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Altered Brain Signal Variability in Patients With Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) is characterized by a chronic, continuous symptom of worry and exaggerated startle response. Although functional abnormality in GAD has been widely studied using functional magnetic resonance imaging (fMRI), the dynamic signatures of GAD are not fully understood. As a vital index of brain function, brain signal variability (BSV) reflects the capacity of state transition of neural activities. In this study, we recruited 47 patients with GAD and 38 healthy controls (HCs) to investigate whether or not BSV is altered in patients with GAD by measuring the standard deviation of fMRI signal of each voxel. We found that patients with GAD exhibited decreased BSV in widespread regions including the visual network, sensorimotor network, frontoparietal network, limbic system, and thalamus, indicating an inflexible brain state transfer pattern in these systems. Furthermore, the correlation between BSV and trait anxiety score was prone to be positive in patients with GAD but negative in HCs. The opposite relationships between BSV and anxiety level in the two groups indicate that the brain with moderate anxiety level may stay in the most stable rather than in the flexible state. As the first study of BSV in GAD, we revealed extensively decreased BSV in patients with GAD similar to that in other mental disorders but with a non-linear relationship between BSV and anxiety level indicating a novel neurodynamic mechanism of the anxious brain.

Keywords: brain signal variability, fMRI, generalized anxiety disorder, neurodynamics, non-linear relationship

INTRODUCTION

Generalized anxiety disorder (GAD) is one of the most prevalent mental disorders characterized by exaggerated startle response and chronic, pervasive, and intrusive worry (1, 2). Based on static analysis methods, many functional magnetic resonance imaging (fMRI) studies have found aberrant brain activation related to cognition and emotion functions in GAD (3, 4). Inefficient intrinsic brain activity associated with integration of interoceptive and somesthetic functions has also been found in anxiety disorders (5–7). These static analysis methods for brain activity or activation have provided abundant evidence for us to understand the neural mechanism of GAD. However, clinically effective biomarker is still lacking. Recently, a mass of studies have shown that dynamic brain activity can provide novel information of neural characteristics for various neural

disorders (8–10). Whether the dynamic brain activity analysis can provide insightful information about the neural mechanism of GAD, however, is unknown.

Human brain activity is naturally variable (11). In previous years, fMRI research had regressed blood oxygen level-dependent (BOLD) signal variance as measurement-related or other confounds (12, 13). However, researchers found that the "noise" variance in data is an important feature of brain function in the recent 10 years (14, 15). In a neuroimaging time series, BSV measures the magnitude of variability from moment to moment (16). The forms of BSV include variance (17) and mean square successive differences (18), especially standard deviation (SD) (14, 15). As the next frontier in brain mapping, the brain signal variability (BSV) reflects the capacity of state transition of neural activities and dynamic range of brain functional systems (16). BSV has been suggested to be an excellent proxy of the characteristics of neural dynamics, cognitive performance, and brain disorders (14, 19–21). Great BSV has been suggested to be associated with increased ability to transfer between brain states (22) and to process varying and unexpected external stimuli (16, 23). Measured with the SD of brain signal, the BSV is more powerful than mean brain signal in predicting neural aging (14). Recently, the quadratic change in lifespan BSV trajectory has been further uncovered (24). Furthermore, a number of studies have demonstrated abnormal BSV in schizophrenia, attention deficit hyperactivity disorder, autism, and patients with disorders of consciousness, reflecting the dynamical dysfunction of neural activities in mental disorders (25, 26). Specifically, the non-linear dynamics of brain signal over a range of temporal scales are mainly decreased compared with those in healthy controls (HCs) (27). The hypothesis of "unhealthy brain is less variable than healthy brain" has been demonstrated in various clinical populations, such as dementia, untreated patients with schizophrenia, autism, and mesial temporal lobe epilepsy (16, 27, 28). In other words, many findings support Pool's opinion that "healthy brain is a chaotic brain" (11).

