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Resting amygdala and medial prefrontal metabolism predicts functional activation of the fear extinction circuit

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Abstract

Objective—Individual differences in ability to control fear have been linked to activation of dorsal anterior cingulate cortex, ventromedial prefrontal cortex, and amygdala. This study investigated whether functional variance in this network can be predicted by resting metabolism in these same regions.

Methods—Healthy subject volunteers were studied with positron emission tomography using [18F]-deoxyglucose to measure resting brain metabolism. This was followed by a two-day fear conditioning and extinction training paradigm in a functional magnetic resonance imaging scanner to measure brain activation during fear extinction and its recall. Skin conductance response was used to index conditioned responding. Resting metabolism in amygdala, dorsal anterior cingulate cortex and ventromedial prefrontal cortex were used to predict responses during fear extinction and extinction recall.

Results—During extinction training, resting amygdala metabolism positively predicted ventromedial prefrontal cortex, and negatively predicted dorsal anterior cingulate cortex, activation. In contrast, during extinction recall, resting amygdala metabolism negatively predicted ventromedial prefrontal cortex, and positively predicted dorsal anterior cingulate cortex, activation. Resting dorsal anterior cingulate cortex metabolism predicted fear expression (skin conductance response) during extinction recall.

Conclusions—Brain metabolism at rest predicts neuronal reactivity and skin conductance changes associated with recall of the fear extinction memory.

Introduction

Much has been learned about the brain network implicated in processing fear learning and its expression. Fear conditioning and extinction are believed to induce synaptic plasticity

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within the amygdala. Amygdala GABAergic neurotransmission modulates both acquisition of fear (1) and its extinction consolidation (2), suggesting that this structure plays a critical function in both fear learning and its extinction. In addition to the amygdala, fear extinction and extinction recall also engage the infralimbic cortex in rodents (3, 4) whereas the more dorsal prelimbic cortex is associated with fear expression (5). In humans, increased activation of the amygdala to conditioned and extinguished cues has been reported in several neuroimaging studies (reviewed in 6). Structure and functional reactivity in the ventromedial prefrontal cortex, the functional homologue to the rat infralimbic cortex, are associated with fear inhibition (7) and extinction recall (8–10). Conversely, structure and functional reactivity in the dorsal anterior cingulate cortex, an apparent functional homologue to the rat prelimbic cortex, is likely critical for maintaining a balance between fear expression and inhibition. In support of this, high structural integrity of the amygdala-ventromedial prefrontal cortex white matter tracts is associated with low anxiety levels (11).

Many of the above rodent studies show that functional variation in infralimbic and prelimbic cortices are associated with variation in conditioned freezing. Human neuroimaging studies show substantial individual variation in the activation of the amygdala, ventromedial prefrontal cortex, and dorsal anterior cingulate cortex during fear extinction. Individual differences in activation of these brain regions correlate with psychophysiological indices of fear expression (9, 12). Moreover, ventromedial prefrontal cortex and dorsal anterior cingulate cortex thicknesses are associated with psychophysiological response during fear extinction (13). These data indicate that there are biological factors that influence the ability to express and control fear, which pre-date exposure to fear-inducing stimuli (14–16).

Much regional cerebral activity in functional magnetic resonance imaging (fMRI) experiments is disregarded (17), because the method relies on contrasting blood oxygenation dependent (BOLD) signal between conditions. Neural reactivity induced by cue presentation, typically measured with BOLD signal, accounts for only 1–10% of the brain's energy consumption, a small portion of total neuronal activity (14–16). Positron emission tomography (PET) using (^{18}F)2-fluoro-2-deoxy-d-glucose (FDG) provides a stable (18) estimate of total, as opposed to cue-induced, brain activity by quantifying regional cerebral metabolism at rest (19, 20), which closely correlates with neuronal signalling (21). Higher amygdala and dorsal anterior cingulate metabolism and lower ventromedial prefrontal cortex metabolism at rest have all been related to anxiety (22–24). Thus, one possibility is that functional brain *reactivity* may depend, to some extent, upon resting regional brain *activity*. If true, resting activity assessed with PET should predict subsequent functional reactivity assessed with fMRI, specifically during fear extinction and/or extinction recall tasks.

To test this hypothesis, resting brain *activity* (metabolism) was measured using FDG PET at rest. Within five days of the PET scan, the same subjects underwent a two-day fear conditioning and extinction protocol (Supplemental Figure 1a) in the fMRI scanner, to measure brain *reactivity* during fear extinction and its recall (9). Skin conductance responses were used as an index of conditioned fear responses. Data analysis focused on *a priori* regions of interest, namely the amygdala, ventromedial prefrontal cortex and dorsal anterior cingulate cortex, based on their involvement in fear conditioning and extinction as reviewed above.

