Supplementary Online Content

Teed AR, Feinstein JS, Puhl M, et al. Association of generalized anxiety disorder with autonomic hypersensitivity and blunted ventromedial prefrontal cortex activity during peripheral adrenergic stimulation: a randomized clinical trial. *JAMA Psychiatry.* Published online February 2, 2022. doi:10.1001/jamapsychiatry.2021.4225

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dDiscussion 1. Study Limitations
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This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods 1. Participants

One hundred thirty-six participants were assessed for eligibility, following study recruitment from outpatients receiving services at the Laureate Psychiatric Clinic and Hospital as well as via newspaper, radio, flyer, and social media advertisements in the Tulsa metropolitan area. Those with current/prior schizophrenia, bipolar disorder, or obsessive-compulsive disorder were excluded. Participants were allowed to continue use of selected psychotropic medications but were instructed not to take any analgesic or other over the counter (OTC) medication within 48 hours of the experimental session and no benzodiazepines, beta-blockers, or tetrahydrocannabinol (THC) containing products within 24 hours of scanning. No participants tested positively for THC or benzodiazepines on the day of scanning. They were further instructed not to have nicotine on the day of the experimental session and to limit their caffeine consumption (i.e., avoid caffeine it was not a daily routine for the participant, and if it was, to reduce their usual amount by half).

Eleven candidates declined to participate and the remaining 125 provided informed written consent. Seventeen participants withdrew prior to the intervention for various reasons (scheduling difficulty, incomplete baseline assessment, or study refusal). Thirty-five additional participants were excluded due to contraindicated medical conditions.

Medical contraindications included: 1) (a) cardiac disease (e.g. bradycardia <40 bpm, any history of diagnoses EKG abnormalities or evidence of 12-lead EKG abnormalities during baseline visit or evidence of frequent premature ventricular contractions during baseline visit), (b) respiratory disease (asthma, pneumonia), (c) endocrine disease (hypothyroidism, diabetes), (d) neurological disease (seizure disorder or reporting a seizure within the last year, head injury with sustained loss of consciousness and memory loss), (e) pain disorder (f) history of hepatic or renal failure, (g) gastrointestinal, hematologic, rheumatologic, or metabolic disease, 4) pregnancy as verified by urine test, 5) intratruncer device (IUD) posing a scanning risk, 6) ages 18 to 55 years, 7) excessive BMI (BMI > 35) preventing scanner entry, 8) MRI contraindications including: (a) cardiac pacemaker, (b) metal fragments in eyes/skin/body (shrapnel), (c) aortic/aneurysm clips, (d) prosthesis, (e) by-pass surgery/coronary artery clips, (f) heart valve replacement, (g) shunt (ventricular or spinal), (h) implanted electrodes, (i) MRI contraindicated metal plates/pins/screws/wires, or neuro/bio-stimulators (TENS unit), (j) persons with a history of professional metal working/welding who showed evidence of intracranial metal on orbital X-ray, history of eye surgery/eyes washed out because of metal, (k) inability to lie still on one’s back for a 1-2 hours, (l) prior neurosurgery, (m) tattoos or cosmetic makeup with metal dyes, (n) unwillingness or inability to remove body piercings, 9) medications that affect the hemodynamic response (e.g. acetazolamide, excessive caffeine intake > 1000 mg per day, 10), non-correctional vision or hearing problems, or 11) vital sign abnormalities during the screening visit (e.g. systolic blood pressure >160 mmHg, diastolic blood pressure >100 mmHg, resting pulse >100 beats per minute).

Of the 73 allocated to the intervention, 72 completed it. One GAD participant withdrew during the infusions due to panic anxiety. Five participants were excluded due to excessive head motion resulting in low data quality (four HCs and one GAD), eight HCs were excluded during the matching process based on age and BMI, and one GAD was excluded for having a BMI too high to appropriately match with a healthy comparator. All participants were financially compensated for their participation.

eMethods 2. Experimental Protocol

Isoproterenol was obtained from Valeant Pharmaceuticals, Laval, QC, Canada and infusions were prepared into 3 mL boluses by a pharmacist who was unblinded. The isoproterenol infusion administration procedure mirrored our previous fMRI cross-over protocol in healthy volunteers; with infusions administered by a nurse seated beside the scanning bed inside of the MRI room who was blinded to infusion condition. For safety monitoring purposes, cardiac rhythm was also recorded continuously using two MRI-compatible ECG leads (lead I and II configuration) (GE Healthcare, Waukesha, WI, USA). These rhythms and vital signs were monitored continuously by the nurse delivering the infusions. As an additional safety precaution, condition order was available to the research assistant sitting in the control room, who was blinded to the study hypotheses.

The randomized sequences for dose order were individually predetermined via a random number generator prior to beginning study sample recruitment. Upon recruitment of each participant, a 3rd party registered nurse (i.e., uninvolved in infusion administration or data collection) selected a randomization code from a set of randomizations generated by the senior study author. The 3rd party nurse then arranged the bolus doses in the predetermined order, and after obtaining verification of this order by a second 3rd party nurse (or nursing assistant), covered the labels. Selection of a randomization order for a given participant was not determined by group membership and occurred in sequential order from the list of randomization orders.

On arrival participants ate a 300 Calorie snack. Each participant was led through a training session approximately one hour before fMRI scanning. During this session, the participant was instructed that they would receive both isoproterenol and saline infusions at different points during the scan. Participants were informed that “you may notice an increase in your heartbeat sensations, and/or may notice increase in your breathing sensations” during the isoproterenol infusions. Also, to familiarize participants with the experience of the infusion setup and isoproterenol-induced sensations, prior to the scan, participants received two practice bolus infusions (saline and 1 microgram, µg) delivered by the nurse in a separate room near the MRI scanning suite. These infusions followed the same time course as those administered during the scanning session and required participants to provide sensation ratings using a dial. We

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administered a 1 µg dose during the practice infusion to avoid a familiarity effect during the subsequent infusion scans, and to ensure that participants received a large enough dose that they were likely to perceive, based on our prior studies. Following the scan session participants ate a 1000 Calorie meal.

**eMethods 3. Primary and Exploratory Behavioral and Physiological Data Analysis**

All statistical tests were performed in R (version 3.5.1; R Core Team, 2016). Linear mixed-effects (LME) regression models were performed using the lme4 package, and statistical degrees of freedom were estimated by Satterthwaite’s approximation via the lmerTest package. We assigned the reference levels for the group, dose, and epoch variables to be the healthy comparator group, the saline condition, and the baseline epoch, respectively. We estimated the chronotropic dose 25 (CD25) by first performing a within-subject linear regression, by ISO dose, on the maximum average heart rate occurring over any rolling 5 second window during the peak and early recovery periods. We used windowed means as opposed to point estimates to reduce potential measurement error due to outliers, as in our previous studies. To provide a baseline for calculating the CD25, we also obtained rolling 5 second windows for the maximum heart rate occurring during the corresponding 40 second period of a resting state scan run before the task. We then calculated each participant’s CD25 estimate using the formula provided in Mills et al., by adding the 25-beat target increase to the resting state value, subtracting the intercept of the linear regression, and dividing the subsequent value by the regression slope. Interoceptive detection was assessed via a chi-square test for independence in R software which counted, for each dose, how many GADs and HCs increased the dial above a threshold of fifteen out of one hundred (this dose detection threshold was chosen to account for inadvertent responses due to the MRI compatible device’s sensitivity profile). Differences in cardiorespiratory interoceptive accuracy were assessed by calculating cross-correlations between continuous heart rate and dial ratings for each individual using custom MATLAB script (as in ).

**eMethods 4. MRI Data Acquisition**

MRI scans were acquired in a GE MR750 3T scanner with an 8-channel head coil. Simultaneous EEG recordings were also collected but were not included in the current analysis. We acquired anatomical images via a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence with sensitivity encoding (SENSE) that lasted 5 min and 40 s. MPRAGE parameters were: 190 axial slices, slice thickness = 0.9 mm, TR/TE = 5/2.012 ms, FOV = 240 x 192 mm², matrix size 256 x 256, flip angle = 8°, inversion time = 725 ms, SENSE acceleration R = 2, with a sampling bandwidth of 31.2. A 240 s, single-shot gradient echo planar imaging (EPI) sequence covering the whole-brain was used for each FMRI scan. In this EPI sequence we obtained axial 39 slices, 2.9 mm thick, with no gap and a voxel size of 1.875 x 1.875 x 2.9 mm³. Additional parameters were TR/TE = 2000/27 ms, FOV = 240 x 240 mm², flip angle = 78°, SENSE acceleration R = 2 with a 96 x 96 matrix.

