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Opinion

Social Preference and Glutamatergic Dysfunction: Underappreciated Prerequisites for Social Dysfunction in Schizophrenia

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Impaired social functioning is pervasive in schizophrenia. Unfortunately, existing treatments have limited efficacy, and possible psychological or neurobiological mechanisms underlying social dysfunction in this disorder remain obscure. Here, we evaluate whether social preference, one key aspect of social processing that has been largely overlooked in schizophrenia research, and *N*-methyl-D-aspartate receptor (NMDAR) dysfunction can provide insights into the mechanism underlying social dysfunction in schizophrenia. Based on evidence from developmental psychology, and behavioral and clinical neuroscience, we propose a heuristic model in which reduced NMDAR function may induce disrupted social preference that can subsequently lead to social cognitive impairment and social disability. We discuss its implications in terms of the pathophysiology of schizophrenia, other disorders with marked social disability, and potential treatments.

Context

Impaired social functioning is pervasive in schizophrenia. Individuals with schizophrenia have difficulty sustaining relationships with family members and friends, and have trouble interacting with colleagues in work settings and acquaintances in leisure settings (Box 1). Unfortunately, existing pharmacological or psychological interventions have seen only limited efficacy in improving social dysfunction. Further, pathways for the development of novel treatments are not obvious, as little is known about the psychological or neurobiological mechanisms underlying social disability in this disorder.

This review focuses on one key aspect of social processing that has direct implications for social disability, but has been largely overlooked in schizophrenia research – social preference. First, we will illustrate that social preference is a fundamental feature of processing social information and is present throughout the lifespan. Second, we will re-evaluate existing studies of schizophrenia and argue that the pattern of findings can be explained by disrupted social preference. Third, we will examine possible neurobiological mechanisms of disrupted social preference in schizophrenia with a focus on the ***N*-methyl-D-aspartate receptor** (NMDAR; see Glossary). Finally, we will propose a heuristic model that links disrupted social preference and dysregulated NMDAR function to social dysfunction in schizophrenia and discuss whether this model could have a broader applicability to other disorders with marked social disability and potential treatment implications for social disability in schizophrenia.

Trends

Impaired social functioning is pervasive in schizophrenia; unfortunately, existing pharmacological or psychological treatments have only limited efficacy in improving social dysfunction.

Little is known about psychological or neurobiological mechanisms underlying social dysfunction in schizophrenia.

Social preference – the tendency to prioritize processing of social over non-social stimuli – represents a fundamental way that human beings process social stimuli and is crucial for the development of social cognitive skills and efficient social functioning.

Emerging evidence strongly suggest that social preference is disrupted in schizophrenia.

Mounting evidence from animal studies suggest that *N*-methyl-D-aspartate receptor (NMDAR) hypofunction is closely related to disrupted social preference. NMDAR hypofunction is also a key neurobiological component of one of leading pathophysiological theories of schizophrenia.

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Box 1. Schizophrenia and Poor Social Functioning

Schizophrenia is a chronic mental illness, affecting approximately 0.7% of the general population around the world [92]. Schizophrenia is typically diagnosed in late adolescence or early adulthood by having at least two of the following characteristic symptoms during a 1-month period: hallucinations (i.e., perception of something not present, such as hearing voices that no one else hears or seeing things that no one else sees); delusions (i.e., a firmly held belief despite having contradictory evidence in reality, often persecutory or grandiose in nature); speech that is too tangential or too loosely associated for others to understand; odd, eccentric or agitated behaviors that would attract others' attention if observed; and negative symptoms such as lack of drive, reduced motivation, or reduced expression of emotions [93].

