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High levels of impulsivity in rats are not accompanied by sensorimotor gating deficits and locomotor hyperactivity

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ABSTRACT

High levels of impulsivity have been linked to a number of psychiatric disorders, including attention-deficit/hyperactivity disorder, drug abuse and schizophrenia. Additionally, schizophrenia patients commonly show deficits in another rather preattentive form of response inhibition, called sensorimotor gating. Given that higher-order functions, such as impulse control, are protected by early and preattentive processes, disturbed gating mechanisms may hamper more complex cognitive-executive functions. In the present study, we therefore tested whether high levels of impulsivity are accompanied by impaired sensorimotor gating in rats. High (HI) and low impulsive (LI) rats were identified based on the number of premature responses in the 5-choice serial reaction time task. Here, LI rats showed higher numbers of omission errors which may suggest attentional deficits while HI rats completed significantly less trials which could indicate a decrease in motivation. However, HI and LI rats did not differ in terms of impulsive decision-making in a delay-based decision-making T-maze task, prepulse inhibition of the acoustic startle response (a measure of sensorimotor gating mechanisms) or locomotor activity levels. Overall, our data indicate that high motor impulsivity is not a suitable predictor of deficient sensorimotor gating and is further not necessarily associated with attentional deficits and/or locomotor hyperactivity in rats.

1. Introduction

High levels of impulsivity are prevalent in numerous psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), drug abuse and schizophrenia (de Wit, 2009; Herpertz and Sass, 1997). Impulsivity is an expression of dysfunctional behavioral inhibition and is often characterized by deficits in motor impulse control reflected by reduced response inhibition (Bari and Robbins, 2013). Schizophrenic patients consistently exhibit impairments in another form of response inhibition called "sensorimotor gating". Sensorimotor gating is considered as a measure of largely involuntary inhibition and refers to a process by which excessive or irrelevant stimuli are automatically filtered or "gated out" of awareness in the early stage of information processing (Braff et al., 2001). Sensorimotor gating deficits are commonly modeled by reduced prepulse inhibition (PPI) of the acoustic startle response (ASR; Fendt and Koch, 2013). In normal PPI, a relatively weak sensory stimulus (prepulse) shortly preceding a startle-inducing stimulus (pulse) suppresses the unconditional ASR (Koch, 1999; Braff et al., 2001). The startle reflex is a ubiquitous, cross-species integrated response to strong exteroceptive stimuli. In rats, whole body startle to acoustic stimuli is typically measured by monitoring animals in a stabilimeter device. In humans, startle response includes the eyeblink reflex, which is assessed by measuring eyelid movements or by electromyography of facial muscles. As PPI is a conserved phenomenon among vertebrates and disorders with dysfunction in brain substrates regulating PPI are accompanied by impaired sensorimotor inhibition, reduced PPI is regarded as a candidate endophenotype for sensorimotor gating deficits (Alsene et al., 2011; Gottesman and Gould, 2003). Besides schizophrenia, deficient PPI is reported in patients with obsessive compulsive disorder (Swerdlow et al., 2006) Huntington's disease (Swerdlow et al., 2006) and Tourette syndrome (Castellanos et al., 1996) all being characterized by a loss of sensorimotor gating (Braff et al., 2001). Impulsive actions (e.g., responding prematurely without foresight) in turn, are regarded as a biomarker of impulsivity in

Abbreviations: 5-CSRTT, 5-choice serial reaction time task; 5-HT, 5-hydroxytryptamine; ADHD, attention-deficit/hyperactivity disorder; ASR, acoustic startle response; BL, baseline; DOI, 2,5-dimethoxy-4-iodoamphetamine; HI, high impulsive; HR, high reward; ISI, interstimulus interval; ITI, intertrial interval; LED, light-emitting diode; LI, low impulsive; LR, low reward; PPI, prepulse inhibition; LH, limited hold; SD, stimulus duration; SHR, spontaneously hypertensive rats; vITI, variable intertrial interval.

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both humans as well as rats and result from a failure in motor impulse control (Bari and Robbins, 2013; Robbins, 2002; Voon et al., 2014; Winstanley et al., 2006). The concept of endophenotypes has gained increasing importance in animal model research, as they are heritable quantitative indices of an individual's susceptibility to neuropsychiatric diseases (Castellanos and Tannock, 2002; Gottesman and Gould, 2003). Due to the complexity of psychiatric syndromes comprising several, often distinguishable symptoms that occur in individually varying degree of severity, modeling endophenotypes may help to study specific characteristics of these complex disorders (Fendt and Koch, 2013). Exemplarily, Dalley et al. (2007) found that trait impulsivity in rats, characterized by increased premature responding in the 5-choice serial reaction time task (5-CSRTT), predicts the probability of self-administering high amounts of cocaine indicating a predisposing potential of impulsivity to drug abuse.

Given that higher-order functions, such as impulse control, are protected by the early and preattentive processes underlying PPI (Chudasama, 2011; Dalley et al., 2004; Koch, 1999), disturbed gating mechanism might impede subsequent and more complex cognitive-executive functions (Minassian et al., 2013; Quednow, 2008). As such, efficient sensorimotor inhibition in healthy subjects is associated with superior executive functioning (Bitsios and Giakoumaki, 2005; Giakoumaki et al., 2006).

