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Review

Neurobiology and treatment of social cognition in schizophrenia: Bridging the bed-bench gap

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ABSTRACT

Social cognition refers to the psychological processes involved in the perception, encoding, storage, retrieval, and regulation of information about others and ourselves. This process is essential for survival and reproduction in complex social environments. Recent evidence suggests that impairments in social cognition frequently occur in schizophrenia, mainly contributing to poor functional outcomes, including the inability to engage in meaningful work and maintain satisfying interpersonal relationships. With the ambiguous definition of social cognition, the neurobiology underlying impaired social cognition remains unknown, and the effectiveness of currently available intervention strategies in schizophrenia remain limited. Considering the advances and challenges of translational research for schizophrenia, social cognition has been considered a high-priority domain for treatment development. Here, we describe the current state of the framework, clinical concerns, and intervention approaches for social cognition in schizophrenia. Next, we introduce translatable rodent models associated with schizophrenia that allow the evaluation of different components of social behaviors, providing deeper insights into the neural substrates of social cognition in schizophrenia. Our review presents a valuable perspective that indicates the necessity of building bridges between basic and clinical science researchers for the development of novel therapeutic approaches in impaired social cognition in schizophrenia.

1. Introduction

Schizophrenia is a complex psychiatric disorder characterized by disruptions in various domains, including perception, emotions, and cognition. Since the introduction of the first antipsychotics, they have been widely used to manage positive symptoms, such as hallucinations, delusions, and disorganized behavior. However, recent clinical evidence has suggested that cognitive dysfunction is the core feature of the illness and an important domain with respect to treatment in schizophrenia for the following reasons (Kahn and Keefe, 2013). First, it has been reported that cognitive impairments are highly prevalent in schizophrenia; 75%-85% of patients with schizophrenia exhibit poor cognitive performance, and family members who have not developed schizophrenia also show mild cognitive dysfunction (Keefe and Fenton, 2007; Reichenberg et al., 2006), suggesting that cognitive impairments are attributable to genetic liability for the illness (Fromer et al., 2016; Hilker et al., 2018; Kavanagh et al., 2015). Second, it has been reported that certain domains of cognitive function decline before the onset of psychotic symptoms and that cognitive dysfunction progressively deteriorates during the course of the disease (Reichenberg et al., 2010). Finally, it is considered that the degree of cognitive dysfunction, rather than the psychotic symptoms, reflects the long-term functional outcomes of patients (Green, 2006).

Cognition can be further divided into neurocognition and social cognition due to differences in roles (van Hooren et al., 2008). Historically, impairments in neurocognitive functions characterized by task processing, such as attention, memory, and executive functioning, have been studied in schizophrenia in relation to functional outcomes, such as community outcomes, social problem solving, and psychosocial skill acquisition (Green et al., 2000; Tolman and Kurtz, 2012; Ventura et al., 2009). However, social cognition has recently gained considerable interest as the ultimate goal of schizophrenia treatment. In general, social cognition refers to how people detect, process, and utilize social information, which provides individuals with the capacity to understand the social world and interact successfully with others (Adolphs, 2001; Penn et al., 1996). Therefore, in patients with schizophrenia, impairments in social cognition appear to affect social, educational, and occupational functioning and the attainment of meaningful interpersonal relationships (Green et al., 2008). Notably, recent studies using structural equation modeling and path analysis have shown that social cognition explains more functional outcome variance than neurocognition (Bowie et al., 2006; Brekke et al., 2007; Fett et al., 2011;

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Kee et al., 2003; Sergi et al., 2007; Vauth et al., 2004), suggesting that treatment of impairments in social cognition can be a high priority to promote functional change in patients with schizophrenia. Accordingly, several researchers have recently discussed and evaluated the use of pharmacotherapy or psychosocial therapy in patients with schizophrenia in order to improve not only neurocognition but also social cognition, which is associated with functional outcomes (Brekke et al., 2007; Buonocore et al., 2018; Couture et al., 2006; Matsuda et al., 2018; Vingerhoets et al., 2013). Despite the medical importance of this domain, development of interventional strategies remains limited due to the inconsistent definitions and complex biological bases of social cognition. Therefore, investigation of neurobiological mechanisms underlying social cognitive impairments and the development of appropriate quantitation methods and therapeutic treatments for social cognitive dysfunction have been the focus of basic and clinical research. In this review, we describe social cognition and schizophrenia, the degree of impaired social cognition in schizophrenia, and the current interventional approaches for impaired social cognition in schizophrenia, highlighting how social cognition became a focus of public health concern and a priority topic within treatment development in schizophrenia. In addition, for the identification and development of therapeutic approaches, it is essential to not only elucidate the neurobiological basis of impairments in social cognition, but also develop translatable brain markers relevant to social cognition in humans and in rodents (Okano et al., 2015). Therefore, we have reviewed information on behavioral abnormalities relevant to social cognition and the potential molecular basis underlying impaired social cognition in rodent models. Since impairments in social cognition are intricately affected by genetic and environmental factors during brain development (Abel et al., 2003; Azar et al., 2017; Fluharty et al., 2018; Germine et al., 2016; Moieni and Eisenberger, 2018; Pin et al., 2009; Riglin et al., 2017), studies using translatable rodent models to track social cognitive deficits can provide valuable insights for future translational research that will ultimately inform the construction of targeted interventions, which might reduce the severity of, or alter the trajectory of impaired social cognition in schizophrenia.

2. Social cognition in schizophrenia

Social cognition is defined as “a cognitive process that is fundamental to interpersonal relationships, including the human ability to understand the intentions and characters of others (Adolphs, 2001).” Patients with schizophrenia have been consistently reported to show impairments in social cognition (Couture et al., 2006), and advances in the early identification of individuals who are at either a clinical or genetic risk of developing schizophrenia have shown that these impairments are present even in the prodromal phase of the illness (Devoe et al., 2018; Pinkham, 2014). Importantly, it has been suggested that these impairments may largely affect social functioning and functional outcomes, such as interpersonal relationships, employment/school attendance, or independent living (Sergi et al., 2007). However, recent advance in this area remains limited because of ambiguous and inconsistent terminology, and the difference in measurement approaches. Thus, at the National Institute of Mental Health workshop in 2006 (Green et al., 2008), social cognition in schizophrenia was proposed to be grouped into five subdomains, as a prioritized research area:

(1) Theory of mind: The theory of mind (ToM) is the ability to infer the mental states of others and to understand that others have beliefs that are different from one’s own (Baron-Cohen et al., 2001). This includes the ability to understand the intentions and beliefs of others, idioms, figurative language, and sarcasm (Caillies and Le Sourn-Bissaoui, 2013; Happe, 1993; Whyte et al., 2014). Deficits in ToM may lead to misreading or failure to read emotions, intentions, or cues from others, resulting in the difficulties in social communication and limited expression of empathy toward others. ToM deficits may also result in one approaching a social situation with assumptions that may not be accurate (Senju, 2012). Therefore, it has been stated that impairment in ToM is suggested to be at the core of many behaviors associated with autism spectrum disorder (ASD) (Korkmaz, 2011). It is thought that abnormalities in this process can account for the development of clinical symptoms of schizophrenia (Brune, 2005; Leitman et al., 2006).
(2) Social perception: Social perception is the ability to understand and assess social rules, roles, and context by using verbal or nonverbal cues in order to make inferences about a social situation (Penn et al., 2002). Social perception may allow one to facilitate interactions with people in social settings or establish relationships. It may also involve making critical appraisals, such as judgements of trustworthiness in other people. Therefore, abnormalities in social perception were reported to be strongly associated with social functioning in schizophrenia (Sergi et al., 2006).
(3) Social knowledge: Social knowledge is the awareness of rules, roles, and goals that characterize interpersonal relationships in social situations or in society (Corrigan et al., 1992; Subotnik et al., 2006). Thus, social perception and social knowledge are often considered together under the domain of social perception; successful social knowledge requires awareness of what cues occur typically in specific social situations (i.e., social perception) and how one is supposed to respond to them (Green et al., 2008). Social knowledge is viewed as an initial step and prerequisite for adequate social competence (Bellack et al., 1994), and thus has been targeted at the first stage of intervention to acquire sociability (Hansen et al., 1985).
(4) Attributional bias: Causal attribution is considered a cognitive framework that humans utilize for inferring or judging the reasons for others’ behaviors or social phenomena. Human behavior can be generally attributed to two types of factors: internal factors such as their own abilities and intentions, and external factors such as situations and contingency (Kelley, 1973). In brief, an attributional bias refers to a bias in attributing a cause to either an internal factor or an external factor. Subjects with schizophrenia tend to show a stronger bias towards external-personal style when explaining negative events, and toward internal-personal style when explaining positive events (Bentall et al., 1991).
(5) Emotional processing: Emotional processing is to perceive, control, and use emotions (Rachman, 1980). An influential model of emotional processing defines emotional intelligence as an asset of four elements (Kohler et al., 2000), including identifying emotions, facilitating emotions, understanding emotions, and managing emotions. This model includes affect perception that is frequently assessed in schizophrenia (Mayer et al., 2001; Salem et al., 1996).

3. Neural basis of social cognition in schizophrenia

Previous studies have suggested that social cognition and neurocognition are largely distinct at the behavioral and neural circuit levels (Green et al., 2015). While the amygdala has been historically emphasized as an important structure that contributes to social behavior (Kluver and Bucy, 1997), Brothers et al. described the human brain network that processes social information as the “social brain (Brothers, 1999).” Thereafter, several studies have determined the neural basis of the social brain using neuropsychological assessments in brain lesion studies and neurophysiological and neuroimaging analyses in healthy controls as well as patients with psychiatric illness. Indeed, multiple brain areas, responsible for the neural activities constituting every subdomain of social cognition, have been reported to be of interest (Green et al., 2015). In fact, various ToM tasks have been studied, including story and cartoon comprehension in social situations. Several brain regions have been consistently suggested as the neural basis of ToM, included the medial prefrontal cortex (PFC), superior temporal sulcus (STS), temporal poles, and the precuneus and temporoparietal

junctions (TPJ) (Amodio and Frith, 2006; Brunet-Gouet and Decety, 2006; Schurz et al., 2014). Previous lesion studies have suggested that the medial PFC and STS appear to play central roles in social perception and social knowledge (Hornak et al., 1996; Koenigs et al., 2007; Pelphrey and Carter, 2008). The ability to recognize emotions from a facial expression or to recognize emotional facial expressions is thought to be mainly associated with the fusiform gyrus (FG), amygdala, STS, PFC and anterior cingulate cortex (Fujiwara et al., 2015; Morris et al., 1998; Motzkin et al., 2015; Ochsner et al., 2012; Quirk and Beer, 2006; Whalen et al., 1998). Since facial expression is often used to communicate emotion, the aforementioned regions are also linked to emotion processing (Gur et al., 2002b; Pinkham, 2014). Finally, it has been demonstrated that the TPJ, precentral gyrus, precuneus, ventrolateral PFC, dorsomedial PFC, and insular cortex may at least in part be involved in attributional biases (Blackwood et al., 2003; Blackwood et al., 2000; Cabanis et al., 2013; Seidel et al., 2010). As a matter of course, it should be noted that social cognition is formed not only by the action of the specific local site in the brain, but also by the extensive and complex network activity in the brain.

