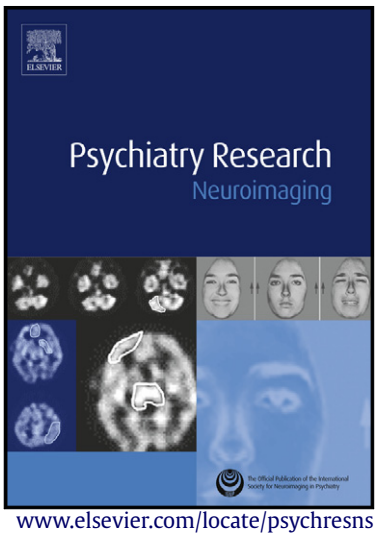


www.elsevier.com/locate/psychresns

Proneness to social anxiety modulates neural complexity in the absence of exposure: A resting state fMRI study using Hurst exponent

Claudio Gentili, Nicola Vanello, Ioana Cristea, Daniel David, Emiliano Ricciardi, Pietro Pietrini

PII: S0925-4927(15)00065-7
DOI: http://dx.doi.org/10.1016/j.pscychresns.2015.03.005
Reference: PSYN10347

To appear in: *Psychiatry Research: Neuroimaging*

Received date: 8 May 2014
Revised date: 7 February 2015
Accepted date: 13 March 2015

Cite this article as: Claudio Gentili, Nicola Vanello, Ioana Cristea, Daniel David, Emiliano Ricciardi, Pietro Pietrini, Proneness to social anxiety modulates neural complexity in the absence of exposure: A resting state fMRI study using Hurst exponent, *Psychiatry Research: Neuroimaging,* http://dx.doi.org/10.1016/j.pscychresns.2015.03.005

Proneness to social anxiety modulates neural complexity in the absence of exposure: A resting state fMRI study using Hurst Exponent

Claudio Gentili,[a,b,*], Nicola Vanello,[c], Ioana Cristea[a,d], Daniel David[d,e], Emiliano Ricciardi[b], Pietro Pietrini[a,b]

a. Clinical Psychology Branch, Department of Neuroscience – Via Roma. 67, Pisa University Hospital, Pisa, Italy
b. Department of Surgical, Medical, Molecular and Critical Area Pathology, Via Paradisa 10, – University of Pisa, Pisa, Italy
c. Department of Information Engineering, Via Diotisalvi 10, – University of Pisa, Pisa, Italy
d. Department of Clinical Psychology and Psychotherapy, Republicii str. 37, – University Babes-Bolyai, Cluj-Napoca, Romania
e. Department of Oncological Sciences - Mount Sinai School of Medicine, 1428 Madison Ave New York, NY, USA

Corresponding Author:

*Claudio Gentili, MD, Ph.D., Clinical Psychology Branch, Department of Neuroscience, Pisa University Hospital, Via Roma 67, I-56126 Pisa, Italy. E-mail: claudio.gentili@med.unipi.it; tel. +39 050 993959

Running Head: Social anxiety modulates resting state brain activity

Abstract

To test the hypothesis that brain activity is modulated by trait social anxiety, we measured the Hurst Exponent (HE), an index of complexity in time series, in healthy individuals at rest in the absence of any social trigger. Functional magnetic resonance imaging (fMRI) time series were recorded in 36 subjects *at rest*. All volunteers were healthy without any psychiatric, medical or neurological disorder. Subjects completed the Liebowitz Social Anxiety Scale (LSAS) and the Brief Fear of Negative Evaluation (BFNE) to assess social anxiety and thoughts in social contexts. We also obtained the fractional Amplitude of Low Frequency Fluctuations (fALFF) of the BOLD signal as an independent control measure for HE data. BFNE scores correlated positively with HE in the posterior cingulate/precuneus, while LSAS scores correlated positively with HE in the precuneus, in the inferior parietal sulci and in the parahippocamus. Results from fALFF were highly consistent with those obtained using LSAS and BFNE to predict HE. Overall our data indicate that spontaneous brain activity is influenced by the degree of social anxiety, on a continuum and in the absence of social stimuli. These findings suggest that social anxiety is a trait characteristic that shapes brain activity and predisposes to different reactions in social contexts.

