Behavioral/Cognitive

Ventromedial Prefrontal Cortex Damage Is Associated with Decreased Ventral Striatum Volume and Response to Reward

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The ventral striatum and ventromedial prefrontal cortex (vmPFC) are two central nodes of the "reward circuit" of the brain. Human neuroimaging studies have demonstrated coincident activation and functional connectivity between these brain regions, and animal studies have demonstrated that the vmPFC modulates ventral striatum activity. However, there have been no comparable data in humans to address whether the vmPFC may be critical for the reward-related response properties of the ventral striatum. In this study, we used fMRI in five neurosurgical patients with focal vmPFC lesions to test the hypothesis that the vmPFC is necessary for enhancing ventral striatum responses to the anticipation of reward. In support of this hypothesis, we found that, compared with age- and gender-matched neurologically healthy subjects, the vmPFC-lesioned patients had reduced ventral striatal activity during the anticipation of reward. Furthermore, we observed that the vmPFC-lesioned patients had decreased volumes of the accumbens subregion of the ventral striatum. Together, these functional and structural neuroimaging data provide novel evidence for a critical role for the vmPFC in contributing to reward-related activity of the ventral striatum. These results offer new insight into the functional and structural interactions between key components of the brain circuitry underlying human affective function and decision-making.

Key words: decision-making; fMRI; lesion; prefrontal cortex; reward; striatum

Significance Statement

Maladaptive decision-making is a common problem across multiple mental health disorders. Developing new pathophysiologically based strategies for diagnosis and treatment thus requires a better understanding of the brain circuits responsible for adaptive decision-making and related psychological subprocesses (e.g., reward valuation, anticipation, and motivation). Animal studies provide evidence that these functions are mediated through direct interactions between two key nodes of a posited "reward circuit," the ventral striatum and the ventromedial prefrontal cortex (vmPFC). For the first time in humans, we demonstrate that damage to the vmPFC results in decreased ventral striatum activity during reward anticipation. These data provide unique evidence on the causal mechanisms by which the vmPFC and ventral striatum interact during the anticipation of rewards.

Introduction

The brain's "reward circuit"—the network of regions encoding various aspects of pleasure, motivation, and value—is a critical biological substrate underlying human emotion, decision-making, and social behavior. Two central nodes of the reward circuit are the ventral striatum/nucleus accumbens and ventromedial prefrontal cortex (vmPFC). The ventral striatum has been particularly associated with the anticipation or prediction of reward, whereas the vmPFC has been linked to reward outcome and subjective value (Knutson et al., 2003; Grabenhorst and Rolls, 2011; Liu et al., 2011; Levy and Glimcher, 2012). Damage to the vmPFC in humans disrupts value-based decision-making and social function (Bechara et al., 1997; Camille et al., 2004, 2011; Koenigs and Tranel, 2007; Koenigs et al., 2007), and dysfunction in this circuit is observed across a broad range of psychopathology (Kalivas and Volkow, 2005; Tremblay et al., 2005; Epstein et al., 2006; Scheres et al., 2007; Harrison et al., 2009; Plichta et al., 2009; Waltz et al., 2009; Koob and Volkow, 2010; Scott-Van Zee-

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land et al., 2010; Figee et al., 2011; Jung et al., 2011; Dichter et al., 2012; Morris et al., 2012; Nielsen et al., 2012; Robinson et al., 2012).

Despite the importance of this brain circuit for mental health and adaptive decision-making, the neural interactions between the vmPFC and ventral striatum are not fully understood. Rodent studies have shown that the vmPFC has direct glutamatergic projections to the ventral striatum (Sesack et al., 1989; Voorn et al., 2004; Gabbott et al., 2005) and that inactivation of the vmPFC alters neuronal activity in the ventral striatum (Ghazizadeh et al., 2012). These studies indicate that the vmPFC may play a role in modulating ventral striatum activity. Human functional imaging studies have yielded additional correlational support for this idea; the vmPFC and ventral striatum exhibit strong functional connectivity at rest (Di Martino et al., 2008; Cauda et al., 2011; Choi et al., 2012) and are often coactivated during reward processing tasks (Cauda et al., 2011). However, there is not yet evidence that the vmPFC actually modulates ventral striatum activity in humans. In other words, whereas animal studies have demonstrated that the vmPFC plays a causal role in modulating ventral striatum activity, there are no comparable data in humans to address whether the vmPFC may be critical for the reward-related response properties of ventral striatum.

In this study, we use fMRI in neurosurgical patients with focal vmPFC lesions to test the hypothesis that the vmPFC is necessary for enhancing ventral striatum responses to the anticipation of reward.

