Neurobiology of Learning and Memory 111 (2014) 65–70

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

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

Rapid Communication

Locus coeruleus neuromodulation of memories encoded during negative or unexpected action outcomes

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ARTICLE INFO

Article history:
Received 16 October 2013
Revised 11 March 2014
Accepted 15 March 2014
Available online 22 March 2014

Keywords:
Locus coeruleus
Outcomes
Functional connectivity
Memory

ABSTRACT

When people experience surprising or sub-optimal performance outcomes, an increase in autonomic arousal helps allocate cognitive resources to adjust behavior accordingly. The locus-coeruleus–norepinephrine (LC–NE) system regulates a central orienting response to behaviorally relevant events, and might therefore signal the need to attend to and learn from performance feedback. Memories of such events also rely on elevated NE, suggesting that LC activity not only responds to salient performance outcomes but also strengthens memory for stimuli associated with their occurrence. In the present study, we used a monetary incentive delay paradigm to determine whether LC functional connectivity during reaction time feedback relates to trial-by-trial memory of preceding photo-objects. We used one psychophysiological interaction (PPI) analysis to examine patterns of LC functional connectivity that were associated with subsequent memory for picture trials in which negative or positive feedback was given, and a second PPI analysis to investigate whether successfully encoded objects from trials with uncertain outcomes were related to distinct patterns of LC functional connectivity across the brain. The PPI results revealed that successfully encoded negative feedback trials (i.e., responses exceeding the response deadline) were uniquely associated with enhanced functional coupling between the LC and left anterior insula. Furthermore, successful memory for objects in low reaction time certainty trials (i.e., responses closest to the response deadline) were linked to positive LC functional coupling with left dorsolateral prefrontal cortex. These findings suggest that noradrenergic influences help facilitate memory encoding during outcome processing via dynamic interactions with regions that process negative or unexpected feedback.

1. Introduction

Adaptive behavior relies on the ability to encode and remember information associated with sub-optimal or unexpected performance outcomes. Autonomic arousal contributes to this process by signaling erroneous action outcomes (Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010; Wessel, Danielmeier, & Ullsperger, 2011) and facilitating learning when task demands fluctuate unpredictably (Raizada and Poldrack, 2007; Yu & Dayan, 2005). Such behaviorally relevant events activate the locus coeruleus (LC), a small brainstem nucleus that serves as the primary supplier of norepinephrine (NE) to the neocortex, (Berridge & Waterhouse, 2003), which in turn initiates a central orienting response that helps reallocate attentional resources to adjust and optimize task performance (Aston-Jones & Bloom, 1981; Aston-Jones & Cohen, 2005; Aston-Jones, Rajkowski, & Kubiak, 1997; Bouret & Sara, 2005; Clayton et al., 2004). This framework is supported by evidence showing that neurophysiological markers of LC activity, including increased pupil dilation (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005; Rajkowski, Kubiak, & Aston-Jones, 1993) and a greater P3 component of event-related potentials (Nieuwenhuis, Aston-Jones, & Cohen, 2005), accompany salient action outcomes, such as errors. In light of these convergent findings, it has been proposed that LC activity promotes both error perception (Ullsperger et al., 2010) and learning during unexpected uncertainty (Yu & Dayan, 2005).

The LC–NE system also augments memory encoding and consolidation of arousing stimuli, particularly during stress (McGaugh & Roozendaal, 2002). Exposure to acute stressors elevates the stress hormones NE and cortisol which each selectively strengthen memory for events associated with their release (Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2011). For instance, neuroimaging studies have demonstrated that LC activity increases during successful encoding of emotionally arousing images

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http://dx.doi.org/10.1016/j.nlm.2014.03.006
1074-7427/

(Sterpenich et al., 2006) and neutral images encoded under stress (Qin, Hermans, van Marle, & Fernández, 2012). Given the importance of LC neuromodulation in both behavioral adjustments and memory, it is possible that the LC interacts with higher brain regions to promote memory of information associated with salient performance feedback. To our knowledge, no previous study has tested this hypothesis in humans.

The goal of the present study was to determine whether feedback-related functional interactions between the LC and rest of the brain predicted subsequent memory for photo-objects associated with specific performance outcomes. To this end, we used functional magnetic resonance imaging (fMRI) to examine LC functional connectivity during the feedback period of a monetary incentive delay (MID) task (e.g., Knutson, Westdorp, Kaiser, & Hommer, 2000; Mather & Schoeke, 2011). Approximately 25 min prior to task-related scanning, a cold pressor stressor (CPS) was used to induce stress, as measured by an increase in the stress hormone cortisol that peaks approximately 15–30 min after stressor onset (Dickerson & Kemeny, 2004). Given evidence that the LC responds to both reward and punishment (Bouret & Sara, 2004; Sara & Segal, 1991), we modeled brain activity during positive and negative feedback periods. Previous research suggests that positive outcomes relate to dopamine release (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006), whereas memory for aversive events has been consistently linked to activity in central nodes within the LC–NE system, including the amygdala (Murty, LaBar, & Adcock, 2012; Sterpenich et al., 2006), insula (Rasch et al., 2009), and LC itself (Knutson et al., 2000). Thus, we hypothesized that enhanced functional connectivity between the LC and aversive-related memory processing regions would predict subsequent memory for pictures encoded in negative but not positive feedback trials. Motivated by evidence that the LC also promotes learning during unexpected uncertainty (Yu & Dayan, 2005), we also examined whether patterns of LC activity following low certainty responses (i.e., reaction times that occurred closest to a dynamic response deadline) were associated with memory of pictures in those trials.