The anxious brain was viewed as an inflexible system, grounded in poor inhibition (29). In patients with GAD, a reduced capacity to inhibit cognitive (worry), behavioral (avoidance), and accompanying physiological manifestations was associated with cognitive rigidity and inflexibility (30). By using the mean-based methods, the core symptom, worry, which predominantly reflected a stimulus-independent mental processing also leads to the inflexible functional brain configurations in the prefrontal cortex, cingulate gyrus, and amygdala (31). However, the respective spatial patterns profiled by the SD-based method (like BSV) and mean-based method were highly different (14). To profile the flexibility of brain, BSV is a brand new effective index. Therefore, we hypothesized that patients with GAD may show decreased BSV compared with HCs in more related core regions.

In this study, we investigated the altered BSV in patients with GAD and healthy participants. To perform comprehensive comparisons, the relationship between BSV and anxiety level was also observed. Notably, this work is the first study of altered BSV in patients with GAD. Therefore, the BSV may be able to provide new insights into understanding the neural dynamics of GAD.

METHODS AND MATERIALS

Participants

Forty-seven patients with GAD were recruited from the mental health center of Chengdu, Sichuan, China. All patients were determined by consensus of two experienced psychiatrists by using the Structured Clinical Interview for DSM-IV (patient edition) (32). Clinical states of the patients were evaluated using the Hamilton anxiety scale (HAMA). Data from one patient was deleted because the BSV is extremely lower than the others (< mean-5 SD). The exclusion criteria included schizophrenia, mental retardation, or personality disorder, history of loss of consciousness, substance abuse, and serious medical or neurological illness. The HC group was composed of 38 age-, gender-, education-, mean frame-wise displacement (FD) (33)-matched healthy participants. The Structured Clinical Interview for DSM-IV non-patient version was employed to ensure the absence of psychiatric illnesses in the HCs. The HCs did not finish the HAMA scale test because the test was only obtained in hospital by two well-trained psychiatrists. None of the HCs had a history of serious medical or neuropsychiatric illness or a family history of major psychiatric or neurological illness in their first-degree relatives. All participants (including GADs and HCs) finished the Chinese vision of Trait Anxiety Inventory (TAI) questionnaire (34), which is often used in clinical application in the diagnostic work-up of mental disorders and has good validity and reliability (35, 36).

Ultimately, 47 patients with GAD and 38 HC were included in the study (**Table 1**). Written informed consent, approved by the research ethical committee of the School of Life Science and Technology at University of Electronic Science and Technology of China, was obtained from each participant.

Data Acquisition

MRI data were acquired using a 3.0T GE 750 scanner (General Electric, Fairfield, Connecticut, USA) equipped with high-speed gradients. An 8-channel prototype quadrature birdcage head coil fitted with foam padding was applied to minimize the head motion. Ear plugs were used to minimize the scanner noise. Participants were instructed to simply rest with their eyes closed, minds relaxed, awake, and motionless. Functional images were acquired using a gradient-recalled echo-planar imaging (EPI) sequence. The parameters were as follows: repetition time/echo time = 2,000 ms/30 ms, 90° flip angle, bandwidth = 250 Hz/pixel, 43 axial slices (3.2 mm slice thickness without gap), 64 × 64 matrix, and 22 cm field of view. For each participant, 255 volumes were obtained.

Data Preprocessing

Functional images were preprocessed using the Data Processing Assistant for resting-state fMRI (DPARSF 2.2, http://www.restfmri.net/forum/DPARSF). The first five volumes were discarded to ensure signal equilibrium and for the participants to familiarize themselves with the scanning environment. The

