Social neuroscience and its potential contribution to psychiatry

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Most mental disorders involve disruptions of normal social behavior. Social neuroscience is an interdisciplinary field devoted to understanding the biological systems underlying social processes and behavior, and the influence of the social environment on biological processes, health and well-being. Research in this field has grown dramatically in recent years. Active areas of research include brain imaging studies in normal children and adults, animal models of social behavior, studies of stroke patients, imaging studies of psychiatric patients, and research on social determinants of peripheral neural, neuroendocrine and immunological processes. Although research in these areas is proceeding along largely independent trajectories, there is increasing evidence for connections across these trajectories. We focus here on the progress and potential of social neuroscience in psychiatry, including illustrative evidence for a rapid growth of neuroimaging and genetic studies of mental disorders. We also argue that neuroimaging and genetic research focused on specific component processes underlying social living is needed.

Key words: Social neuroscience, psychiatry, neurobiological processes, genetics, brain imaging

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The human brain has evolved to attend to, think about, and interact with other people, and we receive immense practice in these processes starting very early in life (1,2). It is therefore easy to underestimate the complexity of the component processes that underlie social living.

As Dunbar (3) has noted, the complexities of deducing better ways to find food, avoid perils, and navigate territories are trivial compared to the complexities of social living. The component processes for social living include: detecting significant stimuli in the environment and differentiating between those that are hospitable vs. hostile; differentiating among objects, nonhuman agents, and other (thinking) individuals; inferring the thoughts, intentions and emotions of other individuals, especially as it pertains to the causes of their behavior; recognizing these individuals despite changes in appearance and roles across situations, events and time; organizing these observations and inferences to provide a coherent, predictive model of others to permit the formation of stable relationships; forming stable attachments or bonds with others, including the ability to confer provisions or benefits to another based on a concern for the other’s welfare; anticipating and coordinating efforts between two or more individuals; learning by social observation; recognizing the shifting status of friends and foes; using language to communicate, reason, teach and deceive others; orchestrating relationships, ranging from pair bonds and families to friends, bands and coalitions; navigating complex social hierarchies, social norms and cultural mandates; subjugating self-interests to the interests of the pair bond or social group in exchange for the possibility of long-term benefits; recruiting support to sanction individuals who violate group norms; and doing all this across time frames that stretch from the distant past to multiple possible futures (4,5).

Deficits in any one of these component processes can result in personal difficulties and interpersonal problems, that are prominent features in a variety of mental disorders (6,7). Both Axis I and II disorders are characterized by a range of cognitive deficits that negatively impact social interactions and/or by specific deficits in social cognition. For instance, autism spectrum disorders include difficulties in social perception, social motivation and/or theory of mind, which results in major impairments in social interactions. Schizophrenia and related personality disorders such as schizotypal disorder include problems in organizing social observations and inferences to develop the coherent, predictive model of others needed to anticipate and coordinate efforts between two or more individuals. Antisocial personality disorder is characterized by an inability to confer a provision or benefit to another based on a concern for the other’s welfare, and a lack of empathy, which makes it difficult to form stable, healthy bonds with others. Hypoactive sexual desire disorder includes the absence or persistent deficiency of desire for sexual activity that causes marked distress or interpersonal difficulty. Several mental disorders, including borderline personality disorder, are marked by unstable relationships and moods, and impulsive behavior such as lashing out in anger. And a deficit of impulse control when interacting with others is a component in a variety of mental disorders.

Social neuroscience is a conceptual perspective focused on the specific delineation of the neural, hormonal, cellular, molecular and genetic mechanisms underlying social structures and processes. As such, social neuroscience offers a valuable perspective...
for understanding important domains of mental disorders (7-12).

THE CHALLENGES OF SOCIAL NEUROSCIENCE IN PSYCHIATRY

The determination of how the human brain works and what to do when disorders develop is one of the grand challenges in science and medicine. Although the human brain shares many design features with those of other organisms, there is no doubt that it also has many unique features. The human brain contemplates the history of the earth, the reach of the universe, the origin of its species, the genetic blueprint of life, and the physical basis of its own unique mental existence. Nevertheless, animal models of mental disorders provide invaluable information about underlying mechanisms, because experiments can be performed in animals that are not possible in humans. The development of animal models is completely reliant upon knowledge gained from patient studies, which identify phenomena to be modeled. Furthermore, highly relevant animal models also exist that are used to study aspects of normal behavior, rather than pathology. These models can be integrated with patient studies and studies of healthy individuals.

