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Absolute Coding of Stimulus Novelty in the Human Substantia Nigra/VTA

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Summary

Novelty exploration can enhance hippocampal plasticity in animals through dopaminergic neuromodulation arising in the substantia nigra/ventral tegmental area (SN/VTA). This enhancement can outlast the exploration phase by several minutes. Currently, little is known about dopaminergic novelty processing and its relationship to hippocampal function in humans. In two functional magnetic resonance imaging (fMRI) studies, SN/VTA activations in humans were indeed driven by stimulus novelty rather than other forms of stimulus salience such as rareness, negative emotional valence, or targetness of familiar stimuli, whereas hippocampal responses were less selective. SN/VTA novelty responses were scaled according to absolute rather than relative novelty in a given context, unlike adaptive SN/VTA responses recently reported for reward outcome in animal studies. Finally, novelty enhanced learning and perirhinal/parahippocampal processing of familiar items presented in the same context. Thus, the human SN/VTA can code absolute stimulus novelty and might contribute to enhancing learning in the context of novelty.

Introduction

Reward-coding dopaminergic midbrain neurons in animals also respond to novelty and habituate when stimuli become familiar without reinforcement (Schultz, 1998). This consistently observed overlap between novelty and reward-processing in the dopaminergic midbrain could suggest a special biological importance for stimulus novelty whereby novelty itself has reward value (Reed et al., 1996) or motivates exploration in the search for potential reinforcers (Kakade and Dayan, 2002; Schultz, 1998). In humans, very little is known about the role of the dopaminergic midbrain in novelty processing. It is uncertain whether the human dopaminergic midbrain responds to stimulus novelty per se and if so whether it prefers stimulus novelty over other dimensions of stimulus salience, such as being unexpected, causing emotional arousal, or requiring a behavioral response (Dommett et al., 2005; Horvitz, 2000; Redgrave et al., 1999). These other forms of salience can be reported by stimuli that are familiar and are therefore not contingent upon stimulus novelty. A preferential response of the dopaminergic midbrain to stimulus novelty would indicate a special biological relevance for novelty as a motivating (Kakade and Dayan, 2002; Schultz, 1998) and/or reinforcing (Reed et al., 1996) stimulus dimension also in humans.

A number of brain regions that provide input into the dopaminergic midbrain are capable of processing not only stimulus novelty but also other forms of stimulus salience. Most notably, the hippocampus and the amygdala are held to be closely functionally linked to the dopaminergic midbrain (Lisman and Grace, 2005) as components of a wider functional dopaminergic system termed the mesolimbic dopaminergic system. The hippocampus appears capable of comparing incoming information with stored memories (Lisman and Grace, 2005) and is sensitive to stimulus novelty (Duzel et al., 2003; Tulving et al., 1996) as well as to other forms of salience such as deviance or rareness and targetness even if reported by highly familiar stimuli (Crottaz-Herbette et al., 2005; Halgren et al., 1980). The amygdala, a structure that, together with noradrenergic nuclei of the brain stem, is critically involved in generating arousal to emotionally salient stimuli and in improving long-term memory for such stimuli (McGaugh, 2004), has a direct projection to the dopaminergic midbrain (Pitkanen, 2000). This projection is functionally relevant for displaying responses to biologically salient stimuli, for instance, for displaying orienting responses in appetitive conditioning (Lee et al., 2005). The orienting response, in turn, includes both autonomic (Lee et al., 2005) and motor (Holland, 1977) components.

An important approach to better understand the functional link between novelty processing and dopaminergic neuromodulation in humans would be to clarify whether the substantia nigra/ventral tegmental area (SN/VTA) of the midbrain, where mesolimbic and mesocortical dopaminergic projections originate, preferentially responds to stimulus novelty or responds also to other forms of salience such as deviance/rareness, negative emotional valence, or targetness. Recent functional magnetic resonance imaging (fMRI) data in healthy humans show that activity of the SN/VTA accompanied hippocampal activity related to memory formation, in that both structures are activated by associative novelty, as a function of recall performance (Schott et al., 2004) and by reward-predicting stimuli that are remembered after long retention intervals (Wittmann et al., 2005). Following a high-reward-predicting cue, both structures show an increased correlation in association with enhanced long-term memory for subsequent scene pictures (Adcock et al., 2006). In view of the close functional links that the hippocampus and the amygdala have with the SN/VTA, it seems plausible that these findings are not only driven by stimulus novelty and reward prediction but also other forms of salience such as rareness/deviance, emotional valence, and targetness.

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Evidence from animal studies show that dopaminergic neuromodulation appears to be critical for synaptic plasticity in the hippocampus (Frey and Morris, 1998). A remarkable observation in rodent studies is that the neuromodulatory influence of novelty on synaptic plasticity occurs both during novelty exploration (Davis et al., 2004) as well as 15 to 30 min beyond exploration (Li et al., 2003; Straube et al., 2003). Rats that were allowed to freely move in a novel spatial environment subsequently have a reduced threshold for LTP induction in a narrow time window after exploration, and this facilitation of LTP in the CA1 region can be blocked by D1/D5 receptor antagonists (Li et al., 2003) suggesting that there is an increase in dopamine release in the context of novelty. These temporally extended effects of novelty exploration raise the possibility that learning of familiar information should be improved in the context of novelty. According to this hypothesis, the additional learning which familiar stimuli would normally undergo due to their repetition should be enhanced in the context of novel stimuli, as compared to a context in which all other stimuli are also familiar.

Another property of the mesolimbic system, however, makes the opposite prediction about how novelty should affect learning of familiar stimuli. Recent evidence suggests that dopaminergic midbrain neurons do not code absolute reward magnitude but instead adapt their response relative to a predicted magnitude in a given context (Tobler et al., 2005). Even a positive reward value can lead to a suppression of dopaminergic neurons if its magnitude is smaller than expected in a given context (Tobler et al., 2005). If an analogous phenomenon of adaptive coding existed for mesolimbic novelty processing, dopaminergic midbrain responses should be scaled according to the highest expected novelty within a context. This would mean that mesolimbic responses to familiar stimuli should be higher within a context where they constitute the relatively most novel stimulus category (that is in a context with other, more highly familiar stimuli), as compared to a context where they are paired with novel stimuli. However, adaptive coding has been observed for reward outcome and not for reward-predicting conditioned stimuli (Tobler et al., 2005). Therefore, if human SN/VTA responses to novelty were scaled in an adaptive manner, this would support the notion that novelty is treated like a reward (Reed et al., 1996), whereas a coding of absolute novelty magnitude in the dopaminergic midbrain would suggest that novelty is treated like a predictive cue (Kakade and Dayan, 2002). This latter possibility would be compatible with computational models in which the dopaminergic midbrain response to novelty is treated as a bonus to explore the environment in the search for a reward rather than coding a reward (Kakade and Dayan, 2002).