We hypothesized that 1) resting metabolism in the amygdala, ventromedial prefrontal cortex and dorsal anterior cingulate cortex would predict fear response measured by skin conductance; 2) resting amygdala metabolism would predict ventromedial prefrontal cortex and dorsal anterior cingulate cortex functional activations during extinction training and recall; 3) ventromedial prefrontal cortex metabolism and dorsal anterior cingulate cortex metabolism would positively and negatively predict, respectively, extinction recall; and 4) given that ventromedial prefrontal cortex functional activation is associated with fear reduction whereas dorsal anterior cingulate cortex activation is associated with fear expression, the metabolism *ratio* between these two regions would predict functional activation of the extinction network during learning and recall (9).

Materials and Methods

Subjects

Twenty-one right-handed healthy volunteer subjects (11 males) between 21 and 40 years old (mean = 26, S.D. = 5) were recruited from the local community. Due to excessive movement, MRI data from three subjects were excluded, yielding a final sample size of 18 (8 males). After a complete description of the study and its procedures, written informed consent was obtained in accordance with the Partners Healthcare System Human Research Committee requirements. Data from this cohort have not been reported in any prior publications.

Fear conditioning, extinction and recall

The experimental protocol was identical to that of previous studies described by Milad and colleagues (9). Briefly, subjects were habituated to all task images (not to be confused with magnetic resonance images) prior to conditioning, during which no shock was presented. During fear conditioning, subjects were shown an image of a room (an office) containing an unlit lamp. The lamp was then “turned on” to reveal one of three colors (blue, red, or yellow; Supplemental Figure 1a) during 32 trials. During 8 trials of each, two colors (reinforced conditioned stimuli) were presented for 6 seconds followed by a highly annoying but not painful shock to the fingers at a 62.5% partial reinforcement schedule, whereas 16 trials of the third color (non-reinforced conditioned stimulus) were not followed by a shock. The inter-trial interval, with no displayed images, was varied between 12 and 18 seconds. No shocks were administered during the subsequent phases of the experiment. Shortly thereafter, during extinction training, subjects were shown images of a second room (library) with a lamp that again “turned on” for 32 trials. Only one of the two reinforced cues (i.e. colors) was extinguished (extinguished conditioned stimulus; 16 trials), whereas the other was not presented (non-extinguished conditioned stimulus). Sixteen trials of the non-reinforced cue were also presented. On the second day of the experiment, extinction recall was tested. Subjects were again shown the library with the light “turning on” for 32 trials. Subjects were presented with the 8 trials each of the extinguished and non-extinguished cues, and 16 trials of the non-reinforced cue. Skin conductance responses to the stimulus presentations were measured throughout the fMRI experiment; see Supplemental Methods and Supplemental Figure 1 for details.

Data preprocessing, analysis and statistical inferences

During all phases of the experiment, fMRI was performed with a Trio 3.0 Tesla whole-body, MRI system (Siemens Medical Systems, Iselin, New Jersey) equipped for echo planar imaging (EPI) with a 32-channel head coil. SPM8 (www.fil.ion.ucl.ac.uk) was used to process PET and MRI data (for additional details on both fMRI and PET data collection, see supplemental material). For PET analysis, each subject's static FDG image was co-registered to individual high-resolution structural MR images. After spatial normalization of the structural images to the SPM8 ICBM Montreal Neurological Institute (MNI) template, the same normalization parameters were applied to the PET images, which were then smoothed (8 mm Full Width Half Maximum) and finally global mean normalized to 50.

Functional images were realigned, corrected for slice timing, co-registered with the structural image, normalized into MNI space using parameters obtained from the structural normalization process, and finally smoothed (8 mm FWHM). After preprocessing, each subject's functional time series was modeled using a general linear model with regressors signifying the stimulus onsets and durations. Based on our previous studies (9, 13, 25–27), during extinction training, the extinguished cue was divided into the first 4 cue presentations (early extinction; reflective of recalling the fear memory), the subsequent 8 cue presentations (mid extinction) and the last 4 cue presentations (late extinction; to capture neural correlates of completed extinction). The context, the non-reinforced cue and the cue offsets were also modeled. During extinction recall, separate regressors modeled the first 4 (early; reflective of extinction recall) extinguished and non-extinguished cues, the subsequent 8 (late, reflective of re-extinction) extinguished and non-extinguished cues, the context, the non-reinforced cue (the cue not paired with shock during conditioning), and the cue offsets. Signal drift, biorhythms and motion artifacts were modeled using high-pass temporal filtering (128s), an autoregressive AR-1 model and six motion parameters (x,y,z, roll, pitch and yaw). Activated voxels in each experimental phase were identified using a statistical model containing boxcar function representing the contrasts of interest, convolved with the SPM8 canonical hemodynamic response function.

