Published in final edited form as:

Eur Neuropsychopharmacol. 2014 May ; 24(5): 759–773. doi:10.1016/j.euroneuro.2013.11.008.

Social interaction and social withdrawal in rodents as readouts for investigating the negative symptoms of schizophrenia

Christina A. Wilson[*] and **James I. Koenig**[1]

Department of Psychiatry, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD 21228, USA

Abstract

Negative symptoms (e.g., asociality and anhedonia) are a distinct symptomatic domain that has been found to significantly affect the quality of life in patients diagnosed with schizophrenia. Additionally, the primary negative symptom of asociality (i.e., withdrawal from social contact that derives from indifference or lack of desire to have social contact) is a major contributor to poor psychosocial functioning and has been found to play an important role in the course of the disorder. Nonetheless, the pathophysiology underlying these symptoms is unknown and currently available treatment options (e.g., antipsychotics and cognitive-behavioral therapy) fail to reliably produce efficacious benefits. Utilizing rodent paradigms that measure social behaviors (e.g., social withdrawal) to elucidate the neurobiological substrates that underlie social dysfunction and to identify novel therapeutic targets may be highly informative and useful to understand more about the negative symptoms of schizophrenia. Accordingly, the purpose of this review is to provide an overview of the behavioral tasks for assessing social functioning that may be translationally relevant for investigating negative symptoms associated with schizophrenia.

Keywords

Schizophrenia; Negative symptoms; Social interaction; Social withdrawal; Rodent model

1. Introduction

Primary negative symptoms (i.e., blunted affect, alogia, asociality, avolition, and anhedonia) are a rather common feature of schizophrenia that represents a distinct and important therapeutic domain (Kirkpatrick et al., 2006). These symptoms affect approximately one-third of patients with the illness and the severity of the negative symptoms is often associated with the course of the illness, as well as the patients' function and quality of life (Breier et al., 1991; Fenton and McGlashan, 1991; Katschnig, 2000; Norman et al., 2000).

[*]Correspondence to: University of Maryland School of Medicine, PO Box 21247, Baltimore, MD 21228, USA Tel.: +1 410 402 7319; fax: +1 410 402 6066. cwilson@mprc.umaryland.edu (C.A. Wilson).

[1]Current address: National Institute of Neurological Disorders and Stroke, NIH, 6001 Executive Blvd. Rm 2107, Rockville, MD 20852, USA.

Contributors

Christina Wilson and James Koenig were responsible for writing the manuscript and editing the final version.

Conflict of interest

The authors have no conflicts to report.

Additionally, the effectiveness of currently available treatment options (e.g., antipsychotics, cognitive-behavioral therapy, and psychosocial treatments) has been found to be inadequate (Keefe et al., 1999; Leucht et al., 2009; Swartz et al., 2007; Wykes et al., 2008).

The negative symptom of asociality (i.e., withdrawal from social contact that derives from indifference or lack of desire to have social contact) is a core behavioral feature in schizophrenia that contributes significantly to poor psychosocial functioning (Puig et al., 2008). Social withdrawal emerges during the premorbid stage, worsens during the prodromal period, and generally persists throughout the course of the illness (Bellack et al., 1990; Cannon et al., 1997; Harvey et al., 2006; Morrison and Bellack, 1987; Pogue-Geile and Harrow, 1985). Further, high levels of social withdrawal have been associated with longer and more debilitating prodromal periods (Binder et al., 1998; Cullen et al., 2011). Although it is apparent that asociality plays an important role in the course of schizophrenia, the processes that underlie social withdrawal are not well understood. Thus, tests that assess different aspects of social engagement may be essential in elucidating the neurobiological substrates that underlie the negative symptoms of schizophrenia as well as to identify novel targets for future drug discovery.

Modeling symptoms of schizophrenia, in general and the negative symptoms, in particular, in animals is challenging because of the relatively poor understanding of the etiology and pathophysiology of the illness, as well as the human nature of the illness (Nestler and Hyman, 2010; Wilson and Terry, 2010; Van den Buuse et al., 2005). Nonetheless, efforts have been made to develop appropriate paradigms for various negative symptoms of schizophrenia including social withdrawal (Desbonnet et al., 2012; Ellenbroek and Cools, 2000; Neill et al., 2010). As rodents exhibit a structured and stable degree of social behavior, measuring social behavior in rats and mice is relatively straightforward (Ellenbroek and Cools, 2000; Meaney and Stewart, 1981). The aim of this review is to discuss the social interaction task as a behavioral paradigm for investigating aspects of social withdrawal relevant to the symptoms associated with schizophrenia. We examine several pharmacological and neurodevelopmental models that exhibit deficits in social interaction as well as the possible neurobiology underlying rodent social behaviors measured throughout the task. Additionally, other models of social behaviors that may further our understanding of social dysfunction are identified in a brief discussion.

2. Social interaction

2.1. Social interaction task

Social behaviors refer to behaviors that occur when two or more individuals of the same species interact. Rodents are highly social animals and when placed into an area in which territory has not been established, they socially engage with one another displaying a number of behavioral acts that can be quantitatively measured (Sams-Dodd, 1995b). These include both playful and aggressive acts such as pouncing, chasing, social grooming, crawling over/under, charging, boxing, wrestling, pinning, anogenital sniffing, and biting (Vanderschuren et al., 1997). Further, social interaction appears to be rewarding to rodents, with behaviors increased by social deprivation and reduced by social satiation (Calcagnetti

and Schechter, 1992; Humphreys and Einon, 1981; Panksepp and Beatty, 1980). Currently, rat and mouse social interaction are tested in several ways.

The social interaction task was initially described for the use of measuring anxiety (File and Hyde, 1978). Social interaction is typically assessed by placing a pair of unfamiliar rodents into an arena under bright lighting condition with an observer scoring the amount of time animals spend engaged with one another (File, 1980). However, with very simple modifications, such as extensive habituation to the arena, close weight-matching of the animals, low lighting conditions and ad-libitum food availability, the task actually minimizes the anxiety-related components of the social interaction task and becomes more relevant to assessing the preference of rodents to engage in social behaviors (File and Hyde, 1978; Lee et al., 2005; Vanderschuren et al., 1997). A significant reduction in social interaction by test subjects is often interpreted as social withdrawal (Sams-Dodd, 1995b; Sams-Dodd, 1996). The social interaction test is typically hand-scored but can also be automated via video-tracking systems, however these systems may be limited by the inability to distinguish aggressive from non-aggressive behaviors, passive interaction (i.e., rats sitting or lying close together, yet there is no other interaction between them) from active interaction, as well as which animal initiates the behavior, which are all critical features of the analysis (Lee et al., 2005; Sams-Dodd, 1995a). Importantly, male rat social interaction, if performed under non-anxiogenic conditions as described above, is also not related to the level of maternal behavior rat pups experience postnatally in distinction to anxiety and depressive phenotypes (Lee et al., 2007; Weaver et al., 2006).

Another version of the task utilizes an arena divided into several chambers and the time the rodent (typically mice) spends in the chamber with a caged unfamiliar conspecific and the empty chambers is scored (Moy et al., 2004). This measure of behavior has been termed social approach and preference for the empty chamber is thought to reflect social avoidance. This task can also be automated for a more objective approach as well as to allow high-throughput scoring (Nadler et al., 2004). The paradigms previously described are commonly utilized, though other variants have been described in the literature. For example, Bitanihirwe and colleagues described a paradigm in which a Y-maze was employed to analyze the time animals spent interacting with a caged conspecific versus a caged “dummy” rat (Bitanihirwe et al., 2010).

While the original intent of social interaction testing was to examine anxious phenotypes, performing either procedure above under less anxiogenic conditions can provide a good indication of rat or mouse social motivation, which may have relevance to the social desire of people with schizophrenia especially if performed in etiologically appropriate animal models as discussed below.

2.2. Pharmacological models that exhibit altered social interaction

Several psychotomimetic agents induce deficits in social interaction and therefore may provide valid pharmacological models of social withdrawal with possible relevance to schizophrenia (Table 1). Phencyclidine (PCP) is a non-competitive NMDA receptor antagonist that elicits psychotic behaviors resembling schizophrenia in healthy individuals as well as mimicking several negative and cognitive symptoms associated with the disorder

(Luby et al., 1959). Additionally, PCP is also known to exacerbate symptoms of patients diagnosed with schizophrenia, thus the agent has been used as one of the primary psychomimetic models in schizophrenia research (Javitt and Zukin, 1991; Malhotra et al., 1997). In accordance, PCP has been found to reliably produce social interaction deficits in rodents when experimental conditions favor social exploration by limiting aversive stimuli (e.g., bright lighting) that could produce anxiety (Gururajan et al., 2010; Sams-Dodd, 1995b). Indeed, numerous studies have found a dose-dependent reduction in social behaviors of adult male rats following acute, subchronic and chronic exposure to PCP (0.5–30 mg/kg) during a social interaction task and in female rats following subchronic exposure (Bruins Slot et al., 2005; Lee et al., 2005; Sams-Dodd, 1995a; Sams-Dodd, 1996; Seillier et al., 2013; Snigdha and Neill, 2008). One study also found that subchronic treatment (15 days) with 10 mg/kg of PCP increased aggressive responses (Audet et al., 2009). Furthermore, the deficits in sociality could be observed as late as 6 weeks posttreatment following sub-chronic administration (Snigdha and Neill, 2008). While PCP has been shown to decrease social interaction time, Lee and colleagues also found that PCP administration modified the quality of social behavior. Rats treated with PCP showed a reduction in contact behaviors and an increase in non-contact behaviors. Interestingly, oxytocin administration into the central nucleus of the amygdala reversed this shift in behavioral quality (Lee et al., 2005). Acute and subchronic PCP administration (5–10 mg/kg) has also been found to be effective in reducing social interaction in mice, with deficits lasting for up to 28 days following subchronic treatment (Haller et al., 2005; Qiao et al., 2001). Furthermore, exposure to PCP during early and late development produced long-term deficits in social interaction in adult rodents (Nakatani-Pawlak et al., 2009; White et al., 2009).

