Anxiety and Brain Activation: How Trait Anxiety Affects Neural Responses Across Task Conditions

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Abstract

We investigated how trait anxiety modulates neural activation across cognitive load and emotional valence in 39 participants, using activation scores from 16 predefined ROIs under ten task conditions. After a reproducible preprocessing pipeline, we first conducted group-level hypothesis tests and identified rdacc and dacc under the highload_neutral condition as significantly different between high and low anxiety ($p<0.01$). Next, region-by-region mixed-effects models with leave-one-subject-out cross-validation showed that only the anxiety×condition interaction terms—rather than anxiety or condition alone—predicted activation, with RMSEs below each region's activation standard deviation in rdacc, ldacc, rvlpfc, lvlpfc, and dacc. Finally, multivariate regression using all 160 activation features (OLS, Ridge, Lasso, and Random Forest, with and without PCA) failed to outperform a mean-only baseline. Together, these results underscore the importance of interaction effects in a small set of ROIs and motivate region-specific modeling as a more fruitful strategy for capturing anxiety-driven neural dynamics.

1 Introduction

Everyone experiences anxiety to some degree, but when it becomes persistent and overwhelming it can interfere with daily life—impacting decision making, attention, and even physiological health. In particular, individuals with high trait anxiety often report difficulty in concentrating when tasks become demanding or when emotional distractions arise. Despite decades of research on anxiety's effects in isolation, we still lack a clear picture of how anxiety interacts simultaneously with cognitive load and emotional context across different brain regions.
In this project, we tackle three core questions:

- Which regions of interest (ROIs) exhibit the largest activation differences between individuals with high versus low trait anxiety?
- How does the interaction between anxiety and task condition (cognitive load and emotional valence) shape neural responses when we account for repeated measurements within each subject?
- Can we reverse the direction of inquiry—using the full pattern of activations across all ROIs—to predict each person's continuous anxiety score?

To address these questions, we leverage a dataset of functional activation measures for 16 ROIs collected under ten task conditions and apply a combination of hypothesis testing, mixed-effects modeling, and multivariate predictive regression. This approach aims to illuminate the neural circuits most sensitive to anxiety, as well as to explore the feasibility of activation-based biomarkers for individual differences in anxiety.

2 Data Preprocessing

2.1 Raw Data and Cleaning

All raw activation values were provided in a wide Excel sheet, where each column name combined a task condition and an ROI mask (e.g. `FearfulVsNeutral_Left_STS_8mm_sphere_mask_cope1`). To make these names analysis-ready and human-readable, we built two mapping dictionaries in Python:

- `cond_map`: translates verbose condition codes like `"HighLoadFearful"` into concise labels such as `"highload_fearful"`.
- `roi_map`: maps long ROI mask names (e.g. `"Left_DLPFC_8mm_sphere_mask_cope1"`) to short region IDs like `"ldlpfc"`.

We then looped over every column (except `Participant` and `Trait Anxiety Score`), split each header on the first underscore, looked up the condition in `cond_map` and the remaining ROI key in `roi_map`, and renamed the column to the format:

`<condition>__<region>`

—for example, `HighLoadFearful_Left_Amygdala_cope1` became `highload_fearful__lamyg`. Finally, we renamed `Participant` to `id` and `Trait Anxiety Score` to `anxiety`, yielding our cleaned short-format table in `data/cleaned_data.csv`. This systematic renaming ensures consistency across downstream analyses.“‘

2.2 Short and Long Formats

We saved the cleaned wide-format table as `data/cleaned_data.csv` containing one row per subject. Then, we also melted the dataset into a long format (`data/long_data.csv`) with columns `id`, `anxiety`, `condition`, `region`, and `activation`, preparing for repeated-measures analysis.

3 Analysis Methods

3.1 Hypothesis Testing

To screen for candidate effects, we dichotomized participants into *high* and *low* anxiety groups at the median, resulting in 22 subjects being assigned to high anxiety class and 17 to the low anxiety class. For each `condition`×`region` cell, we performed Welch's t-test on the activation values of the two groups. Results were saved in `results/hypothesis_test_results.csv`. Significant ROIs under specific conditions are given in Table 1. Out of the 160 tests, 17 of the `condition`×`region` cell are significant, meaning anxiety level do have an impact onto these `condition`×`region` cells.