In parallel with investigating the neural basis for social cognition, several structural and functional imaging studies have provided knowledge of the relationship between impaired social cognition and brain abnormalities in schizophrenia (Bellani and Brambilla, 2008; Pinkham et al., 2008a; Viviano et al., 2018). However, results concerning amygdala function appeared complex, and current work indicated that patients with schizophrenia reveal an increased amygdala response to neutral, rather than emotional stimuli (Anticevic et al., 2012) and that amygdala function may differ across disease states of schizophrenia (Fahim et al., 2005; Gur et al., 2007; Li et al., 2010; Russell et al., 2007; Williams et al., 2004). Findings concerning the STS have also produced mixed results, with some noting no differences (Brunet et al., 2003; Li et al., 2010; Pinkham et al., 2008b) in activation, while at least one other group has found increased activation relative to controls (Mier et al., 2010). Furthermore, neuroimaging studies during ToM tasks have been extensively performed using patients with schizophrenia; however, investigations on schizophrenia are inconsistent and revealed decreased and increased activation in ToM-related brain regions (Andreasen et al., 2008; Benedetti et al., 2009; Brune et al., 2008; Brunet et al., 2003; Lee et al., 2011a; Pedersen et al., 2012; Walter et al., 2009). Therefore, meta-analytic approaches could provide an essential support in understanding the neural basis for abnormalities in ToM and other subdomains in schizophrenia (Jani and Kasparek, 2017; Kronbichler et al., 2017; Li et al., 2010; Sugranyes et al., 2011; Taylor et al., 2012). Alternatively, the diversity of neuroimaging findings might be, at least in part, associated with the relatively small-sized, heterogeneous patient groups or with the different tasks assessing social cognitive domains across the individual studies (Kronbichler et al., 2017). A future study using larger samples with improved psychological assessments would be required to characterize specific brain circuitry and networks associated with impaired social cognitive functioning in schizophrenia.

4. Assessment and degree of social cognition in schizophrenia

Social cognition is a relatively new subfield in the treatment of schizophrenia; thus, appropriate methods for the assessment of this function are limited. For example, the Facial Emotion Identification Test (Kerr and Neale, 1993), Facial Emotion Discrimination Test (Kerr and Neale, 1993), and Penn Emotion Recognition Test (ER-40) (Gur et al., 2002a) have been administered to assess difficulty in recognizing facial emotion in patients with schizophrenia. Within these batteries, the ER-40 is widely used in several clinical settings (Barbato et al., 2015; Gur et al., 2006; Gur et al., 2002c; Pinkham et al., 2018; Rose et al., 2015; Ruocco et al., 2014) and has been nominated as one of the promising candidates for measuring emotion identification and response in schizophrenia (Carter et al., 2009). In addition, the Social Cognition Screening Questionnaire (SCSQ) was developed to measure multiple domains of social cognition and differentiate performance in these domains from non-social cognition. The SCSQ, which can measure non-social domains of verbal memory and schematic inference, as well as the social cognitive domains of ToM, metacognition, and hostile attributional biases, have been suggested to provide comprehensive and efficient measurements of social cognition in schizophrenia (Kanie et al., 2014; Roberts et al., 2011). In recent years, the MATRICS Consensus Cognitive Battery has been widely used to investigate the effects of antipsychotic drugs and psychosocial therapies in social cognition (Vingerhoets et al., 2013) because this battery includes the assessment of neurocognition and social cognition (Green et al., 2005).

The magnitude of impairment of social cognition in schizophrenia has been assessed elsewhere in clinical settings. Savla et al. conducted a meta-analysis based on peer-reviewed studies to compare the effect size (ES) across multiple domains of social cognition between schizophrenia patients and healthy controls (Savla et al., 2013). The mean effect for ToM was large (Hedges' g [ES(g)] = 0.96). The mean effect for social perception was also large ([ES(g)] = 1.04), and the impairment was more severe in hospitalized patients than in outpatients. The mean effect for social knowledge was moderate ([ES(g)] = 0.54) and there were insufficient effects on attributional biases between the two groups. Finally, the mean effect of emotional processing was large ([ES(g)] = 0.88), with a longer duration of the disease associated with a more severe impairment. Heterogeneity in effect sizes between studies within the domains was not accounted for by age, sex, education, or language in the schizophrenia samples. On the other hand, Lee et al. conducted the meta-analysis based on databases as well, comparing the same domains of social cognition between the patients with prodromal psychosis and healthy controls (Lee et al., 2015), indicating that the overall ES of social cognition was medium ([ES(g)] = -0.48). For the subcategories, the ES for attributional biases was the largest ([ES(g)] = -0.78), followed by emotional processing ([ES(g)] = -0.45), ToM ([ES(g)] = -0.43), and social perception ([ES(g)] = -0.38). Previous studies have extensively focused on ToM and emotional perception, but the aforementioned studies may be interesting because impairments in social cognition are present in patients with schizophrenia and are apparent in the prodromal psychosis group. In addition, the ESs for social perception and emotional processing are relatively large in patients with schizophrenia while the ESs might vary depending on the subcategory of social cognition across disease trajectories of schizophrenia. Previous studies suggest that social cognition is considered to have important and identifiable developmental trajectories (Frith and Frith, 2007; Lincoln et al., 2017). Since it is reported that social cognition appears to be influenced by interaction with genetic factors (Lavoie et al., 2013) and social experiences (Gabinio et al., 2018), future long-term longitudinal studies on the course of social cognition changes between patients with the prodromal psychosis, who later convert to schizophrenia or not, may give a new insight into preemptive or presumptive therapy.

5. Clinical interventions for impaired social cognition in schizophrenia

The goal of treatment for schizophrenia is not only to improve psychotic symptoms, but also to restore viability and social functioning. Therefore, a patient is expected to live a satisfying independent life, to have a job, and to recover social functioning necessary and sufficient to build human relationships in a local community. In other words, it is considered necessary to improve not only neurocognition, but also social cognition, which leads to improvement of social functioning. In recent years, several researchers have attempted pharmacological interventions and psychosocial therapeutic interventions for impairments in social cognition.

Table 1
Representative social cognitive rehabilitation programs

Targeted domain	Program name	Abbreviation	Outcome
Targeted programs for social cognition			
Affect recognition	Training of affect recognition	TAR	*(Habel et al., 2010)
Social recognition	Social cognition enhancement training	SCET	*(Choi and Kwon, 2006)
ToM	Instrumental enrichment program	IEP	*(Roncone et al., 2004)
ToM	Emotion and ToM imitation training	ETIT	*(Mazza et al., 2010)
Metacognition	Metacognitive training	MCT	*(Moritz et al., 2013)
Comprehensive programs for social cognition			
Comprehensive	Social cognition and interaction training	SCIT	*(Combs et al., 2007; Roberts and Penn, 2009)
	Social cognitive skill training	SCST	*(Horan et al., 2011)
Integrated programs for social-neurocognition			
Integrated	Integrated psychological therapy	IPT	*(Roder et al., 2011)
	Neurocognition enhancement therapy	NET	*(Bell et al., 2001)
	Cognitive enhancement therapy	CET	*(Eack et al., 2009)
	Integrated Neurocognitive Therapy	INT	*(Mueller et al., 2015)

Abbreviations: ToM, theory of mind.

5.1. Pharmacological interventions in clinics

In order to improve social cognition affecting social functional outcomes, the effects of currently available antipsychotic drugs (especially, atypical antipsychotic drugs) and new therapeutic drugs on social cognition have been examined in several clinical trials (Kucharska-Pietura and Mortimer, 2013). Mizrahi et al. reported that ToM was improved 2 weeks after the administration of clozapine, risperidone, olanzapine, or loxapine (Mizrahi et al., 2007). Sumiyoshi et al. reported that the score of social cognition was improved with the administration of perospirone (Sumiyoshi et al., 2009), and Behere et al. reported that the evaluation task performance in emotion recognition was improved with the administration of risperidone (Behere et al., 2009). Furthermore, Kucharska-Pietura et al. reported that the improvement effect on social cognition is expected to be higher with clozapine than with other atypical antipsychotic drugs (Kucharska-Pietura and Mortimer, 2013). While the mechanism of antipsychotic effects for social cognition remains unknown, catecholamine neurotransmitters, such as serotonin and dopamine, may be involved in the improvement of social cognition. For example, it has been suggested that atypical antipsychotics have a strong affinity for 5-HT2 receptors via the disinhibitory effect of serotonin antagonism on dopamine release in the PFC, likely contributing to improvement in emotional perception and social functioning (Kapur and Remington, 2001). Antipsychotics also affect dopamine regulation in the mesocorticolimbic system, which suggests the potential effect for regulating the amygdala as an emotional manager (Salgado-Pineda et al., 2005). However, there are some negative opinions on the effects of currently-available antipsychotic drugs on social cognition, partly because the bias in clinical trials, such as the number of test samples and lack of long-term assessment, has been indicated. Further investigation using larger samples is required to validate previous findings.

It is expected that cognitive dysfunction involves abnormal activity of the GABA neurons of the PFC (Kimoto et al., 2014), and Buchanan et al. have been investigating the potential of a GABA neuroactive drug for the improvement of social cognition (Buchanan et al., 2011). However, they have reported no improvement in the endpoints of social cognition when MK-0777, a partial agonist of GABAα2/α3, was administered in addition to an antipsychotic drug. This may suggest that improvement in GABA signaling alone cannot provide adequate improvement in social cognition. Finally, the most promising candidate with a clinical potential to improve social cognition is a neuropeptide, since preclinical and clinical evidence have identified various neuropeptides, also termed 'social neuropeptides', which could modulate social behaviors regulated by social brain networks (Meyer-Lindenberg et al., 2011). Neuropeptides, which are widely expressed in the brain, not only directly function as neurotransmitters, but also function as neuromodulators by regulating dopamine, glutamate, serotonin, and GABA neurotransmissions. Indeed, oxytocin, vasopressin, and the corticotropin-releasing factor family have been extensively investigated, and their potential roles relevant to social cognition by using pharmacological and genetic manipulations in rodents has been determined (LaCrosse and Olive, 2013). In contrast, studies of neuropeptide expression levels in schizophrenia have yielded mixed results, with some studies indicating altered levels and others finding no differences compared with controls (Caceda et al., 2007). Studies utilizing nasal administration of oxytocin to patients with schizophrenia have provided inconsistent results with respect to the improvement in social cognition (Jarskog et al., 2017; Pedersen et al., 2011). Therefore, ongoing research into the biological relationship between oxytocin and social cognitive deficits in schizophrenia is warranted to determine future clinical uses of neuropeptides on social functional outcomes of patients with schizophrenia.

