**, 345–355.
- Sonuga-Barke, E., Brandeis, D., Cortese, S., Daley, D., Ferrin, M., Holtmann, M., Stevenson, J., Danckaerts, M., Van Der Oord, S., Dopfner, M., Dittmann, R. W., Simonoff, E., Zuddas, A., Banaschewski, T., Buitelaar, J., Coghill, D., Hollis, C., Konofal, E., Lecendreux, M., Wong, I. C. & Sergeant, J. (2013) Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *American Journal of Psychiatry*, **170**, 275–289.
- Spencer, T. J., Biederman, J., Madras, B. K., Faraone, S. V., Dougherty, D. D., Bonab, A. A. & Fischman, A. J. (2005) In vivo neuroreceptor imaging in attention-deficit/hyperactivity disorder: a focus on the dopamine transporter. *Biological Psychiatry*, **57**, 1293–1300.
- Stevens, L. J., Zentall, S. S., Deck, J. L., Abate, M. L., Watkins, B. A., Lipp, S. R. & Burgess, J. R. (1995) Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder. *The American Journal of Clinical Nutrition*, **62**, 761–768.
- Storebo, O. J., Skoog, M., Damm, D., Thomsen, P. H., Simonsen, E. & Gluud, C. (2011) Social skills training for Attention Deficit Hyperactivity Disorder (ADHD) in children aged 5 to 18 years. *Cochrane Database of Systematic Reviews*, (12), CD008223.
- Swain, J. E., Scahill, L., Lombroso, P. J., King, R. A. & Leckman, J. F. (2007) Tourette syndrome and tic disorders: a decade of progress. *Journal of the American Academy of Child and Adolescent Psychiatry*, **46**, 947–968.
- Szobot, C. M., Rohde, L. A., Bukstein, O., Molina, B. S., Martins, C., Ruaro, P. & Pechansky, F. (2007) Is attention-deficit/hyperactivity disorder associated with illicit substance use disorders in male adolescents? A community-based case-control study. *Addiction (Abingdon, England)*, **102**, 1122–1130.
- Taylor, N., Fauset, A. & Harpin, V. (2010) Young adults with ADHD: an analysis of their service needs on transfer to adult services. *Archives of Disease in Childhood*, **95**, 513–517.
- Thapar, A., Rice, F., Hay, D., Boivin, J., Langley, K., Van Den Bree, M., Rutter, M. & Harold, G. (2009) Prenatal smoking might not cause attention-deficit/hyperactivity disorder: evidence from a novel design. *Biological Psychiatry*, **66**, 722–727.
- Thapar, A., Cooper, M., Eyre, O. & Langley, K. (2013) Practitioner Review: what have we learnt about the causes of ADHD? *Journal of Child Psychology and Psychiatry*, **54**, 3–16.
- Toplak, M. E. & Tannock, R. (2005) Time perception: modality and duration effects in attention-deficit/hyperactivity disorder (ADHD). *Journal of Abnormal Child Psychology*, **33**, 639–654.
- Toplak, M. E., Dockstader, C. & Tannock, R. (2006) Temporal information processing in ADHD: findings to date and new methods. *Journal of Neuroscience Methods*, **151**, 15–29.
- 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.
- Villodas, M. T., Pfiffner, L. J. & McBurnett, K. (2012) Prevention of serious conduct problems in youth with attention deficit/hyperactivity disorder. *Expert Review of Neurotherapeutics*, **12**, 1253–1263.
- Webster-Stratton, C., Reid, J. & Beauchaine, T. (2013) One-year follow-up of combined parent and child intervention for young children with ADHD. *Journal of Clinical Child and Adolescent Psychology*, **42**, 251–261.
- Webster-Stratton, C. H., Reid, M. J. & Beauchaine, T. (2011) Combining parent and child training for young children with ADHD. *Journal of Clinical Child and Adolescent Psychology*, **40**, 191–203.
- Wermter, A.-K., Laucht, M., Schimmelmann, B. G., Banaschewski, T., Sonuga-Barke, E. J., Rietschel, M. & Becker, K. (2010) From nature versus nurture, via nature and nurture, to gene × environment interaction in mental disorders. *European Child and Adolescent Psychiatry*, **19**, 199–210.
- Wilens, T. E., Biederman, J., Brown, S., Tanguay, S., Monuteaux, M. C., Blake, C. & Spencer, T. J. (2002) Psychiatric comorbidity and functioning in clinically referred preschool children and school-age youths with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*, **41**, 262–268.
- Wilens, T. E., Faraone, S. V., Biederman, J. & Gunawardene, S. (2003) Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics*, **111**, 179–185.
- 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.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.