3.2 Mixed-Effects Modeling

We modeled each ROI separately via

$$\text{activation}_{ij} = \beta_0 + \beta_1\,\text{anxiety}_i + \beta_2\,\text{condition}_j + \beta_3\,(\text{anxiety}_i \times \text{condition}_j) + u_i + \varepsilon_{ij},$$

where $u_i \sim \mathcal{N}(0, \sigma_u^2)$ is a random intercept per subject. Models were fit with REML in `statsmodels`. The mixed-effect model were trained and evaluated using leave-one-subject-out cross-validation (LOSO-CV), giving an RMSE per region. These RMSEs were compiled in

Table 1: Significant condition–region pairs (high vs. low anxiety, $p < 0.05$)

Condition	Region	p-value
highload_neutral	rdacc	0.004745
highload_neutral	dacc	0.007411
highload_neutral	ldacc	0.010457
highload_neutral	rdlpfc	0.011063
high_vs_low_load	rsts	0.015398
high_neutral_vs_low_neutral	rsts	0.021508
high_neutral_vs_low_neutral	lracc	0.025044
highload_neutral	lracc	0.030867
highload_neutral	rracc	0.032930
high_fearful_vs_high_neutral	racc	0.033901
high_fearful_vs_high_neutral	lracc	0.034488
highload_fearful	rdacc	0.038990
high_neutral_vs_low_neutral	lsts	0.041890
high_neutral_vs_low_neutral	rracc	0.042508
highload_fearful	dacc	0.042568
highload_neutral	lvlpfc	0.045087
high_fearful_vs_high_neutral	ldlpfc	0.049606

`results/all_regions_rmse.csv` and visualized in Figure 1. As we can see from the plot, the rmses are very close to the region activation scores' standard deviation, meaning the models don't have much prediction power compared to simply predicting using the mean. However, some of the models still have a better rmse than the standard deviation. For example, the models for rdacc, ldacc, rvlpfc, lvlpfc, and dacc all have some prediction power, suggesting these regions' activation could be affected by the anxiety score.
When looking at the coefficient summaries in the `result` folder for these region's models, here are the predictors that are significant (p-value < 0.05):

Table 2: Anxiety × Condition interaction effects by ROI

Region	Predictor	Direction
rdacc	anxiety × highload_neutral	positive
ldacc	anxiety × highload_neutral	positive
rvlpfc	none ($p < 0.05$); near: anxiety × high_vs_low_load, anxiety × lowload_neutral	negative
lvlpfc	none ($p < 0.05$); near: anxiety × highload_neutral	negative
dacc	anxiety × highload_neutral	positive

All of the significant effects in these ROIs are interaction terms between anxiety and task condition. In other words, neither anxiety nor condition on its own fully explains activation differences—it's the combination of the two that drives neural responses.

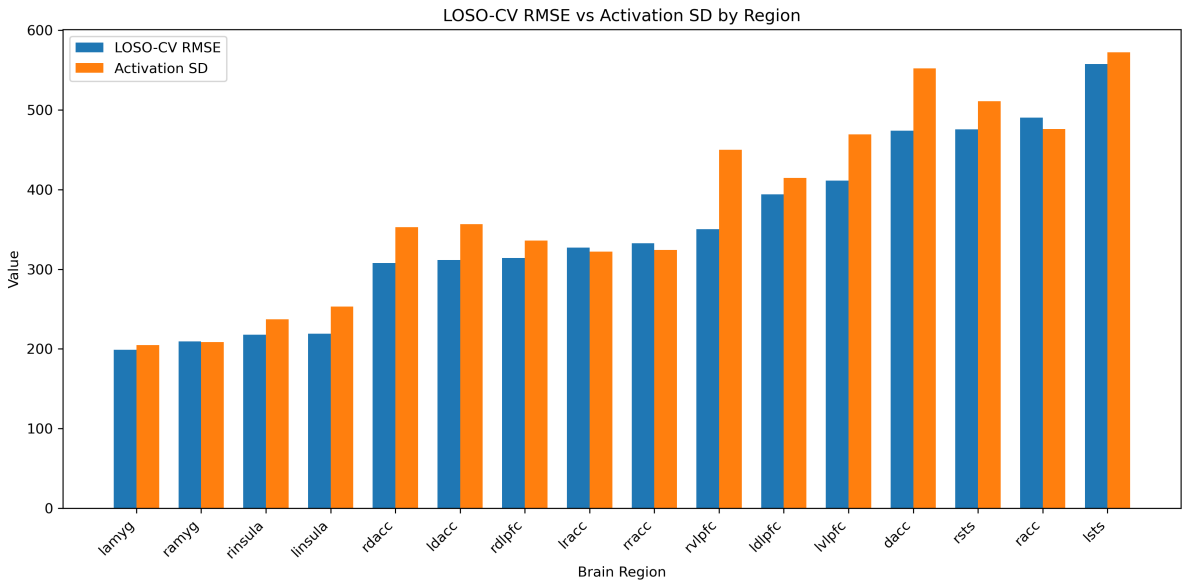

Figure 1: LOSO-CV RMSE for each ROI, indicating how well the anxiety×condition model predicts held-out subjects.

