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Research paper

Spatial complexity of brain signal is altered in patients with generalized anxiety disorder

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ABSTRACT

Background: Is it healthy to be chaotic? Recent studies have argued that mental disorders are associated with more orderly neural activities, corresponding to a less flexible functional system. These conclusions were derived from altered temporal complexity. However, the relationship between spatial complexity and health is unknown, although spatial configuration is of importance for normal brain function.
Methods: Based on resting-state functional magnetic resonance imaging data, we used Sample entropy (SampEn) to evaluate the altered spatial complexity in patients with generalized anxiety disorder (GAD; $n = 47$) compared to healthy controls (HCs; $n = 38$) and the relationship between spatial complexity and anxiety level.
Results: Converging results showed increased spatial complexity in patients with GAD, indicating more chaotic spatial configuration. Interestingly, inverted-U relationship was revealed between spatial complexity and anxiety level, suggesting complex relationship between health and the chaos of human brain.
Limitations: Anxiety-related alteration of spatial complexity should be verified at voxel level in a larger sample and compared with results of other indices to clarify the mechanism of spatial chaotic of anxiety.
Conclusions: Altered spatial complexity in the brain of GAD patients mirrors inverted-U relationship between anxiety and behavioral performance, which may reflect an important characteristic of anxiety. These results indicate that SampEn is a good reflection of human health or trait mental characteristic.

1. Introduction

Being chaotic is thought to be of importance for health (Pool, 1989). Brain signal chaos arises from the interaction of numerous neuronal circuits that operate over a wide range of temporal and spatial scales, enabling the brain to adapt to the ever-changing environment and to perform various mental functions (Yang and Tsai, 2013). Recent studies have suggested that the neural system of patients with mental disorders is accompanied by reduced temporal chaos (Takahashi, 2013; Yang and Tsai, 2013). It means the disordered brain acts more regularly and transforms less frequently from one state to another (Liu et al., 2017; Torre-Luque et al., 2016), resulting in maladaptive behaviors (Dajani and Uddin, 2015). Costa et al. (Costa et al., 2002) suggested that loss of temporal complexity is a generic feature of pathologic dynamics in mental diseases. However, whether spatial complexity is also associated with health is unknown, although spatial configuration is essential for normal brain function (Pang et al., 2018; Wang et al., 2018c).

Sample entropy (SampEn) is widely utilized to evaluate the complexity of a time series in functional magnetic resonance imaging (fMRI), electroencephalogram (EEG), magnetoencephalogram, and other physiological signals (Costa et al., 2002; Courtiol et al., 2016; Gao et al., 2015; Wang et al., 2018a). It has been suggested to be a commendable marker of individual health (Goldberger et al., 2002) and of adaptive capacity in aging and disease (Farzan et al., 2017; Heisz et al., 2015; Torre-Luque et al., 2016). FMRI-based SampEn has been shown to be effective in predicting aging (Sokunbi, 2014), distinguishing brain networks (Mcdonough and Nashiro, 2014), and representing cognitive function (Yang et al., 2013). Because it is robust even in short data segments or reordered data (Courtiol et al., 2016; Grandy et al., 2016),

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SampEn is suitable for studying the complexity of fMRI signal (Smith et al., 2013; Yang et al., 2013). Instead of measuring signal complexity across time, the spatial SampEn evaluates the complexity across brain regions. Specifically, if there are many similar spatial patterns (e.g., a descending pattern: a > b > c) across the brain, the spatial configuration will be very regular, showing low spatial complexity. In contrast, if there are various spatial patterns across the brain, the spatial configuration will be irregular, showing high spatial complexity. Considering that (1) the amplitude distribution across brain regions is reliable during resting state (Raichle, 2015; Zuo et al., 2010) and is changed during cognitive processing (Wang et al., 2018b; Zhang et al., 2015) and (2) particular spatial pattern is closely associated with cognitive functions (Wang et al., 2018b; Xue et al., 2010) and has been utilized to predict brain states (Thavabalasingam et al., 2018; Xia et al., 2018), we suggest that the spatial SampEn could reflect brain functions just like temporal SampEn.

Generalized Anxiety Disorder (GAD) is a prevalent mental disorder characterized by chronic, pervasive and intrusive worry (American Psychiatry Association, 1994). Like other mental disorders, GAD is associated with reduced neural signal complexity compared to healthy controls (HCs) under resting conditions and when retrieving stressful memories (Richman and Moorman, 2000; Takahashi, 2013; Torre-Luque et al., 2016). Meanwhile, cognitive rigidity and inflexibility have been shown in patients with GAD (Ottaviani et al., 2016), in line with reduced brain signal variability (Armbruster-Genç et al., 2016; Wang et al., 2015). With the rise of network neuroscience, researchers have suggested that normal brain functions depend on effective inter-regional cooperation more than solo local neural activity (Bassett and Sporns, 2017). Beyond local alteration, abnormal amygdala-frontal and cortico-cortical functional connections have been reported in patients with GAD, which may change the pattern of spatial configuration across brain regions (Cui et al., 2016; Fonzo and Etkin, 2016; Gold et al., 2016; Makovac et al., 2016; Sylvester et al., 2012). Reduced temporal complexity indicates that temporal signals are more regular in patients with GAD while reduced functional connection suggests that these regular signals are not synchronized between brain regions. That is to say, some new spatial relationships appear in the brain of GAD patients. These more diverse spatial relationships would increase the spatial complexity of the brain in GAD patients.

In the current study, we highlighted the importance of spatial configuration of neural activity for mental health and put forward spatial SampEn to measure the spatial complexity across brain regions in patients with GAD. According to aforementioned studies, we hypothesized that the spatial complexity would be higher in patients with GAD than that in healthy controls. We further calculated the relationship between spatial complexity and anxiety level to test whether the spatial complexity is associated with mental health.

