Social neuroscience in psychiatry: pathways to discovering neurobiological risk and resilience

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Cacioppo et al (1) provide a thoughtful overview of the ways in which social neuroscience can significantly advance our understanding and treatment of mental disorders.

They touch on the way gene regulation, epigenetics and the environment can alter neurodevelopmental trajectories and in turn influence social behavior and social functioning. We would like to emphasize here the importance of future research exploring dynamic social brain changes taking place during adolescence (2,3) as a possible key to understanding the emergence of mental disorders at this critical stage of maturation, when risk for such disorders peaks.

Recent work in our laboratory shows that attenuated growth of the hippocampus and attenuated reduction in putamen volume during age 12 to 16 years are associated with the onset of depression (4). Sex is also a significant factor, since exaggerated amygdala growth in females and attenuated growth in males seems to increase the risk of depression. Taking account of the neurodevelopmental background for boys and girls, relevant to all aspects of cognition, including social cognition, is a necessary prerequisite to understanding mental disorders and their neurobiology.

The prominence of social themes in the characterization of autism spectrum disorders (ASD) also warrants brief discussion. Our recent work on ASD (5) is relevant in being an interdisciplinary study involving biology and engineering, and in linking statistical approaches to biology. Importantly, while the emphasis of most studies has been on discovery of neurobiological risk markers for such disorders, in our study we also identified several single-nucleotide polymorphisms (SNPs) that protected against ASD, that is, might be associated with resilience to development of the disorder.

For example, we found that the SNP rs12317962 protected against ASD (5). This SNP lies in the gene KCNMB4, encoding a potassium channel involved in neuronal excitability, which is highly expressed in the fusiform gyrus and key social brain regions, namely the superior temporal, cingulate and orbitofrontal cortices. Other SNPs, such as variation in rs3796863 in CD38, a gene linked to ASD and known to be involved in oxytocin secretion, has also been linked with activation of the amygdala and in particular the fusiform gyrus, during visual processing of social stimuli in healthy young men (6). We are in the processes of furthering this research in ASD by examining the influence of allelic variation on brain regions using neuroimaging.

Schizophrenia is another disorder that involves deficits in social cognition. Recent theories propose that aberrations in dopaminergic and glutamatergic subcortical-amygdala-prefrontal circuits give rise to dysregulation of salience signaling, causing impairments in emotion-related perception, learning and memory (7), similar to the model of Phillips et al (8) described by Cacioppo et al (1) in the context of depression.

Interdisciplinary research of Walter et al (9) shows that carriers for the psychosis risk variant of the SNP rs1344706 (gene ZNF804A) have abnormal neural activation in the medial prefrontal and left temporo-parietal cortex, as well as in regions of the mirror neuron system, during a theory of mind task. This potential intermediate phenotype derived from functional imaging may have implications for biological treatment of social cognitive impairments in schizophrenia.

One thing that is clear from Cacioppo et al's paper (1) is that, across disorders, common social brain regions are dysfunctional: the amygdala, orbitofrontal cortex, medial prefrontal cortex, superior temporal sulcus, anterior insula and anterior cingulate. Yet, the way in which they deviate from normal functioning (hypo- vs. hyper-activation/mixture of both) depends on the illness being studied and the social processes in question. Therefore, we should study not only across disciplines but also across mental disorders, and in the context of carefully controlled treatment interventions, to provide insights into both risk and resilience factors associated with developing particular disorders.

Oxytocin has been proposed as a potential adjunctive treatment for the social cognitive and behavioural deficits common in social anxiety disorder, ASD, schizophrenia, and borderline personality disorder (10). While there are several oxytocin-related risk alleles that have been linked to social brain functioning, there is little insight into the mechanisms of the actions of oxytocin in the brain. This is a promising avenue for future research in psychiatry.

In conclusion, Cacioppo et al's paper on social neuroscience and mental disorders provides us much food for thought. There is a need for dynamic interdisciplinary (rather than just multidisciplinary) exchange between biological and other sciences; assessing changes in trajectories of brain structure and function; linking these dynamic changes to genes that may bestow risk or resilience to development of illness; and examining the impact of interventions that modulate social

cognition. All of these approaches and their combination present exciting ways forward in understanding some of the most challenging and complex disorders affecting human beings.

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Social neuroscience in psychiatry: of obvious relevance

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Cacioppo et al (1) make the important point that the study of normal and abnormal social behavior is essential in the understanding of mental disorders. Indeed, it is hard to imagine a mental disorder that does not involve, or lead to, abnormalities in social interaction. One could even say that one of the hallmarks of mental illness is that social interactions are affected. Obviously, and as argued by many, the human species is a social species and therefore its brain is developed to support social activities.

The paper provides three examples of psychiatric disorders where abnormalities in social functioning are involved: major depressive disorder, antisocial personality and hypoactive sexual desire disorder. However, the relationship between abnormal social activities and these three disorders may be quite dissimilar. One could argue that in major depression the abnormalities in social interactions are secondary to the disease and may therefore be important in treatment and rehabilitation but not as important in understanding the etiology of the illness (2). In contrast, antisocial personality disorder is characterized at its core by abnormal social interaction, where the abnormality may be lifelong and of a developmental nature. Finally, hypoactive sexual desire disorder may lead to social interaction abnormalities, but these may not be the cause of the illness.

The authors mention, but do not address in detail, two other mental disorders where abnormal social interaction, specifically impaired social cognition, may be a root cause of the illness: autism (3) and schizophrenia (4).

Emotional and cognitive dysfunctions are the core clinical features of schizophrenia (5). Moreover, it has been argued that impairments in emotion recognition and theory of mind (ToM) may even trump the value of general cognition and symptoms in explaining outcome in schizophrenia (6).

In healthy individuals, social cognition has been extensively studied using functional and structural imaging, and a network of brain regions subserving it has been identified (7). In short, the processing of facial expressions depends critically on the amygdala and the orbitofrontal cortex, whereas in mentalizing tasks, such as ToM, the medial and orbitofrontal cortex is critical (8).

In schizophrenia, functional neuroimaging studies have consistently demonstrated reduced activity of the amygdala during processing of facial emotions compared to healthy controls (9), and reduced activation of the prefrontal cortex (PFC) has been related to impaired performance on ToM tasks. Indeed, a recent meta-analysis of functional imaging studies, comprising 450 schizophrenia patients and 422 healthy controls, has shown reduced amygdala and PFC activity in social cognition in schizophrenia (10).

In contrast to the numerous functional neuroimaging studies in schizophrenia, only few structural imaging studies have investigated the relationship between abnormalities of the amygdala and PFC and social cognitive deficits seen in patients. So far, samples have been small (between 16