3.3 Predictive Regression

Beyond univariate ROI models, we evaluated whether whole-brain activation profiles could predict continuous anxiety. We extracted 160 activation features from `cleaned_data.csv` as predictors and compared four algorithms under LOSO-CV:

- Ordinary Least Squares (OLS)
- Ridge regression
- Lasso regression
- Random Forest

Due to the data's nature of high dimensionality (160 predictors and only 39 observations), we also applied Principle Component Analysis (PCA) to the data and compared the performance of these four models on the original data and the PCA data.

We report in Table 3 the LOSO-CV RMSE for each model and present the final coefficients in the `results` folder.

When looking at the RMSE of all the models, the best performing ones have a value around 8, which is very close to the standard deviation of all anxiety scores (7.92). This suggests that the model performances are equivalent to predicting everyone's anxiety scores using the mean, meaning using all 160 activation scores as predictors is not useful in terms of predicting the anxiety score.

When looking closer at the models' coefficients, Ridge Regression drags all variable towards zero, none of the coefficients have a large impacts on the prediction. Same with LASSO, where it penalized every variable to exactly zero, meaning it doesn't think any of the 160 variables have meaningful contribution to the final prediction.

Table 3: LOSO-CV RMSE for regression models predicting anxiety from activation features.

Model	LOSO-CV RMSE
OLS	12.90
Ridge	8.31
LASSO	8.02
Random Forest	8.45
OLS_PCA	9.19
Ridge_PCA	8.31
LASSO_PCA	8.02
Random Forest_PCA	8.52

4 Conclusion

Our hypothesis-testing (Table 1) identified rdacc and dacc under the highload_neutral condition as the most robustly different between high and low anxiety ($p<0.01$). In the mixed-effects analysis, the LOSO-CV RMSE for rdacc, ldacc, rvlpfc, lvlpfc, and dacc all fell below those regions' activation standard deviations (Figure 1), indicating meaningful anxiety–condition coupling. Crucially, when we examined the model coefficients, we found that **only the interaction terms** (anxiety×condition) emerged as significant predictors of activation—neither anxiety nor condition alone retained significance. Finally, a combined predictive model using all 16 ROIs did not outperform the trivial mean predictor, suggesting that distributed activation patterns add little beyond regional interaction effects.

These results point clearly to a strategy of **region-specific modeling**: focus on rdacc, ldacc, rvlpfc, lvlpfc, and dacc, and build detailed models of their anxiety×condition interactions. Such targeted approaches are more likely to yield reliable biomarkers of trait anxiety than global multivariate models in this dataset.

5 Future Suggestions

Based on our findings and limitations, we recommend the following directions for future work:

- **Increase sample size and diversity.** Collecting data from more participants—and ideally from multiple sites—will improve the stability of mixed-effects estimates and enhance the generalizability of predictive models.
- **Focus on region-specific modeling.** Our results point to rdacc, ldacc, rvlpfc, lvlpfc, and dacc as particularly sensitive to anxiety under load. Future analyses should build dedicated models for these ROIs (e.g. hierarchical Bayesian or non-linear approaches) rather than pooling all regions.
- **Integrate functional connectivity.** Beyond univariate activation, exploring dynamic or static connectivity between the key regions may reveal network-level signatures of anxiety that improve prediction and mechanistic insight.
- **Include additional covariates.** Incorporating demographic, behavioral, or physiological measures (e.g. age, heart rate variability) could help explain residual variance and disentangle anxiety effects from confounds.

- **Evaluate nonlinear and ensemble methods.** While our linear and tree-based models gave RMSEs near the baseline, methods such as gradient boosting, support vector regression, or neural networks might capture higher-order interactions in the high-dimensional activation space.

AI Prompts Used: Please revise the grammar of this report to enhance vocabulary, interpretability, and the professional tone in line with consulting standards.