

## Accepted Manuscript

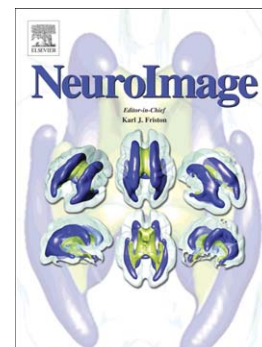
Novelty increases the mesolimbic functional connectivity of the substantia nigra / ventral tegmental area (SN/VTA) during reward anticipation: Evidence from high-resolution fMRI

R.M. Krebs, D. Heipertz, H. Schuetze, E. Duzel

PII: S1053-8119(11)00683-5  
DOI: doi: [10.1016/j.neuroimage.2011.06.038](https://doi.org/10.1016/j.neuroimage.2011.06.038)  
Reference: YNIMG 8420

To appear in: *NeuroImage*

Received date: 7 January 2011  
Revised date: 26 April 2011  
Accepted date: 16 June 2011



Please cite this article as: Krebs, R.M., Heipertz, D., Schuetze, H., Duzel, E., Novelty increases the mesolimbic functional connectivity of the substantia nigra / ventral tegmental area (SN/VTA) during reward anticipation: Evidence from high-resolution fMRI, *NeuroImage* (2011), doi: [10.1016/j.neuroimage.2011.06.038](https://doi.org/10.1016/j.neuroimage.2011.06.038)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Novelty increases the mesolimbic functional connectivity of the  
substantia nigra / ventral tegmental area (SN/VTA) during reward anticipation:  
evidence from high-resolution fMRI**

Authors: Krebs RM<sup>(1,2)</sup>, Heipertz D<sup>(3)</sup>, Schuetze H<sup>(3)</sup>, Duzel E<sup>(3,4,5)</sup>

Affiliations:

<sup>(1)</sup>Department of Experimental Psychology, Ghent University, 9000 Ghent, Belgium

<sup>(2)</sup>Center for Cognitive Neuroscience, Duke University, Durham, NC 27705, US

<sup>(3)</sup>Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke University,  
D-39120 Magdeburg, Germany

<sup>(4)</sup>Institute of Cognitive Neuroscience, University College London, London WC1N 3AR, UK

<sup>(5)</sup>German Centre for Neurodegenerative Disorders (DZNE), Leipziger str 44, D-39120  
Magdeburg, Germany

Corresponding Author: Ruth M. Krebs, Ph.D.

Department for Experimental Psychology, Ghent University

Henri Dunantlaan 2

9000 Ghent, Belgium

Phone: 0032-9-3300297

email: ruthmkrebs@gmail.com

Keywords: novelty; reward; fMRI; midbrain; functional connectivity

**Abstract**

Reward and novelty are potent learning signals that critically rely on dopaminergic midbrain responses. Recent findings suggest that although reward and novelty are likely to interact, different populations of dopamine neurons may be responsive to both. We used high-resolution functional magnetic resonance imaging (fMRI) to isolate neural responses to reward and novelty within the human substantia nigra / ventral tegmental area (SN/VTA) complex to investigate the spatial delineation and integration of reward- and novelty-related activity clusters. We demonstrate that a distinct cluster within the caudal portion of the medial SN/VTA and the lateral portion of the right SN are predominantly modulated by the anticipation of reward, while a more rostral part of the medial SN/VTA was exclusively modulated by novelty. In addition, the caudal medial SN/VTA cluster embodied an interaction between novelty and reward where novelty selectively increased reward-anticipation responses. This interaction, in turn, was paralleled by differences in the functional-connectivity patterns of these SN/VTA regions. Specifically, novel as compared to familiar reward-predictive stimuli increased the functional connectivity of the medial SN/VTA with mesolimbic regions, including the nucleus accumbens and the hippocampus, as well as with the primary visual cortex. This functional correlation may highlight how afferents of the medial SN/VTA provide integrative information about novelty and reward, or, alternatively, how medial SN/VTA activity may modulate memory processes for novel events associated with rewards.

## Introduction

Reward is an effective motivator of behavior and learning (for a review see, Pessoa and Engelmann, 2010; Schultz, 2002; Wise, 2004). Mesolimbic responses to reward, including those arising from the dopaminergic midbrain (comprising the substantia nigra pars compacta and ventral tegmental area, SN/VTA) and the ventral striatum are considered to be crucial for the acquisition of stimulus-reward associations (Schultz, 2004; Zellner and Ranaldi, 2009). Once these stimulus-reward associations are established, mesolimbic responses to reward-predicting stimuli are thought to reflect the magnitude and probability of the anticipated reward (Knutson and Cooper, 2005; O'Doherty, 2004; Schott et al., 2008; Schultz, 1997; Wittmann et al., 2005).

Another important learning signal is stimulus novelty (Mesulam, 1998; Nyberg, 2005; Ranganath and Rainer, 2003; Tulving et al., 1996). More recently, it has been proposed, that novelty signals originating in the hippocampus can modulate the activity of dopamine neurons in the SN/VTA and that an ensuing increase in dopamine release in the hippocampus can promote the long-term persistence of hippocampal memory representations for the novel event (Lisman and Grace, 2005). This notion is supported by observations that dopamine neurons increase their firing rate in response to stimulus novelty (Horvitz et al., 1997; Ljungberg et al., 1992) and by demonstrations that hippocampal memory persistence is critically dependent on hippocampal dopamine (Bethus et al., 2010). In humans, such a mechanism is reflected in increased hemodynamic responses to novel stimuli within the SN/VTA (Bunzeck and Duzel, 2006; Wittmann et al., 2008).

Given the overlapping processing pathways for novelty and reward in the SN/VTA, we recently investigated the potential interaction between reward and novelty using functional

magnetic resonance imaging (fMRI). We found that novelty can increase mesolimbic reward-anticipation responses under circumstances where the novelty-status of stimuli is irrelevant for obtaining reward (Krebs et al., 2009b). These data are compatible with the suggestion from computational modelling that novelty acts as an “exploration bonus” for rewards in that it motivates an organism to explore novel stimuli and situations for future sources of reward (Kakade and Dayan, 2002).

While there is some evidence that the neural responses associated with the processing of reward and novelty in humans are subserved by distinct neuronal clusters within the dopaminergic midbrain (Krebs et al., 2009a), previous fMRI protocols did not allow to directly investigate to what extent activity clusters within the SN/VTA were overlapping or separable. In the present study, we employed high-resolution fMRI to isolate responses to reward and novelty within the SN/VTA. We demonstrate that a distinct cluster within the caudal portions of the medial SN/VTA (henceforth termed caudal VTA) and the more lateral aspects of the SN are predominantly responsive to reward, while a more rostral portion of the medial SN/VTA is exclusively modulated by novelty (henceforth termed rostral VTA). In addition, the caudal VTA cluster embodies an interaction between novelty and reward, indicating a novelty-driven pronunciation of the reward-anticipation signal. Finally, measures of functional connectivity show that the novelty-related activity increase in the caudal VTA covaries with activity patterns in the ventral striatum, the hippocampus, and primary visual cortex.

## Materials and Methods

**Participants.** Twelve healthy right-handed subjects participated in the study (mean age  $\pm$  standard deviation SD:  $24.7 \pm 2.1$ , 7 female). One additional subject had to be excluded

due to poor task compliance. All participants were recruited from the student population of the Otto-von-Guericke University in Magdeburg. The experimental protocols were approved by the ethics committee of the University of Magdeburg, Faculty of Medicine, and all participants gave written informed consent in accordance with the Declaration of Helsinki.