2. Methods and materials

2.1. Participants

A total of forty-seven patients diagnosed with GAD were recruited from the mental health center of Chengdu, Sichuan, China. Thirty-eight age-, gender-, education-, mean frame-wise displacement (FD)-matched HCs were recruited from the community through poster advertisement. All patients were diagnosed by two experienced psychiatrists using the Structured Clinical Interview for DSM–IV (patient edition). Exclusion criteria included schizophrenia, major depressive disorder, mental retardation or personality disorder, history of loss of consciousness, substance abuse, and serious medical or neurological illness. The SCID non-patient version (SCID–NP) was employed to ensure absence of psychiatric illnesses in the HCs. None of the HCs presented a history of serious medical or neuropsychiatric illness or a family history of major psychiatric or neurological illness in their first-degree relatives. The Hamilton anxiety scale (HAMA) was used to evaluate clinical states of patients (Hamilton et al., 1976). All participants were evaluated using the Spielberger Trait Anxiety Inventory (STAI) (Spielberger and Sydeman, 1994), which represents the inherent trait anxiety of the participant. Clinical and demographic data from the 85 participants are shown in Table 1. Written informed consent, approved by the research ethical committee of School of Life Science and Technology at University of Electronic Science and Technology of China (UESTC), was obtained from each participant.

Table 1
Demographic information and characteristics of patients with GAD and HCs.

	GAD	HC	*p* value
Gender (M / F)	47 (17 / 30)	38 (19 / 19)	0.200[a]
Age (years)	38.38 ± 9.08 (mean ± SD)	35.24 ± 10.34	0.139[b]
Education (years)	11.30 ± 3.64	12.37 ± 3.89	0.195[b]
mean FD (mm)	0.0923 ± 0.0470	0.1049 ± 0.0555	0.261[b]
Duration (months)	61.96 ± 73.980	–	–
HAMA	24.28 ± 6.583	–	–
STAI	55.04 ± 8.698	41.29 ± 5.437	<0.001[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	–	–

Note: SD, standard deviation; GAD, generalized anxiety disorder; HC, healthy control; FD, frame-wise displacement; HAMA, Hamilton anxiety rating scale; STAI, Spielberger trait anxiety inventory.
[a] Chi-square test.
[b] Independent-sample *t*-test.

2.2. Medication information

Following previous studies (Pang et al., 2018; Versace et al., 2008), we measured the total medication load index to test whether medication influences spatial complexity. Each anti-anxiety medication was first coded as absent (0), low (1), or high (2). Individuals on level 0 were no-dose subtype, on levels 1 and 2 were coded as low-dose subtype, and on levels 3 and 4 as high-dose subtype. Then, we calculated a composite measure of total medication load for each individual. This measure reflects the dose and variety of medications taken by summing all individual medication codes for each medication category (Pang et al., 2018).

2.3. Imaging acquisition

All the fMRI data were acquired using a 3.0T GE DISCOVERY MR750 scanner (General Electric, Fairfield, Connecticut, USA) at UESTC with the gradient-recalled echo-planar imaging (EPI) sequence. An 8-channel prototype quadrature birdcage head coil fitted with foam padding was applied to minimize the head motion. Patients were instructed to remain motionless with their eyes closed and without thinking of anything in particular. The imaging parameters were as follows: repetition time/echo time = 2000 ms / 30 ms, 90° flip angle, bandwidth = 250 Hz/pixel, 43 axial slices (3.2 mm slice thickness without gap), 64 × 64 matrix, 22 cm field of view (FOV). For each participant, a total of 255 volumes were obtained.

2.4. Imaging preprocessing

Functional images were preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSF 2.2, http://www.restfmri.net/forum/DPARSF). To ensure the scanning environment stabilization, the first five volumes were discarded. The remaining 250 images were slice-time corrected, spatially aligned, spatially normalized to Montreal Neurological Institute (MNI) EPI template, and resampled to $3 \times 3 \times 3\,mm^3$ voxels. After normalization, the blood oxygenation level-dependent (BOLD) signal of each voxel was detrended to abandon the linear drift. Friston 24 head motion parameters, white matter signal, cerebrospinal fluid signal and global signal were further regressed out. SampEn was also calculated based on data without global signal regression, because the regression of global signal has been suggested to change inter-regional relationship (Murphy and Fox, 2017). Finally, band-pass filter was performed with the frequency band 0.01–0.08 Hz to reduce the influences of low-frequency drift and high-frequency physiological noises (Liu et al., 2017). The FD was used to represent instantaneous head motion (Power et al., 2012). No participant was excluded with a FD threshold of 0.5 mm.

2.5. SampEn analysis

The SampEn analysis was developed as a biologically meaningful measure of complexity (Costa et al., 2002; Richman and Moorman, 2000). It is a variant of approximate entropy which could provide a good estimation of entropy even when the match count is low (Richman and Moorman, 2000). The SampEn was obtained by Eq. (1):

$$SampEn(m, r, N) = -log\frac{C^{m+1}(r)}{C^{m}(r)} \quad (1)$$

where m is the pattern length, r (similarity factor) which represents a proportion of the standard deviation (SD) of the signal series is a distance threshold, and N is the length of the signal sequence. $C^m(r)$ is the correlation sum which measures the average likelihood of m-length patterns in a signal series. Two patterns match if the distance is less than r. Prior studies have suggested that data lengths of 10^m–20^m is reasonable to estimate SampEn (Richman and Moorman, 2000; Yang et al., 2013). Therefore, $m = 1$ and $m = 2$ were assessed here, considering the data length of 246. Fig. 1 illustrates the parameters of spatial SampEn.

