common genetic variants in the brain receptors for these prosocial neuropeptides modulate the activity and even structure of these regions in humans (13). As we have recently discussed for the specific case of oxytocin in combination with behavior therapy (13), this opens up a mechanism-guided approach for interfacing the usually separate domains of biological and psychological therapies, as predicted at the conclusion of Cacioppo et al's paper. As emphasized in that paper, a truly interdisciplinary approach to social neuroscience in psychiatry has therefore much to offer for people suffering from mental illness, their clinicians, and science.

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The brain's intrinsic activity and inner time consciousness in schizophrenia

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How is it possible that the brain's neural activity is directly dependent upon environmental contingencies? This is a central question raised by Cacioppo et al's impressive target paper (1), which I will tackle here by bringing in a novel perspective, the brain's intrinsic activity.

C. Sherrington, the British neurologist working at the beginning of the 20th century, considered the brain a mere passive sensorimotor reflex apparatus. Extrinsic stimuli from the environment trigger neural activity in pathways that result in sensorimotor reflexes. This extrinsic view of the brain has been challenged by authors such as G. Brown, K. Lashley and R. Llinas, based on the observation of intrinsically generated activity in the brain (2).

The recent discovery of high resting state activity in a particular set of brain regions, the default-mode network, has once again raised the question of an intrinsic view of the brain's neural activity (3). Since its initial description, the functions of that network have been debated and associated with the self (4) and consciousness (5-9).

What remain unclear, however, are the exact neuronal features of the resting state itself that make possible its interaction with extrinsic stimuli from the world. These neuronal features must be intrinsic to the resting state while at the same time predisposing the brain to the association of its stimulus-induced activity with consciousness and self. We may thus need to develop an intrinsic-extrinsic interaction model with regard to the brain.

The term intrinsic activity describes spontaneous activity generated inside the brain itself (10,11). Since the observation of spontaneous activity implies the absence of extrinsic stimuli and is thus mere rest, the term intrinsic activity is often used interchangeably with resting state activity, especially in an experimental-operational context (10).

One recent proposal suggests that the resting state's slow wave fluctuations in frequency ranges between 0.001 and 4 Hz are central in yielding consciousness (3,5,12). Due to the long time windows of their ongoing cycles, i.e., phase durations, these slow wave fluctuations may be particularly suited to integrating different information. Such information integration may then allow for the respective content to become associated with consciousness (7,9).

Spontaneous fluctuations of neural activity in the resting state are often observed, especially in the default-mode network, where they are characterized predominantly by low frequencies

(<0.1Hz). However, low (and high) frequency fluctuations in neural activity can also be observed in regions other than that network, such as the sensory cortices, motor cortex, insula, and subcortical regions like the basal ganglia and thalamus. Rather than being specific to the default-mode network, low frequency fluctuations appear to be a hallmark feature of neural activity in general.

It is apparent, then, that there is a complex temporal structure and organization to the brain's intrinsic activity. Most importantly, this temporal structure seems to bridge the temporal gaps between different discrete points in time. By linking together neural activities at different points in time, a certain degree of temporal continuity in the brain's intrinsic activity is constituted.

In some psychiatric disorders, abnormalities in the spatiotemporal continuity of both intrinsic activity and consciousness have been described.

Instead of providing a grid or template of spatiotemporal continuity, "inner time and space consciousness" in schizophrenia seems to be characterized by spatiotemporal fragmentation and disruption. These patients no longer experience temporal continuity and thus a dynamic flow of time (and space) in their consciousness. Instead, the stream of consciousness is disrupted and blocked with the three temporal dimensions of past, present and future being disconnected from one other.

The glue between the different discrete points in physical time seems to be missing in the consciousness of time and space. This implies that the different contents, including their distinct discrete points in physical time and space, can no longer be linked to each other in the consciousness; the glue and thus the spatiotemporal continuity is lost. This is very apparent, for instance, in the following quote of a patient with schizophrenia (13): "When I move quickly, it is a strain on me. Things go too quickly for my mind. They get blurred and it is like being blind. It's as if you were seeing a picture one moment and another picture the next".

The patient describes here that the contents of his consciousness, the different pictures, are no longer linked together. There are no longer any transitions between the different discrete points in time and space associated with the different pictures. The pictures are, as it were, experienced as pearls without an underlying chain. Since the underlying chain – the spatiotemporal continuity – seems to be disrupted within itself, the pearls can no longer be put together, ordered, structured and organized in consciousness.

In other words, both the "inner time and space consciousness" and "consciousness of contents" become disordered and disorganized, leading to what may be described as *spatiotemporal disruption*. This leads the patient to experience the contents of consciousness in an abnormal way, as is manifested in many of the schizophrenic symptoms such as ego disorders, thought disorders, hallucinations and delusions.

Numerous studies have recently shown resting state abnormalities in schizophrenia (e.g., 14). Changes in gamma oscillations (and low delta oscillations) have been reported (e.g., 15), indicating abnormal temporal continuity in the brain's intrinsic activity. Much, though, remains unclear at this point. First, the exact nature of these spatial and temporal resting state abnormalities remains to be established. Secondly, their link to the above-described phenomenal abnormalities in the consciousness of time and space in these patients is not clear at this time.

The extrinsic stimuli may encounter an already altered temporal and spatial continuity when interacting with the brain's intrinsic activity. The latter's spatial and temporal abnormalities may be imposed upon the extrinsic stimuli, which are then experienced in abnormal spatial and temporal ways in consciousness. This in turn may account for some of the characteristically difficult symptoms of sufferers of schizophrenia, that could ultimately be described as abnormal spatiotemporal constellations between intrinsic activity and extrinsic stimuli – in short, abnormal rest-stimulus interaction. However, much work remains to be done to establish direct links between the neuronal and phenomenal levels in these patients.

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