Keywords: Social anxiety; Hurst exponent, fMRI, fALFF, Resting state, Default mode network, Social phobia

1.Introduction

According to the Diagnostic Statistic Manual of Mental Disorders – 4th edition text revised (DSM-IV-TR), social anxiety disorder (SAD) is a persistent and excessive fear of social or performance situations in which the person is exposed to unfamiliar people or to scrutiny by others (American Psychiatric Association, 2000).

From a neurobiological point of view, abnormal responses are associated with an altered neural activity in distinct regions, including not only emotion-related ones (Stein et al., 2002; Amir et al., 2005; Gentili et al., 2008), but also areas involved in social perception and interaction, such as the fusiform gyrus, inferior parietal lobule and dorsolateral prefrontal cortex (Gentili et al., 2008; Hattingh et al., 2012). A recent narrative review including 48 reports with fairly different experimental designs highlighted a dysfunctional network in SAD that consisted of the amygdala, pre-frontal regions striatal regions and parietal areas (Freitas-Ferrari et al., 2010). The region most consistently reported as affected in SAD was the amygdala, which has been demonstrated to be hyper-recruited while patients are coping with socially relevant stimuli (Stein et al., 2002; Gentili et al., 2008; Hattingh et al., 2012). Moreover, the degree of social anxiety seemed to correlate with the magnitude of amygdala response to faces both in clinical and non-clinical populations (Killgore and Yurgelun-Todd, 2005; Phan et al., 2006).

Furthermore, recent studies found that even the patterns of functional (Danti et al., 2010) and effective (Liao et al., 2010b) connectivity among the above-mentioned neural structures are altered in SAD. Interestingly, functional connectivity patterns are altered not only when patients are confronted with specific "socially threatening" stimuli, but also when they are *at rest*, that is, in the absence of any stimulation (Liao et al., 2010a). This abnormal activity *at rest* suggests that brain functional alterations may be related to trait characteristics that are present independently of any triggers from socially provoking situations.

Trait characteristics are very important aspects in psychological models of anxiety, including social anxiety (Spurr and Stopa, 2002), and define dimensions varying across a wide range, spanning from healthy individuals to patients. Social anxiety is indeed already recognizable in the common experience of shyness and becomes dysfunctional in patients with social phobia. In line with the conceptualization of trait general anxiety (Spielberg, 1989), we argue that social anxiety may precede and be independent of socially relevant contexts and be responsible for dysfunctional information processing. This dysfunction, in turn, may trigger anxiety in social contexts. The Clark and Wells model (1995) suggested the existence of a stable maintaining factor which contributes to trigger anxiety in social situations (Clark and Wells, 1995), while Spurr and Stopa identified in the self-focused attention a possible trait element responsible for the onset of social anxiety (Spurr and Stopa, 2002). However, predisposing factors have become a focus of interest only recently (Morrison and Heimberg, 2013).

If social anxiety is a trait characteristic, it is plausible that neural activity may be modulated by its degree, not only when individuals are exposed to socially engaging tasks, but also *at rest.* For instance, a significant relationship between strength of effective connectivity *at rest* (e.g., from left amygdala to left inferior temporal gyrus) and social anxiety levels was reported in SAD patients (Liao et al., 2010b).

While connectivity measures provide indications of integrated brain activity among regions, to our knowledge, no neurobiological study has attempted to evaluate the relationship between segregated regional brain activity and social anxiety. An additional approach for the study of brain activity at rest consists in assessing its complexity dimension, which involves the interplay between segregated and integrated activities in brain regions (Takahashi, 2013).