Individuals with schizophrenia also experience high levels of disability in several areas, including self-care, independent living, work, relationships with family members and friends, and interactions with community members in a broader social context (e.g., leisure setting). Indeed, according to the World Health Organization, schizophrenia is among the top 10 leading global causes of disability for both men and women (fifth and sixth, respectively) [94]. In addition to individuals with the diagnosis, individuals who are high risk for developing schizophrenia demonstrate pronounced social dysfunction. For example, in a large population-based prospective study [95], social dysfunction was clearly present as early as 15 years before first hospitalization and deteriorated further 5–8 years before the onset; however, a similar level of impairment or the magnitude of deterioration was not present in other areas of functioning (e.g., work, independent living). Further, social dysfunction was shown to be one of the key predictors of a transition to psychosis among individuals at high risk for developing schizophrenia [96,97]. Notably, even though standard treatments have been effective in alleviating psychotic symptoms in most individuals with schizophrenia, a large number of individuals with schizophrenia experience continuing social dysfunction over the course of illness [98,99].

Social Preference: The Way Humans Process Social Stimuli

Human beings are intrinsically tuned for social stimuli in that we prefer social over nonsocial stimuli. The term social preference refers to this bias or tendency to prioritize processing of social over nonsocial stimuli.

Preferential processing of social stimuli can be easily observed during adulthood. For example, healthy adults identify social stimuli much faster than nonsocial stimuli [1,2] and have more difficulty disengaging from irrelevant social stimuli than from irrelevant nonsocial stimuli [3,4]. People also appear to find social stimuli more rewarding; they show faster learning when feedback is social versus nonsocial stimuli [5,6]. In addition to behavior, social and nonsocial stimuli are processed differently in the brain. For instance, adults have increased activation in the amygdala and medial prefrontal cortex when remembering social information and increased activation in the hippocampus when remembering nonsocial information [7,8]. When processing the reward value of social and nonsocial stimuli, individuals show greater activation in the amygdala for social stimuli but greater activation in the thalamus for nonsocial stimuli [9].

Typically developing children and adolescents show similar tendencies. For example, both younger children (approximately 24 months) [10] and older children (between 9 and 17 years) [11] show greater difficulty disengaging attention away from social compared to nonsocial stimuli. Brain-based measures such as **event-related potentials** (EPRs) reveal that children aged 6–8 years old have larger EPRs, reflecting greater sensitivity, to social reward compared to nonsocial reward [12].

Even babies exhibit preference for social stimuli. Newborns have a preference for social stimuli, such as human faces and voices, over nonsocial stimuli [13,14]. For faces, newborns preferred faces with direct versus averted gaze [15,16], suggesting that they like a more interactive gaze direction. Infants younger than 1 year detect human face targets much faster than other nonsocial targets [17] and have better memory for social over nonsocial targets [18]. Attention to social stimuli (i.e., faces) becomes more robust in 9-month-old, versus 3-month-old, infants [19,20], suggesting that social experience itself may facilitate the preferential processing of social stimuli. As with adults and adolescents, preferential social processing in early life can also be seen at the neural level. Four- to 6-month old infants have preferential processing for faces over both objects and scrambled images, as assessed with steady-state visual evoked potentials

Glossary

Agonist: a chemical that activates a receptor to initiate biological processes after binding to it.
Antagonist: a chemical that blocks the activation of a receptor after binding to it.
Event-related potentials: a noninvasive brain imaging method that uses electroencephalography to assess electrophysiological responses of a brain to a specific sensory, cognitive, or motor event.
γ-Aminobutryic acid (GABA): an inhibitory neurotransmitter in the brain that is involved in reducing neuronal excitability.
Interneuron: a type of neuron that is important for creating neural circuits and is involved in reflexes, neural oscillations, and neurogenesis in the brain.
***N*-Methyl-D-aspartate receptor (NMDAR):** an ionotropic glutamate receptor that becomes activated with the binding of glutamate and glycine and allows positively charged ions to flow through the cell membrane.
Near-infrared spectroscopy: a noninvasive brain imaging method that assesses chromophore concentration of hemoglobin and deoxygenated hemoglobin in the brain using near-infrared light.
Optogenetic: a neuromodulation method that involves the use of light to control neurons that have been genetically modified to be sensitive to light.
Social cognitive skills: a set of mental abilities to recognize and respond to the emotions, intentions and dispositions of others. Schizophrenia patients show impairment on multiple domains of social cognition, including facial affect recognition, affect sharing, mental state attribution, and empathy.
Working memory: a system or mechanism in which information is represented and maintained during a short period of time for further processing of the mental representation.