**Stimuli and Paradigm.** We employed an event-related two-by-two factorial design systematically manipulating both the reward-predictive value (*reward* vs. *no-reward*) and the novelty (*novel* vs. *familiar*) of cue stimuli. This resulted in four trials types, novel stimuli predicting a reward (*novel\_reward*), novel stimuli predicting the absence of reward (*novel\_no-reward*), familiar stimuli predicting a reward (*familiar\_reward*), and familiar stimuli predicting the absence of reward (*familiar\_no-reward*). All stimuli were presented on a grey background and a small black fixation cross was visible throughout the task in the center of the screen (Fig. 1). The cue stimuli were photographs of natural indoor and outdoor scenes that were matched for spatial frequency and luminance.

Prior to the main experiment, participants were familiarized with half of the cue stimuli outside the scanner. For familiarization, the images were presented five times each for 2000 ms in random order intermixed with non-repeat images. Throughout the presentation, participants were asked to indicate whether they have seen the current image before or not in order to estimate the effectiveness of the familiarization.

In the actual fMRI experiment, each trial started with the presentation of the cue stimulus for 2000 ms. The category of the cue (indoor versus outdoor scenes) informed participants whether they will have the chance to obtain a monetary reward in the current trial or not (counterbalanced across subjects). In addition, the cue stimulus could be part of the familiarized image set or a completely novel image. Importantly, the novelty dimension was orthogonal to the reward dimension and was irrelevant to the task. The association

between reward and the indoor/outdoor category of images was explicit and participants were asked to indicate in each trial whether the current cue was predictive of reward or not by pressing one of two buttons with the index and middle finger of the right hand (counterbalanced across subjects). The cue phase was followed by a simple forced choice task with a stimulus onset asynchrony (SOA) of 3300 ms, in which participants indicated via button press whether a single black digit (ranging from 1 to 9) was smaller or greater than 5. This target digit was presented for 100 ms and participants were asked to press one button for digits below 5 and the other button for digits above 5 (counterbalanced across subjects).

Participants were informed that a fast and accurate response to the target digit following reward-predictive cues would result in a gain of 40 ct, while an incorrect and/or slow response would result in a loss of 20 ct. In order to achieve a reward probability of approximately 75% in reward-predictive trials, the response time (RT) window for the forced choice task in reward trials was dynamically adjusted trial-by-trial based on the individual mean RT obtained during the practice session prior to scanning. Depending on the accurate and within-time response to the target digit, participants were presented with a positive (upward green arrow, indicating +40 ct) or negative (downward red arrow, indicating -20 ct) visual feedback, respectively. In no-reward trials, the arrows were replaced by a question mark, independent of the participants' performance. Note that the dynamic adjustment of the response time-out only affected the visual feedback during the experiment, whereas the behavioral analyses (RT and error rates) were performed based on the actual responses within a window of 150 to 1200 ms after target onset. The delay between cue and feedback was pseudo-randomly jittered in 2000 ms steps (SOA 4500 to 8500 ms) in order to separate activations related to reward anticipation from activation

related to the actual reward outcome. Similarly, the onset of the next trial was pseudo-randomly jittered relative to the feedback (SOA 4500 to 8500 ms). Within each run, trial types were pseudo-randomly presented to have at least three but maximal six trials of the same condition in a row to avoid adaptation effects. In addition, four fixation periods, varying between 24 and 54 s were included at randomly selected time points in each run to allow for a proper baseline estimation of the fMRI signal (Josephs and Henson, 1999). The beginning and end of each fixation period was indicated by a “pause” and “play” button presented on the screen, respectively.

-- insert Figure 1 about here --

**fMRI data acquisition.** Prior to the actual fMRI scan, participants performed a short practice session, which also served to obtain the participants' individual mean RTs in the forced-choice task (digit discrimination). Inside the scanner subjects performed two experimental runs, each of 15-minute duration, resulting in a total of 40 trials in each of the four conditions (*novel\_reward*, *novel\_no-reward*, *familiar\_reward*, and *familiar\_no-reward*). fMRI images were acquired using a 3T Siemens Magnetom Trio MRI system (Siemens, Erlangen, Germany) with a standard head-coil system. Each functional run consisted of 460 volumes with 22 T2\*-weighted echo planar slices (EPIs; TR = 2000 ms, TE = 30 ms, FoV = 224 mm, 160\*160 matrix, yielding a voxel size of 1.5\*1.5\*2 mm) acquired as a partial-head volume in an axial slice orientation using an interleaved scanning order.

For each participant, a structural whole-head T1-weighted image (256\*256 matrix; voxel size 1\*1\*1 mm) was acquired to enable coregistration and normalization, as well as a partial-head proton density-weighted (PD) image (320\*320 matrix, voxel size 0.75\*0.75\*2 mm) covering the same acquisition volume as the functional images for localization of the midbrain areas. Throughout the scanning session, the cardiac rate was continuously

acquired using a finger-sensor pulse oxymeter which was placed on the middle finger of the left hand. In order to assess vigilance during the experiment, participants were monitored using an MR-compatible infrared eye-movement recording system (Kanowski et al., 2007).

**Data analysis.** Images were preprocessed and analyzed using Statistical Parametric Mapping (SPM5; University College, London). Anatomical images were co-registered to the SPM template and spatially normalized. Functional EPIs were corrected for acquisition delay and co-registered to the original T1-weighted image. Functional images were normalized and resliced yielding a final voxel size of 1\*1\*1 mm, and smoothed with an isotropic 3-mm full-width half-maximum Gaussian kernel. Before model estimation, a high-pass temporal filter of 128 seconds was applied (Ashburner and Friston, 1999).

A standard two-stage mixed-effects model (Friston et al., 1995) was used for statistical analysis. In the first stage, blood-oxygen level-dependent (BOLD) responses were modeled by delta functions at stimulus onset, which were then convolved with a standard hemodynamic response function (HRF) to form covariates of a general linear model (GLM, Friston et al., 1995). The GLM thus included one regressor for each event type and the corresponding temporal and dispersion derivatives, i.e., four cue types (*novel\_reward*, *familiar\_reward*, *novel\_no-reward*, *familiar\_no-reward*), six feedback types (*novel\_win*, *familiar\_win*, *novel\_loss*, *familiar\_loss*, *novel\_neutral*, *familiar\_neutral*), and one regressor representing all target digits. In addition, six movement parameters derived from the realignment procedure, as well as the cardiac rate were included as additional regressors. Of note, an additional model that did not include the cardiac-rate regressor yielded identical results with respect to the BOLD response within the midbrain region, indicating that the main effects of interest were not significantly affected by residual variance related to cardiac artifacts.

The second level of the analysis consisted of voxel-wise comparisons across subjects (one-sample *t*-tests) that were computed from the single subjects' contrast images based on the HRF amplitude parameter, treating each subject as a random effect (significance threshold  $p < .001$ , cluster size  $k = 10$  adjacent voxels, cluster-level corrected at  $p < .05$ ). Coordinates of significant local maxima are reported in a standard stereotaxic reference space (MNI, Montreal Neurological Institute) and functional overlays are displayed on the average of the subjects' anatomical scans. In order to be able to delineate spatially confined activity clusters within the midbrain, we partitioned the SN/VTA complex into a rostral and a caudal sub-region based on the averaged PD-weighted image. Both the rostral and the caudal part comprised 6 mm, corresponding to a z-coordinate range between -5 to -11 and -12 to -18, respectively (MNI space). We used the *familiar\_no-reward* cues as a baseline condition as it does not elicit a reward anticipation or novelty response. Hence, to isolate effects that are unique to reward, *familiar\_reward* cues were contrasted to *familiar\_no-reward* cues. To isolate effects that are unique to novelty, *novel\_no-reward* cues were contrasted to *familiar\_no-reward* cues. The resulting activity clusters were used to define regions of interest (ROIs) in which we assessed whether these regions were additionally modulated by the other factor (novelty or reward, respectively).

