VU Research Portal

Towards an understanding of unique and shared pathways in the psychopathophysiology of AD/HD

Banaschewski, T.; Hollis, C.; Oosterlaan, J.; Roeyers, H.; Rubia, K.; Willcutt, E.; Taylor, E.

published in

Developmental Science
2005

DOI (link to publisher)

[10.1111/j.1467-7687.2005.00400.x](https://doi.org/10.1111/j.1467-7687.2005.00400.x)

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Banaschewski, T., Hollis, C., Oosterlaan, J., Roeyers, H., Rubia, K., Willcutt, E., & Taylor, E. (2005). Towards an understanding of unique and shared pathways in the psychopathophysiology of AD/HD. *Developmental Science*, 8(2), 132-140. <https://doi.org/10.1111/j.1467-7687.2005.00400.x>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

Towards an understanding of unique and shared pathways in the psychopathophysiology of ADHD

Tobias Banaschewski,¹ Chris Hollis,² Jaap Oosterlaan,³ Herbert Roeyers,⁴ Katya Rubia,⁵ Erik Willcutt⁶ and Eric Taylor⁵

1. University of Göttingen, Germany

2. University of Nottingham, UK

3. Vrije Universiteit, Amsterdam, the Netherlands

4. Ghent University, Belgium

5. Institute of Psychiatry, King's College, University of London, UK

6. University of Colorado, USA

Abstract

Most attention deficit hyperactivity disorder (ADHD) research has compared cases with unaffected controls. This has led to many associations, but uncertainties about their specificity to ADHD in contrast with other disorders. We present a selective review of research, comparing ADHD with other disorders in neuropsychological, neurobiological and genetic correlates. So far, a specific pathophysiological pathway has not been identified. ADHD is probably not specifically associated with executive function deficits. It is possible, but not yet established, that ADHD symptoms may be more specifically associated with motivational abnormalities, motor organization and time perception. Recent findings indicating common genetic liabilities of ADHD and other conditions raise questions about diagnostic boundaries. In future research, the delineation of the pathophysiological mechanisms of ADHD needs to match cognitive, imaging and genetic techniques to the challenge of defining more homogenous clinical groups; multi-site collaborative projects are needed.

Background

Comparisons between ADHD and other disorders are needed for several purposes. Nosologically, it is desirable to establish the discriminative as well as the predictive validity of a condition, and so far this has only been partly achieved. Etiologically, it is crucial to understand whether biological associations are for psychopathology in general or ADHD in particular. Developmentally, it seems that ADHD is heterogeneous clinically (Biederman *et al.*, 1992), genetically (Willcutt, Penninton & DeFries, 2000) and neurophysiologically (Banaschewski *et al.*, 2003a) – and clues to understanding this should come if some components of ADHD can be identified as common to several disorders while others are unique. Clinically, the co-existence of several disorders is so common that it cannot be understood unless we know whether the co-existent conditions are truly different disorders with different associations. If ADHD and the comorbid disorder are each associated with different correlates, a double dissociation between the clinical disorders can be obtained, that is, both disorders can be separated by the

profile of their correlates. Examining the profile of correlates of the comorbid group relative to the single-disorder groups may then suggest the etiology of comorbidity between the two disorders. Such comparisons between groups, however, may fail to be illuminating if the groups are themselves heterogeneous (Mirowsky & Ross, 1989). As long as etiological pathways are unknown, the question of whether the samples investigated are pathophysologically homogeneous cannot be answered conclusively.

The central focus of this selective review of research in the fields of neuropsychology, neuroimaging and genetics is the specificity of the associations of ADHD and the etiological pathways they suggest, understood on the basis of comparisons between ADHD and some other disorders: schizophrenia, autism, oppositional defiant disorder/conduct disorder (ODD/CD), and reading disability (RD). We have not tried to be comprehensive, and recognize the frequency with which ADHD co-occurs with still more problems such as developmental co-ordination disorders, mental retardation, tics and anxiety states. Rather, we have selected disorders for comparison that seem likely to be of particular interest for illuminating the nature of ADHD.

Address for correspondence: Dr T. Banaschewski, Child and Adolescent Psychiatry, University of Göttingen, von-Siebold-Str. 5, D-37075 Göttingen, Germany; e-mail: tbanasc@gwdg.de

Neuropsychology

ADHD

Numerous studies indicate that ADHD is associated with deficits on a variety of neuropsychological measures which come from different psychological models of ADHD (Sergeant, Geurts, Huijbregts, Scheres & Oosterlaan, 2003). Strong evidence indicates that children with ADHD are impaired in various executive function (EF) domains (Barkley, Grodzinsky & DuPaul, 1992; Pennington & Ozonoff, 1996; Sergeant, Geurts & Oosterlaan, 2002). However, mean effect sizes for EF measures seem to be only moderate, suggesting that none of these deficits is a necessary or sufficient cause of ADHD (Willcutt *et al.*, 2003). Furthermore, evidence for other abnormalities has been presented, for example, altered motivational processes (Sagvolden, Johansen, Aase & Russell, in press; Sonuga-Barke, 2002), or an insufficient ability to regulate the state of activation (Kuntsi, Oosterlaan & Stevenson, 2001; Sergeant *et al.*, 2002). Response variability across a variety of tasks is one of the most consistent findings associated with ADHD, particularly when motor decision or effortful response organization is required (Castellanos & Tannock, 2002; Rubia *et al.*, 1999a; Sergeant & Scholten, 1985). Neuropsychological and event-related potential (ERP) studies have found that measures of domains with less of an executive component, such as processing speed, rapid naming, fine and gross motor skills, timing functions, and early and automatic information processing stages, are impaired as well (Banaschewski *et al.*, 2003a; Brandeis *et al.*, 2002; Rubia *et al.*, 1999a; Smith, Taylor, Rogers, Newman & Rubia, 2002; Tannock, Martinussen & Frijters, 2000). An association between ADHD and motor inhibitory control deficits is one of the most consistent findings (Nigg, 2001; Willcutt *et al.*, 2003). Some results suggest that deficient response inhibition may be a marker for a genetic susceptibility to ADHD (Crosbie & Schachar, 2001), but inhibitory control deficits as such are not a unique marker for ADHD, and have also been found in CD, ADHD + ODD/CD (Oosterlaan, Logan & Sergeant, 1998), RD (Purvis & Tannock, 2000; Willcutt *et al.*, 2003), and autism (Geurts, Verté, Oosterlaan, Roeyers & Sergeant, 2004; Nyden, Gillberg, Hjelmquist & Heiman, 1999). Nevertheless, inhibition deficits may be more pervasive in children with ADHD, and different mechanisms may be involved in ADHD from those in other disorders (Purvis & Tannock, 2000).

