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Effects of environmental and pharmacological manipulations on a novel delayed nonmatching-to-sample 'working memory' procedure in unrestrained rhesus monkeys

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HIGHLIGHTS

- Experimentally naïve monkeys learned DNMTS within 60 training days.
- DNMTS forgetting functions were stable over the 6-month experimental period.
- Increasing the intertrial interval enhanced DNMTS performance.
- Δ^9-THC significantly disrupted DNMTS performance, whereas methylphenidate did not alter DNMTS performance.

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ABSTRACT

Background: Working memory is a domain of 'executive function.' Delayed nonmatching-to-sample (DNMTS) procedures are commonly used to examine working memory in both human laboratory and preclinical studies.
New method: The aim was to develop an automated DNMTS procedure maintained by food pellets in rhesus monkeys using a touch-sensitive screen attached to the housing chamber. Specifically, the DNMTS procedure was a 2-stimulus, 2-choice recognition memory task employing unidimensional discriminative stimuli and randomized delay interval presentations.
Results: DNMTS maintained a delay-dependent decrease in discriminability that was independent of the retention interval distribution. Eliminating reinforcer availability during a single delay session or providing food pellets before the session did not systematically alter accuracy, but did reduce total choices. Increasing the intertrial interval enhanced accuracy at short delays. Acute Δ^9-THC pretreatment produced delay interval-dependent changes in the forgetting function at doses that did not alter total choices. Acute methylphenidate pretreatment only decreased total choices.
Comparison with existing methods: All monkeys were trained to perform NMTS at the 1 s training delay within 60 days of initiating operant touch training. Furthermore, forgetting functions were reliably delay interval-dependent and stable over the experimental period (~6 months).
Conclusions: Consistent with previous studies, increasing the intertrial interval improved DNMTS performance, whereas Δ^9-THC disrupted DNMTS performance independent of changes in total choices. Overall, the touchscreen-based DNMTS procedure described provides an efficient method for training and testing experimental manipulations on working memory in unrestrained rhesus monkeys.

1. Introduction

The neuropsychological construct 'executive function' has been broadly defined as self-directed behavior that alters future consequences (Barkley, 1997; Bickel et al., 2012). The executive functions consist of a number of related neurobiological

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and behavioral processes such as working memory, attention, behavioral inhibition/impulsivity and behavioral flexibility closely associated with frontal cortical function (Robbins, 1996). Preclinical research stems from interest in treating mental health disorders and diseases that impact working memory (Buccafusco, 2008). Some examples include attention deficit hyperactivity disorder (Alderson et al., 2013), schizophrenia (Lett et al., 2014), and Alzheimer's (Jahn, 2013). In particular, drug addiction has been suggested to impair working memory in humans (Fernández-Serrano et al., 2011; Ornstein et al., 2000; Tramullas et al., 2007) and correlates with both treatment outcomes and treatment retention rates in drug-addicted individuals (Aharonovich et al., 2006). Moreover, drug addiction is associated with functional and neuroanatomical changes in brain areas such as dorsolateral prefrontal cortex (Liu et al., 2005, 2009), a region thought to be critical for accurate performance in working memory procedures, such as delayed nonmatching-to-sample (DNMTS) (Levy and Goldman-Rakic, 1999). Overall, pharmacological or behavioral approaches that specifically target executive functions such as working memory may therefore provide novel treatment strategies for the development of medications and behavioral interventions for drug addiction (Sofuoglu, 2010; Sofuoglu et al., 2013).

Most preclinical procedures for examining the behavioral and neurobiological mechanisms of working memory utilize a variant of the delayed matching-to-sample (DMTS) procedure (e.g., Blough, 1959; for review, see White, 2013). For example, a subject is required to choose among two comparison stimuli, one of which is physically identical to the sample stimulus presented previously in the trial. When choice of the comparison that matches the previously presented sample is reinforced, the procedure is called (DMTS); whereas, when choice of the other nonmatching sample is reinforced, the procedure is called DNMTS. In general, preference for the reinforced comparison decreases monotonically as a function of the duration of the retention or delay interval interposed between the offset of the sample stimulus and presentation of the comparison stimuli (Rubin and Wenzel, 1996; White, 2001).

