Behavioural Processes 101 (2014) 123–134

Contents lists available at ScienceDirect

Behavioural Processes

journal homepage: www.elsevier.com/locate/behavproc

Dissociations between interval timing and intertemporal choice following administration of fluoxetine, cocaine, or methamphetamine

Sarah R. Heilbronner[a], Warren. H. Meck[b,*]

[a] Department of Pharmacology & Physiology, University of Rochester Medical Center, Rochester, NY 14642, USA
[b] Department of Psychology and Neuroscience, Duke University, Durham, NC 27708, USA

ARTICLE INFO

Article history:
Received 15 May 2013
Received in revised form
19 September 2013
Accepted 21 September 2013

Keywords:
Clock speed
Impulsivity
Self control
Temporal discounting
Dopamine
Serotonin

ABSTRACT

The goal of our study was to characterize the relationship between intertemporal choice and interval timing, including determining how drugs that modulate brain serotonin and dopamine levels influence these two processes. In Experiment 1, rats were tested on a standard 40-s peak-interval procedure following administration of fluoxetine (3, 5, or 8 mg/kg) or vehicle to assess basic effects on interval timing. In Experiment 2, rats were tested in a novel behavioral paradigm intended to simultaneously examine interval timing and impulsivity. Rats performed a variant of the bi-peak procedure using 10-s and 40-s target durations with an additional "defection" lever that provided the possibility of a small, immediate reward. Timing functions remained relatively intact, and 'patience' across subjects correlated with peak times, indicating a negative relationship between 'patience' and clock speed. We next examined the effects of fluoxetine (5 mg/kg), cocaine (15 mg/kg), or methamphetamine (1 mg/kg) on task performance. Fluoxetine reduced impulsivity as measured by defection time without corresponding changes in clock speed. In contrast, cocaine and methamphetamine both increased impulsivity and clock speed. Thus, variations in timing may mediate intertemporal choice via dopaminergic inputs. However, a separate, serotonergic system can affect intertemporal choice without affecting interval timing directly.

This article is part of a Special Issue entitled: Associative and Temporal Learning.

1. Introduction

Intertemporal choice features prominently in decision-making for all animals, including humans (Ainslie and Haslam, 1992; Evenden, 1999b; Meck et al., 2012a,b; Rachlin and Green, 1972). The trade-off between small, immediately available rewards and large rewards only available after a delay is key to understanding decisions about diet, exercise, studying, and investing, to name a few. Mischel and colleagues (Mischel and Metzner, 1962; Mischel et al., 1989) provided early insight into how choice behavior is affected by delays by offering children the opportunity to resist eating one treat (a smaller, sooner option) in order to obtain a more desirable one in the future (a larger, later option). Children who were more patient in this type of delay of gratification task gained a host of advantages over the course of their lifetimes. They achieved greater academic success (Mischel et al., 1989), were better able to cope with rejection and frustration (Shoda et al., 1990), and were less likely to use cocaine according to self-reports (Ayduk et al., 2000). Impulsivity in intertemporal choice tasks more broadly has been linked to gambling (Alessi and Petry, 2003), cigarette smoking (Reynolds et al., 2004), obesity (Seeyave et al., 2009), violent crime (Cherek et al., 1997), and alcohol addiction (Petry, 2001). Decades of research have showed that ability to delay gratification is one of the most useful predictors in a psychologist's toolbox (Bickel and Marsch, 2001). Thus, understanding the nature of self-control and impulsivity is an important goal of behavioral studies (Carlson and Moses, 2001; Crockett et al., 2010; Garcia and Kirkpatrick, 2013; Fantino et al., 1979).

