Published in final edited form as:

Trends Neurosci. 2016 September ; 39(9): 587–596. doi:10.1016/j.tins.2016.06.005.

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

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Abstract

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.

Keywords

NMDAR hypofunction; social preference; social functioning; schizophrenia

Context

Impaired social functioning is pervasive in schizophrenia. Individuals with schizophrenia have difficulty sustaining relationship 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

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Dr. Lee does not have any conflict of interest.

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.

Social Preference: the Way Humans Process Social Stimuli

Human beings are intrinsically tuned for social stimuli in that we prefer social over non-social 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 (around 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 (ERPs) reveal that children aged 6–8 years old have larger ERPs, 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-old 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 [21]. Using near-infrared spectroscopy, 4-month-old infants show greater neural activation in the temporal and prefrontal cortex for faces with direct gaze than faces with averted (i.e., less interactive) gaze [22].

Social Preference and Schizophrenia

As shown above, social preference is present across the entire lifespan, from early stages of development throughout adulthood. However, emerging evidence suggests that social preference is disrupted in schizophrenia. When performing attention or memory tasks, schizophrenia patients do not prioritize social stimuli. For example, whereas healthy controls identified social stimuli better than nonsocial stimuli, schizophrenia patients did not show this benefit [23, 24]. Healthy controls were able to shift their attention toward both social (i.e., gaze) and directional nonsocial cues (e.g., arrows); however, patients shifted attention only toward nonsocial cues, not toward social cues [25, 26]. In a study of recognition memory of social and nonsocial stimuli [27] healthy controls showed better memory on social than nonsocial stimuli, but patients showed equivalent memory for both types of stimuli, failing to benefit from social information. Further, in this study, better social memory was associated with increased activation in the dorsomedial prefrontal cortex in healthy controls, but this association was not observed in schizophrenia.

When evaluating social and nonsocial stimuli, schizophrenia patients appear to be less affected by social stimuli than controls. Healthy controls rated negative social stimuli as more arousing compared with negative nonsocial stimuli; but this effect was not observed in patients [28]. In a study of threat-related detection, healthy controls showed an expected threat-superiority effect (i.e. they detected threat-related stimuli more accurately than non-threat-related stimuli) and that effect was greater for social than nonsocial stimuli [29]. However, schizophrenia patients showed similar levels of threat-superiority effect across both social and nonsocial stimuli (see Figure 1A). Another study examined the bias of socially engaging cues on distance judgment [30]. In this study, as the cues became more socially engaging, healthy controls reported the spatial distance between two cues to be shorter (i.e., greater bias); however, patients failed to show this bias.

Schizophrenia patients also fail to utilize salient information when evaluating social stimuli. When assessing the identity of faces or recognizing fearful or angry expressions, healthy controls tend to focus more on the eye regions than other parts of the face [31, 32]. However, two studies found that schizophrenia patients utilized less information from the eye region and more information from the mouth region when recognizing fearful or angry facial expressions [33, 34].

These findings illustrate that healthy controls find social stimuli more salient than nonsocial stimuli, and process them preferentially. However, this is not the case in schizophrenia. One might wonder whether the reduced preferential processing of social stimuli in schizophrenia is due to a more general impairment in detecting salience in the external world. Existing evidence, however, does not support this possibility. For example, both healthy controls and schizophrenia patients were able to direct attention to salient nonsocial stimuli in a comparable way [35]. When examining working memory of salient versus nonsalient nonsocial items, both patients and controls also showed better working memory for salient items [36]. Thus, schizophrenia patients showed an intact ability to process salient nonsocial stimuli in these studies, suggesting that a non-specific impairment in salience processing does not explain the reduced social preference.

In this section we largely focused on studies that compared social and nonsocial processing with visual stimuli. Schizophrenia patients also have difficulty processing social stimuli in auditory tasks (e.g., prosody perception) [37], so it remains to be established the extent to which disrupted social preference in schizophrenia exists across multiple sensory modalities. Also, the evidence for disrupted social preference in schizophrenia does not mean that difficulties in information processing in schizophrenia are limited to social stimuli. In fact, schizophrenia patients show deficits in many domains of cognition and perception, including early visual and auditory perceptual processing [38–40]. These impairments in early visual and auditory processing have also been linked to social cognitive deficits and social dysfunction in schizophrenia [41, 42]. It remains to be determined whether early perceptual abnormalities are also related to disrupted social preference in this disorder.

Neurobiological Mechanisms of Disrupted Social Preference

One of the prominent theories of the pathophysiology of schizophrenia is NMDAR hypofunction [43, 44]. This theory stems from clinical observations of healthy people who experience psychotic symptoms and negative symptoms after taking NMDAR antagonists such as phencyclidine (PCP) or ketamine. Briefly, this theory posits that NMDAR hypofunction leads to a disruption of the γ -aminobutyric acid (GABA)-ergic system that usually inhibits pyramidal cells, resulting in excessive release of glutamate and disruption of the cortical cellular excitation to inhibition ratio (cellular E/I balance).