**eMethods 5. fMRI Preprocessing**

The first 4 EPI volumes were dropped to allow field stabilization. BOLD signal was scaled to percent change from the time-course mean for each voxel. With respect to motion artifacts, poor quality volumes were censored using interpolation if they exceeded 0.3 mm of mean motion or if >20% of voxels were found to be outliers using AFNI’s 3dtoutcount. Runs were discarded if >20% of volumes were censored. One run was discarded for each of three HC and two GAD participants. We also checked for potential differences in head motion for each of the infusion conditions and found no group differences.

**eMethods 6. Whole-brain fMRI Group Analysis**

We conducted whole-brain analysis using AFNI’s 3dtest++ program and applied the ETAC (Equitable Thresholding and Clustering) option to estimate significant cluster sizes corresponding to a 5% false positive rate at a p < 0.001 voxel-wise threshold. We chose this method to reduce arbitrary judgment in selection of the uncorrected p-value threshold.
eMethods 7. Longitudinal time series analysis with regions of interest

Multivariate sparse functional principal component analysis (mSFPCA) was performed to examine how linear and non-linear temporal dynamics of isoproterenol’s effects on BOLD response, heart rate, and sensation rating trajectories. This technique characterizes the major modes of smoothed variation around the smoothed mean trajectories as FPC coefficients at the subject level using Hamiltonian Markov chain Monte Carlo (MCMC) resampling of the posterior distribution of model parameters in a Bayesian framework. To assist in functional interpretation of our whole-brain results, we generated separate post hoc mSFPCA models for extracted mean PSC from spherical ROIs (5 mm radius) derived from conceptually relevant fMRI meta-analyses reporting clusters in coordinate space near to ours. Seeds for the relevant regions of interest (ROIs) within the vmPFC were obtained from meta-analyses of fMRI studies related to valence processing, sympathetic autonomic control, and self-processing. FPC coefficients for HR, dial, and BOLD ROI trajectories were then entered into LME models with group and dose factors to assess how these factors affect these trajectories. The mSFPCA approach we employed uses sets of eigenfunctions that are allowed to correlate across dependent variables but remain independent with regard to each observation within a variable. Using spline basis functions, each individual’s response was modeled in a multivariate fashion via a matrix of spline coefficients characterizing the major modes of variation as a set of principal components functions (we chose two) around the smoothed mean trajectory. mSFPCA models were created in R using the MASS, Matrix, pracma, and splines packages. mSFPCA was conducted on HR and dial responses after converting the timescale of these variables to 2 second intervals, with the first four intervals dropped to match the BOLD timeseries given the TR of 2 second and the initial 4 volumes being dropped to allow the magnet to reach a steady-state. We generated mean and PC functions by implementing two internal knots yielding model fits via cubic B-spline basis functions. We ran 1,100 MCMC simulations with 100 of those discarded as burn-in.
eFigure 1. Infusion epochs used in the isoproterenol fMRI analysis.

For illustrative purposes, infusion epochs are superimposed on the average time course of heart rate responses during the saline, 0.5 and 2 µg isoproterenol infusions in the healthy comparator sample only. The data shown in the figure includes the complete 43 healthy individual sample tested prior to exclusions for head motion (n=5) and age and BMI group matching (n=9). bpm = beats per minute, µg = micrograms, Sal = saline.

eFigure 2. Subjective Response Assessment

A) Throughout each scan, participants reported their perceived cardiorespiratory sensation intensity ranging using a visual analog scale with a baseline of 0 and maximum of 10 (recorded units of measurement ranged from 0 to 100). B) Immediately after each infusion scan participants provided retrospective ratings of their heartbeat sensation intensity, breathing sensation intensity, anxiety, and arousal felt during the infusions, using an 11-point scale ranging from 0 to 10.
eFigure 3. Respiratory Volume Variability During Isoproterenol Infusion.

Detection responses were operationalized as the generation of a real-time dial rating of greater than 1.5 on a scale of 10. Interoceptive detection rates increased across dose for both groups, but the groups did not show statistically significant differences in rates of detection.
eFigure 5. Group difference in left parietal cortex activity.

The GAD group showed significant attenuation relative to the HC group at a $p<0.001$ voxel-wise threshold during the peak response period for only the 0.5 μg dose.

eFigure 6. Maximum cross-correlations between heart rate and dial response by dose in unmedicated GAD relative to HC.

When medicated GAD participants were removed the mean correlation between HR and perceived cardiorespiratory intensity was significantly higher at the 0.5 μg dose in the unmedicated GAD group relative to HCs at the level of the maximum cross-correlation. Error bars = SE.
eFigure 7. Overlap between whole-brain vmPFC cluster and meta-analysis–derived ROIs.

Overlap (red) between the significant whole-brain BOLD vmPFC cluster identified during the peak response period for the 0.5 μg dose (orange) and the meta-analysis–derived functional ROIs (yellow) is shown below.
eFigure 8. Multivariate Sparse Functional Principal Component Analysis (mSFPCA) model fits to raw data by dose and group.

Spaghetti plots of the mfpca fit (yellow lines) to raw data (black lines) for BOLD percent signal of the self-representation vmPFC ROI (A), heart rate (B), and perceived cardiorespiratory intensity (C) are shown to the left. Mean fpc score curves for healthy comparators (blue) and patients with GAD (green) are shown for each of BOLD (D), heart rate (E), and perceived intensity (F) to the right.
eFigure 9. VmPFC PSC correlations with cardiorespiratory and subjective variables during the peak effect at 0.5µg isoproterenol

Scatterplots with correlation slope line and standard deviation band for relationships between percent signal change extracted from the whole-brain vmPFC selected cardiorespiratory and self-report variables. After Bonferroni-Holm correction for multiple comparisons, significant inverse relationships were seen between PSC and A) change in heart rate from pre-infusion baseline as well as post-infusion self-report of both B) heartbeat intensity and C) respiratory intensity. Negative PSC relationships not surviving Bonferroni-Holm correction were seen for D) perceived cardiorespiratory intensity, though this remained a trend, and E) self-reported anxiety. The relationship with F) CD25 was not significant. CD25 = chronotropic dose 25.
eResults 1. Respiratory Volume Variability (RVV)

We observed dose-related increases in RVV during the peak period but no interaction with group (eFigure 3 and eTable 5), suggesting that group differences in perceived interoceptive intensity were driven preferentially by cardiac signals.

eResults 2. Interoceptive Awareness: Detection and Accuracy Measures

A chi-square test to assess group differences in detection rate of cardiorespiratory changes via increased dial ratings was not significant ($\chi^2(1)=2.54, p=0.111$; eFigure 4). Nor were there clear differences in interoceptive accuracy, as assessed via the cross-correlation of HR with dial responses. The maximum cross-correlation was the only metric showing a trend toward increased accuracy for GADs during a combined peak + early recovery period at 0.5µg ($b=0.09, SE=0.05, t(281.53)=1.79, p=0.075$; eTables 6 and 7).

eResults 3. Reanalysis of Primary Outcomes with Medicated Participants Removed

A reanalysis with the six medicated patients removed revealed a significant difference in age between groups ($t(38.28), p<0.047$) with GADs being older (M=27.96 years) than HCs (M=24.38 years); age was included as a covariate in the subsequent analyses (as it was in the original models). We observed an additional significant result of higher HR for those with GAD compared to HCs at the 2mcg dose during the peak period ($\beta=3.76, t(1475.93)=2.11, p=0.035, 95\% CI[0.30, 7.22]$). The dial response interaction of GAD group by 0.5mcg dose became non-significant during the peak epoch ($\beta=5.42, t(1476.73)=1.57, p=0.118, 95\% CI[-1.30, 12.15]$) but remained significant during early recovery ($\beta=7.62, t(1476.77)=2.00, p=0.028, 95\% CI[0.89, 14.36]$). Finally, the interoceptive accuracy cross-correlation interaction of GAD group by 0.5µg dose became significant ($\beta=0.12, t(252.03)=2.17, p=0.031, 95\% CI[0.01, 0.22]$; eFigure 6). Results relating to BMI, CD25, and all retrospective ratings were unchanged with respect to statistical significance and nearly identical to the previous analysis.