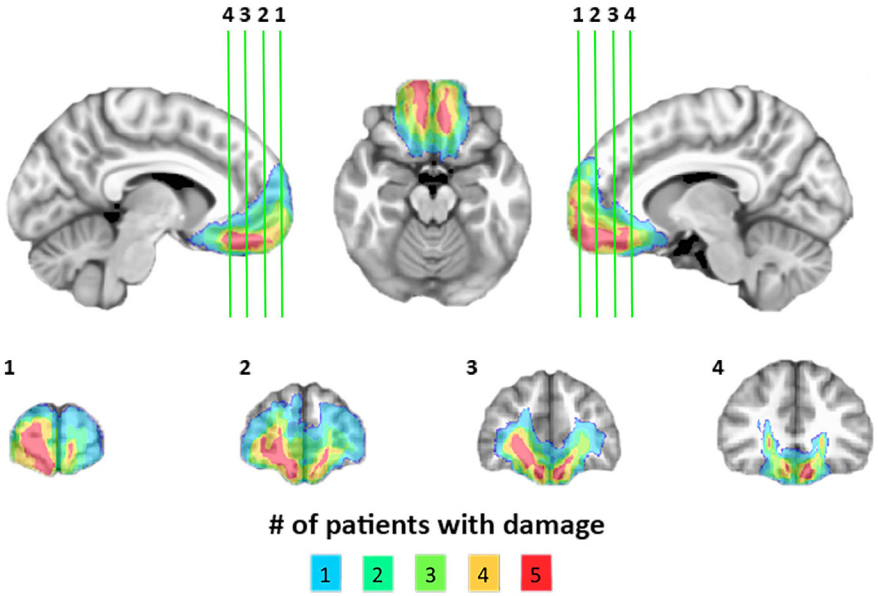

Figure 1. Lesion overlap of vmPFC-lesioned patients. Color indicates the number of overlapping lesions at each voxel. For axial and coronal views, the left side of the brain is displayed on the right.

Materials and Methods

Participants. The target lesion group consisted of five adult neurosurgical patients ($n = 3$ males; $n = 2$ females) with extensive bilateral parenchymal damage, primarily confined to the vmPFC, defined as the medial one-third of the orbital surface and the ventral one-third of the medial surface of the PFC bilaterally (Fig. 1). Each of the five patients underwent surgical resection of a large anterior cranial fossa meningioma via craniotomy. Initial clinical presentations included subtle or obvious personality changes over several months preceding surgery. On postsurgical MRI, although vasogenic edema mostly resolved, there were persistent T_2-weighted signal changes consistent with gliosis and degeneration of white matter fibers in the vmPFC bilaterally. All experimental procedures were conducted >3 months after surgery, when the expected recovery was complete. At the time of testing (range of time elapsed since surgery, 32–75 months), all patients had focal, stable MRI signal changes and resection cavities and were free of dementia and substance abuse. Seventeen healthy adults ($n = 10$ males; $n = 7$ females) with no history of brain injury, neurological or psychiatric illness, or current use of psychoactive medication were recruited as a normal comparison (NC) group. Demographic and neuropsychological data for the vmPFC and NC groups are summarized in Table 1.

fMRI task. To assess ventral striatum activity, we used an fMRI task involving the anticipation of monetary reward (Monetary Incentive Delay task), which has been used extensively to examine reward-related neural responses in healthy and patient populations (Knutson et al., 2008; Ströhle et al., 2008; Beck et al., 2009; Khemiri et al., 2012; Nielsen et al., 2012; Stoy et al., 2012; Gleichgerrcht and Young, 2013). Previous fMRI research with this task has reliably demonstrated ventral striatum activity in response to cues indicating the potential gain of money (Khemiri et al., 2012; Gleichgerrcht and Young, 2013). Hence, this task provides a well established fMRI measure of ventral striatum response to reward. Each trial consists of three periods. During the initial 2 s cue period, the subject views one of six different shapes (with circles indicating potential gains and squares indicating potential losses) displaying the amount of money that could be gained or lost on that trial (+\$0.00, +\$1.00, +\$5.00, −\$0.00, −\$1.00, −\$5.00), followed by a 2 s fixation cross display (anticipation phase). During the following reaction-time task period (performance phase), the subject presses a button in response to a visual prompt (a solid white triangle) as quickly as possible. If the subject responds quickly enough while the prompt is displayed, the subject either gains money or avoids losing money on that trial. The third task period (outcome phase) indicates the monetary result based on the response (e.g., +\$1.00 for a successful response during a gain trial or −\$5.00 for an unsuccessful response during a loss trial) for 2 s. The task difficulty for individual subjects was manipulated based on performance across the task, such that each subject successfully hit the target on ~66% of the trials for each cue type. The entire task consisted of one functional run of ~20 min, consisting of 90 8-s trials (15 trials for each of the six cue types) presented in pseudorandom order, followed by an intertrial interval of 2, 4, or 6 s.

Before scanning, subjects were informed of all cue-outcome contingencies and completed a practice task consisting of 15 trials to ensure task comprehension and accurate reaction time calibration. Subjects completed the practice task twice outside the scanner and once inside the scanner during T_1 acquisition, before the start of the full-length task. At the start of the scanning session, subjects were told that they would receive additional payment corresponding to their cumulative earnings on the full-length reward task.

After the scan, subjects were brought to a separate room and asked to rate their overall arousal and valence for each cue type using a scale ranging from 1 (arousal, "not at all aroused"; valence, "very negative") to 7 (arousal, "highly aroused"; valence, "very positive").

MRI data acquisition. All structural and functional MRI data were acquired using a 3.0 T GE Discovery MR750 scanner equipped with an eight-channel radio-frequency head coil array (GE Healthcare). High-resolution T_1-weighted anatomical images were acquired using an inversion-recovery spoiled gradient recalled acquisition in steady state (spoiled gradient-recalled acquisition in a steady state) sequence (TR, 8.2 ms; TE, 3.2 ms; $\alpha = 12°$; FOV, 256 × 256 mm; matrix, 256 × 256; in-plane resolution, 1 × 1 mm^2; slice thickness, 1 mm; 1024 axial slices).

