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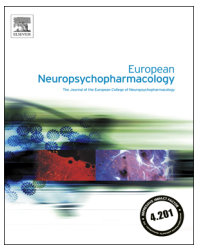

EDITORIAL

IMpACTing on adult ADHD research

In the last 20 years there has been an increasing awareness that attention deficit/hyperactivity disorder (ADHD) not only is the most frequent psychiatric disorder in childhood, but also persists into adulthood in at least 15% of cases (adult ADHD, aADHD) (Faraone et al., 2006). This chronic, substantial impairment as well as the co-morbid conditions being the rule rather than the exception in ADHD call for adequate diagnosis and treatment of this disorder. While the concept of childhood ADHD is still under debate in lay circles – the number of critical, populist and polemic articles not tinted by proper knowledge is legend – but not amongst clinicians and the scientific community, there are still psychiatrists who doubt the existence of persisting ADHD; this despite the overwhelming evidence of continuity from childhood to adulthood. As Thomas Kuhn has said, '[....] paradigms die when their promoters die'— times are changing and the paradigm that ADHD is a disorder limited to childhood and adolescence is finally dying. As stimulant medication has recently been licensed in many European countries for use in adult ADHD, and patients can be offered an effective remedy, awareness of the diagnosis has been further boosted. As a consequence, many psychiatric departments now run specialized outpatient services focusing on diagnosis and treatment of aADHD and its co-morbid conditions. From own experience it has to be said that these are highly beneficial in reducing patients' suffering, although more extensive, integrated programs that combine pharmacotherapy and psychotherapy with neuropsychological training and neurostimulatory techniques or neurofeedback are still scarce.

In striking contrast to the advances in the clinical care of aADHD, research into the underlying pathophysiology falls far short. Despite the fact that persisting ADHD is the most severe, and potentially most genetically loaded and "biological" form of the disease, major questions have not yet been answered. What is the genetic basis of aADHD? Which factors predict persistence vs. remission in adolescence? Are there specific morphological changes in the brain of aADHD patients?, to name but a few (Franke et al., 2012). To address these issues, we founded the International Multicenter persistent ADHD CollaboraTion (IMpACT) in 2007, supported by the ADHD Molecular Genetics Network. The groundwork for IMpACT took place at the World Congress of Psychiatric Genetics in NYC and the ECNP congress in Vienna —the meetings took place back to back, and us two were flying from one to the other. A truly trans-continental effort from the very beginning, indeed! The idea behind IMpACT is to bring together those international research groups that have a strong track record in psychiatric genetics, a research focus on aADHD, clinical expertise in this condition and already existing large patient and control samples that are well phenotypically characterized. The principal investigators of IMpACT are – in addition to the authors of this editorial – Prof. Klaus-Peter Lesch from Würzburg in Germany, Prof. Jan Buitelaar from Nijmegen in The Netherlands, Dr. Bru Cormand and Dr. Josep Antoni Ramos-Quiroga from Barcelona, Spain, Prof. Philip Asherson and Dr. Jonna Kuntsi from London (UK), Prof. Jan Haavik and Prof. Stefan Johansson from Bergen in Norway, Prof. Stephen Faraone and Dr. Erick Mick from Syracuse, New York and Boston, Massachusetts, USA as well as Dr. Claiton Bau from Porto Alegre in Brazil. Together, IMpACT represents the largest sample of aADHD patients for genetic research — at present more than 4000 samples are included in the IMpACT database. Our collaboration has produced numerous conference contributions – also at ECNP meetings – and many collaborative publications in prestigious journals. Given the importance of aADHD, the leading role of IMpACT in the genetic research therein and the chaperoning of ECNP in the formation of our consortium, it is absolutely appropriate that a Special Issue on Adult ADHD featuring cutting edge research from our consortium, now is published in the official ECNP journal. We are greatly indebted to Michael Davidson and the Editorial Board for fostering the idea and their helping hand in preparing this issue, which you are now looking at.