eResults 4. Longitudinal Time-Series Analysis

The mSFPALME revealed an effect of group at 0.5µg for the self-processing ROI ($\beta=0.23, t(112)=2.24, p=0.027, 95\% CI[0.03, 0.44]$) and a trend at 2.0µg ($\beta=0.19, t(112)=1.85, p=0.067, 95\% CI[-0.01, 0.40]$) on FPC1 (Figure 3D, eFigure 8D and eTable 8). For the valence ROI LME, only dose effects were observed for FPC1 but a group effect was seen for FPC2 ($\beta=0.11, t(56)=2.09, p=0.038, 95\% CI[0.01, 0.22]$). The sympathetic autonomic ROI LME showed a trend for a group by dose interaction at 0.5µg on FPC1 ($\beta=0.25, t(112)=1.85, p=0.067, 95\% CI[-0.01, 0.51]$). When PSC values for this ROI were entered in an epoch-based LME, a significant decrease for GAD was seen at 0.5µg during early recovery ($\beta=-0.58, t(840)=-2.17, p=0.030, 95\% CI[-1.09, -0.06]$) (eTable 9; eTables 10 and 11 for other ROIs). Group interactions reflecting differences in HR on FPC2 ($\beta=-0.11, t(112)=-2.28, p=0.025, 95\% CI[-0.20, -0.02]$) and cardiorespiratory dial ratings on FPC1 ($\beta=0.39, t(112)=2.79, p=0.006, 95\% CI[0.12, -0.67]$) were also observed at the 0.5µg dose. In each model, dose effects were again seen on the trajectory of HR and dial ratings (eTable 12).
eTable 1. Diagnostic comorbidities and psychotropic medication status of generalized anxiety disorder and healthy comparator participants.

|                               | GAD     | HC      |
|-------------------------------|---------|---------|
| **Psychotropic medication, N (%)**<sup>a</sup> | 6 (21)  | 0       |
| **Comorbid Diagnoses, N (%)**<sup>b</sup>       |         |         |
| Major depressive disorder (recurrent)             | 15 (52) | 0       |
| Major depressive disorder (partial remission)     | 9 (31)  | 0       |
| Social anxiety disorder                      | 14 (48) | 0       |
| Posttraumatic stress disorder                   | 3 (10)  | 0       |
| **Race/Ethnicity, N (%)**<sup>c</sup>          |         |         |
| Black or African American                  | 2(7)    | 2(7)    |
| American Indian or Alaskan Native             | 1(3)    | 1(3)    |
| Asian                                        | 4(14)   | 5(17)<sup>d</sup> |
| Hispanic or Latino                           | 3(10)   | 3(10)   |
| White                                         | 19(66)  | 18(62)  |
| Other                                         | 0       | 0<sup>e</sup> |

<sup>a</sup> 3 participants reported selective serotonin reuptake inhibitor use (sertraline, paroxetine), 2 reported selective norepinephrine reuptake inhibitor use (bupropion, escitalopram), 1 reported taking both classes of reuptake inhibitor, 1 reported occasional as needed use of a short-acting beta-blocker (propranolol) but abstained for at least one day prior to scanning and 1 reported medicinal tetrahydrocannabinol (THC) use but tested negative on the day of scanning. No participants were taking scheduled benzodiazepines or barbiturates.

<sup>b</sup> For brevity, only comorbid diagnoses with frequency > 5% are listed.

<sup>c</sup> Racial and ethnic categories defined as per the most recent revisions of the federal Office of Management and Budget Directive 15.

<sup>d</sup> One healthy comparator responded as being of Vietnamese and Hispanic ethnicity.

<sup>e</sup> One healthy comparator refused to report ethnicity.
### eTable 2. LME for Heart Rate by Group and Dose for Selected Isoproterenol Time-course Epochs.

| Factor                  | Estimate | Std. Err. | DF  | t-Stat | p-Value | Sig. |
|-------------------------|----------|-----------|-----|--------|---------|------|
| (Intercept)             | 43.60    | 13.79     | 54.15 | 3.16   | 0.003   | **  |
| Period Ant              | -0.04    | 0.84      | 1650.04 | -0.05  | 0.959   |     |
| Period Peak             | -0.86    | 0.84      | 1650.04 | -1.02  | 0.308   |     |
| Period Early            | -1.74    | 0.84      | 1650.04 | -2.06  | 0.039   | *   |
| Period Late             | -1.59    | 0.84      | 1650.04 | -1.89  | 0.059   | ^   |
| Dose 0.5 µg             | 0.24     | 0.84      | 1650.04 | 0.29   | 0.772   |     |
| Dose 2.0 µg             | -0.02    | 0.84      | 1650.04 | -0.02  | 0.984   |     |
| Group GAD               | 27.66    | 14.03     | 56.20 | 1.97   | 0.054   | ^   |
| Age                     | 0.26     | 0.38      | 53.96 | 0.71   | 0.483   |     |
| BMI                     | 0.69     | 0.60      | 53.96 | 1.15   | 0.257   |     |
| Ant X 0.5 µg            | -0.12    | 1.19      | 1650.04 | -0.10  | 0.921   |     |
| Peak X 0.5 µg           | 8.23     | 1.19      | 1650.04 | 6.91   | <0.001 *** |
| Early X 0.5 µg          | 2.13     | 1.19      | 1650.04 | 1.79   | 0.075   | ^   |
| Late X 0.5 µg           | 1.07     | 1.19      | 1650.04 | 0.90   | 0.369   |     |
| Ant X 2.0 µg            | -0.51    | 1.19      | 1650.04 | -0.43  | 0.670   |     |
| Peak X 2.0 µg           | 22.68    | 1.19      | 1650.04 | 19.04  | <0.001 *** |
| Early X 2.0 µg          | 13.79    | 1.19      | 1650.04 | 11.57  | <0.001 *** |
| Late X 2.0 µg           | 5.86     | 1.19      | 1650.04 | 4.92   | <0.001 *** |
| Ant X GAD               | 0.68     | 1.19      | 1650.04 | 0.57   | 0.568   |     |
| Peak X GAD              | 0.33     | 1.19      | 1650.04 | 0.28   | 0.782   |     |
| Early X GAD             | 0.14     | 1.19      | 1650.04 | 0.12   | 0.908   |     |
| Late X GAD              | 0.59     | 1.19      | 1650.04 | 0.49   | 0.623   |     |
| 0.5 µg X GAD            | -0.12    | 1.19      | 1650.04 | -0.10  | 0.921   |     |
| 2.0 µg X GAD            | -0.30    | 1.19      | 1650.04 | -0.25  | 0.801   |     |
| GAD X Age               | -0.30    | 0.38      | 55.16 | -0.80  | 0.427   |     |
| GAD X BMI               | -0.73    | 0.61      | 55.15 | -1.21  | 0.231   |     |
| Ant X 0.5 µg X GAD      | 0.32     | 1.68      | 1650.04 | 0.19   | 0.847   |     |
| Peak X 0.5 µg X GAD     | 5.34     | 1.68      | 1650.04 | 3.17   | 0.002   | **  |
| Early X 0.5 µg X GAD    | 2.02     | 1.69      | 1650.04 | 1.20   | 0.232   |     |
| Late X 0.5 µg X GAD     | 0.71     | 1.69      | 1650.04 | 0.42   | 0.672   |     |
| Ant X 2.0 µg X GAD      | 1.09     | 1.68      | 1650.04 | 0.65   | 0.519   |     |
| Peak X 2.0 µg X GAD     | 3.18     | 1.68      | 1650.04 | 1.89   | 0.060   | ^   |
| Early X 2.0 µg X GAD    | -0.95    | 1.69      | 1650.04 | -0.56  | 0.573   |     |
| Late X 2.0 µg X GAD     | -1.46    | 1.69      | 1650.04 | -0.87  | 0.385   |     |

Note: Sig. = significance. Coded as *** = p<0.001, ** = p<0.01, * = p<0.05, ^ = p<0.1
eTable 3. LME for Continuous Cardiorespiratory Dial Ratings by Group and Dose for Selected Isoproterenol Time-course Epochs.

