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Brain Space and Time in Mental Disorders: Paradigm Shift in Biological Psychiatry

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Abstract:

Contemporary psychiatry faces serious challenges because it has failed to incorporate accumulated knowledge from basic neuroscience, neurophilosophy and brain-mind relation studies. As a consequence, it has limited explanatory power, and effective treatment options are hard to come by. A new conceptual framework for understanding mental health based on underlying neurobiological spatial-temporal mechanisms of mental disorders (already gained by the experimental studies) is beginning to emerge.

Keywords:

EEG; brain; mental disorders; nested hierarchy; metastable balance; neuronal assemblies; functional connectivity; DSM-5

Despite the widespread of psychiatric (mental) disorders[1] and ongoing unprecedented progress in the basic neuroscience[2], there have been disproportionately less advancement in understanding the pathophysiology of such disorders and related to it delay in the development of effective therapies and treatment approaches. We believe this is due to a lack of a consistent paradigm or a theory of psychoneuropathology that incorporates novel knowledge from basic neuroscience, neurophilosophy and theories of the brain-mind relation.

Indeed, there is an increasingly growing understanding in the field that the notion of categorical (discrete) mental disorders adopted in the DSM-III, DSM-IV and even in DSM-5 is far removed from the biological reality of the brain[3-12]. A DSM-informed psychiatric diagnosis is primarily based on criteria derived from the clinician's observations, patient's self-reports of subjective feelings and experiences, as well as patient's behaviour[2,8,13-15]. Despite the fact that these criteria were initially intended to be simple operationalizations of clinical phenomena, over time, such categorical classifications began to be treated as if they were natural and ontologically (i.e., neurobiologically) meaningful taxons with a unique set of causal factors and pathophysiological processes[3-5,10,16]. At the same time, the presence of dimensionality and comorbidity at the level of clinical symptoms and signs that cut across diagnostic boundaries[2,10] suggests that the categorical model of the DSM is a poor fit to the inherent structure of psychopathology[5-8]. Indeed, operationalized criteria that define mental disorder categories are neither backed by a conceptual understanding of normal functioning nor validated by objective biomarkers[9,10,17]. For example, as noted by Petrovic and Castellanos[18] (p. 2-3):

> "many psychiatric symptoms are continuously distributed in the general population. Truncating the range of variation by applying arbitrary cut-points impedes an understanding of underlying mechanisms since it does not mirror the true relationship between symptom levels and neurocognitive levels. […] Another problem is that defining disorders categorically based on whether criteria cut-points are met increases heterogeneity. Two patients can differ on nearly every symptom and still receive the same diagnosis. Moreover, in existing categorical diagnostic systems such as the 5th edition of the DSM or the 10th edition of the International classification of diseases, a particular diagnosis can be partially defined by opposite symptoms. For example, patients with depression can sleep too much or too little, have increased or decreased appetite, or increased or decreased activity levels."

Furthermore, often the subjective symptoms and behavioral patterns of psychopathology do not correlate with objective risk factors for it, as for example, is well documented for depression[19] and other psychopathologies[20,21]. Therefore, reconsideration of the diagnostic classification of mental disorders is needed where the underlying pathophysiology would serve as an entree into mechanistic coding linking psychopathology (signs and symptoms) to pathophysiology. Patients can and should benefit from better diagnoses, as well as more efficacious and safe treatment options stemming from the accumulated body of existing neuroscientific knowledge.