Existing evidence largely supports the relevance of NMDAR hypofunction and GABAergic interneurons to schizophrenia. For example, mice that were treated with ketamine showed increased levels of glutamate expression [45] and reduced levels of parvalbumin GABAergic interneuron expression [46] in the medial prefrontal cortex. Similarly, postmortem studies of schizophrenia patients also showed reduced levels of NMDAR expression [47] and loss of GABAergic interneurons [48]. In healthy human adults, a single sub-anesthetic dose of ketamine was associated increased spontaneous gamma-band oscillation [49] and increased resting state functional connectivity [50, 51], both of which have been reported in schizophrenia and are thought to reflect increased glutamate activity in the brain [51, 52]. Although the exact mechanisms through which NMDAR hypofunction contributes to the pathophysiology of schizophrenia remains to be determined (e.g., the particular cell types in addition to GABAergic interneurons, particular brain regions) [53, 54], it is clear that

substantial evidence supports the role of NMDAR hypofunction and dysregulated GABAergic system in the pathophysiology of schizophrenia.

While NMDA hypofunction is often viewed as the basis of positive symptoms, negative symptoms and cognitive impairments in schizophrenia, it has seldom been discussed in terms of social processing. Interestingly, a growing literature of laboratory studies of rodents indicates a crucial role of NMDAR hypofunction in disrupted social preference.

In animal studies, social preference is typically tested using a three-chamber task, in which a test mouse is placed in one chamber; a strange mouse and an object are placed in the remaining two chambers. Wild-type mice tend to spend more time around a chamber with a strange mouse than an object, indicating preference toward social over nonsocial stimuli. Mice with NMDAR hypofunction, however, fail to show social preference. For example, mice that were genetically modified to have reduced NR1 NMDAR function (referred to as NR1^{neo} $-/-$ mice) spent less time around a strange mouse than an object [55, 56]. Similarly, both NR1-knockdown mice and wild-type mice that were treated with a subchronic dose of an NMDAR antagonist (i.e. MK801) spent less time around a strange mouse (see Figure 1B) [57]. Notably, all of the groups of mice in these studies presented normal levels of anxiety, suggesting that disrupted social preference was not due to heightened general anxiety.

Social preference was also examined in SHANK2 mutant mice, another type of knockout with NMDAR hypofunction. The SHANK2 gene has been linked to schizophrenia [58] as well as autism [59], another disease characterized by severe social dysfunction. SHANK2 mutant mice did not show any preference toward a strange mouse over an object [60]. D-cycloserine, a partial agonist of the NMDAR glycine recognition site, reversed disrupted social preference in SHANK2 mutant mice, further supporting the crucial role of reduced NMDAR function in disrupted social preference.

Several studies also examined how NMDAR hypofunction affects the GABAergic system and, subsequently, social preference. Mice that were genetically modified to have ablated NR1 on parvalbumin-containing interneurons failed to show preference toward other mice over nonsocial objects [61, 62]. Also, baclofen, a GABAB-receptor antagonist normalized social preference in NR1^{neo} $-/-$ mice that had disrupted social preference and elevated cellular E/I balance [56].

Initial evidence indicates that NMDAR hypofunction may critically influence social preference at certain times in development and in certain brain regions. One study directly compared the effects of early postnatal deletion of NR1 versus post-adolescent NR1 deletion with two types of NR1 knockout mice and observed disrupted social preference only in mice with early postnatal deletion [63]. This finding suggests that the quality of NMDAR function early in life is more critical for social preference. Another study examined the effect of disrupting cellular E/I balance in either the medial prefrontal cortex or visual cortex on social preference in mice using optogenetic tools [64]. Disrupted cellular E/I balance in the medial prefrontal cortex, but not in visual cortex, resulted in aberrant social preference. Notably, the medial prefrontal cortex is considered a hub for social information processing in humans [65, 66].

Most of studies described in this section employed genetically modified animals to assess the effect of reduce NMDAR function on social preference. As with any studies of knockout mice or knockdown mice that affect neurodevelopmental processes, it is difficult to rule out the possibility that effects on social preference are due to a compensatory process for the loss of NMDAR function. Nonetheless, several lines of evidence presented here strongly indicate that NMDAR hypofunction is closely associated with disrupted social preference in these animals.

