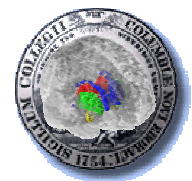


The role of ventromedial prefrontal cortex in anxiety and emotional resilience



Tor D. Wager¹, Christian Waugh², Martin A. Lindquist³, Barbara Fredrickson⁴, Douglas C. Noll⁵, Stephan F. Taylor⁶

1 Department of Psychology, Columbia University 4 Department of Psychology, U. North Carolina
 2 Department of Psychology, University of Michigan 5 Department of Biomedical Engineering, University of Michigan
 3 Department of Statistics, Columbia University 6 Department of Psychiatry, University of Michigan

Cognitive & Affective Control Lab
<http://www.columbia.edu/cu/psychology/tor/>
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INTRODUCTION

The study of brain correlates of emotion in humans has posed a persistent challenge, in part because:
 a) it is difficult to manipulate and maintain strong emotional states
 b) the analysis of state-effects is complicated by low-frequency drift and difficulties in specifying precisely what cognitive and affective operations may give rise to state-related brain activity.

In this study, we induced an emotional state using a silent public speech-preparation task that has been shown to provoke anxiety. Many cognitive and affective processes may occur during performance of this task; we used the following additional information to localize anxiety:

- **State-anxiety-related activity should match the timecourse of subjective anxiety.** We characterize the onset and duration of activity in a data-driven way to look for sustained shifts in fMRI activity.
- **Anxiety-related activity should track physiological indicators of anxiety.** We correlate fMRI activity with heart-rate changes within subjects over time to find regions that a) change with heart rate, and b) show increased correlation with heart rate during anxiety.
- **Anxiety-related fMRI activity should be affected by anxiety-related personality characteristics.** We selected individuals high or low in ego resilience and examined the moderating effects of personality on putative anxiety-related fMRI activity.
- VMPFC is an area of particular interest
 - Implicated in both generation and regulation of stress response
 - Strong projections to brainstem autonomic control centers

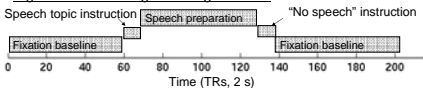
METHODS

Participants. N = 30, selected from a group of 160 to be in the top or bottom quartile on the Ego Resilience Scale (J. Block)

Task design.

- Participants were instructed that during scanning, they would mentally prepare a 7-min long speech that would be later presented to an audience of expert judges. They were told that they would have 2 min to prepare, and that the topic would be presented during scanning.
- 6 min total scanning time. After 2 min of resting baseline participants viewed a screen describing the topic ("Why are you a good friend?") and instructed to prepare silently. After 2 min of preparation, participants were told they would not have to give the speech after all, and they could relax for the remaining 2 min of scanning ("Recovery").

Figure 1. Task design: Anxiogenic task



Data acquisition and analysis.

- Reverse spiral GRE images (D. Noll) acquired on 3 T GE (improved susceptibility artifact reduction), TR = 2s, 3.12 x 3.12 x 3 mm voxels, 215 images
- **HEWMA:** Raw timeseries data linear detrended and subjected to hierarchical exponentially weighted moving average analysis (Lindquist and Wager, 2006, in press): **no a priori model for when activation should begin or end**
 - Locate voxels that deviated significantly from the 2 min baseline period ("random effects")
 - Locate voxels that showed significant differences in timecourse between Resilient vs Nonresilient subjects
 - Characterize onset time and duration of active voxels
- **Brain-physiology correlations.** Correlations (Pearson's r) between heart rate and brain activity timeseries for each subject were assessed voxel-by-voxel using robust regression (Wager et al., 2005).
 - Fisher's r-to-z transformation was used to normalize r values for each subject.
 - Z values tested for significance in the group ("random effects") using robust regression
 - 2nd-level moderation of HR-brain correlations by Resilience was assessed using robust regression (also called "PPI" in SPM).
- **Seed analyses** on timeseries connectivity with brain regions of interest were performed in the same way
- **Thresholds:** HEWMA corrected over time using multivariate-t Monte Carlo and over space using FDR p < .05. Correlations thresholded using FDR p < .05 or p < .001, whichever was more conservative.

SUMMARY

VMPFC is one of only two regions in the brain that, in this study, showed sustained positive activation during an anxiogenic speech-preparation task. Nonresilient individuals showed stronger activity, suggesting at least one rostral subregion is associated with the generation of subjective anxiety. This region may be an analogue of prefrontal cortex in the rat (Sullivan & Gratton; Torrealba; Quirk).

VMPFC activity was strongly correlated with heart rate, and the correlation was strongest for nonresilient individuals. The correlation was stronger during speech preparation than during baseline. VMPFC activity preceded changes in heart rate, suggesting a role in context-based control of autonomic output.

Connectivity analyses showed that VMPFC activity is positively coupled with lateral prefrontal activity, and this connectivity was strongest for nonresilient individuals. This finding suggests that cognitive conceptual/attentional processes contribute to anxiety in nonresilient individuals.

Are VMPFC-heart rate correlations due to vascular artifacts? Probably not; regions around main arteries and veins do not correlate with HR, and the correlation is affected by both task state (speech vs. baseline) and personality (resilience)

RESULTS