For spatial SampEn, the preprocessed data were divided into 246 regions using the Brainnetome Atlas (Fan et al., 2016). This atlas provides functionally meaningful division of brain regions, reducing data redundancy meanwhile (Fan et al., 2016). The values of brain regions were arranged according to label numbers provided by the Brainnetome Atlas. To demonstrate its tolerance to reordered data, the SampEn was also calculated based on data arranged in odd then even labels. At each time point, the spatial SampEn was calculated based on the spatial series consisting of the mean signal of 246 regions. In all calculations, the r value ranged from 0.05 to 0.50 with 0.05 step wise as suggested by previous studies (Grandy et al., 2016; Yang et al., 2013). Lastly, the values of SampEn were averaged across time points to get a representative value of each participant.

2.6. Statistical analysis

Two-sample t test was used to assess the difference of spatial SampEn for all combinations of m and r between two groups of participants. The minimum p value of t test indicates the largest discrepancy between two groups of people, thus was used as an indicator of the optimal parameters of spatial SampEn. Since the SampEn is a nonlinear index (Courtiol et al., 2016), both linear and quadratic relationships between spatial SampEn and STAI score were conducted using partial correlation analysis with age, gender, education, and mean FD as control variables. These correlations were retested without regressing out these variables. For those patients who are on medication, Pearson's correlation between total medication load index and spatial SampEn under each of the aforementioned parameters was calculated.

3. Results

3.1. The optimal parameters of spatial SampEn

In the preliminary calculation, the largest discrepancy of spatial SampEn between GAD and HC groups appeared when $r = 0.30$ and $m = 1$. For $m = 2$, the largest difference between two groups appeared when $r = 0.45$ (see Fig. 2). Results obtained from the combination of these parameters were further analyzed.

3.2. Increased spatial complexity in patients with GAD

As shown in Fig. 3, spatial SampEn was increased in patients with GAD compared with HCs which could pass Bonferroni correction for multiple comparisons ($<0.05/18 = 0.0028$). Considering that m and r were often set as the optimal and constant values (Yang et al., 2013), the current results under parameters of $m = 1$ and $r = 0.3$ were thought to be the primary results, although highly consistent results were observed under other parameter combinations. These results indicated that patients with GAD have a more chaotic spatial configuration of brain activity than HCs.

3.3. Non-linear relationship between spatial SampEn and STAI score

As shown in Fig. 4, an inverted-U relationship between spatial SampEn and STAI score was consistently observed ($r = -0.34$, $p = 0.008$ for $m = 1$ and $r = -0.33$, $p = 0.009$ for $m = 2$), whereas the linear correlation was unapparent ($r = 0.19$, $p = 0.088$ for $m = 1$ and

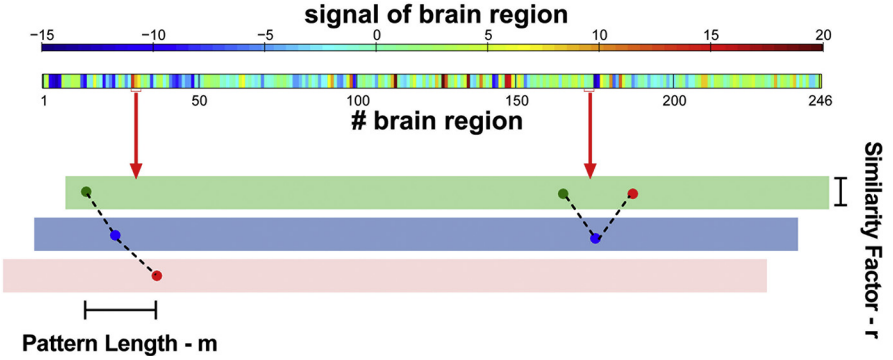

Fig. 1. Illustration for the calculation of SampEn. The width of three horizontal bar at the bottom represent the value of r. The left pattern length is 3 while the right one is 2.

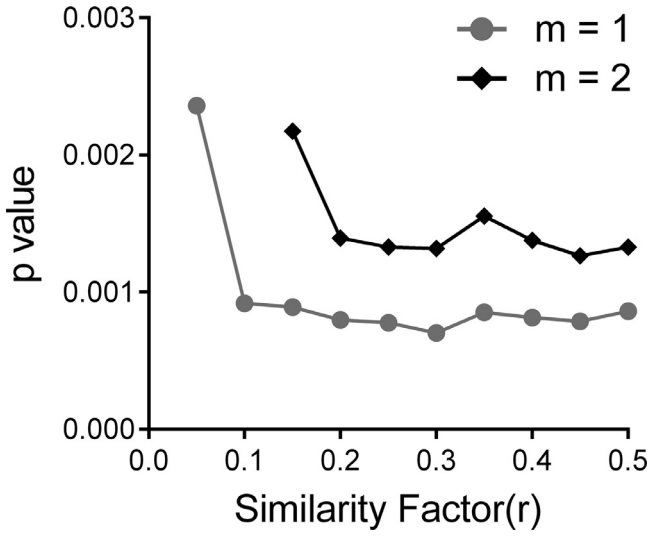

Fig. 2. Parameter selection of spatial SampEn. p values of two-sample t-test between GAD and HC groups are illuminated for all combinations of parameters m and r. For $m = 2$, when r is small, there is no matched pattern for some participants, leading to infinite SampEn. Therefore, p values are missing at some points.

$r = 0.17, p = 0.112$ for $m = 2$). We also tested the linear and quadratic relationships between SampEn and STAI score in HC and patient groups, respectively. Again, the inverted-U relationship was found in HC group ($r = -0.51, p = 0.005$ for $m = 1$ and $r = -0.49, p = 0.009$ for $m = 2$) with significantly linear relationship appearing in neither HC group ($r = 0.23, p = 0.166$ for $m = 1$ and $r = 0.23, p = 0.157$ for $m = 2$) nor patient group ($r = -0.24, p = 0.106$ for $m = 1$ and $r = -0.22, p = 0.130$ for $m = 2$). These consistent findings of inverted-U relationship between spatial SampEn and STAI score indicate a non-linear relationship between anxiety level and the spatial complexity of neural activity, providing novel evidence for the complex neuropsychological mechanism of anxiety. Furthermore, there is no correlation between total medication load index and spatial SampEn (all *ps* are larger than 0.12), indicating that medication has no significant effect on spatial SampEn.