5.2. Psychosocial therapeutic intervention in clinics

Numerous studies have evaluated the efficacy of psychosocial therapeutic investigations for impairments in social cognition. Currently, clinicians tend to develop psychosocial training programs that can remediate cognitive functions with better functional outcome in schizophrenia, based on the idea that cognitive deficits in schizophrenia are not permanent disabilities (Green and Harvey, 2014). Hence, cognitive remediation therapy has been developed as a relatively new intervention approach that aims to enhance cognitive processes (attention, memory, executive function, social cognition, or metacognition) with the goal of durability and generalization (Wykes and Spaulding, 2011). As shown in Table 1, currently available psychotherapeutic programs for social cognition may be classified as three theoretical foundations. The first program type, called targeted programs, is more specific. Each one targets a specific domain of social cognition, such as ToM or emotional recognition. The second type is comprehensive programs, which try to consider all components of social cognition that are impaired in schizophrenia. Finally, integrated programs are the earliest intervention type and are based on the idea that the acquisition of basic cognitive skills increases relational competency. Considering social cognition and neurocognition as independent domains in schizophrenia, there are also comprehensive programs dealing with both neurocognitive functions and social functions. For example, Iwata et al. have reported that cognitive remediation therapy using a computer software program, Cogpack (Japanese version), yields higher significant improvement in cognitive function and social functioning in a cognitive remediation group than in a usual

treatment group (Iwata et al., 2017). Furthermore, Kurtz and Richardson performed a meta-analysis to examine the effects of previously conducted social-cognitive training programs, geared toward one or more areas of social cognition and which measured at least one category of social cognition (Kurtz and Richardson, 2012). They found that social-cognitive training programs provided the moderate-large effect on emotional processing and the small-moderate effect in ToM, whereas effects on social perception and attributional bias were not significant. Another meta-analysis has indicated a similar tendency, and raised awareness of the potential experimental design concerns of previous studies, including measure heterogeneity, modest methodology, and short follow-up periods (Grant et al., 2017). Collectively, current social cognitive rehabilitation does appear to have certain beneficial effects, although future studies using larger cohorts are required to determine how each patient should be treated, and how to identify the appropriate assessment methods and program contents that should be formulated for individual, distinctive impairments in social cognition.

6. Translatable rodent models of social cognition associated with schizophrenia

The development of rodent models that can comprehensively demonstrate schizophrenia-like behavior may prove highly informative and help delineate neurobiological mechanisms and identify novel therapeutic targets for impaired social cognition in schizophrenia. However, modeling of the symptoms of schizophrenia in rodents, particularly those associated with social cognition, may be a challenge owing to the poor understanding of the etiology and pathophysiology of the illness, and because these involve highly sophisticated domains in humans. No single behavioral paradigm in rodents collate the multidimensional nature of social cognition, but it is thought that common fundamental functions exists, while they are achieved in species-specific ways. Based on such, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia initiative has recommended behavioral tasks, based on various cognitive domains, including social cognitive constructs based upon several criteria (e.g.; construct validity, cross-species homology, translatability, reliability, and reproducibility) (Millan and Bales, 2013). Recently, evidence has suggested a translatable perspective of social cognition and measurable social behaviors that play an essential role in rodents and humans (Bicks et al., 2015). For example, social recognition is a part of knowledge of self and others, and is an important construct for other forms of social cognition, such as empathy and moral decision-making. The ability to recognize the facial emotions of others is reported to be impaired in patients with schizophrenia (Edwards et al., 2002; Kohler et al., 2010). Empathy, which is in part associated with ToM, is also compromised in schizophrenia, leading to difficulties in social communication (Lee et al., 2011b). In addition, deficits in social cognition may be associated with disengagement from social interaction, resulting in reduced motivation to engage in social relationships (Brune et al., 2007; Green et al., 2008; Sergi et al., 2007). Impairments in social cognition may also lead to high levels of social anxiety and facilitate the co-occurrence of depressive symptoms through social withdrawal and reduced social motivation (Achim et al., 2013; Corcoran et al., 2011; Green et al., 2008; Lincoln et al., 2011; Nakagami et al., 2010).

Accordingly, to bridge the translational gap in social cognition between rodent model-based studies and clinical application, the ability of social cognition may be frequently assessed using categorical modes of social behaviors such as sociability, social recognition, social motivation, or empathy in rodent models, although these categories of social cognition may not necessarily be mutually exclusive. In rodents, sociability is typically assessed by placing a pair of unfamiliar rodents in an area with an observer measuring the amount of time for which the animals were engaged with each another. Social recognition, also termed as social novelty discrimination, relies on the ability of the experimental rodent to recognize a conspecific as familiar, indicated by either a reduction of social interaction with the familiar conspecific or preference for socially interacting with a novel conspecific. Social motivation is characterized by the motivation of an animal to approach, explore, and interact with a social target. These social behaviors can be frequently measured with behavioral tasks using the “three chamber test” (Moy et al., 2004), “habituation/dishabituation paradigm” (Dantzer et al., 1987) and “conditioned place preference test” (Tzschentke, 2007). Furthermore, quantifying social empathy is a relatively new idea with respect to rodents. In one procedure (Chen et al., 2009), experimental mice observed distressed conspecifics in a conditioned fear situation and thereafter showed significant changes in heart rate or increased freezing corresponding to the behavior of conspecifics and environmental cues. Comprehensive reviews of the behavioral paradigms can be found in the literature (Bicks et al., 2015; Debiec and Olsson, 2017).

Schizophrenia symptom modeling relies on pharmacological, environmental, and genetic manipulations of preclinical models, in part because exposure to a range of environmental factors in early life, as well as genetic components are suggested to increase the risk for schizophrenia. Although no single animal model precisely represents the complexity, subtlety, and multidimensionality of impaired social cognition in patients with schizophrenia, it is essential to investigate how each component biologically associates with the impaired social cognition commonly observed in schizophrenia. The animal models described here are the currently available models, engineered to identify the behavioral phenotypes and neural bases implicated in the cognitive impairments of schizophrenia (see below and Fig. 1).

6.1. Psychotomimetic effects on social cognition relevant to schizophrenia

Several psychotomimetic agents have been used to model aspects of schizophrenia in animals and in human. Among these agents, phencyclidine (PCP) or dizocilpine (MK-801) are non-competitive NMDA receptor antagonists that elicit psychotic behaviors as well as mimic several negative and cognitive symptoms associated with the disease (Javitt and Zukin, 1991; Luisada and Brown, 1976). Therefore, administration (usually sub-chronic) of PCP or MK-801 to adult rodents has been argued to provide valid pharmacological models for the assessment of social behavior with possible relevance to schizophrenia (Mohn et al., 1999; Neill et al., 2014). For example, exposure to PCP during early and late development has been found to reliably produce long-lasting deficits in sociality in rodents, even when experimental conditions favor social exploration by limiting the effects of anxiogenic response (Gururajan et al., 2010; Sams-Dodd, 1995). In other studies, sub-chronic treatment with PCP in adult rats was shown to decrease social motivation, as measured using a conditioned place-preference test (Schwabe et al., 2006). Repeated administration with PCP to juvenile rats was also shown to induce impairments in social recognition, exhibiting reduced exploration of a novel juvenile in adult male rats (Harich et al., 2007). With respect to the effect of medications, studies on antipsychotics in rodent models of NMDA antagonism have yielded inconsistent results, with some indicating a reversal and others finding no effect on social deficits (Wilson and Koenig, 2014). In addition, the administration of antipsychotics has not indicated any long-term effects of treatment in rodent models of NMDA antagonism. At a cellular level, empirical evidence has indicated that the systemic administration of NMDAR antagonists to rodents increases excitatory neuronal activity while reducing the firing of putative inhibitory neuron in the prefrontal cortex (Homayoun and Moghaddam, 2007). Nevertheless, the molecular mechanisms underlying NMDA hypofunction in schizophrenia remain controversial. Future studies such as those characterizing the effect of NMDA receptor antagonisms at the pre-synaptic and post-synaptic levels may provide valuable insight for understanding the neurobiological basis and developing therapeutic agents for cognitive impairments in schizophrenia (Pafundo et al., 2018).

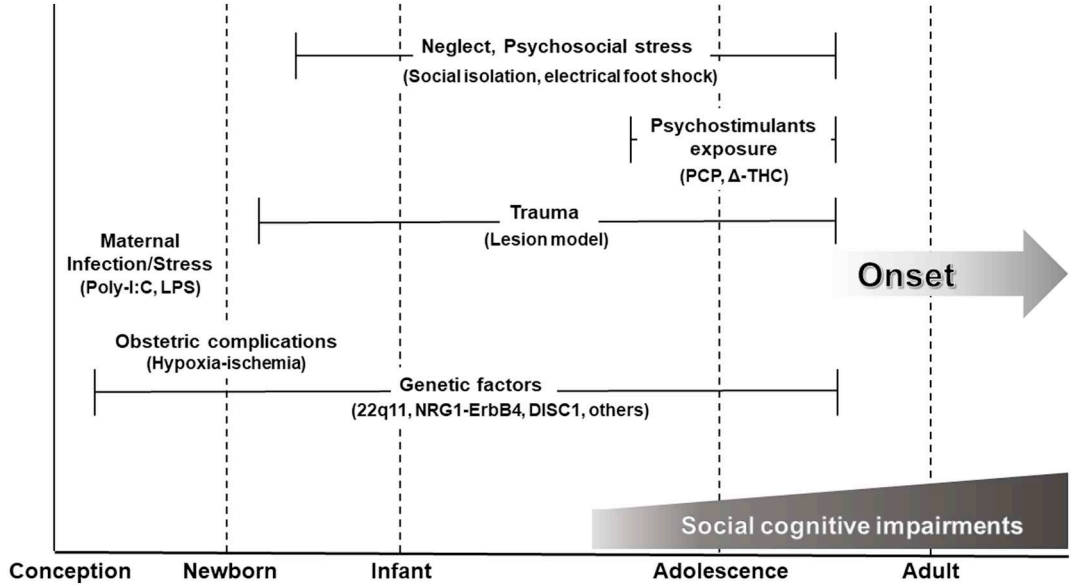

Fig. 1. Schematic representation of the timing of risk factors for social cognition and schizophrenia, and the corresponding rodent models. Exposure to risk factors for social cognition and schizophrenia is detailed from conception through adolescence, and the corresponding rodent models associated with schizophrenia are indicated in parentheses. Abbreviations: Poly-I:C, poly-riboinosinic-polyribocytidylic acid; LPS, lipopolysaccharide; PCP, phencyclidine; Δ-THC, Δ9-Tetrahydrocannabinol; NRG1-ErbB4, neuregulin1-ErbB4; DISC1, Disrupted in schizophrenia 1

6.2. Environmental effects on social cognition relevant to schizophrenia

Maternal infection is well defined by epidemiological studies as a risk factor for neurodevelopmental disorders such as schizophrenia and ASD (Depino, 2013; Hagberg et al., 2012). Several genome-wide association studies have identified variants in genes involved in immune and inflammatory signaling pathways that are associated with schizophrenia (Jia et al., 2010; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Sekar et al., 2016; Shi et al., 2009). In addition, exposure to infections during pregnancy, including evidence of maternal response to infection such as higher serum levels of proinflammatory cytokines (Brown et al., 2004; Rodrigues-Amorim et al., 2017) and inflammatory biomarkers (Canetta et al., 2014; Fond et al., 2018), have shown to be associated with higher rates of schizophrenia in offspring. Accordingly, mouse offspring exposed to maternal immune activation (MIA), which is elicited by poly-riboinosinic-polyribocytidylic acid (Poly-I:C) or lipopolysaccharide (LPS), can reproduce the behavioral, structural, and biochemical abnormalities in schizophrenia (Makinodan et al., 2008; Markham and Koenig, 2011; Scola and Duong, 2017), suggesting that the MIA model triggered by infection is useful in the investigation of the pathophysiology of schizophrenia (Meyer et al., 2005). For instance, administration of Poly-I:C in later pregnancy exhibited deficits in social recognition and anhedonic behavior in both male and female offspring, with alterations in basal neurotransmitter levels (Bitanihirwe et al., 2010). Another study found that prenatal exposure to LPS early in pregnancy is linked with a significant reduction in affiliative/motivational social interaction in male rats (Kirsten et al., 2010). Furthermore, offspring of pregnant rats administrated Poly-I:C in later pregnancy showed alterations in a communicative behavior as measured using ultrasonic vocalizations (Yee et al., 2012), while offspring of pregnant rats administrated Poly-I:C early in pregnancy showed small changes in emotional contagion, a component of the empathy domain (Gonzalez-Liencres et al., 2016). These data suggest that MIA induces different phenotypes depending on the time of the exposure. In addition, future studies determining the molecular pathways that mediate the resulting neuropathology and abnormal behaviors in MIA rodent models would serve as targets for development of new therapeutics.