In order to verify a potential interaction between the reward and novelty dimensions of the cue in a voxel-wise fashion, a two-by-two rANOVA was performed as implemented in SPM5 with factors REWARD (reward vs. no-reward), NOVELTY (novel vs. familiar), and SUBJECT. The main purpose of the ANOVA was to investigate potential voxel-wise interactions rather than the overall main effects of reward and novelty, since these were illustrated using the contrasts above.

Based on the voxel-wise comparisons as well as the rANOVA interaction contrast, we

extracted the mean signal change (%) from ROIs using the Marsbar toolbox (Brett et al., 2002). Spherical ROIs were centered at the local maxima of activated clusters with a radius of 2mm (SN/VTA) and 4mm (remaining regions), respectively. Selected *t*-tests (two-tailed) were conducted to compare conditions of interest.

We then investigated the functional connectivity of the novelty-related increase of the reward-anticipation signal within the caudal VTA (see ROI analysis Fig. 2A). To that end, we conducted a psycho-physiological interaction analysis (PPI) as implemented in SPM5. Specifically, the individual SN/VTA seed activity for the physiological signal was extracted using the contrast *novel\_reward* versus *familiar\_reward*. This contrast reflects the additional enhancement of the reward-anticipation response by novelty. The PPI term was created for each participant by multiplying the deconvolved and mean-corrected BOLD signal with the psychological vector. After convolution with the HRF, mean correction, and orthogonalization, the three regressors (PPI term, physiological vector, and psychological vector) went into the statistical analysis to determine condition-dependent changes of functional connectivity over and above any main effect of task or any main effect of activity in the corresponding brain areas. In the PPI contrasts, the PPI term was computed against implicit baseline. Random-effects analyses were performed on single-subject PPI contrast images ( $p < 0.001$ , uncorrected). An analogous PPI analysis was performed based on the seed contrast *novel\_reward* versus *novel\_no-reward* to investigate potential covariations with respect to the influence of reward during the processing of novel stimuli.

## Results

Participants successfully categorized the cue pictures into reward-predictive and no-

reward-predictive cues, with less than 4 % errors and no significant differences between conditions ( $p$ -values  $>.3$ ). Responses were significantly slower for categorizing reward-predictive as compared to no-reward-predictive images (main effect reward:  $F_{(1,11)}=35.3$ ,  $p<.001$ ). No significant differences were observed between novel and familiar images and there was no interaction between both factors ( $p$ -values  $>.1$ ; see Supplementary Material for a further illustration and discussion in relation to data reported in Krebs et al., 2009b). In the subsequent digit-discrimination task, responses were faster following reward-predictive as compared to no-reward-predictive cues (main effect reward:  $F_{(1,11)}=27.6$ ,  $p<.001$ ), while there was no effect of novelty and no interaction between both factors ( $p$ -values  $>.1$ ). Error rates ranged between 4 and 7 % and did not differ between conditions ( $p$ -values  $>.1$ ). See Table 1 for a full representation of task-performance measures.

-- insert Table 1 about here --

The fMRI data showed that reward-predictive cues elicited stronger BOLD responses than no-reward-predictive cues within the caudal VTA and the right SN (Fig. 2A, left panel), bilateral nucleus accumbens (NAcc), right hippocampus, as well as bilateral anterior insula extending into the inferior frontal gyrus (IFG; Fig. 3). Moreover, additional small activity clusters were observed in the tectal midbrain including in the superior colliculi and more caudally at the level of the pons. Note that the effect of reward was defined by comparing *familiar\_reward* to *familiar\_no-reward* cues. The latter condition therefore served as a baseline condition entailing neither reward nor novelty. Analogously, we compared *novel\_no-reward* cues to the same baseline condition to assess the effect of novelty. This contrast revealed increased activity within the rostral VTA (Fig. 2A, right panel), bilateral hippocampus, bilateral middle occipital cortex, as well as widespread bilateral clusters in

the parahippocampal gyrus (PHG) and the fusiform gyrus (FG; Fig. 3). For a full representation of activity clusters revealed by both contrasts see Table 2.

-- insert Figure 2 and Table 2 about here --

Based on the above contrasts, we extracted the mean BOLD signal change from selected ROIs in order to investigate potential modulations by the respective opposite factor (novelty or reward). In particular, we were interested in how far novelty would modulate reward-sensitive regions, and in how far reward would modulate novelty-sensitive regions. Note that the signal-change values (Fig. 2A) representing the originally contrasted conditions (reward contrast: *familiar\_reward* vs. *familiar\_no-reward*; novelty contrast: *novel\_no-reward* vs. *familiar\_no-reward*), are merely included for completeness rather than being inferential as they naturally reflect the voxel-wise results (Kriegeskorte et al., 2009). The only regions that were significantly modulated by the respective other factor were the caudal VTA (derived from the reward contrast), as well as bilateral hippocampus and FG (derived from the novelty contrast). In particular, activity within the caudal VTA was selectively increased for novel as compared to familiar cues when they were concomitantly predictive of reward (Fig. 2A, left panel). The hippocampus and the FG were concomitantly modulated by reward as reflected in a significant increase for reward-predictive as compared to no-reward-predictive novel cues (Fig. 2B, right panels). All other regions were primarily modulated by either reward or novelty ( $p$ -values  $>.2$ ), however, the right SN and the left NAcc showed a trend similar to the pattern observed within the caudal VTA ( $p$ -values  $<.1$ ). Importantly, the novelty effect in the more rostral part of the VTA was independent of the reward status of cues as indicated by the lack of a significant signal change difference between *novel\_reward* and *novel\_no-reward* cues (Fig. 2A, right panel).

-- insert Figure 3 about here --

The whole-brain ANOVA revealed cortical and subcortical activity clusters that were highly similar to the selective contrasts for both reward and novelty (Table 3). In addition to the main effects of both factors in the SN/VTA region, we observed a voxel-wise interaction within a caudal VTA cluster, consistent with the effects observed in the above ROI analysis based on the selective contrast (Fig. 2A, left panel). As revealed by the extracted signal-change values, the interaction was again driven by a selective activity increase for novel reward-predictive as compared to novel no-reward-predictive cues. In addition, a small cluster within the rostral VTA exhibited an interaction, reflecting the slight asymmetry observed in the selective contrast (Fig. 2A, right panel), which, however, did not reach significance in the ROI-based analysis (see Table 3 for a full representation of the associated main and interaction effects).

By using the BOLD signal extracted from the caudal part of the VTA that was modulated by both reward and novelty as seeds for a whole brain PPI analysis, we sought to explore similar condition-dependent activity patterns in other brain regions (Table 4, Fig. 4). The PPI that focused on novelty-related changes in the context of reward (Fig. 4A; seed contrast: *novel\_reward vs. familiar\_reward*) revealed covariations between the caudal VTA seed region and left NAcc, left hippocampus/PHG, bilateral primary visual cortex (V1), and a small rostral VTA cluster that was highly overlapping with the novelty-sensitive cluster observed in the novelty contrast (compare Fig. 2A, right panel). The second PPI focusing on reward-related changes during the processing of novel stimuli (Fig. 4B; seed contrast: *novel\_reward vs. novel\_no-reward*) primarily revealed covariations in widespread posterior visual-processing areas, including V1, middle and lateral occipital gyri, and posterior FG. A

small cluster was also observed in the right SN, which overlapped with the reward-related cluster (compare Fig. 2A, left panel). These connectivity patterns, which were largely overlapping with the activity clusters in the voxel-wise comparisons, highlight that the VTA's role for the novelty-related modulation of the reward-anticipation response is embedded within a widespread cortical and subcortical network.

-- insert Table 3 and Table 4 about here --

## Discussion

Both reward and novelty have been shown to be potent learning signals that critically rely on dopaminergic midbrain responses (see, Bunzeck and Duzel, 2006; Lisman and Grace, 2005; Wittmann et al., 2005; Zellner and Ranaldi, 2009). Moreover, both stimulus properties seem to interact if presented concurrently (Guitart-Masip et al., 2010a; Krebs et al., 2009b). In the present study we sought to investigate in how far these effects are subserved by overlapping or distinct neuronal clusters within the human SN/VTA using high-resolution fMRI.

