HHS Public Access

Author manuscript

J Cogn Neurosci. Author manuscript; available in PMC 2018 February 22.

Published in final edited form as:

J Cogn Neurosci. 2017 May ; 29(5): 793–804. doi:10.1162/jocn_a_01098.

Mere exposure: Preference change for novel drinks reflected in human ventral tegmental area

Ian C. Ballard[1], **Kelly Hennigan**[2], and **Samuel M. McClure**[3]

[1]Stanford Neurosciences Graduate Training Program, Stanford University, Stanford, CA 94305

[2]Department of Psychology, Stanford University, Stanford, CA 94305

[3]Department of Psychology, Arizona State University, Tempe, AZ 85287

Abstract

Preferences for novel stimuli tend to develop slowly over many exposures. Psychological accounts of this effect suggest that it depends on changes in the brain's valuation system. Subjects consumed a novel fluid daily for 10 days and underwent functional magnetic resonance imaging on the first and last days. We hypothesized that changes in activation in areas associated with the dopamine system would accompany changes in preference. The change in activation in the ventral tegmental area (VTA) between sessions scaled with preference change. Further, a network comprising the sensory thalamus, posterior insula, and ventrolateral striatum showed differential connectivity with the VTA that correlated with individual changes in preference. Our results suggest that the VTA is centrally involved in both assigning value to sensory stimuli and influencing downstream regions in order to translate these value signals into subjective preference. These results have important implications for models of dopaminergic function and behavioral addiction.

Keywords

preference; dopamine; affect; fMRI

Introduction

Many of the sensory experiences people most value, from coffee to music, are initially considered to be neutral or even aversive. With repeated exposure, these stimuli can become increasingly pleasant. This tendency, called the mere exposure effect (Zajonc, 1968), is one of the most replicated phenomena in psychology (for reviews, see (Bornstein, 1989; Zajonc, 2001), and has been an influential idea in fields ranging from political science (Grush, McKeough, & Ahlering, 1978; Winkielman & Berridge, 2003) to marketing (Bargh, 2002; Janiszewski, 1993; Ray & Sawyer, 1971; Rethans, Swasy, & Marks, 1986). Despite its prevalence and long history as a focus of research, the psychological basis of the mere exposure effect remains debated and little is known about its underlying neural basis.

Corresponding Author: Ian C. Ballard, iballard@stanford.edu, (508) 641-2493, Jordan Hall, Building 420, 450 Serra Mall, Stanford, CA 94305.

Repeated exposures are thought to produce changes in stimulus-induced affect or the subjective value assigned to stimuli through a process of conditioning (Zajonc, 2001). Exposure, in the absence of harm, may condition a positive response based on inferred safety. This learning is believed to occur independently from concomitant changes in perceptual fluency, habituation, and other aspects of cognition that change with experience and familiarity. However, diverse empirical findings attributed to the mere exposure effect may in fact be qualitatively distinct. For example, experimental paradigms that rely on rapid presentation of visual symbols (e.g. Chinese ideographs; Zajonc, 1968) may cause changes in preference that depend on short-term changes in brain function such as habituation (Bornstein, 1989). Conversely, changes that develop more slowly through time (e.g. liking of coffee) may depend on slower brain adaptations related to conditioning.

Conditioning and habituation are known to depend on different neurophysiological processes. Habituation is associated with rapid changes in synaptic efficacy that develop over seconds to minutes and that generally do not persist long beyond the original experience (Kandel, 2009). By contrast, conditioning depends on long-term changes in synaptic physiology (size of neurotransmitter vesicle pool, density of postsynaptic receptors, size of dendritic spines, etc.) that develop over hours and persist for weeks or longer (Beste & Dinse, 2013). Most investigations of the mere exposure effect use within-session repeated exposures (but see Birch, McPhee, Shoba, Pirok, & Steinberg, 1987; Stein, Nagai, Nakagawa, & Beauchamp, 2003), which presumably target rapid neural learning mechanisms. In order to separately examine within-session and long-term neurophysiological changes, we employed a protracted experimental design with repeated exposures to novel fluids occurring over ten days.

Our hypothesis was that changes in preference due to repeated exposure should be related to activity in brain networks that encode subjective value. In the brain, valuation is closely associated with the midbrain dopamine system and associated cortical and sub-cortical structures (specifically, the VTA, ventral striatum, and ventromedial prefrontal cortex; (Clithero & Rangel, 2014; Schultz, 1997). We used functional magnetic resonance imaging (fMRI) to measure brain activity before and after an extended period of exposure to novel fluids. Over shorter time periods, habituation is likely to produce decreasing neural responses with subsequent stimulus presentations. We expected that longer-term changes would produce increased responses that scale with changing preferences.

Methods

Subjects and Behavioral Task

Thirty-two subjects were recruited and provided written consent for their participation. One subject dropped out between scan sessions, one did not complete the ratings, and three were excluded due to equipment malfunction, leaving 27 in the reported data (age: mean = 23.3, std= 8.6; 14 female). The task spanned 10 days in order to assess preferences over a time span that is relevant to behavioral change. Scanning occurred on the first and last days of the 10-day experiment. On the first scanning day, subjects tasted and provided ratings for two novel juices. Subjects were asked to rate how much they liked the juice on a Likert scale from −6 to 6 with anchors labeled “Not at all” and “Very much.” They additionally provided

ratings of how familiar the drinks tasted and how healthy they thought the drinks were. The juices were Evolution brand vegetable juices (carrot based: Essential Vegetable, and celery based: Essential Greens), which were chosen based on presumed (and confirmed) novelty. Our funding source, Givaudan, has no connection known to the authors to Evolution brand juices.

After providing ratings, subjects were scanned according to the procedure described below. At the end of the scanning session, subjects were given a supply of one of the juices (the "repeated" juice) to take home. They were instructed to drink ½ a bottle (225 ml) per day and to provide online ratings of how much they wanted the drink (pre-consumption) and how much they like the drink (post-consumption) on the same 13-point scale used in the laboratory. Subjects were given no cover story or motivation to drink the juice (e.g., health), we simply instructed them that drinking the juices and reporting online was a required component of the study. On day 10 of the study, subjects returned for a second scanning session with identical procedures as on day 1. The identity of the repeated and non-repeated (control) juices was counterbalanced across subjects.