During postnatal development, sustained early life stress, such as social isolation rearing or living in densely populated cities, has been implicated as risk factors for psychiatric illnesses such as schizophrenia (Cacioppo and Hawkley, 2009; Krabbendam and van Os, 2005; Mizrahi, 2016). Childhood traumatic experiences such as physical neglect and emotional abuse were also associated with functional and social impairment in adult patients with schizophrenia (Gallagher 3rd and Jones, 2016; Gil et al., 2009). In addition, social withdrawal or asocial tendencies are widely accepted as clinical manifestations of patients with schizophrenia (Sarkar et al., 2015). Accordingly, the post-weaning social isolation models in rodents have been extensively examined, exhibiting behavioral abnormalities with some potential relevance for schizophrenia (Robbins, 2016). Furthermore, it has been suggested that the knowledge of the critical time window that is most vulnerable to inducing social isolation is important to clarify the effect of social isolation on social behavior, as previous studies have produced inconsistent results regarding social behavior in isolation-rearing models (Meng et al., 2010). For example, Makinodan et al. reported that mice isolated for 2 weeks immediately after weaning developed deficits in sociability and working memory, and hypomyelination in the deep layers of the prefrontal cortex (Makinodan et al., 2012). These alterations were also characterized by reduced excitatory synaptic inputs to a subtype of pyramidal cells in the deep layers, which preferentially connect with subcortical regions (Yamamuro et al., 2018). These data suggest that isolation rearing during the critical period of brain development may result in an immature prefrontal network of the brain. This pathological basis may at least in part be attributable to deficits in activity-dependent structural plasticity (Ueno et al., 2017; Van den Heuvel and Pasterkamp, 2008; West and Greenberg, 2011), supporting the notion that disease-related alterations in activity-dependent gene expression could contribute to cognitive impairments in schizophrenia (Kimoto et al., 2014; Kimoto et al., 2015). Since exposure to environmental enrichment is known to positively influence brain plasticity and cognition (Mohammed et al., 2002; van Praag et al., 2000), identifying the molecular substrates of neurobehavioral outcomes, along with highlighting a potential window of opportunity for therapeutic intervention, could support the translatability of rodent models and its potential utility.

6.3. Genetic effects on social cognition relevant to schizophrenia

6.3.1. 22q11 deletion

The 22q11 microdeletion syndrome is the most common copy number variant associated with schizophrenia and accounts for up to 1%–2% of cases (Karayiorgou et al., 2010). It has been well documented that individuals with 22q11DS have poorer social skills (Kiley-Brabeck and Sobin, 2006) and functioning compared to their typically developing peers (Swillen et al., 1999), with morphological brain changes (Mihailov et al., 2017). Norkett et al. reported that patients with 22q11DS had impaired emotion processing and ToM relative to their typically developing peers, while some findings were in part attributable to neurocognitive and intellectual disabilities (Norkett et al., 2017). There is a close homology between human chromosome 22 and portions of mouse chromosome 16, which provides an opportunity to create etiologically valid mutant rodent models (Karayiorgou et al., 2010; Meechan et al., 2015) for studying the 22q11DS deletion. Indeed, several groups have engineered various multigene or single-gene deletion models with respect to this locus and have reported biochemical, anatomical, and behavioral abnormalities relevant to the pathology of schizophrenia and ASD (Kimoto et al., 2012; Lattanzi et al., 2018; Mukai et al., 2008; Paylor et al., 2006; Toritsuka et al., 2013). In particular, septin5 (Sept5), a 22q11.2 locus gene, may play a crucial role in social cognition because Sept5 deficiency in mice has been reported to show impairments in affiliative/motivational social interaction including other behavioral abnormalities (Suzuki et al., 2009). Furthermore, mice overexpressing Sept5 selectively in the amygdala and hippocampus showed elevated levels of active affiliative/motivational social interaction and *vice versa* (Harper et al., 2012). Since previous neuroimaging studies revealed the volume changes in hippocampus and amygdala, or impaired activation in amygdala in patients with 22q11DS (Andersson et al., 2008; Eliez et al., 2001; Flahault et al., 2012; Kates et al., 2006), these data suggest the 22q11.2 gene in these brain regions plays a crucial role in sociability.

6.3.2. Neuregulin 1-ErbB4 signaling

Neuregulin 1 (NRG1), which encodes multiple alternative transcripts that are classified as types I–VI, belongs to the neuregulin family of proteins, sharing a common epidermal growth factor-like domain. Interaction of these domains with membrane-associated tyrosine kinases (ErbB receptors) activates intracellular signaling pathways implicated in important neurodevelopmental processes (Mei and Nave, 2014). Previous studies have shown that NRG1 and its receptor, ERBB4, are associated with genetic susceptibility for schizophrenia (Corfas et al., 2004; Mei and Xiong, 2008). NRG1 gene polymorphism was also reported to be significantly associated with sociality in neurodevelopmental disorders (Yoo et al., 2015). Functionally, NRG1-ErbB4 signaling plays a crucial role in the ontogeny of schizophrenia, and a finding that has been supported by the identification of altered expression levels of NRG1 and ErbB4 in patients with schizophrenia (Chung et al., 2016; Hashimoto et al., 2004; Joshi et al., 2014; Law et al., 2007; Silberberg et al., 2006). Consistent with the results of human studies, several groups have generated gene overexpression/deletion models of NRG1 or ErbB4 in a broad or cell-type specific manner, and they have determined the biochemical, anatomical, electrophysiological, and behavioral abnormalities in rodents relevant to the pathology of schizophrenia. With respect to social cognition, for example, mice selectively overexpressing human NRG1-type IV in neurons exhibit schizophrenia-like behaviors, including impaired social recognition (Papaleo et al., 2016). Deletion of ErbB4 in parvalbumin interneurons (PV-Ins) in mice also show schizophrenia-like behaviors including disrupted social behavior accompanied by lower PV-INs activity (Del Pino et al., 2013). Previous studies have suggested that lower activity of PV-Ins in post-mortem brains has been frequently observed in patients with schizophrenia (Glausier et al., 2014; Lewis et al., 2012), and that loss of PV-Ins function could cause alterations in social behavior in rodents (Brown et al., 2015). Since NRG1-ErbB4 signaling plays a key role in structural and functional plasticity of glutamatergic synapses and regulates GABAergic transmission (Chung et al., 2017; Wen et al., 2010), impairments in social cognition may at least in part be attributable to the altered balance of cortical excitatory-inhibitory neurotransmission (Gao and Penzes, 2015).

6.3.3. Disrupted in schizophrenia 1

Two overlapping and opposite strand genes on chromosome 1, DISC1 and DISC2, are specifically disrupted by a balanced (1,11)(q42.1; q14.3) translocation, in a large Scottish pedigree, resulting in a cohort with several major mental illnesses such as schizophrenia, bipolar affective disorder, and recurrent major depression (Brandon and Sawa, 2011). DISC1 is widely expressed in the central nervous system (Schurov et al., 2004), and it has been shown to be involved in several neurodevelopmental processes such as progenitor cell proliferation (Mao et al., 2009), radial migration (Tomita et al., 2011), dendritic arborization (Duan et al., 2007; Kamiya et al., 2006), and synapse formation (Duan et al., 2007). Studies of various DISC1 mutant models (i.e., haploinsufficiency, point mutation, and transgenic models) have identified both molecular and multiple behavioral abnormalities including social cognition relevant to psychiatric illness. For example, an inducible DISC1 C-terminal fragment transgenic model exhibited abnormal spatial working memory, and reduced sociability, as well as decreased hippocampal dendritic complexity (Li et al., 2007). Inducible expression of mutant hDISC1 also produced sex-specific behavioral alterations in social behavior and spatial memory (Pletnikov et al., 2008; Shevelkin et al., 2017). Mice with the DISC1 Gln31Leu polymorphism showed deficits in social motivation as measured using social-conditioned place-preference, with reduced levels of catecholamines in the nucleus accumbens (Lipina et al., 2013). Mice with dominant-negative DISC1 exhibited deficits in cognition, sociability, and motivation accompanied by decreased PV-Ins activity possibly through increased prefrontal oxidative stress (Johnson et al., 2013). Finally, mouse models considering gene-environmental interactions (i.e., MIA (Abazyan et al., 2010; Ibi et al., 2010)), Δ9-THC (Ballinger et al., 2015), social stress exposures (Niwa et al., 2013) to DISC1 mutant), or gene-gene interactions (co-disruption of DISC1 and NRG1 (Seshadri et al., 2015)) have provided valuable opportunities for understanding the complexity underlying the pathology of psychiatric illnesses (Cash-Padgett and Jaaro-Peled, 2013). Overall, DISC1 dysregulation appears to be linked to multiple mental conditions rather than to schizophrenia specifically (Tomoda et al., 2016).

6.3.4. Others

Many genetic rodent models have been engineered to investigate neurobiological function, including social cognitive function, linked to psychiatric illnesses. Recent studies have indicated loss of function of synaptic adhesion molecules (i.e., neuroligin genes), or scaffolding proteins (i.e., Shank genes) in the postsynaptic density, which appear to contribute to conspicuous deficits in social behavior, particularly in the context of ASD research (Cao and Tabuchi, 2017; Mackowiak et al., 2014; Monteiro and Feng, 2017; Uchino and Waga, 2015). For example, mice with the R451C-substitution in neuroligin-3 (NL3) showed social motivation deficits (Tabuchi et al., 2007), which were most likely due to loss of PV-Ins function in the medial PFC (Cao et al., 2018). In addition, mice with mutations or deletions in various exons of Shank3 have been reported to show abnormalities in social behavior such as sociability, social motivation, and social communication (Bozdagi et al., 2010; Jiang and Ehlers, 2013). In humans, genetic variants in NL3 and shank3 have been recurrently identified in patients with ASD (Durand et al., 2007; Jamain et al., 2003; Leblond et al., 2014) as well as schizophrenia (Gauthier et al., 2010). Indeed, it has become clear that schizophrenia shares some common risk alleles and global gene expression patterns with ASD and other psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013;

Gandal et al., 2018; International Schizophrenia Consortium et al., 2009). In contrast, both clinical schizophrenia and ASD were shown to share some genetic influence with impairments in social communication but reveal distinct developmental profiles in their genetic links (St Pourcain et al., 2018). Accordingly, two lines of shank3 mutant mice associated with schizophrenia and ASD were reported to display both shared and distinct defects in synaptic function and social behavior (Zhou et al., 2016). Therefore, future detailed analysis identifying the subtle phenotypic differences from such mutations would help to understand synaptic development and function associated with social cognition. Optogenetic (Yizhar, 2012) and chemogenetic (Whissell et al., 2016) manipulations of gene expression in rodents (Pisansky et al., 2017; Shemesh et al., 2016) might also provide greater insights into the biological mechanisms underlying phenotypic diversity and the complexity of cognition at the cellular and circuit levels of resolution, contributing valuable information all along the drug discovery pipeline, from target identification to clinical trials.