In line with previous reports, we found that both reward anticipation and novelty elicited robust activity increases within the SN/VTA complex (Bunzeck and Duzel, 2006; D'Ardenne et al., 2008; Wittmann et al., 2005). While reward anticipation in the present study was associated with two distinct activity clusters in the caudal medial SN/VTA and the more lateral portion of the right SN, responses to novelty were primarily observed in a more rostral part of the medial SN/VTA, which was clearly distinguishable from the reward anticipation response. The two regions of the medial SN/VTA will be referred to as caudal and rostral VTA respectively. Novelty modulated reward-related responses within the caudal VTA, with selectively increased responses to novel as compared to familiar reward-

predicting cues.

While earlier comparative fMRI studies of reward and novelty processing did not differentiate between different sub-regions of the SN/VTA (e.g., Guitart-Masip et al., 2010a; e.g., Krebs et al., 2009b; Wittmann et al., 2008), the present high-resolution protocol allowed us to isolate distinct activity clusters associated with both stimulus properties. In line with our earlier observation of inter-individual differences in the responsiveness of the SN/VTA to reward and novelty (Krebs et al., 2009a), the present data suggests that different regions of the SN/VTA complex can be recruited for different types of behaviorally salient information, probably based on differential afferent and efferent connectivity for novelty and reward based information (Cohen et al., 2009; Goto et al., 2007; Marinelli et al., 2006).

The SN/VTA complex comprises different types of dopamine neurons that are part of three major projection systems, mesolimbic, mesocortical and nigrostriatal (for a review, Duzel et al., 2009; Haber and Knutson, 2010). In rodents, there is a clear anatomical distinction between the SN and VTA and this distinction comes together with a separation of mesolimbic projection pathways towards the VTA and nigrostriatal pathways towards the SN (Gasbarri et al., 1997). In primates, on the other hand, there has been an expansion of the size of the SN with the anatomical boundary between the SN and VTA becoming much less apparent. Instead of a dominant SN to VTA distinction of projection pathways, the functional anatomy in primates is dominated by two gradients; a medial to lateral gradient and a dorsal to ventral gradient. Hence, projection neurons to the ventral striatum and hippocampus are more likely to be in the dorsal and medial aspects of the SN/VTA complex, whereas projection pathways to the dorsal striatum are more likely to be in the lateral and ventral aspects of the SN/VTA (Duzel et al., 2009; Haber and Knutson, 2010).

The chemical characteristics of dopamine neurons show that in monkeys, the VTA and the dorsal SN pars compacta form a dorsal continuum of dopamine neurons which express lower levels of mRNA for DAT and D2 receptor than the ventral tier (Haber et al., 1995). It is interesting to note that ventral medial striatal projections to the SN/VTA in primates are concentrated medially in the rostral portions of the SN/VTA and dorsolaterally at central and caudal levels (Haber et al., 2000). Hence, the lateral activity cluster that we have observed for reward (Fig. 2A) in the addition to the caudal VTA cluster may simply reflect these differential projection characteristics from the ventral striatum. Alternatively, this may be related to the medial to lateral gradient of functional connectivity within the SN/VTA according to which more lateral aspects of the SN/VTA complex have a stronger connectivity to the dorsal striatum (Haber et al., 2000). This latter possibility is meaningful because activation of dopamine neurons also signal action propensities (go signals) and recent behavioral and imaging data suggest that reward anticipation responses not only embody the valence of the anticipated outcome but also a bias towards actions that may promote approach and consummatory behavior (Guitart-Masip et al., 2010b). Although a clear delineation between neuron populations of the dorsal and ventral tier is not feasible with the present fMRI resolution, it seems likely that both VTA clusters (caudal and rostral) would substantially overlap with the dorsal tier (Fig. 2A) given that it occupies much of the medial SN/VTA complex in Haber's classification framework (Haber et al., 2000).

Apart from a spatial separation underlying the responses to either reward or novelty, we observed a significant interaction between both factors within the more caudal part of the VTA. In particular, novelty selectively increased the reward-anticipation response, indicating that information about the novelty and the reward-predictive value of a stimulus is integrated in this sub-region. This integration might therefore represent the key mechanism

that gives rise to the preferential processing of novel reward-predicting stimuli which has been described in terms of an “exploration bonus” and biases an organism towards exploring new sources of prospective reward (Kakade and Dayan, 2002). In turn, such a signal is likely to modulate diverse neural processes thereby facilitating the encoding of the current event into long-term memory (Krebs et al., 2009b; Wittmann et al., 2005). Work based on direct recordings in nonhuman primates has led to the proposal that distinct dopaminergic cell types in ventromedial and dorsolateral SN/VTA may code for *motivational value* (positive valence) and *motivational salience*, including positive and negative valence, respectively (Bromberg-Martin et al., 2010). Our paradigm was not designed to directly assess this type of functional gradient and hence it remains unclear how the topography that we have observed relates to this work in nonhuman primates.

Further support for the view that novelty modulates the reward-anticipation response is provided by the functional connectivity results of the present study. In particular, we found that in the context of reward, novelty increases the functional connectivity between the medial SN/VTA and the NAcc, one of the major input and target regions of dopamine neurons that is known to be crucial for establishing stimulus-reward associations (Schultz, 2002; Wise, 2004). A similar functional covariation pattern with the medial SN/VTA was found for the anterior hippocampus/PHG and primary visual cortex (V1). Our data do not allow us to determine whether this pattern of functional connectivity is more related to afferent or efferent connectivity of the SN/VTA. Both possibilities are viable. An afference-related correlation would suggest that visual, medial temporal and ventral striatal regions jointly contribute to establish the novelty related enhancement of reward-anticipation. An efference-related correlation would suggest that the medial SN/VTA signal may act to promote episodic memory for novel reward-predicting stimuli (for related discussions see,

Kakade and Dayan, 2002; Krebs et al., 2009b; Wittmann et al., 2008). This notion appears to be supported by the results of an additional connectivity analysis that focused on the influence of reward on the processing of novel stimuli (*novel\_reward* vs. *novel\_no-reward*). Here, reward appeared to selectively emphasize covariations between the caudal VTA and several clusters in the visual cortices, including middle and lateral occipital cortices, V1, and FG. These results indicate that reward enhances visual processing of novel stimuli, thereby promoting a detailed stimulus analysis. This, in turn, may promote encoding of the novel stimuli (compare, Adcock et al., 2006 and Krebs et al., 2009b).

This reward-related increase in connectivity between the VTA and posterior visual-processing areas appears to be contrasted by the effect of reward on the neural signature of early stimulus encoding within the PHG. In line with numerous previous reports (e.g., Gabrieli et al., 1997; Rombouts et al., 2001), we found that novel “to-be-encoded” stimuli elicited robust responses within the FG/PHG region as compared to familiar stimuli. Interestingly, however, reward appeared to *attenuate* this prototypical response (Fig. 2B, upper right panel). The reason for this type of modulation remains unclear. One speculative possibility is that reward may sometimes bias towards familiarity, that is, it may increase ‘old’ judgments to new items (false alarms; see Krebs et al., 2009b). Another possibility is that these local variations are caused by regional differences in dopamine release within the visual stream.

Considering that the novelty/familiarity of the cue was implicit and irrelevant to the task, it is likely that the observed modulation of the reward-anticipation response within the VTA is triggered relatively automatically by an implicit novelty-detection signal (e.g., Bunzeck et al., 2007; e.g., Ranganath and Rainer, 2003). Notably, the caudal VTA seed region that was associated with the integration of reward and novelty information also covaried with the

rostral VTA region that exhibited a pure novelty response. It is tempting to speculate that the novelty signal in the rostral VTA drives the interaction between reward and novelty within the caudal VTA.

