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Research article

A failed top-down control from the prefrontal cortex to the amygdala in generalized anxiety disorder: Evidence from resting-state fMRI with Granger causality analysis

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ABSTRACT

In generalized anxiety disorder (GAD), abnormal top-down control from the prefrontal cortex (PFC) to the amygdala is a widely accepted hypothesis through which an "emotional dysregulation model" may be explained. However, whether and how the PFC directly exerts abnormal top-down control on the amygdala remains largely unknown. We aimed to investigate the amygdala-based effective connectivity by using Granger causality analysis (GCA). Thirty-five drug-naive patients with GAD and thirty-six healthy controls (HC) underwent resting-state functional MR imaging. We used seed-based Granger causality analysis to examine the effective connectivity between the bilateral amygdala and the whole brain. The amygdala-based effective connectivity was compared between the HC and GAD groups. The results showed that, in the HC group, the left middle frontal gyrus exerted an inhibitory influence on the right amygdala, while in the GAD group, this influence was disrupted (single voxel $P < 0.001$, Gaussian random field corrected with $P < 0.01$). Our findings support and advance the "insufficient top-down control" hypothesis by identifying a failed top-down control from the prefrontal cortex to the amygdala in GAD.

1. Introduction

As the most prevalent anxiety disorder, generalized anxiety disorder (GAD) affects a significant number of people with estimated lifetime prevalence rates of 4–6% [15,17]. The core symptom of GAD is uncontrollable, pervasive worry and anxiety about a variety of events and situations, occurring alongside physical and emotional symptoms, such as restlessness, irritability, muscle tension, difficulties in concentration, and sleep disturbances. Although GAD causes a massive economic burden and substantial individual impacts, the neurobiological basis underpinning the core symptoms are poorly understood.

Aberrant amygdala activity and decreased amygdala-prefrontal connectivity are the most consistent neuroimaging findings in GAD, with the latter being considered to be the underlying neurofunctional correlates of GAD that cause the core symptoms of GAD [14,23]. Decreased functional coupling between the amygdala and prefrontal cortex (PFC) has been reported in both adults [9,21] and adolescents with GAD [24,27]. Decreased amygdala-prefrontal coupling is also correlated with high anxiety rating scores [9,21]. Conversely, it is interesting is that increased amygdala-prefrontal coupling can predict effective emotion regulation [8] or positive reappraisal of negative emotional material [3].

The hypothesis of insufficient top-down emotion control from the PFC to the amygdala has been proposed [2,23] when summarizing the above findings and given that the amygdala is the core hub for emotional processing [18] and that the PFC is one of the most important regions in the goal-directed attention system [10,11]. However, a contrary hypothesis was also proposed by researchers, namely, that GAD involves a hyper-active top-down control system [2,23]. Some studies supporting the second hypothesis found greater PFC activation during the emotional regulation process [4,6]. Notably, the two competing hypotheses are based on evidence that there is altered activation or functional connectivity (Pearson's correlation coefficient between the two BOLD time series) in the amygdala or PFC. However, there has previously been little direct evidence that the PFC exerts abnormal top-down control on the amygdala.

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Effective connectivity using Granger causality analysis (GCA) is a particularly suitable method to investigate the top-down control (directional influence) of the PFC on the amygdala because it can measure the influence of activity in a neural system over that of another [22]. In contrast to other methods used to measure the effective connectivity, GCA does not require any prior knowledge to select an interaction region in advance [7,22,26]. Therefore, GCA can avoid model assumption bias.

Amygdala-based effective connectivity has already been successfully applied to social anxiety disorder [20]. Although there are some similarities between social anxiety disorder and GAD, they are two completely different diagnoses. Moreover, the core symptoms of these disorders are very different. For example, social disorder refers to an excessive fear and/or avoidance of a wide array of social situations; however, the core symptom of generalized anxiety disorder is uncontrollable, pervasive worry and anxiety about a variety of events and situations, including but not limited to, social situations. The neurofunctional correlates of these two diseases may not be exactly the same.

Between-independent component effective connectivity has also been used to investigate the amygdala [26]. However, this study treated the bilateral amygdala as a single component. Previous studies have demonstrated different roles for the left and right amygdala in emotional processing, suggesting a functional lateralization of the amygdala [1,21]. Therefore, treating the bilateral amygdala as two separate regions may provide us with more information. In addition, exploring the effective connectivity between the whole brain and the amygdala in a voxel wise approach may be more comprehensive because it does not have to be limited to an independent component of the brain network. To our knowledge, amygdala-based voxel wise effective connectivity has not been applied to test the two hypotheses in GAD.

