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EDITORIAL

A new opportunity: metabolism and neuropsychiatric disorders

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Neuropsychiatric disorders are associated with significant negative personal and social impacts. Current efforts to treat neuropsychiatric disorders often achieve suboptimal results, leading to recurrent and chronic disease. A remarkable effort has been invested in understanding the genetics and pathophysiology of pediatric and adult neuropsychiatric disorders. Yet we have not made enough progress to offer causal explanation for disturbed behavior, or choosing a treatment based on pathophysiology. Our present knowledge is also incomplete in predicting who will ("susceptible individual") and who will not ("resilient individual") develop a neuropsychiatric disorder. There is a great need to scale up research and also to explore novel concepts to unravel alterations at system level, contributing to disease etiology. Such system-level approach could be "impaired metabolism" in neuropsychiatry. In this special issue of *Journal of Inherited Metabolic Disease*, we have an excellent collection of original articles as well as comprehensive reviews on this matter.

Behavior abnormalities and psychological symptoms are well-known symptoms of many inborn errors of metabolism. Classic metabolic disorders like attenuated forms of urea cycle disorders, MSUD, or propionic acidemia; abnormal synthesis of complex molecules like CDG or cerebrotendinous xantomatosis; porphyria; or storage disorders like Niemann-Pick C disease could all present as psychopathology, even before the classic symptoms of the disease emerge.

Disorders of energy metabolism are rather unique from this aspect. Some billion years ago, one of our single-celled ancestors engulfed a unicellular prokaryote (Roger et al. 2017). These cells continued to evolve together and the endocytosed organism evolved what we know now as mitochondrion. Mitochondria are dynamic organelles and essential components of all eucaryal cells. Mitochondria perform numerous biological tasks and interact with virtually all cellular metabolic processes (Herst et al. 2017).

Neuronal functions are especially dependent on mitochondria which supply our neurons with energy in the form of ATP (Roger et al. 2017). Therefore, a mitochondrial etiology of neuropsychiatric diseases is very likely (Kozicz et al. 2018; Pei and Wallace 2018). Specifically, a variety of neuropsychopathologies, including major depressive disorder, post-traumatic stress disorder, autism, and bipolar disorder as well as Parkinson's and Alzheimer's diseases, have been linked to genetic or acquired deficits in mitochondrial function (DiMauro and Schon 2008; Manji et al. 2012; Morava and Kozicz 2013; Srivastava 2017; Kozicz et al. 2018; Pei and Wallace 2018).

In recent years, an increasing body of evidence—witnessed by the selection of articles and reviews in this special issue too—suggests increased vulnerability to neuropsychopathologies. For example, 50% of patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) present with comorbid major depressive disorder (Anglin et al. 2012). Autism spectrum disorders are frequent in patients with propionic acidemia, especially with chronic amino acid imbalance and lactic acidemia (Al-Owain et al. 2013; Ghaziuddin and Al-Owain 2013). Long-term outcome in MSUD, especially after dietary over-restriction, has been associated with amino acid imbalance and depression (Strauss et al. 1993). Attenuated forms of ornithine transcarbamylase deficiency with mild chronic hyperammonemia show a broad variety of psychopathology (Waisbren et al. 2016). Yet, not all patients with inborn errors of metabolism present with psychopathologies, so it is likely that perturbations in cellular (energy) metabolism are important risk factors and contribute to a certain percentage of explained

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variance in the etiology of neuropsychiatric disorders. For the precipitation of a phenotype, interplay of impaired cellular (energy) metabolism disorder-specific genes superimposed by specific (early) life adversities would be necessary (Kozicz et al. 2018).

But how one can conceptualize the precipitation of a neuropsychiatric phenotype based on altered cellular (energy) metabolism? They can (a) impact (early) brain developmental processes resulting altered brain structure and/or function contributing to susceptibility; (b) act during the pathogenetic period later in life; (c) or might only play an etiological role in proximal symptoms of neuropsychiatric disorders.

Shedding light on the exact genetic and environmental factors in neuropsychiatric disorders is complicated by the complexity of inborn errors of metabolism and interactive pathways. However, increased awareness of clinical clues for a metabolic disturbance or an inborn error of metabolism will optimize referrals and timely metabolic interventions. Psychiatrists and neurologists often ask the question of what they should be aware of when suspecting perturbed cellular (energy) metabolism in the etiology of neuropsychiatric condition. In a recent publication in the pages of this journal, Trakadis et al. provide a comprehensive overview of signs of metabolic alterations, indicative of inborn errors of metabolism (Trakadis et al. 2017). In addition, validated, easily applicable bed-side scoring scales have been developed for mitochondrial disorders (Witters et al. 2018). These could easily be implemented in the clinical diagnostic screening protocols of neuropsychiatric disorders.

While treatment of neuropsychiatric disease by targeting cellular (energy) metabolism is in its infancy, dietary as well as pharmacological treatment for several inborn errors of metabolism is available and may represent an important future therapeutic avenue in treating various neuropsychiatric disorders.

In conclusion, this special on Metabolism and Psychopathology will extend our understanding of (a) why certain individuals are more prone to develop neuropsychopathologies; (b) whether correcting (energy) metabolism could be an effective novel therapeutic option for neuropsychiatric disorders; and (c) whether unique central or peripheral biosignatures of impaired (energy) metabolism could be identified as they relate to susceptibility to neuropsychopathologies.

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