To conclude, high-resolution fMRI allowed us to isolate distinct clusters within the SN/VTA that were preferentially associated with reward anticipation, novelty, as well as their interactions. Beyond unique responses to novelty and reward in the rostral medial SN/VTA and the right lateral SN, respectively, the caudal medial SN/VTA appeared to be one of the key sites where information about the novelty and the reward-predictive value of an event is integrated. In turn, this integrative signal was correlated with neural processes within mesolimbic circuitry (i.e., the ventral striatum and the hippocampus) and the visual cortex. This functional correlation may highlight how afferents of the medial SN/VTA provide integrative information about novelty and reward, or, alternatively, how medial SN/VTA activity may modulate memory processes for novel events associated with rewards.

**Acknowledgements.** The present work was funded by grants from the Deutsche Forschungsgemeinschaft (SFB 779, TP A7, awarded to E. Duzel).

## References

Ashburner, J., Friston, K.J., 1999. Nonlinear spatial normalization using basis functions. *Hum Brain Mapp* 7, 254-266.

Bethus, I., Tse, D., Morris, R.G., 2010. Dopamine and memory: modulation of the persistence of memory for novel hippocampal NMDA receptor-dependent paired associates. *J Neurosci* 30, 1610-1618.

Brett, M., Anton, J.-L., Valabregue, R., Poline, J.-P., 2002. Region of interest analysis using an SPM toolbox (abstract). Available on CD-Rom. *Neuroimage* 16.

Bunzeck, N., Duzel, E., 2006. Absolute coding of stimulus novelty in the human substantia nigra/VTA. *Neuron* 51, 369-379.

Bromberg-Martin, E.S., Matsumoto, M., Hikosaka, O., 2010. Dopamine in motivational control: Rewarding, aversive, and alerting. *Neuron* 68, 815-834.

Bunzeck, N., Schutze, H., Stallforth, S., Kaufmann, J., Duzel, S., Heinze, H.-J., Duzel, E., 2007. Mesolimbic Novelty Processing in Older Adults. *Cereb. Cortex*, bhm020.

Cohen, M.X., Schoene-Bake, J.C., Elger, C.E., Weber, B., 2009. Connectivity-based segregation of the human striatum predicts personality characteristics. *Nat Neurosci* 12, 32-34.

D'Ardenne, K., McClure, S.M., Nystrom, L.E., Cohen, J.D., 2008. BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. *Science* 319, 1264-1267.

Duzel, E., Bunzeck, N., Guitart-Masip, M., Wittmann, B., Schott, B.H., Tobler, P.N., 2009. Functional imaging of the human dopaminergic midbrain. *Trends Neurosci* 32, 321-328.

Friston, K., Holmes, A.P., Worsley, K.J., Poline, J.B., Frith, C.D., Frackowiak, R.S., 1995. Statistical Parametric Maps in Functional Imaging: A General Linear Approach. *Human Brain Mapping* 2, 189-210.

Gasbarri, A., Sulli, A., Packard, M.G., 1997. The dopaminergic mesencephalic projections to the hippocampal formation in the rat. *Prog Neuropsychopharmacol Biol Psychiatry* 21, 1-22.

Goto, Y., Otani, S., Grace, A.A., 2007. The Yin and Yang of dopamine release: a new perspective. *Neuropharmacology* 53, 583-587.

Guitart-Masip, M., Bunzeck, N., Stephan, K.E., Dolan, R.J., Duzel, E., 2010a. Contextual novelty changes reward representations in the striatum. *J Neurosci* 30, 1721-1726.

Guitart-Masip, M., Huys, Q., Fuentemilla, L., Bach, D., Dayan, P., Duzel, E., Dolan, R.J., 2010b. Effects of valence on action learning, an fMRI study. Society for Neuroscience abstract.

Haber, S.N., Fudge, J.L., McFarland, N.R., 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* 20, 2369-2382.

Haber, S.N., Knutson, B., 2010. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* 35, 4-26.

Haber, S.N., Ryoo, H., Cox, C., Lu, W., 1995. Subsets of midbrain dopaminergic neurons in monkeys are distinguished by different levels of mRNA for the dopamine transporter: comparison with the mRNA for the D2 receptor, tyrosine hydroxylase and calbindin immunoreactivity. *J Comp Neurol* 362, 400-410.

Horvitz, J.C., Stewart, T., Jacobs, B.L., 1997. Burst activity of ventral tegmental dopamine neurons is elicited by sensory stimuli in the awake cat. *Brain Res* 759, 251-258.

Josephs, O., Henson, R.N., 1999. Event-related functional magnetic resonance imaging: modelling, inference and optimization. *Philos Trans R Soc Lond B Biol Sci* 354, 1215-1228.

Kakade, S., Dayan, P., 2002. Dopamine: generalization and bonuses. *Neural Netw* 15, 549-559.

Kanowski, M., Rieger, J.W., Noesselt, T., Tempelmann, C., Hinrichs, H., 2007. Endoscopic eye tracking system for fMRI. *Journal of Neuroscience Methods* 160, 10-15.

Knutson, B., Cooper, J.C., 2005. Functional magnetic resonance imaging of reward prediction. *Curr Opin Neurol* 18, 411-417.

Krebs, R.M., Schott, B.H., Duzel, E., 2009a. Personality traits are differentially associated with patterns of reward and novelty processing in the human substantia nigra/ventral tegmental area. *Biol Psychiatry* 65, 103-110.

Krebs, R.M., Schott, B.H., Schutze, H., Duzel, E., 2009b. The novelty exploration bonus and its attentional modulation. *Neuropsychologia* 47, 2272-2281.

Kriegeskorte, N., Simmons, W.K., Bellgowan, P.S., Baker, C.I., 2009. Circular analysis in systems neuroscience: the dangers of double dipping. *Nat Neurosci* 12, 535-540.

Lisman, J.E., Grace, A.A., 2005. The Hippocampal-VTA Loop: Controlling the Entry of Information into Long-Term Memory. *Neuron* 46, 703-713.

Ljungberg, T., Apicella, P., Schultz, W., 1992. Responses of monkey dopamine neurons during learning of behavioral reactions. *J Neurophysiol* 67, 145-163.

Marinelli, M., Rudick, C.N., Hu, X.T., White, F.J., 2006. Excitability of dopamine neurons: modulation and physiological consequences. *CNS Neurol Disord Drug Targets* 5, 79-97.

Mesulam, M.M., 1998. From sensation to cognition. *Brain* 121 ( Pt 6), 1013-1052.

Nyberg, L., 2005. Any novelty in hippocampal formation and memory? *Curr Opin Neurol* 18, 424-428.

O'Doherty, J.P., 2004. Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr Opin Neurobiol* 14, 769-776.

Pessoa, L., Engelmann, J.B., 2010. Embedding reward signals into perception and cognition. *Front Neurosci* 4.

Ranganath, C., Rainer, G., 2003. Neural mechanisms for detecting and remembering novel events. *Nat Rev Neurosci* 4, 193-202.

Schott, B.H., Minuzzi, L., Krebs, R.M., Elmenhorst, D., Lang, M., Winz, O.H., Seidenbecher, C.I., Coenen, H.H., Heinze, H.J., Zilles, K., Duzel, E., Bauer, A., 2008.

Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. *J Neurosci* 28, 14311-14319.

Schultz, W., 1997. Dopamine neurons and their role in reward mechanisms. *Curr Opin Neurobiol* 7, 191-197.

Schultz, W., 2002. Getting formal with dopamine and reward. *Neuron* 36, 241-263.

Schultz, W., 2004. Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. *Curr Opin Neurobiol* 14, 139-147.

Tulving, E., Markowitsch, H.J., Craik, F.E., Habib, R., Houle, S., 1996. Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cereb Cortex* 6, 71-79.