We studied the response properties of the human SN/VTA, as well as other medial temporal and subcortical components of the mesolimbic and mesocortical systems in two event-related fMRI studies using an acquisition protocol that was optimized for the midbrain regions but also allowed the measurement of hippocampal, amygdala, and striatal responses as well as inferior temporal activity. The first fMRI study (Experiment I) was designed to clarify to what extent, in the absence of apparent reward, SN/VTA prefers stimulus novelty over other forms of stimulus salience. We used a modified visual oddball paradigm, in which 66% of all grayscale images depicted a stimulus of neutral emotional valence. This repeatedly presented stimulus served as "standard." Randomly intermixed with the standard were four types of rare or contextually deviant events, each with a probability of 8.3%. These rare events were (1) a neutral stimulus (the "neutral oddball"), (2) a neutral stimulus that required a motor response (the "target oddball"), (3) a stimulus with a negative emotional valence (the "emotional oddball"), and (4) novel stimuli (the "novel oddballs"). Contrasts of these conditions allowed us to assess the response of the SN/VTA to pure stimulus novelty ("novel oddballs versus neutral oddballs"), targetness ("target oddballs versus neutral oddballs"), negative emotional valence ("emotional oddballs versus neutral oddballs"), and to rareness/deviance per se ("neutral oddballs versus standards"). We used stimuli with negative emotional valence as emotional oddballs and refrained from using stimuli with a positive emotional valence in order to avoid confounding SN/VTA and amygdala responses with the rewarding properties of positive emotional valence (Baxter and Murray, 2002).

The second fMRI study (Experiment II) was designed to determine whether, again in the absence of apparent reward, the SN/VTA codes absolute magnitude of novelty or adapts to its relative magnitude in a given context. Using the picture stimuli from the first study, familiar oddballs (pictures that were presented once before scanning) were presented either in the context of novel oddballs (pictures presented for the first time during scanning) or in the context of very familiar oddballs (pictures presented twice before scanning). Moreover, the similarities in the oddball design to the first fMRI study allowed assessment of the reliability of the findings regarding novelty, rareness/deviance, and targetness across the two studies. Behavioral versions (Experiments III, IV, and V) of the second fMRI study were used to assess whether memory for familiar stimuli was improved more strongly in the context of novel stimuli or in the context of very familiar stimuli when tested after short retention intervals (20 min—Experiments III and V) or long retention intervals (1 day—Experiments IV and V) and depending on whether novel and familiar stimuli were behaviorally relevant at study (Experiment V) or did not require a behavioral response (Experiments III and IV).

Results

Behaviorally, in Experiments I–V, target detection and indoor/outdoor discrimination were nearly perfect (hit rate/correct responses > 94% in all experiments), with a mean reaction time (RT) of about 500 ms, and a very low false-alarm (FA) rate/error rate of less than 4% in all experiments (see Table S1 in the Supplemental Data available with this article online).

Experiment I

Statistical parametric maps show that within the midbrain, stimulus novelty (novel oddballs versus neutral oddballs) elicited a prominent response in the right substantia nigra/VTA (Figure 1B; Table 1A), but contextual

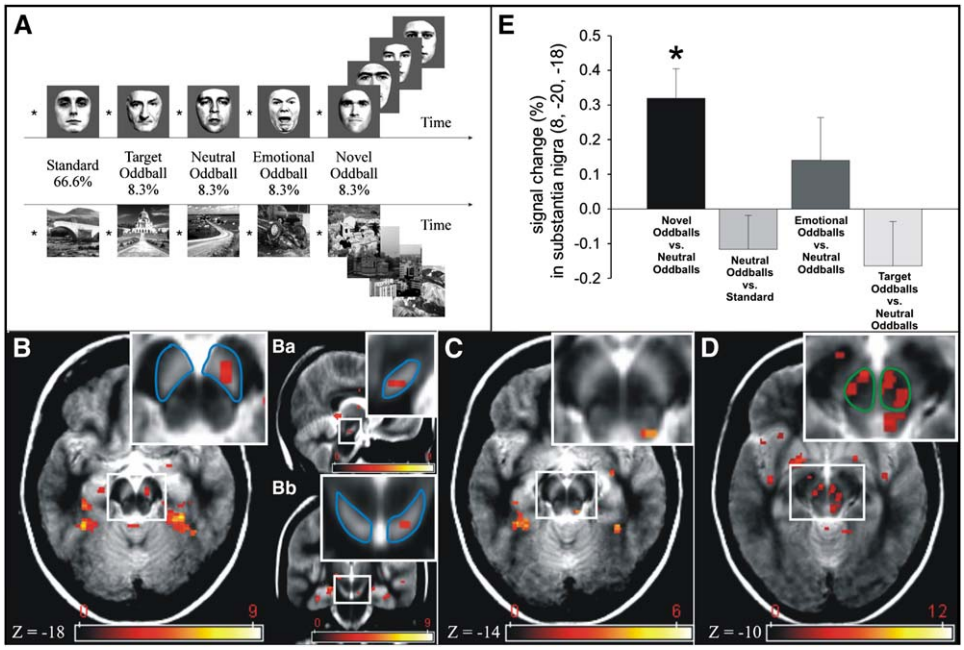

Figure 1. Experimental Design and the fMRI Results for Experiment I

(A) Experimental design. Stimuli and experimental conditions for Experiment I. Numbers denote frequency of occurrence. In one half of the experiment we presented pictures of male faces and in the other half outdoor scenes. The order was counterbalanced across subjects.

(B–E) fMRI results.

(B–D) Results for the contrasts of novel oddballs (B, Ba, and Bb), negative emotional oddballs (C), and target oddballs (D) versus neutral oddballs. Activation maps were superimposed on a magnetization transfer (MT) template (see Experimental Procedures). In (B), the SN/VTA is circled in blue, and in (D), the red nucleus is circled in green.

(E) Estimated percent signal change of the peak hemodynamic response in the SN/VTA (coordinates x, y, z = 8, −20, −18). Error bars denote standard error of the mean and the star denotes the contrasts that elicited significant hemodynamic response differences.

deviance per se (neutral oddballs versus standards), targetness, and negative emotional valence did not (Tables 1B and 2C). A more detailed examination of the peak neural response to stimulus novelty in the substantia nigra/VTA (MNI coordinates x, y, z—8, −20, −18) confirmed that novel oddballs elicited the strongest hemodynamic response in this region (Figure 1E). Negative emotional valence was associated with increased activity in a posterior region of the midbrain that is compatible with the location of the locus coeruleus (Figure 1C; Table 1B), while targetness (target oddballs versus neutral oddballs) was associated with a strong activation of the left and right lateral red nucleus (Figure 1D; Table 1C). Stimulus novelty and negative emotional valence were also associated with red nucleus activity, but, in comparison to targetness, this activity was confined to the right red nucleus. Only targetness elicited the expected activation of the left red nucleus, which is the one contralateral to the response hand.