Variables (Mean ± SD)	GAD	HC	P-value
Gender (Male/Female)	47 (17/30)	38 (19/19)	0.200a
Age (years)	38.38 ± 9.08	35.24 ± 10.34	0.139b
Education (years)	11.30 ± 3.64	12.37 ± 3.89	0.195b
mean FD (mm)	0.0923 ± 0.0470	0.1049 ± 0.0555	0.261b
Course of illness (months)	61.96 ± 73.98	-	-
HAMA score	24.28 ± 6.583	-	-
TAI	55.04 ± 8.698	41.28 ± 5.43	<0.0001 b
Medication load index	1.40 ± 0.85	-	-
ANTIANXIETY MEDICATIONS, NO. OF PATIENTS			
Fluoxetine	1	-	-
Sertraline	5	-	-
Paroxetine	13	-	-
Citalopram	1	-	-
Escitalopram	9	-	-
Fluvoxamine	1	-	-
Venlafaxine	5	-	-
Duloxetine	1	-	-
Mirtazapine	8	-	-

SD, standard deviation; GAD, generalized anxiety disorder; HCs, healthy controls; HAMA, Hamilton Anxiety Rating Scale; TAI, Spielberger Trait Anxiety Inventory. a Chi-square test; b Independent-sample t-test.

remaining 250 images were slice-time corrected, spatially aligned, and spatially normalized to the Montreal Neurological Institute (MNI) EPI template and resampled to $3 \times 3 \times 3$ mm^3 voxels. After signal detrending, the images were spatially smoothed (8 mm full width at half maximum Gaussian kernel). Afterwards, Friston 24 head motion parameters, white matter signal, and cerebrospinal fluid signal were further regressed out. Finally, signal was filtered at 0.04–0.07 Hz because of the less noise contamination within this frequency range (37). The frame-wise displacement (FD) was used to represent instantaneous head motion. The mean FD of each participant was <0.5 mm.

Brain Signal Variability

Firstly, before calculating the BSV, we performed the temporal normalization for each voxel during the entire time of 500 s. The purpose of this step is to eliminate the contamination of the mean signal (14). Secondly, the SD which is simply the square root transformation of variance, was calculated in each voxel cross time series by using a custom-built function in MATLAB (The MathWorks, Inc.). According to Garrett's study, the SD of BOLD signal is temporal variability called BSV (14). The Anatomical Automatic Labeling 90 template was transformed to a binary mask and used to constrain the calculation in the gray matter (21).

Statistical Analysis

Two-sample t-test was used to assess the difference of BSV between the GAD and HC groups. Multiple-comparison correction was performed on the contrast brain map via the

false discovery rate approach ($p < 0.05$). Pearson correlations were calculated between the BSV and TAI score in the two groups, correspondingly, with age, sex, education, and mean FD as control variables. The correlation analysis was performed under the regions with significantly different BSVs between the two groups. We adopted the cross-voxel correlation (21, 38) to evaluate the spatial correlation between the correlation maps of the GAD and HC groups. As suggested by Liang et al., the two 3D maps of correlation coefficient were first transformed into columns and then transformed into z-score by minus mean then divided by SD. Pearson correlation was finally computed between these two columns of data. Then, we built a linear mixed-effects model with State-Trait Anxiety Inventory (STAI) score as a factor to show the differences in these correlations between BSV and STAI score in the two groups.

RESULTS

Decreased BSV in Patients With GAD

Compared with the HC group, patients with GAD show decreased BSV across the widespread brain regions (**Figure 1A**). Significantly low BSV is primarily located in the visual network, sensorimotor network, frontoparietal network, limbic system, and thalamus (**Figure 1B** and **Table 2**).

Correlations Between BSV and Anxiety Severity in GAD and HC

As shown in **Figure 2A**, the correlation between BSV and TAI score in the HC group is mainly negative, whereas that in the GAD group is mainly positive. **Figures 2B,C** show the correlation map for the HC and GAD groups, respectively. The correlation coefficients in the HC group and GAD group are negatively related to each other ($r = -0.285$, $p = 4.12e-274$). In other words, if the correlation between BSV and TAI score in the HC group is negative in one voxel, that correlation in the GAD group is positive in that voxel. The differences of correlations between BSV and STAI score in the two groups are also mainly located in the visual network, sensorimotor network, and frontoparietal network (**Figure 3**).