First-level contrast images were obtained for each subject and then modeled at the second level using a mixed linear model with subject and task factors as independent variables. To test for extinction processes, early trials were contrasted to late trials of the previously reinforced cue (extinguished conditioned stimulus), as defined above. To test for extinction recall the next day, early extinguished cue trials were contrasted to early non-extinguished cue trials, while controlling for order effects with the adjacent trials of the non-reinforced cue. The rationale for trial grouping was based on our previous human studies (9, 13, 25–28) and the animal literature (3), showing that ventromedial prefrontal cortex involvement in extinction recall is only evident during the early phase of extinction recall. Results from the fear-conditioning phase of the experiment are reported elsewhere (Linnman et al., under review).

Statistical inferences

For all analyses, clusters in the resulting SPM map that exceeded 10 voxels and were significant at family wise error (FWE)-corrected $p < 0.05$ were considered significant. Given

our prior studies in fear extinction, and studies conducted by other laboratories, we had strong uni-directional *a priori* hypotheses with respect to the functional reactivity of the ventromedial prefrontal cortex, dorsal anterior cingulate cortex, and amygdala. These regions of interests were the same used in the extraction of metabolic measurements from PET data (see below) with the exception of sphere size. Briefly, the left and right amygdala were defined by the Anatomical Automatic Labeling atlas (30). The ventromedial prefrontal cortex was defined using a 8 mm sphere centered at MNI coordinates (x,y,z = 5, 35, -13) selected on the basis of our previous study on ventromedial prefrontal cortex cortical thickness correlates of extinction memory (14). The dorsal anterior cingulate cortex was defined by a 8 mm sphere centered at MNI coordinates (x,y,z = 2, 22, 29) selected on the basis our previous study of involvement of the dorsal anterior cingulate cortex in conditioned fear (11). Within these *a priori* regions, clusters surviving small volume (8 mm radius sphere, approx. 2100 mm³) correction at $p < 0.05$ FWE corrected were also considered significant.

Metabolism as a predictor of BOLD fMRI and skin conductance responses

A priori we were interested in the roles of the amygdala, the ventromedial prefrontal cortex and the dorsal anterior cingulate cortex in the retention of extinction memory. Individual FDG metabolism measures were calculated from four predefined regions of interest, the bilateral amygdala, the ventromedial prefrontal cortex and the dorsal anterior cingulate cortex with identical definitions as the fMRI regions of interest above, with the exception that the dorsal anterior cingulate and ventromedial prefrontal cortex regions were 5 mm radius spheres. The average metabolism in these regions as well as the ventromedial prefrontal cortex/dorsal anterior cingulate cortex metabolism ratio was calculated for each individual. To correlate resting metabolism with fear during extinction learning and recall, skin conductance indices were calculated (see Supplemental Methods) and entered into a linear regression model with the FDG-PET images. Resting metabolism measures were also entered in linear regression models to investigate their respective influences on BOLD reactivity during extinction training and extinction recall.

Control brain region

For reasons discussed below, we also conducted an additional analysis to examine whether metabolism in primary visual cortex (defined as Broadmann area 17 in the Anatomical Automatic Labeling atlas (30)) predicted its own BOLD reactivity during the presentation of visual stimuli compared to the baseline (with no visual stimuli) during extinction recall.

Results

Skin conductance responses during extinction training and recall

During extinction training, a significant decline in skin conductance responses was observed from the first 4 early extinguished cue trials to the last 4 late extinguished cue trials (see Supplement Figure 1b, center), indicating that extinction learning had occurred. During extinction recall the next day, skin conductance responses to the extinguished cue were significantly lower than to the non-extinguished cue, indicating the recall (retention) of extinction learning (see Supplemental Figure 1b, right).