The scanning task consisted of 2 runs of exposure to both the repeated and non-repeated juices. Each trial consisted of a red or blue image of a droplet that predicted delivery of a particular juice with 100% accuracy. This cue was used to reduce head motion that may result from unexpected juice delivery. The association of color to juice was counterbalanced across subjects and was kept consistent on both scan days for each subject. Two seconds following the visual cue, subjects were delivered a 1 mL bolus of juice. Individual 1mL boluses of juice were delivered to participants via syringe pumps (Harvard Apparatus, Holliston, MA) and 10 m long food-grade plastic tubes. A separate syringe pump and tube was used for each drink. Each bolus of juice was delivered at a flow rate of 1 mL/sec so that juice was delivered slowly (to ease swallowing while avoiding head movement) over 1 second. This design mitigates potential motion or respiration effects of juice delivery. It is possible that these effects do nonetheless occur, but any artifacts related to juice delivery should not affect our main analyses focused on differences between the control and repeated juices. Juice delivery was controlled from the computer running the experiment script. Each juice was delivered 12 times per run in random order. The inter-trial interval was taken from a Poisson distribution with a mean of 6 seconds, a minimum of 4 seconds, and a maximum of 10 seconds.

fMRI Analysis

Imaging was performed on a 3.0 Tesla GE Discovery MR750 scanner. High-resolution T1-weighted scans were acquired using an MP-RAGE sequence. Functional run details were as follows: echo-planar imaging, interleaved acquisition, gradient recalled echo; TR = 2000 ms; TE = 40 ms; flip angle = 90°; 64 × 64 matrix; 26 4 mm axial slices; yielding voxels with dimension 3.3 × 3.3 × 4.0 mm. Although it is possible and advisable to optimize these parameters for imaging of the VTA (D'Ardenne, McClure, Nystrom, & Cohen, 2008), we were interested in investigating mere exposure effects throughout the brain's valuation system and therefore optimized our experimental protocol for imaging of the whole brain.

Our imaging procedures should therefore introduce noise to BOLD responses measured in the midbrain, but should not bias results from these regions (W.-T. Zhang et al., 2006).

Data were analyzed using AFNI (http://afni.nimh.nih.gov/). Functional data underwent slice-time correction as well as motion correction to the third functional scan using six-parameter rigid-body transformation. Following standard AFNI procedures, images were not bandpass filtered, but first, second, and third-order polynomials were added to the GLM to account for low-frequency signal changes of a linear, quadratic, or cubic form. These nuisance regressors were constructed separately for each run. The motion-corrected images were coregistered to each individual's high-resolution structural MRI using a twelve-parameter affine transformation and were subsequently resampled to 2.0 × 2.0 × 2.0 mm. T1-weighted images were normalized to Talairach space using a twelve-parameter affine transformation and this transformation was applied to the coregistered functional images. Normalized functional images were then smoothed using a 4 mm isotropic Gaussian kernel and each voxel was scaled to percent signal change across the task. Scans for which estimated head motion was greater than 1 mm or where more than 10% of brain voxels were considered outliers, using AFNI's automatic outlier detection, were censored from analyses.

Statistical analyses were performed on individual subject's data using a general linear model (GLM). Nuisance regressors included six head motion regressors, the mean signal in a mask of the lateral ventricles of the preprocessed functional data to estimate instrument, nonlinear motion, and physiological noise, and third order polynomial regressors for each run to account for low frequency baseline shifts. Regressors of interest included repeated juice trials and control juice trials, separately for each scan session. Each regressor of interest concatenated events from both runs within a scan session and was convolved with a canonical hemodynamic response function. Additionally, for each regressor of interest, a parametric regressor was constructed that modeled linear changes in response amplitude as a function of trial number within each run to model habituation.

The cue, juice delivery, and swallowing were modeled together as a single event with a 6 second boxcar function. We took this approach for both practical and theoretical reasons. Practically, it was necessary that subjects reliably be able to predict fluid delivery, because the delivery of fluid while lying in the scanner can be startling when unexpected, potentially causing movement and psychological confounds. Theoretically, because both prediction and delivery of juice has been shown to activate reward structures in a manner that scales with preference (Kringelbach, O'Doherty, Rolls, & Andrews, 2003; McClure et al., 2004; O'Doherty, Deichmann, Critchley, & Dolan, 2002), we reasoned that their additive effects should confer increased sensitivity to our preference analyses. The 2 s inter-stimulus interval that we used is expected to produce hemodynamic responses that scale linearly with the sum of anticipated and consummatory reward responses. Although this design does not allow us to discriminate neural activity related to processing of the cue, sensory and motor processes related to juice ingestion, and psychological processes during juice delivery, our analysis approach enabled us to detect activation that specifically scaled with changes in preference.

Contrast images were computed for each subject and were entered into a between subject random effects analysis. For the habituation analysis, the within-session parametric

regression coefficients estimating linear changes in response amplitude (hypothesized to be declining) for each drink and session were averaged together. For preference change analyses, we included behavioral preference change as a covariate at the between-subjects level and examined activations that varied with this measure. This ensures that we detect neural activity whose change in contrast values between days correlates with the degree of observed preference change.

We constructed an additional post-hoc model that was designed to test whether there were nonlinear habituation effects in addition to linear habituation effects. In addition, we were interested in whether we could observe activations that correspond to prediction error. Because our task structure is deterministic, a prediction error regressor for each juice will be exponentially declining for all possible learning rates except for the boundary cases of 0 and 1. Although the slope of this exponential decline could vary across subjects, in practice it makes little difference for modeling of fMRI data (Wilson & Niv, 2015). Therefore, we added to the above model a prediction error regressor taken from a simple value learning model with a learning rate of .3. Importantly, since our task structure was deterministic, it is impossible to discriminate between prediction error responses and exponential habituation responses with this regressor.

We estimated a cluster threshold using Monte Caro simulation through AFNI's AlphaSim. Of note, we used a recent version of AlphaSim (February 11th, 2016) in which a recently discovered bug had been fixed. First, the smoothness of the residual error was estimated for each subject and averaged together to obtain a single estimate of the smoothness of the noise (3.26 × 3.06 × 2.81 mm). We ran a Monte Carlo simulation in a space defined by the group brain mask to obtain a $p<.05$ cluster corrected threshold of 25 voxel extent (2 × 2 × 2 mm) with an individual one-sided voxel significance threshold of $p<.01$. Note that one-sided thresholding for the simulation results in more stringent cluster thresholds, and we used two-sided thresholding for the reported data. This threshold was used for all reported results.

Psycho-physiological interaction (PPI) analyses were implemented using AFNI. We examined the group VTA activation from the analysis reported above, and manually removed voxels determined to be outside of the VTA (see Ballard et al., 2011; Murty et al., 2014) for anatomical boundaries and detail). We extracted time series from this ROI and conducted a standard PPI analysis. The psychological regressor was the juice delivery regressor. All regressors in the models described above (linear decline, nuisance regressors, etc.) were included in the PPI models. We conducted the same correlation analyses as for the preference change analysis described above: We first computed the difference between day 10 and day 1 for the repeated relative to control PPI regressors, and then included behavioral preference change as a between-subject covariate in the group model of this interaction effect.