7. Conclusion

Social cognition is becoming accepted as a reasonable treatment target for schizophrenia, because impairments in social cognition appear to influence the long-term outcome of patients with schizophrenia. Although several approaches using pharmacological and psychosocial interventions have been attempted in clinical practice, the effectiveness and tolerability of such treatments remain unclear. Future studies identifying the timing of individual-level intervention and developing a novel approach may be required to ameliorate impairments in social cognition in schizophrenia. To this end, much work is still needed to build the translational bridges among interdisciplinary research teams in understanding mechanisms and measures of social cognition. Multidimensional studies with cross-species comparisons, delineating abnormalities at the molecular, cellular, and circuit levels may prove useful for understanding the neurobiological substrates that are involved in impaired social cognition, providing valuable insights to develop potential therapeutic treatment for impairments of social cognition in schizophrenia.

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References

Abazyan, B., et al., 2010. Prenatal interaction of mutant DISC1 and immune activation produces adult psychopathology. Biol. Psychiatry 68, 1172–1181.
Abel, K.M., et al., 2003. Ketamine alters neural processing of facial emotion recognition in healthy men: an fMRI study. Neuroreport 14, 387–391.
Achim, A.M., et al., 2013. Impact of social anxiety on social cognition and functioning in patients with recent-onset schizophrenia spectrum disorders. Schizophr. Res. 145, 75–81.
Adolphs, R., 2001. The neurobiology of social cognition. Curr. Opin. Neurobiol. 11, 231–239.
Amodio, D.M., Frith, C.D., 2006. Meeting of minds: the medial frontal cortex and social cognition. Nat. Rev. Neurosci. 7, 268–277.
Andersson, F., et al., 2008. Impaired activation of face processing networks revealed by functional magnetic resonance imaging in 22q11.2 deletion syndrome. Biol. Psychiatry 63, 49–57.
Andreasen, N.C., et al., 2008. Theory of mind and schizophrenia: a positron emission tomography study of medication-free patients. Schizophr. Bull. 34, 708–719.
Anticevic, A., et al., 2012. Amygdala recruitment in schizophrenia in response to aversive emotional material: a meta-analysis of neuroimaging studies. Schizophr. Bull. 38, 608–621.
Azar, S.T., et al., 2017. Social Cognition, Child Neglect, and Child Injury Risk: The contribution of maternal social information processing to maladaptive injury prevention beliefs within a high-risk sample. J. Pediatr. Psychol. 42, 759–767.
Ballinger, M.D., et al., 2015. Adolescent cannabis exposure interacts with mutant DISC1 to produce impaired adult emotional memory. Neurobiol. Dis. 82, 176–184.
Barbato, M., et al., 2015. Theory of mind, emotion recognition and social perception in iindividuals at clinical high risk for psychosis: findings from the NAPLS-2 cohort. Schizophr. Res. Cogn. 2, 133–139.
Baron-Cohen, S., et al., 2001. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J. Child Psychol. Psychiatry 42, 241–251.
Behere, R.V., et al., 2009. Effect of risperidone on emotion recognition deficits in antipsychotic-naive schizophrenia: a short-term follow-up study. Schizophr. Res. 113, 72–76.
Bell, M., et al., 2001. Neurocognitive enhancement therapy with work therapy: effects on neuropsychological test performance. Arch. Gen. Psychiatry. 58, 763–768.
Bellack, A.S., et al., 1994. Evaluation of social problem solving in schizophrenia. J. Abnorm. Psychol. 103, 371–378.
Bellani, M., Brambilla, P., 2008. Social cognition, schizophrenia and brain imaging. Epidemiol. Psychiatr. Soc. 17, 117–119.
Benedetti, F., et al., 2009. Functional and structural brain correlates of theory of mind and empathy deficits in schizophrenia. Schizophr. Res. 114, 154–160.
Bentall, R.P., et al., 1991. Paranoia and social reasoning: an attribution theory analysis. Br. J. Clin. Psychol. 30 (Pt 1), 13–23.
Bicks, L.K., et al., 2015. Prefrontal cortex and social cognition in mouse and man. Front Psychol. 6, 1805.
Bitanihirwe, B.K., et al., 2010. Late prenatal immune activation in mice leads to behavioral and neurochemical abnormalities relevant to the negative symptoms of schizophrenia. Neuropsychopharmacology 35, 2462–2478.
Blackwood, N.J., et al., 2000. Imaging attentional and attributional bias: an fMRI approach to the paranoid delusion. Psychol. Med. 30, 873–883.
Blackwood, N.J., et al., 2003. Self-responsibility and the self-serving bias: an fMRI investigation of causal attributions. Neuroimage 20, 1076–1085.
Bowie, C.R., et al., 2006. Determinants of real-world functional performance in schizophrenia subjects: correlations with cognition, functional capacity, and symptoms. Am. J. Psychiatry 163, 418–425.
Bozdagi, O., et al., 2010. Haploinsufficiency of the autism-associated Shank3 gene leads to deficits in synaptic function, social interaction, and social communication. Mol. Autism. 1, 15.
Brandon, N.J., Sawa, A., 2011. Linking neurodevelopmental and synaptic theories of mental illness through DISC1. Nat. Rev. Neurosci. 12, 707–722.
Brekke, J.S., et al., 2007. How neurocognition and social cognition influence functional change during community-based psychosocial rehabilitation for individuals with schizophrenia. Schizophr. Bull. 33, 1247–1256.
Brothers, L., 1999. The social brain: a project for integrating primate behavior and neurophysiology in a new domain. Concepts Neurosci. 1, 27–51.
Brown, A.S., et al., 2004. Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. Am. J. Psychiatry 161, 889–895.
Brown, J.A., et al., 2015. Inhibition of parvalbumin-expressing interneurons results in complex behavioral changes. Mol. Psychiatry 20, 1499–1507.
Brune, M., 2005. "Theory of mind" in schizophrenia: a review of the literature. Schizophr. Bull. 31, 21–42.
Brune, M., et al., 2007. Mental state attribution, neurocognitive functioning, and psychopathology: what predicts poor social competence in schizophrenia best? Schizophr. Res. 92, 151–159.
Brune, M., et al., 2008. An fMRI study of theory of mind in schizophrenic patients with "passivity" symptoms. Neuropsychologia 46, 1992–2001.
Brunet, E., et al., 2003. Abnormalities of brain function during a nonverbal theory of mind task in schizophrenia. Neuropsychologia 41, 1574–1582.
Brunet-Gouet, E., Decety, J., 2006. Social brain dysfunctions in schizophrenia: a review of neuroimaging studies. Psychiatry Res. 148, 75–92.
Buchanan, R.W., et al., 2011. A randomized clinical trial of MK-0777 for the treatment of cognitive impairments in people with schizophrenia. Biol Psychiatry. 69, 442–449.
Buonocore, M., et al., 2018. Achieving recovery in patients with schizophrenia through psychosocial interventions: a retrospective study. Psychiatry Clin. Neurosci. 72, 28–34.
Cabanis, M., et al., 2013. The precuneus and the insula in self-attributional processes. Cogn. Affect. Behav. Neurosci. 13, 330–345.
Caceda, R., et al., 2007. Involvement of neuropeptide systems in schizophrenia: human studies. Int. Rev. Neurobiol. 78, 327–376.
Cacioppo, J.T., Hawkley, L.C., 2009. Perceived social isolation and cognition. Trends Cogn. Sci. 13, 447–454.
Caillies, S., Le Sourn-Bissaoui, S., 2013. Nondecomposable idiom understanding in children: recursive theory of mind and working memory. Can. J. Exp. Psychol. 67, 108–116.
Canetta, S., et al., 2014. Elevated maternal C-reactive protein and increased risk of schizophrenia in a national birth cohort. Am. J. Psychiatry 171, 960–968.
Cao, X., Tabuchi, K., 2017. Functions of synapse adhesion molecules neurexin/neuroligins and neurodevelopmental disorders. Neurosci. Res. 116, 3–9.
Cao, W., et al., 2018. Gamma oscillation dysfunction in mPFC leads to social deficits in neuroligin 3 R451C knockin mice. Neuron 97 (1253-1260), e1257.
Carter, C.S., et al., 2009. CNTRICS final task selection: social cognitive and affective neuroscience-based measures. Schizophr. Bull. 35, 153–162.
Cash-Padgett, T., Jaaro-Peled, H., 2013. DISC1 mouse models as a tool to decipher gene-environment interactions in psychiatric disorders. Front. Behav. Neurosci. 7, 113.
Chen, Q., et al., 2009. Empathy is moderated by genetic background in mice. PLoS One 4, e4387.
Choi, K.H., Kwon, J.H., 2006. Social cognition enhancement training for schizophrenia: a preliminary randomized controlled trial. Community Ment. Health J. 42, 177–187.
Chung, D.W., et al., 2016. Dysregulated ErbB4 splicing in schizophrenia: selective effects on parvalbumin expression. Am. J. Psychiatry 173, 60–68.