The inference that non-competitive NMDA receptor antagonism in rodents produce deficits in social interaction is further supported by studies utilizing similar agents, dizocilpine (MK-801) and ketamine which also produces psychosis and negative-like symptoms in healthy human subjects (Krystal et al., 1994; Lahti et al., 1995a; Lahti et al., 1995b). For instance, acute and subchronic treatment of MK-801 (0.1–0.3 mg/kg) has been shown to reduce social interaction in adult male rats and mice (de Moura Linck et al., 2008; Matsuoka et al., 2008; Rung et al., 2005). Further, acute and subchronic administration of ketamine (7–30 mg/kg) impaired social interaction in adult male rats (Becker et al., 2003; Silvestre et al., 1997; Uribe et al., 2013). The deficits in social interaction observed in rodents following PCP and other NMDA receptor antagonists seem to correlate to the PCP- and ketamine-induced social withdrawal seen in humans, further supporting social interaction as readout for investigating negative symptoms associated with schizophrenia, more specifically asociality (Sams-Dodd, 1995b).

Amphetamine produces hallucinations and delusions in healthy human subjects, thus is another primary psychomimetic model in schizophrenia research (Snyder, 1973). However, studies suggest that amphetamine does not mimic the social deficits seen with PCP and has even been suggested to produce improvements of these symptoms (Javitt, 1987; Lindenmayer, 1995). This has been supported in several rodent studies which reported that acute and subchronic treatment with amphetamine (4–17 mg/kg) had little effect on social interaction in male rats, and was even suggested to increase social interaction in a study by Guy and Gardner (Der-Avakian and Markou, 2010; Guy and Gardner, 1985; Sams-Dodd,

1995a; Sams-Dodd, 1996). There has also been evidence that exposure to amphetamine (4–8 mg/kg) decreases social interaction in rats, however theses studies were done using an intruder paradigm (i.e., test animal is placed into a stable home colony) used to measure territorial aggressive behaviors instead of a familiar non-territorial environment optimal for testing non-aggressive social behaviors (Gambill and Kornetsky, 1976; Steinpreis et al., 1994; Thurmond, 1975). The pharmacological manipulations listed above support the validity of the rodent social interaction task as a behavioral paradigm for studying social deficits that may be associated with schizophrenia, as the social behaviors observed in the rodents after administration correspond with those seen in healthy human subjects following administration.

Antipsychotic drugs are often used to establish the predictive validity (i.e., the degree to which the model can be used to predict efficacy of a new therapeutic agent in humans) of animal models of schizophrenia (further discussed in section 2.4). The ability of typical and atypical antipsychotics to reverse PCP-induced social deficits has been found to be dependent on the agent, dose and length of treatment. In male rats, subchronic treatment (3 days) with haloperidol (0.01–0.64 mg/kg), clozapine (0.16–10 mg/kg), olanzapine (0.16–2.5 mg/kg), and quetiapine (0.16–10 mg/kg) had no effect on active social interaction deficits produced by subchronic PCP treatment (2.0–2.5 mg/kg) and was even found to further suppress interaction in some instances (Bruins Slot et al., 2005; Sams-Dodd, 1996; Sams-Dodd, 1997). Conversely, subchronic treatment with risperidone (0.02–0.63 mg/kg), aripiprazole (0.04–0.16 mg/kg), and sertindole (0.01–2.5 mg/kg) partially reversed PCP-induced social deficits dose-dependently. In the same studies, chronic antipsychotic treatment (21 days) showed similar results, with haloperidol, olanzapine and quetiapine having no effect on PCP-induced active social interaction in male rats while sertindole reversed the social deficits. However, chronic treatment with risperidone no longer effected active social interaction, while chronic treatment with clozapine was able to partially reverse social deficits produced by PCP. Interestingly, most of the agents produced a minor yet significant dose-dependent increase in passive social interaction, however these effects were seen in both vehicle and PCP-treated rats thus the effects were most likely not specific to PCP-induced social withdrawal (Sams-Dodd, 1997).

In a study using female rats, treatment with ziprasidone (2.5 mg/kg) was found to reverse enduring PCP-induced social deficits, while haloperidol (0.05 mg/kg) and clozapine (2.5 mg/kg) were ineffective (Snigdha and Neill, 2008). In another study, haloperidol (1–3 mg/kg) had no effect on persistent social deficits produced by administration of PCP for 14 days in male mice, whereas subchronic treatment (7 days) with clozapine (10 mg/kg) attenuated these deficits (Qiao et al., 2001). Clozapine (0.3–3 mg/kg) also significantly reversed social interaction impairments in adult male mice induced by neonatal phencyclidine treatment (Nakatani-Pawlak et al., 2009).

Studies of antipsychotics in other rodent models of NMDA antagonism also produced inconsistent results. Acute treatment with clozapine (1–3 mg/kg) was found to significantly reverse the MK-801-induced (0.6 mg/kg) reduction in social encounters in male rats (Gururajan et al., 2011). Conversely, clozapine (2 mg/kg) was unable to reverse MK-801-induced (0.3 mg/kg) social deficits in male mice (de Moura Linck et al., 2008). Additionally,

subchronic treatment (10 days) with clozapine (0.5 mg/kg) and risperidone (0.2 mg/kg) was found to increase non-aggressive social behaviors following administration of ketamine (30 mg/kg for 5 days), while subchronic haloperidol (0.075 mg/kg) had no effect (Becker and Grecksch, 2004). However, in the same study, subchronic treatment with diazepam (0.5 mg/kg) produced results similar to those seen by clozapine and risperidone suggesting that the effects of the atypical antipsychotics may be anxiolytic in nature instead of due to a specific neuroleptic effect.

Thus, social impairments in rats and mice can be induced by administration of psychostimulants that act through glutamate receptor antagonism and second generation antipsychotic drugs appear to reverse many of the social interaction deficits, although results are not consistent. It is also important to note that the positive effects of anti-psychotic treatment on PCP are acute and studies have not yet been able to measure any long-term effects of treatment. This would suggest limited predictive validity (validity that is limited to particular classes of compounds) and thus these pharmacological models may not be useful for identification of a novel class of compounds (Floresco et al., 2005; Sams-Dodd, 1998).

2.3. Neurodevelopmental models that exhibit altered social interaction

Several studies have shown that maternal stress, maternal infection and obstetric complications increase the risk of a child developing schizophrenia later in life, possibly due to disruption in neurodevelopment (Brixey et al., 1993; reviewed in Markham and Koenig (2011)). A number of rodent neurodevelopmental models designed to mimic these insults result in altered social interaction, therefore may provide etiologically appropriate models for understanding social withdrawal associated with schizophrenia (Table 2). For example, gestational disruption of neurodevelopment by treating pregnant rat dams with methylazoxymethanol acetate (MAM) on gestational day 17 (GD17) reduced active social interaction in young adult male offspring (Flagstad et al., 2004). In another study, neonatal ibotenic acid lesion of the ventral hippocampus on postnatal day 7 (PND7) significantly reduced active social interaction at both PND 35 and PND 65 in male rats compared to sham-treated controls, although the reduction may have been indirectly caused by an anxiogenic effect of the lesion as lesioned rats also had a significant reduction in time spent in the center of the arena (Sams-Dodd et al., 1997).

Several prenatal and neonatal rodent immune challenge models are also associated with deficits in social interaction. For instance, prenatal exposure to the viral mimic polyriboinosinic–polyribocytidilic acid (Poly-I:C) on GD 17 led to significant deficits in social interaction in both adult female and male mice, as test animals displayed no preference towards an unfamiliar conspecific versus a dummy rat (Bitanihirwe et al., 2010). Another study found that male and female mice born to mothers infected with human influenza virus (GD 9) also showed a significant reduction in social interaction, although this may be an effect of anxiety as test subjects had a significant reduction in the time spent in the center zone during an open field task (Shi et al., 2003). In another study, prenatal exposure to lipopolysaccharide (LPS; GD 9) reduced play behavior in preadolescent male rats as well as significantly decreased social interaction in adult male rats (Kirsten et al., 2010). Additionally, there was no evidence that the effects on social interaction were a

product of anxiety as no alterations were observed during plus maze studies. In a study by Lancaster and colleagues, neonatal Borna disease virus (BDV) infection was found to significantly reduce active social interaction in male rats both at PND 90 and PND 180 compared to controls, though the amount of time the test animals followed their unfamiliar conspecific was significantly increased (Lancaster et al., 2007).

There have also been a number of rodent models of prenatal and postnatal stress developed that produce impaired social interaction. For example, exposure of pregnant mice to restraint stress twice a day for 30 min, beginning on GD 7 and continuing until delivery, was shown to significantly reduce social interaction in young adult male offspring (Matrisciano et al., 2012). In studies performed in our lab, prenatal exposure *in utero* to a series of unpredictable stresses during the third week of gestation significantly reduced social interaction in both adolescent (PND 35) and young adult (PND 56) male rats (Lee et al., 2007). Furthermore, the quality of social interaction was diminished as prenatally stressed rats spent a significantly larger percentage of their social interaction time engaged in non-contact behavior (e.g., following) compared to controls who spent the majority of social interaction time engaged in contact behaviors (e.g., sniffing, crawling). It is unlikely that the impairments in social interaction were a product of anxiety as male rats exposed to variable prenatal stress perform similarly to controls during behavioral assays designed to measure anxiety (Lee et al., 2007; Wilson et al., 2013). There have also been several studies reporting altered social behaviors in rodents exposed to social isolation during adolescence. Isolation rearing has consistently been found to increase aggressive behaviors in male rats; however the effect on non-aggressive behaviors has been less consistent with some studies showing a significant decrease in social interaction while others found a significant increase in social behaviors (Lukkes et al., 2009; Meng et al., 2010; Van den Berg et al., 1999; Zhao et al., 2009). One possible reason for the contrasting results may be due to the inconsistent period of time rats were socially isolated (2–8 weeks). It is also possible that the results are a product of the anxiogenic-like behaviors induced by isolation rearing shown in several of the studies and thus do not accurately reflect social behaviors. Future studies focusing on a critical time window at which development is most sensitive to social isolation may provide further clarity to the effects of social isolation on social interaction behaviors (Meng et al., 2010).