Of note, our analyses examine changes due to exposures over the intervening days, while averaging over any potential within-session mere exposure effects. When designing the experiment, we chose not to focus on classic within-session mere exposure effects for two reasons. First, we wanted to isolate changes due to preference from potentially antagonistic

changes due to habituation. Second, we were interested in neural changes that persisted over time spans consistent with long-term physiological changes in the relevant circuits.

Results

Behavioral Results

We employed a temporally protracted exposure paradigm with two brain-scanning sessions separated by nine days (Figure 1a). In the first session, subjects provided initial preference ratings for two novel vegetable-based juices and then were given boluses of the juices while undergoing fMRI. On each of the following eight days subjects tasted and provided preference ratings for one of the juices (hereafter: repeated juice). Subjects were not further exposed to the other juice (hereafter: control juice). In the second scanning session, subjects again tasted both liquids while undergoing fMRI and provided final preference ratings.

We quantified the mere exposure effect as the difference in liking ratings for the repeated relative to the control drink across the duration of the experiment. Numerically, this was calculated as

$$\Delta V^i = (V^i_{r,10} - V^i_{r,1}) - (V^i_{c,10} - V^i_{c,1}), \quad \text{(Eq. 1)}$$

where V^i signifies the liking ratings for subject *i*, *r* and *c* the repeated and control drinks respectively, and 1 and 10 the day of the measurement. This measure controls for differences in state, such as thirst and mood, between the scanning sessions insofar as they affect ratings within experimental sessions. Behaviorally, we observed a robust mere exposure effect across the group (Figure 1b, mean ΔV^i = 2.07, t(27) = 3.12, p=.002). The code that generated the behavioral figures and the raw data are available at http://github.com/iancballard/preference-analysis. On average, the drinks were initially rated as slightly aversive to neutral and changed roughly linearly across experiment days so that final ratings were positive on average (Figure 1c, mean slope from daily ratings = .28, t(27)=4.49, p=1.30 × 10^{-4}). We investigated whether there were quadratic trends in the liking ratings by entering both linear and quadratic effects into a multiple linear regression model, and found no evidence of quadratic effects (p=.13). We suspect that the linear trend was due to the relative brevity of the manipulation and that further exposures would have resulted in asymptotic preference ratings.

Despite the robust mere exposure effect evident on average among our participants, there was significant variability in both the size and direction of the mere exposure effect. Roughly half of the subjects (11 of 27) showed either no preference change or reduced preference for the repeated juice. This variability is commonly observed in mere exposure paradigms, and may be especially pronounced for gustatory stimuli (Kahneman & Snell, 1992). For our purpose, this variability was beneficial. It allowed us to study preference-related changes in brain responses while controlling for nuisance effects that derive from task participation, such as familiarity.

In addition, we examined the participant ratings of health and familiarity in the same manner as the liking ratings (Eq. 1). Ratings of familiarity changed for the repeated relative to control drink with exposures (mean ΔF^i = .81, t(27) = 2.66, p=.01). In addition, there was a trend for a change in health ratings (mean ΔH^i = .44, t(27) = 1.94, p=.06) for the repeated relative to the control juice. Interestingly, neither the change in familiarity ratings nor the change in health ratings were correlated with preference change across subjects ($\rho(\Delta V, \Delta F) = -.01$, p=.95; $\rho(\Delta V, \Delta H) = .31$, p=.11). In addition, health and familiarity ratings were not correlated ($\rho(\Delta F, \Delta H) = .02$, p=.90). These results indicate that exposure independently induces changes in the perception of multiple different attributes of the fluids.

Neuroimaging Results

For fMRI analyses, we first searched for brain regions that responded to juice delivery, regardless of juice identity and scan session. This analysis was performed on a voxel-wise basis using the contrast

$$B^i_{r,10}+B^i_{r,1}+B^i_{c,10}+B^i_{c,1}>0, \quad \text{(Eq. 2)}$$

where B^i indicates the BOLD response amplitude for subject *i*. This contrast showed bilateral activation to juice in a broad network involved in sensation and affect, including the occipital lobe (recall, juice delivery was paired with a visual cue), striatum, amygdala, insula, cerebellum, anterior cingulate cortex, primary motor cortex, prefrontal cortex, thalamus, midbrain and pons (Figure 2). These results indicate robust neural responses in regions processing the presentation of the juice cue, the sensory and affective experience of juice consumption, and/or the motor control of swallowing.

Habituation

Stimulus-evoked neural responses are known to decline with repeated stimulus presentation, a phenomenon referred to as habituation or repetition suppression (Grill-Spector, Henson, & Martin, 2006). We therefore expected that, within scan sessions, brain responses to juice anticipation and delivery would decline with time. Indeed, this expectation is what motivated us to employ a multi-day exposure procedure. We separately estimated linear changes in trial-to-trial event-related responses for each drink in both scanning sessions. Testing for linear decline in brain response with trial number identified habituation effects bilaterally in the dorsal caudate, ventrolateral putamen, insula, prefrontal cortex, inferior parietal lobule, cingulate gyrus, as well as the left thalamus (Figure 3a, Table 1). Collectively, these brain regions are implicated in gustatory processing and value representation. These results indicate the importance of our protracted study design, which allows us to separate within-session habituation from potentially slower changes in responses related to value and preference. Further, we observed no differences for the opposite contrast testing for within-session linear increases in activation anywhere within gray matter.

In a post-hoc analysis, we additionally tested for brain regions that showed a nonlinear habituation pattern. We constructed models with both a linear declining term and an exponentially declining term. This exponential decline should capture voxels that show a

nonlinear habituation effect, as well as voxels that show prediction error responses that track the cue to juice pairing. We did not observe any activation in the midbrain for the exponentially declining prediction error regressor. However, we observed non-overlapping activations in the striatum for both the linear and exponential terms, suggesting that different rates of habituation occur in different sub regions of the striatum and that there may be activation correlated with prediction error to the juice cues (Figure 3 b,c).