Table 1. Subject characteristics

	Age (years)	Sex	Edu	IQ	BIS total	BAS total	BAS D	BAS FS	BAS RR	Pos Aff	Neg Aff	BDI-II	STAI-T
vmPFC ($n = 5$)	59.8 (5.2)	3 males/2 females	15.6 (3.6)	105.2 (11.2)	16.4 (1.5)	38.6 (4.2)	11.0 (1.1)	11.6 (1.1)	16.0 (1.4)	37.6 (8.1)	16.2 (7.8)	6.2 (3.3)	33.4 (8.4)
NC ($n = 14$)	62.6 (3.9)	9 males/5 females	17.1 (2.4)	113.0 (6.0)	18.9 (3.5)	38.1 (4.8)	10.6 (2.1)	11.4 (1.9)	16.1 (2.0)	39.9 (7.2)	13.9 (4.2)	3.7 (3.0)	29.6 (5.3)
p (vmPFC vs NC)	0.39	0.86	0.44	0.13	0.11	0.82	0.75	0.96	0.96	0.72	0.62	0.22	0.34

Means are presented with SDs in parentheses. Edu, Years of education; IQ, intelligence quotient estimated by the Wide Range Achievement Test 4, Blue Reading subtest (Wilkinson and Robertson, 2006); BIS/BAS, scores from the Behavioral Inhibition System/Behavioral Approach System, with subtests for drive (D), fun seeking (FS), and reward responsiveness (RR) (Carver and White, 1994); Pos/Neg Aff, scores from the Positive and Negative Affect Schedule (Watson et al., 1988); BDI-II, Beck Depression Inventory-II (Beck et al., 1996); STAI-T, trait version of the Spielberger State Trait Anxiety Inventory (Spielberger et al., 1983). A recently published study from our laboratory (Pujara et al., 2015) demonstrates abnormal value-based decision-making in the same sample of vmPFC-lesioned patients who participated in the current study.

To facilitate lesion segmentation, we collected a separate T_2-weighted fluid-attenuated inversion recovery scan (FLAIR; TR, 8650 ms; TE, 136 ms; $\alpha = 0°$; FOV, 220×220 mm^2; matrix, 512×512; in-plane resolution, 0.43×0.43 mm^2; slice thickness, 5 mm; gap, 1 mm; 25 axial slices).

Baseline resting cerebral blood flow (CBF) was estimated using a 3D fast spin echo spiral sequence with pseudocontinuous arterial spin labeling (pcASL; Dai et al., 2008; Xu et al., 2010; Okonkwo et al., 2014) and background suppression for quantitative perfusion measurements (TR, 4653 ms; TE, 10.5 ms; post-labeling delay, 1525 ms; labeling duration, 1450 ms; eight interleaved spiral arms with 512 samples at 62.5 kHz bandwidth and 38.4-mm-thick slices; number of excitations, 3; scan duration, 4.5 min).

Whole-brain functional scans were acquired using a T_2*-weighted gradient-echo echoplanar imaging (EPI) sequence (TR, 2000 ms; TE, 22 ms; $\alpha = 79°$; FOV, 224×224 mm^2; matrix, 64×64; in-plane resolution, 3.5×3.5 mm^2; slice thickness, 3 mm; gap, 0.5 mm; 38 interleaved axial oblique slices). Field maps were acquired using two separate acquisitions (TR, 600 ms; TE_1, 7 ms; TE_2, 10 ms; $\alpha = 60°$; FOV, 240×240 mm^2; matrix, 256×128; slice thickness, 4 mm; 33 axial oblique slices). Resting-state functional images were collected while subjects lay still and awake, passively viewing a fixation cross for 5 min. Scans were acquired in the following order: pcASL, field map, rest, T_1, task, T_2 FLAIR.

Lesion segmentation and image normalization. Individual vmPFC lesions were visually identified and manually segmented on the T_1-weighted images. Lesion boundaries were drawn to include areas with gross tissue damage or abnormal signal characteristics on T_1 or T_2 FLAIR images. T_1-weighted images were skull stripped, rigidly coregistered with a functional volume from each subject, and then diffeomorphically aligned to the Montreal Neurological Institute (MNI) coordinate system using a Symmetric Normalization algorithm (Avants and Gee, 2004) with constrained cost-function masking to prevent warping of tissue within the lesion mask (Brett et al., 2001). We created the lesion overlap map (Fig. 1) by computing the sum of aligned binary lesion masks for all five vmPFC patients. Alignment parameters computed during this step were used in the subsequent normalization of all anatomical and functional data to MNI space.

fMRI task preprocessing and analysis. Data analysis was conducted using AFNI (Automated Functional Neuro-Imaging; Cox, 1996) and FSL (Functional MRI of the Brain Software Library; http://www.fmrib.ox.ac.uk/fsl) software. The task run was slice time corrected, field map corrected (Jezzard and Clare, 1999), motion corrected, smoothed with a 4 mm full-width half-maximum (FWHM) Gaussian kernel, scaled to percentage signal change (PSC), aligned to MNI space, and resampled to 3 mm^3 isotropic resolution. Anticipatory activity was modeled using a duration-modulated boxcar regressor, beginning at cue onset and spanning the 4 s anticipation phase (cue and fixation cross) before the presentation of the target. All six cue regressors were included in a general linear model (GLM) with six additional regressors for each outcome (gains of \$0, \$1, or \$5; losses of \$0, \$1, or \$5). The GLM also included several regressors of no interest: six motion covariates from rigid-body alignment (Johnstone et al., 2006) and a fourth-order polynomial to model baseline and slow signal drift. To avoid potential confounds introduced by subject motion, volumes in which >10% of voxels were time series outliers were censored before conducting the GLM.

