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# Cognitive emotion regulation modulates the balance of competing influences on ventral striatal aversive prediction error signals

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ABSTRACT

Cognitive emotion regulation (CER) is a critical human ability to face aversive emotional stimuli in a flexible way, via recruitment of specific prefrontal brain circuits. Animal research reveals a central role of ventral striatum in emotional behavior, for both aversive conditioning, with striatum signaling aversive prediction errors (aPE), and for integrating competing influences of distinct striatal inputs from regions such as the prefrontal cortex (PFC), amygdala, hippocampus and ventral tegmental area (VTA). Translating these ventral striatal findings from animal research to human CER, we hypothesized that successful CER would affect the balance of competing influences of striatal afferents on striatal aPE signals, in a way favoring PFC as opposed to 'subcortical' (i.e., non-isocortical) striatal inputs. Using aversive Pavlovian conditioning with and without CER during fMRI, we found that during CER, superior regulators indeed reduced the modulatory impact of 'subcortical' striatal afferents (hippocampus, amygdala and VTA) on ventral striatal aPE signals, while keeping the PFC impact intact. In contrast, inferior regulators showed an opposite pattern. Our results demonstrate that ventral striatal aPE signals and associated competing modulatory inputs are critical mechanisms underlying successful cognitive regulation of aversive emotions in humans.

## 1. Introduction

Ventral striatum is widely known for its role in associative learning, particularly in Pavlovian conditioning (Grace et al., 2007; Liljeholm and O'Doherty, 2012; O'Doherty et al., 2004; Pennartz et al., 2011). It has been repeatedly implicated in aversive Pavlovian conditioning in a variety of human studies (Delgado et al., 2011; Jensen et al., 2003; Klucken et al., 2012; Robinson et al., 2010). Based on computational models of associative learning theory, Pavlovian conditioning is driven by prediction errors (PEs) (Liljeholm and O'Doherty, 2012; Pearce and Bouton, 2001; Rescorla and Wagner, 1972; Schultz and Dickinson, 2000), and a number of studies have demonstrated the encoding of aversive prediction errors (aPEs; PEs related to aversive situations) by the ventral striatum during aversive Pavlovian conditioning (Garrison et al., 2013; Menon et al., 2007; Robinson et al., 2013; Seymour et al., 2007, 2004).

Emotions play an essential role in modulating or controlling motivated behavior (Cardinal et al., 2002; Lang and Bradley, 2010). Animal models of motivated behavior highlight the critical role of ventral striatal activity and its control by diverse competing afferent inputs (Floresco, 2015; Grace et al., 2007; Pennartz et al., 2011; 2009; Sesack and Grace, 2010). Specifically, ventral striatum is seen as an integration area, controlled by a number of afferent regions, including medial and lateral regions of the prefrontal cortex (PFC), ventral

*Abbreviations:* CER, cognitive emotion regulation; aPE, aversive prediction error; PFC, prefrontal cortex; VTA, ventral tegmental area

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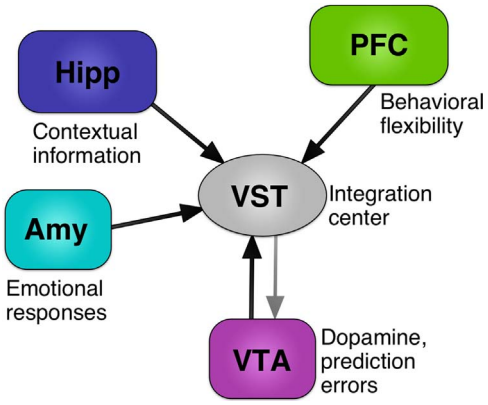


**Fig. 1.** The model of motivated behavior, adapted from (Grace et al., 2007). In the model, ventral striatum (VST) is an 'integration center', influenced by a number of afferent regions: PFC input into ventral striatum is thought to enable behavioral flexibility, hippocampal (Hipp) input to provide contextual and spatial information, amygdala (Amy) to support emotional behavior, particularly cue conditioning, and dopaminergic input from VTA to modulate connections between other afferents and the ventral striatum, possibly via PE signals.

hippocampus, basolateral amygdala, and ventral tegmental area (VTA) (Fig. 1). Roughly, PFC input into ventral striatum is thought to enable behavioral flexibility, hippocampal input to provide contextual and spatial information, amygdala to support emotional behavior, particularly cue conditioning, and dopaminergic input from VTA is suggested to modulate influences of the other afferents on ventral striatum, possibly via PE signals (Floresco, 2015; Grace et al., 2007; Pennartz et al., 2011). While VTA is also an output region of the ventral striatum, PFC, hippocampus and amygdala are its unidirectional afferents, providing input through direct anatomical connections (Floresco, 2015; Grace et al., 2007; Haber and Knutson, 2010; Sesack and Grace, 2010).