2. Methods

2.1 Sample

Twenty-one male participants (age: $M = 23.63$, $SD = 3.95$; range = 18–31) underwent scan sessions on two separate days, and were randomly assigned to the stress or control condition on their first day. Scanning was conducted between 2 and 5 p.m. when cortisol levels are relatively stable. Participants also refrained from eating, caffeine intake, and exercise for at least 1 h and sleeping for at least 2 h prior to arrival. All participants provided written informed consent approved by the University of Southern California (USC) Institutional Review Board. A total of 16 participants' behavioral and fMRI data were analyzed: three participants were excluded due to excessive head motion or technical difficulties with the scanner, and two participants were excluded due to insufficient trials for the fMRI interaction analyses.

2.2 Intake procedure

Upon arrival, participants gave informed consent and drank 8 oz. of water. They then completed the Positive and Negative Affect Scale (PANAS; Watson et al., 1988), subjective ratings of stress, and the 20-item Center for Epidemiological Studies Depression (CES-D; Radloff, 1977), to assess mood, stress level, and depression, respectively. Three repeated-measures ANOVAs determined that these measures did not significantly differ between the stress and control sessions ($ps > .05$). After completing the questionnaires, participants provided a 1 mL baseline saliva sample. This was followed by a brief demonstration of the MID task, then a 10-trial practice version on a computer. Response deadlines for the fMRI task were calibrated to produce a 66% hit rate based on participants' reaction times during the practice.

2.3 Hand immersion task

Participants were told that the ice water could be administered on one or both days of the experiment and did not learn condition assignment before administration. During the CPS, all participants immersed their left hand in ice water (0–3 °C) for at least 1 min and up to 3 min, whereas during the control condition, participants immersed their left hand in warm water (37–40 °C) for up to 3 min. After the hand-immersion task, participants entered the scanner and an unrelated resting-state scan was conducted. Following this scan, participants were instructed to remain still while a second saliva sample was collected using a Sorbette (Salimetrics, LLC, State College, PA, USA).

2.4 Monetary incentive delay paradigm

The MID task (Mather & Schoeke, 2011; Fig. 1) was administered during an fMRI scanning sequence that began approximately 25 min after the onset of hand-immersion. fMRI volumes were collected over a series of 6 blocks. Each block contained 18 trials lasting between 9.5 and 17.5 s. At the beginning of each trial, a monetary cue (win, lose, or none) was displayed for 1000 ms to increase incentive for impending reaction time performance when a picture appeared. These cues indicated whether participants could win or lose $0.25 (or neither) based on whether or not their reaction time was faster than the response deadline. Next, a jittered fixation cross was presented for 2000, 4000, or 6000 ms, followed by a photo-object presented for 1500 ms. Participants were instructed press a button in their right hand as soon as the picture appeared. The picture was followed by another jittered fixation cross with a duration of 1500, 3500, or 5500 ms, followed by positive or negative performance feedback displayed for 2000 ms. The feedback screen indicated the performance outcome and the

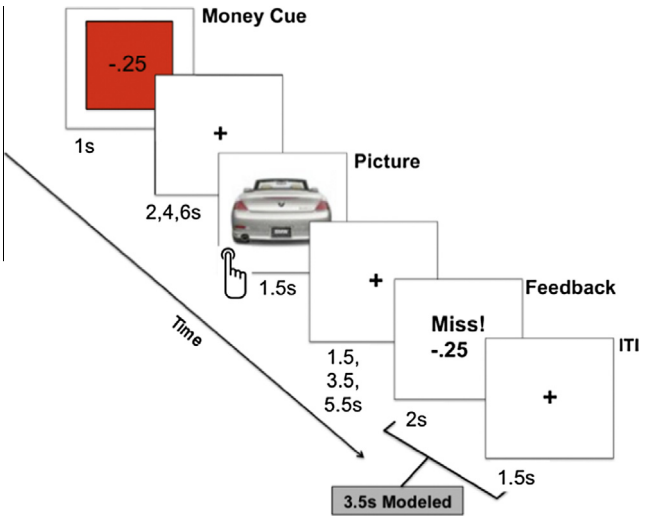

Fig. 1. A sample trial from monetary incentive delay (MID) fMRI task. Positive or negative feedback was given based on whether or not the speed of the button press during picture presentation exceeded a predetermined dynamic response deadline. For the fMRI analysis, whole-brain locus coeruleus (LC) functional connectivity was modeled during the period spanning the feedback and inter-trial-interval slides (for a total of 3.5 s).