Research Review
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Moving beyond symptomatic improvement: from neurobiology to QoL considerations in treating ADHD - May 2011

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Prof. Buitelaar's research interests include neuropsychiatric disorders of children, adolescents and adults such as autism, ADHD and conduct disorder. He is involved in a number of psychopharmacological, psychophysiological, neuroimaging, epidemiological, and genetic studies of these disorders. A prolific researcher, Prof. Buitelaar has authored over 360 scientific publications in peer-reviewed journals.

In addition to serving on the advisory boards and as a reviewer for several other scientific journals, he is currently the chief editor of European Child and Adolescent Psychiatry.

This publication is a summary of a recent presentation by Professor Jan Buitelaar, Radboud University Nijmegen Medical Centre, The Netherlands. In his talks with psychiatrists in New Zealand and Australia during May 2011, Prof. Buitelaar discussed the neurobiology of attention-deficit hyperactivity disorder (ADHD) and how the treatment of this disorder progresses from symptomatic to functional improvement.

Take home messages

- ADHD is a disorder of brain development that differs from a typical child neurological disorder such as a seizure disorder, which has an identifiable locus. Instead, ADHD is a connectivity problem, involving the whole brain, and is a disorder that has a strong genetic loading.
- Environmental and Gene x Environment factors play additional roles
- ADHD is a very persistent disorder; 24 hours/day
- It is important to identify and treat ADHD as a disorder in itself and as a risk factor for other disorders: treatment of ADHD may prevent consequences and complications such as substance abuse, antisocial behaviour, school dropouts, the development of schizophrenia in adult life and even the development of anxiety and depression in adults.
- A comprehensive treatment approach includes a combination of medical and psychological interventions
- Treatment should be systematic, 24 hours/day and long-term.

Clinical issues and course

The key symptoms of inattention and impulsivity/hyperactivity may merge into one domain in DSM-V and new symptoms may eventuate, but Prof. Buitelaar does not expect clinical practice to be affected to a major extent. While worldwide estimates as to the prevalence of ADHD in school-aged children vary from between 5%–15%, in Prof. Buitelaar's opinion, prevalence rates exceeding 5% are inappropriately overinflated and tend to overdiagnose children. Once diagnosed, ADHD has been deemed to persist throughout childhood in many cases, although huge discrepancies exist as to the chronicity of ADHD. For instance, Feldman and colleagues[1] found that 50% of children with ADHD met criteria 4 years after their initial assessment, while Biederman and colleagues[2] found that 85% of boys with ADHD met criteria with impairment after 4 years. Conversely, some studies testify to a low persistence rate, such as Mannuzza and colleagues,[3] whose follow-up study documented the continuation of ADHD symptoms over 16 years in 10% of a cohort diagnosed as hyperactive in childhood.

Thirty years ago, the prevailing thinking was that children would grow out of ADHD – with or without medical intervention. However, this is not supported by the evidence, noted Prof. Buitelaar, who believes there are two reasons for the discrepancy in persistence rates:

- Mannuzza and colleagues[3] defined persistence as symptoms in older age that met the full ADHD DSM diagnostic criteria. However, having four ADHD symptoms as an adult causes relatively more impairment than having seven or eight symptoms as a 10-year-old.
- More critically, Mannuzza and colleagues[3] did not account for functional impairment, i.e., how much ADHD interferes with social life, educational and occupational achievements. If these are accounted for, the persistence rates would look more like those of Biederman and other studies.[2]

Prof. Buitelaar contends that roughly two-thirds of all those with childhood ADHD will continue to have severe symptoms and functional impairments until young adulthood, an observation that is significant for child and adolescent psychiatrists, who need to think about how to successfully transit the paediatric patient through to adult services.

Some of the symptoms may change over time. For example, the observable domain of hyperactivity in childhood may manifest in adult life as inner restlessness, an inability to relax. Impulsivity may lessen over time, and inattention may shift to become more of an inability to organise, plan, and allow for enough time to execute tasks.