DISCUSSION

To the best of our knowledge, this work is the first study on the abnormal BSV in patients with GAD. In accordance with other studies in mental disorders, we observed widely decreased BSV in patients with GAD compared with HCs, suggesting multiple deficits in neural systems of GAD. Interestingly, we observed opposite distributions of linear relationship between TAI score and BSV in the GAD and HC groups, indicating a non-linear relationship between anxiety level and BSV. In other words, the chaotic brain might be not always the healthy one.

Decreased Temporal Variability in Patients With GAD

In line with reduced BSV in other mental disorders, the current study revealed widely decreased BSV in patients with GAD, arguing that reduced BSV is a general characteristic of mental
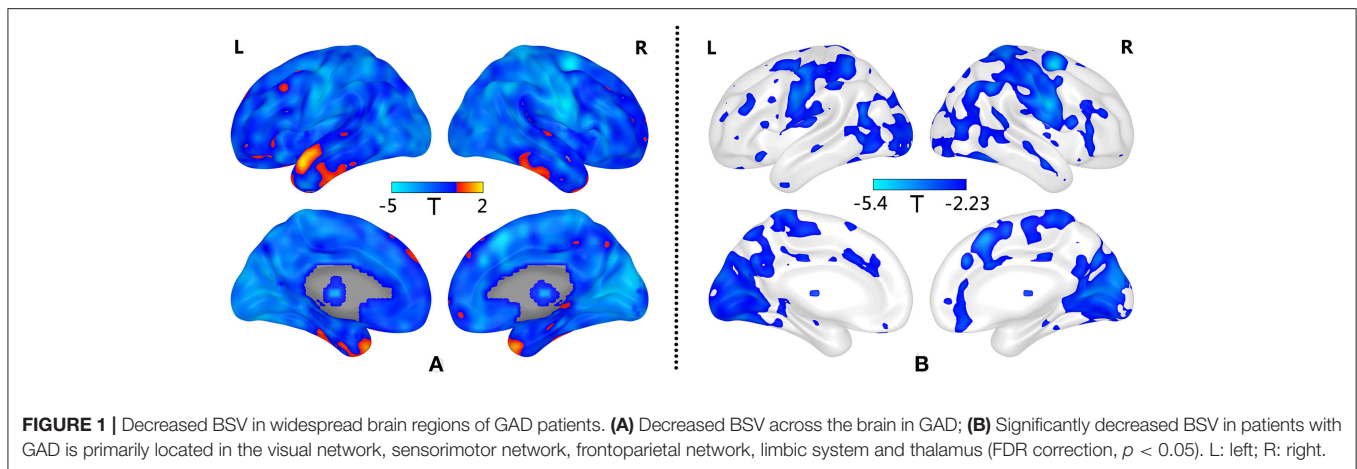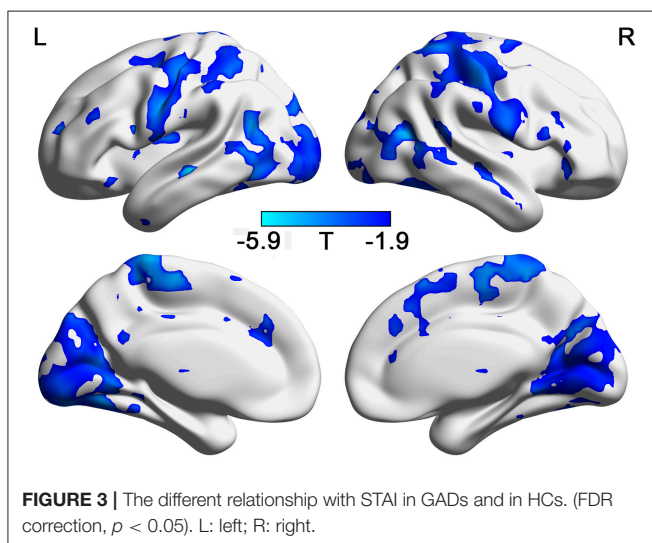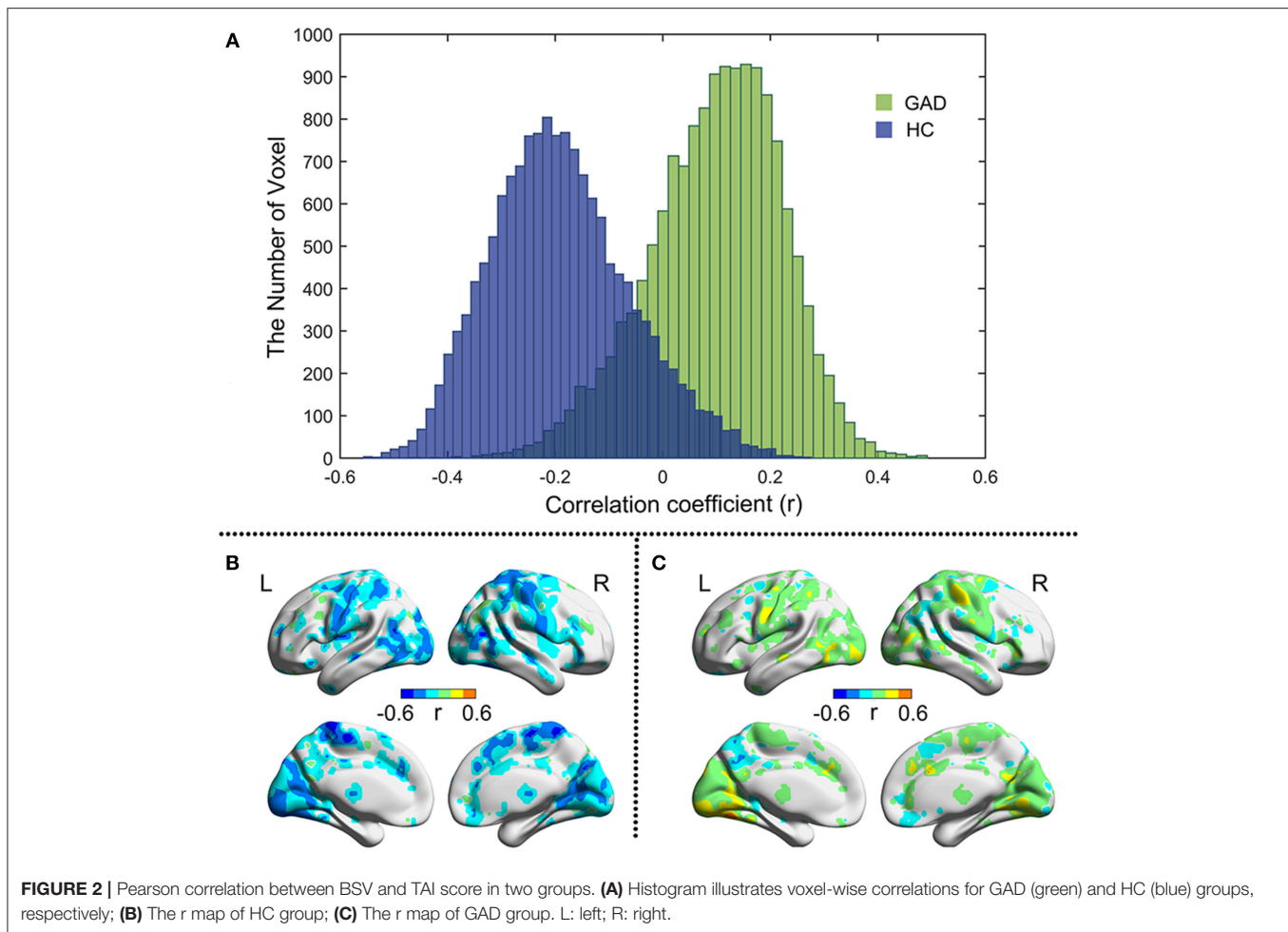
FIGURE 1 | Decreased BSV in widespread brain regions of GAD patients. **(A)** Decreased BSV across the brain in GAD; **(B)** Significantly decreased BSV in patients with GAD is primarily located in the visual network, sensorimotor network, frontoparietal network, limbic system and thalamus (FDR correction, $p < 0.05$). L: left; R: right.