Neural Correlates of Preference Change

We next examined the neural changes associated with exposure to the repeated juice. We contrasted the change in BOLD responses between the two scanning sessions for the repeated drink with the change for the control drink:

$$\Delta B^i = (B^i_{r,10} - B^i_{r,1}) - (B^i_{c,10} - B^i_{c,1}). \quad \text{(Eq. 3)}$$

We found no main effect of exposure in our regions of interest (Figure 4, Table 2). This null result was surprising, as we expected a main interaction effect (ΔB) in value regions given that we observed a group mere exposure effect. However, given that size and direction of the mere exposure effect was highly variable across participants, we next sought to see whether there was a relationship between the size of the neural exposure effect and the size of the behavioral exposure effect. We therefore tested for brain areas where changes in neural activation correlated with our behavioral measure of preference change across subjects (Eq. 1). This approach enabled us to investigate the mere exposure effect while eliminating concerns about other potential contributors to between-session changes in brain activity. We correlated the contrast in brain responses (i.e. ΔB^i) with the contrast of reported subjective value (i.e. ΔV^i). This correlation analysis identified a clusters in the VTA (Figure 5a), caudate (Figure 5b) and insula (Figure 5c), indicating that the difference in activation in the VTA to repeated juice between sessions, relative to the difference in response to the control juice, co-varies with observed preference change (Table 2). A number of patterns in the neural data can yield a positive interaction, and we sought to show that the interaction resulted from relatively increased response to the repeated juice during the second scanning session. This is a challenge because our main result is a correlation between the interaction and preference. For illustrative purposes, we divided the subjects into 3 approximately equally size groups by their preference change (ΔV^i) and plotted the parameter estimates for each juice and each session separately for these groups. This analysis shows relatively increased response to the repeated juice on the second scanning session for subjects with high preference change (Figure 5e). In order to determine whether activation in the VTA specifically tracked changes in preference, rather than other attributes of the juice, we repeated this analysis with both the health and the familiarity ratings and found no correlation with voxels in the VTA, even at liberal thresholds ($p<.01$, uncorrected).

Network Changes Underlying Preference Change

The VTA contains the cell bodies for dopamine neurons that communicate reward information to value-related regions in the forebrain. To the extent that the VTA signals changing preferences across time, we expected that functional connectivity with efferent

forebrain structures should also change. We therefore tested whether VTA connectivity patterns also predict individual preference change. A psycho-physiological interaction analysis was conducted to detect voxels in which changes in correlation with the VTA during juice anticipation and consumption between day 1 and day 10 correlated with individual preference change. We found that only 3 regions showed this pattern: the sensory thalamus, posterior insula, and ventrolateral striatum (Figure 6, Table 2). Using the Talairach-Tournoux atlas, we determined that 80% of the thalamic voxels identified in this analysis were within the ventral posterior (VP) nucleus of the thalamus. The VP nucleus of the thalamus and insula are implicated in gustation, whereas neurons in the ventrolateral striatum have been shown to respond to juice reward in primates (Klein & Platt, 2013). We conclude that preference changes associated with mere exposure to novel gustatory stimuli originate in adapting VTA responses that are communicated to efferent target structures in the basal ganglia, thalamus, and insula. This network supports both behavioral activation and gustatory processing, and the changes we observe with exposure in this system may underlie the subjective change in preference.

Discussion

We found that activation in the VTA tracks individual preference change. No imaging study of the mere exposure effect has reported either neural activity that scales with the preference change as a function of exposure, or exposure-related neural activity in regions known to be involved in the representation of value (Elliott & Dolan, 1998; Green, Bærentsen, Stødkilde-Jørgensen, Roepstorff, & Vuust, 2012; Zebrowitz & Zhang, 2012). Further, although the VTA has been widely implicated in reward learning and the representation of value (Schultz, 1997; Tobler, 2005), as well as the implementation of behavioral preference (Tsai et al., 2009; Witten et al., 2011), this is the first demonstration that human VTA activity tracks changes in preference for non-drug rewards. Importantly, in our task the stimuli were held constant and only the subjects' internal preferences for them changed. Both VTA activation and VTA connectivity with regions involved in taste perception and valuation correlated with this internal change.

Our results arise from a correlation in the variability in individual preference change with individual changes in VTA activation. In spite of observing a mere exposure effect on average across subjects, we did not observe an expected main effect of change in VTA activation for the repeated relative to the control juice. We believe this null result may partially arise from the large variability in individual preference change in our sample, and predict that future work with larger sample sizes will show this effect.

In addition to the finding that VTA activation tracks preference change, we found that the strength of VTA functional connectivity with the sensory (VP) thalamus, posterior insula, and ventrolateral striatum predicted individual changes in preference. The thalamus receives direct input from VTA neurons (Del-Fava, Hasue, Ferreira, & Shammah-Lagnado, 2007). In addition, the VP nucleus of the thalamus receives taste information and projects to somatosensory cortex, including the insula. Although primary taste cortex in nonhuman primates is located in the anterior insula and postcentral gyrus, several studies have shown posterior insula activations related to taste intensity and affective responses to taste

(Nitschke et al., 2006; Small et al., 2003; Zald, Lee, Fluegel, & Pardo, 1998). Finally, the ventrolateral striatum receives input from ventral tier neurons of the VTA (Haber, Fudge, & McFarland, 2000), and has been shown to be involved in anticipation and receipt of primary rewards in humans and in nonhuman primates (Cromwell & Schultz, 2003; McClure, Berns, & Montague, 2003a). These results indicate that preference change with repeated exposure induces persistent physiological changes in the VTA that in turn influence a broad network involved in the perception and valuation of taste. An important question for future research will be to determine precisely how these neural signatures of mere exposure relate to changes in sensory processing or postoral and carbohydrate cues (de Araujo, Lin, Veldhuizen, & Small, 2013).

We assessed changes in preference over the timescale of several days, which is in contrast to a number of other studies that have examined the effect of brief or even subliminal exposures on affective judgments (Bornstein, 1989). Based on the subliminal mere exposure effect, it has been proposed that the effect can be explained entirely as a form of implicit memory, rather than genuine changes in affective judgments (Peretz, Gaudreau, & Bonnel, 1998; Seamon et al., 1997). For instance, according to the nonspecific activation model, subliminal exposure to stimuli activates context-free representations, which in turn make these representations more accessible (Harmon-Jones & Allen, 2001; Jacoby, 1983; Mandler, Nakamura, & Van Zandt, 1987). According to perceptual fluency models (Reber, Winkielman, & Schwarz, 1998) accessibility of representations (via exposure or otherwise) leads to enhanced judgments along any relevant dimension of the activated stimuli – in other words, the influence on affective judgments following subliminal exposure is merely a manifestation of priming. Indeed, some studies have treated the mere exposure effect as a proxy for implicit memory (Elliott & Dolan, 1998). Because we were primarily interested in neural changes that were both dissociable from habituation and persistent over long time scales, our experimental paradigm was not designed to discriminate between these theories. However, both the nonspecific activation model and the perceptual fluency model predict that changes in reported familiarity with the juices should relate to both preference change and neural correlates of preference change. We found no evidence for either relationship. Rather, our results provide evidence that preference change associated with repeated exposure can involve long-term changes within a central component of the brain's valuation network.

