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EDITORIAL

Schizophrenia: from risk genes to outcome and comorbidity

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Dedicated to neurobiology, therapy and outcome of schizophrenia, this issue opens with the effects of the schizophrenia risk gene D-amino acid oxidase activator (DAOA) in healthy probands. During the last years, there is increasing evidence of the involvement of risk genes in the pathophysiology of severe psychiatric diseases, but neurobiological consequences of these gene variants are widely unknown. The DAOA polymorphism has been shown to be associated with a dysfunction of the glutamatergic NMDA receptor that in turn influences dopaminergic and serotonergic metabolism. Andreou et al. [1] investigated effects of DAOA SNPs on the major dopamine metabolite homovanillic acid (HVA), the serotonine metabolite 5-HIAA and the noradrenaline metabolite MHPG in cerebrospinal fluid of healthy probands. They found an association of two polymorphisms with HVA concentrations and one of them with 5-HIAA levels. This suggests DAOA gene variants to possibly affect dopamine turnover. Investigation of gene effects in healthy probands is recommended to avoid the influence of other disease factors and treatment, but as a next step neurobiological consequences should be assessed in schizophrenia patients. Ayesa-Arriola et al. [2] investigated the relationship between elevated plasma homocysteine levels and cognitive deficits in a large sample of first-episode schizophrenia patients and controls. However, despite very sophisticated neuropsychological testing, they found no evidence for a respective tie, which points to another neurobiological background than in neurological diseases. Since plasma levels are probably not representative for alterations in the central nervous system, assessments in post-mortem brain tissue are needed to unravel the neurobiology of schizophrenia.

In a genome-wide microarray study of the superior temporal cortex in schizophrenia, our group (Schmitt et al. [3]) revealed altered gene expression of structural synaptic elements in schizophrenia, influencing proper synaptic function such as synapse stabilization and formation, leading to disturbances of microconnectivity. Both the superior temporal cortex and the inferior parietal lobule belong to the heteromodal association cortex, which has been suggested to be involved in the pathophysiology of a disturbed network in schizophrenia. Palaniyappan and Liddle [4] investigated cortical thickness, surface area and folding in this region in a large group of schizophrenia patients and controls. In the patients' group, the parietal supramarginal gyrus showed reduced gyrification, contracted surface area and thinning, which may originate from a disturbed neurodevelopmental process since the gyrification of the cortex is generated during the perinatal period.

However, in these studies, treatment effects may influence the findings described above. In schizophrenia, different atypical antipsychotics have been suggested to possess different clinical effect sizes. In a prospective observational study, Kilian et al. [5] found that patients under olanzapine medication had lower hospital readmissions compared to other drugs, but showed no differences in clinical outcomes or quality of life. In a 2-year outcome study, Langeveld et al. [6] investigated outcome variables such as symptom severity, remission status, treatment utilization, cognition and social functioning in patients with early-onset schizophrenia (<18 years) compared to adult-onset, first-episode, non-affective psychosis. At baseline,

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early-onset patients were more symptomatically compromised, but after the 2-year period, differences were no longer significant. Thus, older studies reporting worse outcome in teenage onset could not be reconfirmed here.

Comorbid drug and alcohol dependence across European countries were of interest for Carra et al. [7]. They report general odds of dependence being higher in the schizophrenia group ($n = 1{,}208$) than in the general population, but variation between countries and the nine participating centers. Overall, the rates are less than those reported from the USA. From the literature it is known that schizophrenia is comorbid with obsessive–compulsive disorder (OCD) and that neurochemical alterations in the orbitofrontal cortex play a role in the pathophysiology of this disease. Zurowski et al. [8] investigated unmedicated patient with OCD at baseline, and after participating in a 3-month cognitive-behavioral therapy (CBT) study by proton magnetic resonance spectroscopy of the orbitofrontal cortex, striatum and anterior cingulate cortex. They found the concentration of myo-inositol in the orbitofrontal cortex to predict the outcome of subsequent CBT, highlighting neurobiological prediction of effects of psychotherapy. Cognitive dysfunctions have repeatedly been reported in patients with OCD and unaffected relatives. In a neuropsychological study, also examining an antisaccade task, Lennertz et al. [9] reported increased antisaccade error rates in patients and relatives, while prolonged antisaccade latencies and impairments in visouspatial functions, problem-solving and processing speed were found only in the patient's group. The increased antisaccade error rates point to inhibitory deficits and may represent a candidate endophenotype of OCD. Further studies are needed to find well defined endophenotypes of schizophrenia and comorbid disorders to improve diagnostic classification and prediction of outcome.

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