Despite growing evidence demonstrating that impulsive behavior and PPI are partially mediated by identical brain regions and neurotransmitter systems, not much research has been done on a possible relationship between these symptoms so far. In particular, dysregulation of frontostriatal systems comprising the prefrontal cortex and the nucleus accumbens as well as dysfunctional dopaminergic and serotonergic neurotransmission have been associated with both endophenotypes in rats as well as humans (Braff et al., 2001; Feifel et al., 2009; Feja and Koch, 2014b; Meyer-Lindenberg et al., 2002; Nigg and Casey, 2005; Swerdlow and Geyer, 1998). Rodent models have shown that dopamine transporter knockout mice exhibit maladaptive impulsive behavior that correlates with their PPI deficits (Yamashita et al., 2013). Notably, the serotonin (5-hydroxytryptamine,5-HT)$_{2A}$ receptor seems to be a crucial component in the regulation of both PPI and motor impulse control, as systemic administration of the 5-HT$_{2A}$ receptor agonist DOI (2,5-dimethoxy-4-iodoamphetamine) reduced PPI while inducing motor impulsivity in the 5-CSRTT in rats (Koskinen et al., 2000; Koskinen and Sirvio, 2001; Padich et al., 1996; Sipes and Geyer, 1994; Wischhof et al., 2012).

The present study aimed at clarifying a potential relationship between impulsivity and sensorimotor gating deficits. For that purpose, we first identified interindividual differences in the manifestation of motor impulsivity in the 5-CSRTT. Subsequently, we investigated a conceivably differential performance of high and low impulsive rats in PPI, locomotor activity and delay-based decision-making to address the question if high levels of impulsivity may predict sensorimotor gating deficits.

2. Materials and methods

2.1. Animals

The study used 20 adult male Wistar rats (280–350 g) that were bred in our in-house facilities. They were kept in standard Macrolon type IV cages in groups of five under controlled ambient conditions (22 °C, 45–55% humidity, 12 h light/dark cycle, lights on at 7:00 a.m.). The animals received free access to tap water and were maintained on body weights of 85% of those under free-feeding conditions by restricted feeding of 12 g standard laboratory rodent chow (Nohrlin GmbH, Bad Salzuflen, Germany) per rat per day over the entire duration of the experiments. All behavioral testing was done during the rats' light cycle between 9:00 a.m. and 5:00 p.m.. The experiments were performed in accordance with the NIH guidelines for the care and use of laboratory animals for experiments and were approved by local authorities (Senatorische Behörde, Bremen, Germany).

2.2. Apparatus and procedures

2.2.1. 5-choice serial reaction time task

The test apparatus has been described in detail previously (Carli et al., 1983). Briefly, the operant chambers ($26 \times 26 \times 26\,cm^3$) consisted of aluminum walls with stainless steel grid floors and a Perspex roof housed in sound-attenuating and ventilated cubicles. The rear wall of each chamber was concavely curved and contained nine square holes (2.5 cm in diameter, 4 cm deep, and 2 cm above the floor). During the study, holes 2, 4, 6, and 8 were sealed with aluminum inserts. Each of the other five holes was equipped with a yellow light-emitting diode (LED) for stimulus presentation and an infrared beam to detect nose poke responses. The chambers were illuminated by a 3W house light mounted in the center of the ceiling. Food pellets (Bio-Serv, UK Dustless Precision Pellets, 45 mg) were delivered to a tray at the front of the box by a food pellet dispenser. The food tray was fitted with a plastic flap connected to a microswitch enabling to detect head entries. The rats were introduced into the chamber through a hinged Perspex flap in the top half of the front wall. Controlling of the chambers was provided by specific software written in Turandot (Cambridge Cognition Ltd., version 0.7) which was run on a personal computer with the BNC Mark 2 System (Behavioral Net Controller, Campden Instruments Ltd., Loughborough, UK).

2.2.1.1. Habituation and training. The training of the animals was based on procedures extensively described elsewhere (Bari et al., 2008). After two habituation sessions, rats were trained to spatially discriminate and respond to short light stimuli randomly presented in one of the five apertures in order to obtain a food reward. The start of the session was signaled by the illumination of the house light and delivery of a single food pellet into the food magazine. Opening the panel to collect the pellet started the first trial. After a fixed delay of 5 s, the LED at the rear of one of the holes was switched on for a short period. Initially, the stimulus duration (SD) was set to 60 s and then progressively decreased to 1s over the sessions. During a complete session which terminated after 100 trials or 30 min, whichever occurred first, the light stimulus was presented the same number of times in each hole. Nose pokes into a hole while it was illuminated or within 5 s of the light's extinguishing (limited hold, LH) let to the delivery of a food pellet, and a correct response was recorded. Responses into any other aperture during that time (incorrect response) or nose pokes made before the target stimulus occurred (premature responses) just as failures to respond at all during the LH (omissions) resulted in a 5 s time-out during which all lights were turned off. Responses made in the holes while all lights were off restarted the time-out. Additional nose pokes made after correct or incorrect responses in any aperture (perseverative responses) as well as additional responses made at the food magazine before or after pellet delivery were recorded although not punished.

2.2.1.2. Testing. Testing started when the rats showed a stable baseline performance with >70% accuracy and <20% omissions over three consecutive daily sessions with <10% variation. The test schedule consisted of three days of testing with two days of training sessions in between to re-establish the animals' baseline performance. The test session parameters were identical to those used in training but included variable intertrial intervals (vITIs; 4.5,