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Intracranial self-stimulation as a positive reinforcer to study impulsivity in a probability discounting paradigm

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ABSTRACT

Probability discounting is used to study risky decision-making in humans and rodents. In these paradigms, the subject chooses between a small reward that is always delivered and a large reward that is delivered with varying probabilities. Risk-taking is defined as a preference for the large, uncertain reward. The aversive consequence associated with this task involves choosing the large reward and not obtaining it. To study this form of impulsivity in rodents, food reinforcement is commonly used. Using this reinforcer, and the need to food-deprive rodents to enhance task performance, may be problematic in rodent models that exhibit eating disorders, in pharmacological assessments that alter feeding, and for assessments of the neurocircuitry that is engaged by both feeding and risk-taking. We reveal here that electrical intracranial self-stimulation (ICSS) can be used as the positive reinforcer in risk assessments (i.e., probability discounting). ICSS was selected as it is rapidly acquired, the operant procedures are retained for months, and no tolerance or satiety develops to the reinforcer; thus, ICSS can be used in multiple test sessions in a repeated measures design. We developed an efficient, standardized, six phase ICSS-mediated protocol that allowed for the assessments of risk-taking in a probability discounting task. We demonstrated that the discounting behavior remained stable for several weeks. The value of this protocol is discussed in terms of practical as well as theoretical advantages of using ICSS-mediated reinforcement.

1. Introduction

Impulsivity can be regarded as "actions that appear poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation" (Daruna and Barnes, 1993). While some beneficial aspects of impulsivity are known (Dickman, 1990), it is generally recognized as a dysfunctional trait that is frequently associated with numerous neurological and psychiatric disorders including frontal lobe damage, schizophrenia, attention deficit-hyperactive disorder and substance abuse disorders. According to the American Psychiatric Association, impulse control disorders (ICDs) are a form of psychiatric disorder (American Psychiatric Association, 2000). ICDs include trichotillomania, intermittent explosive disorder, pathological gambling, kleptomania, pyromania, hypersexuality, compulsive shopping and others.

To understand impulsivity and ICDs and to subsequently develop therapies targeted to particular aspects of the disorder, laboratory protocols that model attributes of impulsivity are required. Risky decision-making is one facet of impulsivity. A common method used to study risky choice in both humans and laboratory rodents is the probability discounting paradigm (Mobini et al., 2000; Rachlin et al., 1991; Richards et al., 1999). In this task, the subject can choose between a small reward that is always delivered and a large reward that is delivered with varying probabilities. Risky behavior is defined as a preference for the large uncertain reward. The aversive consequence associated with this task involves choosing the large reward and not obtaining it (Cardinal and Howes, 2005). In rodent testing of probability discounting, food is often used as the positive reinforcer and to motivate the animal, salience of the food is enhanced by food-deprivation. This approach presents several disadvantages which can potentially confound outcomes. First, internal factors, such as hunger or thirst, can themselves lead to a change in impulsive behavior in animals (Minamimoto et al., 2009; Schuck-Paim et al., 2004). Second, chronic food restriction can lead to adaptations in dopaminergic (Carlson et al., 1988; Carr et al., 2003, 2009; Collins et al., 2008) and serotonergic signaling (Haleem and Haider, 1996; Huether et al., 1997; Kohsaka et al., 1980). These neurotransmitters also play a role in impulsivity (Adriani et al., 2009; Mehlman et al., 1994; Mobini et al., 2000; Soubrié, 1986; Winstanley et al., 2005). Moreover, this reward

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option may not be possible for assessments of risky choice in rat models of human neuropathologies that present eating disorders or for testing pharmacologics that alter feeding behaviors. Thus, we sought to design a probability discounting paradigm that utilized a positive reinforcer that avoided such shortcomings. To be broadly applicable to a range of laboratory assessments, we determined that criteria for this reinforcer should include the following: (i) It should more directly engage brain "reward centers" than is possible with food reward. (ii) It should be conducive to robust operant task testing. (iii) It should demonstrate a range of reward values that can be discriminated by the rat. (iv) Finally, it should support stable responding for several weeks. We reveal here that intracranial self-stimulation (ICSS) meets these criteria. In ICSS procedures, rats perform an operant task to obtain a positive reinforcing current delivered *via* an electrode implanted in reward regions of the brain (Olds and Milner, 1954). For the current study, we selected the medial forebrain bundle (MFB) at the level of the lateral hypothalamus (LH) as the stimulation target. This structure is well known to readily support ICSS with a large range of stimulation parameters. We detail how this reward parameter can be successfully implemented for probability discounting paradigms, and we verify performance stability and persistence.

2. Methods

Male Sprague–Dawley rats weighing 250–274 g upon arrival (Harlan, Indianapolis, IN) were housed in pairs under environmentally controlled conditions (7:00 AM/7:00 PM light/dark cycle, temperature maintained at 23–25 °C) with access to rat chow and water *ad libitum*. All rats were handled according to established procedures in the *Guide for the Care and Use of Laboratory Animals* (National Research Council, Washington, DC); specific protocols were approved by the Institutional Animal Care and Use Committee at Rush University Medical Center.

