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EDITORIAL

Classification and neurobiological concepts of mania, bipolar disorder and major depression

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In the new DSM-5 and ICD-11 classification systems, pure mania and mania with mild depression are subsumed under bipolar disorder. In a comprehensive review, Angst and Grobler [1] vote for improved differential diagnoses of unipolar mania. This is clinically relevant since the disorder has a prevalence of approximately 1.8 %, and clinical follow-up studies demonstrated good diagnostic stability. Moreover, mania is associated with a hyperthymic temperament, more psychotic symptoms and higher heritability compared with depression. In contrast, the concept of bipolar disorder has been widely investigated in neurogenetic studies. For example, the dopaminergic system has been suggested to be affected in bipolar disorder, but the impact of the genetic variants of the human dopamine transporter DAT1 (SLC6A3) is inconsistent. Huang et al. [2] investigated the association of 18 polymorphisms of the DAT1 gene with bipolar disorder and explored its influence on specific personality traits such as novelty seeking and harm avoidance. Several polymorphisms had a weak association with bipolar disorder, and the promotor G-A-C-G haplotype was overrepresented in their sample of 492 patients compared with 436 healthy controls. Bipolar II patients had the highest harm avoidance score and a significant association between rs40184 of DAT1 and this personality trait in patients with bipolar disorder. G72 (D-amino acid oxidase activator, DAOA) is a susceptibility gene for bipolar disorder and schizophrenia. In a diffusion tensor imaging (DTI) study, Nickl-Jockschat et al. [3] investigated the influence of a G72 susceptibility haplotype on fiber tract integrity in young healthy probands. They found clusters of increased fractional anisotropy in homozygous risk haplotype carriers in the right periinsular and inferior parietal region. Both regions have been hypothesized to be involved in the pathophysiology of bipolar disorder and schizophrenia, and alterations in fractional anisotropy may reflect changes in neuropil such as morphology of dendrites.

In a functional magnetic resonance imaging (fMRI) study using a working memory task, Stegmayer et al. [4] found reduced functional interactions of the right amygdala with cortical regions supporting verbal working memory in 18 bipolar patients compared with 18 healthy controls. The results point to a disturbed right-hemispheric cognitive–emotional interaction between the amygdala and cortical regions, leading to deficits in working memory. In bipolar disorder, poorer prognosis is related to weight gain and obesity. Lackner et al. [5] investigated body mass index, obesity measures, lipometry, metabolic parameters and monoamines in a large sample of bipolar patients compared with healthy controls. In the patient group, they found increased abdominal fat accumulation and measures of the metabolic syndrome along with correlation with epinephrine levels.

The glutamate system has been reported to be involved in the pathophysiology of both bipolar disorder and major depression. Quinolinic acid is produced by activated microglia and is an agonist at the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor. In a postmortem study, Busse et al. [6] investigated immunohistochemistry of quinolinic acid in hippocampal subregions of 12 patients with depression, among them 6 unipolar and 6 bipolar, and 10 healthy controls. Quinolinic-positive microglia was reduced in unipolar and bipolar patients in the right CA1 subregion. A degradation of quinolinic acid may be involved in the

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pathophysiology of both disorders, but since all patients had been treated with antidepressants, treatment effects could not be excluded. Especially in major depression, genetic and environmental factors are hypothesized to interact and induce epigenetic DNA modifications on the level of histone acetylation and DNA methylation. Kaut et al. [7] investigated epigenome-wide methylation analysis in the hippocampus and prefrontal cortex of 6 patients with major depression and 6 healthy controls. Out of 11 hippocampal and 20 genes in the prefrontal cortex, 5 were selected for replication using pyrosequencing. In both regions, the NMDA receptor subunit NR2A (GRIN2A) was found to be hypermethylated in major depression. This alteration may be involved in disturbed synaptic plasticity in depression and link environmental factors to epigenetic modifications, leading to neurobiological-relevant deficits in gene expression.

Furthermore, growing evidence bespeaks the visual system to be involved in the pathophysiology of major depression. Using pattern electroretinogram analysis, Bubl et al. [8] found reduced retinal contrast response and visual evoked potentials (VEP) of the occipital cortex in 40 patients with major depression compared with 28 healthy controls. The VEP amplitude correlated with severity of depression measured by the Hamilton Depression Rating Scale and Beck Depression Scale. The results suggest that the cortical and to a larger extend the retinal response is affected in major depression and may be related to the functional state of the dopaminergic system. Electroconvulsive therapy (ECT) is recommended in treatment-resistant depression. Aten et al. [9] investigated the effects of repeated dose titration method compared with the age-based method on treatment characteristics, clinical outcome and cognition after ECT in 39 patients with unipolar depression. Both methods showed equal clinical outcome and cognition, but the medial ECT course duration was longer in repeated dose titration. In a letter to the editor with reference to the recent publication of Bumb et al. [10] in our April issue, Molendijk and Polyakova [11] state that the hypothesis of seizure quality during ECT correlating with increased peripheral BDNF levels remains unanswered and that high versus low seizure quality should be compared with respect to BDNF levels. Alternatively, a regression weight may show the relation between the variables. Answering this comment, Sartorius et al. [12] added an ANCOVA including an interaction term for the delay of blood sampling and high versus low seizure quality. Since results remained significant, the authors regard Bump et al.'s [10] previous results as robust enough to keep the conclusions but recommend a replication in a larger cohort of patients after ECT. Additionally, for investigation of BDNF levels, blood should be taken more than 2 weeks after the last ECT session.

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