Supplemental Methods and Table S1

Supplemental Methods

Multivatriate pattern classification

For the multivariate pattern classification analysis (1, 2), we converted the relevant individual-level contrast images, masked by the a priori regions of interest described in the main text, or a whole brain gray matter mask, into a matrix of vectors, using the set of 24 controls and 17 patients. Classification dimensions were reduced by recursive feature elimination (1, 2), using in-house tools based on Matlab (3). To do so, we constructed a classifier using all relevant voxels and rank ordered each voxel's contribution to the discrimination. We iteratively removed the 40% worst-discriminating voxels, stopping at the point at which performance of the classifier began to detriorate. This procedure determined the minimum number of required features (voxels). We then performed linear support vector machine-based classification analysis (regularization parameter C=1), with leave-one-out cross-validation. Significance was determined by randomly reassigning class labels in 2000 permutations of the leave-one-out analysis using the voxels identified by the recursive feature elimination process (alpha = $p<0.05$, two-sided).

Results

Correlations with symptom scales

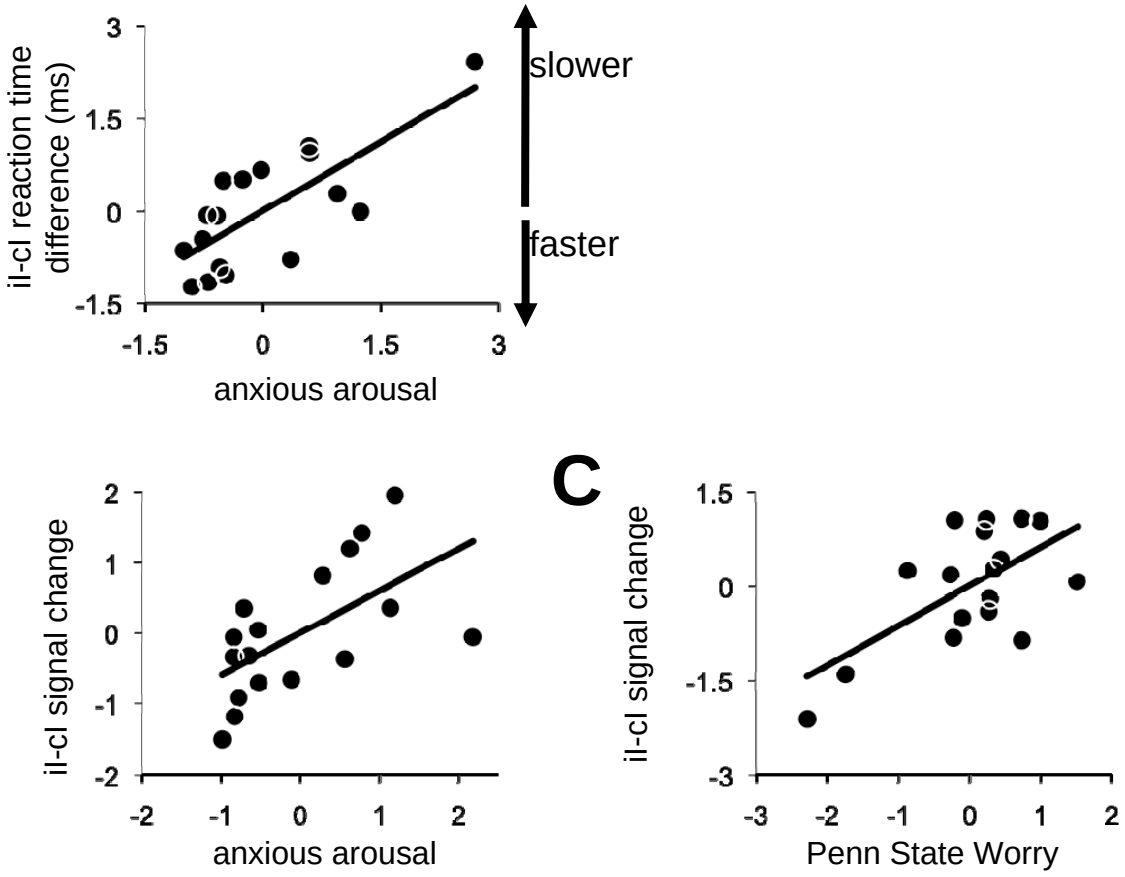
For the patients, we correlated symptom scale scores with the reaction time difference between postincongruent incongruent trials minus postcongruent incongruent trials. The only

