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INDIVIDUAL DIFFERENCES IN IMPULSIVE ACTION AND DOPAMINE TRANSPORTER FUNCTION IN RAT ORBITOFRONTAL CORTEX

J. R. YATES,[a,c†] M. DARNA,[b,d†] J. S. BECKMANN,[a] L. P. DWOSKIN[b,d] AND M. T. BARDO[a,d*]

[a] *Department of Psychology, University of Kentucky, Lexington, KY 40536, USA*

[b] *Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY 40536, USA*

[c] *Department of Psychological Science, Northern Kentucky University, Highland Heights, KY 41099, USA*

[d] *Center for Drug Abuse Research Translation, University of Kentucky, Lexington, KY 40536, USA*

Abstract—Impulsivity, which can be subdivided into impulsive action and impulsive choice, is implicated as a factor underlying drug abuse vulnerability. Although previous research has shown that dopamine (DA) systems in prefrontal cortex are involved in impulsivity and substance abuse, it is not known if inherent variation in DA transporter (DAT) function contributes to impulsivity. The current study determined if individual differences in either impulsive action or impulsive choice are related to DAT function in orbitofrontal (OFC) and/or medial prefrontal cortex (mPFC). Rats were first tested both for impulsive action in a cued go/no-go task and for impulsive choice in a delay-discounting task. Following behavioral evaluation, *in vitro* [^{3}H]DA uptake assays were performed in OFC and mPFC isolated from individual rats. V_{max} in OFC, but not mPFC, was correlated with performance in the cued go/no-go task, with decreased OFC DAT function being associated with high impulsive action. In contrast, V_{max} in OFC and mPFC was not correlated with performance in the delay-discounting task. The current results demonstrate that impulsive behavior in cued go/no-go performance is associated with decreased DAT function in OFC, suggesting that hyperdopaminergic tone in this prefrontal subregion mediates, at least in part, increased impulsive action.

Key words: dopamine transporter, cued go/no-go, impulsive action, delay discounting, impulsive choice, rat.

INTRODUCTION

Impulsivity is a construct that encompasses various behaviors and is typically subdivided into two broad categories: impulsive action and impulsive choice (Winstanley et al., 2010). Impulsive action is conceptualized as motor impulsivity (e.g., the inability to inhibit a prepotent response), and impulsive choice is considered to reflect cognitive impulsivity (e.g., consistently choosing a small, immediate reward over a large, delayed reward). Impulsive action and impulsive choice can be measured in human and laboratory animals with the cued go/no-go task and the delay-discounting task, respectively (Mahrer, 1956; Gross and Weiskrantz, 1962; Rachlin and Green, 1972; Hogg and Evans, 1975; Mazur et al., 1985; Evenden and Ryan, 1996; Harrison et al., 1999). Because impulsive responding in each task has been associated with increased substance abuse liability in humans (Kollins et al., 2005; Weafer et al., 2011), determining the shared neurobiology between impulsive behavior and substance use disorders may lead to improved treatment outcomes for individuals with comorbid impulse-control and substance use disorders.

The role of dopamine (DA) in substance abuse and impulsivity is of particular interest because drugs of abuse, as well as medications used to treat impulse-control disorders (Biederman and Faraone, 2005), increase extracellular DA (Creese and Iversen, 1975; Moghaddam and Bunney, 1989; Kuczenski and Segal, 1997; Jones et al., 1998; Volkow et al., 2002; Caillé and Parson, 2003). Furthermore, DA systems in various subregions of the prefrontal cortex (PFC) are implicated in substance abuse and impulsivity. Specifically, decreased DA transmission is observed in alcoholics (Narendran et al., 2014) and smokers (Luijten et al., 2013). Within PFC, animals exhibiting low levels of either impulsive action or impulsive choice have higher DA D_2 receptor mRNA levels in the prelimbic portion of medial prefrontal cortex (mPFC; Simon et al., 2013). Although mRNA levels do not necessarily reflect differences in receptor protein (Tian et al., 2004), other research has shown that overexpression of DA D_1 receptors in prelimbic mPFC is associated with increased impulsive choice in a delay-discounting paradigm (Sonntag et al., 2014). Despite these DA receptor mRNA and protein differences, little is known about the potential role of presynaptic mechanisms of DA signaling within impulsivity-relevant prefrontal cortical regions.

Medications that are efficacious in treating impulse-control disorders, such as methylphenidate and amphetamine, target the DA transporter (DAT; Ritz and

*Correspondence to: M. T. Bardo, Department of Psychology, University of Kentucky, Lexington, KY, 40536, USA.
E-mail address: mbardo@email.uky.edu (M. T. Bardo).
† These authors contributed equally to the manuscript.
Abbreviations: 5-CSRTT, five-choice serial reaction time task; ACC, anterior cingulate cortex; DA, dopamine; DAT, DA transporter; EDTA, ethylenediaminetetraacetic acid; FR, fixed ratio; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; ILC, infralimbic cortex; ITI, inter-trial interval; MAD, mean adjusted delay; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PLC, prelimbic cortex; VI, variable interval; VI/EXT, VI responses/EXT responses.