Schizophrenia

Subtle cognitive, developmental and social impairments can be observed in children long before the onset of

psychosis (Hollis, 1995). Children of adults with schizophrenia show abnormalities on tasks involving executive control, motor function, sustained attention and rapid information processing – similar to those of children with ADHD (Marcus *et al.*, 1987). Inattention and EF deficits occur in both disorders. In a recent meta-analysis of schizophrenia case-control studies, the largest effect sizes are found for cognitive flexibility (Wisconsin Card Sorting Task, WCST), verbal fluency, interference control (Stroop) and planning (Tower of London/Hanoi, ToH) – very similar to the pattern found in ADHD (Pennington & Ozonoff, 1996). Working memory (WM) impairments have been found both in adult schizophrenia (Gold, Carpenter, Randolph, Goldberg & Weinberger, 1997) and ADHD (Kempton *et al.*, 1999). Similar deficits in verbal and spatial WM performance were found in children with early-onset schizophrenia and children with ADHD (Karatekin & Asarnow, 1998). Evidence to support the hypothesis that a deficit in response inhibition might be more central than a working memory deficit for the pathophysiology of ADHD comes from comparison of eye movement measures. While both schizophrenic and ADHD adult subjects show disinhibition on the delayed oculomotor response task, only schizophrenic subjects show evidence of decreased WM for saccades (Ross, Olincy, Harris, Sullivan & Radant, 2000).

Autism

EF deficits are common in autism too (Pennington & Ozonoff, 1996). Children with autism may also show problems less associated with ADHD – in theory of mind (though studies are contradictory) and in weak central coherence (Booth, Charlton, Hughes & Happe, 2003). A few studies have compared autism and ADHD directly. Ozonoff and Jensen (1999) found a double dissociation between both disorders. Children with autism showed difficulties in planning and cognitive flexibility, but not in inhibition, whereas children with ADHD showed the opposite pattern. Nyden *et al.* (1999) failed to replicate this finding. Both ADHD and autism were associated with a response inhibition deficit, and only children with ADHD showed deficits in flexibility. Geurts *et al.* (2004) also failed to obtain a double dissociation. Children with High Functioning Autism (HFA) demonstrated deficits in all EF domains, except interference control and working memory. ADHD was associated with EF deficits in inhibiting a prepotent response and verbal fluency. Strikingly, EF measures hardly discriminated between ADHD and HFA. Compared to children with ADHD, the HFA group showed more difficulties only with cognitive flexibility and planning.

ODD/CD

Most studies found that ADHD, but not ODD/CD, is associated with deficits in EF. With almost 400 children included, the largest study found evidence for planning deficits in children with ADHD combined type (not inattentive type) that were independent of oppositional and conduct disorders (Klorman *et al.*, 1999). Cognitive flexibility did not discriminate between groups. Clark, Prior and Kinsella (2000) found that adolescents with ADHD performed worse on two EF measures independently of ODD/CD. Similar results were obtained using three different measures of WM (Kalff *et al.*, 2002). In a meta-analysis of the stop task (response inhibition), Oosterlaan *et al.* (1998) concluded that both disorders are associated with inhibitory deficits. More recent studies, however, showed that ADHD, but not ODD or CD, was associated with inhibitory dysfunction (Kooijmans, Scheres & Oosterlaan, 2000; Oosterlaan & Sergeant, 1998; Schachar, Mota, Logan, Tannock & Klim, 2000). Other studies are consistent with the idea that both ADHD and ODD/CD are associated with EF deficits. Thus, adolescents with ADHD as well as those with CD performed poorly on the Stroop task (MacLeod & Prior, 1996). Aronowitz *et al.* (1994) found that CD was associated with poor cognitive flexibility (WCST) and several other EF deficits (Rey-Osterreith complex figure test), while ADHD was associated only with poor flexibility, suggesting that ADHD and ODD/CD may differ in terms of their profile of EF deficits.

Reading disability

Individuals with RD are impaired in several abilities in which children with ADHD are also weak: processing speed (Rucklidge & Tannock, 2002; Tannock *et al.*, 2000), time processing (Smith *et al.*, 2002), EF domains such as verbal WM (Rucklidge & Tannock, 2002; Willcutt *et al.*, 2003), cognitive flexibility (Weyandt, Rice, Linterman, Mitzlaff & Emert, 1998), planning (Klorman *et al.*, 1999), and response inhibition (Purvis & Tannock, 2000; Willcutt *et al.*, 2003). Deficits in phonological processing are more specific to RD (Pennington, Groisser & Welsh, 1993; Wagner & Torgesen, 1987), which may be related to an auditory temporal processing deficit (Tallal, 1980), deficits in rapid sequential processing (Wagner & Torgesen, 1987) or a deficit in the automatization of skills (Nicolson, Fawcett & Dean, 2001). Pennington *et al.* (1993) reported that the comorbid group exhibited significant phonological processing deficits in the absence of the EF deficits typically associated with ADHD. This may have been an artefact of subject selection: most later studies with larger samples found

that the comorbid group exhibited the deficits of both single groups in an additive fashion (Rucklidge & Tannock, 2002; Willcutt *et al.*, 2003).