3.4. Reliability of current results

We retested the aforementioned results using reordered data and the data without global signal regression. Increased spatial SampEn in patients with GAD was consistently observed in these data (see Supplementary Materials Tables S1 and S2). Furthermore, the inverted-U relationship was also duplicated with these two kinds of signals (see Tables S3 and S4). We also retested these results without controlling for age, gender, education and mean FD (Tables S5 and S6). These main results were replicated again. These findings suggested the stability and reliability of both increased spatial complexity in patients with GAD and non-linear complexity-anxiety relationship.

4. Discussion

To the best of our knowledge, this is the first study on the abnormal spatial complexity of neural system in mood disorder. We observed increased spatial complexity in patients with GAD, providing new evidence beyond reduced temporal complexity in mental disorders, and suggesting the neural system of GAD is spatially more diversity and heterogeneity. Another advance is the finding of inverted-U relationship between spatial complexity and anxiety level, suggesting non-linear neural dynamic associated with anxiety. These reliable results under different parameters suggest that spatial complexity, compared with temporal complexity, could provide new insight into understanding the neural dynamic mechanism of GAD.

Essentially, SampEn is indicative of the predictability or complexity of signal (Courtiol et al., 2016). Higher SampEn means less predictability or more complexity. At spatial dimension, higher predictable signal means more regular or similar spatial structures which may reflect higher homogeneous activities across brain regions (Sporns and Betzel, 2016). Therefore, increased spatial SampEn in patients with GAD compared to HCs suggests that the brain of people with GAD appears to be more heterogeneous and less integrated across brain regions. Unlike temporal complexity, the less similarity between brain regions in GAD may be associated with abnormal cortico-cortical and cortico-subcortical functional connectivity in the patients (Cui et al., 2016; Makovac et al., 2016), although the direct link between spatial complexity and functional connectivity is lacking now. Alternatively, the unpredictable spatial structure may reflect unstable energy distribution across brain regions during neural activities, considering that (1) inter-regional energy distribution is stable in normal brain and (2) energy is redistributed during cognitive processing (Baria et al., 2011; Ponce-Alvarez et al., 2015; Wang et al., 2018b; Zuo et al., 2010). Accordingly, the increased spatial SampEn may reflect chaotic energy distribution in the brain of GAD patients which may further disturb cognitive function (e.g., leading to abnormal anxiety level). The psychological and physiological mechanisms of altered spatial SampEn deserve further investigations.

The inverted-U relationship between spatial complexity and anxiety may result from several reasons. First, the SampEn is essentially a non-linear measure of brain signal (Courtiol et al., 2016). Non-linear relationships between brain signal complexity and neural characteristics have been reported elsewhere (Nomi et al., 2017; Zappasodi et al., 2015), which may also contribute to spatial complexity-anxiety relationship. Second, anxiety level has been shown to be linked to behavioral performance in an inverted-U fashion. Specifically, the

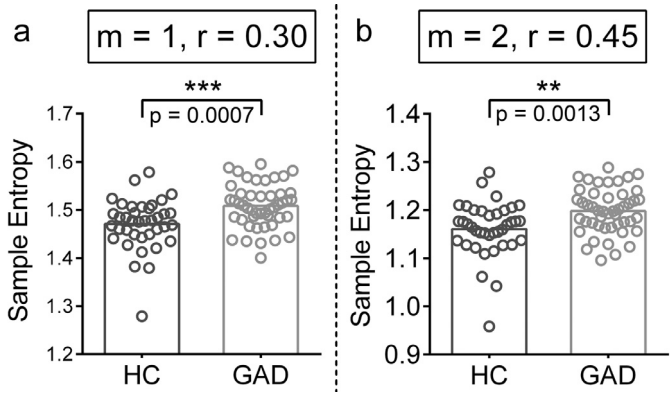

Fig. 3. Significant increase of SampEn in patients with GAD compared with HCs.

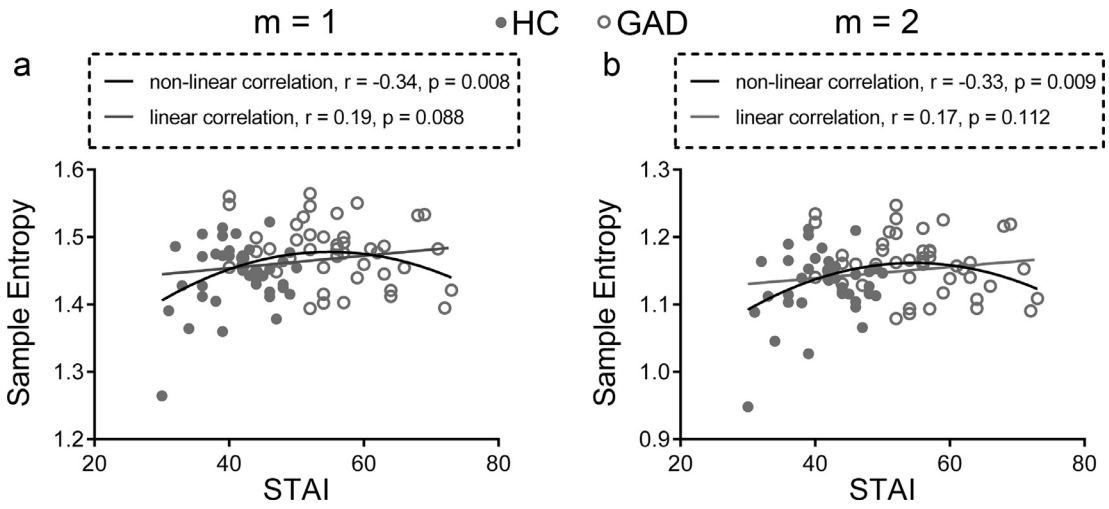

Fig. 4. The correlation between spatial SampEn and STAI. Significant quadratic rather than linear relationships are revealed for $m = 1$ (a) and $m = 2$ (b).