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Kuhar, 1989; Volkow et al., 1998), indicating that DAT is likely an important mediator of impulsivity. Additionally, polymorphisms in the *DAT1* gene are associated with increased impulsivity (Waldman et al., 1998; Paloyelis et al., 2010). Furthermore, GBR12909, a selective DAT inhibitor, reduces impulsive choice in the delay-discounting task in rats (Evenden and Ryan, 1996; van Gaalen et al., 2006; Baarendse and Vanderschuren, 2012), but increases impulsive action in the five-choice serial reaction time task (5-CSRTT; Baarendse and Vanderschuren, 2012), suggesting that DAT may be differentially involved in impulsive choice and impulsive action. Although DAT has been implicated in impulsivity, it is unknown if individual differences in DAT function mediate distinct facets of impulsive behavior. Thus, the purpose of the current study was to determine if inherent variation in DAT function in orbitofrontal cortex (OFC) and mPFC is associated with impulsive action and/or impulsive choice.

EXPERIMENTAL PROCEDURES

Subjects

Eighteen male, experimentally naïve Sprague–Dawley rats (250–275 g; Harlan Laboratories, Indianapolis, IN, USA) were housed individually in a temperature- and humidity-controlled colony with a 12/12-h light/dark cycle. Following 5 days of acclimation, rats were food restricted (85% of free feeding body weight), and had free access to water in their home cages. Experiments were conducted during the light phase. Rats were cared for in accordance with the 2011 edition of the "Guide for the Care and Use of Laboratory Animals" (National Research Council, 2010) and procedures were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

Behavioral apparatus

Operant chambers (28 × 21 × 21 cm; ENV-008; MED Associates, St. Albans, VT, USA) with an aluminum front and back walls and Plexiglas sides were located inside sound-attenuating chambers (ENV-018M; MED Associates, St. Albans, VT, USA). A recessed food tray (5 × 4.2 cm) was located 2 cm above the floor in the bottom-center of the front wall. Retractable levers (4.5 cm) were mounted 6 cm above the floor on each side of the food tray. A 28-V white cue light was located 6 cm above each lever. A white house light was mounted in the center of the back wall. All responses and scheduled consequences were recorded and controlled by a computer interface using Med-IV software.

Experimental design

Each rat was tested in both the cued go/no-go and delay-discounting tasks, with order of testing counterbalanced. Following the last behavioral test day, rats were killed by rapid decapitation and both OFC and mPFC were obtained from each rat to determine the kinetic parameters of DAT function.

Cued go/no-go task. Previously described procedures were used (Marusich et al., 2011). Training began with 3 days of autoshaping (Brown and Jenkins, 1968), in which both levers were extended and the house light was illuminated. During 60-min autoshaping sessions, rats received one sucrose-based pellet (45 mg; F0021 dustless precision pellet, Bio-Serve, Frenchtown, NJ, USA) on a continuous schedule of reinforcement following responses on the active lever. The position of the active lever was counterbalanced across sessions for each rat. To facilitate the acquisition of lever responding, sucrose pellets were delivered non-contingently on a variable time (VT) 100 s schedule of reinforcement. Responses on the inactive lever were recorded, but had no programed consequence. Following either contingent or non-contingent delivery of a sucrose pellet, both levers were retracted for 2 s. Autoshaping sessions ended after delivery of 60 reinforcers or after 60 min elapsed. Following autoshaping, training continued for four consecutive daily 20-min sessions employing a variable interval (VI) schedule (VI-4, VI-8, VI-14, and VI-20 s) of sucrose pellet reinforcement.

The cued go/no-go task was employed for 14 consecutive daily 40-min sessions. Sessions consisted of 2-min "go" components in which reinforcers were available, alternated with 2-min "no-go" components in which reinforcers were not available (extinction). Go components were signaled by cue light illumination. Active lever responses on a VI-20 s schedule resulted in sucrose pellet reinforcement. No-go components were signaled by the absence of cue light illumination; responses on the previously active lever were recorded, but had no programed consequence. During both go and no-go components, responses on the inactive lever were recorded, but had no programed consequence. The cues signaling go and no-go components were not counterbalanced across rats. However, it is important to note that previous work has shown that counterbalancing the cue used to signal each component does not alter performance in this task (Hellemans et al., 2005). The primary dependent measure from the cued go/no-go task was calculated as the number of responses during go trials divided by the number of responses during no-go trials (i.e., VI responses/EXT responses) averaged across the last seven sessions, when stable performance was achieved.

Delay-discounting task. The delay-discounting task was conducted for 21 days using previously described procedures (Perry et al., 2005). Sessions began with house light illumination and ended following completion of 60 trials or when 2 h elapsed. Each session included 15 blocks of four trials. For each block, the first two trials were forced-choice trials, and the last two trials were free-choice trials. During forced-choice trials, only one lever (left or right; counterbalanced across trials) was extended, and the cue light above the extended lever was illuminated. During free-choice trials, both levers were extended, and cue lights above both levers were illuminated. A response on one lever (fixed ratio [FR] 1 schedule of reinforcement) resulted in immediate delivery