EDITORIAL

Neural dynamics in mental disorders

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The search for the pathophysiological substrates of mental disorders remains an important challenge for psychiatric research. While major psychiatric conditions have a biological signature that can be identified with a range of neuroimaging approaches, biomarkers that allow reliable differentiation between different conditions as well as detection at early-illness stages have yielded only modest success. Given the importance of early intervention in a range of disorders as well as the move towards personalized medicine (1), understanding the underlying neurobiology is of crucial importance towards the development of more effective treatments and care.

While the difficulties in the field are also due to nosological overlap between different conditions and poor construct validity of major diagnoses, an impediment has also been the limited understanding and availability of measurement tools to gain insights into the complex neuronal dynamics in large-scale networks and their dysfunctions. In schizophrenia research, for example, the search for the underlying biological signatures of clinical symptoms and cognitive deficits had for a long time focused on the contribution of circumscribed brain regions, such as the prefrontal cortex. In contrast to this view, which was largely inspired by findings from clinical neuropsychology, current research suggests that anatomical alterations involve a large number of cortical and subcortical regions (2). On the basis of these observations and a large body of work highlighting a distributed neural and cognitive impairment, the hypothesis that I would like to advance is that schizophrenia and perhaps other mental disorders are likely to constitute systemic disturbances involving fundamentally a disruption in the dynamics of neural processes in large-scale networks (3).

This is supported by recent data which highlight that cognitive and executive processes during normal brain functioning essentially emerge from the coordinated activity of distributed neuronal populations that are dynamically configured on the backbone of fixed anatomical connections (4,5). The organization of anatomical connections and their contribution towards functional interactions is highlighted in the paper by Van Essen and Barch (6) in this issue of the journal, which summarizes recent advances in both structural and functional neuroimaging, in particular in mapping neural connections in terms of their structural and functional pathways, the so-called "connectome".

The brain's connectome has small-world properties (7), which implies that even neuronal groups distributed across distant cortical areas can communicate with one another either directly or via only a small number of intervening nodes. From this perspective, cognition, consciousness and their disturbances are not properties arising from isolated neuronal units but rather from the distributed and coordinated interplay of a large number of neuronal assemblies (5).

Evidence has accumulated that such neuronal coordination is achieved through modulating the synchrony of rhythmic activity at low and high frequencies. While neural oscillations have a long history in neuroscience, it was the discovery of Singer and colleagues that oscillations in the beta/gamma range (13-30/30-200 Hz) establish precise synchronization between distributed neural responses in the visual cortex (8), which led to the hypothesis that rhythmic activity at high frequencies constitutes a mechanism for establishing temporal windows for neuronal communication (9).

This perspective has contributed to the conceptualization of the brain as a self-organizing complex system in which numerous, densely interconnected but functionally specialized areas cooperate in ever-changing, context- and task-dependent constellations. Important and distinct variables of these dynamic processes are the power and frequency of oscillatory activity in local circuits and the long-range synchronization of these temporally structured activities across brain areas. Oscillatory processes, in particular at gamma-band frequencies, serve the generic cortical computations underlying local encoding of information, while long-range synchronization at low – theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz) – frequencies serves the effective coupling between more remote brain regions (10).

Recent evidence has emerged that the pathophysiology of schizophrenia, but also of autism spectrum disorders and Alzheimer's disease, may fundamentally involve alterations in synchrony and amplitude of neuronal oscillations (neural synchrony) (11), highlighting that a disturbance in neuronal dynamics may lie at the core of these disorders. While it is currently unclear to what extent such impairments may be causal towards the pathogenesis of these syndromes, the hypothesis that changes in the precision and strength of neuronal oscillations are underlying the cognitive deficits and possibly certain clinical symptoms in several conditions is consistent with recent observations that schizophrenia and related disorders are characterized by alterations in the organization of the connectome (12), indicating that changes in the lay-out of cortico-cortical connections could impact on the establishment of large-scale functional interactions (see also 6 in this issue of the journal).

