NeuroImage 157 (2017) 27–33

Contents lists available at ScienceDirect

NeuroImage

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

Linking dopaminergic reward signals to the development of attentional bias: A positron emission tomographic study

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ARTICLE INFO

Keywords:
Selective attention
Reward learning
Dopamine
Dopamine release positron emission tomography
Incentive salience

ABSTRACT

The attention system is shaped by reward history, such that learned reward cues involuntarily draw attention. Recent research has begun to uncover the neural mechanisms by which learned reward cues compete for attention, implicating dopamine (DA) signaling within the dorsal striatum. How these elevated priority signals develop in the brain during the course of learning is less well understood, as is the relationship between value-based attention and the experience of reward during learning. We hypothesized that the magnitude of the striatal DA response to reward during learning contributes to the development of a learned attentional bias towards the cue that predicted it, and examined this hypothesis using positron emission tomography with [^{11}C] raclopride. We measured changes in dopamine release for rewarded versus unrewarded visual search for color-defined targets as indicated by the density and distribution of the available D_2/D_3 receptors. We then tested for correlations of individual differences in this measure of reward-related DA release to individual differences in the degree to which previously reward-associated but currently task-irrelevant stimuli impair performance in an attention task (i.e., value-driven attentional bias), revealing a significant relationship in the right anterior caudate. The degree to which reward-related DA release was right hemisphere lateralized was also predictive of later attentional bias. Our findings provide support for the hypothesis that value-driven attentional bias can be predicted from reward-related DA release during learning.

Introduction

Attention is directed towards stimuli that are physically salient (e.g., bright, high contrast; Theeuwes, 2010) or possess a currently prioritized task-relevant feature (e.g., red stimuli when searching for a red target; Folk et al., 1992). The neural mechanisms of stimulus-driven and goal-directed attention have been extensively studied (e.g., Balan and Gottlieb, 2006; Corbetta and Shulman, 2002). More recently, research has demonstrated that previously reward-associated stimuli automatically capture attention even when explicitly task-irrelevant and physically non-salient (Anderson et al., 2011; see Anderson, 2016a, for a review). Participants first completed a training phase comprising a visual search task in which color-defined targets predicted monetary reward outcomes. Then, in a subsequent test phase, participants performed a different visual search task in which the colors of the stimuli were completely irrelevant to the task. On a subset of trials, one of the non-targets was rendered in a previously reward-associated color, and apart from its reward history this stimulus did not stand out in any salient way. Performance was found to be impaired by the presence of the previously reward-associated stimulus (Anderson et al., 2011), which frequently drew eye movements (Anderson and Yantis, 2012), suggesting automatic attentional processing.

The neural correlates of the attentional processing of previously reward-associated stimuli have been assessed using functional magnetic resonance imaging (fMRI; Anderson, 2017; Anderson et al., 2014; Hickey and Peelen, 2015; Krebs et al., 2011), electroencephalography (MacLean and Giesbrecht, 2015; Qi et al., 2013), magnetoen-

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http://dx.doi.org/10.1016/j.neuroimage.2017.05.062
Received 20 January 2017; Accepted 28 May 2017
Available online 30 May 2017

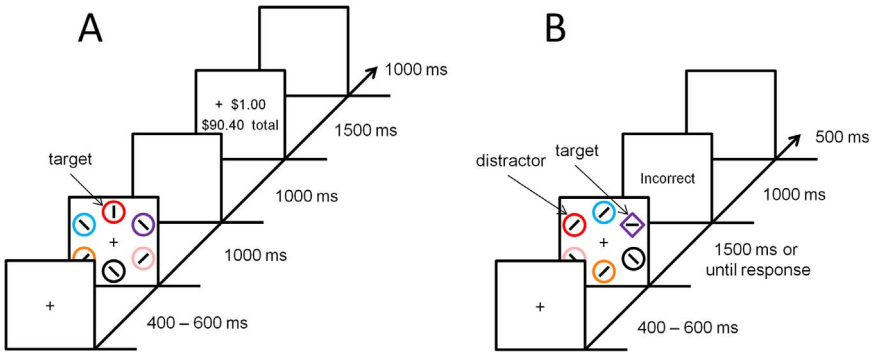

Fig. 1. Experimental task. Time course and trial events for the training phase (A) and test phase (B).

cephalography (Donohue et al., 2016; Hopf et al., 2015), and single unit recording in non-human primates (Hikosaka et al., 2014), consistently implicating elevated neural activity within the posterior parietal cortex and visual corticostriatal loop (see Seger, 2013). These brain areas have been collectively referred to as the value-driven attention network (Anderson, 2017). A recent study utilizing positron emission tomography (PET) further revealed that value-driven attentional bias was strongly related to the release of dopamine (DA) within the dorsal striatum (Anderson et al., 2016b), suggesting a relationship between DA signals within the striatum and the control of visual attention.