To investigate the mutual influence of the biological and social environments and the mechanisms through which these influences operate, social neuroscientists, ranging from physicists to psychologists, epidemiologists to psychiatrists, philosophers to neurobiologists, and entomologists to zoologists, have begun to work together in interdisciplinary scientific teams using animal models, patient studies, and research on healthy individuals. These interdisciplinary collaborations have capitalized on a variety of methods and techniques, ranging from behavioral studies of implicit processes in lesion and split-brain patients to volumetric and neuroimaging studies across scales of neural organization in chimpanzees or healthy humans, to cellular and molecular techniques in genetics and epigenetics. Even well-traveled techniques, such as meta-analyses and electroencephalography, have seen upgrades that, for instance, permit investigations of the source and chronocircuitry of the neural substrates of social processes (13-16). Importantly, the development of experimental manipulations of neural processes in humans through, for instance, the use of pharmacology or transcranial magnetic stimulation has also helped determine the causal significance of specific neural regions in social cognition, emotion and behavior. Finally, increases in computational speed and novel approaches for the analysis of extremely large datasets are creating opportunities to address questions across multiple levels of organization.

The potential for advances in our understanding of mental disorders in their various forms is heightened by an integration of information from multiple levels of scientific inquiry, from the local to the behavioral to the molecular and genetic levels (9). Mapping across systems and levels (from genome to social groups and cultures) requires basic, applied and clinical studies; interdisciplinary expertise; comparative as well as patient studies; innovative methods and integrative conceptual analysis. Multilevel analyses of psychopathology require a range of expertise that is not likely to be found in solitary investigators. One can distinguish multidisciplinary from interdisciplinary approaches in this regard. While multidisciplinary research is characterized by the aggregation of expertise, interdisciplinary research is defined by synergies among experts that can transform both science and scientists. Interdisciplinary scientific research is riskier than multidisciplinary research, since it is a group product rather than the simple sum of its individual products. Accordingly, interdisciplinary teams are more subject to failure than solitary and multidisciplinary scientific efforts. But with this higher risk also comes a potential for higher payoffs. When interdisciplinary teams working on mental disorders succeed, they have the potential to produce significant scientific innovations, make progress in solving what were thought to be intractable problems, and develop more effective diagnostic procedures and treatments.

Social neuroscience facilitates such interdisciplinary development as well as allows an increase in communication and collaborations among scientists and physicians. For the past 20 years, social neuroscience has experienced a dramatic rise in the number of studies investigating mental illness which involve social behavioral disturbances. In the following section, we provide some examples of this research. The scope of social neuroscience and its relevance to psychiatry goes well beyond these examples, however. For instance, important advances have also been made showing: a) how gene regulation changes complex cognitive functions, including learning and memory, and then causes several developmental and mental disorders effects on language and social functioning (17,18); b) a role for epigenetic mechanisms in long-term memory formation (19,20), and c) the effects of early social stress on gene regulation and the epigenome, which then leads to long-lasting changes in behavior, cognition, mood and neuroendocrine responses predisposing to or sheltering from stress-related diseases later in life (21-23).

An example of the impact of social stress on gene regulation is provided by population-based research on older adults, reporting that perceived social isolation (loneliness), a chronic social stressor, is associated with the differential expression of pro-inflammatory and antiviral genes (a pattern known as the conserved transcriptional response to adversity) (24-26). The altered gene expression profiles in plasmacytoid dendritic cells and monocytes appear to be the key cellular mediators of the human immune system’s transcriptional response to chronic loneliness. These two myeloid lineage antigen-presenting cells contributed disproportionately to the set of transcripts differentially expressed in the circulating leukocytes of chronically lonely individuals, whereas genes expressed by other cell types showed little differential expression as a function of loneliness. Consistent with the hypothesis that central
nervous system-mediated differences in neural or endocrine signaling are responsible for such effects, differential expression of monocyte- and dendritic cell-derived transcripts was strongly associated with the subjective experience of social isolation but showed no significant relationship to objective social network size (24).