In this article, we aimed to investigate the amygdala-based effective connectivity by using GCA. We hypothesize that the PFC either exerts hypo-active or hyper-active top-down control on the bilateral amygdala or on one side of the amygdala.

2. Materials and methods

2.1. Participants

This study was approved by the Research Ethics Committee of the People's Hospital of Yuxi City (Yuxi, People's Republic of China). All patients with GAD were recruited from the Department of Rehabilitation Medicine at the People's Hospital of Yuxi City. All participants signed written informed consent agreements. The inclusion criteria for GAD patients were: (a) must conform to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) for diagnosis of GAD; (b) complaints of excessive, uncontrollable and lasting anxiety and worry about everyday events for at least 6 months; (c) free of any anti-anxiety or anti-psychotic drugs at least 1 month before and during the study; (d) had a Hamilton Anxiety Rating Scale (HAM-A) score ≥ 14; (e) younger than 60 years old; and (f) right-handed. Exclusion criteria for GAD patients were: (a) focal abnormality on structural MRI; (b) other psychiatric disorders or a secondary anxiety disorder or substance abuse; (c) past history of depression or episodes of depression; (d) diagnosed with other serious disease, such as diabetes or high blood pressure; (e) pregnant or breastfeeding; and (f) head motion more than or equal to 2.0 mm or 2.0° during the MR imaging. Four GAD patients were excluded because they had abnormal signals on the structural MRI. Four GAD patients were excluded because of head motion. Finally, 35 GAD patients were included in the study.

The study also included 36 gender-, age-, and hand-matched healthy controls (HC). The inclusion criteria for healthy controls were as follows: (a) no history of a neurological or psychiatric disorder; (b) no focal abnormality on the structural MRI; (c) HAM-A score < 7 and a Hamilton Depression Rating Scale (HAM-D) score < 8; and (d) head motion less than 2.0 mm or 2.0° during MR imaging.

Table 1
Demographic, clinical and neuropsychological characteristics of the participants.

Characteristics	GAD (n = 35)	HC (n = 36)	*P* Value
Gender (M/F)	12/23	12/24	0.93[a]
Age (y)	39.43 ± 10.61	38.69 ± 9.20	0.67[b]/0.75[d]
Duration (mo)	29.69 ± 43.86	N/A	N/A
STAI			
State	51.34 ± 11.59	21.17 ± 2.48	< 0.001 [c]
Trait	50.14 ± 9.85	21.19 ± 2.81	< 0.001 [c]
HAM-A	22.69 ± 6.21	1.00 ± 1.80	< 0.001 [c]
HAM-D	16.69 ± 6.05	0.39 ± 1.23	< 0.001 [c]

Note.—Unless otherwise noted, data are mean ± standard deviation.
GAD, Generalized Anxiety Disorder; HC, Healthy Controls; STAI, State-trait Anxiety Inventory; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; N/A, Not Available.
[a] The *P* value was obtained by using chi-square test.
[b] The P value was obtained by using Mann-Whitney *U* test.
[c, d] The P value was obtained by using two-sample t-test.

2.2. Clinical measures

Before the fMRI scan, all participants completed the HAM-A, HAM-D and State–Trait Anxiety Inventory (STAI) scales.

2.3. Data acquisition

Scanning was conducted using a 3.0 T MRI scanner with an eight-channel head coil (Ingenia; Philips, the Netherlands) at the People's Hospital of Yuxi City. Foam pads were used to minimize head motion. During data acquisition, all subjects were instructed to keep their eyes closed, relax their mind, hold still, and not to fall asleep. The resting-state fMRI was acquired using a gradient echo planar imaging sequence (EPI). The sequence parameters were as follows: repeat time/echo time = 2000 ms/35 ms, field of view = 230 × 230 mm, flip angle = 90°, in-plane matrix = 64 × 64, 35 transverse slices with thickness = 3.6 mm and slice gap = 0.7 mm, and voxel size = 3.6 × 3.6 × 3.6 mm^3. For each participant, 240 volumes were acquired, resulting in a total scan time of 480 s.