To some extent, persistence of ADHD into adulthood can be predicted by clinical characteristics or risk factors, which include a family-genetic loading, comorbidity, and environmental stress. The odds of ADHD persisting is documented as being 7 times greater in subjects who have three risk factors.[4] How can prediction of ADHD persistence be improved, in terms of brain correlates and neurobiology? Overall, ADHD in adults is a valid disorder. Evidence from external correlates, neuropsychology, family-genetic studies, brain imaging, treatment response and impairments demonstrate continuity from childhood to adult ADHD.

Adult ADHD: a huge problem

Unquestionably, scientifically, ADHD has been established to be a valid psychiatric syndrome. However, it has been less well accepted in the Psychiatry profession and regulatory environment. In Prof. Buitelaar's opinion, the problem is in the attitude, and in health economics. While he believes the prevalence of childhood ADHD to be around 5% and that of adult ADHD to be around 3%, he notes that due to the volume of the adult population, adult cases would outnumber childhood cases,

which would be a significant cost to the Mental Health system. However, he believes that treating ADHD would be cost-effective, because up to 20%–30% of the patients currently presenting with substance abuse, burnout, sleeping problems, partial response to long-term SSRI treatment for depression and/or anxiety, may have unrecognised ADHD. Prof. Buitelaar believes that all these patients should be screened for ADHD.

Neurodevelopment model of ADHD

The neural underpinnings of ADHD have been extended by Halperin and colleagues,[5,6] whose model proposes that the disorder involves more than the prefrontal cortex and its interconnections with the striatum and other subcortical structures. They hypothesise that ADHD is more of a subcortical problem arising from automatic processing of information, perhaps located in the midbrain and attentional or arousal systems, which are associated with the early onset and with the enduring course of ADHD. Added to this is the cortical dysfunction, which determines the severity and course of ADHD. Thus, according to this model, recovery from ADHD is associated with improved cortical functions, while ADHD-persisters are marked by persisting subcortical dysfunction. All available means (i.e., medication, behaviour therapy, cognitive training) should be used to improve cortical function and aid remission, although Halperin and colleagues are pessimistic as to the odds of improving and curing the key problems of cortical dysfunction.

Brain imaging

Anatomic magnetic resonance imaging (MRI) has demonstrated differences in brain structure and function between healthy controls and cases with ADHD (see Figure 1).[7] According to this research, ADHD is associated with 5%–8% smaller brain volume and fixed brain abnormalities.

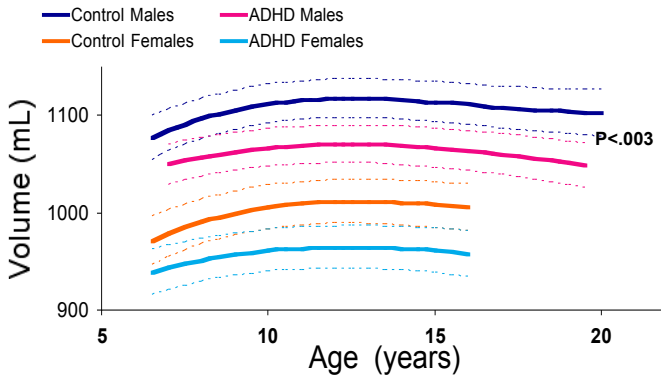

Figure 1. Total cerebral volume growth curves[7]

Anxious parents can be advised that while stimulants can affect up to 15% of children with side effects such as sleeping and eating problems, or nervousness, these are expected to disappear over time. Nevertheless, no experimental preclinical or clinical data are available as to the long-term effects of ADHD medication upon the developing brain. However, the available observational data, including the evidence from Castellanos and colleagues,[7] indicate reassuringly that the medicated ADHD brain is more similar to the normal, healthy brain than the unmedicated ADHD brain (see Figure 2). In addition, stimulants have been available for 50 years, making it unlikely that some hidden problem exists.