Recent studies have been directed toward elucidating the neural mechanisms governing intertemporal choice across species (e.g., Broos et al., 2012; Kim et al., 2008; Louie and Glimcher, 2010; Mobini et al., 2002; Peters and Büchel, 2011; Samanez-Larkin et al., 2011; Sellitto et al., 2011; Winstanley et al., 2004). Choices made about options displaced through time are governed by a variety of brain regions implicated in decision-making, delay and reward representation, and impulsivity more broadly. Serotonin (5-HT) is thought to mediate impulsive decision-making. Decreases in 5-HT levels increase impulsivity in both rodents and humans (e.g., Mobini et al., 2000; Schweighofer et al., 2008; Winstanley et al., 2004; Wogar et al., 1993). Dopamine (DA) levels may also mediate impulsivity and intertemporal choice; however, its effects are inconsistent depending on the behavioral paradigm (Gu et al., 2011;

* Corresponding author at: Department of Psychology and Neuroscience, Genome Sciences Research Building II, 572 Research Drive – P.O. Box 91050, Duke University, Durham, NC 27708, USA.
E-mail address: meck@psych.duke.edu (Warren.H. Meck).

0376-6357/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.beproc.2013.09.013

Harrison et al., 1997; Kayser et al., 2012; Winstanley et al., 2003), and may depend on an intact serotonergic system (Harrison et al., 1997; Winstanley et al., 2006).

Time discrimination, especially as it relates to reward delivery, is obviously an important component of intertemporal choice (Galtress et al., 2012a,b; Kirkpatrick, 2013). In order for organisms to make appropriate decisions about options displaced through time, they must have an intact representation of the relevant time intervals. In addition, they should be able to update their estimation of those intervals according to experience. Interval timing in the seconds-to-minutes range adheres closely to Weber's law, meaning the normal distribution of temporal estimates has a width that scales with the length of the target duration (Allman et al., 2014; Buhusi and Meck, 2005; Oprisan and Buhusi, 2013 – see Killeen, 2013 for a more nuianced analysis of time). Numerical and most sensory estimations also adhere to this rule, often referred to as the scalar property of interval timing (Brannon et al., 2008; Buhusi et al., 2009; Gibbon, 1977; Gibbon et al., 1984; Meck and Malapani, 2004; Treisman, 1964). Several duration perception/production procedures have been developed to assess interval timing in nonhuman animals. The peak-interval (PI) procedure, for example, rewards the first press on a primed lever following a fixed interval, but only on a subset of trials. The unrewarded trials allow investigators to probe time estimations without interruption. Previous studies using the PI procedure in humans and other animals (e.g., Agostino et al., 2011b; Buhusi et al., 2009, 2013; Buhusi and Meck, 2007; Cheng and Meck, 2007; Church et al., 1994; Lake and Meck, 2013; MacDonald et al., 2007; Matell and Meck, 1999; Meck and Williams, 1997; Rakitin et al., 1998) have reliably obtained Gaussian response curves whose peak times and variances fit well with Weber's law.

Unlike the related processes of millisecond timing and circadian timing, which depend mainly on an intact cerebellum and hypothalamus, respectively, interval timing relies most heavily on cortico-striatal circuits (Buhusi and Meck, 2005; Galtress and Kirkpatrick, 2010; Hinton and Meck, 1997, 2004; Matell et al., 2003, 2011; Meck, 2006a,b,c; Meck et al., 2008; Merchant et al., 2013). In particular, the projections of midbrain DA neurons to the dorsal striatum are crucial for interval timing (Coull et al., 2011; Meck, 2006b; Williamson et al., 2008). Patients with Parkinson's disease, characterized by degraded DA neurons in the substantia nigra pars compacta that would normally project heavily to the striatum, exhibit impaired interval timing (Allman and Meck, 2012; Jahanshahi et al., 2010; Jones and Jahanshahi, 2013; Malapani et al., 1998a,b, 2002). Ensemble recordings have revealed that striatal neurons may indeed have some of the necessary properties to conduct interval timing: approximately 20% of neurons are sensitive to time of reward, firing at different rates for the different times being directly investigated (Matell et al., 2003). While the dorsal striatum is clearly important for interval timing, it is at present unknown how this information is transferred to mechanisms of decision-making and what roles DA and glutamate may play in intertemporal choice (Agostino et al., 2011a, 2013; Cheng et al., 2006b; Cheng and Liao, 2007; Coull et al., 2013; Hata, 2011; Jones and Jahanshahi, 2011; Kayser et al., 2012; Kelm and Boettiger, 2013; MacDonald et al., 2012; Merchant et al., 2013).