Relatively few studies have been published analyzing the effects of antipsychotics on social withdrawal associated with rodent neurodevelopmental models of schizophrenia and these results have shown a lack of effect for both typical and atypical agents. For instance, chronic clozapine (0.63–2.5 mg/kg) was unable to reverse social deficits induced by neonatal ventral hippocampal lesion in male rats (Sams-Dodd et al., 1997). Moreover, we found that subchronic treatment with haloperidol (0.3 mg/kg) for 7 days failed to improve the social withdrawal exhibited by rats exposed to a variable prenatal stress paradigm.

The ability of neurodevelopmental models to produce deficits in social interaction further supports the validity of the behavioral task for investigating social withdrawal associated with schizophrenia and the presence of these deficits in both adolescent and adult rodents furthers supports the validity of the task as social deficits are observed in schizophrenic patients before, during and after the first psychotic episode. Additionally, compared to the

pharmacological models previously mentioned, neurodevelopmental models may be more appropriate in elucidating the neuropathology that underlies social dysfunction and identifying novel therapeutic targets due to the lack of etiological validity of pharmacological models as well as the limitations related to a novel therapeutic agent directly attenuating the effects of the animal manipulation itself (i.e., the drug-related effect) instead of what may be disrupted in schizophrenia (Floresco et al., 2005).

2.4. The use of antipsychotics for predictive validity of social interaction tasks

The ability of antipsychotic drug treatment to ameliorate behavioral deficits associated with rodent models of schizophrenia is often used to determine predictive validity. However, the use of these agents to establish predictive validity of models of negative symptoms is not likely to be applicable. While the introduction of second-generation antipsychotics suggested a breakthrough in the treatment of negative symptoms, accumulated results from several clinical studies suggest that currently available treatment options have minimal benefits for these symptoms with studies consistently showing either small effect sizes or inconsistent results (Carpenter and Koenig, 2008; Erhart et al., 2006; Leucht et al., 1999). Additionally, the few beneficial effects observed in patients seem to be coupled to a reduction in positive symptoms (Tandon et al., 2010). Similarly, as discussed in the previous Sections 2.2 and 2.3, rodent studies to determine the ability of antipsychotics to ameliorate deficits of social interaction in models of schizophrenia also produce inconsistent results with slight effects.

While the inconsistent results of antipsychotic drugs on rodent social interaction may be reflective of the modest and diverse effects of these agents on negative symptoms associated with schizophrenia, it is important to recognize that the interpretation of results may be influenced by several factors. Stereotypic behaviors, anxiety and locomotor activity can often be influenced by antipsychotic treatment. The social interaction behavioral task is advantageous in that it is possible to measure several behavioral parameters in a single experiment; however it is possible for these parameters to interact ultimately leading to false positive results for a specific parameter. Further, as the specificity by which a drug can alleviate behaviors resulting from pharmacological or neurodevelopmental manipulations is often evaluated by comparing the drug's effects on vehicle or untreated rodents, it is sometimes difficult to separate specific from non-specific effects (Sams-Dodd, 1997).

2.5. Neurobiology of social interaction relevant to schizophrenia

Several neurotransmitter systems have been implicated in the mediation of social interaction behaviors. As stated previously several pharmacological compounds (e.g., PCP and amphetamine) have been found to disrupt social interaction in rodents, providing pharmacological evidence that the dopaminergic, glutamatergic systems, and possibly the cholinergic and norepinephrine system play an important role in social behaviors (Javitt, 2007; Snyder, 1972; Thomsen et al., 2009). Additionally, it has also been found that injections of GABAergic agonists increase social interaction implicating a role of the GABAergic system (Corbett et al., 1991). In addition, neuropeptides have also been found to be an important mediator of social behavior (Adkins-Regan, 2009; Carter et al., 2008). In male rats, central administration of oxytocin exerted a dose dependent response on social

memory (Popik and van Ree, 1991). Additionally, oxytocin and arginine vasopressin administration in the olfactory bulb was found to facilitate and prolong social recognition (Dluzen et al., 1998a). Furthermore, it was found that the norepinephrine system of the olfactory bulb mediated the effects of oxytocin arginine vasopressin on social recognition (Dluzen et al., 1998b).

It is not surprising that studies have revealed the role of several regions of the forebrain (e.g., amygdala, hippocampus, and frontal cortex) as well as regions of the hindbrain in the modulation of rodent social interaction (see review, File and Seth, 2003). The amygdala is known to play an important role in mediating changes in anxiety and thus has been implicated in the neurobiology underlying anxiety-like behaviors in rodents during the social interaction task. Additionally, several studies have shown that GABAergic and serotonergic modulation of the amygdala may underlie these behaviors. For instance, depletion of amygdaloid serotonin (5-HT) concentrations results in decreased social interaction (File et al., 1981). In another study, infusion of the selective 5-HT1A receptor agonist, 8-OH-DPAT caused an overall reduction in levels of social investigation, while the benzodiazepine receptor agonist, midazolam, increased social interaction suggesting an anxiolytic effect (Gonzalez et al., 1996). The amygdala has also been implicated in mediating social play during social encounters with increased endocannabinoid signaling enhancing social play, possibly through interaction with opioid and dopaminergic neurotransmission (Trezza et al., 2012). Our studies in PCP and prenatally stressed rats targeted amygdala for infusions of oxytocin to reverse social deficits and emphasize the role of the amygdala in social interaction behaviors (Lee et al., 2005, 2007).

The hippocampus has also been implicated in the control of anxiety and is thought to play a possible role in social behavioral responses in the social interaction task. Stimulation of benzodiazepine receptors via bilateral injection of midalzolam into the dorsal hippocampus significantly increased social interaction in rats (Gonzalez et al., 1998). Lesione studies showed varied responses as male rats lesioned with ibotenic acid in the ventral or dorsal hippocampus at 8 weeks of age showed no changes in social interaction, while male rats lesioned at 8 months of age produced a significant increase in social interaction (Becker et al., 1999; Deacon et al., 2002). Another study found that hippocampal neurons discriminate between rats and inanimate objects although they did not discriminate between individual rats (von Heimendahl et al., 2012). In the same study it was also found that social encounters did not induce c-Fos expression in the hippocampus, however there was a social interaction-specific expression in the basolateral amygdala.

The prefrontal cortex and cerebellum have also been implicated in playing a role in social interaction. Lesion of the cerebellar fastigial nucleus, but not of the cerebellar cortical, resulted in significant reductions in social interaction suggesting that ascending fastigial projections to limbic structures may mediate social interaction (Berntson and Schumacher, 1980). Prefrontocortical dopamine loss by injection of 6-hydroxydopamine significantly reduced social interaction in rats, with more extensive impairment in social behaviors among adolescent rats compared to adult rats (Fernandez Espejo, 2003). Another study found that a coronal transection, separating the medial prefrontal cortex (MPFC) from the basal ganglia, significantly enhanced social interaction in male rats without affecting locomotor activity

(Gonzalez et al., 2000). In another study, ibotenic acid lesion of the MPFC (including prelimbic, infralimbic and anterior cingulate) significantly increased active time in social interaction in rats when tested under bright lighting conditions in a novel environment, while MPFC lesions had no effect on social interaction when test parameter included low lighting in a familiar environment (Shah and Treit, 2003). Additionally, using novel optigenetic tools, it has been found that elevations in the cellular balance of excitation and inhibition within the mouse medial prefrontal cortex produce profound, yet reversible, impairments in social function without motor abnormalities or increased anxiety (Yizhar et al., 2011; Yizhar, 2012).

Demonstrating construct validity for animal models of schizophrenia is difficult as neurobiological substrates underlying the deficits associated with schizophrenia have not been clearly established (Wilson and Terry, 2010). However, the suggested neurobiology underling the deficits in social interaction behaviors in rodents are similar to pathophysiological features observed in schizophrenia. The hippocampus, amygdala, prefrontal cortex and cerebellum have all been implicated in the pathophysiology of schizophrenia (Goghari et al., 2010; Yeganeh-Doost et al., 2011). Additionally, there is a large amount of evidence suggesting alterations in several neurotransmitter systems in schizophrenia including the dopaminergic, serotonergic, GABAergic and glutamatergic system (Carlsson et al., 2001). Postmortem studies also suggest that oxytocin neurotransmission may be altered in schizophrenia (Bernstein et al., 1998; Mai et al., 1993). The medial prefrontal cortex and amygdala have been highlighted as playing a specific role in social processing (Amodio and Frith, 2006; Habel et al., 2007). Postmortem studies of patients diagnosed with schizophrenia suggest alterations in PFC inhibitory neurotransmission (Hashimoto et al., 2003; Lewis et al., 2005). Also, studies in patients diagnosed with schizophrenia have shown that amygdala volume and activation are associated with emotional processing deficits and severity of negative symptoms (Gur et al., 2002, 2004). Collectively, these studies further support the validity of the social interaction task for studying negative symptoms associated with schizophrenia.

2.6. Other behavioral paradigms of social behaviors

In humans, the ability to socially interact appropriately requires the capability to construct mental representations about others, oneself, and relations between others and oneself, termed social cognition (Adolphs, 2001). Patients diagnosed with schizophrenia have been found to display deficits in several domains of social cognition including social knowledge, social perceptions, theory of mind (i.e., the ability to understand the behavior and intentions of others in terms of their mental state), and emotional processing (Archer et al., 1994; Corrigan and Addis, 1995; Corrigan and Green, 1993; Greig et al., 2004). Therefore, animal paradigms that are capable of measuring different components of social behaviors (e.g. social memory and social motivation) may be useful in further understanding the social deficits that are associated with schizophrenia.