Analyses also showed that the observed differences of gene expression profiles in antigen-presenting cells do not stem from differences in the prevalence of those cell types within the circulating leukocyte pool, but instead reflect per-cell changes in the expression of inducible genes that are flexibly transcribed depending upon environmental conditions. Thus, among all the cell types within the circulating leukocyte pool, plasmacytoid dendritic cells and monocytes appear to show a unique degree of transcriptional sensitivity to the experienced social environment.

Recent molecular mechanistic analyses have confirmed that experimental induction of social threat in a mouse model (comparable in key respects to the sense of social threat experienced by lonely humans (27)) causally increases bone marrow production of an immature, highly pro-inflammatory subtype of monocyte (28). Pharmacologic and biochemical analyses of glucocorticoid transcriptional control in the mouse model have identified a key role for sympathetic nervous system signaling in driving the hematopoietic production of glucocorticoid insensitive monocytes through a beta-adrenergic receptor-mediated pathway involving the myelopoietic growth factor GM-CSF (28).

Loneliness has been shown to increase a person’s susceptibility to depressive symptomatology (29,30) and is associated with a variety of mental disorders (31). Therefore, future molecular studies focusing on gene expression or other putative functional intermediates have the potential to shed new light on the underlying mechanisms by which loneliness influences susceptibility to mental disease.

THREE ILLUSTRATIVE MENTAL DISORDERS

Recent neuroimaging research in social neuroscience has examined how the functioning of neural circuits in patients differs from that of controls. Rigorous analyses of social behaviors and disorders have identified component processes that may serve as a landmark for better understanding aspects of these disorders. We provide here a brief review of recent work on the neural underpinnings of social behavioral disturbances associated with three mental disorders.

Major depressive disorder

Major depression is a mental disorder with an estimated lifetime prevalence rate of 15-17% (32). Theories of depression point to a disruption of interpersonal processes (33) as well as neural systems involved in socio-emotional processes (34). Individuals suffering from depression, as well as those at risk for depression, evidence a range of social deficits and appear to generate their own stressful social interactions (35-37).

The development of the concept of major depression (38), the experimental study of major depression in animals, and neuroimaging studies in humans have shed new light on how neural systems may be involved in this condition (34,39,40). For instance, with the introduction of functional neuroimaging techniques – such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) – various candidate brain areas/networks for major depression have been proposed (41-43).

A number of studies have examined the neural correlates of abnormal emotion regulation processes, which are a core feature of the disorder (44-50). Because neuroimaging studies generally include a small sample size (e.g., ranging from 9 to 44), many of these neuroimaging studies lack sufficient statistical power (43). Low statistical power reduces chances of detecting true effect (51). It is, therefore, important to keep in mind that the meta-analytic approach to functional imaging studies of major depression often provides a more accurate picture (43).

From the ensemble of these neuroimaging investigations and meta-analytic studies, a cortico-limbic model of major depression has become to emerge (41-43,52-55), postulating a dysfunction of seven key areas (lateral, medial and orbital parts of the prefrontal cortex; the subgenual and rostral parts of the anterior cingulate cortex, the hippocampus and the anterior thalamus) within and beyond the limbic system. Interestingly, this cortico-limbic model of major depression not only suggests a hyperactivity of the limbic system but also a dysregulation of the prefrontal cortex (56).

This model fits with another one proposed by Phillips et al (47,48,57) for emotion regulation, identifying two main parallel systems: a) a ventral system (including the amygdala, insula, ventral striatum, ventral anterior cingulate gyrus, ventromedial prefrontal cortex and medial orbitofrontal cortex), which is important for the bottom-up, automatic emotional evaluation of salient stimuli and the generation of emotional states; and b) a dorsal system (e.g., dorsal anterior cingulate gyrus; dorsal prefrontal cortex), which is assumed to play a crucial top-down cognitive role in the voluntary regulation of these emotional states (47,48).