In the case of human emotional behavior, characterized by both emotion adaption and emotion regulation, a similar macroscopic brain network might be relevant. While emotion adaption is best characterized by ventral striatum-centered PEs in the context of emotional learning, such as Pavlovian conditioning (Floresco, 2015; Grace et al., 2007; Liljeholm and O'Doherty, 2012; Pennartz et al., 2011), cognitive emotion regulation (CER) represents a unique human ability of using cognitive resources in order to face aversive emotional stimuli in a flexible way (Buhle et al., 2014; Gross, 2002; Kalisch, 2009). Studying aPEs in the context of CER thus offers a unique opportunity to better characterize the network of motivated behavior outlined by animal studies. Specifically, we suggest that during CER, the balance among ventral striatal inputs may shift in favor of PFC input, to realize the CER-related behavioral flexibility in response to emotional stimulation. Indeed, previous functional magnetic resonance imaging (fMRI) studies in humans have characterized PFC as a principal region exerting control over ventral striatum during CER, with the effect being related to individual differences in CER ability (Kober et al., 2010; Wager et al., 2008). Furthermore, based on previous studies, aPE-related activity in the ventral striatum was enhanced during specific emotional states such as CER (Mulej Bratec et al., 2015) or stress (Robinson et al., 2013). CER also affects interactions among brain regions. During CER, synchronicity of activity between prefrontal regions (involved in regulation) and 'subcortical' (i.e., non-isocortical) regions such as amygdala (typically suppressed during CER) is increased, with the effect related to participants' reported negative feelings (Banks et al., 2007; Erk et al., 2010; Kohn et al., 2013). Critically, strong PFC activation, akin to that typically seen during CER implementation, was shown to reduce hippocampal and thalamic inputs into the ventral striatum in adult male rats, thus biasing the ventral striatal inputs in favor of cortical and against 'subcortical' inputs (Calhoon and O'Donnell, 2013).

Based on this background, the current study focused on the question of whether CER might affect the balance among competing ventral striatal afferents, and to what extent individual differences in CER ability might play a role in this effect. We therefore measured, in superior (i.e., efficient) and inferior (i.e., inefficient) regulators, the influence of remote brain regions on ventral striatal aPE activity, by way of combining model-based fMRI and psychophysiological interaction analysis (PPI) during aversive Pavlovian conditioning with and without CER. Pavlovian conditioning was chosen as it represents the simplest form of emotional learning and provides the most direct link to animal studies of motivated behavior. The specific strategy of CER was selected due to its pervasiveness in the literature and its effectiveness in relation to other emotion regulation strategies (Buhle et al., 2014). Relying on human studies of CER (Banks et al., 2007; Kober et al., 2010; Mulej Bratec et al., 2015; Wager et al., 2008) and the critical animal study by Calhoon and O'Donnell (Calhoon and O'Donnell, 2013), we hypothesized that a successful CER implementation by superior regulators would shift the balance of ventral striatal inputs in favor of PFC as opposed to 'subcortical' ventral striatal afferents. In contrast, assuming that inferior regulators are unable to successfully recruit the PFC in order to down-modulate the influence of 'subcortical' ventral striatal afferents on ventral striatal aPE activity, we expected to observe an opposite pattern for inferior regulators.

## 2. Materials and methods

To test our hypothesis, we re-analyzed data from a related 'companion' study (Mulej Bratec et al., 2015). While the previous study contrasted differential effects of CER on aversive responses and aPEs, the current study focused on differential modulatory influences on aPE in the ventral striatum during successful CER. The two studies are linked by the idea that CER is associated with crucial effects on aPE activity, a notion currently neglected in CER research. Even though certain methodological particulars can be read elsewhere (Mulej Bratec et al., 2015), we provide a description of all methods to enable uninterrupted reading.

### 2.1. Participants

Twenty-four healthy subjects (all female, mean age=24.8 years, SD=2.3 years) participated in the experiment, all native German speakers, right-handed, with normal or corrected-to-normal vision, and no history of neurological or psychiatric disorders, or intake of psychotropic medication. Two were excluded from further analysis due to excessive head movement (translation > 2 mm, rotation > 2°), and another two due to inadequate performance in the learning task (prediction-outcome correspondence < 10%). Owing to previous reports of gender differences regarding emotion processing and regulation, only female subjects were tested (McRae et al., 2008; Nolen-Hoeksema, 2012; Whittle et al., 2011). The study was approved by a local ethics committee (Technische Universitaet Muenchen) and written informed consent was obtained from all participants.

### 2.2. Experimental design and tasks

There were two experimental runs, CER (i.e., self-distancing) and NoCER (i.e., attentively observing), both of which were completed by every participant. During a conditioning paradigm with varying conditioned-unconditioned stimulus (CS-US) contingencies (Gläscher and Büchel, 2005; Mulej Bratec et al., 2015), a trial started with a fixation cross (1 s), after which the Regulation Instruction ('Distance' for CER and 'Attend' for NoCER) was presented (2 s). Then, a CS (blue square or yellow pentagon) was shown (6 s). Participants indicated whether a negative picture or no picture would follow the CS via a button press in the first 3 s of CS presentation. The US (6 s) was a negative picture from the International Affective Picture System (Lang et al., 1997),