Functional Neuroimaging of Reward Circuitry Responsivity to Monetary Gains and Losses in Posttraumatic Stress Disorder

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Background: Clinical impressions and preclinical work suggest that posttraumatic stress disorder (PTSD) might be associated with dysfunctional reward processing. To pursue this issue, we administered a validated passive-viewing monetary reward task during functional magnetic resonance imaging (fMRI) to subjects with chronic PTSD and to mentally healthy individuals.

Methods: The protocol evaluated fMRI signal changes that anticipated or accompanied monetary gains and losses under varying conditions of controlled expectation. The “expectancy phase” entailed presentation of a promising, unpromising, or intermediate Wheel of Fortune-type spinner, whereas the “outcome phase” was defined by the arrow landing on one of three sectors of that spinner, thereby determining the subjects’ gain or loss for that trial.

Results: Neuroimaging data from 20 PTSD and 26 healthy subjects withstood quality control procedures and were included. In voxelwise and anatomically defined region-of-interest analyses, when gains were contrasted to losses, between-group comparison revealed smaller bilateral striatal activations in the PTSD subjects. In the PTSD group, less striatal activation to gains versus losses was associated with more self-reported motivational and social deficits.

Conclusions: The present data support the hypothesis that PTSD is associated with abnormal processing of monetary outcomes and that this alteration might be related to some aspects of emotional numbing.

Key Words: Corpus striatum, functional magnetic resonance imaging, motivation, posttraumatic, reward, stress disorders

Anxiety symptoms are considered a key component in posttraumatic stress disorder (PTSD) (1), and most functional neuroimaging investigations in these patients have focused on the brain’s fear system (2–4). However, recent research (5,6) also supports the inclusion of PTSD within a reward deficiency spectrum (7,8) comprising personality traits and mental disorders characterized by hypofunctionality of reward circuitry, and manifest as diminution of motivation and capacity to experience pleasure.

Several lines of evidence suggest deficits in the brain reward/reinforcement circuits in PTSD. From a clinical perspective, in addition to high prevalence of substance abuse (9), diagnostic features of PTSD itself suggest reward system dysfunction. The most notable of these are the “emotional numbing” symptoms, including anhedonia (i.e., loss of interest and pleasure) (1), which has been linked with reward function deficits in clinical (10) and mentally healthy (11) samples. The association between PTSD and reward deficits is also supported by animal findings of striatal dopaminergic hypoactivity (12,13) and decreased reward-seeking (14,15) resulting from chronic stress exposure in procedures that hypothetically (16) model the PTSD re-experiencing phenomenon (17).

To validate these clinical impressions and preclinical findings in a laboratory setting, we previously applied behavioral probes of reward function to PTSD subjects (5,6). In one study, we found that male heterosexual combat veterans with current PTSD exerted less effort to extend the viewing time of attractive female faces (5). In a second study, we investigated anticipatory and consummatory aspects of reward processing, assessed by subjective responses during a Wheel of Fortune-type game that provided passive monetary rewards. The PTSD combat veterans reported lower expectancy of and satisfaction with these rewards (6). Neuroimaging investigations have found that PTSD patients show less arousal (18) as well as smaller activations in temporal and parahippocampal brain regions (19) when exposed to pleasant images, and less activation in ventral striatum to positive feedback in a decision-making task (20).

Building upon our pilot behavioral findings (5,6), in the present experiment we used the same validated Wheel of Fortune-type monetary stimuli (6) in conjunction with blood-oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI) to investigate the neural basis of decreased reward responsivity in PTSD. Notably, a previous study in healthy subjects reported significant fMRI signal changes obtained from dopamine terminal fields (striatum, amygdala, and prefrontal cortex) induced by processing of expectancy and experience of monetary gains and losses on this task (21). We hypothesized that PTSD would be associated with decreased fMRI signal in reward-related brain areas during both expectancy and outcome phases of the employed procedure.

Methods and Materials

Procedure

The experimental procedure is detailed elsewhere (21). Subjects were told that an arrow would spin around a disk (spinner) and come to rest in one of three differentially colored sectors representing monetary gains or losses (Figure 1). There were three different spinners: a “good” spinner that generated a large gain ($10.00), a small gain ($2.50), or no gain ($0.00); a “bad” spinner that generated a large loss ($6.00), a small loss ($1.50), or...
no loss ($0.00); and an “intermediate” spinner that generated a small gain ($2.50), a small loss ($1.50), or neither ($0). Gains were set larger than losses to adjust for the greater salience of a loss than a gain of equal magnitude (22). Each subject’s familiarity with the spinners was confirmed via a brief computerized quiz, completion of which was conditioned on the correct understanding of the spinners.