A recent review including 40 fMRI studies and one PET study (44) reinforced (and specified) the role of the cortico-limbic model in major depression by dissecting it with respect to six emotion regulation subprocesses: automatic behavioral control, voluntary behavioral control, automatic attentional control, voluntary attentional control, automatic cognitive control, and voluntary cognitive control. In brief, the review showed that major depression is associated with abnormal hypoactivation of lateral prefrontal cortices, especially during voluntary control of emotional experiences, while automatic emotion regulation is achieved by activation of other brain areas, such as the medial prefrontal regions, including
the rostral and dorsal anterior cingulate gyrus (44).

These neuroimaging results suggest that depression is associated with dysfunctions in specific brain regions involved in emotion regulation, impulse control and affective responding, with social variables playing a role both as a contributing factor and as a consequence of the altered affective processing and executive functioning.

Because of the high heritability of depressive symptoms (58-60), many investigators have examined the role of genetic factors. Several studies have focused on putatively functional polymorphisms, but only a few of these genes have been confirmed in subsequent studies and meta-analyses (61). Pezawas et al (62), for instance, found that subjects with the short allele of a functional promoter polymorphism of the serotonin transporter gene (5-HTTLPR) had a decreased volume of both the amygdala and the subgenual prefrontal cortex, and showed a functional uncoupling of the subgenual–amygdala circuitry. Individuals with this allele had increased anxiety-related temperament traits, increased amygdala reactivity, and an elevated risk of depression. A large meta-analysis supported the interaction of the short allele of 5-HTTLPR and stressors in the etiology of depression (63).

Although genome-wide association studies (64) have identified interesting regions and potential new candidate genes for various mental disorders, early studies were sometimes difficult to replicate (65). Both technical improvements and larger sample sizes have produced more consistent results for major depression, but it is clear that even larger samples and meta-analyses of multiple data sets are required (66,67). The study of intermediate phenotypes provides a valuable approach: these are heritable characteristics that co-segregate with a disorder but are not a direct consequence of the disorder and can be quantified in both affected and unaffected individuals. It has been suggested that intermediate phenotypes may be influenced by a smaller number of genes as compared to mental disorder, simplifying gene discovery. Component social processes that differentiate depressed and non-depressed patients, such as perceived isolation – which has been shown to be about 50% heritable (68,69) – represent a potentially fruitful class of intermediate phenotypes.

The identification of neurobiological markers of depression may help psychiatrists target specific neural processes and regions and to personalize antidepressant treatments. However, when the depression is triggered by a repeatable environmental event (e.g., stressful life circumstances or relationship problems (29,70)), the exclusive reliance on a pharmacologic treatment may leave the patient at risk for relapse. A personalized suite of treatments informed by the field of social neuroscience can significantly improve outcomes.

Antisocial personality and psychopathy

Antisocial personality disorder is marked by a range of social aberrations involving indifference to and violation of the rights of others. The related but more narrowly defined concept of psychopathy focuses on social (e.g., untruthfulness, superficial charm, unresponsiveness in interpersonal relations) and socio-emotional features (e.g., deficits in social emotions such as remorse or shame, incapacity for love, shallow affect) (71,72).

During the past decade, a growing number of neuroimaging studies have investigated the neural substrates of antisocial behaviors and psychopathy (73-82). These investigations indicate that, when individuals with psychopathy imagine or observe others in pain, brain areas necessary for feeling empathy and concern for others (e.g., dorsal anterior cingulate) are less activated or fail to become active, and connections between these regions and other important regions involved in affective processing and decision-making are weaker than in the normal population.

Diminished response to cues of threat or punishment have been hypothesized to mediate the failure to learn from punished responses, the callous exploitation, the lack of remorse, and the focus on immediate rewards that characterize psychopathy. Consistent with this notion, an fMRI investigation revealed that the limbic–prefrontal circuit (involving amygdala, orbitofrontal cortex, anterior insula, and anterior cingulate cortex) that was activated during fear conditioning (using slides of neutral faces) in normal individuals was not activated in psychopaths (83).