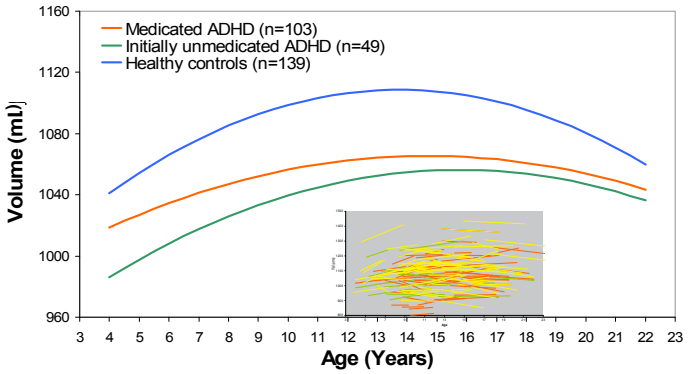

Figure 2. Total cerebral volume in girls and boys (Total: 543 scans)[7]

Besides these fixed structural findings between healthy controls and ADHD cases, there is evidence of a more flexible, delayed framework of maturation. Computational neuroanatomic techniques have plotted peak cortical thickness by age, showing that cortical maturation progresses in a similar manner regionally in both children with and without ADHD.[8] However, whereas peak cortical thickness is attained between ages 5 and 10 years in children without ADHD, cortical areas mature more slowly in children with ADHD, by about 1–2 years.[8]

Functional differences have also been characterised. In the first MRI study in adults with ADHD, Seidman and colleagues[9] reported significant reduction in the volume of the anterior cingulate gyrus and the dorsolateral prefrontal cortex in adults with ADHD compared to normals. These findings are supported by a study using the Counting Stroop, a Stroop variant allowing on-line response time measurements while obviating speech and a task that requires more effortful, focused control than that required by traditional Color Stroop tasks.[10] Functional MRI data reveal significant activity in the cognitive division of the anterior cingulate cortex in normal healthy adults performing the Counting Stroop, whereas no such activation is seen in ADHD cases. Instead, activation has been observed in the bilateral and parietotemporal areas of the brain. Thus, ADHD cases use the brain in a strikingly different way to normal controls.

Defining ADHD in the brain

Rather than trying to define a lesional area in the brain denoting the locus of ADHD, Prof. Buitelaar suggests that it may be more useful to ask where in the brain the problem lies, because accomplishment of a single task requires the collaboration of several areas of the brain. Measurement of structural connectivity between the white matter areas may reveal some answers. For instance, connectivity can be investigated by diffusion-weighted MRI images that trace the local water diffusion profile that indicates the direction of the white matter fibre. Another way of measuring structural quality is to investigate the fibres depicting the cortico-spinal tracts. In addition, functional connectivity enables measurement of activity in one area of the brain and correlation by time series with activity in another area.

Connectivity modelling, or neuronal network analysis, demonstrates that the efficiency of networks depends on having the right balance between short- and long-distance network systems in the brain. Connectivity can be plotted on growth charts over time, as has been shown in data recently submitted for publication.[11] As shown in Figure 3, almost all the children with ADHD are below the average of the connectivity measure of the normally developing group. Prof. Buitelaar noted that if it were possible to predict on an individual level, children could be classified with almost 80% accuracy, thereby supporting the notion that clinical categories may be mapped into a more brain-based connectivity problem.

In this way, ADHD may be conceptualised as a systematic disease of the brain, in the same way that systemic diseases such as lupus and scleroderma are known to affect many different body systems. Prof. Buitelaar believes that this type of analysis will become evident in clinical practice within the next 3–5 years. While such analysis will never replace clinical interviewing, it could serve as an additional clinical tool and one that may monitor treatment.

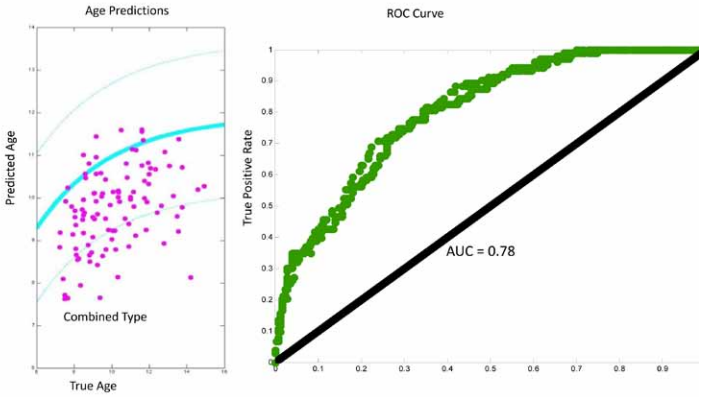

Figure 3. Mapping functional connectivity over age discriminates combined-type of ADHD from controls[11]