One vmPFC-lesioned patient was rescanned because of input device malfunction during the first scan. Three NC subjects ($n = 1$ male; $n = 2$ females) were excluded from task-based analyses because of excessive head motion (>2 mm; Power et al., 2012), for a total sample size of 14 NC subjects ($n = 9$ males; $n = 5$ females). There were no group differences in the percentage of censored volumes ($W = 60.5$, $p = 0.84$) or in mean framewise displacement (NC, 0.06 ± 0.02 mm; vmPFC, 0.07 ± 0.03 mm; $W = 134.0$, $p = 0.31$). Resulting whole-brain maps of voxelwise β values for sustained BOLD responses, in MNI space at 3 mm^3 isotropic resolution, were used for second-level analyses.

To identify brain regions responsive to the anticipation of monetary gain, we first performed a whole-brain, two-tailed paired-sample t test between responses to gain cues (collapsed across magnitude) and the neutral gain cue (+\$0) using only the 14 NC subjects (Chen et al., 2013). All statistical maps were familywise error (FWE) corrected for multiple comparisons across the whole brain at the cluster level ($p_{FWE} < 0.05$), using a height threshold of $p < 0.001$ (Forman et al., 1995; Carp, 2012). A corrected $p_{FWE} < 0.05$ was achieved using a cluster extent threshold of 20 voxels (540 mm^3), calculated using Monte Carlo simulations with 3dClustSim (December 2015 version) in AFNI.

Because of the small sample size of patients with vmPFC lesions, we used nonparametric Mann–Whitney U tests to evaluate our main a priori hypothesis regarding activity of the ventral striatum and behavioral differences between groups (percentage of hits by condition, postscan valence and arousal ratings by condition, target duration by condition, and cumulative money earned from the task). Specifically, we focused our between-group analyses on PSC estimates extracted from functionally derived right and left ventral striatum ROIs (ventral striatum clusters from the gain > neutral contrast in the NC group). We used functional ROIs to ensure that group comparisons were conducted within functionally relevant regions within the ventral striatum (i.e., regions that responded strongly in anticipation of potential gains in healthy subjects; Poldrack, 2007). However, to confirm that group comparisons within functionally derived ventral striatum ROIs reflected differences in ventral striatum activity, we conducted additional between-group tests using values extracted from ROIs in the right and left ventral striatum (number of voxels in masks, $n_{right} = 99$, $n_{left} = 107$), created from subregions in a striatal parcellation atlas derived from functional connectivity to 17 distinct cortical networks in 1000 healthy adults (Choi et al., 2012). The chosen subregions, which correspond to regions 10 and 17 in the 17-network parcellation map (available at http://www.freesurfer.net/fswiki/StriatumParcellation_Choi 2012), demonstrated functional connectivity in the healthy adults to cortical areas corresponding to the region of damage in our vmPFC-lesioned patient sample.

To test the specificity of observed effects to the ventral striatum, we conducted follow-up analyses on PSC values extracted from the remaining functionally derived regions outside the ventral striatum. All tests were considered significant at $p < 0.05$.

Volumetric analysis. The averaged T_1-weighted images were processed using FreeSurfer (Forman et al., 1995; Fischl, 2012). The FreeSurfer tissue segmentation includes volume measurements (in cubic millimeters) for four striatal subregions in each hemisphere. We used nonparametric Mann–Whitney U tests to calculate group differences in volumes of the following striatal subregions: left and right putamen, left and right caudate, left and right accumbens, and left and right pallidum. We also calculated group differences in volumes of two additional subcortical limbic structures—the amygdala and hippocampus—to further examine specificity. All regional volumes were corrected for estimated intracranial volume (Sanfilipo et al., 2004).

Cerebral perfusion analysis. Quantitative CBF images from pcASL were rigidly coregistered with a T_2*-weighted EPI volume from the task scan and normalized to MNI space. Normalized CBF volumes were scaled to

Table 2. Behavioral data

		vmPFC		NC		
	Gain/loss	Mean	SD	Mean	SD	*p*
% Hits	−$0	65.3	5.6	62.1	5.7	0.34
	−$1	53.3	19.4	59.0	10.5	0.92
	−$5	68.0	7.3	65.6	7.1	0.78
	+$0	62.3	7.6	61.5	10.2	0.99
	+$1	66.7	4.7	57.9	12.3	0.21
	+$5	64.0	3.7	60.5	11.0	0.70
Arousal ratings	−$0	2.6	1.5	2.8	1.4	0.85
	−$1	2.8	1.6	3.3	1.5	0.63
	−$5	3.2	2.2	4.5	2.4	0.29
	+$0	3.0	1.6	2.9	1.3	0.92
	+$1	4.4	1.3	4.4	1.3	0.85
	+$5	6.0	0.7	6.0	1.2	0.78
Valence ratings	−$0	3.4	1.3	4.2	0.9	0.34
	−$1	3.8	0.4	3.9	0.8	0.99
	−$5	3.6	2.4	2.7	1.5	0.50
	+$0	3.6	1.1	4.2	0.4	0.39
	+$1	4.6	1.1	4.9	0.6	0.63
	+$5	6.0	1.0	5.8	1.5	0.99
Target duration (ms)	−$0	367	61	352	77	0.69
	−$1	345	77	333	83	0.56
	−$5	350	85	328	71	0.89
	+$0	352	71	354	56	0.96
	+$1	378	67	336	92	0.19
	+$5	334	82	322	84	0.82
Payment		$27.00	$8.06	$22.15	$12.49	0.50