These value-based attentional priority signals were measured in extinction, after learning had already occurred. The neural processes by which such elevated cue reactivity develops remain largely unexplored. One recent study demonstrated that the value-driven attention network responds to the receipt of reward, and does so differently based on the preceding reward cue (in this case, target color), reflecting a reward signal that contains information concerning the preceding visual signal (Anderson, 2017). Thus, reward signals may serve as teaching signals to the visual system during the development of value-based attention, mirroring hypothesized mechanisms of perceptual learning (Roelfsema and van Ooyen, 2005; Seitz and Watanabe, 2005). However, evidence directly linking reward signals to variation in attentional performance is lacking, as is the specific neurotransmitter system involved in shaping the attention system during the learning process.

In the present study, we tested the hypothesis that the DA response to reward in the human striatum serves as a teaching signal to the attention system. Regional concentrations of [^{11}C]raclopride, a radiolabelled D_2/D_3 receptor antagonist, provide a measure of available D_2/D_3 receptors. By comparing the binding potential of [^{11}C]raclopride across rewarded and unrewarded versions of the same task, relative increases or decreases in the release of endogenous DA due to the experience of extrinsic reward were determined (Martin-Soelch et al., 2011; Wong et al., 2006; Volkow et al., 2006). We predicted that greater reward-related DA release during learning would be associated with greater value-driven attentional bias as measured during a subsequent extinction phase (slowing of response time associated with the presence of a previously high-value distractor).

Materials and methods

Participants

Eleven (9 female) healthy adult volunteers (19–33 years of age, mean = 26.7, SD = 4.05) who were free of medical or neuropsychiatric disorders participated in the experiment. Screening criteria included a negative drug test and the exclusion of major medical or neuropsychiatric disorders past or present. Axis I diagnoses were ruled out using the *Structured Clinical Interview for DSM-IV Axis I Disorders—Clinician Version (SCID-CV)* (First et al., 1997), a structured interview to utilize the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*. All participants received a detailed physical exam including vital signs, 12-lead electrocardiogram, blood for complete blood counts with differential, complete metabolic panel, blood clotting parameters, creatinine (CPK) for muscle toxicity, urine for urinalysis, and toxicology for drugs of abuse and alcohol breathalyzer before the PET scans. Informed consent was obtained from all participants, and all procedures were approved by the Institutional Review Board of the Johns Hopkins University School of Medicine and conformed to the principles outlined in the Declaration of Helsinki.

Experimental task

The experiment consisted of a training phase and a test phase. Both phases of the experiment were performed on the same day while the participant lay within the PET scanner, although only during the training phase was PET data acquired – this was done to match the context within which the two phases were completed as much as possible, as value-based attentional biases can be sensitive to contextual information (Anderson, 2015). Participants viewed the stimuli on a LCD monitor using prism mirrors that allow horizontal viewing in the supine position. The experiment was run on a Dell Latitude E6400 computer running Matlab software with Psychophysics Toolbox extensions (Brainard, 1997), and behavioral responses were made using a modified keyboard with all keys except "z" and "m" removed. The test phase was performed immediately after the training phase session that included reward feedback. The test phase took approximately 20 min to complete, leaving at least 55 min of rest between PET scans (see *Acquisition of Neuroimaging Data* section for additional details on the timing of the PET scans).

Training phase

During the training phase (see Fig. 1A), each trial consisted of a fixation display, a search array, and, for the rewarded scan, a feedback display. The fixation display was presented for 400, 500, or 600 ms (randomly determined on each trial), the search array for 1000 ms, and the reward feedback display for 1500 ms. A 1000 ms blank screen was inserted between the search and feedback displays and between trials. Participants were instructed to search for a color-defined target circle and report the orientation of a bar within the target as either vertical or horizontal via a button press ("z" and "m", respectively). Each circle in the search array was approximately 2.3° × 2.3°visual angle in size, placed at equal intervals along an imaginary circle with a radius of 5°.

The training phase consisted of two 720-trial scans. During one scan, participants searched for red and green targets, and during the other scan, participants searched for blue and yellow targets. The target colors for one scan did not appear as non-targets in the other scan (i.e., the same set of non-targets was used in each scan). Half of the trials in each scan contained one color target and half contained the other color target (only one target was presented on each trial); each target color appeared in each of the six possible stimulus positions equally-often. The order of trials was randomized. Participants were provided