Subjects were granted an endowment of $50 and informed that they might lose some or all of this stake, retain it, or increase it. The trial sequence was identical for all subjects and unknown to them it was programmed to a final net winning of $78.50. At the conclusion of the scanning procedures, subjects' estimates of their overall monetary gain or loss were obtained to provide a measure of attention and understanding.

The display consisted of either a fixation point (an asterisk) or one of the three spinners, projected onto a mirror situated within the bore of the scanner. The duration of each trial (a specific spinner presentation) was set at 12 sec, divided into two phases of 6 sec each. The “expectancy phase” constituted viewing one of the three spinners, which remained static for the first .5 sec and was then overlaid by a rotating arrow for 5.5 sec. Subjects were requested, as a measure of attention, to press one of the three buttons to identify the projected spinner during this 6-sec period. The onset of the “outcome phase” was marked by the rotating arrow's halting in one of the spinners’ three sectors. The sector in which it halted then flashed for 5.5 sec to highlight the outcome. The outcome phase was concluded with .5 sec of blank screen.

Subjects

Twenty-eight civilian subjects meeting the DSM-IV-TR criteria for PTSD, diagnosed via the Structured Clinical Interview for DSM-IV (23) and Clinician-Administered PTSD Scale (CAPS) (24), and 33 mentally healthy subjects were recruited by advertisement. After the procedures had been fully explained, each subject gave written informed consent to the protocol approved by the McLean Hospital Institutional Review Board. All subjects were right-handed as assessed with Edinburgh Handedness Inventory (25) and in good physical health as determined by the Cornell Medical Index Health Questionnaire (26). Subjects with a history of schizophrenia; paranoid; other psychotic, bipolar, non-PTSD anxiety; or substance dependence disorder were excluded. Given the high rate of depressive comorbidity in PTSD (9), subjects with onset of major depressive disorder after the traumatic event that caused the PTSD were allowed to participate. Recent drug and alcohol consumption was ruled out by negative results on urine toxicology screen and breathalyzer. We also excluded the use within the previous month of any poten-

tially confounding medications or drugs (e.g., opioids, psychostimulants, cannabinoids, dopaminergic or antidepressant agents including antipsychotics, and mood stabilizers and antidepressants with prominent catecholaminergic effects such as tricyclics, bupropion, mirtazapine, venlafaxine, and duloxetine). Psychotropic medications taken by the PTSD participants included selective serotonin reuptake inhibitors (n = 6), trazodone (n = 2), buspirone (n = 1), gabapentin (n = 1), topiramate (n = 1), and clonazepam (n = 1).

Protocol

The scanning session was subdivided into nine blocks of 19 trials each, separated by 2-min–4-min rest periods. The trial sequence was pseudorandom and fully counterbalanced so that trials of a given type (spinner and outcome) were both preceded and followed equally often by all nine spinner × outcome combinations.

Imaging Procedure

Scans were performed on a 3-Tesla Siemens Trio MR Imaging System (Siemens AG, Erlangen, Germany). A 3-plane scout scan (conventional FLASH sequence with isotropic voxels of 2.8 mm) was acquired. This was used for prescription of the fMRI image stack (gradient echo planar imaging [EPI], repetition time/echo time = 2000/30 msec, 220 mm × 220 mm field of view [FOV], 30 3-mm coronal slices starting from the anterior pole, no gap, right-left readout, 64 × 64 pixel, full k-space acquisition, no sensitivity encoding [SENSE] acceleration; pulse sequence-enhanced version of the Siemens epibold; total acquisition time 9 × 4: 04 min). The imaging volume was chosen to cover the ventral and dorsal striata along with other structures commonly implicated in PTSD neuroimaging studies viz., amygdala and prefrontal cortex (27–29). Automatic second order shimming was performed over the fMRI imaging volume before acquisition. After the functional scans, subjects had a conventional TI scan performed on the same functional prescription and therefore with identical susceptibility distortion (68 T1 weighted coronal slices, FOV = 220 mm × 220 mm, 256 × 256 pixel, 3-mm thick were acquired covering the whole brain, “matched warped”) (30) and a standard T1 weighted magnetization prepared rapid gradient echo (MPRAGE) three-dimensional (FOV = 256 mm × 256 mm × 170 mm, 256 × 256 × 128) for anatomic segmentation and parcellation. Functional MRI images were aligned to the high-resolution T1 weighted MPRAGE images in two steps with FMRIB’s Linear Image Registration Tool (FLIRT). Instead of using a conventional high-signal-to-noise ratio EPI image for the intermediate, we employ a high-resolution, T1-weighted “matched-warped” EPI image that increases the precision of the alignment between the functional dataset and the high-resolution MPRAGE (30). The MPRAGE was then aligned to Montreal Neurological Institute (MNI) space with FLIRT.