Genetics

It has long been observed that ADHD tends to run in families, supported by data indicating inheritability, such as evidence from Faraone and colleagues.[12] Their estimates of heritability from 20 twin studies from the US, Australia, Scandinavia, and the EU revealed a mean heritability estimate of 76%, demonstrating that ADHD is among the most heritable of psychiatric disorders. However, it has proven very difficult to identify genes for ADHD. According to the spectrum of allelic variation, the relative risk of having the common variants that contribute to ADHD are very low (just above 1.0), so very large samples are needed to identify these genetic factors. On the basis of recent evidence from genetic deletion, duplication and chromosomal abnormality studies, it is now known that individuals can have major, rare variants. These may affect only as few as 1/10,000 individuals, but their presence raises the risk for ADHD 10-fold or more.

Why not concentrate on the more commonly occurring variants and simply ignore the rarer ones? Prof. Buitelaar argues that there are two important implications involved in studying the rarer variants:

- Almost certainly, these same variations may affect the same biochemical systems as the common variants. This is therefore a gene-finding strategy. These rare variants may also be linked to glutamatergic systems, which can be affected by more commonly occurring variants that have huge relevance.
- Prof. Buitelaar proposes that if it can be established as to how many ADHD cases are affected by this rare variant (e.g. 10% or more), then a case exists for genetic counselling. It may be important to communicate information about genetic transmission to a family.

The genetic concept of ADHD has advanced from the classic Mendelian view of a monogenetic disease to multi-factorial and now to an oligogenic disease.[13] A meta-analysis[14] of identified genes (mainly of dopaminergic transmission, serotonergic transmission, DAD4 and DAD5 receptor genes) explains only 3%–5% of the gene variance; the total genetic variance is around 75%. Prof. Buitelaar believes that bioinfomatics may be a useful tool to help identify the missing heritability and make sense of large amounts of genetic data, such as the evidence gleaned from single-nucleotide polymorphism (SNP) genotyping of ADHD cases. Notably, a recently published bioinformatics type of analysis indicates that ADHD at the neuronal molecular level is a problem of abnormal connectivity of the neural system, as evidenced by brain imaging studies.[15]

An even more recent bioinformatics analysis investigated the presence of genomic convergence in the top findings of the five published genome-wide association studies (GWASs) of ADHD.[16] Of the 85 top-ranked ADHD candidate genes, 45 were found to encode proteins that fit into a neurodevelopmental network involved in directed neurite outgrowth. This network in ADHD aetiology is further supported by data on copy number variations in patients with ADHD and data from animal studies. Importantly, the data suggest that at the synaptic level, this network describes the way axons in the developing brain grow to make contact with other neurons; a very basic molecular process that may lie at the basis of the disorder.

In summary, we are searching for genes in ADHD. Prof. Buitelaar considers that it is very unlikely that 'ADHD genes' exist – instead, we know that many of these candidate genes are shared between ADHD and other disorders including autism, and schizophrenia. Each of these genes encodes an abnormal protein, which may lead to abnormal cellular functioning and molecular processes that may lead in turn to abnormal cognitive functions and complex phenotypes (see Figure 4). Prof. Buitelaar noted that every level may potentially be affected by epigenetics and environmental input. He believes that this is the most likely model. While new genes may be identified by the clinical phenotype, it may be more efficient and powerful to start with the endophenotype, as for example with the use of MRI, a tool that is being used increasingly to find genes by large studies and research groups.