2.4. Data preprocessing

The data were preprocessed using the SPM12 and the Data Processing Assistant for Resting-State fMRI software (DPARSF, Advanced Edition, V4.3) (http://www.rfmri.org/DPARSF). The first 10 images of each subject were discarded. Then, the resting-state fMRI data were corrected for the temporal differences between slices and head motion. Those participants whose head movement exceeded 2.0 mm or 2.0° were excluded. Next, the corrected fMRI data were spatially normalized to the standard Montreal Neurological Institute (MNI) template and were resampled to 3 × 3 × 3 mm^3. These data were spatially smoothed with a 6 mm full-width at half maximum isotropic Gaussian kernel. We further processed the data to remove linear trends and filtered them temporally (bandpass, 0.01–0.1 Hz). Finally, nuisance signals, including 24 head motion parameters, CSF signals, white-matter signals, and global signals, were regressed out of the MRI data.

2.5. Granger causality analysis

The bilateral amygdala in the automated anatomical labeling (AAL) template were used as the seed regions for the Granger causality analysis. Bivariate first-order coefficient-based voxelwise GCA was implemented on the REST software (http://www.restfmri.net/forum/REST-GCA), using signed-path coefficients [13]. The coefficients were evaluated between the amygdala and the whole brain using a vector autoregression model as described in a previous study [19]. The

Table 2
Between-Group Differences in Effective Connectivity.

	MNI Coordinates	Cluster Size	*T* Values	Mean Causal Influences	
EC	(x, y, z)	(Voxels)	(peak)	HC	GAD
MFG.L→AMYG.R	(−36 45 27)	31	4.63	−1.14 ± 1.24 p < 0.001[#]	0.21 ± 1.09, p = 0.25[#]

GAD, Generalized Anxiety Disorder.
HC, Healthy Controls.
EC, Effective Connectivity.
MFG.L, left middle frontal gyrus; AMYG.R, right amygdala.
[#], one-sample *t*-test.

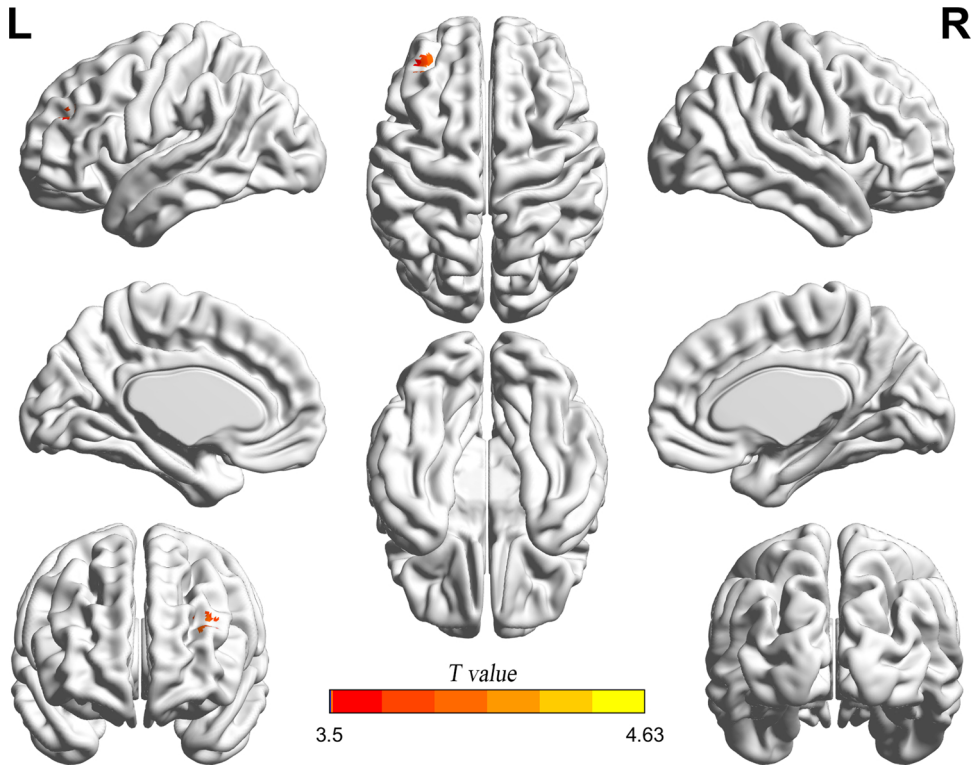


Fig. 1. Between-Group Differences in Effective Connectivity. Compared with HC, patients with GAD showed abnormal Granger causal influences from the left middle frontal gyrus to the right amygdala.