Data Processing and Voxelwise Statistical Analyses

With the exception of a few in-house programs, data processing was performed with FSL release 4.0 (FMRI Analysis Group, Oxford University, United Kingdom; http://www.fmrib.ox.ac.uk/fsl/), specifically FEAT version number 5.92.

Preprocessing procedures included the following steps. First, an in-house despiking filter was applied to all functional datasets. For each voxel and image, a local mean, median, and SD were obtained over an 11-image window centered on the value in question. If this value differed from the local mean by more than 6 local SDs, then the value was replaced by the local median.
simple Gaussian model yields a false-correction rate of $<2 \times 10^{-5}$/test, yielding 12.3 expected false corrections over all voxels, images, runs, and subjects. Second, all images within a scan were aligned to image #60 (in the middle), with mcflirt (31), with 6 degrees of freedom. If the maximum Euclidean deviation from this reference exceeded 3.0 mm (the smaller voxel dimension), the scan was discarded. Third, slice timing correction was performed. Fourth, non-brain voxels were removed. Fifth, spatial filtering was performed, with a Gaussian kernel with 5-mm full width half maximum. Sixth, global normalization was performed, such that the average over all voxels and images was fixed at 10^4.

Seventh, temporal filtering was performed, with a nonlinear high-pass filter with a cut-off of 18 sec. Each nonmotion regressor was subjected to a linear filter modeling the hemodynamic response function, having a gamma impulse response, width of 3 sec and mean lag of 6 sec. Nonmotion regressors were further subjected to the same temporal filter that was applied to the data. Regressors varied in a counterbalanced manner across runs, but each run was identical over all subjects. The results of this analysis were discarded, except for the residuals. A principal-component analysis was performed on the 5000 voxels in the residuals that had the largest variance. The first eight components were retained and used as additional nuisance regressors (without temporal filtering) in a new general linear model, with the same preprocessed functional data (33). From the resulting parameter estimates, the expectancies’ and outcomes’ contrasts were calculated.

Functional results were aligned with the matched T1-weighted scan with 6 degrees of freedom. This scan was in turn aligned with the high-resolution MPRAGE scan with 12 degrees of freedom. Finally, the MPRAGE scan was aligned with the MNI152 standard brain with 12 degrees of freedom. Rendering of the functional results in MNI space was performed once, after concatenating the three alignments into a single matrix. A summary of this functional results in MNI space was performed once, after concatenating the three alignments into a single matrix. A summary of this functional analysis was performed on the 5000 voxels in the residuals that had the largest variance. The first eight components were retained and used as additional nuisance regressors (without temporal filtering) in a new general linear model, with the same preprocessed functional data (33). From the resulting parameter estimates, the expectancies’ and outcomes’ contrasts were calculated.

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Structural Regions-of-Interest

Because the major result of interest in the aforementioned voxelwise analyses suggested activation of bilateral striatal structures to monetary gains minus losses in the outcome phase that was greater in healthy than in PTSD subjects (see Results section), we followed up by extracting BOLD signal responses for each subject from right and left nucleus accumbens, right and left caudate, and right and left putamen subregions, as anatomically determined in structural MRIs according to the Harvard-Oxford cortical and subcortical structural atlas (http://www.fmrib.ox.ac.uk/fsl/fslview/atlas-descriptions.html#ho). Functional MRI data in MNI space were overlaid on the anatomically defined regions-of-interest (ROIs) to determine regional activations. This procedure yielded a single BOLD activation value for each subject in each ROI. These data were then analyzed off-line via analysis of covariance (ANCOVA). In the case of analyses that tested directional hypotheses (i.e., lower responses to reward in PTSD), $p$ values obtained from the ROI analyses were multiplied by .5 when in the predicted direction (35).