Chung, D.W., et al., 2017. Developmental pruning of excitatory synaptic inputs to parvalbumin interneurons in monkey prefrontal cortex. Proc. Natl. Acad. Sci. U S A 114, E629–E637.
Combs, D.R., et al., 2007. Social Cognition and Interaction Training (SCIT) for inpatients with schizophrenia spectrum disorders: preliminary findings. Schizophr. Res. 91, 112–116.
Corcoran, C.M., et al., 2011. The relationship of social function to depressive and negative symptoms in individuals at clinical high risk for psychosis. Psychol. Med. 41, 251–261.
Corfas, G., et al., 2004. Neuregulin 1-erbB signaling and the molecular/cellular basis of schizophrenia. Nat. Neurosci. 7, 575–580.
Corrigan, P.W., et al., 1992. Deficits in social schemata in schizophrenia. Schizophr. Res. 8, 129–135.
Couture, S.M., et al., 2006. The functional significance of social cognition in schizophrenia: a review. Schizophr. Bull. 32 (Suppl. 1), S44–S63.
Cross-Disorder Group of the Psychiatric Genomics Consortium, et al., 2013. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat. Genet. 45, 984–994.
Dantzer, R., et al., 1987. Modulation of social memory in male rats by neurohypophyseal peptides. Psychopharmacology (Berl.) 91, 363–368.
Debiec, J., Olsson, A., 2017. Social fear learning: from animal models to human function. Trends Cogn. Sci. 21, 546–555.
Del Pino, I., et al., 2013. Erbb4 deletion from fast-spiking interneurons causes schizophrenia-like phenotypes. Neuron 79, 1152–1168.
Depino, A.M., 2013. Peripheral and central inflammation in autism spectrum disorders. Mol. Cell Neurosci. 53, 69–76.
Devoe, D.J., et al., 2018. Interventions and social functioning in youth at risk of psychosis: a systematic review and meta-analysis. Early Interv. Psychiatry. https://doi.org/10.1111/eip.12689. [Epub ahead of print].
Duan, X., et al., 2007. Disrupted-In-Schizophrenia 1 regulates integration of newly generated neurons in the adult brain. Cell 130, 1146–1158.
Durand, C.M., et al., 2007. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nat. Genet. 39, 25–27.
Eack, S.M., et al., 2009. Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. Psychiatr. Serv. 60, 1468–1476.
Edwards, J., et al., 2002. Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. Clin. Psychol. Rev. 22, 789–832.
Eliez, S., et al., 2001. Velocardiofacial syndrome: are structural changes in the temporal and mesial temporal regions related to schizophrenia? Am. J. Psychiatry. 158, 447–453.
Fahim, C., et al., 2005. Brain activity during emotionally negative pictures in schizophrenia with and without flat affect: an fMRI study. Psychiatry Res. 140, 1–15.
Fett, A.K., et al., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 35, 573–588.
Flahault, A., et al., 2012. Hippocampal volume reduction in chromosome 22q11.2 deletion syndrome (22q11.2DS): a longitudinal study of morphometry and symptomatology. Psychiatry Res. 203, 1–5.
Fluharty, M.E., et al., 2018. Longitudinal associations of social cognition and substance use in childhood and early adolescence: findings from the Avon longitudinal study of parents and children. Eur. Child Adolesc. Psychiatry 27, 739–752.
Fond, G., et al., 2018. C-reactive protein as a peripheral biomarker in schizophrenia. An updated systematic review. Front. Psychiatry 9, 392.
Frith, C.D., Frith, U., 2007. Social cognition in humans. Curr. Biol. 17, R724–R732.
Fromer, M., et al., 2016. Gene expression elucidates functional impact of polygenic risk for schizophrenia. Nat. Neurosci. 19, 1442–1453.
Fujiwara, H., et al., 2015. Neuroimaging studies of social cognition in schizophrenia. Psychiatry Clin. Neurosci. 69, 259–267.
Gabinio, T., et al., 2018. Early trauma, attachment experiences and comorbidities in schizophrenia. Trends Psychiatry Psychother. https://doi.org/10.1590/2237-6089-2017-0005. [Epub ahead of print].
Gallagher 3rd, B.J., Jones, B.J., 2016. Neglect and hereditary risk: their relative contribution to schizophrenia with negative symptomatology. Int. J. Soc. Psychiatry 62, 235–242.
Gandal, M.J., et al., 2018. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. Science 359, 693–697.
Gao, R., Penzes, P., 2015. Common mechanisms of excitatory and inhibitory imbalance in schizophrenia and autism spectrum disorders. Curr. Mol. Med. 15, 146–167.
Gauthier, J., et al., 2010. De novo mutations in the gene encoding the synaptic scaffolding protein SHANK3 in patients ascertained for schizophrenia. Proc. Natl. Acad. Sci. U S A. 107, 7863–7868.
Germine, L., et al., 2016. Association between polygenic risk for schizophrenia, neurocognition and social cognition across development. Transl. Psychiatry 6, e924.
Gil, A., et al., 2009. The association of child abuse and neglect with adult disability in schizophrenia and the prominent role of physical neglect. Child Abuse Negl. 33, 618–624.
Glausier, J.R., et al., 2014. Altered parvalbumin basket cell inputs in the dorsolateral prefrontal cortex of schizophrenia subjects. Mol. Psychiatry 19, 30–36.
Gonzalez-Liencres, C., et al., 2016. Emotional contagion is not altered in mice prenatally exposed to poly (I:C) on gestational day 9. Front. Behav. Neurosci. 10, 134.
Grant, N., et al., 2017. Social cognition interventions for people with schizophrenia: a systematic review focussing on methodological quality and intervention modality. Clin. Psychol. Rev. 56, 55–64.
Green, M.F., 2006. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J. Clin. Psychiatry. 67 (Suppl. 9), 3–8 discussion 36-42.
Green, M.F., Harvey, P.D., 2014. Cognition in schizophrenia: past, present, and future. Schizophr. Res. Cogn. 1, e1–e9.
Green, M.F., et al., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr. Bull. 26, 119–136.
Green, M.F., et al., 2005. Social cognition in schizophrenia: recommendations from the measurement and treatment research to improve cognition in schizophrenia new approaches conference. Schizophr. Bull. 31, 882–887.
Green, M.F., et al., 2008. Social cognition in schizophrenia: an NIMH workshop on definitions, assessment, and research opportunities. Schizophr. Bull. 34, 1211–1220.
Green, M.F., et al., 2015. Social cognition in schizophrenia. Nat. Rev. Neurosci. 16, 620–631.
Gur, R.C., et al., 2002a. A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. J. Neurosci. Methods 115, 137–143.
Gur, R.C., et al., 2002b. Brain activation during facial emotion processing. Neuroimage 16, 651–662.
Gur, R.E., et al., 2002c. An fMRI study of facial emotion processing in patients with schizophrenia. Am. J. Psychiatry 159, 1992–1999.
Gur, R.E., et al., 2006. Flat affect in schizophrenia: relation to emotion processing and neurocognitive measures. Schizophr. Bull. 32, 279–287.
Gur, R.E., et al., 2007. Limbic activation associated with misidentification of fearful faces and flat affect in schizophrenia. Arch. Gen. Psychiatry 64, 1356–1366.
Gururajan, A., et al., 2010. Current pharmacological models of social withdrawal in rats: relevance to schizophrenia. Behav. Pharmacol. 21, 690–709.
Habel, U., et al., 2010. Training of affect recognition in schizophrenia: neurobiological correlates. Soc. Neurosci. 5, 92–104.
Hagberg, H., et al., 2012. Inflammation during fetal and neonatal life: implications for neurologic and neuropsychiatric disease in children and adults. Ann. Neurol. 71, 444–457.
Hansen, D.J., et al., 1985. Effects of interpersonal problem-solving training with chronic aftercare patients on problem-solving component skills and effectiveness of solutions. J. Consult. Clin. Psychol. 53, 167–174.
Happe, F.G., 1993. Communicative competence and theory of mind in autism: a test of relevance theory. Cognition 48, 101–119.
Harich, S., et al., 2007. Stimulation of the metabotropic glutamate 2/3 receptor attenuates social novelty discrimination deficits induced by neonatal phencyclidine treatment. Psychopharmacology (Berl.) 192, 511–519.
Harper, K.M., et al., 2012. Alterations of social interaction through genetic and environmental manipulation of the 22q11.2 gene Sept5 in the mouse brain. Hum. Mol. Genet. 21, 3489–3499.
Hashimoto, R., et al., 2004. Expression analysis of neuregulin-1 in the dorsolateral prefrontal cortex in schizophrenia. Mol. Psychiatry 9, 299–307.
Hilker, R., et al., 2018. Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish twin register. Biol. Psychiatry 83, 492–498.
Homayoun, H., Moghaddam, B., 2007. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. J. Neurosci. 27, 11496–11500.
Horan, W.P., et al., 2011. Efficacy and specificity of social cognitive skills training for outpatients with psychotic disorders. J. Psychiatr. Res. 45, 1113–1122.
Hornak, J., et al., 1996. Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. Neuropsychologia 34, 247–261.
Ibi, D., et al., 2010. Combined effect of neonatal immune activation and mutant DISC1 on phenotypic changes in adulthood. Behav. Brain Res. 206, 32–37.
International Schizophrenia Consortium, et al., 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460, 748–752.
Iwata, K., et al., 2017. Efficacy of cognitive rehabilitation using computer software with individuals living with schizophrenia: a randomized controlled trial in Japan. Psychiatr. Rehabil. J. 40, 4–11.
Jamain, S., et al., 2003. Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. Nat. Genet. 34, 27–29.
Jani, M., Kasparek, T., 2017. Emotion recognition and theory of mind in schizophrenia: a meta-analysis of neuroimaging studies. World J. Biol. Psychiatry. 1–11.
Jarskog, L.F., et al., 2017. A 12-week randomized controlled trial of twice-daily intranasal oxytocin for social cognitive deficits in people with schizophrenia. Schizophr. Res. 185, 88–95.
Javitt, D.C., Zukin, S.R., 1991. Recent advances in the phencyclidine model of schizophrenia. Am. J. Psychiatry 148, 1301–1308.
Jia, P., et al., 2010. Common variants conferring risk of schizophrenia: a pathway analysis of GWAS data. Schizophr. Res. 122, 38–42.
Jiang, Y.H., Ehlers, M.D., 2013. Modeling autism by SHANK gene mutations in mice. Neuron 78, 8–27.
Johnson, A.W., et al., 2013. Cognitive and motivational deficits together with prefrontal oxidative stress in a mouse model for neuropsychiatric illness. Proc. Natl. Acad. Sci. U S A. 110, 12462–12467.
Joshi, D., et al., 2014. Elevated ErbB4 mRNA is related to interneuron deficit in prefrontal cortex in schizophrenia. J Psychiatr Res. 53, 125–132.
Kahn, R.S., Keefe, R.S., 2013. Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatry 70, 1107–1112.
Kamiya, A., et al., 2006. DISC1-NDEL1/NUDEL protein interaction, an essential component for neurite outgrowth, is modulated by genetic variations of DISC1. Hum. Mol. Genet. 15, 3313–3323.
Kanie, A., et al., 2014. New instrument for measuring multiple domains of social cognition: construct validity of the Social Cognition Screening Questionnaire (Japanese version). Psychiatry Clin. Neurosci. 68, 701–711.
Kapur, S., Remington, G., 2001. Atypical antipsychotics: new directions and new