Fortunately, a novel paradigm that aims to re-orient mental health research toward the discovery of underlying neurobiological and biobehavioral mechanisms of mental disorders is emerging[2,5,10,22]. After years of empirical and theoretical research, modern neuroscience conceptualizes the human brain as a complex nested hierarchy of functionally specialized neuronal assemblies that interact with each other in a spatially (*space*) and temporally (*time*) coherent fashion, maintaining a so-called metastable balance[23-29]. Metastability refers to competition of complementary tendencies of cooperative integration and autonomous fragmentation in the activity of multiple distributed nested neuronal assemblies (REF. 23 for review). In a nested hierarchy (in contrast to a non-nested one), higher levels of functional hierarchy are physically composed of lower levels, and there is no central control of the system which results in weak higher-to-lower level constraints[30,31]. The best way to assess the operations of neuronal assemblies is through the electroencephalogram (EEG) measurement[25,27], because every local EEG-signal is a reflection of synchronization of a shared carrier wave of the outputs of a large number of neurons over the neuronal assembly[32]. It has been further proposed that formation of such functional neuronal assemblies, as well as their dynamical rearrangement in a nested hierarchy of spatial-temporal patterns allows the brain to cognitively and/or phenomenally (subjectively) present sensual inputs as coherent perceptions of the world, create internal images and conscious thoughts, and perform intentional actions and behavior (for reviews, see REF. 25, 32-36).

In normal conditions, the interactions among neuronal assemblies are dynamically arranged according to the moment-to-moment changes in the internal states (emotional, motivational, other), and the number and type of available external sensory stimuli, whilst, at the same time, keeping a metastable balance[24,25,27,34,37]. Empirical research shows that the loss of such a metastable balance in favor of either independent or hyper-ordered processing leads to pathologic states that underpin neuropsychiatric or neurological syndromes constituting a particular disorder (for an illustration see Fig. 1)[3,24,28,38-41]. In this view, the symptoms of a given psychiatric disorder, which are instantiated by interacting neuronal assemblies, are not just the passive psychometric indicators but are active constituent ingredients that, together, form a unique but dynamically choreographed network that defines a disorder (see also REF. 42). Thus, the complexity of psychiatric phenotypes and their diversity directly reflect the complexity and diversity of the underlying brain processes. In other words, the complexity inherent to a nested hierarchy of spatial-temporal patterns of interacting neuronal assemblies during adaptive reconfiguration of metastable balance between integration and segregation provides many avenues for ‘failure’, each of which would be accompanied by a characteristic set of symptoms, specific to either a concrete mental disorder or a genetic risk for mental illness[3,24,28]. In relation to this conceptualization Northoff proposed[43,44] a new term – “Spatiotemporal Psychopathology”. Unlike Biological Psychiatry that focuses on various neurological correlates of cognitive or affective (dys)functions, Spatiotemporal Psychopathology concentrates on the spatial and temporal patterns of interacting neuronal assemblies that underlie the psychopathological symptoms (for review, see REF. 37).