Wise, R.A., 2004. Dopamine, learning and motivation. *Nat Rev Neurosci* 5, 483-494.

Wittmann, B.C., Daw, N.D., Seymour, B., Dolan, R.J., 2008. Striatal activity underlies novelty-based choice in humans. *Neuron* 58, 967-973.

Wittmann, B.C., Schott, B.H., Guderian, S., Frey, J.U., Heinze, H.J., Duzel, E., 2005. Reward-related fMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. *Neuron* 45, 459-467.

Zellner, M.R., Ranaldi, R., 2009. How conditioned stimuli acquire the ability to activate VTA dopamine cells: a proposed neurobiological component of reward-related learning. *Neurosci Biobehav Rev* 34, 769-780.

## Figure Legends

**Figure 1.** Stimuli and paradigm. **(A)** Each trial started with a cue stimulus (presented for 2000 ms) indicating if responses to the upcoming target will be rewarded or not (as indicated by the indoor vs. outdoor category of scenes). The cue was followed by a forced-choice task, in which participants had to indicate whether the presented target digit (presented for 100 ms) was smaller or greater than 5. After a variable delay, participants received visual feedback (1500 ms) depending on their performance (SOA: stimulus onset asynchrony). **(B)** Two-by-two factorial design. The cues not only indicated the potential reward category (indoor vs. outdoor), but could furthermore belong to a set of stimuli that have been familiarized before, or could be completely novel. The novelty/familiarity manipulation, however, was entirely irrelevant to the task, but resulted in four main cue types, i.e., *novel\_reward*, *novel\_no-reward*, *familiar\_reward*, and *familiar\_no-reward*. **(C)** The partial-head volume of the functional acquisition sequence is overlaid on the T1-weighted scan averaged across participants.

**Figure 2.** Neural activity within the SN/VTA related to reward (blue) and novelty (red). **(A)** Both reward and novelty alone elicited distinct activity clusters within the SN/VTA (overlaid on the PD-weighted scan averaged across participants). While reward-related activity was observed within the caudal VTA [MNI x y z: 3 -15 -16] and the right SN [9 -19 -14], novelty-related activity was observed in a more rostral VTA cluster [1 -11 -8] (the respective cutting planes are illustrated in the center panel). In addition to reflecting the results of the voxel-wise comparisons (colored asterisks), the BOLD signal values revealed that activity in the reward-sensitive VTA region was further increased for novel stimuli as reflected in a

significant difference between reward-predictive novel and familiar cues (delineation of the dorsal and ventral tier of the SN/VTA complex based on Haber et al., 2000). **(B)** Main effects and voxel-wise interaction between reward and novelty. The ANOVA revealed highly overlapping activity clusters with respect to the selective contrast in (A). In addition, two VTA clusters additionally exhibited an interaction, reflecting the ROI-based analysis pattern of the selective contrasts. Note that the main effect of novelty in the rostral VTA was only significant on a more lenient threshold ( $^{\#}p < .001$ , uncorrected) due to the interaction pattern in this region.

**Figure 3.** Neural activity related to reward and novelty outside the SN/VTA. Several regions were primarily modulated by either reward (left panels) or novelty (right panels; overlaid on the T1-weighted scan averaged across participants). Analogous to the ROI analyses in Fig. 2, colored asterisks highlight the results of the voxel-wise comparisons. The novelty effect in FG/PHG and hippocampus/PHG was concomitantly modulated by reward as reflected in a significant difference between reward-predictive and no-reward-predictive novel cues.

**Figure 4.** Functional connectivity (PPI) with the caudal VTA. **(A)** Functional connectivity between the reward-sensitive caudal VTA region and left NAcc, left hippocampus/PHG, bilateral V1, and rostral VTA is increased for novel as compared to familiar reward-predictive stimuli. The individual participants' seed-region activity was derived by contrasting *novel\_reward* and *familiar\_reward* cues representing the joint neural activity enhancement by novelty and reward. **(B)** An analogous PPI was performed contrasting *novel\_reward* and *novel\_no-reward*, thereby focusing on the effect of reward on novel

stimuli alone, Here, activity within the caudal VTA covaried with activity in a wide range of posterior visual-processing regions, including V1, middle and lateral occipital cortices, posterior FG, as well as with a small cluster in the right SN. The positive PPI contrasts are overlaid on the PD-weighted (VTA, SN) and T1-weighted scan (NAcc and cortical regions) averaged across participants. *Hip*, hippocampus; *LOC*, lateral occipital gyrus.

