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Association of Generalized Anxiety Disorder With Autonomic Hypersensitivity and Blunted Ventromedial Prefrontal Cortex Activity During Peripheral Adrenergic Stimulation
A Randomized Clinical Trial

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Supplemental content

IMPORTANCE β-Adrenergic stimulation elicits heart palpitations and dyspnea, key features of acute anxiety and sympathetic arousal, yet no neuroimaging studies have examined how the pharmacologic modulation of interoceptive signals is associated with fear-related neurocircuitry in individuals with generalized anxiety disorder (GAD).

OBJECTIVE To examine the neural circuitry underlying autonomic arousal induced via isoproterenol, a rapidly acting, peripheral β-adrenergic agonist akin to adrenaline.

DESIGN, SETTING, AND PARTICIPANTS This crossover randomized clinical trial of 58 women with artifact-free data was conducted from January 1, 2017, to November 31, 2019, at the Laureate Institute for Brain Research in Tulsa, Oklahoma.

EXPOSURES Functional magnetic resonance imaging was used to assess neural responses during randomized intravenous bolus infusions of isoproterenol (0.5 and 2.0 μg) and saline, each administered twice in a double-blind fashion.

MAIN OUTCOMES AND MEASURES Blood oxygen level–dependent responses across the whole brain during isoproterenol administration in patients with GAD vs healthy comparators. Cardiac and respiratory responses, as well as interoceptive awareness and anxiety, were also measured during the infusion protocol.

RESULTS Of the 58 female study participants, 29 had GAD (mean [SD] age, 26.9 [6.8] years) and 29 were matched healthy comparators (mean [SD] age, 24.4 [5.0] years). During the 0.5-μg dose of isoproterenol, the GAD group exhibited higher heart rate responses (b = 5.34; 95% CI, 2.06-8.61; P = .002), higher intensity ratings of cardiorespiratory sensations (b = 8.38; 95% CI, 2.05-14.71; P = .01), higher levels of self-reported anxiety (b = 1.04; 95% CI, 0.33-1.76; P = .005), and significant hypoactivation in the ventromedial prefrontal cortex (vmPFC) that was evident throughout peak response (Cohen d = 1.55; P < .001) and early recovery (Cohen d = 1.52; P < .001) periods. Correlational analysis of physiological and subjective indexes and percentage of signal change extracted during the 0.5-μg dose revealed that vmPFC hypoactivation was inversely correlated with heart rate (r_{56} = −0.51, adjusted P = .001) and retrospective intensity of both heartbeat (r_{56} = −0.50, adjusted P = .002) and breathing (r_{56} = −0.44, adjusted P = .01) sensations. Ventromedial prefrontal cortex hypoactivation correlated inversely with continuous dial ratings at a trend level (r_{56} = −0.38, adjusted P = .051), whereas anxiety (r_{56} = −0.28, adjusted P = .27) and chronotropic dose 25 (r_{56} = −0.14, adjusted P = .72) showed no such association.

CONCLUSIONS AND RELEVANCE In this crossover randomized clinical trial, women with GAD exhibited autonomic hypersensitivity during low levels of adrenergic stimulation characterized by elevated heart rate, heightened interoceptive awareness, increased anxiety, and a blunted neural response localized to the vmPFC. These findings support the notion that autonomic hyperarousal may be associated with regulatory dysfunctions in the vmPFC, which could serve as a treatment target to help patients with GAD more appropriately appraise and regulate signals of sympathetic arousal.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02615119

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