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Lewis rats have greater response impulsivity than Fischer rats

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HIGHLIGHTS

- Lewis and Fischer rats were compared on a measure of response impulsivity.
- Lewis rats had greater response impulsivity than Fischer rats.
- Lewis and Fischer rats provide a valid rodent model of response impulsivity.

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ABSTRACT

Impulsivity, a tendency toward immediate action without consideration of future consequences, is associated with a wide array of problematic behaviors. Response impulsivity, a type of behaviorally-assessed impulsivity characterized by behavioral disinhibition, is also associated with health risk behaviors. Response impulsivity is distinct from choice impulsivity, which is characterized by intolerance for delay. Lewis rats have higher levels of choice impulsivity than Fischer rats (Anderson & Woolverton, 2005; Madden et al., 2008; Stein et al., 2012). However, no studies have examined whether Lewis and Fischer rats have different levels of response impulsivity. The present research examined response impulsivity in the two rat strains. Subjects were 16 male Lewis and Fischer rats. Rats' response impulsivity was measured using the Five Choice Serial Reaction Time Task (5-CSRTT). In addition, their locomotor activity was measured in locomotor activity chambers. Lewis rats had more premature responses than Fischer rats during the 5-CSRTT assessment [$F(1, 14) = 5.34$, $p < 0.05$], indicating higher levels of response impulsivity. Locomotor activity did not differ between rat strain groups [$F(1, 14) = 3.05$, $p = .10$], suggesting that overall movement did not account for group differences in response impulsivity on the 5-CSRTT. It can be concluded from this research that Lewis rats have higher levels of response impulsivity than Fischer rats, and therefore provide a valid rat model of individual differences in impulsivity.

1. Introduction

Impulsivity involves a tendency to act rapidly with diminished regard for future consequences (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001) and is associated with multiple risk behaviors including substance use, gambling, drunk-driving, violence, and disordered eating (Dawe & Loxton, 2004; de Wit, 2009; Kalichman, Greenberg, & Abel, 1997; Perry & Carroll, 2008; Potenza, 2008). Impulsivity can be deconstructed into two types of behaviorally-assessed impulsivity, response impulsivity and choice impulsivity (Winstanley, Eagle, & Robbins, 2006). Response impulsivity is characterized by behavioral disinhibition and is indexed by a diminished ability or willingness to withhold a prepotent response. Response impulsivity differs from choice impulsivity, a diminished ability or willingness to tolerate delay. Response impulsivity and choice impulsivity are two distinct dimensions of impulsivity that frequently correlate weakly or not at all (Lane, Cherek, Rhoades, Pietras, & Tcheremissine, 2003; Meda et al., 2009; Reynolds, Ortengren, Richards, & de Wit, 2006), and each deserves focused research attention given their relationships with clinically relevant measures in people. However, the present research was focused specifically on behaviorally-assessed response impulsivity because of its relationships with drug use and addiction (Belin, Mar, Dalley, Robbins, & Everitt, 2008; de Wit, 2009), conditions in which disinhibition is a main component.

Response impulsivity is measured by tasks that require inhibition of a behavioral response until the presentation of a stimulus, such as a light or tone, signals that the appropriate time for responding has begun. The

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Five Choice Serial Reaction Time Task (5-CSRTT) is a commonly-used task that measures response impulsivity in rat models; premature responding on the task provides an index of response impulsivity (Robbins, 2002). The 5-CSRTT has been used to investigate response impulsivity in rats of various strains and ages, including adolescent and adult Sprague–Dawley rats (Burton & Fletcher, 2012; Jentsch & Taylor, 2003), adult Lister-hooded rats (Belin et al., 2008), and adult Wistar rats (Amitai & Markou, 2011; Diergaarde, Pattij, Nawijn, Schoffelmeer, & De Vries, 2009). However, no studies have examined the differences in response impulsivity between two rat strains, a research question that has utility for identifying a rat model of response impulsivity.

The Lewis and Fischer rat strains differ on variables that are relevant to addiction and other risk behaviors. Lewis rats have a higher intake of and preference for drugs including cocaine, morphine, ethanol, and nicotine (Horan, Smith, Gardner, Lepore, & Ashby, 1997; Kosten & Ambrosio, 2002; Suzuki, George, & Meisch, 1988; Suzuki, Otani, Koike, & Misawa, 1988). They also demonstrate the differences from Fischer rats in stress measures (including corticosterone levels), drug responsiveness (including amphetamine-induced locomotion) and brain function (including ventral striatal differences), and these differences have been linked to specific genetic locations between the different strains (Potenza et al., 2004; Potenza et al., 2008). Lewis and Fischer rats differ with respect to dopamine (DA) neurotransmission, with Lewis rats having higher levels of DA release in response to stimulants (Camp, Browman, & Robinson, 1994; Strecker, Eberle, & Ashby, 1995), as well as lower levels of DA receptors and DA transporters (Flores, Wood, Barbeau, Quirion, & Srivastava, 1998) than Fischer rats. Because DA neurotransmission is implicated in choice impulsivity and response impulsivity (van Gaalen, Brueggeman, Bronius, Schoffelmeer, & Vanderschuren, 2006; van Gaalen, van Koten, Schoffelmeer, & Vanderschuren, 2006), each of these differences in DA neurotransmission may predispose Lewis rats to elevated levels of impulsivity. Lewis rats also demonstrate higher levels of choice impulsivity than Fischer rats (Anderson & Woolverton, 2005; Madden, Smith, Brewer, Pinkston, & Johnson, 2008). In addition, Lewis rats were found to have a superior performance to Fischer rats on cognitive measures, including measures of attention, learning, and memory (Fole et al., 2011; Richards et al., 2013; van der Staay, Schuurman, van Reenen, & Korte, 2009). However, no studies have directly compared response impulsivity in Lewis and Fischer rats.