| Factor               | Estimate | Std. Err. | DF    | t-Stat | p-Value | Sig. |
|----------------------|----------|-----------|-------|--------|---------|------|
| (Intercept)          | 8.97     | 7.18      | 56.41 | 1.25   | 0.217   |      |
| Period Ant           | 0.46     | 1.63      | 1650.55 | 0.28   | 0.776   |      |
| Period Peak          | 2.51     | 1.63      | 1650.55 | 1.54   | 0.123   |      |
| Period Early         | 3.75     | 1.63      | 1650.55 | 2.30   | 0.021 * |      |
| Period Late          | 2.81     | 1.63      | 1650.55 | 1.73   | 0.084 ^ |      |
| Dose 0.5 µg          | -0.14    | 1.63      | 1650.55 | -0.09  | 0.931   |      |
| Dose 2.0 µg          | 0.51     | 1.63      | 1650.55 | 0.31   | 0.754   |      |
| Group GAD            | -13.75   | 7.96      | 75.44 | -1.73  | 0.088 ^ |      |
| Age                  | -0.19    | 0.19      | 53.74 | -0.98  | 0.331   |      |
| BMI                  | -0.14    | 0.31      | 53.74 | -0.45  | 0.655   |      |
| Ant X 0.5 µg         | 0.14     | 2.30      | 1650.55 | 0.06   | 0.952   |      |
| Peak X 0.5 µg        | 3.91     | 2.30      | 1650.55 | 1.70   | 0.090 ^ |      |
| Early X 0.5 µg       | 1.34     | 2.30      | 1650.55 | 0.58   | 0.560   |      |
| Late X 0.5 µg        | -1.20    | 2.30      | 1650.55 | -0.52  | 0.602   |      |
| Ant X 2.0 µg         | 0.39     | 2.30      | 1650.55 | 0.17   | 0.866   |      |
| Peak X 2.0 µg        | 25.27    | 2.30      | 1650.55 | 10.97  | <0.001 *** |      |
| Early X 2.0 µg       | 27.14    | 2.30      | 1650.55 | 11.79  | <0.001 *** |      |
| Late X 2.0 µg        | 4.57     | 2.30      | 1650.55 | 1.99   | 0.047 *  |      |
| Ant X GAD            | 0.24     | 2.30      | 1650.55 | 0.11   | 0.916   |      |
| Peak X GAD           | -0.18    | 2.30      | 1650.55 | -0.08  | 0.938   |      |
| Early X GAD          | -1.53    | 2.31      | 1650.61 | -0.66  | 0.508   |      |
| Late X GAD           | 0.01     | 2.31      | 1650.61 | 0.01   | 0.995   |      |
| 0.5 µg X GAD         | 0.45     | 2.30      | 1650.55 | 0.20   | 0.844   |      |
| 2.0 µg X GAD         | 0.24     | 2.30      | 1650.55 | 0.11   | 0.917   |      |
| GAD X Age            | 0.30     | 0.21      | 65.82  | 1.47   | 0.148   |      |
| GAD X BMI            | 0.25     | 0.33      | 64.56  | 0.76   | 0.450   |      |
| Ant X 0.5 µg X GAD   | 0.41     | 3.26      | 1650.55 | 0.13   | 0.901   |      |
| Peak X 0.5 µg X GAD  | 8.38     | 3.26      | 1650.55 | 2.57   | 0.010 * |      |
| Early X 0.5 µg X GAD | 9.11     | 3.26      | 1650.58 | 2.80   | 0.005 ** |      |
| Late X 0.5 µg X GAD  | 1.88     | 3.26      | 1650.58 | 0.58   | 0.564   |      |
| Ant X 2.0 µg X GAD   | 0.44     | 3.26      | 1650.55 | 0.13   | 0.893   |      |
| Peak X 2.0 µg X GAD  | 6.06     | 3.26      | 1650.55 | 1.86   | 0.063 ^ |      |
| Early X 2.0 µg X GAD | 3.36     | 3.26      | 1650.58 | 1.03   | 0.303   |      |
| Late X 2.0 µg X GAD  | -1.19    | 3.26      | 1650.58 | -0.37  | 0.714   |      |

Note: Sig. = significance. Coded as *** = p<0.001, ** = p<0.01, * = p<0.05, ^ = p<0.1
**eTable 4. LME for Retrospective Ratings by Group and Dose.**

| Factor           | Estimate | Std. Err. | DF  | t-Stat | p-Value | Sig. |
|------------------|----------|-----------|-----|--------|---------|------|
| **Heartbeat Intensity** |          |           |     |        |         |      |
| (Intercept)      | 5.27     | 1.89      | 52.68 | 2.79   | 0.007 **|      |
| Dose 0.5 µg      | 0.79     | 0.31      | 278.98 | 2.54   | 0.012 * |      |
| Dose 2.0 µg      | 5.35     | 0.31      | 279.27 | 17.12  | <0.001 ***|     |
| Group GAD        | -3.04    | 2.40      | 52.88 | -1.27  | 0.210   |      |
| Age              | -0.05    | 0.05      | 52.04 | -1.05  | 0.297   |      |
| BMI              | -0.13    | 0.08      | 51.86 | -1.57  | 0.122   |      |
| 0.5 µg X GAD     | 2.21     | 0.44      | 278.81 | 5.04   | <0.001 ***|    |
| 2.0 µg X GAD     | 0.50     | 0.44      | 278.96 | 1.14   | 0.257   |      |
| GAD X Age        | 0.05     | 0.06      | 51.78 | 0.73   | 0.469   |      |
| GAD X BMI        | 0.09     | 0.10      | 51.83 | 0.97   | 0.336   |      |
| **Respiratory Intensity** |          |           |     |        |         |      |
| (Intercept)      | 4.40     | 1.88      | 52.39 | 2.34   | 0.023 * |      |
| Dose 0.5 µg      | 0.85     | 0.29      | 276.49 | 2.90   | 0.004 **|      |
| Dose 2.0 µg      | 4.27     | 0.29      | 275.76 | 14.86  | <0.001 ***|    |
| Group GAD        | -2.46    | 2.39      | 52.52 | -1.03  | 0.309   |      |
| Age              | -0.03    | 0.05      | 51.68 | -0.58  | 0.566   |      |
| BMI              | -0.11    | 0.08      | 52.08 | -1.36  | 0.181   |      |
| 0.5 µg X GAD     | 1.51     | 0.41      | 276.00 | 3.70   | <0.001 ***|    |
| 2.0 µg X GAD     | 0.48     | 0.41      | 275.62 | 1.18   | 0.238   |      |
| GAD X Age        | 0.04     | 0.06      | 51.50 | 0.67   | 0.506   |      |
| GAD X BMI        | 0.07     | 0.10      | 51.88 | 0.67   | 0.507   |      |
| **Anxiety**      |          |           |     |        |         |      |
| (Intercept)      | 2.43     | 2.01      | 52.71 | 1.21   | 0.231   |      |
| Dose 0.5 µg      | 0.47     | 0.26      | 281.50 | 1.81   | 0.072   |      |
| Dose 2.0 µg      | 1.63     | 0.26      | 281.09 | 6.34   | <0.001 ***|    |
| Group GAD        | 0.19     | 2.54      | 52.80 | 0.07   | 0.942   |      |
| Age              | -0.02    | 0.05      | 51.97 | -0.31  | 0.756   |      |
| BMI              | -0.05    | 0.09      | 52.83 | -0.54  | 0.593   |      |
| 0.5 µg X GAD     | 1.04     | 0.37      | 281.32 | 2.84   | 0.005 **|      |
| 2.0 µg X GAD     | 1.22     | 0.36      | 281.11 | 3.36   | 0.001 ***|    |
| GAD X Age        | 0.06     | 0.07      | 51.95 | 0.96   | 0.341   |      |
| GAD X BMI        | -0.05    | 0.10      | 52.60 | -0.52  | 0.604   |      |
| **Excitement**   |          |           |     |        |         |      |
| (Intercept)      | 4.09     | 2.21      | 51.91 | 1.85   | 0.071 ^|      |
| Dose 0.5 µg      | -0.02    | 0.18      | 256.70 | -0.10  | 0.922   |      |
| Dose 2.0 µg      | 0.14     | 0.18      | 256.62 | 0.76   | 0.450   |      |
| Group GAD        | -3.20    | 2.81      | 51.99 | -1.14  | 0.260   |      |
| Age              | 0.35     | 0.26      | 256.69 | 1.37   | 0.173   |      |
| BMI              | 0.18     | 0.26      | 256.89 | 0.69   | 0.489   |      |
| 0.5 µg X GAD     | 0.04     | 0.06      | 51.67 | 0.70   | 0.486   |      |
| 2.0 µg X GAD     | 0.07     | 0.04      | 51.80 | 1.57   | 0.123   |      |
| GAD X Age        | -0.15    | 0.10      | 52.26 | -1.55  | 0.128   |      |
| GAD X BMI        | -0.07    | 0.06      | 51.80 | -1.19  | 0.239   |      |

