On the long-term outcome of ADHD: the socioeconomic burden of a neglected condition

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1. Summary

ADHD is the most prevalent neuropsychiatric disorder of childhood. The disorder persists into adulthood in at least 15% of the cases. The prevalence in adults lies between 2,4 and 6,6%, which leads to an estimate of 19 million affected adults in the EU today. Persistence into adulthood profoundly compromises functioning in multiple areas and significantly contributes to a variety of adverse health, social and economic outcomes. Affected individuals are at significantly increased risk for poor occupational achievement despite normal cognitive and intellectual abilities, low income, under employment, impaired social skills and relationships, family dysfunction with increased rate of divorce, legal difficulties and delinquency. Direct medical costs for adult ADHD in the EU amount to 46 billion Euro on a yearly basis. An annual cost of 17 billion Euro needs to be added to this based on lost work performance. Due to lack of representative studies, no estimates of additional costs for crime, accidents, risk-taking behavior or divorce are available.

In sharp contrast to the well documented impact of ADHD persistence on patients, families and society there is a critical lack of knowledge from suitably powered large-scale studies regarding the genetic, molecular and neural basis for the disorder in adults. Understanding the factors that lead to persistence of ADHD in adults, the long-term outcome of treatment, the factors that lead to remission of ADHD some cases, as well as those that increase coping strategies for the disease in adults, will enable improved prediction of outcomes and the development of measures to prevent the progression of ADHD into adulthood and cost-effective treatments.

Given the high heritability of ADHD in conjunction with the evidence of cognitive and neurological anomalies in the disorder, it is very likely that markers of persistence exist and may be useful in increasing remission and/or coping in adulthood. The potential impact of such studies becomes clear from the fact that achieving remission for only an additional 10% of ADHD patients could reduce disease-associated costs by 6,3 billion Euros per year in the EU.

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We strongly suggest implementing a multinational study on the long-term outcome of ADHD, which would focus on elucidating the genetic, molecular, neural and cognitive factors that lead to persistence of ADHD in adults, as well as resilience factors for remission and coping; and would also include observational studies of the long-term effects of treatment of ADHD in childhood and adulthood. The findings should translate into developing new and more effective clinical treatment strategies (pharmacological, psychological, and/or environmental) to enhance remission and prevent persistence into adulthood.

2. Introduction

While it is well established that attention deficit/hyperactivity disorder (ADHD) is the most prevalent and impairing neuropsychiatric disorder in childhood, less attention has been paid to the fact that this disorder persists into adulthood in many cases: the full diagnosis of ADHD persists in at least 15% of ADHD children. An additional 50% have a partial diagnosis in adulthood with persistence of some symptoms leading to continued impairments (Faraone et al., 2006), and most of these 'partial remission' cases are expected to be re-classified as meeting full criteria for ADHD in adulthood by the future diagnostic criteria (DSM-V) for ADHD. Symptoms of persistent ADHD include inattention, forgetfulness, poor concentration, distractibility, lack of conscientiousness, disorganization and emotional dysregulation including mood instability and irritability. Hyperactive symptoms are often attenuated as compared to the childhood condition, yet increased motor activity and fidgetiness, impatience, risk taking behavior and sensation seeking are commonly seen and are highly impairing in some cases.

While these core symptoms of ADHD persist in adults, compensatory strategies and adjustments to the environment mean that that are not always apparent; however co-morbid conditions that often arise as a consequence of the underlying disorder are a hallmark of ADHD and cause additional impairment and suffering. ADHD in adults is characterized by high comorbidity rates of severe depression, anxiety disorders and alcohol/drug abuse and dependency, in addition to long term problems with low self-esteem and the development of personality disorders. High rates of ADHD are found in addiction, forensic psychiatry and youth offender units and among prison inmates (see below). Behavioral sequelae also include overt risk taking behavior with consequences such as increased accidents and medical conditions (sexually transmitted diseases, trauma), an increased rate of divorce and broken home situations.