In the rest of the scanned volume (Table S2), stimulus novelty was associated with a strong response in the left hippocampus and parahippocampal cortex (including the perirhinal cortex; Figure 2A), right caudate nucleus, and left pallidum. Negative emotional valence elicited

Table 1. fMRI Activations within the Midbrain for Experiment I

Anatomical Structure	Hemisphere	Cluster Size (Voxel)	Uncorrected p Value	Corrected p Value (SVC)	Peak Z Score	T Value	Peak Coordinates MNI (mm) x	y	z
(A) Novel Oddballs versus Neutral Oddballs									
Substantia nigra/VTA	R	3	0.001	0.039	3.09	3.85	8	−20	−18
Red nucleus	R	4	0.001		2.97	3.65	8	−22	−10
(B) Negative Emotional Oddballs versus Neutral Oddballs									
Red nucleus	R	6	0.001		3.19	4.04	6	−22	−6
Locus coeruleus	R	3	0.001		3.07	3.81	8	−34	−14
(C) Target Oddballs versus Neutral Oddballs									
Red nucleus	L/R	19	<0.001	0.002	3.83	5.36	−6	−18	−8

Contrasts include novel oddballs versus neutral oddballs (A), negative emotional oddballs versus neutral oddballs (B), and target oddballs versus neutral oddballs (C). Data are thresholded at $p < 0.005$ (uncorrected).

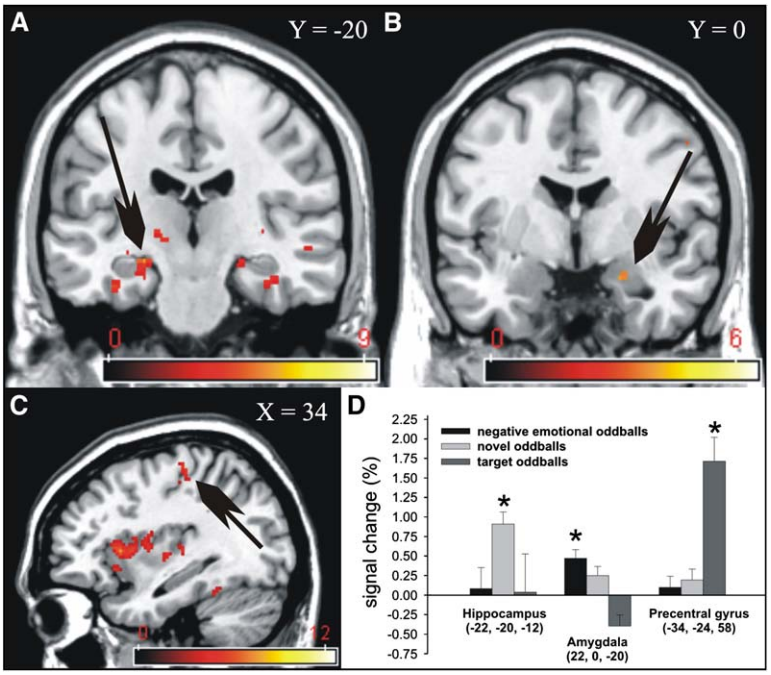

Figure 2. Activation Pattern for Experiment I Observed outside the Midbrain for Novel Oddballs, Negative Emotional Oddballs, and Target Oddballs in Comparison to Neutral Oddballs

(A) Novel oddballs; (B) negative emotional oddballs; (C) target oddballs.

Black arrows point to activations in the hippocampus (coordinates x, y, z = −22, −20, −12) (A), the amygdala (coordinates x, y, z = 22, 0, −20) (B), and the left precentral gyrus (coordinates x, y, z = −34, −24, 58) (C). All activations were superimposed on the T1-weighted MNI brain.

(D) Estimated percent signal change of the peak hemodynamic responses. Error bars denote standard error of the mean, and stars denote contrasts that elicited significant hemodynamic response differences.

activation in right amygdala (Figure 2B) and bilateral parahippocampal cortex, while targetness was associated with activation of the right cerebellum, bilateral thalamus, and left precentral gyrus (motor cortex; Figure 2C). Additional analyses of the peak activations in hippocampus (−22, −20, −12), amygdala (22, 0, −20), and precentral gyrus (−34, −24, 58) showed that the strongest hippocampal response was to stimulus novelty, and the strongest response of the left motor cortex was to targetness (Figure 2D). In the amygdala, activity for negative emotional valence was reliably higher than activity for targetness, but not stimulus novelty (Figure 2D). An additional analysis of variance (2 × 2 ANOVA) between regions (substantia nigra/VTA and amygdala) and conditions (novel oddballs versus neutral oddballs and negative emotional oddballs versus neutral oddballs) revealed a significant interaction between both variables ($F(1,13) = 4.74$; $p = 0.048$). A post hoc analysis showed a significant difference between the hemodynamic response elicited by negative emotional valence (negative emotional oddballs versus neutral oddballs) and novelty (novel oddballs versus neutral oddballs) in substantia nigra (one-sample t test; $p = 0.05$, one-tailed) but not in the amygdala (Figure S2). Furthermore, contextual deviance per se activated the anterior cingulate, parahippocampal cortex (Figure 3A), and a portion of the left hippocampus (Figure 3B) which was more posterior to that observed in response to stimulus novelty (Table S2).

Experiment II

fMRI data confirmed the results of Experiment I by showing activations in SN/VTA, hippocampus, parahippocampal cortex (including PPA and perirhinal cortex), for "novel stimuli" in comparison to neutral oddballs (Figures 4A–4D). Also consistent with Experiment I, target oddballs activated the red nucleus, precentral gyrus, cerebellum, thalamus, and basal ganglia. A list of activated structures (novel oddballs versus neutral oddballs and target oddballs versus neutral oddballs) is provided in Table S3. Further analyses of novelty associated peak voxels in SN/VTA, hippocampus, perirhinal cortex, and PPA are shown in Figures 4E–4H. Compared to neutral oddballs, the strongest activation in all four regions is to novel oddballs with a significant decrease for very familiar oddballs (i.e., pictures presented for the third time; $p < 0.05$, one-sample t test). Hemodynamic responses for familiar stimuli in SN/VTA (Figure 4E), hippocampus (Figure 4F), and PPA (Figure 4H; $p > 0.05$) were not affected by novelty context, in that there was no activity difference between familiar pictures presented in the same context as novel pictures and familiar pictures presented in the same context as very familiar pictures. Thus, there was no evidence that SN/VTA coded relative novelty in a given context, and instead, the findings show that absolute novelty is coded.

In a region bordering between posterior perirhinal cortex and anterior parahippocampal cortex, however, context did influence neural response to familiar pictures. In the context with novel pictures, familiar pictures

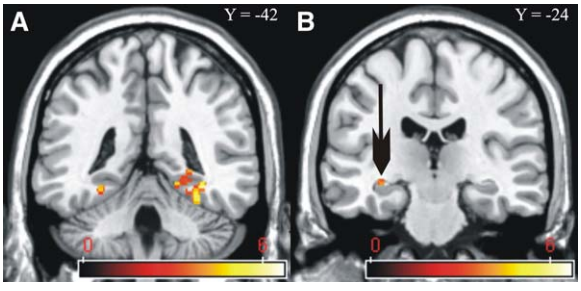

Figure 3. Activation Pattern Observed for Contextual Deviance (or Rareness, Neutral Oddballs versus Standards) in Experiment I

In Experiment I, contextual deviance activated the parahippocampal/fusiform region (A) and in the left hippocampus (B). Activation maps are superimposed on the T1-weighted MNI brain.

