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Modeling Social Behavior in Rodent Models of Psychiatric Illness.

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The global prevalence of psychiatric disorders that result in abnormal social behaviors has sparked the desire to model and study these behaviors in rodent models of brain diseases. According to recent estimates, approximately 1 in 160 individuals has autism spectrum disorder, 350 million are diagnosed with depression, 21 million people are schizophrenic, and 10% have attention deficit or attention deficit hyperactivity disorder [1–4]. Individuals diagnosed with these disorders often exhibit atypical social behaviors [for example 5–8].

One of the major challenges to studying these diseases in animal models is that the cellular and molecular underpinnings are still unknown. Currently there are no objective tests for their diagnosis and most of the diagnostic criteria consist of behavioral abnormalities and self reported emotions. With these challenges to overcome, many of the current animal models consist of genetic manipulations of genes that have been identified to correlate with these diseases or likely candidate genes based on their known roles in neuronal function. Since mice have been the model rodent of choice for genetic manipulations, most of the genetic models for neuropsychiatric and neurodevelopmental disorders are mouse models [9–11]. The problem with the majority of these models being mouse models is that mice are not an ideal system for the study of complex social behaviors, similar to those that are disrupted in these illnesses. This is particularly apparent with the study of juvenile play fighting. As opposed to many of the behavioral tests used to asses animal models of psychiatric disorders, such as learned helplessness or forced swim tests, play fighting is part of the normal behavioral repertoire of many animal species [12], and there are many similarities between this behavior in humans and non-human animals [13]. Both human children and juvenile rats will have deficits later in life if they are deprived of the opportunity for play fighting, and there is a shared sex difference in which both boys and ale rats exhibit higher levels of play fighting relative to females [14–22].

In a comparison of play fighting complexity between rats and mice, rats were given a complexity score of 0.94, the highest score out of all of the rodents included in the analysis, while mice received a score of 0.13, the second lowest score [19]. Importantly, the aforementioned study included an analysis on wild mice, which may engage in play fighting more than the inbred strains used for most genetic models [20]. In a particularly interesting study, Poole and Fish [21] compare play between laboratory rats and mice and demonstrate that mice did not demonstrate social play behavior even when solicited for play by a rat.

Recently, there has been an increase in studies demonstrating a very complex form of social behavior in rodents, empathy. This is another behavior that is disrupted in mental illnesses [22]. In mice these studies have been an expansion of the traditional Pavlovian fear conditioning paradigm in which one animal receives a foot shock paired with a cue, thus learning to freeze when presented with the cue in the absence of the shock [23]. In the empathy paradigm, another animal watches this fear conditioning procedure and exhibits signs of distress, including freezing and heart deceleration, however not all strains of mice exhibit these behaviors [24,25]. The paradigms that have been employed in rats have been a little more sophisticated in that they do not rely on one animal observing another in pain, rather the observer watches another animal in non- painful distress and then works to rescue the other. In one example, rats learned to rescue a conspecific from a restraint chamber, while in another a rat learned to rescue a conspecific soaked in water [26,27]. In both cases, the rats helped the conspecific before attempting to retrieve a food reward [26,27]. It will be interesting to see whether the typically less social mice would be willing to help a conspecific before seeking a food reward or if they would have a reaction to a conspecific in an unpleasant situation in the absence of physical pain.

CRISPR (clustered regularly interspaced short palindromic repeats) gene-editing technology presents an excellent opportunity to generate genetic models of psychiatric illnesses in rats where complex social behaviors can be readily analyzed [28]. This technology has the added benefit of being generated in outbred strains rather than generating inbred rat strains, which helps to ensure that naturally occurring behaviors, such as juvenile play fighting will not be lost through inbreeding. To make better use of the already existing genetic mouse models of psychiatric diseases, backcrossing to wild mice could help to regain some of the social behaviors that have been lost through numerous generations of inbreeding [29].

Incorporating these techniques to generate better models of psychiatric illnesses will help to incorporate models of complex social behavioral disruptions in these diseases to aid in our understanding of the social brain and how social networks dysfunction in disease.

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