Complex systems are characterized by a) the presence of a large number of interdependent elements that interact nonlinearly and that are organized at different hierarchical spatial and temporal scales; b) an *emergent* behavior (i.e., an observed phenomenon cannot be predicted studying single constituents); c) self-organization properties, meaning that the system can change and adapt its structure (Baranger, 2001; Bassett and Gazzaniga, 2011; Ladyman et al., 2013). The brain fits these properties well. In fact, it is constituted by about 86 billion neural cells and by a similar number of non-neural cells (Azevedo et al., 2009). All these constituents interact to form short-range and long-range mutual connections, resulting in an interplay between segregation and integration at different hierarchical spatial and temporal scales. Interestingly, connectivity properties of neural networks have shown properties related to the spectrum profile of brain activity both in simulated (Steinke and Galán, 2011) and in real datasets (Ding et al., 2011; Tomasi and Volkow, 2011; Baria et al., 2013), and results discussed in terms of networks complexity. In particular, regions that show higher power at a low frequencies also show higher connectivity (Baria et al., 2013) and peculiar topological organization (Ding et al., 2011). These observations support the relevance of the use of the functional magnetic resonance imaging (fMRI) data power spectrum to study brain complexity features. In particular, the spectrum profile of the fMRI signal during rest has been found to show a 1/f-like behavior (where *f* is frequency) (Zarahn et al., 1997; Bullmore et al., 2001; Shimizu et al., 2004). Among different models of 1/f-like behaviors, those based on fractional Gaussian Noise (fGN) (Mandelbrot and Van Ness, 1968) are particularly relevant since they can describe both short and long range time dependencies. In particular, these models can describe processes whose power spectrum can be written as $S(f) \propto 1/|f|^{\beta}$ with $\beta < 1$ which is a model of fractality, or self-similarity at different temporal scales, and time-series predictability (Mandelbrot, 1971). For fGn parameter β can be written as $\beta = 2^{2}\ HE - 1$, where HE is an index ranging from 0 to 1 called the Hurst Exponent (HE), which allows a parsimonious description of different time series behaviors. In fact, time series can be divided into three categories according to HE values. A HE smaller than 0.5 is related to an anticorrelated time series, and the underlying generating process is called anti-persistent. In this case, the dynamics of the process are reversing in time, and an increase in the time-series will be, on average, followed by a decrease and vice-versa. A HE bigger than 0.5 is related to a positively correlated or persistent behavior, meaning that the generating process, on average, causes changes along time that go in the same direction. In this case the process is said to have a long memory, and the time-series is more predictable. When HE is equal or close to 0.5, the time course is a random white noise series. In this latter case, the process is considered 'without memory', meaning with low predictability. The power spectrum of a long memory persistent process is 1/f-like and the low frequency, slowly varying components, are more relevant. A process with HE < 0.5 is characterized by higher frequencies (i.e. rapidly changing components) (Fig. 1). Therefore, HE can be seen as a measure of brain activity complexity.

INSERT FIGURE 1 ABOUT HERE

HE was recently applied to BOLD (blood oxygen level dependent) signal measured under both physiological and pathological conditions. Changes in HE were shown to be related to normal and pathological aging, cholinergic modulation, autism spectrum disorders and different personality traits (Wink et al., 2006; Lai et al., 2010; Hahn et al., 2012; Lei et al., 2013; Sokunbi et al., 2014). For instance, Lei and colleagues showed an inverse relationship between HE in the default mode network (DMN) and extraversion (Lei et al., 2013).

Given the growing knowledge on the importance of 1/f phenomena in the understanding of spontaneous neuronal activity, we were interested in assessing whether the complexity of regional brain activity *at rest* was modulated by social anxiety levels. We expected such a modulation to be present also in the absence of socially relevant stimuli and to affect spontaneous brain activity across a wide range of degrees of social anxiety. To test this hypothesis, we evaluated whether social anxiety modulated HE in healthy volunteers, whose social anxiety levels varied from hardly present to high. Moreover, as an independent measure to validate HE results, we also calculated the fractional Amplitude of Low Frequency Fluctuations (fALFF). fALFF is a measure of low frequency oscillation (LFO) and in particular of the relative weight of LFO with respect to the total spectrum. fALFF has been found to be more robust to physiological confounds with respect to the Amplitude of Low Frequency Fluctuations (ALFF) parameter (Zou et al., 2008). Moreover, convergent evidence supports the relationship of both ALFF and fALFF to connectivity properties (Turner 2013). In particular, a reduction of fALFF and ALFF measures in schizophrenia was associated with a reduction in the connectivity within occipital lobe, superior parietal lobe and precuneus areas. A recent work showed a positive correlation between fALFF and HE (Jao et al., 2013). Therefore, we expected that fALFF, although not itself a measure of complexity, would provide an index of convergent validity for our HE results.