Neurobiology

ADHD

Structural studies in ADHD have shown reduced volumes – especially in right frontal brain regions, caudate, corpus callosum and cerebellum – and also in parietal, temporal and occipital brain regions (Castellanos *et al.*, 2002; Sowell *et al.*, 2003). The largest structural study conducted so far using combined cross-sectional and longitudinal design revealed that these volumetric abnormalities seem to be evident early in life, persist with age, and show parallel and non-progressive developmental growth curves (except for the caudate where group differences disappeared with age, Castellanos *et al.*, 2002). Abnormalities were not related to medication. Functional imaging studies using SPECT and fMRI have found abnormal brain activation patterns during attention tasks and response inhibition – predominantly in frontal lobes and caudate, but also in parietal lobes. The reduced caudate activation was consistent across all these studies, while the prefrontal lobe has been reported both as overactivated (Vaidya *et al.*, 1998) and underactivated (Rubia, Sergeant, Taylor & Taylor, 1999b).

Schizophrenia

In schizophrenia, as in ADHD, reduced grey matter has been observed in frontal, temporal and parietal brain regions (Rapoport *et al.*, 1997), but with different developmental trajectories. As opposed to the parallel growth curves in ADHD, strikingly *progressive* decline has been found in early-onset schizophrenia in region-specific grey matter loss of parietal, temporal and frontal lobes without changes in white matter (Thompson *et al.*, 2001), suggesting a progressive neurodevelopmental process. Ventricular volume enlargement is described in schizophrenia rather than ADHD (Rapoport *et al.*, 1997). The only study comparing functional imaging data between the two disorders found mirror image activation patterns between adolescent ADHD and adult schizophrenic patients in prefrontal lobes (underactivation in right dorsolateral prefrontal lobe in ADHD, but in left dorsolateral prefrontal lobe in schizophrenia) and in caudate (underactivation in ADHD and overactivation in schizophrenia) during response inhibition (Rubia, 2002). This last finding is in line with anatomical studies finding larger sized caudate, putamen and globus

pallidus in schizophrenia (Gordon *et al.*, 1994), as opposed to the reduced size of these regions in ADHD. A preattentive information processing deficit has been reported both in adolescents with schizophrenia and ADHD (Rund, Oie & Sundet, 1996). Abnormal early sensory processing – evidenced by lack of normal P50 suppression to a second paired auditory stimulus – appears specific for schizophrenia (Olincy *et al.*, 2000). The P50 effect in schizophrenia has a large effect size (1.5) and may reflect specific temporal lobe pathology (Bramon, Rabe-Hesketh, Murray & Frangou, 2004). In contrast, the P300 amplitude attenuation is a non-specific finding. However, differences in lateralization of the P300 are reported: reduction over the left temporal lobe in schizophrenia (Salisbury *et al.*, 1998) and the right hemisphere in ADHD (Oades, Dittmann-Balcar, Schepker, Eggers & Zerbin, 1996).

Autism

In autism, as opposed to ADHD, anatomical studies found *larger* total brain and white matter volumes in most cortical brain regions and in the cerebellum, caudate and globus pallidum (Piven, Arndt, Bailey & Andreasen, 1996). A shared anatomical dysmorphology between autism and ADHD appears to be a smaller corpus callosum (Saitoh, Courchesne, Egaas, Lincoln & Schreibman, 1995). In functional imaging studies, the most consistent finding has been that of reduced frontal and parietal activation during a wide range of tasks (Baron-Cohen *et al.*, 1999), which may not be very different for ADHD.

ODD/CD

No modern imaging studies exist on pure CD independent from its comorbidity with ADHD. Recent ERP studies (Bauer & Hesselbrock, 1999) did show abnormalities in prefrontal lobe activation. Furthermore, electrophysiological activity has been observed to differ between comorbid ADHD + ODD/CD groups and pure ADHD or pure ODD/CD groups (Banaschewski *et al.*, 2003a; Rothenberger *et al.*, 2000). Interestingly, comorbid children appear to be less deviant than either children with ADHD only or children ODD/CD only regarding performance parameters and P3a-amplitudes to cues linked to attentional orienting (Banaschewski *et al.*, 2003a).

Reading disability

The most consistent imaging findings in dyslexia have been those of reduced volume in specific focal brain

regions mediating speech and learning such as bilateral inferior prefrontal lobes (pars triangularis) and anterior lobe of the cerebellum, but also left hemispheric temporal and parietal brain regions, in particular planum temporale and parietale (Klingberg *et al.*, 2000; Pennington *et al.*, 1999). In line with these structural findings, functional imaging studies have observed abnormal left prefrontal and left temporo-parietal brain activation in relation to linguistic stimuli (Breier *et al.*, 2003).