We interpret our findings as evidence that the VTA is centrally involved in both assigning value to sensory stimuli and influencing downstream regions in order to translate these value signals into a subjective preference. In contrast to recent findings suggesting that valuation depends on orbital and ventral regions of the primate prefrontal cortex (Padoa-Schioppa, 2011; Rangel, Camerer, & Montague, 2008), we found no evidence of involvement of these regions in preference change during mere exposure. Although negative findings must be interpreted with caution, particularly in regions such as ventral prefrontal cortex that have strong susceptibility artifacts, our results support a model in which affective reactions to stimuli develop as a result of synaptic modification in subcortical circuits under the modulatory influence of dopamine. These affective responses may serve as inputs to prefrontal regions during more complex cognitive tasks in which value becomes task-

relevant, such as those involving value-comparison (Grueschow, Polania, Hare, & Ruff, 2015).

In addition, the finding that VTA correlates with preference may seem surprising given the focus on the role of dopamine neurons in signaling prediction error and novelty for the purpose of learning. Importantly, little learning was possible in our design because participants were instructed that juices were 100% predicted by the cues. We see no evidence for midbrain prediction error responses related to the stochasticity in trial order. However, midbrain dopamine neurons display considerable heterogeneity in firing patterns beyond prediction errors (Schultz, 2013). In particular, dopamine neurons appear to track stimulus values in the absence of learning, and adapt these values based on uncertainty (de Lafuente & Romo, 2011), temporal delay (Roesch, Calu, & Schoenbaum, 2007), and reward size (Tobler, 2005). Finally, mesolimbic dopamine is important for adjusting behavioral activation to rewarding stimuli (Berridge & Robinson, 1998; McClure, Daw, & Read Montague, 2003b). Based on our connectivity results, we propose that changes in connectivity between perceptual and behavioral activation systems underlie the gradual formation of preferences.

These findings present a challenge for theories of dopaminergic involvement in reinforcement learning (Nakahara, Itoh, Kawagoe, Takikawa, & Hikosaka, 2004; Schultz, 1997). Reinforcement learning models of dopamine neurons function are based on the Markov assumption that reward values are fixed and do not depend on the history of behavior (Sutton & Barto, 1998). The finding that stimuli can transition from being negatively to positively valued over a relatively small number of exposures raises the question of how an organism can incrementally learn about reward contingencies when the reward values of the stimuli change. Although fMRI cannot be used to measure the activity of dopamine neurons, our results, in combination with others (Redish, 2004), point to the need for a more nuanced model of VTA dopamine neuron responsivity that incorporates history-dependent changes in reward value.

There has been growing support for the idea that behavioral addictions, such as gambling, shopping, viewing pornography, and exercise, arise in part due to changes in the mesolimbic dopamine system similar to those observed in drug addiction (Grant, Potenza, Weinstein, & Gorelick, 2010a; 2010b; Potenza, 2008; Volkow, Wang, Fowler, Tomasi, & Baler, 2012). However, this idea is controversial because addictive drugs, unlike other reinforcers, perturb synaptic function to increase dopamine release or efficacy. Our findings that repetition alone is sufficient to enhance activity in the VTA lends credence to the idea that repetition of reinforcing behaviors causes changes in dopaminergic function akin to those observed in drug addiction. Elucidating which stimulus properties preferentially alter affective systems underlying preference may be an important step towards a mechanistic understanding of the development of behavioral addictions.

Acknowledgments

This work was supported by a grant from the Givaudan Corporation (SMM).

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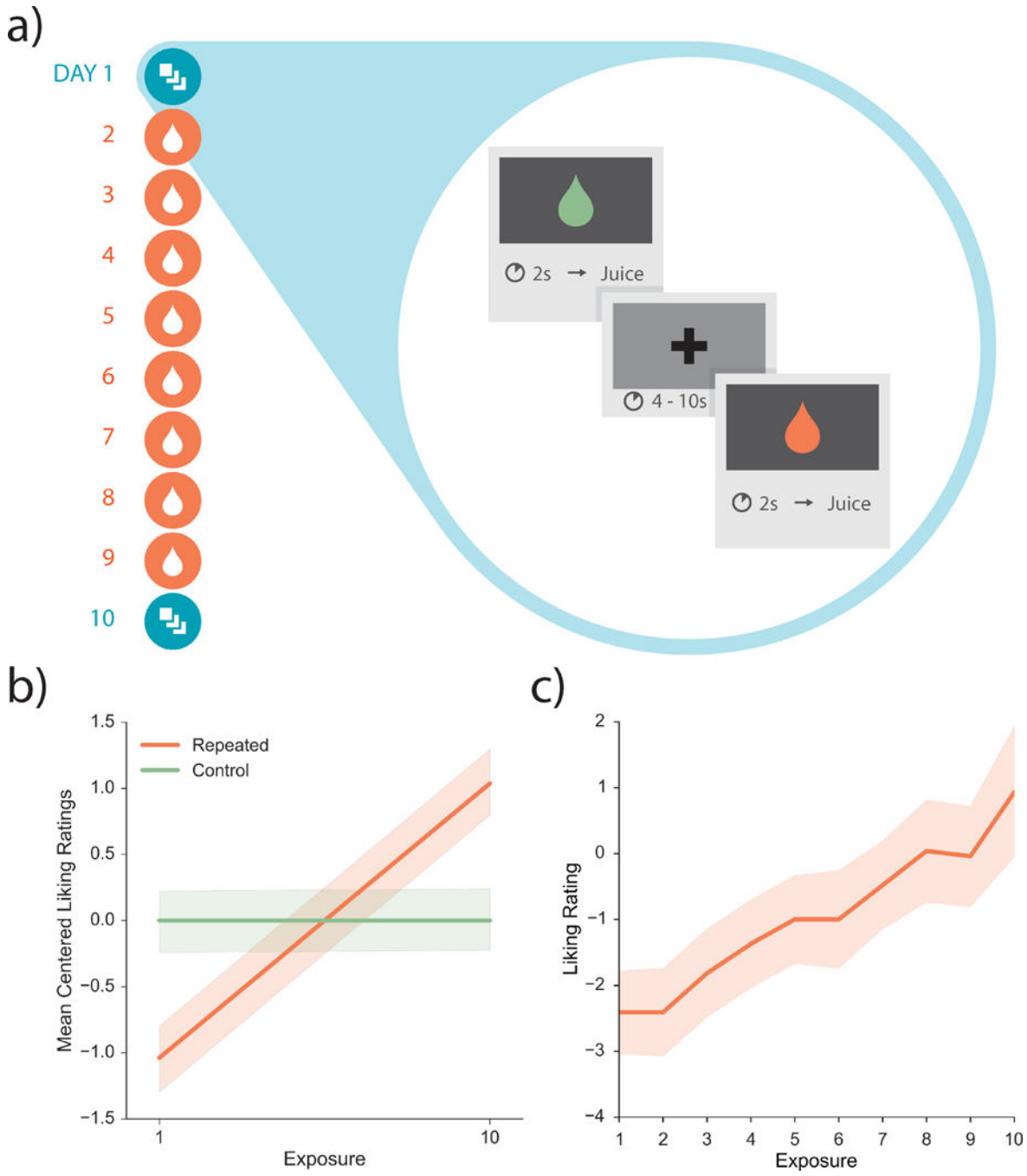

Figure 1. Task and results

(A) The experimental task spanned 10 days with scanning on day 1 and day 10. The task involved exposure to 2 novel juices. Each trial consisted of a colored image of a droplet that indicated that a specific juice would be delivered in 2 seconds. Subjects were given a supply of one of the juices to drink for the intervening 8 days. **(B)** Preference ratings on the first and last day indicate that, on average, preference increased for the repeated, but not control juice. The shaded area indicates bootstrapped 68% confidence intervals across subjects. **(C)** Daily ratings of the repeated juice indicate that preference increased roughly linearly across the 10

exposures. The shaded area indicates the bootstrap estimated standard error of the mean preference rating for each exposure.

