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EDITORIAL

Autism spectrum disorder: underlying neurobiology

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Introduction

Over the recent years, a lot of progress has been made on eliciting the underlying neurobiology of Autism spectrum disorder (ASD). This severe and disabling neurodevelopmental disorder is characterized by pervasive impairments in social interaction, communication, and repetitive or stereotyped behaviour, and is associated with a significant burden not only to the affected children and their families but also to the society as a whole (Lavelle et al. 2014). Fuelled by strong public and private support for ASD research, especially in the US, large scale genetic, but also phenotypic studies have been performed. These studies have indicated a continuum of the autism specific social interaction and communication abilities as well as stereotyped behaviours and special interests, which cross the old diagnostic boundaries of DSM-IV TR and ICD-10. This continuum idea has now been integrated in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Autism spectrum disorder (ASD) now comprises former DSM-IV TR diagnoses autism, Asperger's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder—not otherwise specified (American Psychiatric Association 2000; American Psychiatric Association 2013) which are roughly comparable to the ICD-10 diagnoses autism, Asperger Syndrome, Childhood Disintegrative Disorder, and atypical autism (World Health Organization 1992). Over the past years, a number of research studies have already been performed in this integrated way investigating combined samples.

With regard to current neurobiological research in ASD, the following core topics and research questions are starting to emerge: (1) What are the specific characteristics of ASD compared to other child psychiatric disorders? This question is specifically relevant for the question of differential diagnosis and differential treatment of all ASD as a group versus other child psychiatric disorders. (2) Within ASD, can we describe more homogeneous neurobiologically defined subtypes, which may share the same aetiology? This question is specifically relevant to provide a basis for research on specific treatment options for some children with ASD who share an underlying neurobiology, as has been described, for example, for Fragile-X-Syndrome (Berry-Kravis et al. 2012).

This special issue of the *Journal of Neural Transmission* combines a comprehensive collection of original and review articles trying to answer these two core research questions.

Genetic and gene-expression studies

Over recent years, huge progress on the genetics of ASD has been made. Especially, the role of rare and de-novo variants, either copy number variations (CNV) or single

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nucleotide variations (SNV), has been delineated by large scale genetic studies involving multiple sites and large samples. The role of common genetic variation, e.g. single nucleotide polymorphisms or common CNVs, has not been in the focus of genetic studies over the last years despite a likely role of common genetic variation in ASD (Devlin et al. 2011). Many studies on the genetics of ASD have taken a hypothesis-free approach aiming at finding new risk variants and describing the involved pathways based on their study results. The two studies on the genetics of ASD presented in this special issue, in contrast, started with the hypothesis, that the glutamatergic system will be involved in ASD, which was confirmed, and indicates a role for rare and common variants in glutamatergic candidate genes in ASD aetiology (Chiocchetti et al., Waltes et al.). Other approaches to study the underlying neurobiology of ASD are gene-expression and proteomic studies. Gene-expression and proteomic studies have the advantage over genetic studies, that gene products are measured directly, after splicing and translation processing. The original proteomic and gene-expression study included here (Taurines et al.) describes a convergent ASD specific pattern compared to attention-deficit/hyperactivity disorder (ADHD).

Brain imaging studies

With the technology-driven transformation of cognitive neuroscience research and the proliferation of various neuroimaging modalities, a wide and still growing array of novel phenotypes of ASD has been delineated. The application of structural and functional MRI, diffusion tensor imaging (DTI), electro-encephalography (EEG), and magnetoencephalography (MEG) has revealed abnormalities in neuronal patterning, cortical connectivity, synaptic organization, and electrophysiology in subjects with ASD. However, so far, many inconsistent findings have emerged, and still, our understanding of brain dysfunction in subjects with ASD is very limited. It is likely that many different neural pathways are involved in ASD, with a specific combination of differentially neurobiologically influenced pathways in specific individuals with ASD. Thus, there is an urgent need to bridge the gap between cognitive neuroscience research, multimodal brain imaging techniques, and human genetics to elucidate the molecular mechanisms underlying quantitative neurocognitive phenotypes, and to further our understanding of the brain's structural and functional architecture in subjects with ASD.

Recent evidence from neurophysiological studies such as EEG, MEG or TMS studies for such an approach has been summarized by Luckhardt et al. in the present issue. The authors argue that by tracking down abnormal neural activation patterns associated with key cognitive or perceptual functions to more basic neuronal functions such as deficits in cortico-cortical connectivity might help to better bridge the gap between genetic and brain imaging findings in ASD. Ambrosino and colleagues followed these suggestions and investigated functional brain connectivity during cognitive control in subjects with ASD using a multivariate data-driven approach. During the last years, advances in the field of structural brain imaging also allow to investigate different aspects of typical and atypical structural brain maturation in a more sophisticated way. For example, the structure of the cortex itself as well as the thickness of the cortex in the same areas can be analyzed in parallel and it has been recently demonstrated that surface area and cortical thickness are genetically distinct from one another (Peper et al. 2007). Ecker et al. used this approach and demonstrated that differences in the neurodevelopmental trajectory of maturation for both measures need to be taken into account when interpreting case–control differences at the group-level in adolescents with ASD.

Neuropsychological studies

Before the development of functional brain imaging in the 1980s, behavioural neurocognitive studies were the core studies aiming at describing brain function in a sophisticated way. They still have a number of advantages today compared to brain imaging studies. For example, they are easy to implement in clinical settings, and can, therefore, be used during every-day diagnostic work up to describe neurocognitive function related to specific ASD subtypes or to outcomes of psychotherapy and pharmacological interventions. Given that ASD is a neurodevelopmental disorder, it is of strong importance to study the developmental course of neurocognitive impairments. Greimel et al. thus investigated face processing abilities in different age groups, and also reflects on the question if ASD shows a developmental delay or a deviant development with regard to face processing. Another important change in the DSM-5 classification is that the ASD diagnoses no longer preclude the diagnoses of ADHD. Given the fact that DSM-5 now allows to simultaneously diagnosing ASD and ADHD in one individual, studies on overlap and specificity of ADHD, ASD, and the impact of comorbidity on neurocognitive dysfunction become even more important. De Vries and Geurts investigated the ADHD related aspects of working memory and inhibitory task performance in children with ASD, and found a small ASD subgroup with impairments in both areas. Pankert et al. focussed on reward processing abilities, which also have been described in ADHD before, and investigated the specific impact of familiar versus unfamiliar social reward relative to non-social, monetary reward.

As guest editors, we feel that this special issue illustrates the breadth of issues and opportunities presented by the interface of psychiatry, genetics and neuroscience, and hopefully will stimulate further debate and research. We would like to thank all contributors for their high-quality papers and the Editor-in-Chief of the *Journal of Neural Transmission*, Professor Peter Riederer, for affording us the chance to guest edit this special issue.

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