challenges in the treatment of schizophrenia. Ann. Rev. Med. 52, 503–517.
Karayiorgou, M., et al., 2010. 22q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. Nat. Rev. Neurosci. 11, 402–416.
Kates, W.R., et al., 2006. Temporal lobe anatomy and psychiatric symptoms in velocardiofacial syndrome (22q11.2 deletion syndrome). J. Am. Acad. Child. Adolesc. Psychiatry 45, 587–595.
Kavanagh, D.H., et al., 2015. Schizophrenia genetics: emerging themes for a complex disorder. Mol. Psychiatry 20, 72–76.
Kee, K.S., et al., 2003. Is emotion processing a predictor of functional outcome in schizophrenia? Schizophr. Bull. 29, 487–497.
Keefe, R.S., Fenton, W.S., 2007. How should DSM-V criteria for schizophrenia include cognitive impairment? Schizophr. Bull. 33, 912–920.
Kelley, H.H., 1973. The process of causal attribution. Am. Psychol. 28, 107–128.
Kerr, S.L., Neale, J.M., 1993. Emotion perception in schizophrenia: specific deficit or further evidence of generalized poor performance? J. Abnorm. Psychol. 102, 312–318.
Kiley-Brabeck, K., Sobin, C., 2006. Social skills and executive function deficits in children with the 22q11 deletion syndrome. Appl. Neuropsychol. 13, 258–268.
Kimoto, S., et al., 2012. Selective overexpression of Comt in prefrontal cortex rescues schizophrenia-like phenotypes in a mouse model of 22q11 deletion syndrome. Transl. Psychiatry 2, e146.
Kimoto, S., et al., 2014. Lower expression of glutamic acid decarboxylase 67 in the prefrontal cortex in schizophrenia: contribution of altered regulation by Zif268. Am. J. Psychiatry. 171, 969–978.
Kimoto, S., et al., 2015. Altered markers of cortical gamma-aminobutyric acid neuronal activity in schizophrenia: role of the NARP gene. JAMA Psychiatry 72, 747–756.
Kirsten, T.B., et al., 2010. Prenatal lipopolysaccharide reduces social behavior in male offspring. Neuroimmunomodulation 17, 240–251.
Kluver, H., Bucy, P.C., 1997. Preliminary analysis of functions of the temporal lobes in monkeys. 1939. J. Neuropsychiatry Clin. Neurosci. 9, 606–620.
Koenigs, M., et al., 2007. Damage to the prefrontal cortex increases utilitarian moral judgements. Nature 446, 908–911.
Kohler, C.G., et al., 2000. Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. Biol. Psychiatry 48, 127–136.
Kohler, C.G., et al., 2010. Facial emotion perception in schizophrenia: a meta-analytic review. Schizophr. Bull. 36, 1009–1019.
Korkmaz, B., 2011. Theory of mind and neurodevelopmental disorders of childhood. Pediatr. Res. 69, 101R–108R.
Krabbendam, L., van Os, J., 2005. Schizophrenia and urbanicity: a major environmental influence–conditional on genetic risk. Schizophr. Bull. 31, 795–799.
Kronbichler, L., et al., 2017. Abnormal brain activation during theory of mind tasks in schizophrenia: A meta-analysis. Schizophr. Bull. 43, 1240–1250.
Kucharska-Pietura, K., Mortimer, A., 2013. Can antipsychotics improve social cognition in patients with schizophrenia? CNS Drugs 27, 335–343.
Kurtz, M.M., Richardson, C.L., 2012. Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. Schizophr. Bull. 38, 1092–1104.
LaCrosse, A.L., Olive, M.F., 2013. Neuropeptide systems and schizophrenia. CNS Neurol. Disord. Drug Targets 12, 619–632.
Lattanzi, G.M., et al., 2018. Genetic and clinical features of social cognition in 22q11.2 deletion syndrome. J. Neurosci. Res. https://doi.org/10.1002/jnr.24265.
Lavoie, M.A., et al., 2013. Social cognition in first-degree relatives of people with schizophrenia: a meta-analysis. Psychiatry Res. 209, 129–135.
Law, A.J., et al., 2007. Disease-associated intronic variants in the ErbB4 gene are related to altered ErbB4 splice-variant expression in the brain in schizophrenia. Hum. Mol. Genet. 16, 129–141.
Leblond, C.S., et al., 2014. Meta-analysis of SHANK mutations in autism spectrum disorders: a gradient of severity in cognitive impairments. PLoS Genet. 10, e1004580.
Lee, J., et al., 2011a. Theory of mind in schizophrenia: exploring neural mechanisms of belief attribution. Soc. Neurosci. 6, 569–581.
Lee, J., et al., 2011b. Schizophrenia patients are impaired in empathic accuracy. Psychol. Med. 41, 2297–2304.
Lee, T.Y., et al., 2015. Social cognitive functioning in prodromal psychosis: a meta-analysis. Schizophr. Res. 164, 28–34.
Leitman, D.I., et al., 2006. Theory of Mind (ToM) and counterfactuality deficits in schizophrenia: misperception or misinterpretation? Psychol. Med. 36, 1075–1083.
Lewis, D.A., et al., 2012. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. 35, 57–67.
Li, W., et al., 2007. Specific developmental disruption of disrupted-in-schizophrenia-1 function results in schizophrenia-related phenotypes in mice. Proc. Natl. Acad. Sci. U S A. 104, 18280–18285.
Li, H., et al., 2010. Facial emotion processing in schizophrenia: a meta-analysis of functional neuroimaging data. Schizophr. Bull. 36, 1029–1039.
Lincoln, T.M., et al., 2011. Negative symptoms and social cognition: identifying targets for psychological interventions. Schizophr. Bull. 37 (Suppl. 2), S23–S32.
Lincoln, S.H., et al., 2017. A developmental perspective on social-cognition difficulties in youth at clinical high risk for psychosis. Harv. Rev. Psychiatry 25, 4–14.
Lipina, T.V., et al., 2013. Disrupted-in-schizophrenia-1 Gln31Leu polymorphism results in social anhedonia associated with monoaminergic imbalance and reduction of CREB and beta-arrestin-1,2 in the nucleus accumbens in a mouse model of depression. Neuropsychopharmacology 38, 423–436.
Luisada, P.V., Brown, B.I., 1976. Clinical management of the phencyclidine psychosis. Clin. Toxicol. 9, 539–545.
Mackowiak, M., et al., 2014. Neuroligins, synapse balance and neuropsychiatric disorders. Pharmacol. Rep. 66, 830–835.
Makinodan, M., et al., 2008. Maternal immune activation in mice delays myelination and axonal development in the hippocampus of the offspring. J. Neurosci. Res. 86, 2190–2200.
Makinodan, M., et al., 2012. A critical period for social experience-dependent oligodendrocyte maturation and myelination. Science 337, 1357–1360.
Mao, Y., et al., 2009. Disrupted in schizophrenia 1 regulates neuronal progenitor proliferation via modulation of GSK3beta/beta-catenin signaling. Cell 136, 1017–1031.
Markham, J.A., Koenig, J.I., 2011. Prenatal stress: role in psychotic and depressive diseases. Psychopharmacology (Berl.) 214, 89–106.
Matsuda, Y., et al., 2018. Feasibility and effectiveness of a cognitive remediation programme with original computerised cognitive training and group intervention for schizophrenia: a multicentre randomised trial. Neuropsychol. Rehabil. 28, 387–397.
Mayer, J.D., et al., 2001. Emotional intelligence as a standard intelligence. Emotion 1, 232–242.
Mazza, M., et al., 2010. Could schizophrenic subjects improve their social cognition abilities only with observation and imitation of social situations? Neuropsychol. Rehabil. 20, 675–703.
Meechan, D.W., et al., 2015. Modeling a model: mouse genetics, 22q11.2 Deletion Syndrome, and disorders of cortical circuit development. Prog. Neurobiol. 130, 1–28.
Mei, L., Nave, K.A., 2014. Neuregulin-ERBB signaling in the nervous system and neuropsychiatric diseases. Neuron 83, 27–49.
Mei, L., Xiong, W.C., 2008. Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. Nat. Rev. Neurosci. 9, 437–452.
Meng, Q., et al., 2010. Peri-adolescence isolation rearing alters social behavior and nociception in rats. Neurosci. Lett. 480, 25–29.
Meyer, U., et al., 2005. Towards an immuno-precipitated neurodevelopmental animal model of schizophrenia. Neurosci Biobehav. Rev. 29, 913–947.
Meyer-Lindenberg, A., et al., 2011. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat. Rev. Neurosci. 12, 524–538.
Mier, D., et al., 2010. Neuronal correlates of affective theory of mind in schizophrenia out-patients: evidence for a baseline deficit. Psychol. Med. 40, 1607–1617.
Mihailov, A., et al., 2017. Morphological brain changes associated with negative symptoms in patients with 22q11.2 deletion syndrome. Schizophr. Res. 188, 52–58.
Millan, M.J., Bales, K.L., 2013. Towards improved animal models for evaluating social cognition and its disruption in schizophrenia: the CNTRICS initiative. Neurosci. Biobehav. Rev. 37, 2166–2180.
Mizrahi, R., 2016. Social stress and psychosis risk: common neurochemical substrates? Neuropsychopharmacology 41, 666–674.
Mizrahi, R., et al., 2007. The effect of antipsychotic treatment on Theory of Mind. Psychol. Med. 37, 595–601.
Mohammed, A.H., et al., 2002. Environmental enrichment and the brain. Prog. Brain Res. 138, 109–133.
Mohn, A.R., et al., 1999. Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. Cell 98, 427–436.
Moieni, M., Eisenberger, N.I., 2018. Effects of inflammation on social processes and implications for health. Ann. N Y Acad. Sci. 1428, 5–13.
Monteiro, P., Feng, G., 2017. SHANK proteins: roles at the synapse and in autism spectrum disorder. Nat. Rev. Neurosci. 18, 147–157.
Moritz, S., et al., 2013. Complementary group Metacognitive Training (MCT) reduces delusional ideation in schizophrenia. Schizophr. Res. 151, 61–69.
Morris, J.S., et al., 1998. Conscious and unconscious emotional learning in the human amygdala. Nature 393, 467–470.
Motzkin, J.C., et al., 2015. Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. Biol. Psychiatry 77, 276–284.
Moy, S.S., et al., 2004. Sociability and preference for social novelty in five inbred strains: an approach to assess autistic-like behavior in mice. Genes Brain Behav. 3, 287–302.
Mueller, D.R., et al., 2015. One-year randomized controlled trial and follow-up of integrated neurocognitive therapy for schizophrenia outpatients. Schizophr. Bull. 41, 604–616.
Mukai, J., et al., 2008. Palmitoylation-dependent neurodevelopmental deficits in a mouse model of 22q11 microdeletion. Nat. Neurosci. 11, 1302–1310.
Nakagami, E., et al., 2010. The prospective relationships among intrinsic motivation, neurocognition, and psychosocial functioning in schizophrenia. Schizophr. Bull. 36, 935–948.
Neill, J.C., et al., 2014. Acute and chronic effects of NMDA receptor antagonists in rodents, relevance to negative symptoms of schizophrenia: a translational link to humans. Eur. Neuropsychopharmacol. 24, 822–835.
Niwa, M., et al., 2013. Adolescent stress-induced epigenetic control of dopaminergic neurons via glucocorticoids. Science 339, 335–339.
Norkett, E.M., et al., 2017. Social cognitive impairment in 22q11 deletion syndrome: a review. Psychiatry Res. 253, 99–106.
Ochsner, K.N., et al., 2012. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Ann. N Y Acad. Sci. 1251, E1–24.
Okano, H., et al., 2015. Brain/MINDS: brain-mapping project in Japan. Philos. Trans. R. Soc. Lond. B Biol. Sci. 370.
Pafundo, D.E., et al., 2018. Presynaptic effects of N-Methyl-D-Aspartate receptors enhance parvalbumin cell-mediated inhibition of pyramidal cells in mouse prefrontal cortex. Biol. Psychiatry 84, 460–470.
Papaleo, F., et al., 2016. Behavioral, neurophysiological, and synaptic impairment in a transgenic neuregulin1 (NRG1-IV) murine schizophrenia model. J. Neurosci. 36, 4859–4875.
Paylor, R., et al., 2006. Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: implications for 22q11 deletion syndrome. Proc. Natl. Acad. Sci. U S A 103, 7729–7734.
Pedersen, C.A., et al., 2011. Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. Schizophr. Res. 132, 50–53.