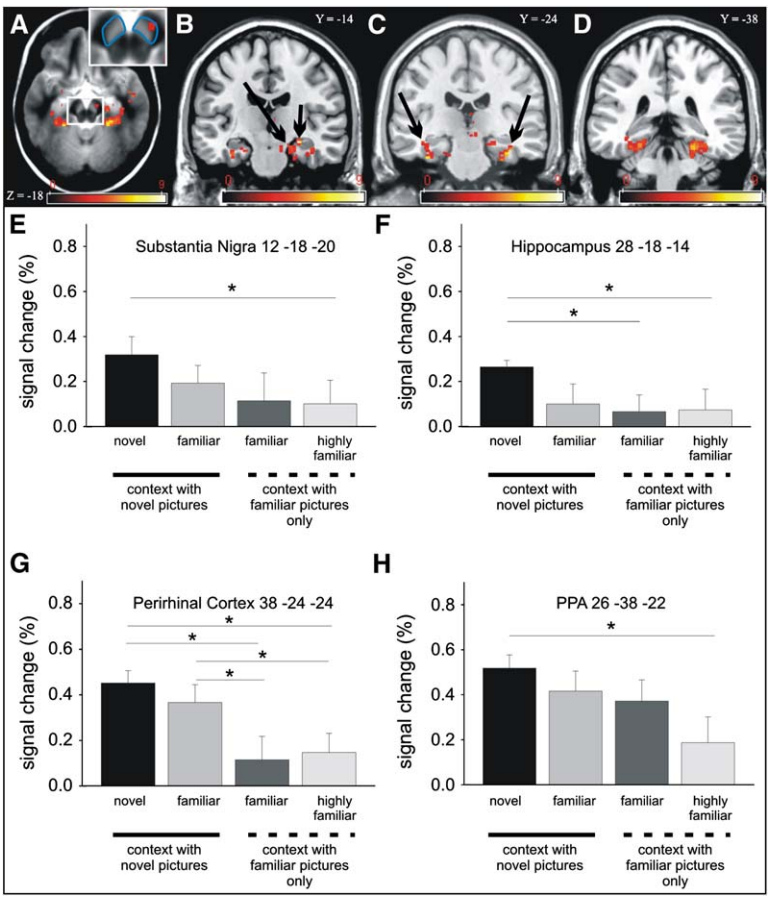

Figure 4. Novelty (Novel Oddballs versus Neutral Oddballs) Responses in Experiment II in the SN/VTA, the Hippocampus, Perirhinal/Parahippocampal Region, and a Region that Corresponds to the PPA

(A) SN/VTA; (B) hippocampus; (C) perirhinal/parahippocampal region; (D) region that corresponds to the PPA.

In (A), the midbrain activation is superimposed in the MT template, and the SN/VTA is circled in blue. The activations outside the midbrain (B, C, and D) are superimposed on the T1-weighted MNI brain.

(E–H) Estimated regional hemodynamic responses. The data are derived from the peak voxels of novelty (novel oddballs versus neutral oddballs) activations. Asterisks indicate significant differences between conditions (one-sample t test; $p < 0.05$), and error bars denote standard error of the mean.

activated the perirhinal cortex significantly stronger than in the context with very familiar pictures (Figure 4G). The direct comparison of "familiar oddballs in novel context versus familiar oddballs in familiar context" confirmed this by showing a hemodynamic response difference in right parahippocampal/perirhinal cortex but not in hippocampus, SN/VTA, or PPA (Figure S3). It should be noted that this pattern does not indicate relative coding of novelty in the posterior perirhinal/anterior parahippocampal cortex. Rather it shows the opposite pattern of enhanced familiarity responses in the context of novelty.

Experiments III and IV

Recognition memory as indicated by corrected "remember rate" ([hits remember − false-alarms remember]/all old pictures), corrected "know rate" ([hits know − false-alarms know]/all old pictures), and corrected hit rate ([corrected remember rate + corrected know rate]/all old pictures) for novel oddballs, familiar oddballs in context with novel oddballs ("novelty context"), familiar oddballs in context with very familiar oddballs ("familiarity context") and "very familiar oddballs" is shown in Table 2. To asses the effect of repetition on recognition memory, a 3 × 2 analysis of variance (ANOVA) with the factors repetition (corrected hit rate for novel oddballs, "familiar oddballs" [collapsed over both contexts], and very familiar oddballs) and retrieval quality (corrected remember rate and corrected know rate) was designed. In both experiments (III and IV), repetition had a significant main effect (Experiment III—$F(2,12) = 9.345$; $p = 0.004$; Experiment IV—$F(2,10) = 18.63$; $p < 0.001$), indicating that recognition performance increased with the number of repetitions. The effect of novelty context on recognition memory was assessed in a three-way ANOVA with the factors context (novelty, familiarity) and retrieval quality (corrected remember rate, corrected know rate) as within-subjects factors and delay (20min, 24 hr) as between-subjects factor. This yielded a main effect of context ($F(1,26) = 5.35$; $p = 0.029$) and retrieval quality ($F(1,26) = 8.87$; $p = 0.006$) while all other factors and their interactions were not significant (all p's > 0.1). Post hoc t tests of the corrected hit rate for familiar pictures from the novelty context compared to familiar pictures from the familiarity context confirmed an improvement in the short delay (two-tailed; $df = 13$; $p = 0.047$; $T = 2.2$) but not 1 day after encoding (two-tailed; $df = 13$; $p = 0.264$; $T = 1.17$). However, the corrected hit rates 1 day after encoding did not significantly differ from chance level (one-sample t test, two-tailed, $df = 13$; familiar pictures in novelty context—$p = 0.23$, $T = 1.25$; familiar pictures in familiarity context—$p = 0.44$, $T = 0.79$) which makes it difficult to interpret the absence of the context effect in this condition. Therefore, we reanalyzed data from Experiments III and IV using results only from those subjects whose corrected hit rate was at least 10% above their false-alarm rate. Such breaking down of recognition performance into good and bad performers is a common strategy in memory research (e.g., Shanks et al., 2003). In this