2.6.1. Social recognition—Social recognition, also termed social novelty discrimination or social memory, relies on the ability of the experimental rodent to recognize a conspecific as familiar indicated by either a reduction in social interaction with the familiar conspecific

or preference for socially interacting with a non-familiar conspecific (Engelmann et al., 1995; Kaidanovich-Beilin et al., 2011). While not as well studied as social interaction, there have been several research studies analyzing impaired social recognition in animal models of schizophrenia. For example, acute treatment with MK-801 (0.1 mg/kg) produced diminished discriminative capabilities for a familiar versus novel conspecific in both male rats and mice (Zou et al., 2008). Additionally, pretreatment with clozapine (0.3–1 mg/kg), but not haloperidol (0.01–0.1 mg/kg), significantly attenuated the effects of MK-801 in male rats (Shimazaki et al., 2010). In a study by Harich and colleagues, treatment with PCP (10 mg/kg) on PND 7, 9, and 11 significantly reduced exploration of a novel juvenile in adult male rats (Harich et al., 2007). In the same study, acute treatment with clozapine (3 mg/kg) significantly enhanced novelty discrimination indices in rats neonatally treated with PCP, though clozapine was found to inhibit social interaction in both PCP-naive and PCP-treated rats. In another study, vasopressin deficient Brattleboro rats which have previously been shown to have several natural schizophrenia-like deficits, exhibited impaired social discrimination that could be restored by acute administration of 10 mg/kg clozapine (Feifel et al., 2009). Therefore, the results suggest validity of social recognition paradigms for studying social deficits associated with schizophrenia. Additionally, it is possible that paradigms of social recognition may further our understanding of the different underlying mechanisms involved in social interaction and social memory, as well as provide useful information on how these social components differ in their susceptibility to therapeutic treatments (e.g. antipsychotics).

2.6.2. Social conditioned place preference—Conditioned place preference is one of the most popular paradigms for studying motivation and reward (for review see Tzschentke, 2007). In studies using social interaction for conditioning, both rats and mice prefer an environment in which a social partner was previously located regardless of age (e.g., adolescent and adult), suggesting a rewarding aspect of social interaction (Calcagnetti and Schechter, 1992; Panksepp and Lahvis, 2007; Stewart and Grupp, 1985). Unfortunately, relatively few studies have been published analyzing social conditioned place preference in animal models of schizophrenia. In one study, subchronic treatment (7 days) with 5 mg/kg PCP was found to significantly decrease preference for the social chamber in male rats (Schwabe et al., 2006). In another study, socially-conditioned wild-type mice had a strong preference for the location where social interactions took place, whereas mice with disrupted-in-schizophrenia-1 Gln31Leu polymorphism spent more time in the compartment where they were isolated during the conditioning sessions (Lipina et al., 2013). These results suggest that the social conditioned place preference task may also be useful for studying social deficits associated with schizophrenia; however more specific studies are necessary to determine the validity of the paradigm. Additionally, similar to the social interaction task, controlling for factors such as anxiogenic-like behaviors or hyperactivity is necessary for accurate behavioral assessment.

2.6.3. Social empathy—Recent studies suggest the possibility that social empathy occurs in rodents and describe behavioral paradigms that may be capable of quantifying this behavior (for review see Panksepp and Lahvis, 2011). In one experimental procedure, experimental mice observed distressed conspecifics undergoing a series of tone-shock foot

pairings (Chen et al., 2009). Experimental mice had significant changes in heart rate when distress vocalizations were emitted from con-specifics as well as increased freezing responses to environmental cues that predicted social distress. Additionally, genetic background was found to substantially influence the magnitude of these responses. In another experimental procedure, experimental rats were placed in an arena with a cagemate trapped in a restrainer (Ben-Ami Bartal et al., 2011). Experimental rats learned to intentionally open the restrainer to free their cagemate but left empty or object-containing restrainers alone. While the results of this specific procedure could be interpreted as social empathy, as previously stated social interaction appears to be rewarding in rodents and thus cannot be ruled out as a possible underlying motivation for opening the restrainer. A considerable amount of research is still required to further our understanding of the behaviors observed in these paradigms, however if valid, the paradigm could prove to be crucial in elucidating the underlying mechanisms involved in social cognition.

2.6.4. Social communication—Social communication is an important component of successful social interactions and has been found to be affected in a number of neuropsychiatric disorders including schizophrenia and autism (DeLisi, 2001; Frith and Happé, 1994). In rodents, pups often emit ultrasonic vocalizations as an early communicative behavior between pup and mother, which increase when exposed to stressors (Goodwin et al., 1994; Shair, 2007). Additionally, complex vocalizations are emitted by juveniles engaged in social interactions as well as adult males in response to female pheromones (Knutson et al., 1998). Interestingly, one study found that ultrasonic vocalizations were a strong predictor of the extent of social interaction in mice (Panksepp et al., 2007). Therefore, it has been suggested that measures of ultrasonic vocalization may be useful in studying deficits in social communication. In one model of schizophrenia, offspring of pregnant rats administered poly I:C (4.0 mg/kg; GD 15) were found to have increased affective ultrasonic communication during fear learning (Yee et al., 2012). In another model, pups prenatally exposed to LPS (100 μg/kg; GD 15 and 16) had a significant decrease in the number and duration of ultrasonic vocalization calls at PND 3 and PND 5 (Baharnoori et al., 2012). Further, clozapine (10 mg/kg) but not haloperidol (0.2 mg/kg) significantly enhanced isolation-induced pup ultrasonic vocalization calls (Li et al., 2011). Unfortunately, however, it is premature to suggest that this endpoint has significant relevance to any aspect of schizophrenia symptomatology and further studies will be needed to gain a clearer understanding of the relationship between vocalizations and social behaviors later in life.

3. General discussion

Positive social interactions are essential for the emotional well-being, healthy development, and reproductive success of both humans and animals. Rodent paradigms that evaluate social behaviors are necessary to identify the mechanisms that underlie social dysfunction. As the negative symptom, asociality, is a core behavioral feature in schizophrenia, social behavioral paradigms may prove useful in investigating the negative symptoms associated with schizophrenia as well as discovering novel therapeutic treatments.

A number of rodent pharmacological and neurodevelopmental models of schizophrenia produce deficits in social interaction. To date, the most well studied of the models is pharmacological treatment with the psychotomimetic agent, PCP. PCP has consistently been found to induce social withdrawal in rodents whether administered acutely or chronically, producing enduring deficits lasting at least six weeks following withdrawal (Sams-Dodd, 1995a, b, 1996; Snigdha and Neill, 2008). However, while the results of pharmacological models support the face validity of the behavioral task for investing social withdrawal associated with schizophrenia, neurodevelopmental models may be more appropriate as they are etiologically valid and may be useful when studying the course of the negative symptoms. Whereas, pharmacological models produce deficits that endure for several weeks, neurodevelopmental models are capable of producing lasting deficits observed from preadolescence through late adulthood. Additionally, in drug development, pharmacological models have limitations related to the novel therapeutic agent directly attenuating the effects of the compound used for animal manipulation itself. Further, neurodevelopmental animal models also produce abnormalities in multiple neural systems associated with schizophrenia; thus, better approximating the pathophysiology of the disorder.

There is also evidence that treatment with atypical anti-psychotics is capable of reversing the social deficits associated with the models of schizophrenia supporting predictive validity of the model (Qiao et al., 2001; Sams-Dodd, 1996). However results of these studies were inconsistent. This is not surprising as results of studies analyzing antipsychotic use for negative symptoms in patients with schizophrenia have also been inconsistent, with the effectiveness of the treatment found to be inadequate (Erhart et al., 2006; Leucht et al., 1999). While it is necessary to determine the predictive validity of animal models that exhibit social deficits associated with schizophrenia, it may not be feasible until more effective therapeutics are developed which consistently reduce negative symptoms such as social withdrawal in schizophrenia patients.

Determining construct validity of social deficits produced by rodent models of schizophrenia is difficult since the processes that underlie social interaction are not well understood. Additionally, as schizophrenia is associated with dysfunction of several neurotransmitter systems as well as a wide range of symptoms it becomes difficult to separate out the precise mechanism of action of a specific deficit associated with the disorder. Nevertheless, the social interaction task appears to have validity for some pathophysiological features of schizophrenia that may be related to negative symptoms. For instance, hippocampus, amygdala, prefrontal cortex and cerebellum have been implicated in playing specific roles in both social interaction and negative symptoms (File and Seth, 2003; Goghari et al., 2010; Yeganeh-Doost et al., 2011). Additionally, there is a large amount of evidence suggesting several neurotransmitter systems (e.g., dopaminergic and glutamatergic) involved in social interaction are also altered in schizophrenia (Carlsson et al., 2001).

It is also important to note that deficits in social interaction have also been observed in several purported rodent models for autism (Moy and Nadler, 2008; Patterson, 2011). This is not surprising as social dysfunction is a central feature of the disorder (Volkmar, 2011). Due to the similarities of the social deficits produced by rodent models of schizophrenia and autism, the behavioral paradigms may not be able to differentiate between the social

dysfunction associated with the two disorders. Thus, while the social interaction task may be useful in investigating the negative symptoms associated with schizophrenia, the behaviors more likely reflect a general social dysfunction associated with several neuropsychiatric disorders. Though, once therapeutic agents become available to treat the negative symptoms associated with schizophrenia and/or the social dysfunction associated with autism, it may be possible to determine differences (if any) between the social deficits observed in animal models of the two disorders.

Nonetheless, studies of the social interaction task support the paradigm for investigating the negative symptoms of schizophrenia, particularly asociality. However, the ability to socially interact appropriately requires intact social cognition. Utilizing several rodent paradigms that are capable of measuring different components of social behaviors may further our understanding of the different underlying mechanisms involved in social behaviors, how the components interact, and how the components differ in their susceptibility to therapeutic treatments.

Acknowledgments

The authors are supported by NIH Grants T32 MH067533 (CAW) and P50 MH082999 (Project 1 and Core 3 – JIK).

Role of the funding source

Neither Christina Wilson nor James Koenig received funding for the preparation of this manuscript.

References

Adkins-Regan E. Neuroendocrinology of social behavior. ILAR J. 2009; 50:5–14. [PubMed: 19106448]

Adolphs R. The neurobiology of social cognition. Curr. Opin. Neurobiol. 2001; 11:231–239. [PubMed: 11301245]

Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. Nat. Rev. Neurosci. 2006; 7:268–277. [PubMed: 16552413]

Archer J, Hay DC, Young AW. Movement, face processing and schizophrenia: evidence of a differential deficit in expression analysis. Br. J. Clin. Psychol. 1994; 33:45–61.