Functional MRI responses during extinction training and recall

As previously stated, extinction training was divided into an early (reflecting recall of the acquired fear association) and a late (reflecting extinction learning) phase. We observed amygdala deactivation from the early to late trials of the extinguished cue (MNI coordinates $x,y,z = -26, 2, -16$, $t(17) = 3.42$, $p_{FWE}=0.019$), a finding that is consistent with reduced expression of the conditioned fear response as extinction proceeded. In contrast, an observed ventromedial prefrontal cortex activation ($x,y,z = 10, 48, -8$, $t(17) = 3.37$, $p_{FWE}=0.022$, Figure 1 left) from early to late trials of the extinguished cue is consistent with a role for this structure in extinction learning. During extinction recall the next day, contrasting BOLD responses between the early extinguished versus non-extinguished cue trials revealed ventromedial prefrontal cortex activation ($x,y,z = 10, 42, -18$, $t(17) = 3.43$, $p_{FWE} = 0.018$, Figure 1 right), replicating earlier findings (8, 9) and consistent with a role for this brain region also in the recall of the previous day's extinction training. Significant activations and deactivations observed outside the *a priori* regions of interest are reported in Supplemental Table 1. An additional analysis examined the responsiveness of the ventromedial prefrontal cortex during extinction recall to the early extinguished and non-extinguished cue trials relative to the fixation baseline. Results indicated that relative to baseline, the ventromedial prefrontal cortex was activated by the extinguished cue but deactivated by the non-extinguished cue (see Supplemental Figure 2).

Regional brain metabolism as a predictor of skin conductance responses

In none of our *a priori* regions of interest did regional metabolism predict skin conductance responses during extinction learning. During extinction recall, however, dorsal anterior cingulate cortex metabolism positively predicted skin conductance response ($x,y,z = 8, 32, 26$, $t(17) = 5.21$, $p_{FWE} = 0.015$, $r = 0.80$, Figure 2), the latter of which is indicative of poorer recall of fear extinction.

Regional brain metabolism as a predictor of BOLD activations

Examining the association between resting amygdala metabolism and subsequent BOLD reactivity in the contrast between early versus late trials of the extinguished cue during extinction training, left amygdala metabolism was found *negatively* to predict dorsal anterior cingulate cortex activation ($x,y,z = 8, 14, 26$, $t(17) = 3.74$, $p_{FWE} = 0.035$, $r = -0.68$, Figure 3a), whereas right amygdala metabolism *positively* predicted ventromedial prefrontal cortex activation ($x,y,z = -4, 48, -18$, $t(17) = 3.87$, $p_{FWE} = 0.020$, $r = 0.70$, Figure 3b). Moreover, ventromedial prefrontal cortex metabolism positively predicted left amygdala activation ($x,y,z = -22, -4, -26$, $t(17) = 3.80$, $p_{FWE} = 0.035$, $r = 0.69$, Figure 4). Neither metabolism in the dorsal anterior cingulate cortex nor the ventromedial prefrontal cortex/dorsal anterior cingulate cortex metabolism ratio significantly predicted BOLD responses during extinction training.

Regional metabolism was then examined in relation to BOLD reactivity during extinction recall in the contrast between early extinguished and non-extinguished cue trials. In marked contrast to extinction training, left amygdala metabolism now *positively* predicted dorsal anterior cingulate cortex activation ($x,y,z = 16, 12, 30$, $t(17) = 4.27$, $p_{FWE} = 0.032$, $r = 0.73$, Figure 3a), whereas right amygdala metabolism *negatively* predicted ventromedial prefrontal

cortex activation ($x,y,z = 14, 56, -10$, $t(17) = 3.86$, $p_{FWE} = 0.021$, $r = -0.69$, Figure 3b). Scatter plots of the observed correlations are presented in Supplementary Figure 3. The ventromedial prefrontal cortex/dorsal anterior cingulate cortex metabolism ratio positively predicted rostral anterior cingulate activation ($x,y,z = -4, 42, 4$, $t(17) = 3.67$, $p_{FWE} = 0.035$, $r = 0.68$, Figure 5); rostral anterior cingulate cortex is a component of ventromedial prefrontal cortex. Neither ventromedial prefrontal cortex nor dorsal anterior cingulate cortex metabolism alone predicted functional activations during extinction recall, including activations in their own regions; the latter also applied to amygdala. In contrast, metabolism in the primary visual cortex control region did significantly predict its own functional reactivity in response to all visual stimuli presented during recall compared to non-visual baseline (see Supplementary Figure 4).