Genetics

Twin studies have shown considerable heritability of ADHD with genetic factors explaining 70% to 80% of the phenotypic variance in the population (Thapar, Holmes, Poulton & Harrington, 1999). Molecular genetic studies have linked ADHD to various polymorphisms. However, the known risk alleles are widely distributed in the population and each accounts only for a small increase of risk. No single allele is either necessary or sufficient. Twin and family studies strongly support the role of genetic factors in schizophrenia (explaining about 80% of the phenotypic variance, Harrison & Owen, 2003), autism (about 90%, Shastri, 2003), RD (30–60%, Stevenson, Pennington, Gilger, DeFries & Gillis, 1993), and to some extent in ODD/CD, depending on the source of information. Several regions of the chromosomes, which, it has been suggested, harbour risk genes for autism – 2q24, 15q, 16p13, 17p11 – have also been highlighted in genome-wide scans for ADHD (Smalley *et al.*, 2002). Some common genetic influences may also contribute to the comorbidity of RD and ADHD. A quantitative trait locus study revealed significant bivariate linkage of the chromosome 6p region to both disorders (Willcutt *et al.*, 2002). More recently, suggestive linkage to RD was found in four chromosomal regions including regions on 16p and 17q that had previously been implicated in ADHD (Loo *et al.*, 2004).

Implications for understanding ADHD pathophysiology

(1) Unique and shared pathways

The studies we have reviewed indicate a mixed pattern: many of the findings in ADHD characterize other disorders too, but some may be more specific. The most specific seem to be some of the anatomical changes. Some good candidates (such as delay aversion) have not yet been tested in other disorders. ADHD may not be fully explainable by a primary deficit of behavioural inhibition

causing secondary deficits in other EFs, and thus leading to behavioural symptoms (as proposed by Barkley, 1997). Inhibitory control problems may also be a secondary consequence of attentional problems (Banaschewski *et al.*, 2004; Brandeis *et al.*, 2002), altered motivational processes (Sagvolden *et al.*, in press; Sonuga-Barke, 2002), or an insufficient ability to regulate the state of activation (Kuntsi *et al.*, 2001; Sergeant *et al.*, 2003). More fundamental, simpler problems could also be underlying ADHD deficits, such as a more generalized deficit of processing speed, time processing, motor response organization, or attentional orienting (Brandeis *et al.*, 2002; Sagvolden *et al.*, in press; Sergeant, Oosterlaan & Van der Meere, 1999; Smith *et al.*, 2002). While there is evidence for the hypothesis that EF deficits play a role in the etiology of ADHD (Willcutt *et al.*, 2003), many deficits are shared with other disorders and some differences between ADHD and other disorders may be quantitative rather than qualitative. Comparative neurofunctional and neuroanatomical studies between different psychopathological disorders are needed to establish the specificity of aetiopathophysiology of ADHD. At the present state of research, it appears that while identical brain regions, including the association cortices, the basal ganglia and the cerebellum, are sensitive to a wide range of developmental abnormalities, there seem to be specific differences between ADHD and the other psychiatric disorders in either the development of these brain abnormalities, the exact location, the size of abnormalities, or the laterality.

(2) Heterogeneity

The construct validity of the various psychological processes implicated in ADHD (e.g. attention, response inhibition, working memory, executive function and timing) is often uncertain. The validity of the tasks used to measure these processes needs to be investigated more rigorously (Miyake *et al.*, 2000). Many tasks tap more than one latent dimension of functioning (Tannock, 1998). We also recognize that distinct neuropsychological constructs may partly rely on the same interconnected neuronal circuits (Goldman-Rakic, 1998); and similar neuropsychological processes may rely on different neuronal structures in clinical and control groups. Developmental effects and compensatory processes need to be taken into account. More work needs to be done on the possibility several distinct neuropsychological changes can all result in ADHD behaviour. For instance, Sonuga-Barke (2002) has emphasized the independence of a motivational pathway (delay aversion) and a disinhibitory change; and they seem to be independently associated with the diagnosis of ADHD (Solanto *et al.*,

2001). We do not yet know whether these will be separately associated with other disorders, but it should repay investigation (see Coghill, Nigg, Rothenberger, Sonuga-Barke & Tannock, 2005, this issue). The fronto-striatal circuits considered above may be disrupted at numerous loci with similar functional consequences (Fletcher, 2000). Dysfunctions of these circuits could also be affected by dysfunctions of posterior cortical regions, the cerebellum or ascending arousal systems, which closely interact with the prefrontal cortex and have also been implicated in ADHD. Recent neuropsychological evidence demonstrating temporal processing deficits and non-executive memory deficits suggests the involvement of wider brain systems. The common perception of ADHD as a cortico-striato-thalamo-cortical disorder may be too limited. The overlap of genetic influences on ADHD and comorbid disorders could indicate that some influences have multiple behavioural consequences (pleiotropy); or could result from uncertainties and overlaps in the definitions of the phenotypes. This raises questions about diagnostic boundaries: the mapping of different cognitive and behavioural abnormalities on to the various DNA changes should be encouraged.

(3) Development

It is difficult to determine through cross-sectional studies whether neurocognitive correlates represent a primary abnormality or a secondary compensation mechanism. Longitudinal studies of developmental trajectories are required using age-appropriate task versions. For example, as long as developmental studies on EF in ADHD are lacking, any hypotheses concerning an etiological primacy of a deficit in EF seems to remain somewhat speculative.

(4) Comorbidity

The specificity of ADHD correlates may be dependent on the presence or absence of comorbid disorders. Stratification according to certain comorbidities is appropriate to study homogeneous ADHD subgroups. For example, ADHD and autism often co-occur, and inclusion of the comorbid group in research is urgently needed. Concerning the comorbidity of ADHD with ODD/CD, some studies suggest that the comorbid condition may constitute a biologically distinct subtype (Banaschewski *et al.*, 2003a; Faraone, Biederman, Mennin, Russell & Tsuang, 1998); others do not. In contrast, recent studies suggest more clearly that the comorbidity of ADHD + RD may represent a true comorbidity, with characteristics of both disorders, caused partly by common genetic influences (Purvis & Tannock, 2000; Willcutt *et al.*, 2003).