ADHD is highly heritable with meta-analysis of numerous twin studies estimating an average heritability of 76% (Faraone et al., 2005). Current data suggest that ADHD has a complex mode of inheritance involving multiple genes of small effect, interacting with each other and with environmental risk factors (Buitelaar, 2005; Faraone and Khan, 2006). Recent data indicate that rare variants with major effect size are also relevant for the etiology of ADHD (Elia et al., 2009; Lesch et al., 2010), but at this stage it is unclear what proportion of ADHD is explained by rare variants, pending further studies. Cognition is impaired in ADHD in several cognitive domains (Dickstein et al., 2006). Systematic reviews and meta-analyses indicate that response inhibition and other aspects of executive functioning (working memory, and planning) are impaired in subjects with ADHD (Willcutt

et al., 2005; Oosterlaan et al., 1998; Sergeant et al., 2010). Next to that, impairments in non-executive processes including state regulation deficits, impairments of sensitivity to reward contingencies, impulsive responding including delay aversion and anticipation to reward are also documented in ADHD (Luman et al., 2005; Scheres et al., 2008; Scheres et al., 2007; Johnson et al., 2009). Brain imaging data reflect these abnormalities in brain function, but also indicate structural abnormalities in patients with the disorder. Reduced total and right cerebral brain volume, smaller prefrontal structures, smaller size of the splenium of the corpus callosum; and smaller volumes of right caudate and of cerebellar regions are implicated in ADHD (Valera et al., 2007). In addition to smaller brain volumetric measures, children and adults with ADHD were shown to have a relatively thin cortex particularly in regions important for attentional control (medial and superior prefrontal and precentral regions) compared to controls (Shaw et al., 2006; Makris et al., 2007; Narr et al., 2009). Furthermore, studies report structural brain connectivity (i.e. white matter integrity) to be abnormal in motor and attentional networks in children and adults with ADHD (Ashtari et al., 2005; Makris et al., 2008; Hamilton et al., 2008). Furthermore, neuroimaging with different modalities (i.e. electroencephalography [EEG] and functional magnetic resonance imaging) proves functional connectivity to be abnormal in several regions of the brain in ADHD (Murias et al., 2007; Mazaheri et al., 2010; Rubia et al., 2009; Cubillo et al., 2010; Wolf et al., 2009; Tian et al., 2006; Helps et al., 2010; Yang et al., 2010; Cao et al., 2010; Cao et al., 2009).

Estimates of the prevalence of ADHD in adults range from 2,4 to 6,6% (Simon et al. 2009, Fayyad et al., 2007; Kessler et al., 2006; Faraone and Biederman, 2005; Kessler et al., 2005a; Kooij et al., 2005). Taking an average population prevalence of 4,5% as a starting point, this translates into 19 million persons older than 15 years living in the European Union in 2010 (a population of 501,1 Mio. x 84,3% x 4,5%) suffering from ADHD. Persistent ADHD thus has important implications for patients, health care systems and society. There have, however, been relatively few investigations of the genetic, molecular, neural and cognitive factors that influence the developmental trajectory from childhood through to adulthood and as a result little is known about the factors that influence prognosis of childhood ADHD and the processes involved in remission versus persistence. Even more importantly, it can only be speculated upon why a large portion of ADHD patients develop co-morbid disorders such as depression, substance abuse or anti-social personality disorder, while others are able to cope with the disorder or even manage to utilize symptoms of persistent ADHD in a beneficial manner.

Considering the manifold consequences and the frequency of ADHD, there is a surprising dearth of data on the socioeconomic impact of persistent ADHD. The estimated yearly income loss for adults with persistent ADHD in the US is $ 77 billion (Biederman and Faraone, 2006). Data from the USA indicate direct medical costs per adult ADHD patient per year of 2.500 € (Hinnenthal et al., 2005), translating to roughly 46 billion € for all persistent ADHD patients in the EU. However, indirect costs are much higher and are suggested to be comparable to those of substance use disorders (including alcohol abuse) (Schlander, 2010). An American study estimated the annual cost due to lost work performance at $ 4.336 p.a. per patient (Kessler et al., 2009), with a 1,9% prevalence in the examined working population. Assuming an overall employment rate of 65% in the EU, these numbers reflect an annual cost due to lost work performance of 17 billion €. Due to lack of respective studies other aspects of burden of disease – e.g. due to violence, drug abuse and crime (with prevalence of ADHD in male prison inmates as high as 45% (Rosler et al., 2009; Rosler et al., 2004), accidents, risk-taking behavior, divorce, etc. – cannot be provided, yet the direct medical cost and loss due to decreased

productivity already add up to more than 63 billion Euro per year in the EU. Given the enormous socioeconomic impact of this disorder, the lack on data on prevention and prediction is surprising and detrimental.