Discussion

The unique feature of the present work is the use of a multi-modal approach to examine the relationship between resting regional brain *activity* (i.e., metabolism) and subsequent psychophysiological and functional neuroimaging *reactivity* in the network of brain regions involved in fear extinction training and extinction recall. With regard to functional reactivity (fMRI) during extinction training and extinction recall, we largely replicated previous findings from our group and others (6, 8–10, 25). We also determined the extent to which preceding resting metabolism obtained via FDG PET could predict fMRI responses. Results revealed several interesting correlations. During extinction training, higher resting amygdala metabolism predicted transient dorsal anterior cingulate cortex deactivations and ventromedial prefrontal cortex activations. These associations are consistent with the critical involvement of the amygdala in the extinction learning process as opposed to its separate roles in fear learning and fear expression. However, the above predictive relationships reversed during extinction recall, such that higher resting amygdala metabolism now predicted activation of dorsal anterior cingulate cortex and deactivation of ventromedial prefrontal cortex. This result is consistent with a role for of ventromedial prefrontal cortex in inhibiting the amygdala's expression of the fear response during extinction recall, and a role for the dorsal anterior cingulate cortex in promoting it. Electrophysiological data in the rat show that at least two separate populations of neurons exist within the amygdala, one that signals fear acquisition and expression, and another that signals fear extinction (29). The present results, however, did not reveal that amygdala metabolism was predictive of extinction learning as measured by skin conductance response. Future studies with higher resolution to allow the parceling of amygdala subregions may reveal such a relationship. Further animal studies, possibly employing of optogenetic tools (30), are also needed to examine the interaction between different populations of amygdala neurons with different prefrontal regions during fear acquisition and extinction.

The lack of correlations between resting metabolism in amygdala, ventromedial prefrontal cortex, and dorsal anterior cingulate cortex with their own functional reactivity during any phase of the experiment may appear counterintuitive. However, we did observe such a relationship in the visual cortex region, where the higher this region's resting metabolism, the higher its BOLD reactivity to visual stimuli during extinction recall. Results in this control brain region demonstrate that the methodology employed here is capable of

detecting such an intraregional predictive relationship where it exists in the brain. Results in our *a priori* regions of interest suggest that a simple intraregional baseline activity-functional reactivity association model possesses insufficient explanatory value in the higher integrative cortical areas that are implicated in fear conditioning and extinction, which have more complex excitatory and inhibitory anatomical connections and functional roles.

It is also important to note that results in our *a priori* regions are consistent with several findings obtained with different experimental modalities. For example, in healthy subjects, the S-allele of the serotonin transporter promoter polymorphism is associated with elevated threat-related reactivity of the amygdala (31), but baseline blood flow appears unaffected by this polymorphism (32). In social phobia, amygdala resting blood flow is normal (33), but amygdala reactivity is elevated. Thus, our data and those of others suggest that within a region, resting metabolism and functional reactivity are not necessarily linked. Rather, according to our results, resting activity in particular regions appear to relate to transient reactivity in functionally connected regions dependent on the experimental context. More studies are needed to further examine the relationship between resting metabolism and functional reactivity across modalities within the human brain.

Given our previous studies showing opposite structural and functional correlations between the dorsal anterior cingulate cortex and ventromedial prefrontal cortex during fear expression and extinction recall, we hypothesized that resting metabolic activity within these two regions would oppositely predict extinction recall performance. In support of this hypothesis, resting dorsal anterior cingulate cortex metabolism did predict skin conductance response during extinction recall, but resting ventromedial prefrontal cortex metabolism did not. Further investigation of this hypothesized opposite relationship is warranted.

Several caveats resulting from this study's multi-modal design should be considered while interpreting the current findings. First, the inferred predictive value of regional brain metabolism for fear extinction and recall relies on stability over time. We have recently demonstrated that individual extinction recall responses in our psychophysiological paradigm are reliable over 12 weeks (28). With regard to metabolism, activity in cortical structures has been found to be more stable over time compared with subcortical structures (18). Given that the duration of time between the PET and fMRI phases of the experiment was no longer than 5 days (2 days on average), we expect the PET measures would be stable. However, PET and MRI data acquisition within the same experimental session is a next step (34). Recent studies also indicate that resting state functional connectivity may be used as a predictor of subsequent functional and behavioral responses (35), an exciting concept that complements the current approach. Another caveat is that both PET and fMRI have limited spatial resolution and thus likely obscure finer anatomical details, especially in small structures such as the amygdala, which contain substructures that may exert opposing influences on behavior. The development of imaging techniques with greater spatial and temporal resolution should help to address this problem. Lastly, the correlation coefficients observed in the present study may be inflated due to sample size and multiple comparisons despite the statistical corrections employed; accordingly, they should be interpreted with caution.