Note that, because of a computer malfunction, the behavioral data for one NC subject was not available.

whole-brain CBF (after masking out the lesion in vmPFC patients) and smoothed with a 6 mm FWHM Gaussian kernel. To rule out differences in baseline cerebral perfusion, we examined group differences in mean whole-brain CBF and differences in scaled CBF for all functionally defined ROIs using nonparametric Mann–Whitney *U* tests.

Results

Behavioral data

Groups did not significantly differ with respect to task performance (percentage of hits by condition, postscan valence and arousal ratings by condition, target duration by condition, and cumulative money earned from the task; all comparisons $p > 0.19$). These behavioral data for the vmPFC and NC groups are summarized in Table 2.

fMRI task data

Relative to the neutral cue, gain anticipation elicited robust bilateral striatum activity in the NC subjects (Fig. 2; Table 3). To examine group differences in striatum activity, we extracted PSC estimates from these functionally derived right and left striatum ROIs. In support of our main hypothesis, patients with vmPFC lesions exhibited significantly less activity in the right striatum ($W = 64.0$, $p = 0.005$) and left striatum ($W = 59.0$, $p = 0.03$) during gain anticipation than did NC subjects (Fig. 2). This effect was present for the high gain $5 cue > $0 cue contrast (right striatum, $W = 64.0$, $p = 0.005$; left striatum, $W = 60.0$, $p = 0.02$) but not the low gain $1 cue > $0 cue contrast (right striatum, $W = 54.0$, $p = 0.09$; left striatum, $W = 47.0$, $p = 0.30$). Consistent with the results based on functionally derived ROIs, we observed a significant group difference for the $5 cue > $0 cue contrast for the a priori right ventral striatum ROI ($W = 28.0$, $p = 0.04$) and a trend-level group difference for the $5 cue > $0 cue contrast for the a priori left ventral striatum ROI ($W = 30.0$, $p = 0.07$).

To test the anatomical specificity of group differences in activity related to gain anticipation (Table 3), we conducted follow-up analyses in the three remaining functionally derived ROIs from the gain > neutral cue contrast [e.g., left paracentral lobule/medial frontal gyrus (MFG), left inferior parietal lobule (IPL), and right caudate] and found similar group differences (left MFG, $W = 68.0$, $p = 0.0007$; left IPL, $W = 64.0$, $p = 0.005$; right caudate, $W = 63.0$, $p = 0.007$).

To ensure that the hypothesized group differences in the functionally defined striatum regions were not attributable to baseline differences in perfusion after vmPFC damage, we estimated CBF using pcASL before the functional scan in all subjects. There were no significant differences between groups for whole-brain CBF ($W = 26$, $p = 0.44$) or for either of the functionally defined striatum ROIs (right, $W = 50.0$, $p = 0.19$; left, $W = 41.0$, $p = 0.62$).

Volumetric data

Compared with the NC group, the vmPFC group had significantly smaller volumes of the accumbens subregion of the left ventral striatum ($W = 57.0$, $p = 0.04$) and a trend-level difference for the right accumbens subregion of the ventral striatum ($W = 54$, $p = 0.09$; Fig. 3). There were no significant group differences for any other region of the striatum (right putamen, $W = 33.0$, $p = 0.49$; left putamen, $W = 38.0$, $p = 0.76$; right caudate, $W = 29.0$, $p = 0.32$; left caudate, $W = 28.0$, $p = 0.28$; right pallidum, $W = 34.0$, $p = 0.54$; left pallidum, $W = 46.0$, $p = 0.82$), amygdala (right, $W = 44.0$, $p = 0.93$; left, $W = 35.0$, $p = 0.59$), or hippocampus (right, $W = 52$, $p = 0.49$; left, $W = 45.0$, $p = 0.88$; Table 4).

Discussion

Through a novel application of fMRI in patients with bilateral vmPFC damage, we have demonstrated a critical role for the vmPFC in modulating the reward-related activity and structure of the ventral striatum. Specifically, we found that vmPFC lesions were associated with decreased ventral striatal activity during the anticipation of reward and decreased volumes of the accumbens subregion of the ventral striatum. These results are germane to neural circuitry models of reward processing and mental illness.