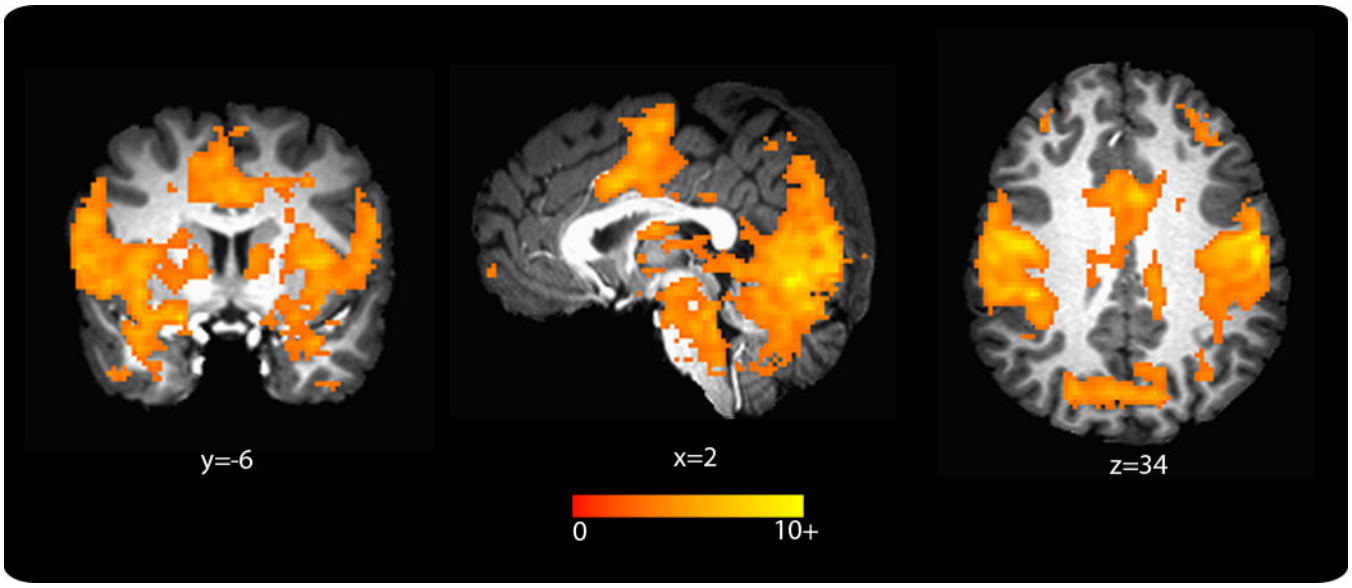

Figure 2. Juice Delivery

Contrast map showing the main effect of juice cue and delivery, pooled across both fluids and scanning sessions ($p<0.05$, cluster corrected). Coordinates are in Talairach space.

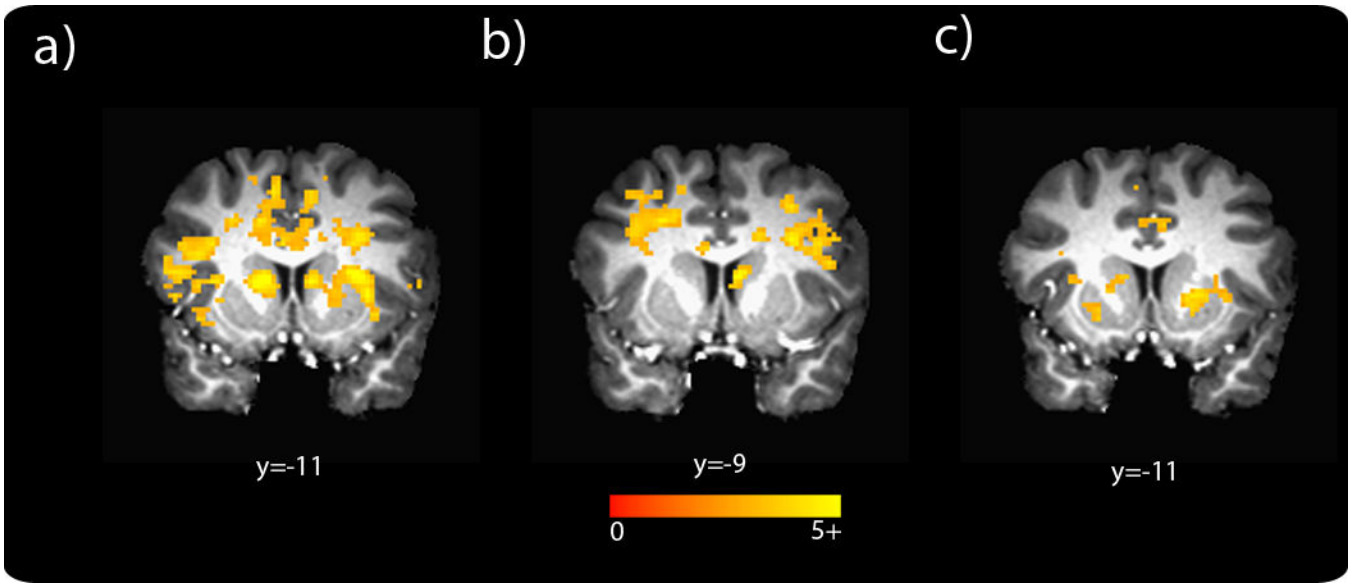

Figure 3. Habituation

(A) Contrast map showing voxels whose activation declined with exposure to the fluids, pooled across both fluids and scanning sessions ($p<0.05$, cluster corrected). This response is consistent with neural habituation in these regions. (**B)** Contrast showing the voxels with an exponential habituation profile. (**C)** Contrast showing voxels with a linear habituation profile. Coordinates are in Talairach space.

