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EDITORIAL

Impaired recovery in affective disorders and schizophrenia: sharing a common pathophysiology?

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Patients with mood disorders and schizophrenia share psychotic and affective symptoms such as delusions, cognitive deficits, depression and mania. Most importantly, however, longitudinal studies have revealed a subgroup of patients which is characterized by enduring functional disability that crosses traditional diagnostic boundaries [1]. At the level of psychopathological commonalities, Angst et al. [2] described a spectrum concept of mania ranging from patients with major depression (MDD) alone, over subthreshold manic syndromes to bipolar (BD)-II and -I disorders. According to Serafini et al. [3], patients with residual depressive symptoms exhibit a longer duration of the current illness episode and more lifetime psychotic symptoms than those without residual symptoms. During inter-episodic periods of BD, manic predominant polarity, depressive symptoms and illness severity showed to be strongly associated with functional impairment [4]. In schizophrenia (SZ), a deficit subtype, including negative symptoms and diminished emotionality, is known to be related to functional impairment compared to the low-symptom group [5]. The improvement of residual symptoms by developing pathophysiology-based treatment strategies may thus foster functional recovery in patients with affective psychoses and SZ.

Both, affective and psychotic disorders are most likely controlled by neurodevelopmental and environmental alterations such as obstetric complications, childhood trauma and stress hitting the maturing brain within critical time windows. Additionally, a genetic overlap has been reported between patients with MDD, BD, and SZ [6]. It has been proposed that several hits in the form of genetic and environmental risk factors may interact in a complex way during neurodevelopment, leading to the onset of the disease in young adulthood, when fine-grained interactions between complex neural networks emerge. These time-dependent hits may not only produce manifold multi-level pathological alterations but, importantly, also impair the brain's capacity to establish compensatory mechanisms [7]. The capacity for recovery in patients with MDD, BD and SZ may be controlled by a continuum of clinical and neurobiological processes based on gene–environment interactions cutting through the established phenotypic boundaries of these disorders. On the one hand, these dynamic trajectories of risk for impaired recovery include cognitive, social, and interpersonal domains and are critically moderated by neurobiological processes and the effectiveness of treatment. Reciprocally, outcome may impact these trajectories and also mediate response to treatment. Within these mutual psycho-biological interactions, impaired recovery may itself trigger adverse neurobiological cascades and clinical phenotypes across disease boundaries, thus fueling a vicious circle involving brain pathology and residual symptoms plus increasing cognitive disability.

Understanding the mechanisms of recovery hence demands a transnosological approach leveraging the growing insight into the multi-scale risk patterns operating across these disorders. Studies have shown that affective and psychotic syndromes co-occur along the disease trajectory and aggregate within families. Unfavorable outcomes affect 10–15% of patients with mood disorders, while only 15–20% of patients with SZ fully recover. A prevalence rate of 50% presenting negative symptoms and of 40% depressive symptoms, respectively, have been reported for SZ patients after remission of psychosis [8]. In patients with MDD, BD and SZ, brain phenotypes involve shared alterations of limbic, paralimbic, and prefrontal regions [9], and intersecting proteomic, transcriptomic, and genetic signatures map to a common dysregulation of maturational and immunoregulatory pathways [10]. Since cross-sectional case–control paradigms still prevail in neurobiological research, links between those levels unfortunately have been blurred by the large unexplained heterogeneity characterizing the course of

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these disorders. Promising approaches to deconstruct diagnoses into underlying phenotypes, such as the NIH-based Research Domain Criteria (RDoC) or the European Roadmap for Mental Health Research (ROAMER), recently have tried to bridge the gap between the observable behavioral level and biological pathology. Because of the overlap of symptoms and underlying pathophysiology, the current diagnostic and pharmacological paradigms anyhow are being increasingly questioned. A salient approach to disentangle phenotypic heterogeneity in patients with affective disorders and schizophrenia into both clinically and neurobiologically valid entities is thus urgently needed.

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