Concluding comments

Specific pathophysiological pathways for ADHD have not been identified. Many components of the etiological pathways may well be shared with other conditions, while others may be unique to ADHD. Future studies will need to examine the validity of the complex neuro-cognitive constructs, decompose the distinct component processes that are involved and develop methods to investigate whether poor task performance reflects the same underlying dysfunction across development and in groups with different disorders. Group differences in cognitive strategies, effort, motivation, or compensation strategies need to be considered. Comparison of pure and comorbid groups will be useful and may need advances in how to measure comorbid states. This will require the use of an extensive battery of well-defined and theoretically based tasks, including several measures of each construct to provide the accurate assessment of the multiple aspects of these multifaceted EF constructs and the investigation of putatively etiologically homogeneous subgroups of the ADHD phenotype. Research on epidemiological samples would be helpful, because at least some inconsistencies across studies using clinical samples, which may be conditioned by referral patterns, might reflect differences in sample composition (Willcutt *et al.*, 2003). The combination of techniques required calls for increasing collaboration between research groups.

References

- Aronowitz, B., Liebowitz, M., Hollander, E., Fazzini, E., Durlach-Misteli, C., Frenkel, M., Mosovich, S., Garfinkel, R., Saoud, J., DelBene, D., Cohen, L., Jaeger, A., & Rubin, A.L. (1994). Neuropsychiatric and neuropsychological findings in conduct disorder and attention-deficit hyperactivity disorder. *Journal of Neuropsychiatry and Clinical Neurosciences*, **6** (3), 245–249.
- Banaschewski, T., Brandeis, D., Heinrich, H., Albrecht, B., Brunner, E., & Rothenberger, A. (2003a). Association of ADHD and conduct disorder – brain electrical evidence for the existence of a distinct subtype. *Journal of Child Psychology and Psychiatry*, **44** (3), 356–376.
- Banaschewski, T., Brandeis, D., Heinrich, H., Albrecht, B., Brunner, E., & Rothenberger, A. (2004). Questioning inhibitory control as the specific deficit of ADHD – evidence from brain electrical activity. *Journal of Neural Transmission*, **111**, 841–864; published on-line 24 October 2003, DOI 10.1007/s00702-003-0040-8.
- Barkley, R.A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin*, **121** (1), 65–94.
- Barkley, R.A., Grodzinsky, G., & DuPaul, G.J. (1992). Frontal lobe functions in attention deficit disorder with and without hyperactivity: a review and research report. *Journal of Abnormal Child Psychology*, **20** (2), 163–188.
- Baron-Cohen, S., Ring, H.A., Wheelwright, S., Bullmore, E.T., Brammer, M.J., Simmons, A., & Williams, S.C. (1999). Social intelligence in the normal and autistic brain: an fMRI study. *European Journal of Neuroscience*, **11** (6), 1891–1898.
- Bauer, L.O., & Hesselbrock, V.M. (1999). P300 decrements in teenagers with conduct problems: implications for substance abuse risk and brain development. *Biological Psychiatry*, **46** (2), 263–272.
- Biederman, J., Faraone, S.V., Keenan, K., Benjamin, J., Krifcher, B., Moore, C., Sprich-Buckminster, S., Ulagia, K., Jellinek, M.S., Steingard, R., Spencer, T., Norman, D., Kolodny, R., Kraus, I., Perrin, J., Keller, M.B., & Tsuang, M.T. (1992). Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred samples. *Archives of General Psychiatry*, **49** (9), 728–738.
- Booth, R., Charlton, R., Hughes, C., & Happe, F. (2003). Disentangling weak coherence and executive dysfunction: planning drawing in autism and attention-deficit/hyperactivity disorder. *Philosophical Transactions of the Royal Society of London Series B – Biological Sciences*, **358** (1430), 387–392.
- Bramon, R.A., Rabe-Hesketh, S., Murray, R.M., & Frangou, S. (2004). Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophrenia Research*, **70** (2–3), 315–329.
- Brandeis, D., Banaschewski, T., Baving, L., Georgiewa, P., Blanz, B., Warnke, A., Steinhausen, H.C., Rothenberger, A., & Scheuerpflug, P. (2002). Multicenter P300 brain mapping of impaired attention to cues in hyperkinetic children. *Journal of the American Academy of Child and Adolescent Psychiatry*, **41** (8), 990–998.
- Breier, J.I., Simos, P.G., Fletcher, J.M., Castillo, E.M., Zhang, W., & Papanicolaou, A.C. (2003). Abnormal activation of temporoparietal language areas during phonetic analysis in children with dyslexia. *Neuropsychology*, **17** (4), 610–621.
- 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., Zijdenbos, A., Evans, A.C., Giedd, J.N., & Rapoport, J.L. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Medical Association*, **288** (14), 1740–1748.
- Castellanos, F.X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nature Reviews. Neuroscience*, **3** (8), 617–628.
- Clark, C., Prior, M., & Kinsella, G.J. (2000). Do executive function deficits differentiate between adolescents with ADHD and oppositional defiant/conduct disorder? A neuropsychological study using the six elements test and Hayling sentence completion test. *Journal of Abnormal Child Psychology*, **28** (5), 403–414.
- Coghill, D., Nigg, J., Rothenberger, A., Sonuga-Barke, E., & Tannock, R. (2005). Whither causal models in the neuroscience of ADHD? *Developmental Science*, **8** (2), 105–114.

