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LETTER TO THE EDITOR

Is Molecular Inflammatory Profiling a Useful Tool for Personalized Brain Stimulation in Psychiatric Disorders?

To the Editor:

A plethora of noninvasive and invasive brain stimulation modalities has emerged for a variety of psychiatric disorders (depression, obsessive–compulsive disorder, Tourette syndrome, schizophrenia) (1). As yet, though, measures predicting individual brain-stimulation responsiveness and allowing personalized brain stimulation paradigms are not established in clinical routine (2). Given that the efficacy of brain stimulation is characterized by substantial heterogeneity across individuals, a neuroscience-driven development of predictive biomarkers is indispensable (2). Available preclinical and clinical data indicate altered neuro-immune communication across a broad range of psychiatric diseases. Despite its potential to improve diagnostic and therapeutic precision as well as outcome prediction (3), systematic, longitudinal molecular pattern profiling of inflammatory markers in different biofluids (e.g., cerebrospinal fluid, saliva, and plasma) remains an under-investigated concept in brain stimulation for psychiatric disorders.

Inflammation as a response to endogenous or exogenous stimuli occurs in distinct steps with specific cellular and molecular patterns (recognition, recruitment, response, and resolution). Mediators of inflammation (cytokines/chemokines) have the capability to cross the blood–brain-barrier and act by either modulating afferent properties of the vagal nerve or by evoking synthesis of pro-inflammatory neuropeptides by innate immune cells of the brain (microglia activation). Specific brain regions (hypothalamus-pituitary axis, hippocampus, or the brainstem) interfere with multifunctional cytokine transmission (e.g., IL-1β, 4, 6, 10, 13, TNF-α, INF-γ, brain-derived neurotropic factor BDNF) and corresponding receptor domains in order to establish a well-balanced neuro-immune state, thus maintaining a physiological brain response or inducing a cascade leading to a permanent deteriorated behavioral state. Impairment of this vulnerable homeostasis evokes a pro-inflammatory response that has been clearly linked with the molecular etiology of psychiatric disorders (3).

For instance, it has been suggested that the previously observed effects of the autonomic nervous system in depression and schizophrenia may in part be driven by the neuro-immune properties of the vagal nerve (4). Based on these findings and on the inflammatory hypothesis of psychiatric disorders, molecular assays exploring changes in inflammatory mediators have been utilized in studies involving electroconvulsive therapy (ECT) for depression, the majority of which were limited in providing relational evidence due to a biased study design (5). In a recent review, Yrandi and colleagues assessed clinical trials aimed at determining the value of cytokine analysis and found altered plasma levels of pro-inflammatory IL-1β, IL-6, and TNF-α in patients with depression under adjunctive first ECT treatment. A sufficient conclusion was limited mainly due to the uncontrolled and small-scale study designs published so far (5). Another uncontrolled clinical cohort study assessed changes in serum concentration of oxytocin and its possible relation to acute (first session) ECT treatment in a mixed study population (n = 33) including patients with schizophrenia, depression, mania, and non-affective-psychosis; this study found no correlation between ECT responsiveness and changes in serum levels of oxytocin (5). In view of the low level of evidence, experimental, and in particular clinical exploration of mechanisms of neuroimmune communication in subjects treated with brain stimulation is highly recommended to close gaps between neuroscience and clinical practice. In contrast to other approaches, peripheral biofluids (saliva, serum) are easily accessible and suitable for wide-spread application and data acquisition in future clinical trials (3).

At this stage, both the pragmatic potential and the integration of molecular inflammatory profiling into personalized brain stimulation concepts deserves substantial clarification for several reasons.

For one, the dynamic and heterogeneous (interindividual and intraindividual variability) nature of psychiatric illness *per se* represents a considerable confounder for diagnosis, patient selection, and treatment response in a currently undefined frame (2,3). Secondly, as suggested by panel recommendations and expert opinions, several randomized-controlled, comparative studies have been conceptualized to analyze different interventions and ensure rigorous assessment of standardized stimulation parameters (i.e., dose–response relationship) (3). In view of the rapid technical progression and availability of the applied noninvasive and invasive brain stimulation technologies, such systematically-driven data acquisition of stimulation parameters (target, frequency, intensity, duration) will help establish reliable dose–response relationships relevant for distinct psychiatric disease subtypes (biotyping), identified through imaging, electrophysiology, psychosocial

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characteristics, advanced statistical models, and (epi-) genetics (2–5).

Given the inconsistent findings in earlier brain stimulation studies of inflammation assays, future research on targeted brain stimulation should attempt to integrate molecular pattern assays in relation to brain stimulation outcome in a controlled study design. Inflammation research as a potential predictive tool for brain stimulation should initially aim at detecting disease-specific characteristics, and, in a second step, attempt to predict brain stimulation effects on a molecular level, thus supporting existing biotype screening modalities and allowing for an individualized approach for both diagnosis and treatment (2). In a first step, distinct subsets of clustered patients have to be identified by applying advanced statistical models (categorical dimensional driven construct) and by gathering multimodal (saliva, serum, CSF) molecular data in order to develop a mechanistic model. By accomplishing the first step, the second will be the integration of biotype-tailored brain stimulation patterns relative to the suitable classified biotype, hence promoting a predictive system for a subset of subjects, rather than patterns based on predictions at the individual-level (2). Advanced statistical models capable of performing categorical-based biotyping may enhance the pragmatic value of molecular profiling, help to homogenize distinct subtypes more likely to respond to brain stimulation, and, together with other pre-stimulation screening tools, process high loads of data consisting of multimodal (-level) screening modalities across individuals classified under a common nosocomial diagnosis. It is important to note that such approaches may generate large amounts of data. Hence, artificial pattern recognition systems, mobile health system applications (digital phenotyping), and deep learning-algorithms may become indispensable adjunctive tools. Several expert panels and recommendations proposed a novel classification framework for research of psychiatric disorders that integrates multi-level data such as genetics, neuroscience, and behavioral science.

Molecular profiling of inflammatory mediators may lead the direction of research toward the identification of quantitative measures by molecular means and may become instrumental in better understanding interindividual/intraindividual variations in clinical phenotypes, treatment outcome, and stratification of brain stimulation concepts. Ultimately, the subsequent integration of suitable molecular patterns in real clinical practice depends on variables revealing questions far beyond those in the laboratory.

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