Note: Sig. = significance. Coded as *** = p<0.001, ** = p<0.01, * = p<0.05, ^ = p<0.1
### Table 5. LME for Respiratory Volume Variability by Group and Dose for Selected Isoproterenol Time-course Epochs.

| Factor                      | Estimate | Std. Err. | DF    | t-Stat | p-Value | Sig. |
|-----------------------------|----------|-----------|-------|--------|---------|------|
| (Intercept)                 | 15.59    | 3.87      | 54.63 | 4.03   | <0.001  | ***  |
| Period Ant                  | 1.37     | 0.59      | 1649.87| 2.32   | 0.021   | *    |
| Period Peak                 | 0.23     | 0.59      | 1649.87| 0.39   | 0.697   |      |
| Period Early                | -0.65    | 0.59      | 1649.87| -1.10  | 0.270   |      |
| Period Late                 | -0.81    | 0.59      | 1649.87| -1.38  | 0.169   |      |
| Dose 0.5 µg                 | -1.14    | 0.59      | 1649.87| -1.94  | 0.052   | ^    |
| Dose 2.0 µg                 | -3.07    | 0.59      | 1649.87| -5.21  | <0.001  | ***  |
| Group GAD                   | 1.16     | 4.11      | 65.40 | 0.28   | 0.778   |      |
| Age                         | 0.20     | 0.10      | 53.46 | 1.89   | 0.065   | ^    |
| BMI                         | -0.16    | 0.17      | 53.46 | -0.94  | 0.352   |      |
| Ant X 0.5 µg                | 0.13     | 0.83      | 1649.87| 0.16   | 0.872   |      |
| Peak X 0.5 µg               | 2.77     | 0.83      | 1649.87| 3.33   | <0.001  | ***  |
| Early X 0.5 µg              | -0.76    | 0.83      | 1649.87| -0.92  | 0.360   |      |
| Late X 0.5 µg               | -0.07    | 0.83      | 1649.87| -0.08  | 0.935   |      |
| Ant X 2.0 µg                | -0.30    | 0.83      | 1649.87| -0.36  | 0.719   |      |
| Peak X 2.0 µg               | 6.18     | 0.83      | 1649.87| 7.41   | <0.001  | ***  |
| Early X 2.0 µg              | -0.42    | 0.83      | 1649.87| -0.51  | 0.610   |      |
| Late X 2.0 µg               | -0.29    | 0.83      | 1649.87| -0.35  | 0.727   |      |
| Ant X GAD                   | 0.34     | 0.83      | 1649.87| 0.41   | 0.681   |      |
| Peak X GAD                  | 0.19     | 0.83      | 1649.87| 0.22   | 0.823   |      |
| Early X GAD                 | 0.03     | 0.84      | 1649.89| 0.04   | 0.970   |      |
| Late X GAD                  | 0.40     | 0.84      | 1649.89| 0.48   | 0.631   |      |
| 0.5 µg X GAD                | -0.33    | 0.83      | 1649.87| -0.40  | 0.688   |      |
| 2.0 µg X GAD                | 0.32     | 0.83      | 1649.87| 0.38   | 0.702   |      |
| GAD X Age                   | -0.21    | 0.11      | 59.97 | -1.93  | 0.058   | ^    |
| GAD X BMI                   | 0.15     | 0.17      | 59.63 | 0.89   | 0.375   |      |
| Ant X 0.5 µg X GAD          | -0.77    | 1.18      | 1649.87| -0.66  | 0.512   |      |
| Peak X 0.5 µg X GAD         | 0.15     | 1.18      | 1649.87| 0.13   | 0.900   |      |
| Early X 0.5 µg X GAD        | -0.43    | 1.18      | 1649.88| -0.36  | 0.718   |      |
| Late X 0.5 µg X GAD         | -0.59    | 1.18      | 1649.88| -0.50  | 0.614   |      |
| Ant X 2.0 µg X GAD          | 0.33     | 1.18      | 1649.87| 0.28   | 0.780   |      |
| Peak X 2.0 µg X GAD         | -1.24    | 1.18      | 1649.87| -1.05  | 0.293   |      |
| Early X 2.0 µg X GAD        | -0.60    | 1.18      | 1649.88| -0.51  | 0.612   |      |
| Late X 2.0 µg X GAD         | -0.67    | 1.18      | 1649.88| -0.57  | 0.572   |      |

Note: Sig. = significance. Coded as *** = p<0.001, ** = p<0.01, * = p<0.05, ^ = p<0.1
### eTable 6. LME for Cross Correlations (CC) Between Real-time Dial Responses and Heart Rate.

| Factor          | Estimate | Std. Err. | DF    | t-Stat | p-Value | Sig. |
|-----------------|----------|-----------|-------|--------|---------|------|
| **Zero-Lag CC** |          |           |       |        |         |      |
| (Intercept)     | 0.09     | 0.14      | 332.08| 0.62   | 0.538   |      |
| Dose 0.5 µg     | 0.17     | 0.04      | 280.94| 4.44   | <0.001  ***|
| Dose 2.0 µg     | 0.63     | 0.04      | 280.94| 16.36  | <0.001  ***|
| Group GAD       | -0.06    | 0.18      | 332.56| -0.36  | 0.721   |      |
| Age             | 0.00     | 0.00      | 313.91| -0.83  | 0.407   |      |
| BMI             | 0.00     | 0.01      | 301.96| -0.44  | 0.664   |      |
| 0.5 µg X GAD    | 0.05     | 0.05      | 281.12| 0.88   | 0.380   |      |
| 2.0 µg X GAD    | -0.07    | 0.05      | 281.12| -1.34  | 0.181   |      |
| GAD X Age       | 0.00     | 0.00      | 332.12| 0.82   | 0.411   |      |
| GAD X BMI       | 0.00     | 0.01      | 318.40| 0.02   | 0.983   |      |
| **Max CC**      |          |           |       |        |         |      |
| (Intercept)     | 0.25     | 0.13      | 336.37| 1.95   | 0.052   ^|
| Dose 0.5 µg     | 0.21     | 0.04      | 281.27| 5.69   | <0.001  ***|
| Dose 2.0 µg     | 0.54     | 0.04      | 281.27| 14.87  | <0.001  ***|
| Group GAD       | -0.06    | 0.16      | 336.20| -0.39  | 0.700   |      |
| Age             | 0.00     | 0.00      | 325.11| 1.07   | 0.286   |      |
| BMI             | -0.01    | 0.01      | 310.95| -1.09  | 0.276   |      |
| 0.5 µg X GAD    | 0.09     | 0.05      | 281.53| 1.79   | 0.075   ^|
| 2.0 µg X GAD    | -0.01    | 0.05      | 281.53| -0.19  | 0.846   |      |
| GAD X Age       | 0.00     | 0.00      | 337.00| -0.82  | 0.416   |      |
| GAD X BMI       | 0.01     | 0.01      | 328.38| 1.01   | 0.311   |      |
| **Lag-time at Max CC** | | | | | |
| (Intercept)     | 9.55     | 20.32     | 279.00| 0.47   | 0.639   |      |
| Dose 0.5 µg     | -14.04   | 6.37      | 279.00| -2.20  | 0.028   ^|
| Dose 2.0 µg     | -17.47   | 6.05      | 279.00| -2.89  | 0.004   **|
| Group GAD       | -15.44   | 25.67     | 279.00| -0.60  | 0.548   |      |
| Age             | -0.29    | 0.55      | 279.00| -0.54  | 0.592   |      |
| BMI             | 0.22     | 0.87      | 279.00| 0.25   | 0.800   |      |
| 0.5 µg X GAD    | 5.57     | 8.83      | 279.00| 0.63   | 0.529   |      |
| 2.0 µg X GAD    | 13.33    | 8.47      | 279.00| 1.57   | 0.117   |      |
| GAD X Age       | 0.30     | 0.66      | 279.00| 0.46   | 0.649   |      |
| GAD X BMI       | -0.22    | 1.03      | 279.00| -0.21  | 0.831   |      |

Note: Sig. = significance. Coded as *** = p<0.001, ** = p<0.01, * = p<0.05, ^ = p<0.1
### Table 7. LME for Cross Correlations (CC) Between Continuous Dial Responses and Respiratory Volume Variability.