Audet MC, Goulet S, Doré FY. Impaired social motivation and increased aggression in rats subchronically exposed to phencyclidine. Physiol. Behav. 2009; 96:394–398. [PubMed: 19046980]

Baharnoori M, Bhardwaj SK, Srivastava LK. Neonatal behavioral changes in rats with gestational exposure to lipopolysaccharide: a prenatal infection model for developmental neuropsychiatric disorders. Schizophr. Bull. 2012; 38:444–456. [PubMed: 20805287]

Becker A, Grecksch G. Ketamine-induced changes in rat behaviour: a possible animal model of schizophrenia. Test of predictive validity. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2004; 28:1267–1277. [PubMed: 15588753]

Becker A, Grecksch G, Bernstein HG, Höllt V, Bogerts B. Social behaviour in rats lesioned with ibotenic acid in the hippocampus: quantitative and qualitative analysis. Psychopharmacology (Berl). 1999; 144:333–338. [PubMed: 10435405]

Becker A, Peters B, Schroeder H, Mann T, Huether G, Grecksch G. Ketamine-induced changes in rat behaviour: a possible animal model of schizophrenia. Prog. NeuroPsychopharmacol. Biol. Psychiatry. 2003; 27:687–700. [PubMed: 12787858]

Bellack AS, Morrison RL, Wixted JT, Mueser KT. An analysis of social competence in schizophrenia. Br. J. Psychiatry. 1990; 156:809–818. [PubMed: 2207511]

Ben-Ami Bartal I, Decety J, Mason P. Empathy and pro-social behavior in rats. Science. 2011; 334:1427–1430. [PubMed: 22158823]

Bernstein HG, Stanarius A, Baumann B, Henning H, Krell D, Danos P, Falkai P, Bogerts B. Nitric oxide synthase-containing neurons in the human hypothalamus: reduced number of immunoreactive cells in the paraventricular nucleus of depressive patients and schizophrenics. Neuroscience. 1998; 83:867–875. [PubMed: 9483570]

Berntson GG, Schumacher KM. Effects of cerebellar lesions on activity, social interactions, and other motivated behaviors in the rat. J. Comp. Physiol. Psychol. 1980; 1980(94):706–717. [PubMed: 7410630]

Binder J, Albus M, Hubmann W, Scherer J, Sobizack N, Franz U, Mohr F, Hecht S. Neuropsychological impairment and psychopathology in first-episode schizophrenic patients related to the early course of illness. Eur. Arch. Psychiatry Clin. Neurosci. 1998; 248:70–77. [PubMed: 9684915]

Bitanihirwe BK, Peleg-Raibstein D, Mouttet F, Feldon J, Meyer U. Late prenatal immune activation in mice leads to behavioral and neurochemical abnormalities relevant to the negative symptoms of schizophrenia. Neuropsychopharmacology. 2010; 35:2462–2478. [PubMed: 20736993]

Breier A, Schreiber JL, Dyer J, Pickar D. National Institute of Mental Health longitudinal study of chronic schizophrenia: prognosis and predictors of outcome. Arch. Gen. Psychiatry. 1991; 48:239–246. [PubMed: 1671741]

Brixey SN, Gallagher BJ 3rd, McFalls JA Jr, Parmelee LF. Gestational and neonatal factors in the etiology of schizophrenia. J. Clin. Psychol. 1993; 149:447–456. [PubMed: 8315050]

Bruins Slot L, Kleven MS, Newman-Tancredi A. Effects of novel antipsychotics with mixed D2 antagonist/5-HT1A agonist properties on PCP induced social interaction deficits in the rat. Neuropharmacology. 2005; 49:996–1006. [PubMed: 16009387]

Calcagnetti DJ, Schechter MD. Place conditioning reveals the rewarding aspect of social interaction in juvenile rats. Physiol. Behav. 1992; 51:667–672. [PubMed: 1594664]

Cannon M, Jones P, Gilvarry C, Rifkin L, McKenzie K, Foerster A, Murray RM. Premorbid social functioning in schizophrenia and bipolar disorder: similarities and differences. Am. J. Psychiatry. 1997; 154:1544–1550. [PubMed: 9356562]

Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML. Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. Annu. Rev. Pharmacol. Toxicol. 2001; 41:237–260. [PubMed: 11264457]

Carpenter WT, Koenig JI. The evolution of drug development in schizophrenia: past issues and future opportunities. Neuropsychopharmacology. 2008; 33:2061–2079. [PubMed: 18046305]

Carter CS, Grippo AJ, Pournajafi-Nazarloo H, Ruscio MG, Porges SW. Oxytocin, vasopressin and sociality. Prog. Brain Res. 2008; 170:331–336. [PubMed: 18655893]

Chen Q, Panksepp JB, Lahvis GP. Empathy is moderated by genetic background in mice. PLoS One. 2009; 4:e4387. [PubMed: 19209221]

Corbett R, Fielding S, Cornfeldt M, Dunn RW. GABA-mimetic agents display anxiolytic-like effects in the social interaction and elevated plus maze procedures. Psychopharmacology (Berl). 1991; 104:312–316. [PubMed: 1681557]

Corrigan PW, Addis IB. The effect of cognitive complexity on a social sequencing task in schizophrenia. Schizophr. Res. 1995; 16:137–144. [PubMed: 7577767]

Corrigan PW, Green MF. Schizophrenic patients' sensitivity to social cues: the role of abstraction. Am. J. Psychiatry. 1993; 150:589–594. [PubMed: 8465875]

Cullen K, Guimaraes A, Wozniak J, Anjum A, Schulz SC, White T. Trajectories of social withdrawal and cognitive decline in the schizophrenia prodrome. Clin. Schizophr. Relat. Psychos. 2011; 4:229–238.

de Moura Linck V, Herrmann AP, Goerck GC, Iwu MM, Okunji CO, Leal MB, Elisabetsky E. The putative antipsychotic alstonine reverses social interaction withdrawal in mice. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2008; 32:1449–1452. [PubMed: 18539376]

Deacon RM, Bannerman DM, Rawlins JN. Anxiolytic effects of cytotoxic hippocampal lesions in rats. Behav. Neurosci. 2002; 116:494–497. [PubMed: 12049331]

DeLisi LE. Speech disorder in schizophrenia: review of the literature and exploration of its relation to the uniquely human capacity for language. Schizophr. Bull. 2001; 27:481–496. [PubMed: 11596849]

Der-Avakian A, Markou A. Withdrawal from chronic exposure to amphetamine, but not nicotine, leads to an immediate and enduring deficit in motivated behavior without affecting social interaction in rats. Behav. Pharmacol. 2010; 21:359–368. [PubMed: 20571366]

Desbonnet L, O'Tuathaigh CM, Waddington JL. Modeling schizophrenia: uncovering novel therapeutic targets. Expert Rev. Clin. Pharmacol. 2012; 5:667–676. [PubMed: 23234324]

Dluzen DE, Muraoka S, Engelmann M, Landgraf R. The effects of infusion of arginine vasopressin, oxytocin, or their antagonists into the olfactory bulb upon social recognition responses in male rats. Peptides. 1998a; 19:999–1005. [PubMed: 9700747]

Dluzen DE, Muraoka S, Landgraf R. Olfactory bulb norepinephrine depletion abolishes vasopressin and oxytocin preservation of social recognition responses in rats. Neurosci. Lett. 1998b; 254(3): 161–164. [PubMed: 10214982]

Ellenbroek BA, Cools AR. Animal models for the negative symptoms of schizophrenia. Behav. Pharmacol. 2000; 11:223–233. [PubMed: 11103877]

Engelmann M, Wotjak CT, Landgraf R. Social discrimination procedure: an alternative method to investigate juvenile recognition abilities in rats. Physiol. Behav. 1995; 58:315–321. [PubMed: 7568435]

Erhart SM, Marder SR, Carpenter WT. Treatment of schizophrenia negative symptoms: future prospects. Schizophr. Bull. 2006; 32:234–237. [PubMed: 16492797]

Feifel D, Mexal S, Melendez G, Liu PY, Goldenberg JR, Shilling PD. The brattleboro rat displays a natural deficit in social discrimination that is restored by clozapine and a neurotensin analog. Neuropsychopharmacology. 2009; 34:2011–2018. [PubMed: 19322170]

Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes: II. positive and negative symptoms and long-term course. Arch. Gen. Psychiatry. 1991; 48:978–986. [PubMed: 1747021]

Fernandez Espejo E. Prefrontocortical dopamine loss in rats delays long-term extinction of contextual conditioned fear, and reduces social interaction without affecting short-term social interaction memory. Neuropsychopharmacology. 2003; 28:490–498. [PubMed: 12629528]

File SE. The use of social interaction as a method for detecting anxiolytic activity of chlordiazepoxide-like drugs. J. Neurosci. Methods. 1980; 2:219–238. [PubMed: 6120260]

File SE, Hyde JR. Can social interaction be used to measure anxiety? Br. J. Pharmacol. 1978; 62:19–24. [PubMed: 563752]

File SE, James TA, MacLeod NK. Depletion in amygdaloid 5-hydroxytryptamine concentration and changes in social and aggressive behaviour. J. Neural Transm. 1981; 50:1–12. [PubMed: 7193710]

File SE, Seth P. A review of 25 years of the social interaction test. Eur. J. Pharmacol. 2003; 463:35–53. [PubMed: 12600701]

Flagstad P, Mørk A, Glenthøj BY, van Beek J, Michael-Titus AT, Didriksen M. Disruption of neurogenesis on gestational day 17 in the rat causes behavioral changes relevant to positive and negative schizophrenia symptoms and alters amphetamine-induced dopamine release in nucleus accumbens. Neuropsychopharmacology. 2004; 29:2052–2064. [PubMed: 15199377]

Floresco SB, Geyer MA, Gold LH, Grace AA. Developing predictive animal models and establishing a preclinical trials network for assessing treatment effects on cognition in schizophrenia. Schizophr. Bull. 2005; 31:888–894. [PubMed: 16079387]