TABLE 2 | Decreased BSV in patients with GAD compared with HC group.

	Brain regions	BA	Cluster size	T value	MNI coordinates		
					X	Y	Z
Cluster 1	Right superior frontal gyrus	5\6\17\18\32	13576	−5.4	21	0	57
	Bilateral postcentral gyrus						
	Bilateral supplementary motor area						
	Bilateral precentral gyrus						
	Bilateral occipital cortex						
	Dorsal anterior cingulate cortex						
Cluster 2	Right medial frontal gyrus	10	57	−4.10	9	66	27
Cluster 3	Left thalamus		194	−3.65	−3	−9	9
	Right caudate						
Cluster 4	Right inferior temporal gyrus	20\21	83	−3.61	60	−6	21
	Right middle temporal gyrus						
Cluster 5	Medial frontal gyrus	24	251	−3.45	6	39	−18
	Bilateral anterior cingulate						
Cluster 6	Left middle frontal gyrus	46	144	−3.42	−33	39	15

BA, Brodmann's area; MNI, Montreal Neurological Institute; X, Y, Z, coordinates of primary peak locations in the MNI space; T statistical value of peak voxel showing BSV decreased. All the clusters survived $p < 0.05$, FDR corrected, and a minimum cluster size of 50 voxels. Degree of freedom= 78.

disorders. Recent studies have shown that low amplitude of low-frequency fluctuation (ALFF) in the left supplementary motor area, right middle occipital gyrus, cerebellum, prefrontal-limbic system, and thalamus is associated with high-trait anxiety (32, 39, 40). Because ALFF is the square root of power (41) and power is equivalent to BSV (21). The BSV may reflect similar neural mechanisms to ALFF but in a non-linear way (21). Specifically, decreased BSV is associated with small potential kinetic energy to handle external environmental demands (16, 22) and low ability to transfer between different brain states (i.e., rest state and task state) (42). In patients with anxiety disorder, the functional deficit of environmental detection and the inflexible functional brain configurations has been found (31, 43). Therefore, the widely decreased BSV in patients with GAD may be associated with limited ability to adapt different external conditions and inflexible pattern of information transfer.

Low BSV in GAD is mainly located in the visual cortex, somatosensory cortex, anterior cingulate cortex (ACC), and thalamus. Multiple studies have documented deficits in the visual cortex in different anxiety disorders (44–46). Visual cortex plays a core role in the social brain network during visual and emotion processing (47). Visual cortex is also involved in the processing of fear generalization (48), which may greatly contribute to the GAD psychopathology (49, 50). The postcentral gyrus, as a critical substrate of interoceptive processing (51), is responsible for receiving, integrating, and interpreting most of the sensory information transmitted by the thalamus (52, 53). As shown by many studies, the thalamus is also strongly involved in interoceptive awareness (54–57). Abnormal connectivity between the postcentral gyrus and thalamus has been found in panic disorder, which may be associated with the typical symptoms (e.g., the extreme feeling of heartbeat) of panic disorder

FIGURE 2 | Pearson correlation between BSV and TAI score in two groups. **(A)** Histogram illustrates voxel-wise correlations for GAD (green) and HC (blue) groups, respectively; **(B)** The r map of HC group; **(C)** The r map of GAD group. L: left; R: right.

FIGURE 3 | The different relationship with STAI in GADs and in HCs. (FDR correction, $p < 0.05$). L: left; R: right.

(6). In general, as a hub of the interoceptive network, the ACC participates in mediating visceromotor activity and has projections into motor systems (56). Decreased functional connections between the ACC and thalamus was negatively correlated with HAMA in GAD, which may cause some somatic disturbed symptoms, such as rapid heart rate, low skin conductance, and difficulty breathing (58). Above all, the reduction of variability in these brain areas may be related to biased perception in processing exogenous and endogenous information (6, 59), which is implicated in the GAD pathological mechanism.

