Social neuroscience and mechanisms of risk for mental disorders

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In their thoughtful paper, Cacioppo et al (1) emphasize the role of social neuroscience as an integrative meeting ground of a variety of methodological approaches, "neural, hormonal, cellular, molecular and genetic", and call for a truly "interdisciplinary" approach. We fully endorse this viewpoint and would like to emphasize the importance to apply this strategy at another important, but underexamined juncture between disciplines: the connection between psychiatric epidemiology and psychiatric neuroscience. Specifically, we propose that there is growing evidence that an important facet of risk for severe mental illness can be understood as altered neural processing of specifically social stimuli, and that this may have therapeutic and preventive applications in the future.

It is well known that impoverished or abusive social contexts contribute to the risk for mental illness (2). Recent work also supports the view that epidemiologically validated risk factors such as urban living and upbringing and migration have a social component, as proposed by the social defeat hypothesis (3). Specifically, work from our laboratory has suggested a specific impact of social stress on activation in a perigenual cingulate-amygdalar circuit in healthy populations exposed to urban living and upbringing (4) and migration. Since previous work, as highlighted by Cacioppo et al, has shown that the same circuit is impacted by (serotonergic) candidate genes that show gene-environment interactions (5,6), we have recently proposed that this circuit, the limbic regions (such as ventral striatum and hippocampus) linked to it, and regions of evolutionarily more recent medial and lateral prefrontal cortex that regulate it, may be a core convergence pathway for risk for mental disorders arising through social stressors (7). In fact, given preclinical evidence, it also appears possible that socially adverse environments early in brain development are causal for the dysfunction specific to social stress observed in adults exposed to risk. Since this circuit and those linked to it are found abnormal and related to symptomatology in patients (as demonstrated by the three clinical conditions discussed by Cacioppo et al), they may also be important for treatment. Seen this way, the social environment remains relevant throughout the trajectory of mental illness, as it is configured, unfolds and gets addressed. Clarifying these interacting genetic, neural and environmental mechanisms further is thus important for therapy, and possibly even prevention.

This suggests an ambitious, but actionable work program spanning several layers of description. Evidence for mechanisms supporting gene-environment interaction on the systems level should be supplemented by research to clarify its cellular basis in humans. This is challenging as the primary tissue of interest is not available in man, but methods such as genome wide methylation analysis in peripheral tissues may help to identify some of the genes and pathways modified by social environmental stress (8). A further level of description may be added through the study of human neurons derived through induced pluripotent stem cell technology (9), although most epigenetic programming is removed in the process of generating these cells. Gene-environment interaction effects in brain should be confirmed directly by combining social exposures with imaging in genotyped subjects.

Based on these data, the neural underpinnings of subcomponents of the social environment that could contribute to the epidemiological evidence we have highlighted need to be analyzed further (examining effects such as social defeat, discrimination, and loneliness – as emphasized in Cacioppo et al's paper). This will require close interactions with the social sciences in providing scales that measure these facets of the social landscape with precision. In addition to laboratory paradigms, this will also require field studies that combine neuroimaging and biomarker ascertainment with experience-based assessment, mobile neuropsychological testing and tracking of subjects in spatially and socially well defined real-life contexts (10).

Based on epidemiological evidence that time periods such as the perinatal period, early childhood and adolescence are especially vulnerable for these environmental exposures, an account must be developed on which neurobiological changes underlie vulnerability across the lifespan. This requires longitudinal and ecological human studies that combine neuroscience approaches with the power of epidemiological methods, such as the European IMAGEN study (11). We have recently begun a study that uses these methods combined with imaging and urban geography to highlight aspects of the urban social environment.

A better understanding of these neural circuits will also enable back-translation into a generation of more specific animal models that can be used in early drug discovery (12), and could enable the identification of molecular targets for social dysfunction through cellular and (epi-)genetic approaches. Further into therapy development, this neuroscience information can also constrain pharmacological and psychotherapeutic strategies targeting the identified circuits. For example, the prosocial neuropeptides oxytocin and vasopressin can be shown to act on precisely the core perigenual cingulate-amygdalar regulatory circuit for gene-environment interaction, and

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