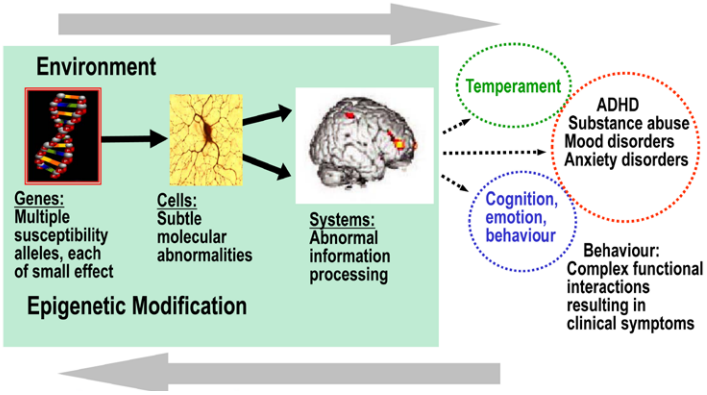

Figure 4. Interactions between genes and environment in ADHD

Treatment

The key targets of treatment include the following:

– Reduce symptoms of ADHD
– Reduce comorbid symptoms
– Reduce risk of further complications
– Educate the patient and caregivers/teachers about the disorder
– Adapt the environment to the patient's needs
– Enhance coping skills of the patient, parent, teacher, etc
– Change maladaptive views

Prof. Buitelaar advocates that treatment should not aim only for symptom reduction, but for remittance or normalisation. It is important to be proactive and go beyond symptoms to address functional impairments.

Efficacy of interventions

A number of evidence-based treatments are available that have proven short-term effects, although on the group level, long-term effects are not well documented beyond 2 years. Parent management training has proven effective, as well as school-based behavioural interventions.

Various psychotherapies can be introduced to the patient, such as self-management and social competence, as well as self-instruction training. Prof. Buitelaar stressed that pure cognitive behavioural therapy is less effective, unless provided within the context of a broader contingency management plan.

An important message provided by the Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (the MTA study) is that a huge difference exists between care as usual and optimised medication.[17] That study randomised 579 children aged 7 to 9.9 years with ADHD combined type to 14 months of medication management (titration followed by monthly visits); intensive behavioural treatment (parent, school, and child components, with therapist involvement gradually reduced over time); the two combined; or standard community care (treatments by community providers). The first analysis showed that both optimised medication arms were superior to behavioural treatment alone and to community care. Prof. Buitelaar noted that the community care arm is analogous to the treatment being provided in most clinics.

Considering that 67% of patients in the community care arm received medication as usual, what accounts for the difference between optimised medication and care as usual? Prof. Buitelaar suspects there are several reasons:

- Pharmacotherapy was provided in the medication management arms by a double-blind titration procedure, a complicated process that Prof. Buitelaar would not recommend for clinical practice.
- More importantly, the mean daily dosage was slightly higher than normal (30mg immediate-release methylphenidate) and dosing was given 3 times a day. This covered more of the day and also after-school hours.
- Also, the study employed very regular medication visits (once-monthly half-hour visits with psychoeducational support (including self-help material) and coaching
- Those visits looked for any "room for improvement" (a structured probing for functional impairment as a means of optimising medication)
- A daily report card.

Prof. Buitelaar believes that long-acting medications have improved treatment approaches. The short-acting formulation of methylphenidate (Ritalin®) given twice daily is associated with fluctuating plasma levels. In contrast, plasma levels of the extended-release formulation of Concerta® are smoother, avoiding peaks and troughs, and the effects last up to 12 hours. Ritalin LA® contains half the dose as immediate-release methylphenidate and the other half as delayed-release methylphenidate, and is somewhat shorter in efficacy (6–8 hours). Concerta has lower initial drug release, with a 22% immediate-release component and 78% extended-release component, providing a longer duration of action throughout the day.[18] Prof. Buitelaar suggests that the lower initial drug release of Concerta can be mitigated by giving the medication immediately upon awakening, so that the drug level is built-up by school time, combined with the longer duration of action over the day. Having a choice of medications allows for more targeted treatment, to more closely match symptoms.

Prof. Buitelaar encourages psychiatrists to make a difference to those adolescents or adults with undiagnosed ADHD. Appropriate treatment can have a positive effect even after having the disorder for a significant time period without treatment.

Go beyond symptoms

When treating ADHD, it is very important to go beyond symptoms. Many of the associated problems are broader,[19,20] such as:

- poor school performance (>90%)
- 30%–45% of cases experiencing some form of special education services
- lower academic achievement (10–15 pt. deficit)
- learning disabilities (affecting 24%–70%) including reading, spelling, maths, written expression
- 32% of cases do not complete high school
- 75%–95% fail to complete college.