An additional important determinant of burden of disease of adult ADHD is the frequency of co-morbid conditions. In surveys, those are often not identified as being due to the underlying ADHD persistence, so that the "true" socioeconomic impact of persisting ADHD is difficult to estimate, yet is most likely much higher than the numbers given above. A clue might be derived from studies on persistent ADHD comorbidities. For example, lifetime co-morbidity with mood disorders was found to be 57%, with anxiety disorders 27%, and with substance use disorders 45% (Jacob et al., 2007). Especially the latter number should be considered in the light of the fact that development of substance use disorders can be prevented by appropriate treatment of childhood ADHD.

3. What could be changed?

As indicated above, ADHD remits in a proportion of patients. This suggests that remission might be influenced if the predictors and mechanisms of remission where known. So far, however, only a small number of studies have looked into potential predictors of persistence and remission of ADHD. Being generally of only small size, they have produced inconsistent results. Suffering from the combined subtype of ADHD, as well as symptom severity, impairment, comorbidity and adverse environmental factors have been reported to predict a persistent course of ADHD (Biederman et al., 1996; Lara et al., 2009); another study found symptom severity as well as childhood treatment to be relevant (Kessler et al., 2005b). The cognitive, genetic, and neural mechanisms that underlie persistence versus remission of ADHD are largely unknown. Halperin and Schulz (Halperin and Schulz, 2006) proposed a neurodevelopmental model of ADHD and hypothesized that (1) ADHD is due to an early onset dysfunction of subcortical brain areas that persists throughout life, and (2) the prefrontal cortex, which typically develops throughout childhood and adolescence, mediates top-down executive function processes that compensate for the subcortical dysfunctions. Remission of ADHD over the course of development would be associated with improvements in executive control functions. In testing their hypothesis, persistent ADHD was associated with deficits in effortful executive processes compared to remitting ADHD and controls at follow-up in late adolescence. Both persisters and remitters had deficient perceptual sensitivity and response variability, indexing subcortical dysfunction (Halperin et al., 2008). The literature on the prognostic value of genetic factors, like the ADHD risk factor in the dopamine D4 receptor (*DRD4*) gene is contradictory (Shaw et al., 2007; Langley et al., 2009; Biederman et al., 2009b). Our own work on another candidate gene, the dopamine transporter (*DAT1*) gene, suggests that a different allele of is associated with persistence of ADHD in adults from that reported to be associated with childhood ADHD (Franke et al., 2008; Franke et al., 2010).

As described above, ADHD is associated with various abnormalities of neural structures and neural functions (altered performance in various cognitive domains as well as altered functional brain connectivity), but it is still unclear whether these neural measures reflect symptom severity or index the course of ADHD.

Treatment is another factor potentially influencing ADHD outcome. Stimulant medications have been evaluated extensively in hundreds of empirical studies (Faraone and Buitelaar, 2010) and are considered a first-line treatment for ADHD. Methylphenidate (MPH) is the best-studied stimulant medication for ADHD, with results from a number of studies demonstrating that it significantly improves behavioral and attention-related symptoms of ADHD and academic and social functioning (Pelham et al., 2001; Biederman et al., 2003; Swanson et al., 2003; Taylor et al., 2004) and at the same time reduces sequelae, such as the development of psychiatric disorders (The MTA Cooperative Group, 1999) as well as substance use and abuse (Wilens et al., 2003; Wilens et al., 2008). Atomoxetine, which has been shown to be effective in relapse prevention (Prasad and Steer, 2008; Bakken et al., 2008), is considered a second-line treatment option. There is clear evidence suggesting a better clinical outcome of children that stay in treatment for ADHD (Goksoyr and Nottestad, 2008; Halmoy et al., 2009; Barbaresi et al., 2007; Biederman et al., 2009a). However, the current rate of retention of children in treatment is low (Weiss et al., 2006; Atzori et al., 2009; Janols et al., 2009).