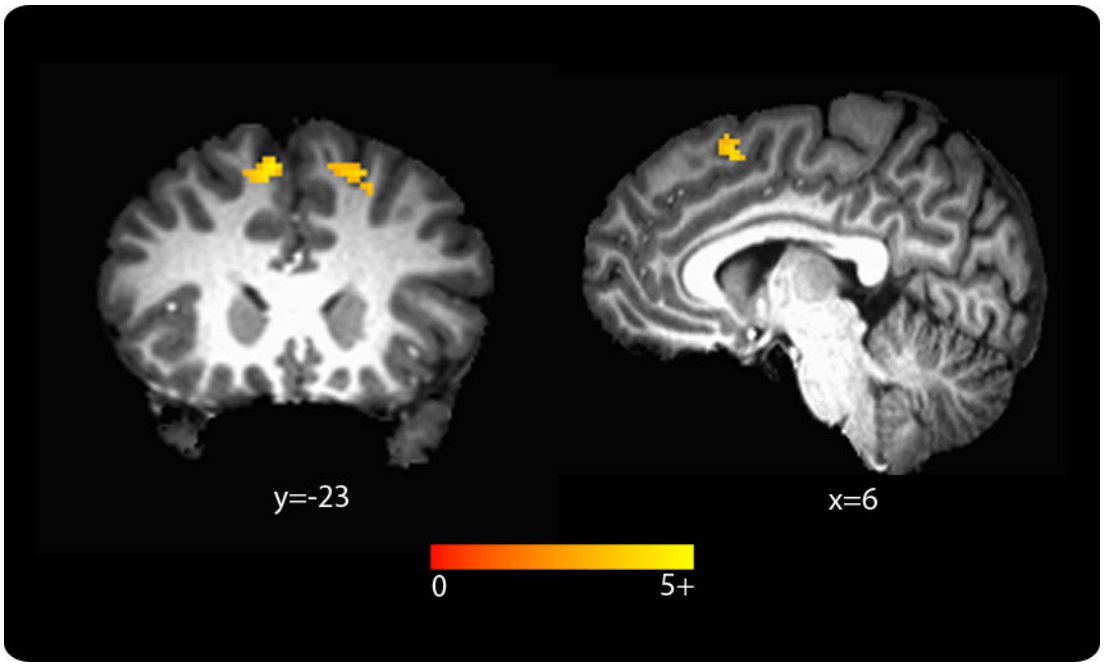

Figure 4. Main Effect of Preference Change

Result of an analysis comparing the change in response between days to the repeated juice to that of the control juice. We observed activations in the bilateral supplementary motor area. Coordinates are in Talairach space.

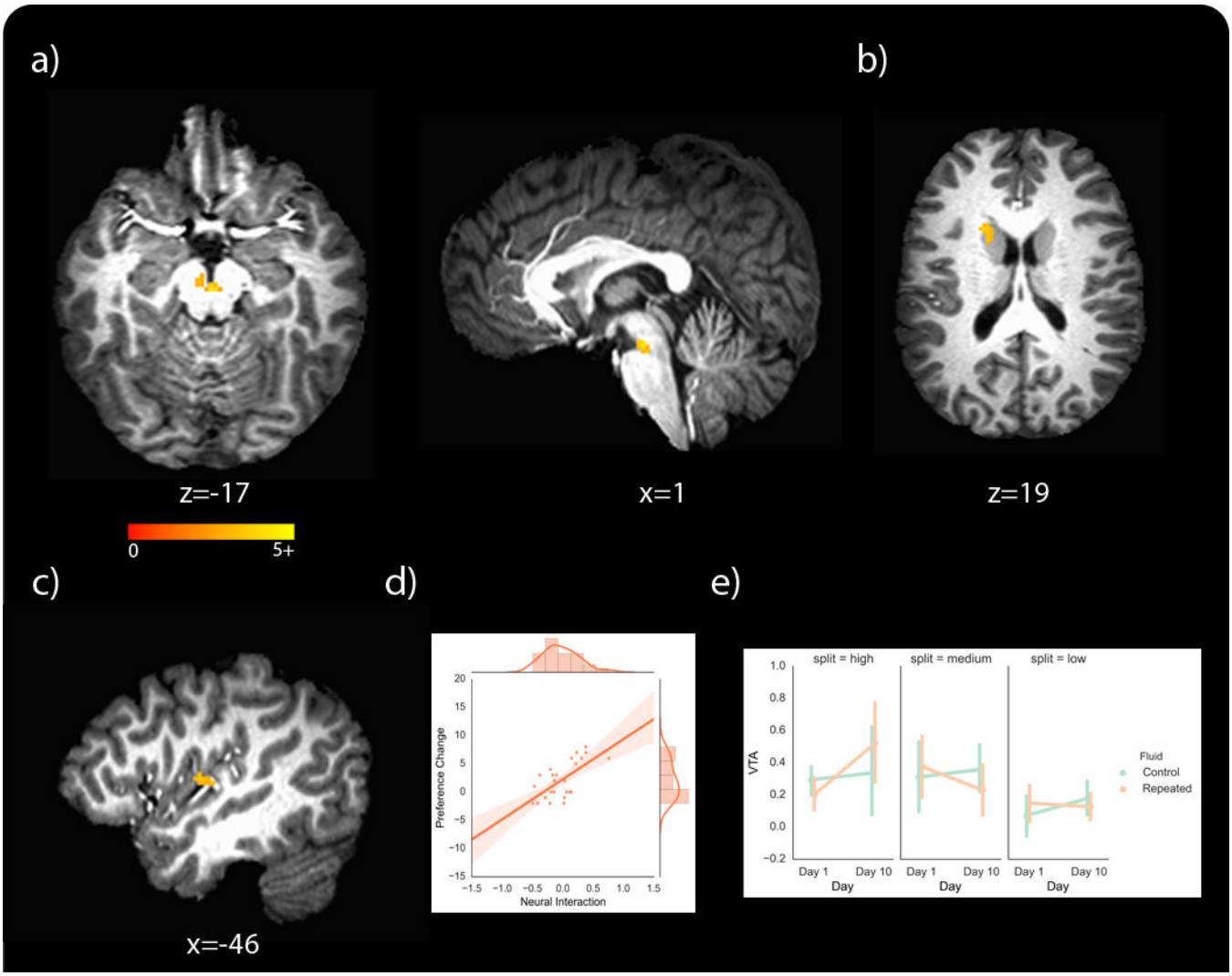

Figure 5. Neural Correlates of Preference Change

(A) In the VTA, the change in BOLD response to the repeated, relative to control, juice between days tracks the magnitude of the mere exposure effects between subjects ($p<0.05$, cluster corrected). **(B)** Results of the same analysis in the caudate. **(C)** Results of the same analysis in the insula. (**D)** Correlation of the neural interaction in the VTA (β values from regression) with our behavioral measure of preference change (contrast of "liking" ratings). Side panels show the marginal distributions of each variable. Shaded error shows bootstrapped 95% confidence intervals of the regression estimates. The VTA ROI was not selected independently of preference change, and we show this figure only to visualize the data that gave rise to the whole-brain corrected effect. **E)** We divided the subjects into 3 approximately equally size groups by their preference change and plotted the parameter estimates for each juice and each session separately for these groups. Error bars show bootstrapped 68% confidence intervals across subjects. The high preference change group showed the expected pattern, that is the magnitude of response to the repeated juice is increased during the second scanning session.