correlation that survived a Bonferroni correction for the six comparisons made was between greater scores on the anxious arousal subscale of the mood and anxiety symptom questionnaire and progressively greater reaction time difference scores (i.e. greater sensitization; $r=0.68$, $p<0.005$). This correlation is particularly interesting, because this subscale was designed to differentiate anxiety from depression (4, 5). Indeed, after controlling for the same questionnaire's depression-specific measure, the anhedonic depression subscale, which was not significantly correlated with either the reaction time difference scores ($r=0.32$, $p>0.2$) or the anxious arousal subscale ($r=–0.1$, $p>0.7$), the correlation between the anxious arousal subscale and the reaction time difference scores rose to $r=0.75$ ($p=0.001$; see Figure S1A). Independence from outliers in this correlation was confirmed with robust regression (data not shown) as well as by removing the potential outlier value at the top-right of the plot in supplemental Figure S1A ($r=0.54$, $p<0.05$).

Correlations were also made between symptom scale scores with the average difference between postincongruent incongruent trials minus postcongruent incongruent trials for the group contrast clusters in the pregenual cingulate and dorsomedial prefrontal cortices. After Bonferroni correction, the anxious arousal subscale and Penn State Worry Questionnaire were found to correlate with greater inappropriate dorsomedial prefrontal activation in postincongruent incongruent trials (anxious arousal: $r=0.64$, $p=0.005$; worry: $r=0.68$, $p<0.005$; see supplemental Figure S1B and S1C). After removing variance associated with the anhedonic depression subscale, which did not correlate with dorsomedial prefrontal activity ($r=0.04$, $p>0.8$), as well as worry scores, the correlation between dorsomedial prefrontal activity and the anxious arousal subscale remained strong ($r=0.6$, $p<0.05$; see supplemental Figure S1B). Likewise, dorsomedial prefrontal activity correlated with worry scores after removing variance associated with anxious

arousal and anhedonic depression scores (r=0.63, p=0.01, see supplemental Figure S1C). Worry scores and anxious arousal scores were not significantly correlated (r=0.35, p>0.15).

FIGURE S1. Correlations Between Anxiety Symptoms and Reaction Times



(A) A significant positive correlation in patients between the anxious arousal subscale of the Mood and Anxiety Symptom Questionnaire and reaction time difference scores for the contrast of postincongruent incongruent trials minus postcongruent incongruent trials (iI-cI), indicating worse performance, rather than facilitation, to repeated incongruent trials in more anxious individuals. Psychometric and behavioral data are expressed as Z-scores after accounting for variance related to the anhedonic depression subscale of the same questionnaire. (B, C) Greater inappropriate dorsomedial prefrontal activation is correlated with higher levels of anxiety. Correlations between iI-cI signal for patients in the group difference dorsomedial prefrontal cluster from Figure 3C and anxious arousal subscale scores adjusted for anhedonic depression subscale and worry scores (B), or the correlation with scores on the Penn State Worry Questionnaire (C), after adjusting for anxious arousal and anhedonic depression scores, all expressed as Z-scores.

Multivariate pattern classification

We implemented a linear support vector machine pattern classification approach, using recursive feature elimination for feature reduction and leave-one-out cross-validation, to determine whether fMRI signal in the emotional conflict task can discriminate between patients and controls. Within our *a priori* regions of interest, significant classification using the contrast of incongruent trials preceded by incongruent trials minus incongruent trials preceded by congruent trials was achieved in the pregenual cingulate (accuracy 88%, $p<0.0005$; sensitivity 88%, specificity 88%), and the dorsomedial prefrontal cortex (accuracy 76%, $p<0.01$; sensitivity 59%, specificity 88%), but not in the amygdala (accuracy 66%, $p>0.1$; sensitivity 24%, specificity 96%). Using whole brain data, we were able to achieve 95% accuracy ($p<0.0005$, sensitivity 94%, specificity 96%). Successful classification could also be achieved using reaction time difference scores (accuracy 73%, $p<0.0005$; sensitivity 53%, specificity 88%).

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TABLE S1: Reaction Times (standard deviations in parenthesis)

Healthy subjects		**Current trial**	
		congruent	incongruent
Previous trial	congruent	736.6 (95.6)	850.2 (152.4)
	incongruent	762.9 (84.8)	821.4 (117.1)

Patients		**Current trial**	
		congruent	incongruent
Previous trial	congruent	810.7 (233.4)	905.8 (226.8)
	incongruent	851.1 (263)	922.0 (252.3)