2.Methods

2.1. Subjects

Thirty-six healthy subjects (16 F; mean age±S.D.=27±4 years) were enrolled in the study. All subjects were drug free and received a clinical examination to exclude history or presence of any medical, neurological, or psychiatric disorders - including substance abuse disorders - that could affect brain function. No history of psychiatric disorders in first-degree relatives was reported. All participants gave their written informed consent to the study, which was approved by the Ethical Committee at the University of Pisa.

2.2. Psychological measurements

All subjects completed the following scales for the assessment of social anxiety:

2.2.1. Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1993). The LSAS is an instrument designed to measure social anxiety by assessing the fear and avoidance individuals might experience in social interaction and performance situations. The self-report version, which has minimal differences as compared with the original clinician-based version (Fresco et al., 2001), was used in this study;

2.2.2. Brief Fear of Negative Evaluation (BFNE) (Leary, 1983). The BFNE measures a core cognitive component of social anxiety, the fear of being negatively evaluated and the negative reappraisals of social situations. For the present study, we used a modified version of the BFNE, considered to be the most valid variant of the scale (Rodebaugh et al., 2011).

2.3 MRI acquisition

A single Echo Planar Imaging sequence consisting of 450 time-points (15 min duration) was obtained in each fMRI session on a 1.5T GE scanner. The sequence had the following parameters: 26 contiguous 4-mm-thick axial slices (repetition time/echo time = 2000/40 ms, flip angle = 90◦, field of view= 24 cm, resolution = 64×64 pixels). A high-resolution anatomical brain scan was acquired with a T1-weighted spoiled gradient recall sequence (124 slices, 1.2-mm-thick sagittal images, field of view = 24 cm).

Subjects, all scanned after a full night of sleep, were instructed to lie in the scanner with eyes closed and to relax without falling asleep.

2.4. Data analysis

2.4.1 Data preprocessing

We used the AFNI package (Cox, 1996) for spatial and time registration. Spatial registration was performed with the program 3dvolreg. Motion parameters were recorded and used in the HE calculation. For time registration we used the program 3dTshift.

Residual movement related effects were first removed using a linear regression approach. In fact, signal changes related to head movements cannot be fully compensated by spatial realignment. These artifactual signals are generated by movement-dependent modulation of magnetization history of voxels (Friston et al., 1996). Six time series describing three rigid body translations and three rigid body rotations of the head across time were obtained from a volume registration algorithm. These series were used in a multiple regression model at each voxel. A time dependent regressor was also included to linear detrended voxel time series. Time series were consequently obtained as the residuals of the model.

2.4.2. HE calculation

As pointed out by Maxim (Maxim et al., 2005), fMRI noise, after these pre-processing steps, can be described as fGn. In particular, fGn can be modeled as a stochastic process, whose behavior can be characterized by its auto-covariance function. The auto-covariance function is related to correlation of the process observed at two time points. In the case of fGn, the covariance function depends upon the distance among time points and upon the HE. With HE=0.5, the fGn is reduced to independent Gaussian noise, meaning the samples in the sequences originated from independent variables. HE values that are different from 0.5 introduce time dependencies among the samples in the series, thus leading to persistent or anti-persistent behavior, as discussed in the introduction. In this study, we exploited the relationship between fGn and fractional Brownian motion (fBm). In particular, fGn can be seen as the increment of a fBm sequence. This implies that a fractional Brownian motion sequence $B_{HE}(n)$ can be obtained as

$$B_{HE}(n) = \sum_{k=0}^{n} G_{HE}(k) \qquad (1)$$

where $G_{HE}(k)$ are the samples of a fGn sequence. With HE=0.5, since the fGn reduces to independent Gaussian noise, $B_{HE}(n)$ reduces to Brownian motion. The equation (1) was used in this work to obtain a fractional Brownian motion (fBm) sequence from the movement corrected and linear detrended voxel time-series. Then, the discrete second-order derivative approach (Istas and Lang, 1997; Kiviniemi et al., 2009) was used to estimate HE from fBm sequence. To perform this latter operation we used the *wfbmesti* function of the Wavelet Toolbox of the Matlab package.