- Crosbie, J., & Schachar, R. (2001). Deficient inhibition as a marker for familial ADHD. *American Journal of Psychiatry*, **158** (11), 1884–1890.
- Faraone, S.V., Biederman, J., Mennin, D., Russell, R., & Tsuang, M.T. (1998). Familial subtypes of attention deficit hyperactivity disorder: a 4-year follow-up study of children from antisocial-ADHD families. *Journal of Child Psychology and Psychiatry*, **39** (7), 1045–1053.
- Fletcher, P.C. (2000). The functional neuroimaging of memory disorders. In J.C. Mazziotta, A.W. Toga & R.S.J. Frackowiak (Eds.), *Brain mapping: The disorders* (pp. 201–215). San Diego: Academic Press.
- Geurts, H.M., Verte, S., Oosterlaan, J., Roeyers, H., & Sergeant, J.A. (2004). How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? *Journal of Child Psychology and Psychiatry*, **45** (4), 836–854.
- Gold, J.M., Carpenter, C., Randolph, C., Goldberg, T.E., & Weinberger, D.R. (1997). Auditory working memory and Wisconsin card sorting test performance in schizophrenia. *Archives of General Psychiatry*, **54** (2), 159–165.
- Goldman-Rakic, P.S. (1998). The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. In A.C. Roberts, T.W. Robbins & L. Weiskrantz (Eds.), *The prefrontal cortex: executive and cognitive functions* (pp. 87–102). Oxford: Oxford University Press.
- Gordon, C.T., Frazier, J.A., McKenna, K., Giedd, J., Zametkin, A., Zahn, T., Hommer, D., Hong, W., Kaysen, D., Albus, K.E., & Rapoport, J.L. (1994). Childhood-onset schizophrenia: an NIMH study in progress. *Schizophrenia Bulletin*, **20** (4), 697–712.
- Harrison, P.J., & Owen, M.J. (2003). Genes for schizophrenia? Recent findings and their pathophysiological implications. *Lancet*, **361** (9355), 417–419.
- Hollis, C. (1995). Child and adolescent (juvenile onset) schizophrenia. A case control study of premorbid developmental impairments. *British Journal of Psychiatry*, **166** (4), 489–495.
- Kalff, A.C., Hendriksen, J.G., Kroes, M., Vles, J.S., Steyaert, J., Feron, F.J., van Zeben, T.M., & Jolles, J. (2002). Neurocognitive performance of 5- and 6-year-old children who met criteria for attention deficit/hyperactivity disorder at 18 months follow-up: results from a prospective population study. *Journal of Abnormal Child Psychology*, **30** (6), 589–598.
- Karatekin, C., & Asarnow, R.F. (1998). Working memory in childhood-onset schizophrenia and attention-deficit/hyperactivity disorder. *Psychiatry Research*, **80** (2), 165–176.
- Kempton, S., Vance, A., Maruff, P., Luk, E., Costin, J., & Pantelis, C. (1999). Executive function and attention deficit hyperactivity disorder: stimulant medication and better executive function performance in children. *Psychological Medicine*, **29** (3), 527–538.
- Klingberg, T., Hedeus, M., Temple, E., Salz, T., Gabrieli, J.D., Moseley, M.E., & Poldrack, R.A. (2000). Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging. *Neuron*, **25** (2), 493–500.
- Klorman, R., Hazel-Fernandez, L.A., Shaywitz, S.E., Fletcher, J.M., Marchione, K.E., Holahan, J.M., Stuebing, K.K., & Shaywitz, B.A. (1999). Executive functioning deficits in attention-deficit/hyperactivity disorder are independent of oppositional defiant or reading disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, **38** (9), 1148–1155.
- Kooijmans, R., Scheres, A., & Oosterlaan, J. (2000). Response inhibition and measures of psychopathology: a dimensional analysis. *Neuropsychology, Development, and Cognition. Section C, Child Neuropsychology*, **6** (3), 175–184.
- Kuntsi, J., Oosterlaan, J., & Stevenson, J. (2001). Psychological mechanisms in hyperactivity: I response inhibition deficit, working memory impairment, delay aversion, or something else? *Journal of Child Psychology and Psychiatry*, **42** (2), 199–210.
- Loo, S.K., Fisher, S.E., Francks, C., Ogdie, M.N., MacPhie, I.L., Yang, M., McCracken, J.T., McGough, J.J., Nelson, S.F., Monaco, A.P., & Smalley, S.L. (2004). Genome-wide scan of reading ability in affected sibling pairs with attention-deficit/hyperactivity disorder: unique and shared genetic effects. *Molecular Psychiatry*, **9** (5), 485–493.
- MacLeod, D., & Prior, M. (1996). Attention deficits in adolescents with ADHD and other clinical groups. *Child Neuropsychology*, **2**, 1–10.
- Marcus, J., Hans, S.L., Nagler, S., Auerbach, J.G., Mirsky, A.F., & Aubrey, A. (1987). Review of the NIMH Israeli Kibbutz-City Study and the Jerusalem Infant Development Study. *Schizophrenia Bulletin*, **13** (3), 425–438.
- Mirowsky, J., & Ross, C.E. (1989). Psychiatric diagnosis as reified measurement. *Journal of Health and Social Behavior*, **30** (1), 11–25; discussion, 26–40.
- Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A., & Wager, T.D. (2000). The unity and diversity of executive functions and their contributions to complex ‘frontal lobe’ tasks: a latent variable analysis. *Cognitive Psychology*, **41** (1), 49–100.
- Nicolson, R.I., Fawcett, A.J., & Dean, P. (2001). Developmental dyslexia: the cerebellar deficit hypothesis. *Trends in Neurosciences*, **24** (9), 508–511.
- Nigg, J.T. (2001). Is ADHD a disinhibitory disorder? *Psychological Bulletin*, **127** (5), 571–598.
- Nyden, A., Gillberg, C., Hjelmquist, E., & Heiman, M. (1999). Executive function/attention deficits in boys with Asperger syndrome, attention disorder and reading/writing disorder. *Autism*, **3**, 213–228.
- Oades, R.D., Dittmann-Balcar, A., Schepker, R., Eggers, C., & Zerbin, D. (1996). Auditory event-related potentials (ERPs) and mismatch negativity (MMN) in healthy children and those with attention-deficit or tourette/tic symptoms. *Biological Psychiatry*, **43** (2), 163–185.
- Olincy, A., Ross, R.G., Harris, J.G., Young, D.A., McAndrews, M.A., Cawthra, E., McRae, K.A., Sullivan, B., Adler, L.E., & Freedman, R. (2000). The P50 auditory event-evoked potential in adult attention-deficit disorder: comparison with schizophrenia. *Biological Psychiatry*, **47** (11), 969–977.
- Oosterlaan, J., Logan, G.D., & Sergeant, J.A. (1998). Response inhibition in ADHD, CD, comorbid ADHD + CD, anxious,