First, with respect to neural circuitry models of reward processing, the study results fill an empirical gap between previous animal and human research findings. Human fMRI studies have consistently shown that the vmPFC and ventral striatum exhibit coincident activity (Di Martino et al., 2008; Cauda et al., 2011; Choi et al., 2012). However, a fundamental limitation of this correlational approach is that it does not distinguish between cause and consequence within the network of observed activity. In other words, is the observed coactivation of the vmPFC and ventral striatum during reward processing in these studies attributable to vmPFC activity modulating ventral striatum activity or vice versa? Or are activity changes in these areas just parallel, coincidental downstream effects triggered by activity elsewhere in the brain? Animal research suggests a causal effect of vmPFC activity on ventral striatum activity. Rodent studies have shown that the vmPFC has direct glutamatergic projections to the ventral striatum (Sesack et al., 1989; Voorn et al., 2004; Gabbott et al., 2005) and that inactivation of the vmPFC alters neuronal activity in the ventral striatum (Ghazizadeh et al., 2012). Lesioning or inactivating both the vmPFC and ventral striatum/accumbens disrupts behavioral responding during reward learning and reaction time tasks, indicating that adaptive decision-making depends on concurrent activation of both regions (Christakou et al., 2004; Peters et al., 2008; Bossert et al., 2012; St Onge et al., 2012; Richard and Berridge, 2013; Smith and Graybiel, 2013; Feja and Koch, 2015). The present study yields the first human evidence suggesting that the vmPFC does in fact have a causal influence on modulating ventral striatum activity, in that deprivation of vmPFC

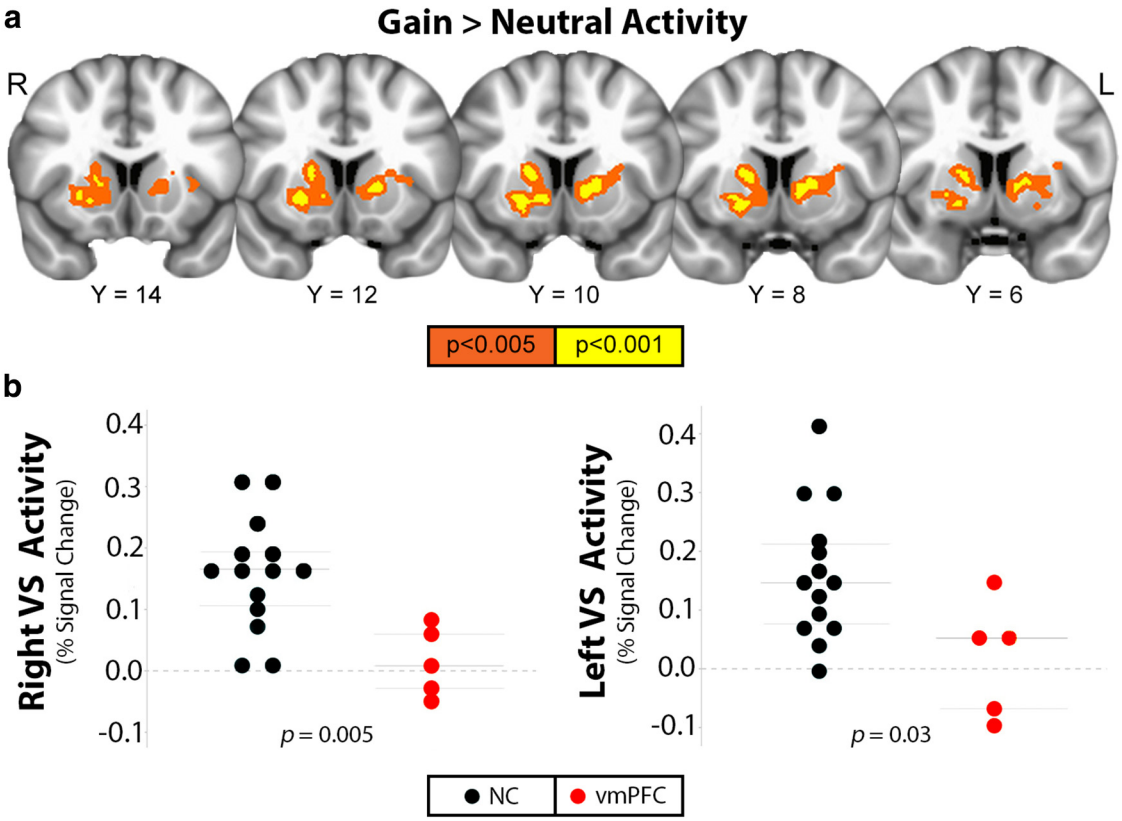

Figure 2. a, Striatal regions with greater activation to gain, relative to neutral, cues in 14 NC subjects. Significant striatum clusters from the gain > neutral contrast at $p < 0.005$ uncorrected in orange and $p < 0.001$ in yellow ($p_{FWE} < 0.05$) for display. Slice coordinates (in millimeters) are presented in MNI template space. b, Plots depict the distribution of individual PSC values for vmPFC-lesioned patients (red circles) and NC subjects (black circles) in response to gain (+5, +1) minus neutral (+0) cues within each striatum cluster at $p < 0.001$ uncorrected, $p_{FWE} < 0.05$. Light gray horizontal lines on the plots represent the mean and the first and third quartiles of PSC values for each group.

Table 3. Brain regions sensitive to anticipatory cues in the NC group

		Cluster		Peak voxel			
Contrast	Structure	Size	p_{FWE}	T	x	y	z
Gain > neutral	L Striatum	26	<0.001	5.40	+15.5	−9.5	+3.5
	R Striatum #1	34	<0.001	5.92	−20.5	−9.5	−5.5
	R Striatum #2	29	<0.001	6.76	−17.5	−6.5	+9.5
	L MFG	218	<0.001	7.21	+6.5	+20.5	+66.5
	L IPL	192	<0.001	7.31	+27.5	+44.5	+39.5
	R Caudate	29	<0.001	6.76	−17.5	−6.5	+9.5
Loss > neutral	—	—	—	—	—	—	—

Cluster size in number of voxels ($3 \times 3 \times 3$ mm^3). Corrected p thresholds indicate minimum FWE-corrected p value for each cluster. Peak voxel coordinates (millimeters) are presented in MNI space. BA, Brodmann area; L, left; R, right.

input (via focal lesion) results in reduced ventral striatum activity during the anticipation of reward. This finding accords with human lesion studies that demonstrate impairments in value-based decision-making after vmPFC damage (Zald and Andreotti, 2010; Fellows, 2011). In the context of these behavioral effects, our fMRI data suggest a critical role for the vmPFC in modulating anticipatory ventral striatal responses to potential rewards.