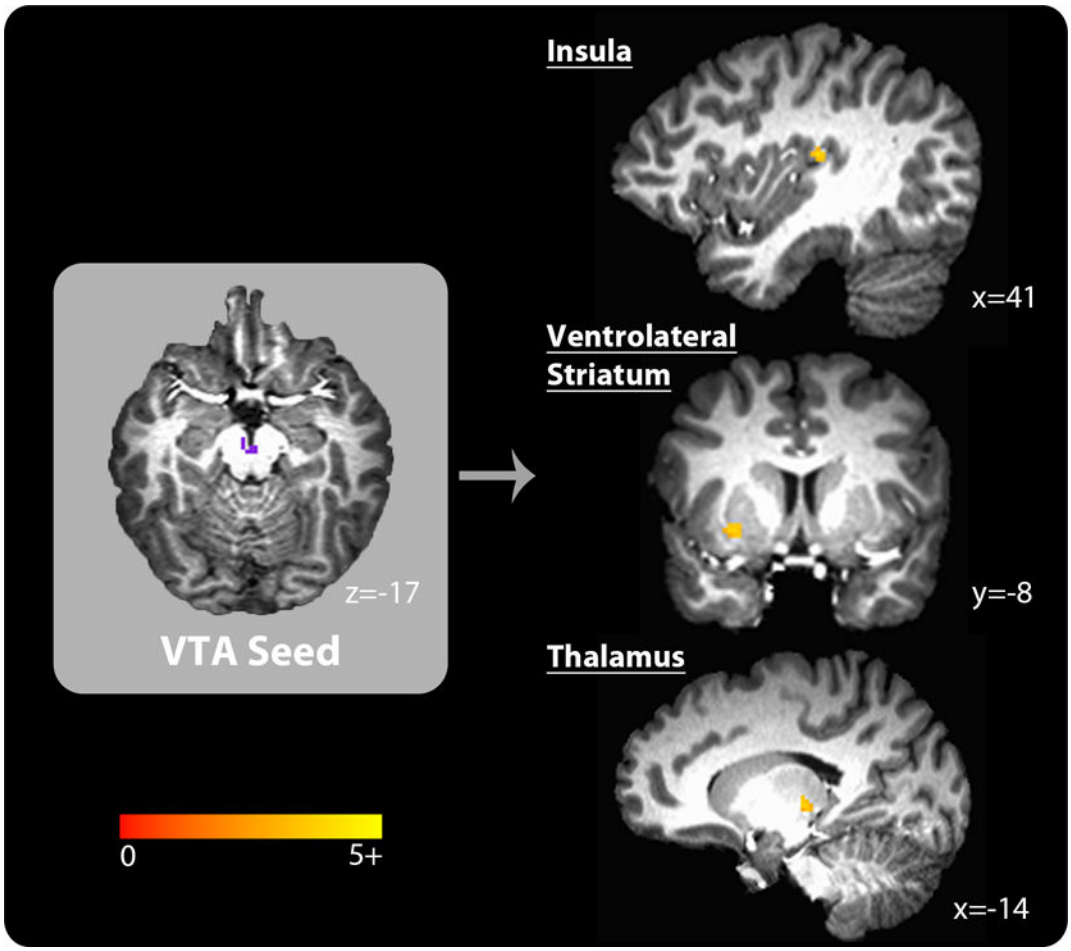

Figure 6. Functional connectivity correlated with preference change

Functional connectivity between the VTA and the insula, ventrolateral striatum, and thalamus correlate with magnitude of the mere exposure effect across subjects ($p<0.05$, cluster corrected). Coordinates are in Talairach space.

Table 1

Table of activations for habituation contrast (Figure 3)

Region	Extent	X	Y	Z	Peak T
Middle frontal gyrus, cingulate, caudate, putamen, medial frontal gyrus, inferior frontal gyrus, superior frontal gyrus	5154	−35	−5	24	−7.21
Left dorsolateral prefrontal cortex	1489	33	−31	20	−7.43
Left motor/premotor cortex	436	15	−3	58	−5.19
Ventricle	275	19	37	12	5.55
Inferior parietal lobule, postcentral gyrus	209	53	21	28	−5.04
Cingulate	178	−3	11	22	−4.99
Ventricle	171	−29	41	4	+6.0
Left Inferior Parietal Lobule	56	39	37	42	−4.14
Right Inferior Parietal Lobule	46	−61	31	32	−4.0
Right Inferior Parietal Lobule	46	−37	37	48	−4.80
Left Thalamus	41	3	17	−2	−4.15
Right postcentral gyrus	39	−37	15	28	−4.48

Full list of activations detected in the habituation analysis in Figure 3. Extent denotes the number of voxels in the cluster. Coordinates of the peak voxel are in Talairach space, and are given in units of mm.

Table 2

Table of activations for preference change correlation and connectivity

Region	Extent	X	Y	Z	Peak T
Exposure contrast: $\Delta V^i = (V^i_{r,10} - V^i_{r,1}) - (V^i_{c,10} - V^i_{c,1})$					
Left supplemental motor area	97	17	−25	52	5.47
Right supplemental motor area	39	−7	−23	54	4.74
Posterior cingulate cortex, white matter	34	19	53	20	−3.49
Preference Change Correlation					
superior temporal gyrus, precentral gyrus, insula	37	−49	15	6	3.63
middle temporal gyrus, superior temporal gyrus	35	−61	45	6	3.93
precentral gyrus, postcentral gyrus	32	−27	27	52	3.82
caudate	31	−19	−15	20	3.79
inferior parietal lobule, postcentral gyrus	31	45	33	28	3.80
VTA	26	1	21	−16	4.26
VTA Connectivity					
thalamus	42	−13	21	2	3.86
insula	39	41	23	16	3.94
putamen	36	−27	−7	−4	3.86
white matter	32	−5	41	12	−3.90
white matter	26	−33	35	32	−4.03

Full list of activations detected in the preference change analysis. Extent denotes the number of voxels in the cluster. Coordinates of the peak voxel are in Talairach space. Subheadings refer to 1) the main effect of exposure (Figure 2), 2) Figure 5a,b,c (regions whose change in activity scales with preference change) and 3) Figure 6 (regions whose change in connectivity with the VTA scales with preference change). Coordinates of the peak voxel are in Talairach space, and are given in units of mm.