Pedersen, A., et al., 2012. Theory of mind in patients with schizophrenia: is mentalizing delayed? Schizophr. Res. 137, 224–229.
Pelphrey, K.A., Carter, E.J., 2008. Brain mechanisms for social perception: lessons from autism and typical development. Ann. N Y Acad. Sci. 1145, 283–299.
Penn, D.L., et al., 1996. The relationship of social cognition to ward behavior in chronic schizophrenia. Schizophr. Res. 20, 327–335.
Penn, D.L., et al., 2002. Social perception in schizophrenia: the role of context. Psychiatry Res. 109, 149–159.
Pin, T.W., et al., 2009. A review of developmental outcomes of term infants with post-asphyxia neonatal encephalopathy. Eur. J. Paediatr. Neurol. 13, 224–234.
Pinkham, A.E., 2014. Social cognition in schizophrenia. J. Clin. Psychiatry 75 (Suppl. 2), 14–19.
Pinkham, A.E., et al., 2008a. Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. Schizophr. Res. 99, 164–175.
Pinkham, A.E., et al., 2008b. An investigation of the relationship between activation of a social cognitive neural network and social functioning. Schizophr. Bull. 34, 688–697.
Pinkham, A.E., et al., 2018. Social cognition psychometric evaluation: results of the final validation study. Schizophr. Bull. 44, 737–748.
Pisansky, M.T., et al., 2017. Oxytocin enhances observational fear in mice. Nat. Commun. 8, 2102.
Pletnikov, M.V., et al., 2008. Inducible expression of mutant human DISC1 in mice is associated with brain and behavioral abnormalities reminiscent of schizophrenia. Mol. Psychiatry 13, 173–186, 115.
Quirk, G.J., Beer, J.S., 2006. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. Curr. Opin. Neurobiol. 16, 723–727.
Rachman, S., 1980. Emotional processing. Behav. Res. Ther. 18, 51–60.
Reichenberg, A., et al., 2006. Premorbid intellectual functioning and risk of schizophrenia and spectrum disorders. J. Clin. Exp. Neuropsychol. 28, 193–207.
Reichenberg, A., et al., 2010. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. Am. J. Psychiatry 167, 160–169.
Riglin, L., et al., 2017. Schizophrenia risk alleles and neurodevelopmental outcomes in childhood: a population-based cohort study. Lancet Psychiatry. 4, 57–62.
Robbins, T.W., 2016. Neurobehavioural sequelae of social deprivation in rodents revisited: modelling social adversity for developmental neuropsychiatric disorders. J. Psychopharmacol. 30, 1082–1089.
Roberts, D.L., Penn, D.L., 2009. Social cognition and interaction training (SCIT) for outpatients with schizophrenia: a preliminary study. Psychiatry Res. 166, 141–147.
Roberts, D., Fiszdon, J., Tek, C., 2011. Initial validity of the Social Cognition Screening Questionnaire (SCSQ). Schizophr. Bull. 37, 280 Suppl. 1.
Roder, V., et al., 2011. Effectiveness of integrated psychological therapy (IPT) for schizophrenia patients: a research update. Schizophr. Bull. 37 (Suppl. 2), S71–S79.
Rodrigues-Amorim, D., et al., 2017. Cytokines dysregulation in schizophrenia: a systematic review of psychoneuroimmune relationship. Schizophr. Res. https://doi.org/10.1016/j.schres.2017.11.023. Epub ahead of print.
Roncone, R., et al., 2004. Rehabilitation of theory of mind deficit in schizophrenia: a pilot study of metacognitive strategies in group treatment. Neuropsychol. Rehabil. 14, 421–435.
Rose, A., et al., 2015. Randomized controlled trial of computer-based treatment of social cognition in schizophrenia: the TRuSST trial protocol. BMC Psychiatry 15, 142.
Ruocco, A.C., et al., 2014. Emotion recognition deficits in schizophrenia-spectrum disorders and psychotic bipolar disorder: Findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. Schizophr. Res. 158, 105–112.
Russell, T.A., et al., 2007. Neural responses to dynamic expressions of fear in schizophrenia. Neuropsychologia 45, 107–123.
Salem, J.E., et al., 1996. More evidence for generalized poor performance in facial emotion perception in schizophrenia. J. Abnorm. Psychol. 105, 480–483.
Salgado-Pineda, P., et al., 2005. Dopaminergic contribution to the regulation of emotional perception. Clin. Neuropharmacol. 28, 228–237.
Sams-Dodd, F., 1995. Distinct effects of d-amphetamine and phencyclidine on the social behaviour of rats. Behav. Pharmacol. 6, 55–65.
Sarkar, S., et al., 2015. Conceptualization and treatment of negative symptoms in schizophrenia. World J. Psychiatry 5, 352–361.
Savla, G.N., et al., 2013. Deficits in domains of social cognition in schizophrenia: a meta-analysis of the empirical evidence. Schizophr. Bull. 39, 979–992.
Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011. Genome-wide association study identifies five new schizophrenia loci. Nat. Genet. 43, 969–976.
Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511, 421–427.
Schurov, I.L., et al., 2004. Expression of disrupted in schizophrenia 1 (DISC1) protein in the adult and developing mouse brain indicates its role in neurodevelopment. Mol. Psychiatry 9, 1100–1110.
Schurz, M., et al., 2014. Fractionating theory of mind: a meta-analysis of functional brain imaging studies. Neurosci. Biobehav. Rev. 42, 9–34.
Schwabe, K., et al., 2006. Behavioural effects of neonatal lesions of the medial prefrontal cortex and subchronic pubertal treatment with phencyclidine of adult rats. Behav. Brain Res. 168, 150–160.
Scola, G., Duong, A., 2017. Prenatal maternal immune activation and brain development with relevance to psychiatric disorders. Neuroscience 346, 403–408.
Seidel, E.M., et al., 2010. Who is to blame? Neural correlates of causal attribution in social situations. Soc. Neurosci. 5, 335–350.
Sekar, A., et al., 2016. Schizophrenia risk from complex variation of complement component 4. Nature 530, 177–183.
Senju, A., 2012. Spontaneous theory of mind and its absence in autism spectrum disorders. Neuroscientist 18, 108–113.
Sergi, M.J., et al., 2006. Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. Am. J. Psychiatry 163, 448–454.
Sergi, M.J., et al., 2007. Social cognition in schizophrenia: relationships with neurocognition and negative symptoms. Schizophr. Res. 90, 316–324.
Seshadri, S., et al., 2015. Interneuronal DISC1 regulates NRG1-ErbB4 signalling and excitatory-inhibitory synapse formation in the mature cortex. Nat. Commun. 6, 10118.
Shemesh, Y., et al., 2016. Ucn3 and CRF-R2 in the medial amygdala regulate complex social dynamics. Nat. Neurosci. 19, 1489–1496.
Shevelkin, A.V., et al., 2017. Expression of mutant DISC1 in Purkinje cells increases their spontaneous activity and impairs cognitive and social behaviors in mice. Neurobiol. Dis. 103, 144–153.
Shi, J., et al., 2009. Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature 460, 753–757.
Silberberg, G., et al., 2006. The involvement of ErbB4 with schizophrenia: association and expression studies. Am. J. Med Genet. B Neuropsychiatr. Genet. 141B, 142–148.
St Pourcain, B., et al., 2018. ASD and schizophrenia show distinct developmental profiles in common genetic overlap with population-based social communication difficulties. Mol. Psychiatry 23, 263–270.
Subotnik, K.L., et al., 2006. Neurocognitive and social cognitive correlates of formal thought disorder in schizophrenia patients. Schizophr. Res. 85, 84–95.
Sugranyes, G., et al., 2011. Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. PLoS One. 6, e25322.
Sumiyoshi, T., et al., 2009. Effect of perospirone on P300 electrophysiological activity and social cognition in schizophrenia: a three-dimensional analysis with sloreta. Psychiatry Res. 172, 180–183.
Suzuki, G., et al., 2009. Sept5 deficiency exerts pleiotropic influence on affective behaviors and cognitive functions in mice. Hum. Mol. Genet. 18, 1652–1660.
Swillen, A., et al., 1999. Neuropsychological, learning and psychosocial profile of primary school aged children with the velo-cardio-facial syndrome (22q11 deletion): evidence for a nonverbal learning disability? Child Neuropsychol. 5, 230–241.
Tabuchi, K., et al., 2007. A neuroligin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. Science 318, 71–76.
Taylor, S.F., et al., 2012. Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. Biol. Psychiatry 71, 136–145.
Tolman, A.W., Kurtz, M.M., 2012. Neurocognitive predictors of objective and subjective quality of life in individuals with schizophrenia: a meta-analytic investigation. Schizophr. Bull. 38, 304–315.
Tomita, K., et al., 2011. Disrupted-in-Schizophrenia-1 (Disc1) is necessary for migration of the pyramidal neurons during mouse hippocampal development. Hum. Mol. Genet. 20, 2834–2845.
Tomoda, T., et al., 2016. Utility and validity of DISC1 mouse models in biological psychiatry. Neuroscience 321, 99–107.
Toritsuka, M., et al., 2013. Deficits in microRNA-mediated Cxcr4/Cxcl12 signaling in neurodevelopmental deficits in a 22q11 deletion syndrome mouse model. Proc. Natl. Acad. Sci. U S A 110, 17552–17557.
Tzschentke, T.M., 2007. Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. Addict. Biol. 12, 227–462.
Uchino, S., Waga, C., 2015. Novel therapeutic approach for autism spectrum disorder: Focus on SHANK3. Curr. Neuropharmacol. 13, 786–792.
Ueno, H., et al., 2017. Region-specific impairments in parvalbumin interneurons in social isolation-reared mice. Neuroscience 359, 196–208.
Van den Heuvel, D.M., Pasterkamp, R.J., 2008. Getting connected in the dopamine system. Prog. Neurobiol. 85, 75–93.
van Hooren, S., et al., 2008. Social cognition and neurocognition as independent domains in psychosis. Schizophr. Res. 103, 257–265.
van Praag, H., et al., 2000. Neural consequences of environmental enrichment. Nat. Rev. Neurosci. 1, 191–198.
Vauth, R., et al., 2004. Does social cognition influence the relation between neurocognitive deficits and vocational functioning in schizophrenia? Psychiatry Res. 128, 155–165.
Ventura, J., et al., 2009. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. Schizophr. Res. 113, 189–199.
Vingerhoets, W.A., et al., 2013. Pharmacological interventions for the MATRICS cognitive domains in schizophrenia: what's the evidence? Front. Psychiatry. 4, 157.
Viviano, J.D., et al., 2018. Resting-state connectivity biomarkers of cognitive performance and social function in individuals with schizophrenia spectrum disorder and healthy control subjects. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2018.03.013. Epub ahead of print.
Walter, H., et al., 2009. Dysfunction of the social brain in schizophrenia is modulated by intention type: an fMRI study. Soc. Cogn. Affect. Neurosci. 4, 166–176.
Wen, L., et al., 2010. Neuregulin 1 regulates pyramidal neuron activity via ErbB4 in parvalbumin-positive interneurons. Proc. Natl. Acad. Sci. U S A. 107, 1211–1216.
West, A.E., Greenberg, M.E., 2011. Neuronal activity-regulated gene transcription in synapse development and cognitive function. Cold Spring Harb. Perspect. Biol. 3.
Whalen, P.J., et al., 1998. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J. Neurosci. 18, 411–418.
Whissell, P.D., et al., 2016. The use of DREADDs to deconstruct behavior. Front. Genet. 7, 70.
Whyte, E.M., et al., 2014. Idiom, syntax, and advanced theory of mind abilities in children with autism spectrum disorders. J. Speech. Lang Hear Res. 57, 120–130.
Williams, L.M., et al., 2004. Dysregulation of arousal and amygdala-prefrontal systems in paranoid schizophrenia. Am. J. Psychiatry 161, 480–489.
Wilson, C.A., Koenig, J.I., 2014. Social interaction and social withdrawal in rodents as readouts for investigating the negative symptoms of schizophrenia. Eur. Neuropsychopharmacol. 24, 759–773.
Wykes, T., Spaulding, W.D., 2011. Thinking about the future cognitive remediation

therapy–what works and could we do better? Schizophr. Bull. 37 (Suppl. 2), S80–S90.
Yamamuro, K., et al., 2018. Social isolation during the critical period reduces synaptic and intrinsic excitability of a subtype of pyramidal cell in mouse prefrontal cortex. Cereb. Cortex. 28, 998–1010.
Yee, N., et al., 2012. Increased affective ultrasonic communication during fear learning in adult male rats exposed to maternal immune activation. J. Psychiatr. Res. 46, 1199–1205.
Yizhar, O., 2012. Optogenetic insights into social behavior function. Biol. Psychiatry 71, 1075–1080.
Yoo, H.J., et al., 2015. Genetic association analyses of neuregulin 1 gene polymorphism with endopheontype for sociality of Korean autism spectrum disorders family. Psychiatry Res. 227, 366–368.
Zhou, Y., et al., 2016. Mice with Shank3 mutations associated with ASD and schizophrenia display both shared and distinct defects. Neuron 89, 147–162.