The present findings may also help inform neural circuitry models of mental illness. Clinical neuroimaging studies have consistently identified abnormalities in reward circuit function and decision-making across a range of psychiatric disorders, including major depression (Tremblay et al., 2005; Epstein et al., 2006; Robinson et al., 2012), schizophrenia (Waltz et al., 2009; Morris et al., 2012; Nielsen et al., 2012), substance use disorders (Kalivas and Volkow, 2005; Koob and Volkow, 2010), attention-deficit hyperactivity disorder (Scheres et al., 2007; Plichta et al., 2009), obsessive-compulsive disorder (Harrison et al., 2009; Figee et al., 2011; Jung et al., 2011), and autism (Scott-Van Zeeland et al., 2010; Dichter et al., 2012). Clarifying the functional architecture of this circuit is thus an important step in advancing the neuropathophysiological understanding of mental illness. The present results suggest that vmPFC dysfunction may contribute to psychopathology by disrupting ventral striatal activity.

In addition to the diminished reward-related activity in the ventral striatum, we also observed reduced ventral striatum volumes in the vmPFC-lesioned patients. Importantly, this volume reduction was specific to the accumbens subregion of the striatum; the volumes of all other striatal subregions (caudate, putamen, pallidum) and other limbic subregions (amygdala, hippocampus) did not significantly differ between groups. The specificity of this finding mirrors known anatomical connections between the vmPFC and striatum, which share a particularly high density of reciprocal axonal connections (Haber and Knutson, 2010; Rigoard et al., 2011). It is possible that the ventral striatum volume reduction among vmPFC-lesioned patients is attributable to diminished input from vmPFC and/or retrograde degeneration from damaged axonal connections. Regardless, the complementary fMRI and volumetric findings underscore the tight link between structure and function in this brain circuit.

Although our study hypothesis focused on the ventral striatum, we also observed activity related to gain anticipation in the lateral parietal cortex. This finding accords with electrophysiological studies of nonhuman primates, which have consistently demonstrated reward-related neuronal activity in the lateral parietal cortex during decision-making and reinforcement learning (Platt and Glimcher,

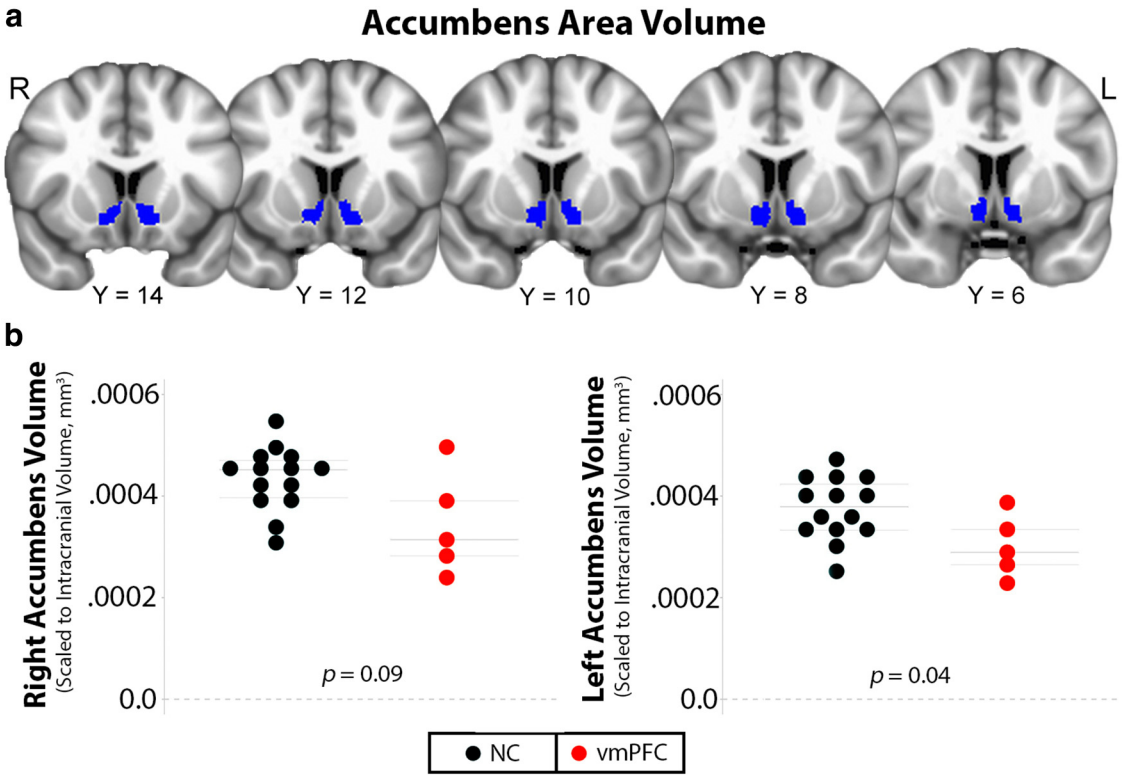

Figure 3. a, Accumbens area (ventral striatum) subregions of a representative subject. b, Plots depict the distribution of individual volume values (in cubic millimeters) for vmPFC-lesioned patients (red circles) and NC subjects (black circles) for each accumbens area region of interest, scaled to total estimated intracranial volume. Light gray horizontal lines on the plots represent the mean and the first and third quartiles of volume values for each group.