Disrupted social preference, NMDAR hypofunction, and social dysfunction in schizophrenia

As already shown, social preference is a fundamental way that humans process social information, and this distinction between social and nonsocial stimuli occurs very early in life. What are the implications of social preference for social functioning? Prioritizing social stimuli increases the opportunity to perceive and experience social stimuli and to respond appropriately, thereby facilitating the development of social cognitive skills and resulting in efficient social behaviors. Along these lines, emerging evidence indicates that a preference for social stimuli predicts later social cognitive ability and social functioning. For instance, infants with a stronger early preference towards social over nonsocial stimuli are better able to detect others' gaze and understand their intention later in life (around 4-years old) and have more adaptive social behavior [67–69]. Children with greater detection of other's gaze from 15 to 34 months of age also have better social skills at age 5 [70]. Additional evidence suggests that the association between social preference and social behavior can be observed beyond childhood. Two cross-sectional studies of young adults found that individuals with greater sensitivity to social over nonsocial stimuli had better self-reported social functioning [5, 71].

As reviewed earlier, findings in schizophrenia indicate that patients have a disruption in social preference. Mounting evidence from animal studies demonstrates the crucial role of NMDAR hypofunction and associated dysregulated GABAergic functioning in disrupted social preference. These are key neurobiological components of prominent theories of the pathophysiology of schizophrenia. Putting these somewhat disparate findings together, we propose a multi-level heuristic model in which reduced NMDAR function leads to disrupted social preference, which in turn leads to diminished social interaction (Figure 2). In this model, the reduced social interaction preempts effective development of social cognitive skills in individuals with schizophrenia, ultimately resulting in social dysfunction. We believe that the effect of disrupted social preference on social cognitive skills and social interaction starts early in life, and continues in an interactive fashion throughout the life span. We hypothesize a bi-directional influence between diminished social interaction and less effective development of social cognitive skills, such that individuals with poor social cognitive skills engage in fewer social interactions, further hindering the development of social cognitive skills and efficient social functioning.

This model is consistent with several prominent features of schizophrenia. For example, one would expect to see diminished social interaction and less effective social cognitive

development at early life among those who later develop schizophrenia. Indeed, it is well established in both prospective and retrospective studies that children who were less sociable than matched controls at a young age are more likely to later develop schizophrenia [72–74]. Similarly, compared to a typically developing cohort, individuals who were considered to be in the psychosis spectrum showed a development delay that was larger in social cognition than other types of cognition, starting as early as 8 years old [75]. A disproportionate impairment of social cognition versus nonsocial cognition is also observed over the course of illness [76, 77]. There is also indirect evidence for the association between disrupted social preference and reduced social cognition in schizophrenia. When performing a mentalizing task, a measure of social cognition, patients paid significantly less attention to gaze orientation of cartoon characters than they did to objects in cartoon, a pattern not shown by healthy controls. Further, the reduced gaze orientation in patients explained their poor performance on the mentalizing task [78].

Other neuropsychiatric disorders aside from schizophrenia have marked social dysfunction. Hence, the proposed model may be more broadly applicable. For instance, autism spectrum disorder is another neurodevelopmental disorder that is also characterized by severe social dysfunction. Relevant to this discussion, individuals with autism spectrum disorder show a performance pattern consistent with disrupted social preference [79–81] as well as impairments on various social cognitive tasks [82–84]. There is also longitudinal evidence linking social preference to social functioning in autism spectrum disorder; children with autism spectrum disorder who could better detect others' gaze during early childhood (around 4 years old) later showed better social functioning in adulthood [85]. However, the types of social cognitive deficits in schizophrenia and autism spectrum disorder may be distinct, though the findings are not consistent. Both groups showed similar levels of impairment on social cognitive tasks using visual stimuli [83, 84, 86], but individuals with autism spectrum disorder do not always show impairment on auditory social cognitive tasks [82, 86]. Thus, it remains to determine the extent to which the proposed model is applicable to other disorders with social impairment.

It should be noted that NMDAR hypofunction has been implicated in other processes in schizophrenia that could also lead to social dysfunction (Figure 2). For instance, NMDAR antagonists induces features similar to negative symptoms (e.g., blunted affect and social withdrawal) in healthy individuals [87] and negative symptom is a key determinant of social dysfunction in schizophrenia [88]. Similarly, NMDAR hypofunction is associated with impairments in early visual and auditory processing [37, 89], both of which are associated with impaired social cognition in schizophrenia [90, 91]. By focusing on one aspect that has received little attention in schizophrenia, namely disrupted social preference, this study provides one plausible pathway that links NMDAR hypofunction to social disability through disrupted social preference and raises a possibility that this model may be applicable to other disorders with social disability, such as autism spectrum disorder.