ACCEPTED MANUSCRIPT

Figure 1

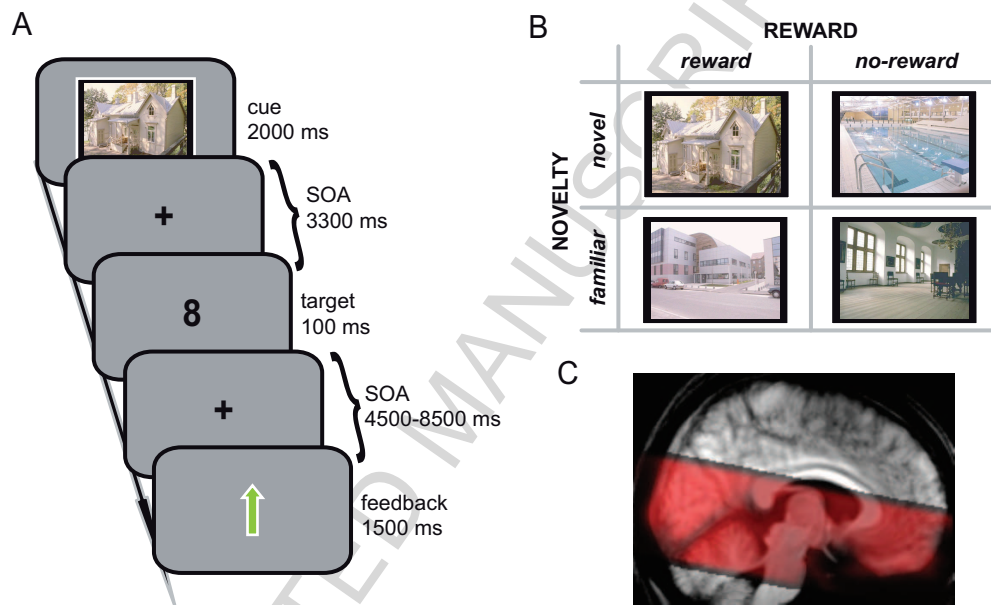


Figure 2

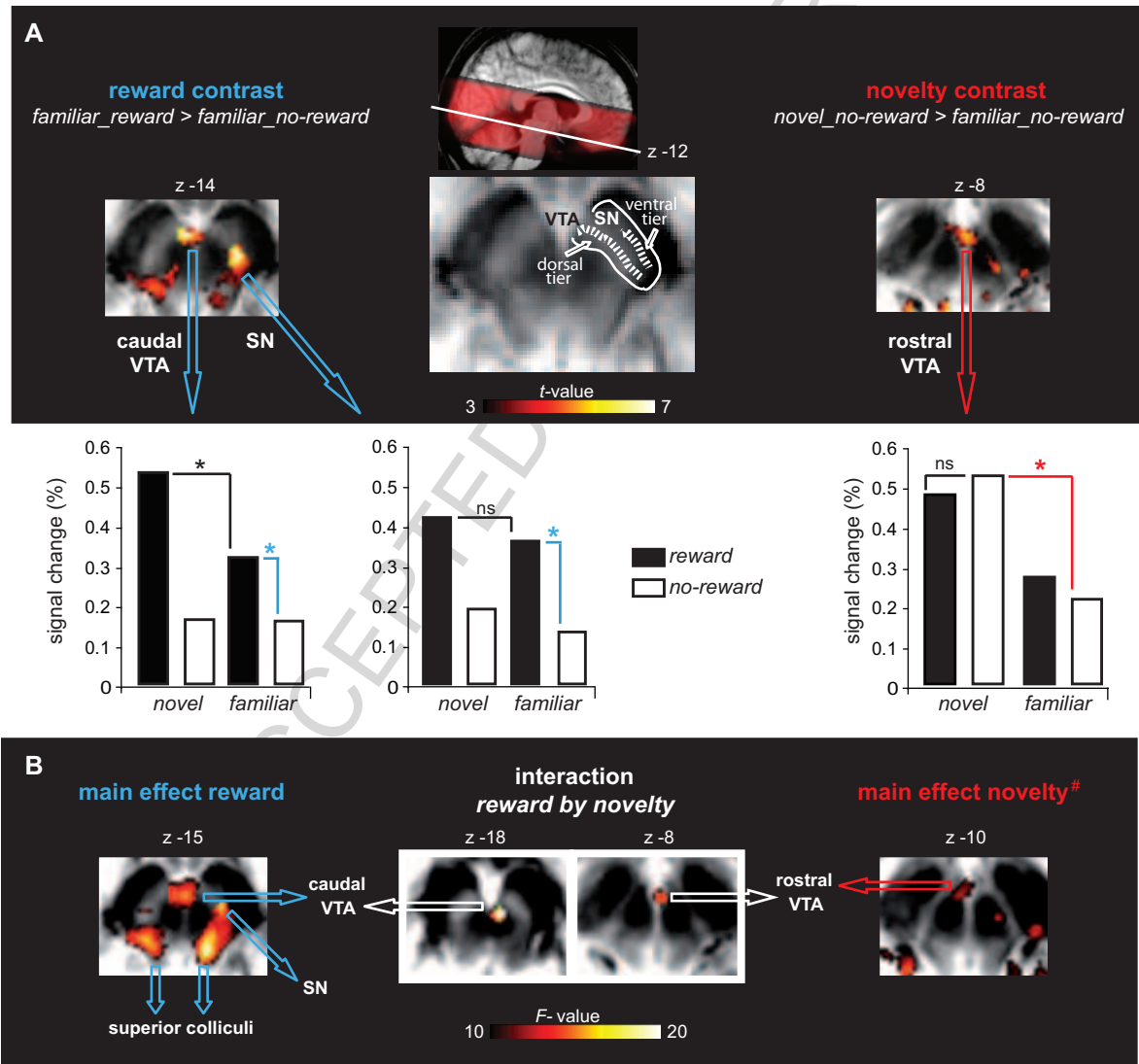


Figure 3

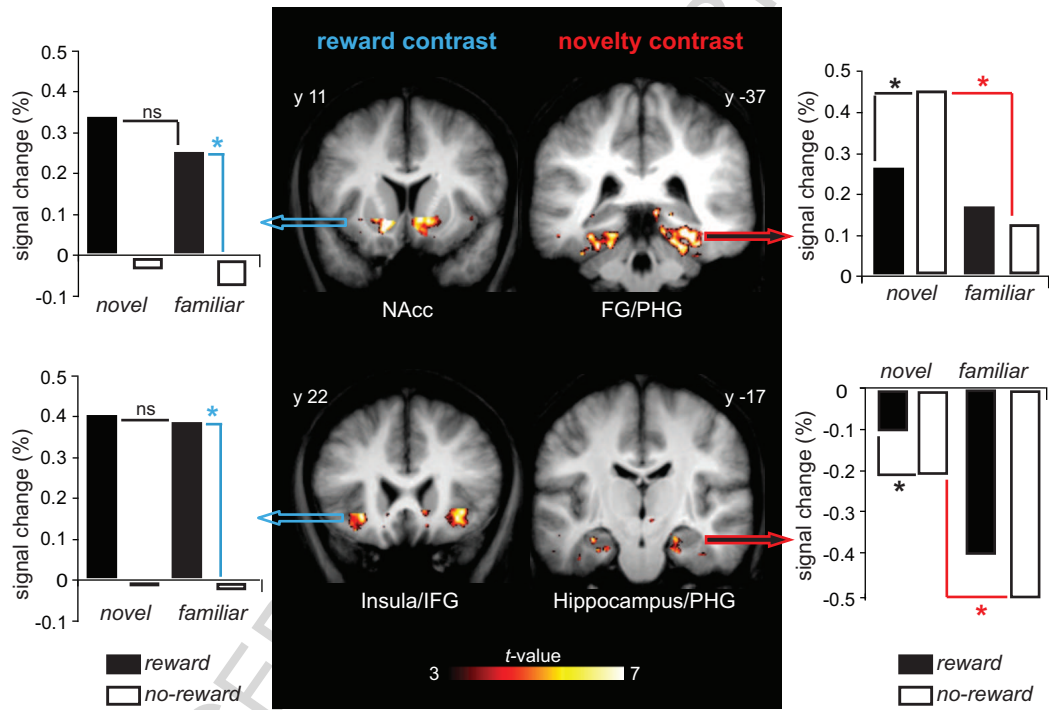
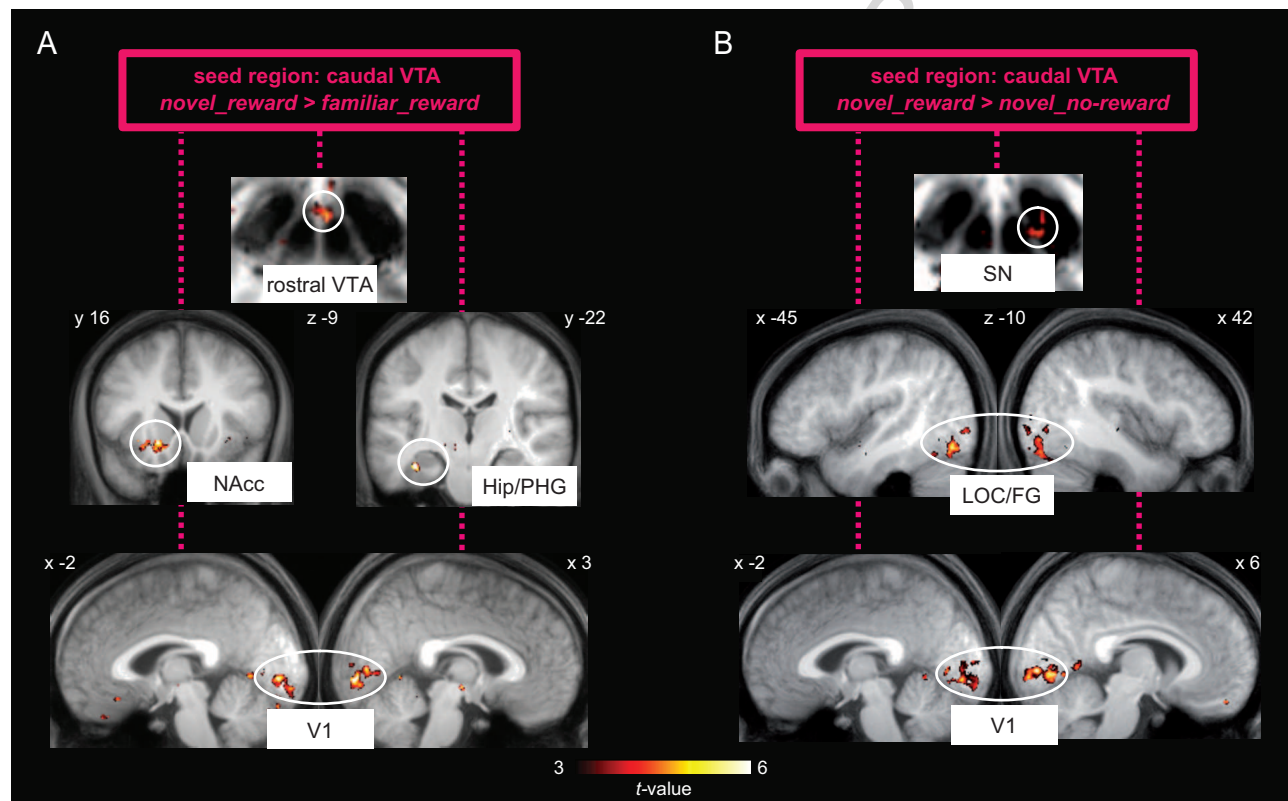