moderate-intensity of anxiety rather than the lowest or the highest anxiety level is associated with the best performance, indicating that moderate anxiety level may reflect the optimal brain state (King et al., 1987; Raglin and Turner, 1993; Sonstroem and Bernardo, 1982). On the other side, the highest variability of brain signal facilitates the transition among various potential brain states, improving the flexibility of cognition (Garrett et al., 2014; Guitart-Masip et al., 2016; Wang et al., 2014a; Wang et al., 2016). Therefore, both higher anxiety and lower anxiety are associated with reduced flexibility of cognition and spatial complexity. Third, the inverted-U relationship may be modulated by the dopamine system. Both brain signal variability and anxiety level are associated with dopamine level in the cortico-striatum system (Guitart-Masip et al., 2016; Mp et al., 2010; Schneier et al., 2009), while the functional affection of dopamine level manifests an inverted-U curve (Bromberg-Martin et al., 2010; Cools and D'Esposito, 2011). Fourth, different trends of direction for linear correlation between spatial complexity and anxiety level in patient and HC groups may be responsible for the inverted-U relationship. Although the linear correlations are not significant, there are somewhat positive and negative trends of spatial complexity-anxiety correlation in HC and patient groups, respectively. These trends indicate that the spatial configuration is more regular as anxiety increases or decreases from moderate level. However, the two kinds of regularities may direct to different states: normal and abnormal (Fonzo and Etkin, 2016; Yang and Tsai, 2013). Therefore, the opposite spatial complexity-anxiety relationship may reflect different neural dynamical mechanisms in patients with GAD and healthy people. Overall, the mechanism of inverted-U relationship between spatial SampEn and anxiety level is far from clear and warrants further multi-modal studies combining behavioral, neuroimaging, and biochemical techniques.

There is no rigorous guideline for choosing optimal parameters of SampEn (Costa et al., 2002; Mizuno et al., 2010; Yang et al., 2013). Usually, the estimation of SampEn in short time series of BOLD signal is sufficient for $m = 1$ and $m = 2$ (Yang et al., 2013). When m increases, the accuracy of entropy is deteriorated (Wang et al., 2014b). On the other hand, similarity factor is critical to describe the nonlinear dynamics (Xie et al., 2010). When r is too small, the dissimilarity between two systems may primarily be caused by noise; when r is too large, the matching criteria is too loose to capture some signal details. Hence, it is best that the r value is large enough to allow the algorithm to distinguish signal from noise, but small enough to allow the algorithm to evaluate the detail of signal (Chen et al., 2009; Sokunbi, 2014). Following these principles, we chose $r = 0.30$ for $m = 1$ and $r = 0.45$ for $m = 2$. Our selection of m and r is based on the largest discrepancy between GAD and HC groups, which is also compatible with previous fMRI studies (Yang et al., 2015; Yang et al., 2013).

Although the results about SampEn are interesting and reliable, several questions remain. First, the length of signal series in fMRI studies is shorter than that in EEG studies. Although SampEn is stable in relative short signal (Grandy et al., 2016; Sokunbi, 2014), long fMRI data may benefit investigations of signal complexity. Second, we used ROI-wise analysis rather than voxel-wise analysis due to two reasons: (1) the divisional brain regions have been demonstrated to be functional meaningful (Fan et al., 2016); (2) the signal of single voxel is vulnerable to preprocessing operations such as spatial smooth. The ROI-wise analysis and voxel-wise analysis reflect different spatial sampling rates just like different temporal sampling rates of EEG and fMRI, expressing distinctive characteristics of signal complexity. Therefore, voxel-wise analysis deserves further investigations. Third, the mechanism of inverted-U relationship between spatial complexity and anxiety level could not be determined in this study. Whether the nonlinear relationship is specific to anxiety or could be broadened to other relationships between brain signal complexity and psychological characteristics are still unclear. Fourth, although increased spatial complexity in patients with GAD is consistently observed under different parameters, the sample is relative small ($n = 85$) and most patients are on medication (see Table 1). Although there is no correlation between medication and spatial complexity, medication may make the brain function of patients with GAD similar to that of healthy controls (Mochcovitch et al., 2014; Whalen et al., 2008). Therefore, these results should be treated with caution and be verified in big data with first-episode, drug-naïve patients. Fifth, the relationship between spatial complexity and functional connectivity is undetermined. Spatial complexity is a global index obtained at each time point or the overall time course while the functional connectivity measures inter-regional dependence by calculating temporal correlation between two time courses. Therefore, the relationship between them cannot be directly assessed, although some previous studies have suggested confusing relationship between temporal complexity and functional connectivity (Ghanbari et al., 2015; Mcdonough and Nashiro, 2014; McIntosh et al., 2014). Last, there are various measures derived from graph theory that have been applied to study the spatial configuration of patients with mental disorders. However, only a few of them reflect the global characteristic of brain activity such as the small-world property. Like the significance of global signal in schizophrenia (Yang et al., 2017), the spatial complexity as a global index may provide useful information for neural dynamics of mental disorders, which deserves more investigations.