| Factor          | Estimate | Std. Err. | DF  | t-Stat | p-Value | Sig. |
|-----------------|----------|-----------|-----|--------|---------|------|
| **Zero-Lag CC** |          |           |     |        |         |      |
| (Intercept)     | 0.00     | 0.16      | 331.09 | 0.02  | 0.982   |      |
| Dose 0.5 µg     | 0.03     | 0.04      | 281.73 | 0.66  | 0.511   |      |
| Dose 2.0 µg     | 0.00     | 0.04      | 281.73 | -0.02 | 0.981   |      |
| Group GAD       | 0.03     | 0.20      | 331.89 | 0.17  | 0.866   |      |
| Age             | 0.00     | 0.00      | 311.58 | 0.16  | 0.870   |      |
| BMI             | 0.00     | 0.01      | 300.58 | -0.58 | 0.564   |      |
| 0.5 µg X GAD    | -0.06    | 0.06      | 281.89 | -1.06 | 0.292   |      |
| 2.0 µg X GAD    | -0.03    | 0.06      | 281.89 | -0.45 | 0.650   |      |
| GAD X Age       | 0.00     | 0.01      | 329.85 | 0.29  | 0.774   |      |
| GAD X BMI       | 0.00     | 0.01      | 316.10 | -0.14 | 0.888   |      |
| **Max CC**      |          |           |     |        |         |      |
| (Intercept)     | 0.35     | 0.12      | 334.24 | 2.83  | 0.005   ** |
| Dose 0.5 µg     | 0.10     | 0.03      | 281.77 | 3.04  | 0.003   ** |
| Dose 2.0 µg     | 0.23     | 0.03      | 281.77 | 6.90  | <0.001   *** |
| Group GAD       | -0.26    | 0.16      | 334.28 | -1.66 | 0.099   ^   |
| Age             | 0.00     | 0.00      | 319.23 | 0.56  | 0.574   |      |
| BMI             | -0.01    | 0.01      | 306.22 | -1.10 | 0.273   |      |
| 0.5 µg X GAD    | 0.06     | 0.05      | 281.98 | 1.21  | 0.229   |      |
| 2.0 µg X GAD    | 0.03     | 0.05      | 281.98 | 0.69  | 0.488   |      |
| GAD X Age       | 0.00     | 0.00      | 335.41 | 0.11  | 0.913   |      |
| GAD X BMI       | 0.01     | 0.01      | 323.27 | 1.70  | 0.091   ^   |
| **Lag-time at Max CC** |      |           |     |        |         |      |
| (Intercept)     | 12.29    | 28.80     | 278.92 | 0.43  | 0.670   |      |
| Dose 0.5 µg     | -4.79    | 8.73      | 242.07 | -0.55 | 0.584   |      |
| Dose 2.0 µg     | -3.46    | 8.30      | 242.55 | -0.42 | 0.677   |      |
| Group GAD       | -7.19    | 36.34     | 278.80 | -0.20 | 0.843   |      |
| Age             | -0.63    | 0.77      | 274.03 | -0.82 | 0.415   |      |
| BMI             | -0.07    | 1.21      | 262.65 | -0.05 | 0.957   |      |
| 0.5 µg X GAD    | -0.38    | 12.11     | 242.32 | -0.03 | 0.975   |      |
| 2.0 µg X GAD    | -3.42    | 11.61     | 242.09 | -0.30 | 0.768   |      |
| GAD X Age       | 0.55     | 0.94      | 278.24 | 0.59  | 0.558   |      |
| GAD X BMI       | -0.44    | 1.44      | 274.14 | -0.31 | 0.759   |      |

Note: Sig. = significance. Coded as *** = p<0.001, ** = p<0.01, * = p<0.05, ^ = p<0.1
Table 8. LMEs for FPC Score Reflecting Signal Change Timeseries for Meta-analysis–derived vmPFC ROIs.

| Factor | Value | Std. Err. | DF   | t-value | p-value | Sig. |
|--------|-------|-----------|------|---------|---------|------|
| **Self ROI: Functional Principal Component 1** |       |           |      |         |         |      |
| (Intercept) | -0.35 | 0.06      | 146.00 | -5.64 | <.001 *** |      |
| Group GAD | 0.00 | 0.09      | 146.00 | 0.01 | 0.944 |      |
| Dose 0.5 µg | 0.22 | 0.07      | 112.00 | 2.99 | 0.004 ** |      |
| Dose 2.0 µg | 0.60 | 0.07      | 112.00 | 8.11 | <.001 *** |      |
| 0.5 µg X GAD | 0.23 | 0.10      | 112.00 | 2.24 | 0.027 * |      |
| 2.0 µg X GAD | 0.19 | 0.10      | 112.00 | 1.85 | 0.067 ^ |      |
| **Self ROI: Functional Principal Component 2** |       |           |      |         |         |      |
| (Intercept) | -0.06 | 0.04      | 162.85 | -1.49 | 0.138 |      |
| Group GAD | 0.09 | 0.06      | 162.85 | 1.52 | 0.129 |      |
| Dose 0.5 µg | 0.10 | 0.05      | 112.00 | 1.85 | 0.067 ^ |      |
| Dose 2.0 µg | 0.03 | 0.05      | 112.00 | 0.52 | 0.607 |      |
| 0.5 µg X GAD | -0.05 | 0.08 | 112.00 | -0.66 | 0.509 |      |
| 2.0 µg X GAD | -0.11 | 0.08 | 112.00 | -1.41 | 0.160 |      |
| **Valence ROI: Functional Principal Component 1** |       |           |      |         |         |      |
| (Intercept) | -0.38 | 0.08      | 138.39 | -4.93 | <.001 *** |      |
| Group GAD | 0.07 | 0.11      | 138.39 | 0.63 | 0.528 |      |
| Dose 0.5 µg | 0.21 | 0.09      | 112.00 | 2.34 | 0.021 * |      |
| Dose 2.0 µg | 0.69 | 0.09      | 112.00 | 7.73 | <.001 *** |      |
| 0.5 µg X GAD | 0.16 | 0.13 | 112.00 | 1.31 | 0.194 |      |
| 2.0 µg X GAD | 0.12 | 0.13 | 112.00 | 0.96 | 0.341 |      |
| **Valence ROI: Functional Principal Component 2** |       |           |      |         |         |      |
| (Intercept) | -0.01 | 0.04      | 138.46 | -0.28 | 0.779 |      |
| Group GAD | 0.12 | 0.06      | 138.46 | 2.09 | 0.038 * |      |
| Dose 0.5 µg | 0.03 | 0.05      | 112.00 | 0.55 | 0.584 |      |
| Dose 2.0 µg | -0.11 | 0.05 | 112.00 | -2.21 | 0.029 * |      |
| 0.5 µg X GAD | -0.10 | 0.06 | 112.00 | -1.19 | 0.237 |      |
| 2.0 µg X GAD | -0.07 | 0.06 | 112.00 | -0.88 | 0.382 |      |
| **Autonomic ROI: Functional Principal Component 1** |       |           |      |         |         |      |
| (Intercept) | -0.41 | 0.08      | 144.63 | -5.10 | <.001 *** |      |
| Group GAD | -0.00 | 0.11      | 144.63 | -0.03 | 0.976 |      |
| Dose 0.5 µg | 0.16 | 0.10      | 112.00 | 1.67 | 0.097 |      |
| Dose 2.0 µg | 0.88 | 0.10      | 112.00 | 9.27 | <.001 *** |      |
| 0.5 µg X GAD | 0.25 | 0.13 | 112.00 | 1.85 | 0.067 ^ |      |
| 2.0 µg X GAD | 0.09 | 0.13 | 112.00 | 0.69 | 0.494 |      |
| **Autonomic ROI: Functional Principal Component 2** |       |           |      |         |         |      |
| (Intercept) | -0.04 | 0.05      | 133.05 | -0.86 | 0.394 |      |
| Group GAD | 0.11 | 0.06      | 133.05 | 1.67 | 0.097 ^ |      |
| Dose 0.5 µg | 0.09 | 0.05 | 112.00 | 1.77 | 0.080 ^ |      |
| Dose 2.0 µg | -0.11 | 0.05 | 112.00 | -2.13 | 0.036 * |      |
| 0.5 µg X GAD | -0.09 | 0.07 | 112.00 | -1.22 | 0.224 |      |
| 2.0 µg X GAD | 0.04 | 0.07 | 112.00 | 0.58 | 0.560 |      |

Note: Sig. = significance. Coded as *** = p<0.001, ** = p<0.01, * = p<0.05, ^ = p<0.1