2.4.3. fALFF calculation

The fALFF parameter was estimated from fMRI timeseries as in Zou et al. (Zou, et al. 2008) as the ratio of the power spectrum estimated between 0.01 and 0.08 Hz to the power spectrum at all available frequencies (0-0.25 Hz for our dataset). To calculate fALFF, we adopted two different approaches. In a first approach ($fALFF_0$) it was estimated directly on preprocessed fMRI time series. In a second approach, ($fALFF_{WM}$) two time series obtained from two spherical regions of interest (ROIs) (4-mm radius) centered in the left lateral ventricle and in the corpus callosum were added to the multiple regression model described in 2.4.1 to control for white matter (WM) and cerebrospinal fluid (CSF) signals, respectively. In both cases, fALFF was estimated with the program 3dRFSC of the AFNI package.

2.4.4. Group analysis

To perform the group analysis, the maps of the HE and fALFF of each subject were re-sampled into standardized Talairach space (Talairach and Tournoux, 1988). We then performed a linear regression analysis (with the *3dRegAna* program of AFNI package) on the whole brain where the score of each scale was used as the predictor to estimate the HE and fALFF (criterion), respectively. We considered significant a p value < 0.01 and a cluster size > 180 µl - corresponding to a p value < 0.05 FWE correction for false positive - as estimated by Monte Carlo simulation through the *3dClustSim* command of the AFNI package. For this simulation, we estimated the mean full width half maximum (FWHM) of the spatial structure of the noise with the command *3dFWHMx* applied on a time series of residuals obtained with option –errts of the command *3dDeconvole* both of AFNI package. The final mean FWHM values for the three dimensions were 3.29; 3.38 and 3.01. The simulation was performed on a mask (989.882 voxels) including only voxels common to all subjects.

We were also interested in evaluating whether significant clusters obtained from LSAS and BFNE would overlap. To this aim, we performed a conjunction analysis using the significant clusters from the two maps (p<0.01 uncorrected). In the resulting map we considered significant only the clusters over the cluster size (> 180 µl) defined before.

2.4.5. HE and fALFF comparison with ROI analysis

A post-hoc ROI analysis was performed to explore more in detail possible correlations of fALFF parameter with the psychological scales. Significant cluster for the linear regression analysis using LSAS and BFNE to predict HE were used as ROI. Mean fALFF for each ROI was extracted from each subject. These values were entered in correlation analyses with LSAS and BFNE, respectively.

3.Results

3.1. Psychological scales

In our sample the mean LSAS score was 23.58 ± 6.85 (S.D.), ranging between 3 and 84 (maximum score 144), while the mean BFNE score was 26.11 ± 18.65, ranging between 30 and 35 (maximum score 60). Because Grubb's test for outliers identified a female subject with an LSAS score of 84 as an outlier ($p<0.05$), this subject was removed from the analysis. The new mean scores for the LSAS and the BFNE were 23.22 ± 6.61 (range 3-76) and 24.45 ± 16.03, respectively. The scores of the two scales were significantly correlated (Pearson's r: 0.64, $p<0.0001$).

3.2. fMRI data analysis

3.2.1. Hurst Exponent calculation

Mean global HE was 0.69±0.05. Correlational analyses between global HE and the BFNE and LSAS were not significant ($r=0.05$ and $r=0.08$, respectively). We found significant positive correlations between BFNE scores and HE in the precuneus/posterior cingulate regions. This means that the higher the fear of negative evaluation is, the more the time course of the BOLD signal is predictable and the less the complexity is. Moreover, LSAS scores were, in the same way, positively correlated with HE in the precuneus and in bilateral inferior parietal sulcus (IPS) and right parahippocampus (Table 1; Fig. 2) ($p<0.01$, corrected). No other significant clusters were found.

Scatterplots illustrating correlations between LSAS and BFNE scores and the HE of each cluster are shown in Fig. 3.

- INSERT FIGURES 2, 3 and TABLE 1 ABOUT HERE -

Conjunction analysis showed areas of overlapping in the precunues/posterior cingulate and in the parahippocampal gyrus (Fig. 4)

- INSERT FIGURE 4 ABOUT HERE -

3.2.2. fALFF whole brain analysis

LSAS scores were found to correlate with $fALFF_{wm}$ in the precuneus/posterior cingulate region and in the parahippocampus (Fig. 5, Table 2). While no significant clusters were found for the correlation between the BFNE and $fALFF_{wm}$. No significant correlations were found using $fALFF_0$.