Table 2. Behavioral Results for Experiments III–V

	Novel Oddballs	Familiar Oddballs in Context with Novel Oddballs	Familiar Oddballs in Context with Very Familiar Oddballs	Very Familiar Oddballs
Experiment III (Recognition Test 20 min after Encoding)				
High-confidence hit rate	0.06 (0.07)	0.18 (0.07)	0.13 (0.07)	0.2 (0.08)
Corrected remember rate	0.07 (0.08)	0.13 (0.1)	0.12 (0.11)	0.18 (0.12)
Corrected familiarity rate	−0.01 (0.2)	0.04 (0.25)	0.01 (0.23)	0.02 (0.24)
Corrected hit rate	0.16 (0.4)	0.3 (0.04)	0.24 (0.04)	0.32 (0.04)
Corrected remember rate	0.08 (0.03)	0.14 (0.03)	0.13 (0.04)	0.19 (0.04)
Corrected familiarity rate	0.08 (0.03)	0.16 (0.03)	0.12 (0.03)	0.13 (0.02)
Experiment IV (Recognition Test 1 Day after Encoding)				
High-confidence hit rate	−0.08 (0.04)	0.07 (0.05)	0.04 (0.05)	0.1 (0.05)
Corrected remember rate	0.01 (0.1)	0.10 (0.13)	0.09 (0.13)	0.13 (0.12)
Corrected familiarity rate	−0.09 (0.11)	−0.03 (0.13)	−0.05 (0.13)	−0.04 (0.1)
Corrected hit rate	0.00 (0.05)	0.20 (0.04)	0.17 (0.04)	0.21 (0.03)
Corrected remember rate	0.05 (0.04)	0.16 (0.04)	0.15 (0.04)	0.2 (0.04)
Corrected familiarity rate	−0.05 (0.03)	0.05 (0.04)	0.02 (0.04)	0.01 (0.03)
Experiment V (Recognition Memory Tested 20 min after Encoding)				
High-confidence hit rate	0.17 (0.03)	0.32 (0.04)	0.26 (0.04)	0.54 (0.4)
Corrected remember rate	0.1 (0.02)	0.17 (0.03)	0.13 (0.02)	0.31 (0.05)
Corrected familiarity rate	0.07 (0.02)	0.15 (0.04)	0.13 (0.03)	0.22 (0.05)
Experiment V (Recognition Memory Tested 1Day after Encoding)				
High-confidence hit rate	0.14 (0.03)	0.27 (0.03)	0.25 (0.02)	0.43 (0.4)
Corrected remember rate	0.05 (0.02)	0.09 (0.03)	0.09 (0.03)	0.2 (0.04)
Corrected familiarity rate	0.09 (0.02)	0.17 (0.03)	0.16 (0.03)	0.23 (0.05)

Recognition memory performance is indicated by the mean corrected hit rate, corrected remember rate, and corrected know rate. For Experiments III and IV, upper panels show recognition memory performance for all subjects, lower panels for subjects whose corrected hit rate for familiar pictures was at least 10% above their false alarm (FA) rate (n = 11 in Experiment III, and n = 8 in Experiment IV). Numbers in brackets denote standard error of the mean.

analysis the context effects of novelty were even stronger ($F(1,17) = 10.09$; $p = 0.006$), while all other factors and interactions were not significant (all p's > 0.1). Post hoc t tests of corrected hit rate for familiar pictures from the novelty context compared to familiar pictures from the familiarity context confirmed a robust improvement in the short delay (one-sample t test, two-tailed; df = 10; $p = 0.013$; $T = 3.01$) but not 1 day after encoding (one-sample t test, two-tailed; df = 7; $p = 0.15$; $T = 1.62$). Importantly, in this analysis the subjects' corrected hit rate was significantly different from chance level in both the early and 24 hr recognition testing (one-sample t test, two-tailed, df = 7; familiar pictures in novelty context—$p = 0.002$, $T = 4.73$; familiar pictures in familiarity context—$p = 0.005$, $T = 4.1$). The corrected hit rates for both contexts and experiments are shown in Figure 5.

Experiment V

Recognition memory performance 20 min after encoding and 1 day after encoding is shown in Table 2. Similar to Experiments III and IV, a main effect of repetition on memory performance was observed in a 3 × 2 ANOVA with the factors repetition ("novel pictures," "familiar pictures," [collapsed over both contexts] and "very familiar pictures") and retrieval quality (corrected remember rate and corrected know rate), where recognition performance increased with the number of repetitions (recognition test after 20 min—$F(2,12) = 99.48$, $p < 0.001$; recognition test after 1 day—$F(2,12) = 47.12$, $p < 0.001$). The effect of novelty context on recognition memory was tested by a three-way ANOVA with the factors context (novelty, familiarity), retention interval (20 min, 24 hr), and retrieval quality (corrected remember rate and

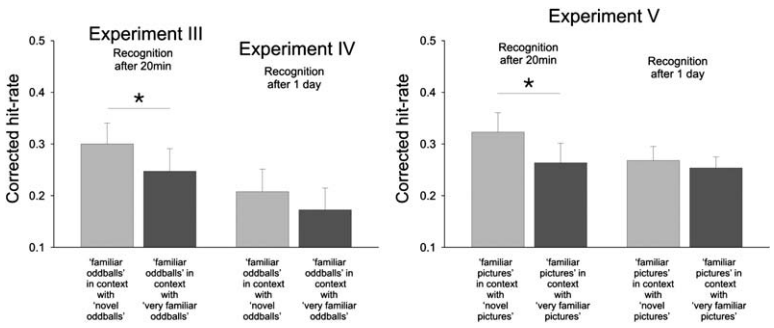

Figure 5. Effects of Novelty Context on Recognition Memory Performance

Bars denote corrected hit rate, asterisks indicate a significant difference between conditions (one-sample t test, two-tailed; $p < 0.05$), and error bars denote standard error of the mean. The results on the left panel are from Experiments III and IV (only subjects with a corrected hit rate above 10% were considered—n = 11 in Experiment III, and n = 8 in Experiment IV) and the right panel from Experiment V (n = 14).

corrected know rate). As in Experiments III and IV, it yielded a robust main effect of context ($F(1,13) = 6.61$; $p = 0.023$), while all other factors and interactions were not significant (all p's > 0.1). Post hoc t tests of corrected hit rate for familiar pictures from the novelty context compared to familiar pictures from the familiarity context confirmed a robust improvement in the short delay (two-tailed; $df = 13$; $p = 0.019$; $T = 2.67$) but not 1 day after encoding (two-tailed; $df = 13$; $p = 0.39$; $T = 0.89$). As in Experiments III and IV (analysis that included only those subjects with a corrected hit rate above 10% over chance), there was no significant main effect of retrieval quality ($F(1,13) = 0.56$; $p = 0.468$), which indicates the memory effect was not specific to either remembering or knowing. The corrected hit rate for both recognition memory test intervals is shown in Figure 5.

Discussion

Stimulus Novelty

The SN/VTA region preferred stimulus novelty over other forms of stimulus salience in both fMRI studies. The other forms of stimulus salience used in our experiments were associated with anatomically specific activations outside the SN/VTA. In both studies, rareness/deviance per se activated the hippocampus (Crottaz-Herbette et al., 2005; Halgren et al., 1980) and the sensorimotor integration that is necessary for the motor responses to target stimuli activated the red nucleus (contralateral to the response hand; Houk, 1991). In the first study, negative emotional stimuli activated the amygdala (McGaugh, 2004) and, compatible with recent animal studies, a midbrain region that potentially could overlap with the locus coeruleus, a noradrenergic midbrain nucleus which is functionally and anatomically connected with the amygdala (Bouret et al., 2003). Importantly, therefore, the lack of a SN/VTA response to rareness/deviance, targetness, and negative emotional arousal was not due to weak experimental effects of these forms of salience.