Both choice impulsivity and response impulsivity have been associated with relevant aspects of addictive behaviors across species (Fineberg et al., 2014). The gravity of the consequences of risk behaviors associated with response impulsivity highlights the importance of examining response impulsivity in Lewis and Fischer rats, strains that might be used to examine for biological (including genetic) differences relating to this construct and substance-use behaviors. Toward this end, the performance of Lewis and Fischer rats on the 5-CSRTT was compared in the present research. It was hypothesized that response impulsivity would be greater in Lewis rats than in Fischer rats.

2. Methods

2.1. Subjects and housing

Subjects in the experiment were 8 adult male Lewis rats and 8 adult male Fischer rats (Charles River Laboratories). Within rat strain, animals were pair-housed in standard rat cages (42.5 × 20.5 × 20 cm) on hardwood chip bedding (Pine-Dri) with access to food (Harlan Teklad 4% Mouse/Rat Diet 7001) and water. Rats were pair-housed to avoid potentially stressful effects of crowding (Brown & Grunberg, 1995) or isolation (Parker & Radlow, 1974). Cagemates were housed together throughout the entire training and testing phases. Rats were approximately 26 days old upon arrival, and approximately 46 days old at the start of the 5-CSRTT training. Sixteen Lewis and 16 Fischer rats were trained on the 5-CSRTT, and 8 Lewis rats and 8 Fischer rats were included in the experiment based on whether they met the training criterion (described below). At the start of the experiment (after the 5-CSRTT training had concluded), rats were approximately 144 days old; the Fischer rats' mean weight was 274.3 g while the Lewis rats' mean weight was 388.8 g. The strain difference in body weights was expected because Lewis rats are generally larger than Fischer rats (Gomez-Serrano, Tonelli, Listwak, Sternberg, & Riley, 2001). Animals were maintained at 85% to 90% of free-feeding body weight to motivate performance in the 5-CSRTT, which is an operant task with a food reward. Free-feeding body weight was determined by feeding ad libitum two additional pairs of Lewis rat cagemates and Fischer rat cagemates (a total of four rats) that were the same age as the experimental rats, and weighing them daily. Restricting food intake is a standard procedure in the experiments using operant tasks with a food reward to ensure that animals are sufficiently motivated to work in order to obtain the food reward (Bari, Dalley, & Robbins, 2008; Blondel, Sanger, & Moser, 2000; Burton & Fletcher, 2012; Carli, Robbins, Evenden, & Everitt, 1983; Diergaarde et al., 2009; Humby, Wilkinson, & Dawson, 2005).

Housing room was maintained at 68–72 °F with 40% humidity and a 12 h reverse light cycle, with lights off at 7:00 a.m. Because rats are nocturnal animals, maintaining a reverse light cycle caused their active (dark) phase to occur during the daytime, allowing all daytime behavioral testing to take place during the rats' active (dark) phase. This experimental protocol was approved by the USUHS Institutional Animal Care and Use Committee and was conducted in full compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (NIH, 1996).

2.2. 5-CSRTT

2.2.1. Apparatus

The 5-CSRTT equipment consisted of four operant conditioning chambers, each housed in a sound-attenuating box (Med Associates, Inc.). The rear wall of each chamber was a curved metal surface containing a row of five nose-poke apertures. An infra-red photocell beam traversed each aperture to detect nose pokes, and a yellow LED light was fixed at the rear of each aperture. In each chamber, on the opposite wall from the apertures, a pellet dispenser delivered 45 mg pellets (Noyes precision pellets) into a food-hopper. Chamber illumination was provided by a house light located above the food tray. Data collection and presentation of stimuli and rewards were controlled by a computer (Med-PC version 4.0, Med Associates, Inc.). In the 5-CSRTT, rats were required to respond to brief flashes of light randomly presented in one of the five apertures by making a nose-poke in the illuminated aperture. In the 5-CSRTT, the total number of premature responses indexed response impulsivity, with more premature responses indicating more response impulsivity. Premature responses were responses that occurred before a cue-light was illuminated, or during a time-out period. The accuracy variable is a measure of the capacity of the rat to sustain spatial attention divided among multiple locations and multiple trials. The accuracy measure is the proportion of correct detections plus errors of commission (i.e., incorrect responses in apertures where the visual target had not been presented (Robbins, 2002)). Omissions could reflect sensory, motor, or motivational factors (Robbins, 2002). An omission was recorded when a rat failed to make a nose-poke response in an aperture either when the aperture was illuminated or in the 2-second period immediately following the illumination.

2.2.2. Training

Rats were trained on the 5-CSRTT following the procedures of van Gaalen, Brueggeman, Bronius, Schoffelmeer, and Vanderschuren (2006) and van Gaalen, van Koten, Schoffelmeer, and Vanderschuren (2006). Training lasted approximately 12 weeks and consisted of five phases: two acquisition (autoshaping) phases, two training phases, and a discrimination phase. During the first acquisition phase, pellets