Frith U, Happé F. Language and communication in autistic disorders. Philos. Trans. R. Soc. Lond. B Biol. Sci. 1994; 346:97–104. [PubMed: 7886159]

Gambill JD, Kornetsky C. Effects of chronic d-amphetamine on social behavior of the rat: implications for an animal model of paranoid schizophrenia. Psychopharmacology (Berl). 1976; 50:215–223. [PubMed: 826965]

Goghari VM, Sponheim SR, MacDonald AW 3rd. The functional neuroanatomy of symptom dimensions in schizophrenia: a qualitative and quantitative review of a persistent question. Neurosci. Biobehav. Rev. 2010; 34:468–486. [PubMed: 19772872]

Gonzalez LE, Andrews N, File SE. 5-HT1A and benzodiazepine receptors in the basolateral amygdala modulate anxiety in the social interaction test, but not in the elevated plus-maze. Brain Res. 1996; 732:145–153. [PubMed: 8891278]

Gonzalez LE, Ouagazzal AM, File SE. Stimulation of benzodiazepine receptors in the dorsal hippocampus and median raphé reveals differential GABAergic control in two animal tests of anxiety. Eur. J. Neurosci. 1998; 10:3673–3680. [PubMed: 9875346]

Gonzalez LE, Rujano M, Tucci S, Paredes D, Silva E, Alba G, Hernandez L. Medial prefrontal transection enhances social interaction. I: behavioral studies. Brain Res. 2000; 887:7–15. [PubMed: 11134584]

Goodwin GA, Molina VA, Spear LP. Repeated exposure of rat pups to isolation attenuates isolation-induced ultrasonic vocalization rates: reversal with naltrexone. Dev. Psychobiol. 1994; 27:53–64. [PubMed: 8112488]

Greig TC, Bryson GJ, Bell MD. Theory of mind performance in schizophrenia: diagnostic, symptom, and neuropsychological correlates. J. Nerv. Ment. Dis. 2004; 192:12–18. [PubMed: 14718771]

Gur RE, Kohler C, Turetsky BI, Siegel SJ, Kanes SJ, Bilker WB, Brennan AR, Gur RC. A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. Biol. Psychiatry. 2004; 55:512–517. [PubMed: 15023579]

Gur RE, McGrath C, Chan RM, Schroeder L, Turner T, Turetsky BI, Kohler C, Alsop D, Maldjian J, Ragland JD, Gur RC. An fMRI study of facial emotion processing in patients with schizophrenia. Am. J. Psychiatry. 2002; 159:1992–1999. [PubMed: 12450947]

Gururajan A, Taylor DA, Malone DT. Current pharmacological models of social withdrawal in rats: relevance to schizophrenia. Behav. Pharmacol. 2010; 21(8):690–709. [PubMed: 20847646]

Gururajan A, Taylor DA, Malone DT. Effect of cannabidiol in a MK-801-rodent model of aspects of schizophrenia. Behav. Brain Res. 2011; 222:299–308. [PubMed: 21458498]

Guy AP, Gardner CR. Pharmacological characterisation of a modified social interaction model of anxiety in the rat. Neuropsychobiology. 1985; 13:194–200. [PubMed: 2864655]

Habel U, Windischberger C, Derntl B, Robinson S, Kryspin-Exner I, Gur RC, Moser E. Amygdala activation and facial expressions: explicit emotion discrimination versus implicit emotion processing. Neuropsychologia. 2007; 45:2369–2377. [PubMed: 17408704]

Haller J, Szirmai M, Varga B, Ledent C, Freund TF. Cannabinoid CB1 receptor dependent effects of the NMDA antagonist phencyclidine in the social withdrawal model of schizophrenia. Behav. Pharmacol. 2005; 16:415–422. [PubMed: 16148446]

Harich S, Gross G, Bespalov A. Stimulation of the metabotropic glutamate 2/3 receptor attenuates social novelty discrimination deficits induced by neonatal phencyclidine treatment. Psychopharmacology (Berl). 2007; 192:511–519. [PubMed: 17318501]

Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophr. Bull. 2006; 32:250–258. [PubMed: 16221995]

Hashimoto T, Volk DW, Eggan SM, Mirnics K, Pierri JN, Sun Z, Sampson AR, Lewis DA. Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. J. Neurosci. 2003; 23:6315–6326. [PubMed: 12867516]

Humphreys AP, Einon DF. Play as a reinforcer for maze learning in juvenile rats. Anim. Behav. 1981; 29:259–270.

Javitt DC. Negative schizophrenic symptomatology and the PCP (phencyclidine) model of schizophrenia. Hillside J. Clin Psychiatry. 1987; 9:12–35. [PubMed: 2820854]

Javitt DC. Glutamate and schizophrenia: phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions. Int. Rev. Neurobiol. 2007; 78:69–108. [PubMed: 17349858]

Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am. J. Psychiatry. 1991; 140:1301–1308. [PubMed: 1654746]

Kaidanovich-Beilin O, Lipina T, Vukobradovic I, Roder J, Woodgett JR. Assessment of social interaction behaviors. J. Vis. Exp. 2011; (48) http://dx.doi.org/10.3791/2473.

Katschnig H. Schizophrenia and quality of life. Acta Psychiatr. Scand. 2000; 407(suppl):33–37.

Keefe RS, Harvey PD, Lenzenweger MF, Davidson M, Apter SH, Schmeidler J, Mohs RC, Davis KL. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetaipaine,

risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials. Schizophr. Res. 1999; 35:51–68. [PubMed: 9988841]

Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr. Bull. 2006; 32:214–219. [PubMed: 16481659]

Kirsten TB, Taricano M, Maiorka PC, Palermo-Neto J, Bernardi MM. Prenatal lipopolysaccharide reduces social behavior in male offspring. Neuroimmunomodulation. 2010; 17:240–251. [PubMed: 20203530]

Knutson B, Burgdorf J, Panksepp J. Anticipation of play elicits high-frequency ultrasonic vocalizations in young rats. J. Comp. Psychol. 1998; 112:65–73. [PubMed: 9528115]

Krystal JH, Karper LP, Seibyl JP. Subanaesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch. Gen. Psychiatry. 1994; 51:199–214. [PubMed: 8122957]

Lahti AC, Holcomb HH, Medoff DR, Tamminga CA. Ketamine activates psychosis and alters limbic blood flow in schizophrenia. Neuroreport. 1995a; 6:869–872. [PubMed: 7612873]

Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology. 1995b; 13:9–19. [PubMed: 8526975]

Lancaster K, Dietz DM, Moran TH, Pletnikov MV. Abnormal social behaviors in young and adult rats neonatally infected with Borna disease virus. Behav. Brain Res. 2007; 176:141–148. [PubMed: 16860408]

Lee PR, Brady DL, Shapiro RA, Dorsa DM, Koenig JI. Prenatal stress generates deficits in rat social behavior: reversal by oxytocin. Brain Res. 2007; 1156:152–167. [PubMed: 17540347]

Lee PR, Brady DL, Shapiro RA, Dorsa DM, Koenig JI. Social interaction deficits caused by chronic phencyclidine administration are reversed by oxytocin. Neuropsychopharmacology. 2005; 30:1883–1894. [PubMed: 15798779]

Leucht S, Kissling W, Davis JM. Second-generation antipsychotics for schizophrenia: can we resolve the conflict? Psychol. Med. 2009; 39:1591–1602. [PubMed: 19335931]

Leucht S, Pitschel-Walz G, Abraham D, Kissling W. Efficacy and extrapyramidal side effects of the new antipsychotics olanzapine, quetiapine, risperidone and sertindole compared to conventional antipsychotics and placebo. A metaanalysis of randomized controlled trials. Schizophr. Res. 1999; 35:51–68. [PubMed: 9988841]

Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nature Rev. Neurosci. 2005; 6:312–324. [PubMed: 15803162]

Li M, He W, Heupel K. Administration of clozapine to a mother rat potentiates pup ultrasonic vocalization in response to separation and re-separation: contrast with haloperidol. Behav. Brain Res. 2011; 222:385–389. [PubMed: 21473887]

Lindenmayer JP. New pharmacotherapeutic modalities for negative symptoms in psychosis. Acta Psychiatr. Scand. 1995; 388(Suppl):15–19.

Lipina TV, Fletcher PJ, Lee FH, Wong AH, Roder JC. Disrupted-in-schizophrenia-1 Gln31Leu polymorphism results in social anhedonia associated with monoaminergic imbalance and reduction of CREB and β-arrestin-1,2 in the nucleus accumbens in a mouse model of depression. Neuropsychopharmacology. 2013; 38:423–436. [PubMed: 23011268]

Luby ED, Cohen BD, Rosenbaum G, Gottlieb JS, Kelley R. Study of a new schizophrenomimetic drug; sernyl. AMA Arch. Neurol. Psychiatry. 1959; 81:363–369.

Lukkes JL, Mokin MV, Scholl JL, Forster GL. Adult rats exposed to early-life social isolation exhibit increased anxiety and conditioned fear behavior, and altered hormonal stress responses. Horm. Behav. 2009; 55(1):248–256. [PubMed: 19027017]

Mai JK, Berger K, Sofroniew MV. Morphometric evaluation of neurophysin-immunoreactivity in the human brain: pronounced inter-individual variability and evidence for altered staining patterns in schizophrenia. J. Hirnforsch. 1993; 34:133–154. [PubMed: 8228177]

Malhotra KA, Pinals AD, Adler MC, Elman I, Clifton A, Pickar D, Breier A. Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. Neuropsychopharmacology. 1997; 17:141–150. [PubMed: 9272481]

Markham JA, Koenig JI. Prenatal stress: role in psychotic and depressive diseases. Psychopharmacology (Berl). 2011; 214:89–106. [PubMed: 20949351]

Matrisciano F, Tueting P, Maccari S, Nicoletti F, Guidotti A. Pharmacological activation of group-II metabotropic glutamate receptors corrects a schizophrenia-like phenotype induced by prenatal stress in mice. Neuropsychopharmacology. 2012; 37:929–938. [PubMed: 22089319]

Matsuoka T, Tsunoda M, Sumiyoshi T, Takasaki I, Tabuchi Y, Seo T, Tanaka K, Uehara T, Itoh H, Suzuki M, Kurachi M. Effect of MK-801 on gene expressions in the amygdala of rats. Synapse. 2008; 62:1–7. [PubMed: 17948890]

Meaney MJ, Stewart J. A descriptive study of social development in the rat (Rattus norvegicus). Anim. Behav. 1981; 29:34–45.