Social-emotional consequences[19,21] include:

- rejection/isolation from peers
- association with antisocial friends
- pregnancy (impulsivity, forgetfulness)
- sexually transmitted diseases.

Problems with family life[19] include:

- 50% or more of ADHD cases have had individual or family therapy
- increased parent-child conflict, with greater parental hostility and inconsistent discipline
- greater parent and family stress
- interference with 'launch into adulthood'.

Social-emotional consequences with the peer group[19,20] include:

- 50%–70% have poor peer relations, with less sharing, cooperative behaviour and turn-taking
- intrusive, angry and inconsistent behaviour
- peers shun owing to unpredictability
- up to 70% have no close friends by 4th grade (9–10 years)
- 25%–45% develop antisocial behaviour
- unlikely to respond to social skills training
- antisocial behaviour accelerates once they affiliate with deviant peers.

Changing environmental factors can be helpful, as shown in Figure 5. Prof. Buitelaar explained that highly structured settings are those that provide clear expectations of the child in a particular context, with consequences for behaviour.

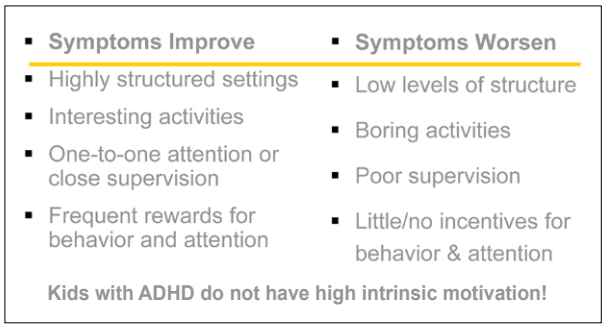

Figure 5. Environmental factors that can affect symptom expression

Principles that can be given to parents and teachers to manage behaviour include:

- Provide unconditional acceptance
- Give personal attention
- Become an ADHD expert
- Model and teach good values
- Provide structure at home/school with clear rules
- Monitor compliance and check behaviour regularly
- Inspire confidence as parent/teacher-coach.

Educator/parent characteristics that can enhance positive outcomes include:

- Have positive expectations
- Check work/behaviour
- Provide clear rules/instructions
- Remain flexible to meet individual's needs
- Show warmth, patience and humour
- Maintain structure
- Demonstrate firmness
- Communicate often with parents/educators/health professionals.

Q&A session

Q: Do children grow out of ADHD or adapt to the disorder?

A: Maybe a third, around 30%–40%, will grow out of it. The majority do not. No brain imaging data are available to support the neurological foundation. If we could understand remittance in terms of biology, we would probably have some biological targets for treatment. The MTA data showed that at a group level, the longer follow-up did not support effectiveness of treatment for longer than two years. However, a later analysis of the subgroups revealed one subgroup that had a very strong response in the first two years and then stabilised. Another subgroup had a very strong response and then relapsed after stopping the more intensive treatment, while a third group had a very slow, enduring response over the two-year period. Of these three groups, the first may not need any more intensive treatment after the first two years. The second group may need the same intensive treatment for longer, while the third group appears to need a very persistent, constant type of treatment over the years. Prof. Buitelaar advocates treating for as long as is needed. Treatment extension should be based on the individual situation of the child and family, with perhaps yearly evaluation. Medication may be withdrawn in certain situations, if the patient is responding well; if there is a relapse, this underscores the need for the medication.

Q: Is training of teachers and parents best given on a one-to-one situation, or in a group, and if group-based is best, how large should that group be? Where do resources come from?

A: Prof. Buitelaar's service starts with psychoeduation in a parent group with two therapists (a junior and senior therapist), in the evenings, providing information about ADHD. Prof. Buitelaar also provides parents with a booklet detailing practical tips and tricks. Parents are then offered a parent group for behavioural treatment, enabling parents to meet one another and share helpful ways of coping. Group-based teaching is efficient in terms of financing and budgeting.

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