2.1. Implantation of electrode into the lateral hypothalamus

Eight rats were anesthetized with sodium pentobarbital (50 mg/kg ip; Sigma, St. Louis, MO), and placed into a small animal stereotaxic instrument (David Koft, Tujunga, CA) with the nose piece set at 3.3 mm below the horizontal. A midline scalp incision was made and a hole was drilled through the skull at −2.8 mm posterior to bregma and 1.8 mm lateral to midline. A bipolar stimulating electrode (MS303/3-B/SPC; Plastics One, Roanoak, VA) was stereotaxically lowered −8.4 mm from dura into the LH. Electrodes were secured to the skull with stainless steel screws and dental acrylic, and the incision was sutured. Rats were returned to their home cage following full recovery from anesthesia, and one week later, testing in the operant chambers was initiated.

2.2. Test apparatus

Rats were tested in operant chambers (30.5 cm × 24.1 cm × 21.0 cm; Med-Associates, St. Albans, VT), enclosed in ventilated, sound attenuated boxes outfitted on one wall with two retractable levers and a stimulus light above each lever. On the opposite wall, a single 100 mA house light was located in the top center. Intracranial stimulation was delivered by constant current stimulators (PHM-152/2 Dual programmable ICSS stimulator) *via* bipolar leads connected to 2-channel commutators (Plastics One, Roanoak, VA) mounted above the chamber.

2.3. Behavioral testing protocol

Acquisition of the probability discounting task was accomplished with a six phase protocol. Each phase included ongoing assessments of individual task performance, and the protocol was designed to sequentially fine-tune and verify the ICSS parameters as the rats progressed through the phases in order acquire the probability discounting task. As rats advanced, they were trained to build on prior task performance in order to meet standardized phase milestones. Table 1 illustrates the time-line for the protocol, as well as the objectives, criteria and maximal number of sessions necessary for rats to complete phase criteria. The methodologies associated with each phase, along with an explanation of data analyses, are provided below.

2.3.1. Phase 1: shaping

Following one week recovery from surgery, rats were trained to lever press to obtain a positively reinforcing electrical brain stimulation (EBS) using shaping procedures modified from Chester et al. (2006). At the beginning of a 30 min session, one of the two levers was extended. Shaping occurred by successive approximation, during which experimenter-applied EBS was used to initially direct the rat towards the lever, and then to aid the rat in making the association between a lever press and receiving an EBS. At the start of this process, each EBS consisted of biphasic 100 μA square wave pulses 200 μs applied as a 100 Hz for 500 μs. With the EBS frequency and pulse duration remaining constant, the current intensity was adjusted for individual rats based on their performance to approach and ultimately press the lever. The procedure used for this adjustment was as follows: lack of behavioral responses (e.g., sniffing, rearing, and approaching the lever) resulted in 20 μA increasing increments. If responses indicative of aversion occurred (freezing, crouching, and twitching) the current was decreased by 20 μA increments until aversive behaviors were no longer observed. Once the rat pressed the extended lever eight times in approximately 1 min, that lever was retracted and the other lever was extended and shaping proceeded (the order of left *vs*. right lever presentation was counter balanced across sessions). The minimum criteria set for this phase was steady lever pressing (∼eight presses/min) on both levers. Once lever pressing was established, the current intensity was incremented until no further increase in lever pressing rate was seen. This intensity level was used for the remaining Phases.

2.3.2. Phase 2: training on fixed ratio (FR)-1

The purpose of this Phase was to demonstrate stable lever pressing rates. To do so, one lever was extended during each 30 min session (right and left levers were counter balanced across sessions) and the number of lever presses was recorded. To complete this phase, rats had to meet the following minimum criteria in consecutive sessions: (1) lever press at least five times within the first 2 min of the session (i.e., to initiate the session) and (2) display a minimum average of eight lever presses/min in the session. Lever pressing rates for the last two sessions were averaged for each rat and group means ± SEM are reported. Data were analyzed using a paired *t*-test with significance set at $p < 0.05$.

2.3.3. Phase 3: rate–current intensity functions

The purpose of this Phase was to determine the effect of various LH stimulation parameters on the rate of lever pressing. A single lever was used in a session which was approximately 30–40 min in duration (right and left levers were presented in a counter balanced order across sessions). To evaluate the impact of various current intensities on lever press response rate, *rate–intensity functions* were generated for each rat. In this task, the LH stimulation frequency (100 Hz) and train duration (500 μs) where held constant while various intensities were pseudo-randomly presented. In the first 30 s of the session, rats had access to the lever which was set to deliver the current intensity used to meet Phase 2 criteria. This was used as a protocol 'reminder'; these data were