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Editorial

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Back to the brain: for a third-millennium psychiatry

Liliana Dell'Osso

Department of Clinical and Experimental Medicine, University of Pisa, Italy

Liliana Dell'Osso

Last century's psychiatry left us with an important and heavy legacy. A legacy of great changes, but also of unfulfilled goals and unsatisfactory assumptions. We thought that neuroscience would have provided an answer to all our questions, like a *deus ex-machina*, but those answers never came. Neuroscientific research tirelessly focused on the hope of isolating specific biological markers of diseases, conceptualized as genetically pure phenotypes. Genetic research focused on identifying possible specific mutations associated with the main categories of mental disorders. But despite the unthinkably wide literature production, we reached the conclusion that, in most cases, mental disorders are instead underlain by complex polygenic inheritances, which interact with epigenetic modifications and environmental factors for determining the actual manifestations of the disorder. Although highlighting an undeniable basis of hereditability, the possibility of pure determinism in the field of psychiatry has progressively faded. It is no coincidence that research is now increasingly focusing on the interaction between neurobiological asset and environment, because this is actually the direction in which we need to proceed. On the other hand, the failure of the goal of finding a correspondence between the nosographic categories provided by the Diagnostic and Statistical Manual of Mental Disorders (DSM) and specific biological markers, played a role in the current crisis of the nosographic system itself. In the absence of a well-defined biological counterpart, it could be hypothesized that a given nosological category, defined on a syndromic basis, should be better conceptualized as a pattern, a dimension without a well-defined threshold, and whose diagnostic boundaries are blurred. In light of the increasingly spreading dimensional approach to psychopathology, the issue of psychiatric diagnoses should be regarded critically. It should be noted that the difficulties in finding a specific correspondence between real-life clinical cases and DSM categories are not only a research paradigm problem, but it is an issue that challenges all of us during the clinical practice on a daily basis: all psychiatrists have experienced that, in order to assess most of their patients, they have to refer to multiple comorbid diagnoses, including also personality disorders. Since early 2000s, the operative model of "spectrum" allowed overcoming this problem [1]. Through the spectrum model, it is possible to identify and measure those mild manifestations and symptoms that, although below the clinical threshold, isolated or atypical, are not qualitatively different from the full-fledged disorders described in the DSM. A dimensional approach allows us to describe a clinical case by specifying which symptomatologic clusters are fully expressed and which are instead detectable in a sub-clinical form. During daily clinical practice, the psychiatrists are still pushed to focus on what is called the index episode, and on identifying the clinically prevalent symptoms, ignoring the broad range of sub-threshold manifestations and traits that the subject may show at the time of clinical assessment, having likely been present in various degrees throughout her/his life. Sub-threshold comorbidity, on the other hand, is of the utmost importance for truly understanding the clinical picture, often constituting the vulnerability ba-

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Correspondence:
Liliana Dell'Osso
liliana.dellosso@med.unipi.itl

sis for the entire psychopathological trajectory: hence the need to focus on sub-clinical symptomatology. From this perspective, the stereotype of episodic course of psychiatric disorders also needs to be reconsidered. As a matter of fact, the arbitrarily identified clinical thresholds give an episodic appearance to a chronic and life standing condition with different grades of severity during lifetime. While the episode is identified only when symptoms exceed the diagnostic threshold, broader and milder manifestations of the same sign persist and shape subjects' life, often anticipating the clinical onset and remaining as an inter-episodic and residual condition. A third-millennium medicine, prevention-oriented, should certainly change this paradigm and focus on addressing sub-clinical manifestations, rather than simply on treating the acute phases, thus contributing on the prevention of the so called clinical onset. As described above, the spectrum model is based on a dimensional approach to psychopathology, according to which the chronic presence of sub-clinical traits, usually detectable since the developmental period, significantly contribute in shaping the subject's personality, conditioning life choices and constituting the vulnerability basis for developing a full-fledged psychopathological trajectory. It would be wrong to believe, however, that this model is in contrast with a neurobiological approach to psychiatry. It is, in fact, quite the opposite: the spectrum model may allow a novel approach to neurobiological research in psychiatry that, without trying to push neurobiology into abstract categories, or to link the latters to specific brain circuits whose specificity appears equally abstract, would be more compliant with the most recent findings in the field of brain functioning. Recent researches pointed out how the central nervous system is a tightly interconnected and flexible structure, where a given function is underlain by complex interactions between different areas, overcoming the concept of compartmentalization. On the basis of this model, which seems in agreement with the dimensional presentations of psychiatric conditions, it has been proposed that mental disorders might be better conceptualized not as alterations of specific brain mechanisms, but as "globalopathies", which would feature an impairment of the whole brain functioning and of its complex network of connections [2]. A further advancement in this hypothesis has been made through the study of neurodevelopmental disorders, and in particular through the autism spectrum model. Familial aggregation studies have long emphasized the heritability of Autism Spectrum Disorder (ASD) not only considering its clinical presentation, but also as a "Broad autism phenotype", a condition very common among first degree relatives of ASD patients, featuring manifestations qualitatively similar to the full-blown disorder but of reduced intensity. Growing research is stressing how autistic traits seems to be distributed along a continuum in the general population, being particularly common among patients with other kinds of mental disorders. The presence of autistic traits, even when sub-threshold, seems to be associated with increased risk for the development of other mental disorders as well as suicidal ideation and behaviors, enhancing vulnerability toward stressful life events. Based on these findings, and in accordance with the "globalopathies" theory, it has been hypothesized that a neurodevelopmental alteration could be at the basis of different psychiatric conditions: the interaction of the specific type, severity and timing of the alteration with prenatal and postnatal environmental influences, including stressful life events, may shape the specific psychopathological trajectory, including the pattern of mental disorders developed [3]. In this framework, the recently renewed focus on the catatonia spectrum, and its associations with the autism spectrum, may provide additional insights to the proposed model [4,5]. To date, we find us at a turning point in the field of psychiatry: through the matter of neurodevelopment, we glimpse the chance to finally merge psychopathological and neurobiological approaches in a coherent model, possibly as never happened before. It is, now, all about understanding whether we can meet this challenge, and to which new frontiers this may lead us.

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