Our aim was to address several important issues in the current state of affairs in adult ADHD research. These should include epidemiological, genetic, neuroimaging and clinical research. We aimed for a balance of scholarly reviews and original research on these topics. Genetic modeling in a large twin study of young adults by Merwood

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and co-workers shows how ADHD symptoms relate to temperament dimensions; hyperactivity/impulsivity as well as inattention appear related to novelty seeking, while inattention is also related to harm avoidance traits. Sanchez-Mora and Weissflog present candidate gene studies along the research rationales of their respective working group: while the Catalan group follows the approach of investigating functionally connected gene sets (here, genes that regulate neurotransmitter release) through a gene-system association study in ADHD across the lifespan, the Franconian strategy is to focus on genes (in this case *KCNIP4*) with converging evidence from GWAS, linkage and other studies. In their well-powered studies, Sanchez-Mora and coworkers provide first evidence for the involvement of *SYT2* and *STX1A* in the genetic predisposition to adult ADHD, the former also being relevant for childhood ADHD; the study by Weissflog and colleagues suggests that *KCNIP4* is involved not only in aADHD, but also in personality disorders. Importantly, the study by Carpentier et al. shows that subdividing aADHD according to the presence and absence of particular co-morbidities – in this case substance use disorders (SUDs) – can strongly improve genetic association studies. The data presented suggest that the *DBH* gene is associated with aADHD particularly in cases without SUDs, while *OPRM1* seems linked to aADHD with co-morbid occurrence of SUDs.

Downstream of gene-finding, the mechanisms leading from gene to disease are still largely elusive in (a)ADHD. Using genetic imaging approaches, the experimental studies by Fallgatter and Hoogman show how progress in this area can be achieved. For the well-established ADHD candidate genes *LPHN3* (Ribasés et al., 2011; Lange et al., 2012) and *DAT1* (Franke et al., 2010) they provide more information on potential brain substrates. Fallgatter and co-workers show in a large electroencephalography study how the ADHD risk haplotype in *LPHN3* alters event-related potentials elicited by a Continuous Performance Test. The functional magnetic resonance imaging genetics approach by Hoogman and colleagues shows in the hitherto largest sample of cases and controls that the *DAT1* genetic risk factor for aADHD is not relevant for striatal brain activity during reward anticipation while performing a modified monetary incentive task; this disproves earlier findings in smaller samples. In addition to these experimental studies, review papers by Lesch and Rivero critically summarize the present knowledge on two pathophysiologically relevant molecular mechanisms in ADHD: those downstream of latrophilins (including *LPHN3*) and the glutamatergic system in the review by Lesch et al., and those mediating effects of the *CDH13* gene in the RIVERO paper.

Clinical issues related to the pharmacological treatment of aADHD are addressed in five additional papers. Review articles by Frederiksen and Surman summarize available evidence for safety and efficacy of stimulant treatment in this group of patients. Frederiksen presents evidence for the long-term efficacy of stimulant and atomoxetine treatment of adults with ADHD; Surman's review of the literature concludes that stimulant treatment leads to measurable improvement in daily function for adults with ADHD. The meta-analysis performed by Mick and co-workers investigates cardiovascular safety of stimulants for aADHD. The authors report evidence for small increases in resting heart rate and systolic blood pressure in stimulant users of as yet unclear clinical significance. Experimental data presented by Bron about the connection between stimulant treatment and nicotine craving in aADHD provide first evidence that tobacco consumption and nicotine craving increase acutely and stabilize at increased levels after three-months of methylphenidate use; this finding can form a basis for the initiation of randomized controlled trials on this issue. Lastly, Contini and coworkers performed a review of pharmacogenetic studies of methylphenidate response in aADHD, speaking to the dearth of data on this important area of biomarker research.

Taken together, we here put together a special issue full of state-of-the-art research papers and review articles dealing with crucial issues in aADHD research, both preclinically and clinically. While we are of course proud of the overall quality of research done within IMpACT and the success of the collaboration, this issue is rather meant as a contribution to the just recently emerging field of research on aADHD. We strongly believe that our group has made an IMpACT, but much more research is necessary to improve diagnosis and treatment of the large arsenal of patients suffering from this severely impairing chronic form of ADHD. Unfortunately, funding for such research has not been readily forthcoming yet, potentially due to the stigma that is still attached to aADHD. Thus, an important task for the IMpACT members lies in educating the public and decision makers about ADHD in adults and its impact on society. Fortunately, and probably most importantly, we will take these challenges in our consortium by not only working together efficiently and effectively, but also as the good friends we have become in the last five years. Also in this respect we are looking forward to next five years of IMpACT! As for now, we hope you will enjoy reading our special issue.

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Barbara Franke*
Radboud University Nijmegen Medical Centre, The Netherlands
E-mail address: B.Franke@gen.umcn.nl

Andreas Reif
University of Würzburg, Germany
E-mail address: reif_a@klinik.uni-wuerzburg.de

*Corresponding author. Tel.: +31 24 3610181; fax: +31 24 3616658.