This perspective furthermore predicts that the mechanisms that are involved in assuring the generation of coordinated neuronal states are likely to be dysfunctional in mental disorders and thus could offer novel treatment targets and possibilities for early intervention. During normal brain functioning, networks of mutually interacting GABAergic interneurons are crucially involved as pacemakers in the generation of high-frequency oscillations in local circuits. In addition, AMPA- and NMDA-receptor mediated activation of GABAergic interneurons is essential for the generation of oscillatory activity and is involved in the long-range synchronization of spatially segregated cell groups (3).

Impaired high-frequency oscillations in schizophrenia but also in autism spectrum disorders are consistent with dysfunctions in GABAergic interneurons as a core impairment in these disorders (13). Moreover, animal models demonstrate that diverse genetic and environmental risk factors converge on specific defects in the development and function of interneurons (3), highlighting that such deficits constitute a critical pathway common to several syndromes which lead to impaired generation of rhythmic activity and cognitive deficits.

Data on GABAergic dysfunctions is accompanied by findings emphasizing the importance of aberrant glutamatergic neurotransmission in psychiatric conditions. In schizophrenia, hypofunctioning of the NMDA receptor is thought to be critically implicated in cognitive deficits as well as in psychotic symptoms, as blockade of that receptor can recreate many features of the disorder in human participants and animal models (14).

In order to further advance the role of aberrant neural dynamics in the explanation of major mental disorders and establish close links with underlying neurobiological parameters, a crucial prerequisite are non-invasive imaging tools that have sufficient temporal and spatial resolution. Until recently, studies investigating the spatial organization of large-scale cortical networks could only be conducted with functional magnetic resonance imaging (fMRI), because advanced source-analysis techniques for electrophysiological data which complement the excellent temporal resolution of electro/magnetoencephalography (EEG/MEG) were not available. However, recent studies which have mapped oscillatory cortical networks during cognitive and executive processes have demonstrated the feasibility of this approach, highlighting that modulations in the synchrony between brain regions are particularly crucial for cognitive processes (10).

While EEG/MEG approaches have the required temporal resolution to capture neuronal dynamics at realistic time scales, a distinct advantage of these approaches is also the fact that they are ideally suited for translational research. Neural oscillations and the molecular mechanisms and circuits that underlie them are highly conserved across a range of species (15), thus allowing hypotheses regarding the biological mechanisms that underlie impaired neural oscillations to be directly tested in animal models and *in vitro* preparations. This possibility may not be offered by other imaging techniques, such as fMRI, for which the biological mechanisms of signal generation are less clear and the direct translation of findings from data obtained with human experiments to animal models is more difficult.

Moreover, crucial insights into the pathophysiology of major mental disorders are also likely to require a focus on at-risk populations. Major psychiatric syndromes, such schizophrenia and Alzheimer's disease, involve an extended prodromal period prior to the full manifestation of clinical symptoms and diagnosis, during which cognitive impairments are already manifested. As the treatments available do not reverse circuits dysfunctions once clinical symptoms reach current diagnostic thresholds, development of biomarkers for targeted early intervention are crucial. EEG/MEG approaches may be ideally suited for this goal, as the wide range of oscillation frequencies provides a parameter space that can be used to delineate disorder-specific neuronal dynamics, which can then be used to identify the underlying pathophysiological mechanisms in pre-clinical research.

Moreover, such studies may also reveal insights into the neurobiology that may be closer to the essential core of mental disorders. For example, it is conceivable that certain clinical manifestations, such as the positive symptoms of schizophrenia, reflect the system's adaptive response towards a more fundamental disturbance in neuronal dynamics. From this perspective, genetic and environmental risk factors cause a primary disturbance that leads to a disruption of large-scale dynamics and cognitive dysfunctions. This view is consistent with previous formulations which have emphasized a differentiation between primary or basic symptoms and secondary or accessory phenomena in schizophrenia, the latter essentially representing compensatory and adaptive phenomena towards a fundamental disruption of neuronal processes.

While some of the issues raised in this paper reflect long-standing debates in both cognitive neuroscience and psychiatry with regard to the nature of brain functions and their disturbances, it is perhaps only now, with the increased knowledge and technology available to examine large-scale dynamics, that insights into the pathophysiology of mental disorders may be in reach. Such insights would not only be of tremendous value for scientific purposes, but also allow for more effective early intervention as well as for the development of rational treatments aimed at reducing the human and social costs associated with major mental disorders.

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