As a preliminary study, we introduced the spatial SampEn to measure brain signal complexity of patients with GAD and demonstrated

increased heterogeneity across brain regions in GAD patients, uncovering different scenarios from temporal complexity. The relationship between spatial complexity and anxiety level, mirrors the inverted-U relationship between behavioral performance and anxiety, implying an important mechanism of neural dynamics in GAD. These findings shed new light on the neurodynamic mechanism of GAD, suggesting that spatial SampEn could serve as a good reflection of health and an effective biomarker of GAD.

Ethical statement

This study was approved by the research ethical committee of the University of Electronic Science and Technology of China. The oral and written information about the aims, contents, and scanning procedures were first presented to all participants. This study also comply with the latest revision of the Declaration of Helsinki and registered at ClinicalTrials.gov (Identifier: NCT02888509; https://www.clinicaltrials.gov/ct2/show/NCT02888509?term=NCT02888509&rank=1).

Written informed consents were then obtained from both the healthy controls and patients with generalized anxiety disorder.

Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Yifeng Wang, Qian Cui, Zongling He, and Huafu Chen designed the study; Liyuan. Li, Xuezhi Yang, Qijun Zou, Pu Yang, and Dongfeng Liu collected the data; Yifeng Wang, Xinqi Wang, Liangkai Ye, and Qi Yang analyzed the data; Yifeng Wang, Xinqi Wang, Liangkai Ye, Qian Cui, and Huafu Chen wrote the paper; All authors contributed to and have approved the final manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.12.107.

References

American Psychiatry Association, 1994. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). American Psychiatric Publishing, Washington DC.
Armbruster-Genç, D.J.N., Ueltzhöffer, K., Fiebach, C.J., 2016. Brain signal variability differentially affects cognitive flexibility and cognitive stability. J. Neurosci. 36, 3978–3987.
Baria, A.T., Baliki, M.N., Parrish, T., Apkarian, A.V., 2011. Anatomical and functional assemblies of brain BOLD oscillations. J. Neurosci. 31, 7910–7919.
Bassett, D.S., Sporns, O., 2017. Network neuroscience. Nat. Neurosci. 20, 353–364.
Bromberg-Martin, E.S., Matsumoto, M., Hikosaka, O., 2010. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron 68, 815–834.
Chen, W., Zhuang, J., Yu, W., Wang, Z., 2009. Measuring complexity using FuzzyEn, ApEn, and SampEn. Med. Eng. Phys. 31, 61–68.
Cools, R., D'Esposito, M., 2011. Inverted-U–Shaped Dopamine actions on human working memory and cognitive control. Biol. Psychiatry 69, e113–e125.
Costa, M., Goldberger, A.L., Peng, C.K., 2002. Multiscale entropy analysis of complex physiologic time series. Phys. Rev. Lett. 92, 705–708.
Courtiol, J., Perdikis, D., Petkoski, S., Müller, V., Huys, R., Sleimen-Malkoun, R., Jirsa, V.K., 2016. The multiscale entropy: guidelines for use and interpretation in brain signal analysis. J. Neurosci. Methods 273, 175–190.
Cui, H., Zhang, J., Liu, Y., Li, Q., Li, H., Zhang, L., Hu, Q., Cheng, W., Luo, Q., Li, J., 2016. Differential alterations of resting-state functional connectivity in generalized anxiety disorder and panic disorder. Hum. Brain Mapp. 37, 1459–1473.
Dajani, D.R., Uddin, L.Q., 2015. Demystifying cognitive flexibility: implications for clinical and developmental neuroscience. Trends Neurosci. 38, 571–578.
Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A.R., Fox, P.T., Eickhoff, S.B., Yu, C., Jiang, T., 2016. The human brainnetome atlas: a new brain atlas based on connectional architecture. Cereb. Cortex 26, 3508–3526.
Farzan, F., Atluri, S., Mei, Y., Moreno, S., Levinson, A.J., Blumberger, D.M., Daskalakis, Z.J., 2017. Brain temporal complexity in explaining the therapeutic and cognitive effects of seizure therapy. Brain 140, 1011–1025.
Fonzo, G.A., Etkin, A., 2016. Brain connectivity reflects mental and physical states in generalized anxiety disorder. Biol. Psychiatry 80, 733–735.
Gao, J., Hu, J., Liu, F., Cao, Y., 2015. Multiscale entropy analysis of biological signals: a fundamental bi-scaling law. Front. Comput. Neurosci. 9, 64.
Garrett, D.D., McIntosh, A.R., Grady, C.L., 2014. Brain signal variability is parametrically modifiable. Cereb. Cortex 24, 2931–2940.
Ghanbari, Y., Bloy, L., Edgar, J.C., Blaskey, L., Verma, R., Roberts, T.P.L., 2015. Joint analysis of band-specific functional connectivity and signal complexity in autism. J. Autism Dev. Disord. 45, 444–460.