Figure 4



**Table 1. Behavioral responses to the cue and the target digit.**

<b>NOVELTY</b>		<b>cue</b>		<b>target digit</b>	
		<b>reward</b>	<b>no-reward</b>	<b>reward</b>	<b>no-reward</b>
<b>novel</b>	RT ms (SD)	620 (144)	571 (113)	426 (58)	471 (59)
	errors % (SD)	2.3 (7.2)	3.5 (4.9)	4.6 (6.1)	3.5 (5.8)
<b>familiar</b>	RT ms (SD)	649 (108)	595 (111)	419 (64)	458 (64)
	errors % (SD)	3.1 (7.8)	3.1 (7.5)	5.0 (5.0)	6.9 (7.5)

*RT: response time; SD: standard deviation*

**Table 2. Contrasts to define regions of interest for reward and novelty.**

region	L/R	k	MNI coordinates			T-value
			x	y	z	
<b>familiar_reward vs. familiar_no-reward (in the absence of novelty)</b>						
Nucleus accumbens (Nacc)	L	289	-12	12	-8	7.0
Nucleus accumbens (Nacc)	R	176	12	6	-11	6.2
Insula / inferior frontal gyrus (IFG)	L	226	-27	24	-11	9.0
Insula / inferior frontal gyrus (IFG)	R	174	34	20	-7	6.4
Superior colliculus	R	26	7	-28	-5	6.3
Superior colliculus	L	20	-4	-28	-8	7.3
VTA	L/R	19	3	-15	-16	5.4
SN	R	11	9	-19	-14	5.4
Hippocampus	R	26	34	-17	-15	8.2
Locus coeruleus	L	22	-8	-29	-21	8.3
<b>novel_no-reward vs. familiar_no-reward (in the absence of reward)</b>						
Fusiform / parahippocampal gyrus (FG/PHG)	R	3047	27	-32	-28	12.5
Fusiform / parahippocampal gyrus (FG/PHG)	L	2342	-24	-32	-23	9.4
Hippocampus	R	129	19	-14	-20	9.9
Hippocampus	L	492	-22	-9	-26	6.3
Calcarine sulcus (V1)	L	38	-5	-82	-1	8.3
VTA	L/R	12	1	-11	-8	4.6

L: left hemisphere; R: right hemisphere; k: cluster size; MNI: Montreal Neurological Institute; ctx: cortex  
T-value: FDR-corrected significance threshold for clusters at  $p < .05$  (FDR: false discovery rate)

**Table 3. Main and interaction effects of reward and novelty based on a voxel-wise ANOVA.**

region	L/R	k	MNI coordinates			F-value
			x	y	z	
<b>main effect REWARD</b>						
Nucleus accumbens (Nacc)	L	453	-11	11	-8	47.5
Nucleus accumbens (Nacc)	R	920	9	11	-6	46.4
Insula / inferior frontal gyrus (IFG)	R	857	33	25	-4	42.2
Insula / inferior frontal gyrus (IFG)	L	594	-29	24	-7	35.0
SN	R	18	10	-19	-15	30.9
VTA	L/R	25	1	-16	-15	25.5
Superior colliculus	L	26	-6	-28	-10	23.0
Superior colliculus	R	23	9	-23	-7	23.0
Hippocampus	L	51	-28	-7	-27	22.4
Hippocampus	R	11	25	-13	-25	17.2
Locus coeuleus	L	12	-5	-32	-25	17.8
<b>main effect NOVELTY</b>						
Fusiform / parahippocampal gyrus (FG/PHG)	R	9121	33	-38	-15	53.1
Fusiform / parahippocampal gyrus (FG/PHG)			18	-41	-11	50.0
Fusiform / parahippocampal gyrus (FG/PHG)	L	7093	-23	-40	-15	47.6
Fusiform / parahippocampal gyrus (FG/PHG)			-30	-46	-11	43.3
Middle occipital gyrus	R	1280	47	-79	7	34.0
Middle occipital gyrus			44	-83	0	23.2
Middle occipital gyrus	L	1290	-36	-79	-18	32.2
Middle occipital gyrus			-46	-71	-9	31.1
Hippocampus	L	324	-25	-11	-29	25.1
Hippocampus			-26	-19	-26	17.8
Inferior temporal gyrus	L	644	-53	-57	-17	24.6
Hippocampus	R	232	25	-19	-21	23.1
Hippocampus			19	-13	-21	22.6
Thalamus / pulvinar	R	178	20	-31	-1	18.1
VTA	L/R	6	-1	-13	-10	10.6 <sup>#</sup>
<b>interaction REWARD by NOVELTY</b>						
VTA	L/R	25	3	-22	-19	25.6
VTA	L/R	29	2	-13	-8	15.9

L: left hemisphere; R: right hemisphere; k: cluster size; MNI: Montreal Neurological Institute; ctx: cortex  
 F-value: FDR-corrected significance threshold for clusters at  $p < .05$  (FDR: false discovery rate); <sup>#</sup>  $p < .001$ , uncorrected

**Table 4. Functional connectivity using the caudal VTA as seed region.**

region	L/R	k	MNI coordinates			T-value
			x	y	z	
<b>seed contrast:</b>						
<b>novel_reward vs. familiar_reward</b>						
Nucleus accumbens (Nacc)	L	100	-16	11	-12	8.5
Nucleus accumbens (Nacc)			-16	16	-8	5.7
Calcarine sulcus (V1)	L/R	434	6	-84	0	6.4
Calcarine sulcus (V1)			-6	-82	-3	5.4
Occipital pole	L	94	-10	-102	-13	6.2
Putamen	L	76	-26	6	-9	6.5
Hippocampus / parahippocampal gyrus (PHG)	L	44	-37	-20	-23	7.7
VTA	L/R	7	3	-12	-9	4.8
<b>novel_reward vs. novel_no-reward</b>						
Lateral occipital gyrus	L	107	-47	-78	-3	8.3
Middle occipital gyrus	L	237	-36	-85	-8	7.6
Middle occipital gyrus	R	151	26	-69	-2	7.4
Calcarine sulcus (V1)	L/R	189	6	-71	-3	7.3
Lateral occipital gyrus	R	347	42	-74	-15	6.7
Calcarine sulcus (V1)	L/R	348	6	-84	0	6.7
Middle occipital gyrus	R	67	25	-92	4	6.6
Fusiform gyrus (FG)	L	64	-23	-43	-19	6.1
Middle occipital gyrus	R	96	34	-88	5	6.0
Fusiform gyrus (FG)	R	67	22	-46	-15	5.9
Fusiform gyrus (FG)	R	83	28	-33	-24	5.9
Putamen	R	18	20	12	-13	5.9
Lateral occipital gyrus	L	231	-37	-76	-19	5.6
Calcarine sulcus (V1)	L/R	43	-2	-83	-4	5.6
Fusiform / parahippocampal gyrus (FG/PHG)	R	146	22	-42	-9	5.9
Fusiform gyrus (FG)	R	117	33	-46	-21	5.2
SN	R	14	12	-17	-8	4.8

L: left hemisphere; R: right hemisphere; k: cluster size; MNI: Montreal Neurological Institute; ctx: cortex  
T-value: significance threshold  $p < .001$ , uncorrected