Training of DMTS or DNMTS procedures in nonhuman primates has been previously reported to take greater than 12 months (Weed et al., 1999; Gould et al., 2012, 2013). In addition to these protracted training periods, baseline accuracy has been shown to increase over time necessitating individual subject adjustments of both delays and distractors for the DMTS procedure to maintain a delay-dependent decrease in performance (Weed et al., 1999; Bain et al., 2003; Gould et al., 2013; Uslaner et al., 2013; Kromrey et al., 2015). Thus, the aim of the present study was to develop an automated DNMTS procedure in experimentally naïve rhesus monkeys using a touch-sensitive screen attached to the home cage. DNMTS was used to facilitate comparison to prior studies in rhesus monkeys (Weed et al., 1999) and because this task engages brain regions exhibiting abnormal functioning in opioid addicted humans (Levy and Goldman-Rakic, 1999; Liu et al., 2005, 2009). We hypothesized that the use of two unidimensional stimuli (white and black boxes) would facilitate DNMTS training and reliably maintain a delay-dependent decrement in accuracy. Additionally, the effects of environmental manipulations that consisted of either manipulating the magnitude of the reinforcer (extinction and prefeeding) or manipulating the intertrial interval, and two pharmacological manipulations, acute Δ^9-tetrahydrocannabinol and methylphenidate, were determined to validate the procedure. These environmental (Odum et al., 2005; Taffe, 2004) and pharmacological (Aigner, 1988; Schulze et al., 1988) manipulations have been previously examined on DMTS or DNMTS performance in preclinical studies.

2. Method

2.1. Subjects

Four adult male rhesus monkeys (*Macaca mulatta*) served as subjects. All monkeys were experimentally naïve at the beginning of the study. Monkeys weighed 7–10 kg and were maintained on a diet of fresh fruit and food biscuits (Lab Diet High Protein Monkey Biscuits No. 5045; PMI Nutrition, St. Louis, MO) provided following daily experimental sessions. Water was continuously available in the home cage via an automatic watering system. A 12-h light–dark cycle was in effect (lights on from 06:00 to 18:00 h). Animal research and maintenance were conducted according to the 8th edition of the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health (National Academies Press, 2011). Animal facilities were licensed by the United States Department of Agriculture and accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. The Institutional Animal Care and Use Committee approved the research protocol. Monkeys had visual, auditory, and olfactory contact with other monkeys throughout the study. Operant procedures and foraging devices were provided for environmental manipulation and enrichment. Videos were played daily in animal housing rooms to provide additional environmental enrichment.

2.2. Apparatus

Monkeys were housed individually in well-ventilated, stainless steel chambers (66 cm × 76 cm × 94 cm) that also served as experimental chambers. Each chamber was equipped with a custom-made, stainless steel screen enclosure (Lafayette Instrument, Lafayette, USA), which was mounted on the front wall of the chamber to provide access to a 15″ touch-sensitive screen (33.6 cm × 26.4 cm Model 1537L; Elo TouchSystems, Menlo Park, CA). Each chamber was also equipped with a pellet dispenser (Model ENV-203-1000; Med Associates, St Albans, VT) mounted on a shelf above the chamber. All experimental events and data were collected using custom programming in ABET II Touch software (Lafayette Instrument, Lafayette, USA) in tandem with a Whisker server (Cambridge University, UK) controlled the touch-sensitive apparatus. Touchscreen stimuli were made in Microsoft PowerPoint for Mac 2011 using the hue-saturation-brightness slider. Sample and comparison stimuli were different shades of gray constructed by adjusting the hue and saturation to 0.0 and varying brightness/intensity. Brightness was set at 1.8% (black) and 100.0% (white) throughout the present study.

2.3. Touch response training

Monkeys were first trained to touch the screen at a central location under a fixed-ratio (FR) 1 schedule for 1-g banana-flavored pellets (5TUR, Test Diets, Richmond, IN). Sessions ended after either 80 pellets were earned or 2 h, whichever occurred first. A custom grid with dimensions of 800 × 600 pixels, divided into 48, 100 × 100 pixel boxes was used throughout the present study. During the first training phase, the entire screen was signaled active by a white display and each touch (FR 1) produced a food pellet and was followed by a 3 s intertrial interval (ITI) in which the screen was blank (black). Subsequent training phases consisted of progressively decreasing dimensions of the active response location until reliable responding (≥60 pellets earned per session) within the final 200 × 200 pixel (9.6 cm × 8.8 cm) dimensions was established. This required one intermediate active location size (500 × 500 pixel) and no more than 10 sessions for any monkey. After the terminal size of the active location was established, the fixed-ratio requirement