Gold, A.L., Shechner, T., Farber, M.J., Spiro, C.N., Leibenluft, E., Pine, D.S., Britton, J.C., 2016. Amygdala–cortical connectivity: associations with anxiety, development, and threat. Depress. Anxiety 33, 917–926.
Goldberger, A.L., Peng, C.K., Lipsitz, L.A., 2002. What is physiologic complexity and how does it change with aging and disease? Neurobiol. Aging 23, 23–26.
Grandy, T.H., Garrett, D.D., Florian, S., Markus, W.B., 2016. On the estimation of brain signal entropy from sparse neuroimaging data. Sci. Rep. 6, 23073.
Guitart-Masip, M., Salami, A., Garrett, D., Rieckmann, A., Lindenberger, U., Bäckman, L., 2016. BOLD variability is related to dopaminergic neurotransmission and cognitive aging. Cereb. Cortex 26, 2074–2083.
Hamilton, M., Schutte, N., Malouff, J., 1976. Hamilton anxiety scale (HAMA). Sourcebook Of Adult Assessment. Applied Clinical Psychology, pp. 154–157.
Heisz, J., Gould, M., Mcintosh, A., 2015. Age-related shift in neural complexity related to task performance and physical activity. J. Cogn. Neurosci. 27, 605–613.
King, M.A., Padman, L., Nicholls, K., Clarke, P.J., Gudmundsson, G.H., Kulessa, B., Shepherd, A., 1987. Relationship between competitive state anxiety inventory-2 subscale scores and pistol shooting performance. J. Sport Psychol. 9, 33–42.
Liu, F., Wang, Y., Li, M., Wang, W., Li, R., Zhang, Z., Lu, G., Chen, H., 2017. Dynamic functional network connectivity in idiopathic generalized epilepsy with generalized tonic–clonic seizure. Hum. Brain Mapp. 38, 957–973.
Makovac, E., Meeten, F., Watson, D.R., Herman, A., Garfinkel, S.N., Critchley, H., Ottaviani, C., 2016. Alterations in amygdala-prefrontal functional connectivity account for excessive worry and autonomic dysregulation in generalized anxiety disorder. Biol. Psychiatry 80, 786–795.
Mcdonough, I.M., Nashiro, K., 2014. Network complexity as a measure of information processing across resting-state networks: evidence from the Human Connectome Project. Front. Hum. Neurosci. 8, 409.
McIntosh, A.R., Vakorin, V., Kovacevic, N., Wang, H., Diaconescu, A., Protzner, A.B., 2014. Spatiotemporal dependency of age-related changes in brain signal variability. Cereb. Cortex 24, 1806–1817.
Mizuno, T., Takahashi, T., Cho, R.Y., Kikuchi, M., Murata, T., Takahashi, K., Wada, Y., 2010. Assessment of EEG dynamical complexity in Alzheimer's disease using multiscale entropy. Clin. Neurophysiol. 121, 1438–1446.
Mochcovitch, M.D., da Rocha Freire, R.C., Garcia, R.F., Nardi, A.E., 2014. A systematic review of fMRI studies in generalized anxiety disorder: evaluating its neural and cognitive basis. J. Affect. Disord. 167, 336–342.
Mp, D.L.M., Gallegos, C.A.G.Y., Marcellino, D., Fuxe, K., 2010. Role of dopamine receptor mechanisms in the amygdaloid modulation of fear and anxiety: Structural and functional analysis. Prog. Neurobiol. 90, 198–216.
Murphy, K., Fox, M.D., 2017. Towards a consensus regarding global signal regression for resting state functional connectivity MRI. Neuroimage 154, 169–173.
Nomi, J.S., Bolt, T.S., Ezie, C., Uddin, L.Q., Heller, A.S., 2017. Moment-to-moment BOLD Signal variability reflects regional changes in neural flexibility across the lifespan. J. Neurosci. 37, 5539–5548.
Ottaviani, C., Watson, D.R., Meeten, F., Makovac, E., Garfinkel, S.N., Critchley, H.D., 2016. Neurobiological substrates of cognitive rigidity and autonomic inflexibility in generalized anxiety disorder. Biol. Psychol. 119, 31–41.
Pang, Y., Chen, H., Wang, Y., Long, Z., He, Z., Zhang, H., Liao, W., Cui, Q., Chen, H., 2018. Transdiagnostic and diagnosis-specific dynamic functional connectivity anchored in the right anterior insula in major depressive disorder and bipolar depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 85, 7–15.
Ponce-Alvarez, A., He, B.J., Hagmann, P., Deco, G., 2015. Task-driven activity reduces the cortical activity space of the brain: experiment and whole-brain modeling. PLoS Comput. Biol. 11, e100445.
Pool, R., 1989. Is it healthy to be chaotic? Science 243, 604–607.
Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59, 2142–2154.
Raglin, J.S., Turner, P.E., 1993. Anxiety and performance in track and field athletes: a comparison of the inverted-U hypothesis with zone of optimal function theory. Personal. Individ. Differ. 14, 163–171.
Raichle, M.E., 2015. The brain's default mode network. Annu. Rev. Neurosci. 38, 433–447.
Richman, J.S., Moorman, J.R., 2000. Physiological time-series analysis using approximate entropy and sample entropy. Am. J. Physiol. Heart Circulatory Physiol. 278, H2039.