Concluding remarks

We evaluated whether social preference, a key aspect of social processing that has been largely overlooked in schizophrenia research, and NMDAR dysfunction could provide

insight into potential mechanisms underlying social dysfunction in schizophrenia. Based on available evidence in developmental neuroscience, behavioral neuroscience, and clinical science, we proposed a heuristic model in which reduced NMDAR function in schizophrenia is associated with disrupted social preference, and this disruption is, in turn, associated with social cognitive impairment and social disability. This model is consistent with several prominent features of schizophrenia although this model has not yet been empirically tested (see outstanding questions). We believe that this model provides one potential mechanism underlying social disability in schizophrenia by allowing us to view social disability in the context of current pathophysiological theories of the illness. In addition to testing the model in a systematic way, it remains to be determined whether this model is more relevant to certain groups of patients (e.g., those with severe social disability) considering that schizophrenia is regarded as a highly heterogeneous disorder. This model may be also applicable to other disorders with severe social disability. Finally, this model has treatment implications for improving social cognitive impairments and social disability in schizophrenia. Drugs targeting NMDAR hypofunction or GABAergic dysregulation normalized disrupted social preference in mice [56, 60] and pharmacological agents with similar mechanisms of action may have positive effects on disrupted social preference, social cognitive impairments, and social disability in schizophrenia.

Acknowledgments

The authors wish to thank Jonathan K. Wynn and Gerhard S. Helleman for helpful comments on an earlier version of the draft. This work is supported by MH102567 (JL), Brain & Behavior Research Foundation NARSAD Young Investigator Award (JL) and MH087618 (MFG). Dr. Green has served as a consultant for AbbVie, ACADIA, DSP, Forum, and Taketa, been on a scientific board for Luc, and received research support from Amgen and Forum.

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

Interneuron

a type of neuron that is important for creating neural circuits and is involved in reflexes, neural oscillations, and neurogenesis in the brain

Near-infrared spectroscopy

a noninvasive brain imaging method that assesses chromophore concentration of hemoglobin and deoxygenated hemoglobin in the brain using near-infrared light

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.

Optogenetic

a neuromodulation method that involves the use of light to control neurons that have been genetically modified to be sensitive to light

Gamma-aminobutyric acid (GABA)

an inhibitory neurotransmitter in the brain that is involved in reducing neuronal excitability

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

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Text Box 1**Schizophrenia and poor social functioning**

Schizophrenia is a chronic mental illness, affecting approximately 0.7 percent 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 (5th and 6th, 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 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].

Outstanding Questions Box

- Is disrupted social preference in schizophrenia related to indirect measures of reduced NMDAR function in the brain such as the levels of glutamate or glutamine assessed with magnetic resonance spectroscopy?
- Does the relationship between disrupted social preference, social cognitive skills, and social disability change over the course of illness in schizophrenia? That is, would similar relationship be present among individuals at high-risk for developing schizophrenia, individuals with recent-onset schizophrenia and individuals with chronic schizophrenia?
- Is it possible to test the hypothesized causal relationship between disrupted social preference, social cognitive skills and social disability in the proposed model with a longitudinal study on individuals at high-risk for developing schizophrenia or individuals with recent-onset schizophrenia?
- Can pharmacological compounds that modulate NMDAR hypofunction improve disrupted social preference and thereby reduce social disability in schizophrenia?
- Are other abnormalities that are linked to NMDAR hypofunction, such as increased resting state connectivity, increased neuroinflammation and abnormal neural plasticity, related to disrupted social preference in schizophrenia?
- Is the proposed heuristic model that includes relationships among NMDAR hypofunction, disrupted social preference and social disability applicable to other neuropsychiatric disorders with marked social disability (e.g., autism) as well as non-clinical samples with similar problems (e.g., social isolation)?

Trends Box

- 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 nonsocial 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 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.

Figure 1.

A) The Y axis represents threat ratio index, in which values greater than 1 indicate faster detection for threat-related stimuli than non-threat-related stimuli. When detecting threat-related stimuli, healthy controls showed a higher threat ratio index for social stimuli than nonsocial stimuli. However, schizophrenia patients showed similar levels of threat ratio index across nonsocial and social stimuli (adapted from [29]). B) Bar graphs show the amount of time a test mouse (either NR1-knockdown mice or wild-type mice treated with MK801) spent around a strange mouse versus a nonsocial stimuli on a three-chamber task over a 10-minute period. The NR1-knockdown mice spent less time around a strange mouse compared to wild type mice (left panel). Similarly, mice treated with NMDAR antagonist, MK801, spent less time around a strange mouse compared to mice treated with saline (right panel). (** $p < .005$, Student t test) (Adapted from [57]).

Figure 2.

In this heuristic model for social disability in schizophrenia (parts depicted in brown), reduced N-methyl-D-aspartate receptor (NMDAR) function leads to disrupted social preference, which in turn leads to diminished social interaction. In this model, diminished social interaction hinders effective development of social cognitive skills in individuals with schizophrenia, ultimately leading to social disability. The effect of disrupted social preference on social cognitive skills and social interaction is hypothesized to start early in life and continues in an interactive fashion throughout the life span. Previous studies suggested that reduced NMDAR function might influence social disability through negative symptoms and through impaired early sensory processing (parts depicted in green).