Relatedly, psychopathy has been associated with deficient autonomic responding in anticipation of threatening events (84) and inhibited startle to negative emotional stimuli (e.g., victim scenes) (85). Prefrontal functional impairments have been proposed to relate to the behavioral and affective deficits seen in psychopathy (86), as structural studies suggest that antisocial personality disorder is associated with reduced prefrontal gray matter volume and that these prefrontal gray deficits are reflected in diminished electrodermal responses (87).

Hicks et al (88) investigated the hypothesis that primary psychopathy (affective-interpersonal features) is predominantly heritable, whereas secondary psychopathy (social deviance) is primarily environmentally determined. Trait-based indices of primary and secondary psychopathic tendencies were assessed using the Multidimensional Personality Questionnaire (MPQ) to estimate fearless dominance and impulsive antisociality, respectively, and the environmental contexts of family, school, peers, and stressful life events were also evaluated. MPQ impulsive antisociality was primarily associated with environmental risk factors, and these environmental influences were greater than for MPQ fearless dominance. However, MPQ fearless dominance and impulsive antisociality exhibited similar heritability, and genetic effects appeared to mediate the associations between MPQ impulsive antisociality and environmental contexts. The authors concluded that gene-environment interactions rather than main effects of genes and en-
Hypoactive sexual desire disorder

There is now a sizeable literature in psychiatry and psychology on female hypoactive sexual desire disorder, which is defined in the DSM-IV as “persistent or recurrently deficient (or absent) sexual fantasies and desire for sexual activity” that cause “marked distress or interpersonal difficulty”. Epidemiological studies report that about 40% of American women between 20 and 70 years of age have problems with low sexual desire (89). The disorder has a negative impact on quality of life of both the individual and the couple (89-91).

Social neuroscientists have begun to investigate hypoactive sexual desire disorder because of the importance of understanding the brain regions and networks involved if new and more effective interventions are to be developed. Although this is still a nascent area of research, the extant work suggests the importance of central, in contrast to peripheral, processes in both healthy individuals and patients (92), and the brain regions and networks associated with sexual desire vs. love are beginning to be identified.

In healthy subjects, recent neuroimaging studies have shown that sexual desire involves not only emotion-related limbic areas, such as the amygdala, hypothalamus, hippocampus, ventral striatum, and insula, but also a distributed cortical network including (but not restricted to) three main areas: anterior cingulate, parietal lobule, and middle temporal gyrus/posterior superior temporal sulcus (93). The distributed nature of this network in healthy subjects highlights how sexual desire involves brain areas that mediate different functions, such as reward mechanisms (e.g., ventral striatum) and higher-order cognitive processes associated with social cognition, self-representation, body image, and attention (94). Together, the functions of this brain network support the view of sexual desire as a phenomenon driven not only by bottom-up influences but also top-down influences from past and integrated rewarding bodily self-related experiences, combined with sensory (e.g., visual) and emotional processing (93,94).

Neuroimaging studies in people with sexual desire disorders constitute a unique opportunity to investigate the putative role of these underlying brain processes (95-98). Using PET, Stoleru et al (95) demonstrated differential brain activation to visual erotic stimuli between men with hypoactive sexual desire disorder and healthy men. Whereas healthy men showed decreased activity in the medial orbitofrontal region, men with the disorder showed no such decreased activity to the erotic stimuli. The authors interpreted this difference as due to the maintenance of inhibitory control when men with the disorder viewed erotic stimuli. Men with hypoactive sexual desire disorder, compared to controls, also displayed greater deactivation in emotion-related brain regions (such as the anterior cingulate) and in brain regions mediating motor imagery processes, somatic experiences, and self-representation (e.g., the secondary somatosensory cortex).

Subsequent neuroimaging studies in this field, performed with fMRI and female participants (97,98), reinforced Stoleru’s findings. In brief, these studies revealed two distinct types of neural changes in participants with hypoactive sexual desire disorder relative to healthy controls. Women with the disorder showed a hypoactivation in the sexual desire brain network that is typically activated in healthy participants (e.g., posterior insula); and a hyperactivation in three specific brain regions that are not typically activated in healthy participants: the inferior parietal lobule, inferior frontal gyrus, and extra-striate visual cortex.