Reduced BSV in patients with GAD is also found in the dorsolateral prefrontal cortex and inferior parietal lobe, which are the key brain regions of the frontoparietal network (FPN). The deficiencies in FPN have been found in individuals with high-trait anxiety who have poor cognitive control and are easily distracted by emotional distractors from external environment (60, 61). Individuals with high anxiety generally require additional attentional control even in the absence of threat-related stimuli (62). The FPN is also a flexible hub during brain state transition (63). Low variability in the FPN may be associated with low ability to transfer between different brain states (42). Therefore, low BSV in the FPN may be associated with inflexible information to transform patterns facing the external world in patients with GAD.

Opposite Relationships Between BSV and Anxiety in the GAD and HC Groups

The opposite correlations between the BSV and TAI score in the HC group and in the GAD group has been found in the present study, indicating that the moderate anxious brain has small BSV. Moderate anxiety is associated with the best performance (64–66), and BSV has been demonstrated to be closely related to behavior performance (19, 24). In certain brain regions, maintaining great signal stability is also a critical marker of good task performance (22). In other words, the direction of correlation between BSV and behavioral performance depends on both cognition and brain region (21, 24, 67). Therefore, the opposite relationships between BSV and anxiety level may indicate that (1) moderate anxiety is associated with the most stable brain state and the best performance, and (2) increased BSV in subjects with high anxiety and low anxiety may be related to distinctive brain states, leading to different performances. Considering that (1) the dopaminergic system is closely associated with both anxiety and BSV (68, 69), (2) the non-linear relationship between dopaminergic system and behavioral performance (70), and (3) the quadratic relationship between anxiety and behavioral performance (66), the opposite BSV-anxiety relationship may reflect different neural dynamical configurations mediated by the dopaminergic system in patients with GAD and healthy people. Furthermore, the negative correlation between the HC group and GAD group suggests that the neuropsychological association in HC and patients with GAD may be driven by the same mechanism rather than independent from each other. This hypothesis deserves further investigations.

Although increased anxious levels in GADs showed increased BSV which indicated the great capacity of detection, the mechanism of this seemingly increasing ability can be totally different from healthy participants. In patients with GAD, the excessive activation is an apparent clinical symptom (1, 2), which might be associated with the high detection. In addition, this conclusion still needs further research. Meanwhile, the great BSV in some regions can be a compensation mechanism of an inefficient brain (14).

Overall, the opposite correlations between the BSV and TAI score in two groups indicate close relationships among dopaminergic system, behavioral performance, anxiety level, and BSV. These relationships can be described by the U law. Therefore, BSV is not always linearly related to brain health (24). These results provide valuable insights into understanding the relationship between BSV and health.

LIMITATIONS

Some limitations remain in this study. First, the sample is relatively small ($n=85$), impeding the uncovering of a strong correlation between BSV and anxiety level. Second, the HAMA score is lacking in the HC group because these participants were tested at the university rather than at the hospital, hindering the full investigation of clinical relevance of BSV. Third, some undiagnosed comorbid psychological disorders may exist in this sample, which may mix the true relationship between BSV and anxiety. A large sample with accurate diagnosis and complete scale collection is needed in future studies.

CONCLUSION

In summary, the decreased BSV in patients with GAD and different neuropsychological relationships in patients with GAD and HCs may reveal a novel neurodynamic mechanism, suggesting that the chaotic brain is not always the healthy one.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 and the applicable revisions at the time of investigation. Informed consent was obtained from all patients included in the study.

AUTHOR CONTRIBUTIONS

LL, YW, and HC designed the study. LY, WC, DL, and HX wrote the computing scripts. QC and ZH interviewed all patients by using the DSM-IV. LL managed the literature searches and analyses, acquired, and analyzed the data, and wrote the first manuscript draft. All authors contributed and have approved the final manuscript. The authors thank all subjects participating in this study.

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