Finding a cognitive or biological marker of persistent ADHD would provide a means of distinguishing children with ADHD who are at risk for a persistent course into adulthood and poor clinical and psychosocial outcomes. The technical advances of genetic analysis (including the availability of next generation sequencing), proteomics- and metabolomics-based systems analysis, and the availability of established cell-based and animal-based model systems for the evaluation of genes and their interaction with the environment, finally brings the identification of biological markers for persistence of ADHD into close reach. Combining biological marker data with those from the analysis of neuroimaging, neuropsychology and neuropsychopharmacology, makes the establishment of tests for ADHD persistence with high sensitivity and specificity feasible. Such markers would provide a basis for targeted treatment approaches for the group at risk of persistence. In addition, resilience factors that increase the chance of remission and allow the development of strategies for better coping with the disorder can also be identified in this way. Targeting processes that naturally lead to remission in a proportion of cases, may lead to the development of new treatments to prevent progression of the disorder in cases where ADHD would usually persist. The potential impact of such studies becomes clear from the fact that achieving an additional remission for only 10% of adult ADHD patients could reduce disease-associated costs by 6,3 billion € per year in the EU; assuming treatment costs of 2.000 € p.a. and the conservative estimate of direct and indirect costs of 6.000 € p.a. as outlined above.

Taken together, there are clear arguments for large-scale, systematic studies exploring factors predicting long-term outcome of the disease; and the possibilities to use those factors in the clinic to improve treatments for ADHD in adults, halt the progression of the disorder and associated comorbidities and/or improve coping when the disorder does persist. We therefore strongly suggest establishing a multinational study on the long-term outcome of ADHD, including the **identification of genetic, molecular, neural and cognitive factors promoting ADHD persistence as well as resilience factors for remission and coping**. This also includes the **long-term effects of treatment** of ADHD in childhood / adulthood. Finally, these findings should **translate into clinical treatment strategies** (be it pharmacological, psychological or environmental) to enhance remission.

4. An EU project on the long-term outcome of ADHD

The following objectives should be addressed in such a project:

1. Identification of genetic, molecular, neural and cognitive factors involved in persistence of ADHD
2. Identification of factors enhancing remission and protective factors (resilience factors)
3. Assessment of long-term effects of treatment
4. Translation of the findings into developing new and more effective clinical treatment strategies

A combination of various strategies is needed to achieve these objectives, which involve the evaluation of biological, psychological and environmental factors, in longitudinal designs. This can be achieved by utilizing the following essential resources: 1) already existing well-established large integrated databases of phenotypic, neural, cognitive and genetic data; 2) existing long-term observational studies, and 3) animal and cell models. Clearly, this calls for large international collaborations including research-oriented clinical departments (child and adolescent psychiatry, adult psychiatry, psychology) as well as strong basic research groups (genetics, molecular and systems neuroscience, behavioral physiology).

To reach objective 1 in a time- and cost-efficient manner, information should be generated from two sources, i.e. through following up existing well-characterized clinical samples of children with ADHD and through assessments of population data from existing registries.

To reach objectives 1-3, psychological, pharmacological and environmental factors need to be explored. This is best carried out using the following tools:

- Neuroimaging based on functional and structural magnetic resonance imaging (MRI), near-infrared spectroscopy (NIRS), EEG
- Existing data on neuropsychopharmacology
- Next generation sequencing, proteomics and metabolomics
- Cell biological techniques
- Animal models (mouse, rat, zebrafish)

To reach objective 4, the results obtained in parts 1-3 are to be translated into (clinical) strategies involving lifestyle modification, personalized medicine as well as coping strategies.

The authors of this white paper are in a perfect position to carry out such a project. They have at their availability all necessary expertise and facilities, either at their own institutes, or through already existing collaborations. As a group, they represent the top-ranks of the ADHD research field, with regard to the availablity of integrated phenotype databases, biobanks and access to ADHD clinical patient populations.

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