Meng Q, Li N, Han X, Shao F, Wang W. Peri-adolescence isolation rearing alters social behavior and nociception in rats. Neurosci. Lett. 2010; 480(1):25–29. [PubMed: 20638959]

Morrison RL, Bellack AS. Social functioning of schizophrenic patients: clinical and research issues. Schizophr. Bull. 1987; 13:715–725. [PubMed: 3326165]

Moy SS, Nadler JJ. Advances in behavioral genetics: mouse models of autism. Mol. Psychiatry. 2008; 13:4–26. [PubMed: 17848915]

Moy SS, Nadler JJ, Perez A, Barbaro RP, Johns JM, Magnuson TR, Piven J, Crawley JN. Sociability and preference for social novelty in five inbred strains: an approach to assess autistic-like behavior in mice. Genes Brain Behav. 2004; 3:287–302. [PubMed: 15344922]

Nadler JJ, Moy SS, Dold G, Trang D, Simmons N, Perez A, Young NB, Barbaro RP, Piven J, Magnuson TR, Crawley JN. Automated apparatus for quantitation of social approach behaviors in mice. Genes Brain Behav. 2004; 3:303–314. [PubMed: 15344923]

Nakatani-Pawlak A, Yamaguchi K, Tatsumi Y, Mizoguchi H, Yoneda Y. Neonatal phencyclidine treatment in mice induces behavioral, histological and neurochemical abnormalities in adulthood. Biol. Pharm. Bull. 2009; 32:1576–1583. [PubMed: 19721235]

Neill JC, Barnes S, Cook S, Grayson B, Idris NF, McLean SL, Snigdha S, Rajagopal L, Harte MK. Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDA receptor antagonism. Pharmacol. Ther. 2010; 128:419–432. [PubMed: 20705091]

Nestler EJ, Hyman SE. Animal models of neuropsychiatric disorders. Nat. Neurosci. 2010; 13:1161–1169. [PubMed: 20877280]

Norman RM, Malla AK, McLean T, Voruganti LP, Cortese L, McIntosh E, Cheng S, Rickwood A. The relationship of symptoms and level of functioning in schizophrenia to general wellbeing and the quality of life scale. Acta Psychiatr. Scand. 2000; 102:303–309. [PubMed: 11089732]

Panksepp J, Beatty WW. Social deprivation and play in rats. Behav. Neural Biol. 1980; 30:197–206. [PubMed: 7447871]

Panksepp JB, Jochman KA, Kim JU, Koy JJ, Wilson ED, Chen Q, Wilson CR, Lahvis GP. Affiliative behavior, ultrasonic communication and social reward are influenced by genetic variation in adolescent mice. PLoS One. 2007; 2:e351. [PubMed: 17406675]

Panksepp JB, Lahvis GP. Social reward among juvenile mice. Genes Brain Behav. 2007; 6:661–671. [PubMed: 17212648]

Panksepp JB, Lahvis GP. Rodent empathy and affective neuroscience. Neurosci. Biobehav. Rev. 2011; 35:1864–1875. [PubMed: 21672550]

Patterson PH. Modeling autistic features in animals. Pediatr. Res. 2011; 69(5 Pt 2):34R–40R. [PubMed: 20940665]

Pogue-Geile MF, Harrow M. Negative symptoms in schizophrenia: their longitudinal course and prognostic importance. Schizophr. Bull. 1985; 11:427–439. [PubMed: 4035306]

Popik P, van Ree JM. Oxytocin but not vasopressin facilitates social recognition following injection into the medial preoptic area of the rat brain. Eur. Neuropsychopharmacol. 1991; 1:555–560. [PubMed: 1668316]

Puig O, Penadés R, Gastó C, Catalán R, Torres A, Salamero M. Verbal memory, negative symptomatology and prediction of psychosocial functioning in Schizophrenia. Psychiatry Res. 2008; 158:11–17. [PubMed: 18001844]

Qiao H, Noda Y, Kamei T, Nagai T, Furukawa H, Miura H, Kayukawa Y, Ohta T, Nabeshima T. Clozapine, but not haloperidol, reverses social behavior deficit in mice during withdrawal from chronic phencyclidine treatment. NeuroReport. 2001; 12:11–15. [PubMed: 11201068]

Rung JP, Carlsson A, Rydén Markinhuhta K, Carlsson ML. (+)-MK-801 induced social withdrawal in rats; a model for negative symptoms of schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry. 2005; 29:827–832.

Sams-Dodd F. Automation of the social interaction test by a video-tracking system: behavioural effects of repeated phencyclidine treatment. J. Neurosci. Methods. 1995a; 59:157–167. [PubMed: 8531482]

Sams-Dodd F. Distinct effects of d-amphetamine and phencyclidine on the social behaviour of rats. Behav. Pharmacol. 1995b; 6:55–65. [PubMed: 11224312]

Sams-Dodd F. Phencyclidine-induced stereotyped behaviour and social isolation in rats: a possible animal model of schizophrenia. Behav. Pharmacol. 1996; 7:3–23. [PubMed: 11224390]

Sams-Dodd F. Effect of novel antipsychotic drugs on phencyclidine-induced stereotyped behaviour and social isolation in the rat social interaction test. Behav. Pharmacol. 1997; 8:196–215. [PubMed: 9833015]

Sams-Dodd F. A test of the predictive validity of animal models of schizophrenia based on phencyclidine and D-amphetamine. Neuropsychopharmacology. 1998; 18(4):293–304. [PubMed: 9509497]

Sams-Dodd F, Lipska BK, Weinberger DR. Neonatal lesions of the rat ventral hippocampus result in hyperlocomotion and deficits in social behaviour in adulthood. Psychopharmacology (Berl). 1997; 132:303–310. [PubMed: 9292631]

Schwabe K, Klein S, Koch M. Behavioural effects of neonatal lesions of the medial prefrontal cortex and subchronic pubertal treatment with phencyclidine of adult rats. Behav. Brain Res. 2006; 168:150–160. [PubMed: 16387372]

Seillier A, Martinez AA, Giuffrida A. Phencyclidine-induced social withdrawal results from deficient stimulation of cannabinoid CB_1 receptors: implications for schizophrenia. Neuropsychopharmacology. 2013; 38(9):1816–1824. [PubMed: 23563893]

Shah AA, Treit D. Excitotoxic lesions of the medial prefrontal cortex attenuate fear responses in the elevated-plus maze, social interaction and shock probe burying tests. Brain Res. 2003; 969:183–194. [PubMed: 12676379]

Shair HN. Acquisition and expression of a socially mediated separation response. Behav. Brain Res. 2007; 182:180–192. [PubMed: 17379325]

Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. J. Neurosci. 2003; 23:297–302. [PubMed: 12514227]

Shimazaki T, Kaku A, Chaki S. D-Serine and a glycine transporter-1 inhibitor enhance social memory in rats. Psycho-pharmacology (Berl). 2010; 209:263–270.

Silvestre JS, Nadal R, Pallarés M, Ferré N. Acute effects of ketamine in the holeboard, the elevated-plus maze, and the social interaction test in Wistar rats. Depress. Anxiety. 1997; 5:9–33.

Snigdha S, Neill JC. Efficacy of antipsychotics to reverse phencyclidine induced social interaction deficits in female rats - a preliminary investigation. Behav. Brain Res. 2008; 187:489–494. [PubMed: 18037171]

Snyder SH. Catecholamines in the brain as mediators of amphetamine psychosis. Arch. Gen. Psychiatry. 1972; 27(2):169–179. [PubMed: 4339577]

Snyder SH. Amphetamine psychosis: a “model” schizophrenia mediated by catecholamines. Am. J. Psychiatry. 1973; 130:61–67. [PubMed: 4345465]

Steinpreis RE, Sokolowski JD, Papanikolaou A, Salamone JD. The effects of haloperidol and clozapine on PCP- and amphetamine-induced suppression of social behavior in the rat. Pharmacol. Biochem. Behav. 1994; 47:579–585. [PubMed: 8208777]

Stewart RB, Grupp LA. Some determinants of the motivational properties of ethanol in the rat: concurrent administration of food or social stimuli. Psychopharmacology (Berl). 1985; 87:43–50. [PubMed: 3933036]

Swartz MS, Perkins DO, Stroup TS, Davis SM, Capuano G, Rosenheck RA, Reimherr F, McGee MF, Keefe RS, McEvoy JP, Hsiao JK, Lieberman JA. CATIE Investigators. Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. Am. J. Psychiatry. 2007; 164:428–436. [PubMed: 17329467]

Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, “just the facts” 5. Treatment and prevention. Past, present, and future. Schizophr. Res. 2010; 122:1–23. [PubMed: 20655178]

Thomsen MS, Christensen DZ, Hansen HH, Redrobe JP, Mikkelsen JD. Alpha(7) Nicotinic acetylcholine receptor activation prevents behavioral and molecular changes induced by repeated phencyclidine treatment. Neuropharmacology. 2009; 56(6–7):1001–1009. [PubMed: 19233218]

Thurmond JB. Technique for producing and measuring territorial aggression using laboratory mice. Physiol. Behav. 1975; 14:879–881. [PubMed: 1237905]

Trezza V, Damsteegt R, Manduca A, Petrosino S, Van Kerkhof LW, Pasterkamp RJ, Zhou Y, Campolongo P, Cuomo V, Di Marzo V, Vanderschuren LJ. Endocannabinoids in amygdala and nucleus accumbens mediate social play reward in adolescent rats. J. Neurosci. 2012; 32:14899–14908. [PubMed: 23100412]

Tzschentke TM. Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. Addict. Biol. 2007; 12:227–462. [PubMed: 17678505]