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| Factor                        | Value | Std. Err. | DF   | t-stat | p-value | Sig. |
|------------------------------|-------|-----------|------|--------|---------|------|
| (Intercept)                  | 0.10  | 0.22      | 836.00 | 0.45   | 0.653   |      |
| Early                       | -0.26 | 0.13      | 836.00 | -1.93  | 0.054   | ~    |
| Late                        | -0.15 | 0.13      | 836.00 | -1.11  | 0.268   |      |
| Peak                        | -0.50 | 0.13      | 836.00 | -3.78  | <0.001  | ***  |
| Ant                         | -0.50 | 0.13      | 836.00 | -3.76  | <0.001  | ***  |
| Dose 0.5 µg                 | 0.12  | 0.13      | 836.00 | 0.87   | 0.387   |      |
| Dose 2.0 µg                 | 0.60  | 0.13      | 836.00 | 4.55   | <0.001  | ***  |
| Group GAD                   | 0.09  | 0.28      | 836.00 | 0.31   | 0.758   |      |
| Age                         | 0.00  | 0.01      | 836.00 | 0.20   | 0.841   |      |
| BMI                         | 0.00  | 0.01      | 836.00 | 0.52   | 0.601   |      |
| Early X 0.5 µg              | -0.13 | 0.19      | 836.00 | -0.68  | 0.495   |      |
| Late X 0.5 µg               | -0.03 | 0.19      | 836.00 | -0.16  | 0.871   |      |
| Peak X 0.5 µg               | -0.41 | 0.19      | 836.00 | -2.20  | 0.028   | *    |
| Ant X 0.5 µg                | -0.04 | 0.19      | 836.00 | -0.21  | 0.835   |      |
| Early X 2.0 µg              | -1.62 | 0.19      | 836.00 | -8.63  | <0.001  | ***  |
| Late X 2.0 µg               | -0.02 | 0.19      | 836.00 | -0.12  | 0.909   |      |
| Peak X 2.0 µg               | -1.32 | 0.19      | 836.00 | -7.02  | <0.001  | ***  |
| Ant X 2.0 µg                | -0.05 | 0.19      | 836.00 | -0.24  | 0.809   |      |
| Early X GAD                 | 0.07  | 0.19      | 836.00 | 0.36   | 0.722   |      |
| Late X GAD                  | -0.05 | 0.19      | 836.00 | -0.29  | 0.776   |      |
| Peak X GAD                  | -0.13 | 0.19      | 836.00 | -0.69  | 0.493   |      |
| Ant X GAD                   | -0.20 | 0.19      | 836.00 | -1.08  | 0.280   |      |
| Dose 0.5 µg XGAD            | 0.22  | 0.19      | 836.00 | 1.18   | 0.237   |      |
| Dose 2.0 µg XGAD            | 0.14  | 0.19      | 836.00 | 0.72   | 0.471   |      |
| GAD X Age                   | 0.00  | 0.01      | 836.00 | 0.12   | 0.904   |      |
| GAD X BMI                   | 0.00  | 0.01      | 836.00 | -0.30  | 0.763   |      |
| Early X 0.5 µg X GAD        | -0.58 | 0.27      | 836.00 | -2.16  | 0.031   | *    |
| Late X 0.5 µg X GAD         | -0.07 | 0.27      | 836.00 | -0.25  | 0.799   |      |
| Peak X 0.5 µg X GAD         | -0.40 | 0.27      | 836.00 | -1.52  | 0.129   |      |
| Ant X 0.5 µg X GAD          | -0.04 | 0.27      | 836.00 | -0.16  | 0.875   |      |
| Early X 2.0 µg X GAD        | -0.13 | 0.27      | 836.00 | -0.48  | 0.633   |      |
| Late X 2.0 µg X GAD         | -0.10 | 0.27      | 836.00 | -0.37  | 0.710   |      |
| Peak X 2.0 µg X GAD         | -0.46 | 0.27      | 836.00 | -1.74  | 0.083   | ^    |
| Ant X 2.0 µg X GAD          | 0.02  | 0.27      | 836.00 | 0.06   | 0.954   |      |

Note: Sig. = significance. Coded as *** = $p<0.001$, ** = $p<0.01$, * = $p<0.05$, ^ = $p<0.1$
## eTable 10. LME for BOLD PSC for the Meta-analysis–derived Self-processing vmPFC ROI.

| Factor                                      | Value  | Std. Err. | DF    | t-stat | p-value | Sig. |
|----------------------------------------------|--------|-----------|-------|--------|---------|------|
| (Intercept)                                  | 0.00   | 0.11      | 836.00| 0.01   | 0.990   |      |
| Early                                        | 0.02   | 0.07      | 836.00| 0.25   | 0.805   |      |
| Late                                         | -0.04  | 0.07      | 836.00| -0.52  | 0.606   |      |
| Peak                                         | 0.00   | 0.07      | 836.00| 0.00   | 0.998   |      |
| Ant                                          | -0.16  | 0.07      | 836.00| -2.36  | 0.018   | *    |
| Dose 0.5 µg                                  | 0.07   | 0.07      | 836.00| 0.98   | 0.330   |      |
| Dose 2.0 µg                                  | 0.23   | 0.07      | 836.00| 3.45   | 0.001   | ***  |
| Group GAD                                    | -0.02  | 0.14      | 836.00| -0.14  | 0.893   |      |
| Age                                          | 0.00   | 0.00      | 836.00| 0.58   | 0.564   |      |
| BMI                                          | 0.00   | 0.00      | 836.00| -0.26  | 0.796   |      |
| Early X 0.5 µg                               | -0.07  | 0.10      | 836.00| -0.72  | 0.473   |      |
| Late X 0.5 µg                                | 0.01   | 0.10      | 836.00| 0.09   | 0.927   |      |
| Peak X 0.5 µg                                | -0.32  | 0.10      | 836.00| -3.32  | 0.001   | ***  |
| Ant X 0.5 µg                                 | 0.04   | 0.10      | 836.00| 0.43   | 0.670   |      |
| Early X 2.0 µg                               | -0.52  | 0.10      | 836.00| -5.41  | <0.001  | ***  |
| Late X 2.0 µg                                | 0.01   | 0.10      | 836.00| 0.12   | 0.907   |      |
| Peak X 2.0 µg                                | -0.62  | 0.10      | 836.00| -6.43  | <0.001  | ***  |
| Ant X 2.0 µg                                 | -0.11  | 0.10      | 836.00| -1.16  | 0.249   |      |
| Early X GAD                                  | 0.04   | 0.10      | 836.00| 0.39   | 0.695   |      |
| Late X GAD                                   | -0.01  | 0.10      | 836.00| -0.13  | 0.894   |      |
| Peak X GAD                                   | -0.05  | 0.10      | 836.00| -0.53  | 0.600   |      |
| Ant X GAD                                    | -0.12  | 0.10      | 836.00| -1.23  | 0.220   |      |
| 0.5 µg X GAD                                 | 0.19   | 0.10      | 836.00| 1.95   | 0.052   | ^    |
| 2.0 µg X GAD                                 | 0.13   | 0.10      | 836.00| 1.36   | 0.173   |      |
| GAD X Age                                    | 0.00   | 0.00      | 836.00| -0.36  | 0.720   |      |
| GAD X BMI                                    | 0.00   | 0.01      | 836.00| 0.51   | 0.608   |      |
| Early X 0.5 µg X GAD                         | -0.38  | 0.14      | 836.00| -2.83  | 0.005   | **   |
| Late X 0.5 µg X GAD                          | -0.11  | 0.14      | 836.00| -0.79  | 0.429   |      |
| Peak X 0.5 µg X GAD                          | -0.29  | 0.14      | 836.00| -2.17  | 0.031   | *    |
| Ant X 0.5 µg X GAD                           | -0.16  | 0.14      | 836.00| -1.20  | 0.231   |      |
| Early X 2.0 µg X GAD                         | -0.32  | 0.14      | 836.00| -2.34  | 0.019   | *    |
| Late X 2.0 µg X GAD                          | -0.09  | 0.14      | 836.00| -0.65  | 0.519   |      |
| Peak X 2.0 µg X GAD                          | -0.21  | 0.14      | 836.00| -1.52  | 0.128   |      |
| Ant X 2.0 µg X GAD                           | 0.08   | 0.14      | 836.00| 0.61   | 0.542   |      |

Note: Sig. = significance. Coded as *** = p<0.001, ** = p<0.01, * = p<0.05, ^ = p<0.1
### eTable 11. LME for BOLD PSC for the Meta-analysis–derived Valence vmPFC ROI.