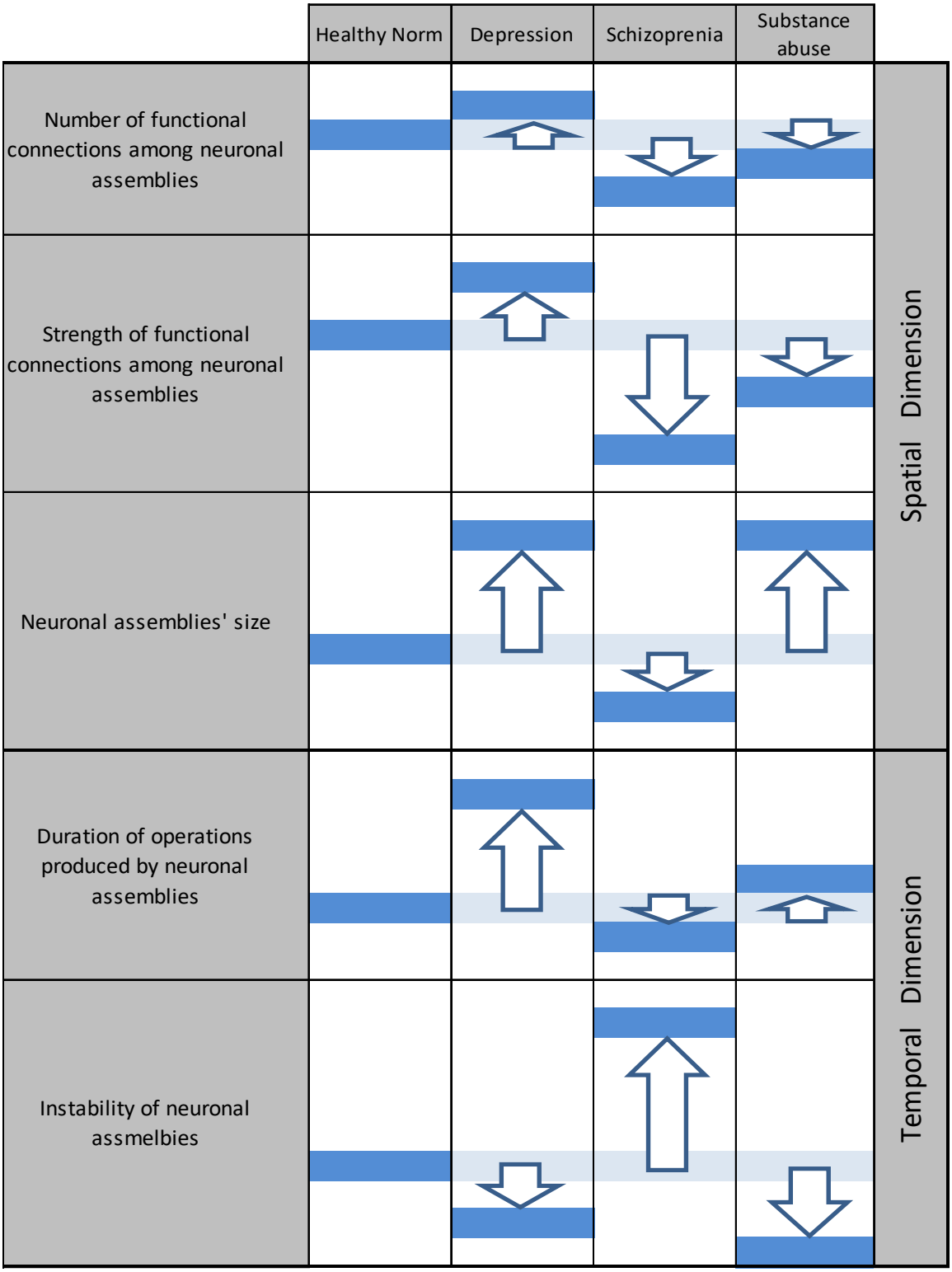

Figure 1. Schematic illustration of the main elements of brain metastable balance (indexed by EEG attributes) for several psychopathological conditions. The rest condition with closed eyes in healthy subjects is taken as a reference functional state with a healthy metastable balance and it is marked by a dark blue colour in the 'Healthy Norm' column and a light blue colour for the following columns. The increase and decrease of a concrete element of the metastable balance for a given psychopathological condition are shown by the vertical arrows. This illustrative scheme is based on real experimental data summarized in REF 24.

From such novel perspective, the understanding of many mental disorders could gain a new insight. For example, even though the modern model of major depression stresses the key role of anterior asymmetry – the so-called cognitive anterior model of depression[45,46], from the viewpoint of metastable balance hypothesis outlined above, major depression could generally be viewed as a disorder of disturbed neuronal assemblies' plasticity, characterized by an inadequate relationship between multiple operations produced by many interacting neuronal assemblies[37,47-51]. Indeed, major depression can be conceptualized as a syndrome of thalamocortical dysrhythmia[52,53] with limbic hyperactivity and prefrontal hypoactivity[54] marked by the persistent resonance of EEG theta and alpha oscillations. Also, an overall increase in brain functional connectivity (synchrony among operations produced by multiple neuronal assemblies) during rest[47] suggests that patients with major depression tend to expend energy in a potentially excessive or inefficient neural processing manner[51]. Importantly, the alterations in spatio-temporal EEG connectivity pattern demonstrated quite high specificity[47]: they were proportional to major depressive severity. In this context different spatial-temporal EEG patterns may reflect different underlying mechanisms/functions/symptoms and point to the existence of several subgroups within major depression that are not represented within current diagnostic systems[51].