coefficients characterized the signed strength and direction of the relationship between the amygdala and the whole brain. We followed Chen's extended model as follows:

$$Y_t = \sum_{i=1}^{p} A_i X_{(t-i)} + \sum_{i=1}^{p} B_i Y_{(t-i)} + CZ_t + \varepsilon_t$$

$$X_t = \sum_{i=1}^{p} A_i' Y_{(t-i)} + \sum_{i=1}^{p} B_i' X_{t-i} + C'Z_t + \varepsilon_t'$$

where: Y_t is the BOLD time series of one voxel in the brain at time *t*; *Xt* is the BOLD time series of the seed region at time *t*; Z_t is a $q \times 1$ vector containing exogenous variables (covariates or confounds) at time *t*; ε^t is the error term; *p* and *q* are the number of lags and confounds, respectively; A_i is the signed path coefficient at time lag *i* ($i = 1,\ldots, p$); and B_i is the autoregression coefficient. In the present study, the number of lags $p = 1$ (1 TR = 2 s).

If A_i is significantly different from zero, then it is said that *X* Granger causes *Y*. If the path coefficient $A_{i\ =}$ + 1, this result suggests that one unit of change in the time series *X* in a specific direction results in a unit change in the time series Y in the same direction, representing excitatory influences and vice versa [25]. It is worth noting that the voxelwise GCA calculates causal influences of a time series of the seed region for that of every voxel in the brain (X to Y) and the time series of every voxel in the brain for that of the seed region (Y to X). Thus, 4 GCA maps (2 seed regions × 2 directions of GCA influences) were generated for each subject.

2.6. Statistical analysis

Differences in age between the GAD and HC groups were compared by using the Mann-Whitney *U* test Between-group differences in STAI, HAM-A and HAM-D were compared by using the two-sample t-test. Differences in gender were assessed by using chi-squared test.

First, the 4 GCA maps were analyzed using one-sample t tests for GAD and the HC group separately with an uncorrected P < 0.001 and cluster size > 10. Then, we made 4 masks by combining every 2 resulting maps (GAD + HC) from the above one-sample t tests to constrain the subsequent two-sample t-tests.

Second, between-group differences in the GCA maps were compared by using two-sample t tests with age and gender imported as covariates. Multiple comparisons were corrected by a Gaussian random field (GRF) method implemented in the DPABI software (DPABI version 3.0, Data Processing & Analysis for (Resting-State) Brain Imaging) [29] and using significant corrected thresholds of P < 0.01 combined with single voxel P < 0.001.

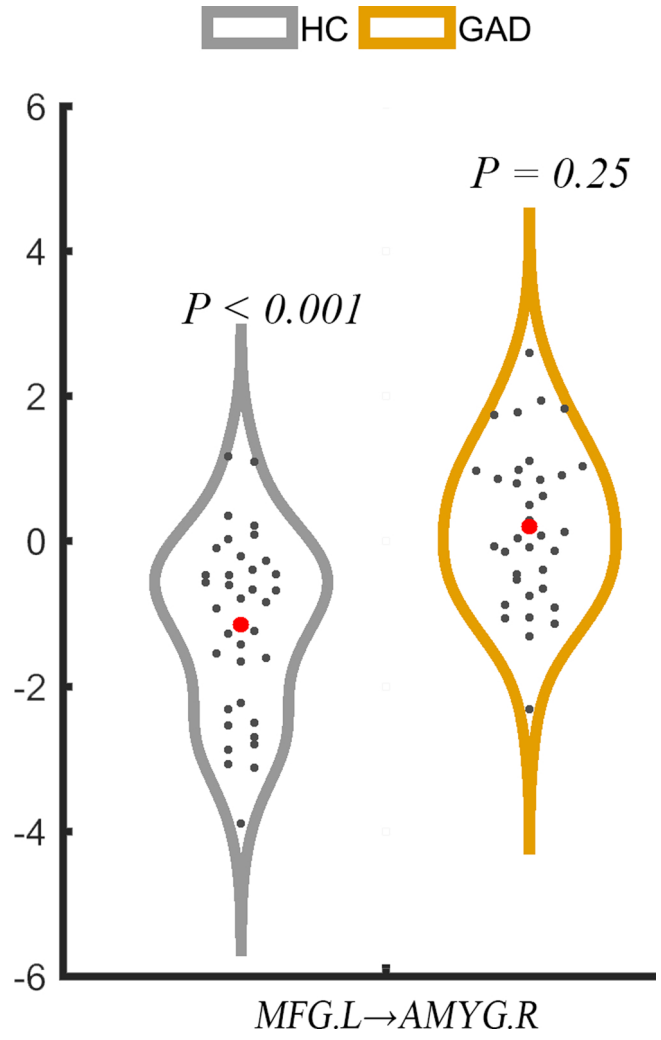


Fig. 2. Follow-up one-sample t tests found that, in controls, the left middle frontal gyrus exerted a significant inhibitory influence on the right amygdala (P < 0.001), while in the GAD patients, this influence was not statistically significant (P = 0.25).
MFG.L, Left middle frontal gyrus; AMYG.R, right amygdala.