- and control children: a meta-analysis of studies with the stop task. *Journal of Child Psychology and Psychiatry*, **39** (3), 411–425.
- Oosterlaan, J., & Sergeant, J.A. (1998). Effects of reward and response cost on response inhibition in ADHD, disruptive, anxious, and normal children. *Journal of Abnormal Child Psychology*, **26** (3), 161–174.
- Ozonoff, S., & Jensen, J. (1999). Brief report: specific executive function profiles in three neurodevelopmental disorders. *Journal of Autism and Developmental Disorders*, **29** (2), 171–177.
- Pennington, B.F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry*, **37** (1), 51–87.
- Pennington, B.F., Groisser, D., & Welsh, M.C. (1993). Contrasting cognitive deficits in Attention Deficit Hyperactivity Disorder versus Reading Disability. *Developmental Psychology*, **29**, 511–523.
- Pennington, B.F., Filipek, P.A., Lefly, D., Churchwell, J., Kennedy, D.N., Simon, J.H., Filley, C.M., Galaburda, A., Alarcon, M., & DeFries, J.C. (1999). Brain morphometry in reading-disabled twins. *Neurology*, **53** (4), 723–729.
- Piven, J., Arndt, S., Bailey, J., & Andreasen, N. (1996). Regional brain enlargement in autism: a magnetic resonance imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry*, **35** (4), 530–536.
- Purvis, K.L., & Tannock, R. (2000). Phonological processing, not inhibitory control, differentiates ADHD and reading disability. *Journal of the American Academy of Child and Adolescent Psychiatry*, **39** (4), 485–494.
- Rapoport, J.L., Giedd, J., Kumra, S., Jacobsen, L., Smith, A., Lee, P., Nelson, J., & Hamburger, S. (1997). Childhood-onset schizophrenia. Progressive ventricular change during adolescence. *Archives of General Psychiatry*, **54** (10), 897–903.
- Ross, R.G., Olincy, A., Harris, J.G., Sullivan, B., & Radant, A. (2000). Smooth pursuit eye movements in schizophrenia and attentional dysfunction: adults with schizophrenia, ADHD, and a normal comparison group. *Biological Psychiatry*, **48** (3), 197–203.
- Rothenberger, A., Banaschewski, T., Heinrich, H., Moll, G.H., Schmidt, M.H., & van't Klooster, B. (2000). Comorbidity in ADHD-children: effects of coexisting conduct disorder or tic disorder on event-related brain potentials in an auditory selective-attention task. *European Archives of Psychiatry and Clinical Neuroscience*, **250** (2), 101–110.
- Rubia, K. (2002). The dynamic approach to neurodevelopmental psychiatric disorders: use of fMRI combined with neuropsychology to elucidate the dynamics of psychiatric disorders, exemplified in ADHD and schizophrenia. *Behavioural Brain Research*, **130** (1–2), 47–56.
- Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S.C., Simmons, A., & Bullmore, E.T. (1999a). Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *American Journal of Psychiatry*, **156** (6), 891–896.
- Rubia, K., Sergeant, J., Taylor, A., & Taylor, E. (1999b). Synchronization, anticipation and consistency of motor timing in dimensionally defined children with Attention Deficit Hyperactivity Disorder. *Perceptual and Motor Skills*, **89**, 1237–1258.
- Rucklidge, J.J., & Tannock, R. (2002). Neuropsychological profiles of adolescents with ADHD: effects of reading difficulties and gender. *Journal of Child Psychology and Psychiatry*, **43** (8), 988–1003.
- Rund, B.R., Oie, M., & Sundet, K. (1996). Backward-masking deficit in adolescents with schizophrenic disorders or attention deficit hyperactivity disorder. *American Journal of Psychiatry*, **153** (9), 1154–1157.
- Sagvolden, T., Johansen, E.B., Aase, H., & Russell, V.A. (in press). A dynamic developmental theory of Attention-Deficit/Hyperactivity Disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behavioral and Brain Sciences*.
- Saitoh, O., Courchesne, E., Egaas, B., Lincoln, A.J., & Schreibman, L. (1995). Cross-sectional area of the posterior hippocampus in autistic patients with cerebellar and corpus callosus abnormalities. *Neurology*, **45** (2), 317–324.
- Salisbury, D.F., Shenton, M.E., Sherwood, A.R., Fischer, I.A., Yurgelun-Todd, D.A., Tohen, M., & McCarley, R.W. (1998). First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in P300 amplitude over left temporal lobe. *Archives of General Psychiatry*, **55** (2), 173–180.
- Schachar, R., Mota, V.L., Logan, G.D., Tannock, R., & Klim, P. (2000). Confirmation of an inhibitory control deficit in attention-deficit/hyperactivity disorder. *Journal of Abnormal Child Psychology*, **28** (3), 227–235.
- Sergeant, J.A., & Scholten, C.A. (1985). On resource strategy limitations in hyperactivity: cognitive impulsivity reconsidered. *Journal of Child Psychology and Psychiatry*, **26** (1), 97–109.
- Sergeant, J.A., Oosterlaan, J., & Van der Meere, J.J. (1999). Information processing and energetic factors in attention-deficit/hyperactivity disorder. In H.C. Quay & A. Hogan (Eds.), *Handbook of disruptive behavior disorders* (pp. 75–104). New York: Plenum Press.
- Sergeant, J.A., Geurts, H., & Oosterlaan, J. (2002). How specific is a deficit of executive functioning for attention-deficit/hyperactivity disorder? *Behavioural Brain Research*, **130** (1–2), 3–28.
- Sergeant, J.A., Geurts, H., Huijbregts, S., Scheres, A., & Oosterlaan, J. (2003). The top and the bottom of ADHD: a neuropsychological perspective. *Neuroscience & Biobehavioral Reviews*, **27** (7), 583–592.
- Shastri, B.S. (2003). Molecular genetics of autism spectrum disorders. *Journal of Human Genetics*, **48** (10), 495–501.
- Simonoff, E. (2001). Genetic influences on conduct disorder. In J. Hill & B. Maughan (Eds.), *Conduct disorder in childhood and adolescence* (pp. 202–234). Cambridge: Cambridge University Press.
- Smalley, S.L., Kustanovich, V., Minassian, S.L., Stone, J.L., Ogdie, M.N., McGough, J.J., McCracken, J.T., MacPhie, I.L., Francks, C., Fisher, S.E., Cantor, R.M., Monaco, A.P., & Nelson, S.F. (2002). Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region