Schizophrenia is another mental disorder whose pathophysiological mechanisms could be better understood by treating it as a disbalance between large-scale integration (formation of spatiotemporal patterns) and independent processing (local transient neuronal assemblies) in the brain, favoring independent operations[24,55-58]. Such low-level of functional synchrony among the operations produced by different neuronal assemblies may signify a well-documented pattern of mental impairment in schizophrenics that expresses a lack of integration of different cognitive functions for effective problem solving, deficits in abstract concept formation, set maintenance, set shifting, behavioral control, and problems in the regulation of affect and behaviour[37,59,60]. Furthermore, such an approach may be extremely useful for delineating the brain network disorganization that is always present when a clinical psychosis takes place in general (independently from a clinical diagnosis) from diagnostically more specific brain network functional patterns that are specific for the clinical expressions of concrete disorder like for example schizophrenia or bipolar disorder (for the promising results see REF. 61), as well as different sub-types within the same disorder[62].

Autism spectrum disorders (ASD) are yet another nosological group which recently has started to gain insight from applying the brain activity metastable balance strategy in research efforts to elucidate the etiology of autism. Indeed, despite the notable heterogeneity associated with ASD, a single neurobiological mechanism linking ASD symptoms to aberrant neuronal nets connectivity has recently been proposed[63]. Further research has confirmed that such connectivity abnormality is characterized by malfunctioning of brain metastability with local over-connectivity and long-distance under-connectivity[64,65].

Importantly, when the spatial-temporal patterns of brain activity (nested functional synchrony among the operations produced by different neuronal assemblies and measured by EEG) are treated as 'phenotypes'[66], they could reliably predict the effectiveness of drug interventions, while nosological or behavioural grouping do not[67]. For example, effective treatment of the refractory depression[68] or attention-deficit/hyperactivity disorder (ADHD)[69] was achieved when it was based on prospectively identified EEG phenotypes related to different subtypes within diagnostic group, thus stressing that nosological heterogeneity is well reflected in the multiplicity of saptio-temporal parameters of electrical (EEG) brain activity.

To conclude, looking at psychiatric/mental problems as disturbances in the temporal and metastable structure of brain activity, where this temporal structure could be either more irregular (uncorrelated randomness) or more regular (excessive order) than normal, we believe the future of neuropsychotherapy lies in its ability to design such therapeutic procedures (pharmaceutical compounds, psychosocial and behavioral interventions or devices such as transcranial magnetic stimulation) that can restore the normal temporal structure and metastable structure of brain activity[70]. This approach seems more physiologically adequate to integrative, nonstationary and self-organized nature of brain processes[23,71-73] and is in keeping with a novel understanding of the dynamic nature of mental disorders, where so-called "time disbalance" is more prominent (especially in the early stages of the disease) than "structural disbalance"[74-78]. In this context, future studies that focus on how different neuropsychotherapeutic approaches can modify temporal/metastable structure of brain activity in psychiatric patients are encouraged. The hope is that the partitioning of patients into subgroups characterized by different neurophysiological processes responsible for pathological conditions will allow researchers to understand how usually adaptive processes may become part of vicious circles that result in pathology, and, eventually, lead the way toward new nosology and treatment. To us such a perspective seems to be neuroscientifically informed, clinically useful, and practically achievable. It is also synergistic with the currently proposed initiative of National Institute of Mental Health to redefine psychiatric nosology in terms of the underlying neuro-biology using the Research Domain Criteria (RDoC)[5,22].

Contributors

This Personal View was conceptualised by AnA and AlA. AnA and AlA did literature search. AnA drafted the manuscript. AlA revised the paper for important intellectual content.

Declaration of interests

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Search strategy and selection criteria

Relevant articles published between 1980 and 2018 were identified through searches in the authors' personal files, in Google Scholar, and ResearchGate. Relevant articles resulting from these searches were reviewed.

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