Table 4. Volumetric data

	NC		vmPFC			
Region	Mean	SD	Mean	SD	*W*	*p*
Striatum						
L NAc	568.8	126.2	481.14	129.8	57.0	**0.04**
R NAc	658.5	121.4	549.9	184.1	54.0	0.09
L caudate	3397.1	573.4	3773.8	381.4	28.0	0.28
R caudate	3645.2	679.7	4059.6	641.7	29.0	0.32
L putamen	5248.1	724.0	5557.4	620.6	38.0	0.76
R putamen	5052.2	651.1	5427.2	502.9	33.0	0.49
L pallidum	1319.2	182.3	1407.9	260.6	46.0	0.82
R pallidum	1447.5	257.6	1527.9	190.0	34.0	0.54
Amygdala						
L amygdala	1527.7	260.2	1634.6	221.4	35.0	0.59
R amygdala	1680.1	272.0	1753.2	417.5	44.0	0.93
Hippocampus						
L hippocampus	3943.8	296.9	4199.2	486.8	45.0	0.88
R hippocampus	4138.6	324.3	4314.5	453.1	52.0	0.49
Total estimated ICV	1507627.1	146862.7	1587332.61	145817.2	23.0	0.30

Significant group differences are in bold. L, Left; R, right; NAc, nucleus accumbens; ICV, intracranial volume.

1999; Dorris and Glimcher, 2004; Sugrue et al., 2004; Peck et al., 2009; Seo et al., 2009; Louie and Glimcher, 2010). Our finding that reward-related activity in the parietal cortex was significantly reduced in the vmPFC-lesioned patients suggests that vmPFC damage may attenuate reward-related signals outside the striatum.

One limitation of the present study is the inability to determine whether the vmPFC was engaged in response to reward cues in normal subjects. Unfortunately, the area of vmPFC damage in our patient sample corresponds almost exactly to the area of maximal fMRI signal dropout attributable to magnetic field inhomogeneities. In addition, the lesions almost certainly involved damage to white matter pathways in and around the vmPFC. Hence, we are unable to determine whether vmPFC damage disrupted local processing during the task, or perhaps impaired communication between the striatum and other cortical areas via damage to underlying white matter. To account for the absence of a lesion control group, we assessed baseline cerebral perfusion. Because ASL data indicated no gross alterations of perfusion in the vmPFC patients (either globally or in ventral striatum), the observed group differences in task activation cannot be readily explained by group differences in cerebral perfusion.

Another limitation of this study is that the Monetary Incentive Delay (MID) fMRI paradigm does not provide a sensitive behavioral measure of reward processing. To more conclusively determine the behavioral relevance of the observed abnormalities in ventral striatum structure and function, future studies could examine the link between striatal neurobiology and established behavioral measures of reward learning or value-based decision-making. In addition, it will be important to determine whether vmPFC damage is associated with less improvement in behavioral performance based on incentives relative to neurologically healthy subjects. One early study reported a "small but reliable tendency" for reaction time decreasing with higher reward magnitude on a task of 250 rewarded trials (Stillings et al., 1968). Another study reported an effect of reward magnitude on reaction time on a task that included a total of 300 trials (Park et al., 2012). Our MID task only included 30 rewarded trials, because it was tailored specifically for fMRI data collection to address the hypothesis regarding ventral striatum activation. There are a few possible ways to assess behavioral differences between groups in future studies. One would be to use a longer version of the MID task outside of the scanner with a greater number of rewarded trials. Another would be to use a delay discounting task, which

has been included as a behavioral test outside the scanner to complement the MID task in the scanner (Luo et al., 2009; Benningfield et al., 2014). A recent study examined incentivization by reward in vmPFC-lesioned patients using a speeded saccade task with an auditory incentive cue (Manohar and Husain, 2016). Consistent with our fMRI findings, vmPFC damage resulted in reduced saccadic velocity and autonomic pupil responses for rewards.

One feature of this study that warrants consideration is the limited sample size of vmPFC-lesioned patients ($n = 5$). For this study, we used extremely stringent selection criteria for our target group; lesions had to involve substantial portions of vmPFC bilaterally but could not extend significantly outside vmPFC. Furthermore, because the study involved fMRI, we could not include patients with metallic implants, such as aneurysm clips. To meet these criteria, we selected a group of patients who had all undergone surgical resection of large orbital meningiomas. So, although our sample size may be small by conventional vmPFC-lesioned patient standards (which typically feature 5–12 vmPFC-lesioned patients), it is unique with respect to the homogeneity of etiology, uniformity, and selectivity of bilateral vmPFC lesions and compatibility with fMRI.

In summary, these findings indicate a role for the vmPFC in contributing to reward-related activity of the ventral striatum. Our results offer new insight into the functional and structural interactions between the vmPFC and ventral striatum, two key components of the brain circuitry underlying human affective function and decision-making.

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