Table 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PTSD (n = 20)</th>
<th>Healthy (n = 26)</th>
<th>t(44)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yr)</td>
<td>33.0 ± 10.5</td>
<td>28.0 ± 8.2</td>
<td>1.82</td>
<td>.08</td>
</tr>
<tr>
<td>Education (Yr)</td>
<td>14.5 ± 2.4</td>
<td>15.9 ± 1.9</td>
<td>2.24</td>
<td>.03</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>12/8</td>
<td>11/15</td>
<td>.37*</td>
<td></td>
</tr>
<tr>
<td>Race (W/B)</td>
<td>16/4</td>
<td>21/5</td>
<td>.99*</td>
<td></td>
</tr>
<tr>
<td>Outcome estimate ($)</td>
<td>54.6 ± 38.6</td>
<td>54.5 ± 63.9</td>
<td>.005</td>
<td>1.0</td>
</tr>
<tr>
<td>BDI Score</td>
<td>18.4 ± 13.5</td>
<td>3.0 ± 6.3</td>
<td>4.9</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Spinner Identification (#)</td>
<td>17.1 ± 4.4</td>
<td>14.2 ± 3.8</td>
<td>2.41</td>
<td>.02</td>
</tr>
<tr>
<td>Psychotropic Medications</td>
<td>SSRIs (n = 6), trazodone (n = 2), buspirone (n = 2), gabapentin (n = 1), topiramate (n = 1), and clonazepam (n = 1)</td>
<td></td>
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</tr>
</tbody>
</table>

Means ± SDs or ratios.

PTSD, posttraumatic stress disorder; BDI, Beck Depression Inventory; SSRIs, selective serotonin reuptake inhibitors.

*Fisher’s exact test.
Results

Subjects

Neuroimaging data from 20 PTSD (mean CAPS score; 70.8 ± 17.9) and 26 healthy subjects who had quality control procedures and were included in the analyses. Types of traumatic events in the PTSD subjects included rape (n = 6), physical assault (n = 5), and witnessing of violent death or injury (n = 9). As presented in Table 1, PTSD subjects were significantly less educated, had higher Beck Depression Inventory (BDI) scores, and made more mistakes on the spinners’ identification assignment. However, PTSD and healthy subjects made similar estimates of their net monetary gains across the experiment. Race and gender distributions were not significantly different between the groups.

Voxelwise Analyses

In the expectancy phase, between-group analyses of anticipation of probable monetary gain versus loss (i.e., response to the presentation of the good vs. bad spinner) in PTSD versus healthy subjects (i.e., group × spinner interaction) failed to produce any significant clusters of activation. Separate analyses in healthy subjects revealed a significant cluster of activation to the good minus bad spinner that comprised right nucleus accumbens, caudate, and putamen (MNI x, y, and z coordinates of the peak voxel: 16, 13, −2, respectively; cluster volume: 5.33 mL; corrected p = 0.02). Analyses in PTSD subjects revealed no significant clusters of greater activation to the good minus bad spinner. No significant activations across all subjects or activation differences between groups were revealed to the bad versus good spinner.

In the outcome phase, between-group analyses of experiencing gains versus losses collapsed across spinner types produced two significant clusters of activation in right and left nucleus accumbens, caudate, and putamen—both in the direction of more activation in healthy than in PTSD subjects (x, y, and z coordinates of the peak voxel on the right = 25, 2, −1, respectively; cluster volume: 3.71 mL; corrected p = 0.01; x, y, and z coordinates of the peak voxel on the left = −2, 8, 11, respectively; cluster volume: 2.92 mL; corrected p = 0.03), as shown in Figure 2. Separate analyses in healthy subjects revealed a single large significant cluster of greater activation to gains minus losses that comprised nucleus accumbens, caudate, putamen, pallidum, amygdala, insular cortex, cingulate gyrus, orbitofrontal cortex, frontal pole, and superior frontal gyrus, all bilateral (x, y, and z coordinates of the peak voxel: 26, 7, −8, respectively; cluster volume: 73.36 mL; corrected p < 0.001). No significant clusters of activations to gains minus losses were observed in PTSD subjects.

Anatomically Defined ROI Analysis

Because there were no significant group × subregion (i.e., right and left nucleus accumbens, right and left caudate, and right and left putamen), group × laterality, or group × subregion × laterality interactions, these 6 subregions were combined into a single anatomically defined ROI designated “striatum.” Parallel to the voxelwise results, healthy subjects showed significantly greater activation to gains minus losses [t(44) = 2.89, one-tailed p = 0.003] but exhibited a similar effect in a related reward structure, amygdala [t(44) = 0.98, one-tailed p = 0.17] (Figure 3). Striatal BOLD time courses (Figure 4) confirm PTSD patients’ hyporeactivity to the monetary stimuli.