In addition to interval timing affecting intertemporal choice, the discounted value of a reward based on delay to acquisition may have an impact on the process of interval timing. Presumably, an interval is timed more effectively when decisions will be made with the temporal information gathered. Valuation will thus alter the interval-timing process. The importance of DA projections to the striatum for value-based learning, temporal discounting, and control of impulsivity only underscores the linked nature of interval timing and reward (Asgari et al., 2006; Body et al., 2004, 2005, 2006, 2013; Ho, 1996; Kurti and Matell, 2011; MacDonald et al., 2012; Schultz et al., 1997; Wiener et al., 2008; Willuhn et al., 2010). Surprisingly, the relationship between hyperbolic discounting and timing remains almost wholly unstudied – but see Cui (2011) and Galtress et al. (2012a,b) for recent initiatives. Our goal in the present experiment was to develop a novel version of the PI procedure using two different target durations (e.g., bi-peak procedure) in order to allow us to investigate the relationship between intertemporal choice and interval timing in rats (MacDonald and Meck, 2004, 2005, 2006; Matell et al., 2006; Meck et al., 2012a,b). By adjusting the bi-peak procedure to allow for "defection" with the possibility of immediate reward, we were able to determine an animal's estimate of time and valuation of rewards displaced through time. The addition of the defection lever effectively mixes a bi-peak procedure with a delay of gratification procedure, in which the smaller sooner option is available throughout the delay (Reynolds et al., 2002). We then used this hybrid procedure to measure the effects of a selective 5-HT reuptake inhibitor (fluoxetine) and indirect DA agonists (cocaine and methamphetamine) on both interval timing and intertemporal choice because of their known impact on time perception and prediction (Ardayfio et al., 2008; Barr et al., 2004; Coull et al., 2011; Daw et al., 2002; Sysoeva et al., 2010; Wiener et al., 2011).

2. Materials and methods

2.1. Subjects

The temporal control of behavior was studied in eight (Experiment 1) and fifteen (Experiment 2) male Sprague-Dawley rats weighing 250–400 g (Charles-River Laboratories, Raleigh, NC, USA) and approximately 3 months of age when the experiments began. Rats were housed in pairs in a 12:12 light/dark (LD) cycle with lights on from 7:00 A.M. to 7:00 P.M. Rats were given continuous access to water and were maintained at 85% free-feeding weight. They were fed a ration of Purina chow after each daily session conducted during the light phase of the LD cycle. Experiments were conducted in accordance with procedures approved by the Institutional Animal Care and Use Committee of Duke University.

2.2. Apparatus

All experimental data were obtained in eight identical lever boxes (Model ENV-007, MED Associates, St. Albans, VT) housed in ventilated cubicles designed to provide light and sound isolation (Model ENV-019, MED Associates, St. Albans, VT). Lever boxes had dimensions of 24 cm × 31 cm × 31 cm. Tops, sidewalls, and doors were constructed of clear acrylic plastic; front and back walls were constructed of aluminum. The floor consisted of 19 parallel stainless steel bars. A pellet dispenser (Model ENV-203, MED Associates, St. Albans, VT) delivered 45 mg food pellets (Research Diets, New Brunswick, NJ) to a food cup located 1 cm above the floor on the front wall. Each lever box was equipped with two retractable response levers (Model ENV-112, MED Associates, St. Albans, VT) situated on the front wall of the lever box to the left and right of the food cup. In addition, each lever box contained one non-retractable response lever situated in the middle of the front wall, centered, above the food cup. A 28-V house light was mounted at the center of the top of the front wall. A speaker system (Model ENV-225, MED Associates, St. Albans, VT) was mounted on the opposite wall from the levers and was used to present white-noise signals at 75-dB. An IBM-PC compatible computer running MED-PC Version IV Research Control & Data Acquisition System software (MED Associates, St. Albans, VT) was attached to an electronic interface (Models DIG-700 and SG-215, MED Associates, St. Albans, VT) used to control the experimental equipment and record the data. The time of each lever press was recorded to an accuracy of 10 ms and placed into 1-s