| Factor                  | Value | Std. Err. | DF   | t-stat | p-value | Sig. |
|-------------------------|-------|-----------|------|--------|---------|------|
| (Intercept)             | 0.00  | 0.10      | 836.00 | -0.01  | 0.990   |      |
| Early                   | -0.04 | 0.06      | 836.00 | -0.63  | 0.529   |      |
| Late                    | -0.03 | 0.06      | 836.00 | -0.58  | 0.563   |      |
| Peak                    | -0.15 | 0.06      | 836.00 | -2.42  | 0.016 * |      |
| Ant                     | -0.15 | 0.06      | 836.00 | -2.52  | 0.012 * |      |
| Dose 0.5 µg             | 0.06  | 0.06      | 836.00 | 1.02   | 0.308   |      |
| Dose 2.0 µg             | 0.25  | 0.06      | 836.00 | 4.08   | <0.001 *** |    |
| Group GAD               | 0.09  | 0.13      | 836.00 | 0.68   | 0.498   |      |
| Age                     | 0.00  | 0.00      | 836.00 | 0.29   | 0.776   |      |
| BMI                     | 0.00  | 0.00      | 836.00 | 0.42   | 0.676   |      |
| Early X 0.5 µg          | -0.12 | 0.09      | 836.00 | -1.38  | 0.168   |      |
| Late X 0.5 µg           | -0.01 | 0.09      | 836.00 | -0.17  | 0.869   |      |
| Peak X 0.5 µg           | -0.19 | 0.09      | 836.00 | -2.21  | 0.027 * |      |
| Ant X 0.5 µg            | -0.01 | 0.09      | 836.00 | -0.07  | 0.944   |      |
| Early X 2.0 µg          | -0.63 | 0.09      | 836.00 | -7.44  | <0.001 *** |   |
| Late X 2.0 µg           | -0.02 | 0.09      | 836.00 | -0.19  | 0.852   |      |
| Peak X 2.0 µg           | -0.50 | 0.09      | 836.00 | -5.85  | <0.001 *** |   |
| Ant X 2.0 µg            | -0.07 | 0.09      | 836.00 | -0.83  | 0.405   |      |
| Early X GAD             | -0.05 | 0.09      | 836.00 | -0.64  | 0.526   |      |
| Late X GAD              | -0.06 | 0.09      | 836.00 | -0.75  | 0.454   |      |
| Peak X GAD              | -0.15 | 0.09      | 836.00 | -1.73  | 0.083 * |      |
| Ant X GAD               | -0.17 | 0.09      | 836.00 | -1.96  | 0.050 * |      |
| 0.5 µg X GAD            | 0.08  | 0.09      | 836.00 | 0.98   | 0.327   |      |
| 2.0 µg X GAD            | 0.03  | 0.09      | 836.00 | 0.41   | 0.684   |      |
| GAD X Age               | 0.00  | 0.00      | 836.00 | 0.00   | 0.997   |      |
| GAD X BMI               | 0.00  | 0.00      | 836.00 | -0.15  | 0.883   |      |
| Early X 0.5 µg X GAD    | -0.22 | 0.12      | 836.00 | -1.79  | 0.074 * |      |
| Late X 0.5 µg X GAD     | -0.01 | 0.12      | 836.00 | -0.09  | 0.931   |      |
| Peak X 0.5 µg X GAD     | -0.14 | 0.12      | 836.00 | -1.16  | 0.248   |      |
| Ant X 0.5 µg X GAD      | -0.03 | 0.12      | 836.00 | -0.25  | 0.807   |      |
| Early X 2.0 µg X GAD    | -0.08 | 0.12      | 836.00 | -0.68  | 0.498   |      |
| Late X 2.0 µg X GAD     | -0.01 | 0.12      | 836.00 | -0.07  | 0.943   |      |
| Peak X 2.0 µg X GAD     | -0.14 | 0.12      | 836.00 | -1.17  | 0.243   |      |
| Ant X 2.0 µg X GAD      | 0.09  | 0.12      | 836.00 | 0.77   | 0.439   |      |

Note: Sig. = significance. Coded as *** = p<0.001, ** = p<0.01, * = p<0.05, ^ = p<0.1
### eTable 12. LMEs for Heart Rate and Dial Response FPC Scores.

| Factor                  | Value | Std. Err. | DF | t-value | p-value | Sig. |
|-------------------------|-------|-----------|----|---------|---------|------|
| **Heart Rate Functional Principal Component 1** |       |           |    |         |         |      |
| (Intercept)             | -0.50 | 0.13      | 64.46 | -3.78   | <0.001  |      |
| Group GAD               | 0.22  | 0.19      | 64.46 | 1.18    | 0.241   |      |
| *Dose 0.5 µg*           | 0.24  | 0.06      | 112.00| 4.07    | <0.001  | ***  |
| *Dose 2.0 µg*           | 0.85  | 0.06      | 112.00| 14.14   | <0.001  | ***  |
| *0.5 µg X GAD*          | 0.15  | 0.09      | 112.00| 1.75    | 0.083   |      |
| *2.0 µg X GAD*          | -0.01 | 0.09      | 112.00| -0.11   | 0.913   |      |
| **Heart Rate Functional Principal Component 2** |       |           |    |         |         |      |
| (Intercept)             | 0.25  | 0.05      | 79.09 | 5.21    | <0.001  |      |
| Group GAD               | 0.05  | 0.07      | 79.09 | 0.80    | 0.426   |      |
| *Dose 0.5 µg*           | -0.18 | 0.03      | 112.00| -5.36   | <0.001  | ***  |
| *Dose 2.0 µg*           | -0.56 | 0.03      | 112.00| -16.50  | <0.001  | ***  |
| *0.5 µg X GAD*          | -0.11 | 0.05      | 112.00| -2.28   | 0.025   | *    |
| *2.0 µg X GAD*          | -0.07 | 0.05      | 112.00| -1.39   | 0.166   |      |
| **Dial Rating Functional Principal Component 1** |       |           |    |         |         |      |
| (Intercept)             | -0.49 | 0.09      | 133.35| -5.58   | <0.001  |      |
| Group GAD               | -0.04 | 0.12      | 133.35| -0.28   | 0.777   |      |
| Dose 0.5 µg             | 0.10  | 0.10      | 112.00| 1.02    | 0.311   |      |
| *Dose 2.0 µg*           | 1.13  | 0.10      | 112.00| 11.37   | <0.001  | ***  |
| *0.5 µg X GAD*          | 0.39  | 0.14      | 112.00| 2.79    | 0.006   | **   |
| *2.0 µg X GAD*          | 0.21  | 0.14      | 112.00| 1.47    | 0.144   |      |
| **Dial Rating Functional Principal Component 2** |       |           |    |         |         |      |
| (Intercept)             | 0.12  | 0.06      | 152.58| 2.22    | 0.028   |      |
| Group GAD               | -0.01 | 0.08      | 152.58| -0.12   | 0.906   |      |
| Dose 0.5 µg             | -0.11 | 0.07      | 112.00| -1.62   | 0.109   |      |
| *Dose 2.0 µg*           | -0.15 | 0.07      | 112.00| -2.23   | 0.028   | *    |
| *0.5 µg X GAD*          | -0.04 | 0.10      | 112.00| -0.41   | 0.680   |      |
| *2.0 µg X GAD*          | -0.14 | 0.10      | 112.00| -1.44   | 0.152   |      |

Note: Sig. = significance. Coded as *** = p<0.001, ** = p<0.01, * = p<0.05, ^ = p<0.1
Discussion 1. Study Limitations

Our focus on females with GAD was based on the fact that females outnumber males on a 2:1 basis. Future research will need to establish whether the current results may extend to males. Recent studies have suggested a divergence of symptom clusters in GAD females vs. males such that females are more likely to report somatic symptoms whereas males are more likely to report mood and motor symptoms. Thus, it is possible that the findings observed in the current study may represent a subtype expression of the disorder specific to females. Although we allowed participants who were taking psychotropic medications to enter the study, we do not think this impacted our findings, for several reasons: 1) they were stably medicated, 2) we would have expected to see disrupted action across all doses and epochs, and 3) the main effects of hypersensitivity and blunted vmPFC signal remained even after removing the medicated participants in follow-up analyses. Finally, given the high degree of comorbidity in GAD and our diagnostic focus, future work will need to test this paradigm in dimensionally and categorically defined samples (as in ) to see if a similar pattern of vmPFC hypoactivity during adrenergic stimulation is evident across other anxiety disorders.
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