A subsequent analysis controlled for potential habituation effects by including trial number as an additional predictor in the calculation of BOLD signal changes; analyses of these data yielded an essentially unchanged result [t(44) = 2.94, one-tailed p = 0.003].

Figure 2. Clusters of activation (colored) obtained from voxel contrasts of monetary gains minus losses collapsed across spinner type in healthy (n = 26) > posttraumatic stress disorder (n = 20) subjects projected onto a background (grayscale) representing subjects’ mean high-resolution anatomic image (apparent activation in a ventricle represents artifact). Coordinates are in accordance with the Montreal Neurological Institute (MNI) space.

Figure 3. Group means (± SEM) for the striatum and amygdala regions-of-interest (ROIs)’ blood-oxygen-level-dependent (BOLD) signal changes in response to gains minus losses collapsed across spinner type. Because there were no significant laterality effects or group × laterality interactions, the same anatomic regions in the right and left hemisphere were combined into a single ROI PTSD, posttraumatic stress disorder.
Figure 4. Single trial analysis is shown as mean BOLD timecourses of responses to best minus worst outcome within striatum for PTSD and healthy subjects. Striatal ROI responses to the best and the worst outcome was averaged over all runs for each subject. Time course statistics were computed across subjects for both groups and are presented as mean ± SEM. The abscissa is the time relative to the onset of the outcome phase (when the rotating arrow halts in one of the spinners' three sectors). The ordinate displays the percent activation relative to the mean value over time. Note that, due to the hemodynamic lag, maximal response is observed approximately 8 sec after the outcome onset. Abbreviations as in Figure 3.

After adjusting the latter analysis for three potentially confounding variables that significantly differed between groups (Table 1) (viz., education, BDI score, and number of correct spinner identifications), via ANCOVA, this effect still remained significant \(F(1,41) = 8.03, \) half-tailed \(p = .004\). Repeating the latter analysis after excluding the nine subjects with current depression or current medication use (all in the PTSD group), the effect again remained significant \(F(1,32) = 4.52, \) half-tailed \(p = .02\).

To determine the potential contributions to group differences of gains and losses separately, ANCOVAs contrasted brain ROI responses to the best or the worst outcomes versus the intermediate outcomes. The results indicate significantly lower responsivity in the PTSD group to gains \(\{.09 ± .19 ± .22\}, F(1,41) = 3.60, \) half-tailed \(p = .03\) but not to losses \(\{.05 ± .3 vs. -.17 ± .3\}, F(1,41) = 2.98, p = .09\). However, note that the latter result would be significant at half-tailed \(p < .05\).

Exploratory analyses within the PTSD group revealed significant negative Pearson product-moment correlations between striatal BOLD response to gains minus losses and subscores on the CAPS items “markedly diminished interest in significant activities” \(r(18) = -.45, p < .05\) and “feelings of detachment or estrangement from others” \(r(18) = -.55, p = .01\) (Figure 5) but not “restricted range of affect” \(r(18) = -.09, p = .70\) or “sense of foreshortened future” \(r(18) = .17, p = .47\).

Discussion

We found that, during the passive experiencing of monetary gains compared with losses and monetary gains compared with intermediate outcomes, subjects with PTSD showed significantly smaller bilateral striatal activations. Thus, the present results extend our earlier work with behavioral probes and self-report in which we also found PTSD-related decrements in reward function, as indicated by reduced motivation for viewing beautiful female faces (5) and self-reported expectancy and satisfaction with monetary rewards (6). Although there were methodological similarities between the latter and current study (e.g., enrollment of PTSD subjects and use of the same monetary reward task), there were also important differences, including the neuroimaging component and the focus on civilian rather than combat-related PTSD. Furthermore, the present data demonstrate an association in PTSD subjects between diminished striatal response to monetary reward and self-reported symptoms of emotional numbing (viz., decreased interest and detachment from others). Numbing of responsiveness to positive stimuli and anhedonia are common in PTSD patients (1) and are considered by some to be the most specific diagnostic features of the disorder (36).

