5.5.3 Clinical Research Unit 125, Attention-Deficit/Hyperactivity Disorder – Translational Research Focus on Molecular Pathogenesis and Treatment across the Life Cycle

The primary goals are based on the following concept: By joining preclinical and clinically oriented research groups, who work on ADHD-specific molecular mechanisms of nerve cell function as well as molecular genetic and developmental biological essentials of brain function, and on structural-functional basis of the complex behavior of ADHD, predictors and differential strategies for therapy during the long-term course of illness are being developed. Moreover, evolutionary conserved ADHD-relevant principles of structure and function of the brain as well as syndrome-typical behavior (e.g., hyperactivity, attention-deficit, impulsivity, aggression, substance use) are being defined by comparative investigations of different species (humans, nonhuman primates, mice). Finally, the preexisting areas of convergence between the fields of neuropsychology, psychobiology as well as child and adolescent, and adult psychiatry will strengthen the connections between the individual disciplines by establishing new research groups, who will investigate common topics. In that, new opportunities for the study of the molecular foundations in the etiopathogenesis and long-term course of ADHD have been put into practice.

**Major Research Interests**

ADHD (MIM 143465) is the most common behavioral disorder in childhood with a prevalence of 4-8% and with substantial heritability which is likely due to multiple genes of small effect size. Longitudinal studies demonstrated persistence into adulthood with a lifetime prevalence estimated at approximately 2-4%. Epidemiological studies suggested high co-morbidity with other psychiatric disorders; lifetime prevalence rates of anxiety disorders in adult ADHD approach 50%. Affective disorders and alcohol/drug dependence also display a remarkable frequency (Fig. 1). A co-morbidity with antisocial personality disorder was reported to be increased in several clinical cohorts. The burden of disease cannot be overestimated by accounts of social and economic problems as well as impaired academic achievement and work performance. Particularly, disruptive family environment may harm offspring development.

By integrating the concepts of molecular genetics, neurobiology, and cognitive psychology, the psychiatric neurosciences have witnessed remarkable progress in the understanding of the relationship between neurodevelopment, neural function, and behavior related to ADHD. In this context particularly animal models such as genetically modified mice or nonhuman primates contributed important insight. On the other hand improvement of methodological tools in psychology and psychiatry permitted the accumulation of new information on the psychological and neurobiological basis of behavior and its alteration in ADHD. The human genome project and the sequencing of mouse and rhesus macaque genomes shifted the focus also to investigations of gene function in psychiatry. This development will allow better understanding of both the molecular and cellular foundation of ADHD and the relevance of genetic variation for disease-related behavior such as hyperactivity, attentional and cognitive deficits, emotional dysregulation, and drug use. Finally, the design of novel therapeutic strategies requires translational approaches with interdisciplinary cooperation of basic research and clinical medicine.

The KFO 125 is divided into ten tightly interconnected subprojects (Fig. 2): Two subprojects (SP 1 and 2) focus on clinical aspects including diagnostic evaluation of ADHD and co-morbid disorders across the life cycle as well as ascertainment of patients and their families for genetic study. In addition, these two subprojects assess etiological heterogeneity, clinical symptoms of subtypes and outcome, as well as psychosocial impact of ADHD within the framework of a family-centered outpatient unit. In contrast to previous longitudinal studies, a multi-layer analysis facilitates a novel understanding of ADHD.
approach in follow-up research which is likely to provide a more profound understanding of the interaction between genetic disposition and environmental influences on the course of juvenile and adult ADHD. In synergy to SP 1 and 2 a BMBF-supported study entitled “Effects and Mechanisms of Psychotherapy in the Treatment of ADHD in Children and Adults – The First Randomized Multicentre Study” exclusively focuses on the treatment of ADHD across the life cycle.

Three subprojects (SP 3-5) represent an integrated approach toward elucidation of specific molecular genetic and neurobiological mechanisms of complex behavior related to ADHD. Genome-wide linkage scans using 50K SNP arrays are being performed on extended multigenerational families with high density of ADHD and a sample of affected sib pairs. In addition, application of a 500K SNP array in genome-wide association (GWA) studies will provide a profound basis for subsequent studies on genetically modified mouse models of ADHD. Furthermore, three subprojects (SP 6-8) attempt to define endophenotypes of ADHD by electrophysiological and neuropsychological paradigms as well as functional magnetic resonance imaging (fMRI). Finally, all aspects of the clinical and neurobiological research program are integrated by a subproject on genetic epidemiology/biostatistics (SP 9) and by a junior research group on imaging of genetic variation (SP 10 - JRG). The primary goal of the JRG is the elucidation of the effects of genetic variation on the functional neuroanatomy of attention, impulsivity as well as emotion and its relevance for ADHD using different brain imaging techniques like EEG, NIRS, fMRI and PET.

The basis for the pursuit of these concepts and goals is the interdisciplinary composition of KFO 125 and its integration into the research structures of the University of Wuerzburg (e.g. SFB 581, GRK 1156, GRK 1263, GSLS, IZKF) as well as into a wide spectrum of national (e.g. BMBF Multicentre Study, Nationales Schwerpunktnetzwerk ADHS, MPI für Molekulare Genetik) and international collaborations (e.g. EU Neuro10, NIMH, NHGRI, NIDA, NI- AAA, Tgen Research Institute). This resulted in a specific and long-term configuration of competence at the Clinical Institute of the University of Wuerzburg with focus on future-oriented translational research of etiopathogenetic mechanisms and novel therapeutic options of ADHD.

Teaching

The unique configuration of competence for translational research of the KFO 125 together with the SFB 581 and Graduate Programs within the Internationale Graduate School of Life Sciences (GSLS) provides an excellent platform for competent education and training of a wide variety of junior researchers including Bachelor and Master students, M.D. and Ph.D. students as well as Postdocs from the Faculties of Medicine, Biology, Physics, and Humanities. The enhancement of the interdisciplinary teaching in the psychiatric neurosciences is therefore an ultimate goal of the KFO 125. Complex approaches to neurobiological questions and the joint use of techniques and methods derived from molecular biology, genetics, and imaging are the hallmarks of modern psychobiological research, making psychiatric neurosciences interdisciplinary by definition.