Schneier, F.R., Abidargham, A., Martinez, D., Slifstein, M., Hwang, D.R., Liebowitz, M.R., Laruelle, M., 2009. Dopamine transporters, D2 receptors, and dopamine release in generalized social anxiety disorder. Depress. Anxiety 26, 411–418.
Smith, R.X., Yan, L., Wang, D.J., 2013. Multiple time scale complexity analysis of resting state FMRI. Brain Imaging Behav. 8, 284–291.
Sokunbi, M.O., 2014. Sample entropy reveals high discriminative power between young and elderly adults in short fMRI data sets. Front. Neuroinform. 8, 69.
Sonstroem, R.J., Bernardo, P., 1982. Intraindividual pregame state anxiety and basketball performance: a re-examination of the inverted-U curve. J. Sport Psychol. 4, 235–245.
Spielberger, C.D., Sydeman, S.J., 1994. State-Trait Anxiety Inventory and State-Trait Anger Expression Inventory. Lawrence Erlbaum Associates, Inc.
Sporns, O., Betzel, R.F., 2016. Modular brain networks. Annu. Rev. Psychol. 67, 613–640.
Sylvester, C.M., Corbetta, M., Raichle, M.E., Rodebaugh, T.L., Schlaggar, B.L., Sheline, Y.I., Zorumski, C.F., Lenze, E.J., 2012. Functional network dysfunction in anxiety and anxiety disorders. Trends Neurosci. 35, 527–535.
Takahashi, T., 2013. Complexity of spontaneous brain activity in mental disorders. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 45, 258–266.
Thavabalasingam, S., O'Neil, E.B., Lee, A., 2018. Multivoxel pattern similarity suggests the integration of temporal duration in hippocampal event sequence representations. Neuroimage 178, 136–146.
Torre-Luque, A.D.L., Bornas, X., Balle, M., Fiol-Veny, A., 2016. Complexity and nonlinear biomarkers in emotional disorders: a meta-analytic study. Neurosci. Biobehav. Rev. 68, 410–422.
Versace, A., Almeida, J.R.C., Hassel, S., Walsh, N.D., Novelli, M., Klein, C.R., Kupfer, D.J., Phillips, M.L., 2008. Elevated left and reduced right orbitomedial prefrontal fractional anisotropy in adults with bipolar disorder revealed by tract-based spatial statistics. Arch. Gen. Psychiatry 65, 1041–1052.
Wang, N., Wu, H., Xu, M., Yang, Y., Chang, C., Zeng, W., Yan, H., 2018a. Occupational functional plasticity revealed by brain entropy: a resting-state fMRI study of seafarers. Hum. Brain Mapp. 39, 2997–3004.
Wang, Y.-F., Dai, G.-S., Liu, F., Long, Z.-L., Yan, J.H., Chen, H.-F., 2015. Steady-state BOLD response to higher-order cognition modulates low frequency neural oscillations. J. Cogn. Neurosci. 27, 2406–2415.
Wang, Y.-F., Liu, F., Long, Z.-L., Duan, X.-J., Cui, Q., Yan, J.H., Chen, H.-F., 2014a. Steady-state BOLD response modulates low frequency neural oscillations. Sci. Rep. 4, 7376.
Wang, Y., Chen, W., Ye, L., Biswal, B.B., Yang, X., Zou, Q., Yang, P., Yang, Q., Wang, X., Cui, Q., Duan, X., Liao, W., Chen, H., 2018b. Multiscale energy reallocation during low-frequency steady-state brain response. Hum. Brain Mapp. 39, 2121–2132.
Wang, Y., Zhu, L., Zou, Q., Cui, Q., Liao, W., Duan, X., Biswal, B., Chen, H., 2018c. Frequency dependent hub role of the dorsal and ventral right anterior insula. Neuroimage 165, 112–117.
Wang, Y.F., Long, Z., Cui, Q., Liu, F., Jing, X.J., Chen, H., Guo, X.N., Yan, J.H., Chen, H.F., 2016. Low frequency steady-state brain responses modulate large scale functional networks in a frequency-specific means. Hum. Brain Mapp. 37, 381–394.
Wang, Z., Li, Y., Childress, A.R., Detre, J.A., 2014b. Brain entropy mapping using FMRI. PLoS One 9, e89948.
Whalen, P.J., Johnstone, T., Somerville, L.H., Nitschke, J.B., Polis, S., Alexander, A.L., Davidson, R.J., Kalin, N.H., 2008. A functional magnetic resonance imaging predictor of treatment response to venlafaxine in generalized anxiety disorder. Biol. Psychiatry 63, 858–863.
Xia, T., Zhuang, L., Xu, X., Qi, Z., Luo, W., 2018. How do different emotional states represent in human brain?——Evidence from multi-variate pattern analysis based on functional MRI. Chin. Sci. Bull. 63, 241–247.
Xie, H.B., Guo, J.Y., Zheng, Y.P., 2010. Fuzzy approximate entropy analysis of chaotic and natural complex systems: detecting muscle fatigue using electromyography signals. Ann. Biomed. Eng. 38, 1483–1496.
Xue, G., Dong, Q., Chen, C., Lu, Z., Mumford, J.A., Poldrack, R.A., 2010. Greater neural pattern similarity across repetitions is associated with better memory. Science 330, 97–101.
Yang, A.C., Hong, C.J., Yin-Jay, L., Huang, K.L., Huang, C.C., Liu, M.E., Men-Tzung, L., Huang, N.E., Peng, C.K., Lin, C.P., 2015. Decreased resting-state brain activity complexity in schizophrenia characterized by both increased regularity and randomness. Hum. Brain Mapp. 36, 2174–2186.
Yang, A.C., Huang, C.C., Yeh, H.L., Liu, M.E., Hong, C.J., Tu, P.C., Chen, J.F., Huang, N.E., Peng, C.K., Lin, C.P., 2013. Complexity of spontaneous BOLD activity in default mode network is correlated with cognitive function in normal male elderly: a multiscale entropy analysis. Neurobiol. Aging 34, 428–438.
Yang, A.C., Tsai, S.J., 2013. Is mental illness complex? From behavior to brain. Prog. Neuro-psychopharmacol. Biol. Psychiatry 45, 253–257.
Yang, G.J., Murray, J.D., Glasser, M., Pearlson, G.D., Krystal, J.H., Schleifer, C., Repovs, G., Anticevic, A., 2017. Altered global signal topography in schizophrenia. Cereb. Cortex 27, 5156–5169.
Zappasodi, F., Marzetti, L., Olejarczyk, E., Tecchio, F., Pizzella, V., 2015. Age-related changes in electroencephalographic signal complexity. PLoS One 10, e0141995.
Zhang, H., Zhang, L., Zang, Y., 2015. Fluctuation amplitude and local synchronization of brain activity in the ultra-low frequency band: an fMRI investigation of continuous feedback of finger force. Brain Res. 1629, 104–112.
Zuo, X.-N., Di Martino, A., Kelly, C., Shehzad, Z.E., Gee, D.G., Klein, D.F., Castellanos, F.X., Biswal, B.B., Milham, M.P., 2010. The oscillating brain: complex and reliable. Neuroimage 49, 1432–1445.