This is in line with current hypotheses about reduced sexual desire (99), which suggest that hypoactive sexual desire disorder may result from hypofunctional excitation, hyperfunctional inhibition, or some mix of the two. Interestingly, these findings also echo Masters and Johnson’s, Kaplan’s and Barlow’s clinical concept of “spectatoring” (100,101), which assumes that deficits in sexual functioning may be (at least partly) associated with inhibited excitement due to a disruption in the processing of erotic stimuli and a shift in attentional focus from erotic stimuli to self-monitoring of sexual response (i.e., self-focus attention).

This hypothesis needs further testing, but these results provide insights into the brain processes underlying sexual desire disorders as well as anomalies in social information processing in hypoactive sexual desire disorder. More generally, this work illustrates the potential value of social neuroscience – from analyses of regional brain activity to the dissection of component social structures and processes – to better specify the mechanisms underlying a mental disorder and to develop more proximal and effective targets (e.g., pharmacologic, neural, cognitive, social) for intervention.

FUTURE PERSPECTIVES

The human brain is among the most complex biological structures known. Given the complexity of the brain and its outputs, what is perhaps remarkable is that the appearance of a mental disorder across a lifetime is not more common. The original focus on the genetics and neural regions associated with psychiatric diagnostic categories was an important initial step, but such an approach assumes that these categories can be mapped in a 1:1 fashion to specific underlying causes. Given the complexity of the human brain and the vagaries of mental disorders, it is
not surprising that targeting specific endophenotypes within each mental disorder is proving to be more informative. This research is gaining momentum, with the list of biological and behavioral intermediate phenotypes increasing rapidly. Given that among the most important functions of the human brain are the production of an organized mental existence and the orchestration of behavior, including our recognition and interaction with others, it may prove informative to also specify the component social structures and processes that are involved in mental disorders.

Correlating complex mental disorder with regions of activation in the brain is only a preliminary step toward specifying the brain mechanism responsible for any such disorder. The brain does not operate exclusively at the spatial level of molecules, cells, nuclei, regions, circuits or systems, nor does it operate exclusively at the temporal level of milliseconds, seconds, minutes, hours or days. Any single neuroimaging methodology provides a partial view of brain activity within a very limited range of spatial and temporal levels. Therefore, converging methods that gauge neural events at different temporal and spatial scales should be used to provide a more complete picture of brain function.

The equilateral triangle depicted in Figure 1 represents the equal importance of three converging approaches that may help us to understand the brain mechanisms underlying mental disorders (102): a) behavioral assessment, or the specification of component information processing operations, including specific component social processes; b) experimental manipulations; and c) physiological measurements. Neuroimaging is a correlative measure, so experimental studies including lesion, transcranial magnetic stimulation and pharmacological interventions (e.g., ligands, drugs) in human and nonhuman animal are essential to further elucidate the causal role of any given neural structure, circuit or process in a given task. Each of these angles has limitations, but the confluence of the three can facilitate advances in our understanding of the neural mechanisms underlying mental disorders.

CONCLUSIONS

Technological and computational developments over the past few decades have transformed the nature and amount of data available on brain structure and function at various scales. However, with these advancements have come distinctive methodological, analytical and conceptual frameworks, and increased subdisciplinary specialization, interests and pressures toward segregation. Although understandable, this specialization can work against the integration of data across levels of analysis, especially when it is associated with eliminative reductionism rather than constructive reductionism, which favors the study of the part to better understand the whole. A contribution of the multilevel integrative approach of social neuroscience to psychiatry may therefore be the way in which data at various levels of organization of brain function and behavior (including social behavior) are related to one another.

Although not unique in psychiatry, social neuroscience may represent a hospitable meeting ground articulating and integrating theories, methods and data from various levels of organizations and disciplinary perspectives to better understand the causes and treatment of mental disorders. Moreover, psychiatry has been split into two subdisciplines, one focused on pharmacological and biological treatment of disease and the other focused on talk therapy. Social neuroscience may serve as a meeting ground between these perspectives, as well as one in which pharmacological intervention could be viewed as a strategy for improving social function.

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