These data provide evidence in favor of a recent model suggesting a functional hippocampal-SN/VTA loop (Lisman and Grace, 2005) from a vantage point of stimulus novelty. They clarify that, in the absence of apparent reward, activation of this loop is driven by stimulus novelty rather than other forms of stimulus salience. Previous imaging studies have either compared novel oddballs to standard stimuli (Strange and Dolan, 2001; Yamaguchi et al., 2004) or familiar oddballs to standard stimuli (Crottaz-Herbette et al., 2005) but did not allow the direct comparison of rareness/deviance and stimulus novelty. The present findings go a step beyond these previous studies by showing that the hippocampus can detect rareness/deviance and stimulus novelty even if both are presented within the same experimental context. Despite this dual capability, a functional relationship to the SN/VTA is evident only on the basis of stimulus novelty because rareness/deviance does not lead to a notable activation of the SN/VTA. The recently reported improvement of hippocampus-dependent encoding of novel stimuli by reward anticipation in humans is thus likely to result from an additive effect of SN/VTA activation by stimulus novelty and by reward (Adcock et al., 2006; Wittmann et al., 2005). Nevertheless, our data do not rule out the possibility that stimulus novelty and other forms of salience (e.g., emotional valence) could also have an additive effect on SN/VTA activity (Ungless, 2004) and that emotional stimuli of positive valence could activate the SN/VTA in the absence of novelty. The data are also neutral with respect to the notion that the SN/VTA and the hippocampus jointly code changes in learned sequences of familiar stimuli, such as places in a learned environment (Lisman and Grace, 2005).

Data from the second fMRI experiment show that the mesolimbic response to stimulus novelty decreases as a function of the number of previous exposures to a stimulus. That is, there is a slight (nonsignificant) decrease with one previous exposure and a stronger (significant) decrease with two previous exposures (Figures 4E–4H). The amount of decrease appeared to be equivalent in the mesolimbic system, with no apparent difference between SN/VTA and the hippocampus (Figures 4E–4F). This pattern of a stepwise decrease as a function of exposures, rather than a strong decrease from novelty to a single previous exposure, seems important in understanding the mechanisms behind the recently demonstrated contribution of dopamine precursor substitution to learning by repetition in humans (Knecht et al., 2004). Our findings suggest that even though the mesolimbic system prefers stimulus novelty, it still seems capable of making a contribution to the learning of stimuli that are repeated. Compatible with this possibility, recognition memory and recollection was incrementally improved by number of repetitions in the three behavioral experiments (Table 2).

It has been suggested that a hippocampal novelty signal might be conveyed to the SN/VTA indirectly through the ventral striatum (nucleus accumbens) and the ventral pallidum (Lisman and Grace, 2005). Our data are partly compatible with such a model inasmuch as they show coactivation of SN/VTA, hippocampus, and ventral pallidum by stimulus novelty. Rareness/deviance per se was associated with activity of the dorsal striatum and did not elicit ventral striatal/ventral pallidal activation, compatible with previous observations that the dorsal striatum responds to such salient stimuli (Zink et al., 2003). Our data contribute to the functional understanding of striatal processing of novelty and salience by showing that an output target of the ventral striatum (the ventral pallidum) prefers novel stimulus information over other forms of salience and components of the dorsal striatum respond to both. It should be noted that novel stimuli could activate the SN/VTA at a much earlier level of visual stimulus processing, as suggested by the recently demonstrated very early visual input from the superior colliculus (Dommett et al., 2005). We did not observe evidence that this pathway might be implicated in our study since there was no activation of the superior colliculus by stimulus novelty and it seems unlikely that the colliculus is capable of discriminating novel and repeated pictures of faces or complex scenes.

Contextual Effects of Novelty

Data from the second fMRI experiment show that the decrease of the SN/VTA novelty response as a function of the number of previous exposures to a stimulus was a reflection of absolute rather than relative novelty (Figure 4E). Familiar stimuli elicited the same hemodynamic

response in the SN/VTA irrespective of whether they were relatively less novel (in the context with novel stimuli) or relatively more novel (in the context with very familiar stimuli) than the other stimuli in the context. In a recent animal study, SN/VTA activity coded the magnitude of anticipated reward in an absolute manner, whereas the magnitude of reward outcome was coded adaptively (Tobler et al., 2005). A reward outcome of medium magnitude elicited increased firing when it was the higher of two possible reward outcomes but decreased firing when it was the lower of two possible reward outcomes (Tobler et al., 2005). Absolute coding of novelty as observed in our study is therefore compatible with temporal difference models that see novelty as a motivating bonus to explore an environment in the search for reward rather than being a reward itself (Kakade and Dayan, 2002). This novelty bonus decreases gradually if repeated in the absence of reward (Kakade and Dayan, 2002), compatible with the gradual decrease of SN/VTA novelty responses as a function of repetition observed in the current study. Behavioral data from Experiments III, IV, and V also do not support the possibility of adaptive coding of novelty in the SN/VTA. With adaptive coding, recognition memory for familiar pictures should have been better in the context in which they were relatively more novel, but we observed the opposite pattern in Experiments III and V (Figure 5). Furthermore, the behavioral data from Experiment V make it unlikely that adaptive coding mechanisms did not come into play because novel and familiar stimuli were not behaviorally relevant. In Experiment V, subjects had to respond to each novel and familiar stimulus, but the pattern of memory improvement for familiar stimuli remained incompatible with adaptive coding. Although the presence of adaptive coding of novelty in the SN/VTA—and perhaps in the hippocampus—cannot be ruled out by the present findings, it seems unlikely that they operate under standard conditions of list learning. They could come into play under conditions where novelty is manipulated as the outcome of cued expectations. Such a scenario would be closer to the experimental conditions under which adaptive coding of reward magnitude has been observed (Tobler et al., 2005), albeit being less related to real-life learning situations.

In rodent studies, the dopaminergic neuromodulatory influence of novelty on synaptic plasticity in the hippocampus was found to extend several minutes beyond the exploration of novelty (Li et al., 2003; Straube et al., 2003), raising the possibility that hippocampus-dependent memory might be improved in the context of novelty. While the behavioral data from Experiments III and V indeed show an improvement of memory in the context of novelty, this was probably not entirely hippocampus-dependent. A hippocampus-dependent mechanism would have been more likely with a selective improvement of recollection (Brown and Aggleton, 2001; Duzel et al., 2001; Mishkin et al., 1998), while we observed an overall improvement of recognition memory. Also, hemodynamic response increases in the context of novel stimuli occurred in a region bordering between the posterior perirhinal cortex and the anterior portions of the parahippocampal cortex (Figure 4G), a region that is thought to be sufficient for recognition memory but not for recollection (Brown and Aggleton, 2001; Duzel et al., 2001; Mishkin et al., 1998). Animal studies suggest that the contextual enhancement of hippocampal plasticity by novelty could operate over longer time scales (around 30 min, e.g., Li et al. [2003]; Straube et al. [2003]) than the separation of experimental blocks with and without novel stimuli in Experiment II (6 min). The behavioral enhancement observed here therefore appears to highlight an additional, more immediate, though perhaps more short-term and nonhippocampal enhancement by novelty. The dopaminergic mechanisms involved in this enhancement remain to be elucidated but could be related to the recently demonstrated D2 receptor-mediated modulation of perirhinal learning in nonhuman primates (Liu et al., 2004). It is also evident from recent reward-related SN/VTA activation studies that less contextual and more stimulus-related SN/VTA activations do have a close relationship to very long-term hippocampus-dependent memory (Wittmann et al., 2005; Adcock et al., 2006).