In summary, the data gathered from the present study suggest that resting dorsal anterior cingulate cortex and/or ventromedial prefrontal cortex metabolism might predict the magnitude of fear learning and fear extinction in healthy individuals. As recent studies have shown that fear extinction is impaired in patients with psychiatric disorders (36–39) and that the functional activation of the dorsal anterior cingulate and ventromedial prefrontal cortices are abnormal in the context of fear extinction within posttraumatic stress disorder (37, 40), future studies delineating whether resting metabolism measurements predict the degree of successful extinction recall in anxiety disorders, and the degree of treatment response, are indicated. In support of this possibility, two recent twin studies found that elevated resting dorsal anterior cingulate cortex metabolism and functional responsivity are risk factors for developing PTSD (24, 41). Furthermore, patients with PTSD have been found to display altered subgenual anterior cingulate cortex and amygdala functional connectivity at rest (42, 43). Pharmacological anti-anxiety treatment has been reported to decrease resting amygdala and increase ventromedial prefrontal cortex metabolism (22, 44). An additional question is whether regional brain metabolism can predict the success, or lack thereof, of cognitive behavioral therapy for anxiety disorders, as been found for functional activation (45). Ability to predict treatment response to therapy with neuroimaging tools might help guide treatment selection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BOLD signal during Extinction learning

BOLD signal during Extinction recall

Figure 1. BOLD activations during extinction training and extinction recall

The BOLD responses during extinction training (left) represent activations to the conditioned stimulus during late extinction contrasted with early extinction. The recall contrast (right) represents activations to the extinguished cue contrasted with activations to the non-extinguished cue. Activation maps are illustrated with a threshold of $t(17) > \pm 2.11$ ($p_{\text{uncorrected}} < 0.05$) and overlaid on a template structural MRI image.

dACC metabolism predicts differential SCR during extinction recall

Figure 2. Resting pre-training dorsal anterior cingulate cortex metabolism predicts differential skin conductance responses during extinction recall

Whole brain correlation map showing that dorsal anterior cingulate cortex metabolism was positively correlated with skin conductance responses to the extinguished cue (minus the CS-; $r = -0.80$), indicative of spontaneously recovered fear. Correlated responses are illustrated with a threshold of $t(17) > \pm 2.11$ ($p_{\text{uncorrected}} < 0.05$) and overlaid on the average metabolism PET maps from the study.

Figure 3. Resting amygdala metabolism predicts functional activations in dorsal anterior cingulate cortex and ventromedial prefrontal cortex during extinction training and extinction recall

Resting metabolisms in the left and the right amygdala were extracted and used to predict BOLD activations elicited during extinction training and extinction recall. Left amygdala metabolism (**a**) negatively predicted dorsal anterior cingulate cortex responses during extinction training, but it positively predicted dorsal anterior cingulate cortex responses during extinction recall. Right amygdala metabolism (**b**) positively predicted ventromedial prefrontal cortex responses during extinction training, but it negatively predicted ventromedial prefrontal cortex responses during extinction recall. Correlated responses are illustrated with a threshold of $t(17) > \pm 2.11$ ($p_{\text{uncorrected}} < 0.05$) and overlaid on a template structural MR image.

Pre training vmPFC
metabolism...

...predicts reactivity during
Extinction Learning

Figure 4. Resting pre-training ventromedial prefrontal cortex metabolism predicts amygdala functional activity during extinction training

Metabolism in the ventromedial prefrontal cortex was extracted and used to predict BOLD activations during extinction training. Ventromedial prefrontal cortex metabolism positively predicted left amygdala responses ($r = 0.76$). Correlated responses are illustrated with a threshold of $t(17) > \pm 2.11$ ($p_{\text{uncorrected}} < 0.05$) and overlaid on a template structural MRI image.

Figure 5. Ventromedial prefrontal cortex/dorsal anterior cingulate cortex resting metabolic ratio predicts prefrontal cortex functional activity during extinction recall

The ratio of ventromedial prefrontal cortex to dorsal anterior cingulate cortex metabolism was calculated and used as to predict BOLD activations elicited during extinction recall. The ventromedial prefrontal cortex/dorsal anterior cingulate cortex ratio was positively correlated to genual anterior cingulate extinction recall responses ($r = 0.65$). Correlated responses are illustrated with a threshold of $t(17) > \pm 2.11$ ($p_{\text{uncorrected}} < 0.05$) and overlaid on a template structural MRI image.