Uribe E, Landaeta J, Wix R, Eblen A. Memantine reverses social withdrawal induced by ketamine in rats. Exp. Neurobiol. 2013; 22(1):18–22. [PubMed: 23585718]

Van den Berg CL, Van Ree JM, Spruijt BM, Kitchen I. Effects of juvenile isolation and morphine treatment on social interactions and opioid receptors in adult rats: behavioural and autoradiographic studies. Eur. J. Neurosci. 1999; 11(9):3023–3032. [PubMed: 10510167]

Van den Buuse M, Garner B, Gogos A, Kusljic S. Importance of animal models in schizophrenia research. Aust. N Z. J. Psychiatry. 2005; 39:550–557. [PubMed: 15996135]

Vanderschuren LJ, Niesink RJ, Van Ree JM. The neurobiology of social play behavior in rats. Neurosci. Biobehav. Rev. 1997; 21:309–326. [PubMed: 9168267]

Volkmar FR. Understanding the social brain in autism. Dev. Psychobiol. 2011; 53:428–434. [PubMed: 21678390]

von Heimendahl M, Rao RP, Brecht M. Weak and nondiscriminative responses to conspecifics in the rat hippo-campus. J. Neurosci. 2012; 32:2129–2141. [PubMed: 22323725]

Weaver IC, Meaney MJ, Szyf M. Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. Proc. Natl. Acad. Sci. USA. 2006; 103:3480–3485. [PubMed: 16484373]

White IM, Minamoto T, Odell JR, Mayhorn J, White W. Brief exposure to methamphetamine (METH) and phencyclidine (PCP) during late development leads to long-term learning deficits in rats. Brain Res. 2009; 1266:72–86. [PubMed: 19245799]

Wilson C, Terry AV Jr. Neurodevelopmental animal models of schizophrenia: role in novel drug discovery and development. Clin. Schizophr. Relat. Psychos. 2010; 4:124–137.

Wilson CA, Vazdarjanova A, Terry AV Jr. Exposure to variable prenatal stress in rats: effects on anxiety-related behaviors, innate and contextual fear, and fear extinction. Behav. Brain Res. 2013; 238:279–288. [PubMed: 23072929]

Wykes T, Steel C, Everitt B, Tarrier N. Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. Schizophr. Bull. 2008; 34:523–537. [PubMed: 17962231]

Yee N, Schwarting RK, Fuchs E, Wöhr M. Increased affective ultrasonic communication during fear learning in adult male rats exposed to maternal immune activation. J. Psychiatr. Res. 2012; 46:1199–1205. [PubMed: 22687817]

Yeganeh-Doost P, Gruber O, Falkai P, Schmitt A. The role of the cerebellum in schizophrenia: from cognition to molecular pathways. Clinics (Sao Paulo). 2011; 66:71–77. [PubMed: 21779725]

Yizhar O. Optogenetic insights into social behavior function. Biol. Psychiatry. 2012; 71:1075–1080. [PubMed: 22341368]

Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, Sohal VS, Goshen I, Finkelstein J, Paz JT, Stehfest K, Fudim R, Ramakrishnan C, Huguenard JR, Hegemann P, Deisseroth K. Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature. 2011; 477:171–178. [PubMed: 21796121]

Zhao X, Sun L, Jia H, Meng Q, Wu S, Li N, He S. Isolation rearing induces social and emotional function abnormalities and alters glutamate and neurodevelopment-related gene expression in

rats. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2009; 33(7):1173–1177. [PubMed: 19563853]

Zou H, Zhang C, Xie Q, Zhang M, Shi J, Jin M, Yu L. Low dose MK-801 reduces social investigation in mice. Pharmacol. Biochem. Behav. 2008; 90:753–757. [PubMed: 18577395]

Eur Neuropsychopharmacol. Author manuscript; available in PMC 2015 June 26.

Table 1

Pharmacological models that exhibit altered social interaction. The specifics of the pharmacological treatments are listed as well as their effects on social interaction and responsiveness to antipsychotics and anxiolytics.

Pharmcological compound	Dose	Length of treament	Time at testing	Model type	Sex of test subjects	Effect on social interaction	Effects of antipsychotics and anxiolytics	References
PCP	2–8 mg/kg	Acute	45 min postinjection	Rat	Male	Reduced active social interaction		Sams-Dodd (1995a, b)
	2–30 mg/kg	3–5 days	45 min postfinal injection	Rat	Male	Decreased active social interaction	Chronic treatment with clozapine (0.16–10 mg/kg) and subchronic treatment with risperidone (0.15–0.32 mg/kg) partially normalized interaction; treatment with aripiprazole (0.04–0.16 mg/kg) reversed deficts	Sams-Dodd (1995b, 1996, 1997) and Bruins Slot et al. (2005)
	2–16 mg/kg	14–21 days	45 min postfinal injection	Rat	Male	Reduced active social interaction		Sams-Dodd (1996) and Lee et al. (2005)
	10 mg/kg	17 days	18–22 h postinjection	Rat	Male	Initiated less affiliative contacts and increased aggressive responses		Audet et al. (2009)
	2 mg/kg	7 days	6weeks postfinal injection	Rat	Female	Significantly reduced time spent engaged in social behaviors	Acute treatment with ziprasidone (2.5 mg/kg) significantly reversed PCP-induced deficits; haloperidol (0.05 mg/kg) and clozapine (2.5 mg/kg) had no effect	Snigdha and Neill (2008)
	5 mg/kg	Acute	45 min postinjection	Mouse	Male	Reduced social interaction		Haller et al. (2005)
	3–10 mg/kg	7–14 days	3–28 days postfinal injection	Mouse	Male	Decreased social interaction in a dose- and time- dependent manner	Subchronic treatment with clozapine (10 mg/kg) but not haloperidol (1–3 mg/kg) reversed social deficits	Qiao et al. (2001)
	10 mg/kg	3 days (PND 7,9,11)	15–19 weeks posttreatment	Mouse	Male	Reduced social interaction	Clozapine (0.3–1 mg/kg) reversed	Nakatani-Pawlak et al. (2009)

Pharmcological compound	Dose	Length of treament	Time at testing	Model type	Sex of test subjects	Effect on social interaction	Effects of antipsychotics and anxiolytics	References
							impairments in social interaction impairments in social interaction	
	9 mg/kg	2 days (PND 50–51)	7–28 days postfinal injection	Rat	Male	Reduced social interaction		White et al. (2009)
Amphetamine	0.125–4 mg/kg	3–5 days	45 min postfinal injection	Rat	Male	Slight decrease in active social interaction		Sams-Dodd (1995b, 1996)
	10 mg/kg	7 days	1–3 days postwithdrawal	Rat	Male	No effect on social interaction		Der-Avakian and Markou (2010)
	4 mg/kg	Acute	5 min postinjection	Rat	Male	Reduced social behaviors during an intruder paradigm	Haloperidol (0.025) reversed the effects of amphetamine on specific social behaviors, while clozapine (2 mg/kg) had no effect	Steinpreis et al. (1994)
MK-801	0.2–0.6 mg/kg	Acute	20–30 min postinjection	Rat	Male	Reduced social interaction	Clozapine (1–3 mg/kg) normalized social behavior	Rung et al. (2005) and Gururajan et al. (2011)
	0.13 mg/kg	14 day	45 min postfinal injection	Rat	Male	Decreased social interaction		Matsuoka et al. (2008)
	0.3 mg/kg	Acute	30 min postinjection	Mouse	Male	Reduced social interaction	Clozapine (2.0 mg/kg) had no effect	de Moura Linck et al. (2008)
Ketamine	7 mg/kg	Acute	30 min postinjection	Rat	Male	Decreased active social interaction		Silvestre et al. (1997)
	30 mg/kg	5 days	5–14 days postfinal injection	Rat	Male	Decreased non-aggressive behaviors	Clozapine (0.5 mg/kg), risperidone (0.2 mg/kg), and diazepam (0.5 mg/kg) increased non-aggressive behaviors	Becker et al. (2003), Becker and Grecksch (2004) and Uribe et al. (2013)

Table 2

Neurodevelopmental models that exhibit altered social interaction. The specifics of the models are listed as well as their effects on social interaction and responsiveness to antipsychotics and anxiolytics.

Neurodevelopmental model	Age at testing	Model type	Sex of test subjects	Effect on social interaction	Evidence of anxiety	Effects of antipsychotics and anxiolytics	References
Antimitotic agent – MAM (GD17)	PND 58–60	Rat	Male	Reduced active social interaction	No		Flagstad et al. (2004)
Neonatal ventral hippocampal lesion (PND 7)	PND 35 and PND 65	Rat	Male	Reduced social interaction	Yes	Chronic treatment with clozapine (0.63–2.5 mg/kg) further reduced active social interaction	Sams-Dodd et al. (1997)
Poly I:C immune challenge (GD 17)	PND 80	Mouse	Male and female	Produced deficits in social interaction	No		Bitanihirwe et al. (2010)
Human influenza virus immune challenge (GD 9)	5–9 weeks	Mouse	Male and female	Reduced social interaction	Yes		Shi et al. (2003)
LPS immune challenge (GD 9)	Preadolescent and adult	Rat	Male	Reduced play behavior and reduced social interaction	No		Kirsten et al. (2010)
Borna disease virus immune challenge (PND 1)	PND 90 and PND 180	Rat	Male	Reduced active social interaction and decreased aggressive behaviors	No		Lancaster et al. (2007)
Prenatal restraint stress (GD7 – birth)	PND 60	Mouse	Male	Reduced social interaction	No		Matrisciano et al. (2012)
Variable prenatal stress (third week gestation)	PND 35 and PND 56	Rat	Male	Reduced social interaction and diminished quality of social interaction	No	Subchronic treatment with haloperidol (0.3 mg/kg) failed to improve social deficits	Lee et al. (2007)
Isolation rearing (PND 21–77)	7–11 weeks	Rat	Male	Increased aggressive behaviors and altered social interaction	Yes		Lukkes et al. (2009), Meng et al. (2010), Van den Berg et al. (1999) and Zhao et al. (2009)