Even patients with relatively selective hippocampal injury, whose extrahippocampal medial temporal lobes seem intact, do not have entirely normal recognition-memory performance (Duzel et al., 2001; Squire et al., 2004). Our findings now raise the possibility that impaired mesolimbic novelty processing as a consequence of the selective hippocampal injury could eliminate positive contextual effects of novelty in these patients, thereby having a net negative effect also on the perirhinal/parahippocampal components of recognition memory. However, our data are not fully conclusive as to whether such a mechanism would affect recognition memory across short or long retention intervals. Although the context effect was robust after the short but not the long delay, analyses of variance did not reveal a significant interaction between improvement and retention interval, indicating a weak effect also across longer delays.

To summarize, computational models favor the notion that novelty-related phasic dopaminergic midbrain responses signal an exploration bonus (Kakade and Dayan, 2002). Our data are fully compatible with such a computational notion of SN/VTA novelty responses in humans. Moreover, the data extend this notion by the possibility that increased motivation for exploration induced by novelty also affects the medial temporal processing and encoding of familiar stimuli presented in the same context. As a final note, fMRI is currently the only imaging technique that allows event-related studies of SN/VTA activity in humans. Although the relationship between hemodynamic SN/VTA and activity of dopaminergic neurons remains inferential, fMRI studies have been successful in translating questions raised in animal physiology to studies in humans. The integration of molecular genetic approaches into neuroimaging (Schott et al., 2006) and pharmacology might help to further elucidate the role of neuromodulatory transmitter systems in human novelty processing.

Experimental Procedures

Subjects

In each experiment fourteen healthy, right-handed adults (Experiment I—age range, 20–36; mean = 23.86; SD = 4.19; nine female and five male; Experiment II—age range, 21–30; mean = 24.0; SD = 2.77; seven female and seven male; Experiment III—age range, 22–31; mean = 24.92; SD = 3.06; ten female and four male;

Experiment IV—age range, 19–27; mean = 22.78; SD = 2.45; seven female and seven male; Experiment V—age range, 18–29; mean = 22.93; SD = 2.97; eight female and six male) were recruited for paid participation in the studies which were run under the protocol approved by the local ethics committee.

Experimental Design and Task

Experiment I

Subjects completed twelve blocks of the visual oddball paradigm. In each block there were 80 standards, 10 target oddballs, 10 neutral oddballs, 10 negative emotional oddballs, and 10 novel oddballs, yielding a total of 120 stimuli per oddball class in the entire experiment (Figure 1A). To avoid category-specific habituation and allow for generalization of our findings over different categories of visual stimuli, we presented pictures of male faces in one half of the session and pictures depicting outdoor scenes in the other half (counterbalanced across subjects). We chose these categories instead of abstract images to make stimulus exploration biologically relevant. The target stimulus was presented prior to the experimental session for 4.5 s, and subjects were required to make a simple button press to each of its subsequent appearances in the experiment using their right index finger. No motor responses were associated with any of the other stimulus classes. During the experiment, the pictures were presented for 500 ms followed by a white fixation cross on gray background (gray value = 127) using an interstimulus interval (ISI) of 2.7 s. ISI was jittered between −300 ms and +300 ms (uniformly distributed). The order of stimuli was optimized for efficiency (Hinrichs et al., 2000).

Experiment II

This experiment consisted of two phases that were performed while participants lay in the scanner. fMRI data acquisition was realized in phase II only. In contrast to Experiment I, only pictures of scenes but not faces were presented. In phase I, subjects were familiarized with 150 scene pictures: 100 pictures were presented once and 50 pictures were shown twice. Amidst those stimuli a target picture was shown 40 times. All pictures were randomly presented for 1 s and were separated by a white fixation cross on gray background for 3 s. Subjects were instructed to watch the pictures and respond as fast and as correct as possible to the target (which was also presented for 4 s before the beginning of phase I) with a simple button press. During fMRI data acquisition in phase II, ten blocks of a visual oddball paradigm were conducted. Each of those blocks contained 80 standard stimuli, 10 target oddballs, 10 neutral oddballs, and 10 familiar oddballs (pictures that were presented once in phase I). In one-half of the blocks, additionally 10 novel oddballs were shown. In the other half, the additional oddball category contained 10 very familiar oddballs (pictures that were presented twice in phase I). Taken together, in one-half of the blocks the familiar pictures were presented in the context with novel pictures, and in the other half the familiar pictures were presented in the context with very familiar pictures only. Prior to each block, a target was presented for 4.5 s. As in phase I, subjects were instructed to watch the pictures and respond as fast and as correct as possible to the target with a simple button press using their right index finger. Randomization, picture duration, ITI, and jittering followed the procedure of Experiment I.

Experiments III and IV

Both experiments followed the exact procedures as described in Experiment II except from two points. First, they were performed outside of the scanner at a personal computer. Second, recognition performance for the presented pictures was tested 20 min after (Experiment III) or one day after (Experiment IV) phase II (encoding). The subjects received a "remember/know" recognition task with 200 pictures from phase II (50 novel oddballs, 50 familiar oddballs in context with novel oddballs, 50 familiar oddballs in context with very familiar oddballs, and 50 very familiar oddballs) together with 100 new distracters that had not been presented either in phase I or in phase II. All pictures were randomly presented. During recognition testing, subjects first made an "old/new" decision to each individually presented picture using their right index or middle finger. Following a "new" decision, subjects were prompted to indicate whether they were confident ("certainly new") or unsure ("guess"), again using their right index and middle finger. After an "old" decision, subjects were prompted to indicate whether they were able to remember something specific about seeing the scene at study ("remember" response), just felt familiarity with the picture without any recollective experience ("know" response), or were merely guessing that the picture was an old one ("guess" response). The subject had 4 s to make each of both judgments and there was a break of 10 s after 75, 150, and 225 pictures.

