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

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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.

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). 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).

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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