For regions showing significant group differences, mean signed-path coefficients were extracted and follow-up one-sample t tests were performed to investigate the Granger causal influences in each group separately.

3. Results

3.1. Demographic and clinical variables

As shown in Table 1, the GAD patients and HC showed no significant differences in gender ($P = 0.93$) or age ($P = 0.67$). The GAD group had higher STAI, HAM-A and HAM-D than those of the HC group (all $P < 0.001$).

3.2. Granger causality analysis

Compared with the HC, GAD patients showed disrupted Granger causal influences from the left middle frontal gyrus (dorsolateral prefrontal cortex, DLPFC) to the right amygdala (Table 2 and Fig. 1). Follow-up one-sample t tests found that, in controls, the left DLPFC exerted a significant inhibitory influence on the right amygdala (P < 0.001), while in the GAD patients, this influence was not statistically significant (P = 0.25) (Fig. 2).

4. Discussion

This study investigated amygdala-based effective connectivity (directional connectivity) in HCs and patients with GAD at the resting state. Our main finding showed that, in HCs, the left DLPFC exerted a significant inhibitory influence on the right amygdala (a significant negative coefficient); however, in the GAD patients, the inhibitory influence disappeared (there was no significant coefficient). This result suggests a failed top-down control from the DLPFC to the amygdala in GAD at the resting state. Our results align with the "insufficient top-down control" hypothesis and provide some new insight into the pathophysiological mechanism of GAD.

In line with the "insufficient top-down control" hypothesis, many studies have found decreased activation in the PFC or decreased functional connectivity between the PFC and amygdala [2,9,14,21,23,24,27]. A recent study using functional network modeling and graph-theory found lower betweenness centrality and a lower degree in the PFC, also suggesting weakened inhibitory control of the PFC. In addition, using average time courses as an independent component, Jianping Qiao et al. found the effective connectivity in GAD was decreased from the middle frontal gyrus to the amygdala [26]. In the present study, using effective connectivity with voxel wise analysis, we also found a failed top-down control from the left DLPFC to the right amygdala in GAD with a relatively large sample. Together with the findings by Jianping Qiao et al. [26], our findings might deepen the understanding of the "insufficient top-down control" hypothesis.

Decreased functional coupling between the PFC and amygdala is a reasonable explanation for the two common abnormalities in GAD: decreased activation of PFC and increased activation of the amygdala [5,12,14,21,23]. Disrupted top-down control from the DLPFC to the amygdala might assist in the decreased functional coupling to explain these two consistent findings in GAD. In the HC, the DLPFC exerts an inhibitory influence on the amygdala. If the causal link between these regions is disrupted in GAD, the amygdala can very possibly lose control and show increased activation. In contrast, the prefrontal cortex might lose positive feedback, thereby reducing activation. Future studies will be needed to test this hypothesis.

Deficits in top-down inhibition are not unique to GAD but also exist in a variety of diseases related to stress, fear, and anxiety [16]. For example, insufficient top-down governance from higher cortical control areas (especially the PFC) to the amygdala in a person with a panic disorder may lead to fundamental amygdala hyper responsivity to subtle environmental cues, triggering full-scale threat-related responses [16]. Previous studies found insufficient top-down governance over the amygdala by the medial prefrontal cortex in posttraumatic stress disorders [28]. A decreased regulatory influence of the orbitofrontal cortex over the amygdala was also found in a previous study [20]. Together with previous studies, the present study suggests that the deficits in top-down inhibition are trans diagnostic characteristics of diseases that are related to stress, fear, and anxiety. Our results also suggest a functional lateralization of the amygdala [1]. In the present study, we only found an abnormality in the right amygdala but not in the left amygdala. The present findings are consistent with a recent study that found a relatively lower connectivity between the right amygdala and the PFC [21].

Our study had several limitations. First, this study is a cross-sectional study, and the findings cannot provide longitudinal alteration data on patients with GAD. Second, we cannot clearly identify the effective connectivity during emotional regulation tasks due to the present study only including resting-state fMRI information.

Overall, our data offer an explanation for the "insufficient top-down control" hypothesis in GAD.

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