Experiment V

In Experiment V, testing delay was manipulated as a within-subject variable and novel and familiar stimuli were made behaviorally relevant during encoding in that subjects made an indoor/outdoor judgment to each of them. Furthermore, familiar and novel stimuli were not oddballs, allowing us to determine whether contextual effects of novelty generalize to more standard learning situations. In phase I of the experiment, subjects were familiarized with 270 images of scenes, of which 180 were presented once and 90 six times. There were also 60 repetitions of three images, which later served as a "standard." Images appeared for 1 s and were separated by a white fixation cross on gray background for 3 s. The subjects were instructed to decide as fast and as accurately as possible whether an image depicted an indoor or outdoor scene (ratio 1:1). In phase II (5 minutes later), six pseudorandomized "context" blocks were performed. Half of the blocks constituted the novelty context. These blocks contained 30 novel pictures (pictures that were not presented during familiarization), 30 familiar pictures (presented once during familiarization), and ten presentations of each of the three standards (i.e., 30 presentations). The other half of the blocks constituted the familiarity context. These blocks contained 30 familiar pictures (presented once during familiarization), 30 very familiar pictures (presented six times during familiarization), and again ten presentations of each of the three standards. Within each block, pictures from the different conditions were pseudorandomly intermixed. Stimuli and order of blocks were counterbalanced across subjects. After encoding, subjects received an interpolated distracter task in which they wrote down as many capital cities of the world as possible within 1 min. This task aimed to ensure that short term or working memory effects on the immediate recognition memory performance were eliminated. Recognition memory was tested 20 min and 1 day after encoding using the same remember/know task as in Experiments III and IV. Here, half of the pictures from phase II (i.e., 45 novel pictures, 45 familiar pictures from the novelty context, 45 familiar pictures from the familiarity context, and 45 very familiar pictures) were intermixed together with 45 new pictures (distracters) that had not been presented in either phase I or II. The task (remember/know) and timing of picture judgment during the recognition test followed the procedure of Experiments III and IV.

The performance of target detection in Experiments I–IV was assessed by analyzing the hit rate (correct responses to the target) and false-alarm rate (responses to nontarget pictures). The indoor/outdoor discrimination in Experiment V was assessed using correct responses and the error rates (incorrect answers, double responses, and misses).

All stimuli were carefully prepared. The scalp hair and ears of faces were removed artificially and the outdoor scenes did not include faces. All pictures were gray-scaled and normalized to a mean gray value of 127 and a standard deviation of 75. The pictures were projected onto the center of a screen and the participants watched them through a mirror mounted on the head coil, subtending a visual angle of about 8°. The pictures were taken from different sources (neutral faces, The Psychological Image Collection at Stirling (PICS), http://pics.psych.stir.ac.uk/; the emotional face, Ekman and Friesen (1976); the emotional scene, the international affective picture system [IAPS; Lang et al., 2001]). The emotional scene picture depicted a negatively rated car accident without exhibiting any persons.

fMRI Methods

In both Experiments I and II, fMRI was performed on a 3-Tesla whole-body MRI system (Siemens Magnetom Trio, Erlangen, Germany) with echo planar imaging (EPI) using an eight channel head coil. The slices were acquired parallel to the brainstem in an odd-even interleaved direction. In the functional session, 24 T2*-weighted echo planar images per volume with blood oxygenation level-dependent (BOLD) contrast were obtained (matrix, 64 × 64, 24 slices per volume; FoV, 192 × 192 mm; spatial resolution, 3 × 3 × 3 mm; gap = 0.3mm; TE = 30 ms; TR = 1500 ms; flip angle = 75°). These partial

volumes covered the hippocampus, amygdala, brainstem (including diencephalon, mesencephalon, pons, and medulla oblongata), and parts of the prefrontal cortex and cerebellum (Figure S1). For each subject, functional data were acquired in six (Experiment I) or five (Experiment II, each scan comprising one block with and one without novel oddballs) scanning sessions containing 440 volumes per session. Six additional volumes per session were acquired at the beginning of each functional session and subsequently discarded from the analysis to allow for steady-state magnetization. Images of each subjects' entire brain were collected by T1-weighted inversion recovery prepared EPI (IR-EPI) sequences (matrix, 64 × 64, 60 slices; FoV, 192 × 192 mm; spatial resolution, 3 × 3 × 3 mm; gap = 0.3 mm; TE = 33 ms; TI = 1450 ms; TR = 15000 ms). To improve the identification of SN/VTA, magnetization transfer (MT) images of 33 subjects were acquired (matrix, 256 × 256, 48 slices; FoV, 250 × 250 mm; spatial resolution, 0.98 × 0.98 × 3 mm; TE = 20 ms; TR = 2600 ms; flip angle = 90°) to create an MT template (see below). This was derived by averaging the 33 individual MT images after they were spatially normalized to the standard MNI template supplied by SPM99. The individual MT images were acquired from nine subjects that participated in the first study (Experiment I) and 24 subjects that did not participate in any of the experiments (age range, 20–36; mean, 23.58; SD, 3.12; 14 female and 19 male). The averaged MT template derived from averaging the MT images from the nine subjects that participated in Experiment I and the averaged MT template derived from the 24 subjects that did not participate in either of the experiments revealed no differences.

The fMRI data were preprocessed and statistically analyzed by the general linear model approach (Friston et al., 1994) using SPM99 software package (Wellcome Department of Cognitive Neuroscience, University College, London, UK) and MATLAB 6.1 (The Mathwork Inc.). All functional images were corrected for odd/even slice intensity differences with reference to the middle slice acquired in time, corrected for motion artifacts by realignment to the first volume, and spatially normalized to a standard T1-weighted SPM template (Ashburner and Friston, 1999). The normalization was realized by warping the subjects anatomical IR-EPI to the SPM template and applying these parameters to the functional images. The images were resampled to 2 × 2 × 2 mm and smoothed with an isotropic 4 mm full-width half-maximum Gaussian kernel. The time-series fMRI data were highpass-filtered (cutoff 120 s) and globally scaled over voxels and scans within each session. A statistical model for each subject was computed by applying a canonical response function and its temporal derivatives (Friston et al., 1998). To capture residual movement-related artifacts, six covariates per session were included (the three rigid-body translations and three rotations determined from initial realignment). Regionally specific condition effects were tested by employing linear contrasts for each subject and different conditions. The resulting contrast images were submitted to a second level random-effects analysis. Here, one-sample t tests were used on images obtained for each subjects' volume set and different conditions. Given our a priori hypotheses, the results were thresholded at $p < 0.005$ (uncorrected) and $k = 3$ voxel. The significance of activated clusters within the SN/VTA region and the red nucleus was assessed using a small volume correction (SVC; Worsley et al., 1996). The corresponding small volumes are depicted on the MT template for the SN/VTA region in Figure 1B and for the red nucleus in Figure 1D. Unlike the SN/VTA region and the red nucleus, the locus coeruleus cannot be structurally identified on MRI images (its location can only be approximated in relation to other midbrain structures). To verify the anatomical localization of SN/VTA responses, the activation maps were superimposed on the MT template. While the SN/VTA region can be easily distinguished from surrounding structures on MT images as a bright stripe (Eckert et al., 2004) the adjacent red nucleus appears dark. The anatomical localization of significant activations outside of the midbrain was assessed with reference to the standard stereotaxic atlas by superimposition of the SPM maps on a standard brain template (Montreal Neurological Institute) provided by SPM99.

Supplemental Data

Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/51/3/369/DC1/.

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