The pattern of results obtained in the healthy subjects (viz., striatal activation to gains accompanied by striatal deactivation to losses) is consistent with prior observations (21,37–43). Interestingly, the present PTSD subjects showed not only less striatal activation to gains but also a trend toward less striatal deactivation to losses (which would have been statistically significant had this result been predicted a priori). This pattern suggests that PTSD patients, in addition to being unmoved by life’s rewards, might also be indifferent to at least some of life’s punishments. More research is needed to pursue the latter possibility. Addi-

Figure 5. Scatterplots relating individual BOLD signal changes in a bilateral striatal ROI within PTSD subjects to their Clinician-Administered PTSD Scale (CAPS) scores for (A) “markedly diminished interest in significant activities” (DSM-IV-TR criterion C4), and (B) “feelings of detachment or estrangement from others” (DSM-IV-TR criterion C5). \(r = \) Pearson product-moment correlation coefficient. Abbreviations as in Figure 3.

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tionally, clinical PTSD assessments might benefit from specific questioning concerning the emotional and motivational significance not only of positively but also of negatively valenced material to enhance psychopathology characterization and formulation of treatment plans.

The question regarding specificity of neural responses to expectancy versus outcome phases of rewards is still being debated (21,44). Even though the fixed trial length employed in the present study necessarily entailed some degree of correlation between expectancy and outcome regressors that would tend to decrease the efficiency with which activations during these two phases could be separated, their dissociability was nevertheless supported by the present findings of striatal activations that were more pronounced during the outcome phase and by significant between-groups differences that were confined to this condition. An alternate interpretation is rooted in behavioral economics’ conceptualization of money as a conditioned reinforcer that creates an expectancy of subsequent material rewards (45–47) and might therefore engage expectancy regions.

Prevailing theories on reward neurobiology ascribe different roles to ventral and dorsal striatal subregions, with the former relating to reward salience and prediction and the latter relating to action planning and initiation in the context of past experiences (48,49). Being a conditioned reinforcer (50,51), money can be processed as a reward per se as well as a stimulus to strategize subsequent actions to obtain more tangible rewards. Our findings of reduced ventral and dorsal striatal activations suggest that both processes are impaired in PTSD. Even though the procedure employed did not allow us to segregate these processes, basic (52,53) and clinical (54,55) research suggests that they are mediated by the same neurotransmitter (viz., dopamine), released in the ventral and dorsal striatum. Indeed, abnormalities in D2 dopamine receptors, located in ventral and dorsal striatal regions (56), have been observed in PTSD (57–59), but see 60) as well as in other disorders that are included within a “reward deficiency” spectrum (7,8,61,62).

It should be noted that in the voxelwise analyses of the two groups separately, the PTSD subjects failed to show activation in some brain areas (other than striatum) in which the non-PTSD subjects did show activation, including pallidum and amygdala as well as insular, cingulate, orbitofrontal, and frontal cortices. This raises the possibility that PTSD subjects fail to activate a broader brain system in response to reward presentations. However, in the absence of statistically significant between-group differences in the aforementioned areas, this remains only a possibility deserving of further investigation.

A limitation of the cross-sectional design of this study is its inability to resolve the risk factor versus acquired origin of hyposensitive reward in PTSD, which will require prospective and/or twin studies. Another caveat that should be considered in interpreting these data pertains to medication status. There is a considerable amount of preclinical (63,64) and clinical (65,66) data supporting the attribution of reward changes to pharmacotherapy with serotoninergic and other (67) agents used by our patients. Even though—after excluding subjects with current medication use—the diminished reward effect in the PTSD group remained significant, the question regarding the precise role of PTSD pharmacotherapy in modulation of reward function still remains open, and more research controlling for medications status is warranted. Additionally, although possible attentional confounds were reasonably controlled through overall monetary outcome estimates and spinners identification, with regard to the latter task, several factors other than attention (e.g., motor-spatial skills, working memory, and executive functions) might have influenced performance on an assignment that involves locating and pressing an unseen button while in the scanner. Fully addressing this issue would require disentangling the aforesaid components via an exclusively passive procedure that does not employ motoric output.

As noted in the preceding text, the striatum seems to play a substantial role not only in reward function but also in both stress and anxiety (12–15). This raises the possibility of a functional reciprocity between heightened stress reactivity and emotional numbing in PTSD (68), which is a testable hypothesis that could be evaluated in PTSD subjects by juxtaposing responses to functional neuroimaging probes that reliably activate both brain stress and reward regions. Finally, the current findings could have important treatment implications, because they suggest the use of reward-enhancing behavioral or pharmacological interventions for PTSD symptom amelioration. In this respect, it is noteworthy that atypical antipsychotics, which have been suggested to correct reward system deficits that might characterize negative symptoms of schizophrenic patients (69,70), have been tried with some success in PTSD (71–73). It would be of interest to test whether atypical antipsychotics are able to reverse the reward dysfunction in PTSD observed here.

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