- implicated in autism. *American Journal of Human Genetics*, **71** (4), 959–963.
- Smith, A., Taylor, E., Rogers, J.W., Newman, S., & Rubia, K. (2002). Evidence for a pure time perception deficit in children with ADHD. *Journal of Child Psychology and Psychiatry*, **43** (4), 529–542.
- Solanto, M.V., Abikoff, H., Sonuga-Barke, E., Schachar, R., Logan, G.D., Wigal, T., Hechtman, L., Hinshaw, S., & Turkel, E. (2001). The ecological validity of delay aversion and response inhibition as measures of impulsivity in ADHD: a supplement to the NIMH multimodal treatment study of ADHD. *Journal of Abnormal Child Psychology*, **29** (3), 215–228.
- Sonuga-Barke, E.J. (2002). Psychological heterogeneity in ADHD – a dual pathway model of behaviour and cognition. *Behavioural Brain Research*, **130** (1–2), 29–36.
- Sowell, E.R., Thompson, P.M., Welcome, S.E., Henkenius, A.L., Toga, A.W., & Peterson, B.S. (2003). Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *Lancet*, **362** (9397), 1699–1707.
- Stevenson, J., Pennington, B.F., Gilger, J.W., DeFries, J.C., & Gillis, J.J. (1993). Hyperactivity and spelling disability: testing for shared genetic aetiology. *Journal of Child Psychology and Psychiatry*, **34** (7), 1137–1152.
- Tallal, P. (1980). Auditory temporal perception, phonics, and reading disabilities in children. *Brain and Language*, **9** (2), 182–198.
- Tannock, R. (1998). Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. *Journal of Child Psychology and Psychiatry*, **39** (1), 65–99.
- Tannock, R., Martinussen, R., & Frijters, J. (2000). Naming speed performance and stimulant effects indicate effortful, semantic processing deficits in attention-deficit/hyperactivity disorder. *Journal of Abnormal Child Psychology*, **28** (3), 237–252.
- Thapar, A., Holmes, J., Poulton, K., & Harrington, R. (1999). Genetic basis of attention deficit and hyperactivity. *British Journal of Psychiatry*, **174**, 105–111.
- Thompson, P.M., Vidal, C., Giedd, J.N., Gochman, P., Blumenthal, J., Nicolson, R., Toga, A.W., & Rapoport, J.L. (2001). Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, **98** (20), 11650–11655.
- Vaidya, C.J., Austin, G., Kirkorian, G., Ridlehuber, H.W., Desmond, J.E., Glover, G.H., & Gabrieli, J.D. (1998). Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. *Proceedings of the National Academy of Sciences of the United States of America*, **95** (24), 14494–14499.
- Wagner, R.K., & Torgesen, J.K. (1987). The nature of phonological processing and its causal role in the acquisition of reading skills. *Psychological Bulletin*, **101**, 192–212.
- Weyandt, L.L., Rice, J.A., Linterman, I., Mitzlaff, L., & Emert, E. (1998). Neuropsychological performance of a sample of adults with ADHD, developmental reading disorder, and controls. *Developmental Neuropsychology*, **14**, 643–656.
- Willcutt, E.G., Pennington, B.F., & DeFries, J.C. (2000). Twin study of the etiology of comorbidity between reading disability and attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics*, **96** (3), 293–301.
- Willcutt, E.G., Pennington, B.F., Smith, S.D., Cardon, L.R., Gayan, J., Knopik, V.S., Olson, R.K., & DeFries, J.C. (2002). Quantitative trait locus for reading disability on chromosome 6p is pleiotropic for attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics*, **114** (3), 260–268.
- Willcutt, E.G., DeFries, J.C., Pennington, B.F., Olson, R.K., Smith, S.D., & Cardon, L.R. (2003). Genetic etiology of comorbid reading difficulties and ADHD. In R. Plomin, J.C. DeFries, P. McGuffin & I. Craig (Eds.), *Behavioral genetics in a postgenomic era* (pp. 227–246). Washington D.C.: American Psychological Association.

Copyright of Developmental Science is the property of Blackwell Publishing Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.

Copyright of Developmental Science is the property of Blackwell Publishing Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.