INSERT FIGURE 5 AND TABLE 2 ABOUT HERE

3.2.3. fALFF ROI analysis

fALFF metrics correlate with BFNE scores in the precuneus ROI while they significantly correlate with LSAS score in the ROIs placed in the precuneus, PCC/precuneus, bilateral IPS and right parahippocampus (Table 1).

4. Discussion

This study aimed to evaluate whether the psychological dimension of social anxiety may influence spontaneous brain activity *at rest*. We assessed the relationship between social anxiety, as measured by the LSAS and the BFNE, and HE, an index that describes the fractal complexity of time-series, which is related to its predictability. To obtain an independent validation of HE results, we also estimated, fALFF a measure of LFO of the BOLD signals, which has been found to correlate with HE measures (Jao et al., 2013).

Although none of our subjects had any history of psychiatric morbidity, 11 of 35 had a LSAS score greater than 30, which has been used as a threshold for SAD screening in the general population (Rytwinski et al., 2009). The 93.9% of the patients with a diagnosis of social phobia, according to the DSM-IV-TR criteria, score 30 or more on the LSAS (Rytwinski et al., 2009). While a LSAS score greater than 30 is not by itself sufficient for a diagnosis of SAD, the large range of LSAS scores among the volunteer sample reflects a wide array of social anxiety levels. It is also important to underline that in our sample there were subjects with very low levels of social anxiety (namely scores of 3 over 144 at LSAS). Therefore, the linear relationship we found in our data indicates that also from a neurobiological point of view, social anxiety spans across a continuum.

Fractal dimensions are used to describe several biological phenomena. The HE has already been used to describe fractal properties of biophysical signals, including also the electrocardiogram (Costa and McCrae, 1992) and EEG (Ignaccolo et al., 2010). As described in the introduction, HE provides a parsimonious description of different possible behaviors of the auto-covariance of the fMRI signal.

Several methods have been used to estimate the HE in biological signals. A recent article (Rubin et al., 2013) analyzes the robustness of different algorithms with respect to possible fMRI artifacts and time series lengths. In particular, the relevance of preprocessing steps as motion correction, detrending and filtering were evaluated both on simulated and real fMRI data, while other preprocessing steps like segmentation were not evaluated, although they may have an impact on

HE determination and likely deserve specifically designed studies. The second order derivative approach adopted in the present work was found to be consistent with other approaches and, moreover, to be robust with respect to spikes in the data This method has the advantage of being applicable to a time series of any length, in contrast to other validated methods, which have to be applied on time series with a length of 2^x time points (where x is a natural number) (Maxim et al., 2005).

The HE of fMRI time series is generally higher in gray matter than in white matter (Maxim et al., 2005), augments in the hippocampus with aging, and decreases with cholinergic transmission enhancement (Wink et al., 2006). Nonetheless, these findings do not warrant the conclusion that a higher HE is related to worse brain functioning. For instance, a reduction of HE has been observed in autistic and schizophrenic patients (Lai et al., 2010; Sokunbi et al., 2014). Therefore, it seems more plausible that the HE reflects some inherent pattern of spontaneous discharge and that it can be modulated by psychological or psychopathological variables.

Since the HE can describe long and short range memory dynamics, it has been proposed as a measure of online information-processing efficiency: higher HEs are related to long memory dynamics and to higher temporal redundancy and less freedom to vary (He, 2011). Thus, we suggest that differences of long-range memory in spontaneous regional brain activity may represent a possible neurobiological correlate of trait social anxiety. Furthermore, as described in Section 1, the HE is related to 1/f-like behaviors. Interestingly, recent findings support the possibility that the power spectrum profile of the fMRI time series power spectrum reflects connectivity properties of neural networks. In particular, low frequency changes of the BOLD signal may reflect both segregated and integrated information (Ding et al., 2011; Tomasi and Volkow, 2011; Baria et al., 2013). For instance, Baria et al. (2013) observed that a greater distribution of power at lower frequencies was found in regions characterized by a higher functional connectivity, as in primary sensory areas and cortical areas of the DMN.

We found a positive correlation between the HE and social anxiety scores in DMN regions including the posterior cingulate, the precuneus and bilateral IPS. We also found a positive correlation between LSAS scores and the HE in the parahippocampus.

In a trait condition of low social anxiety, the subject is able to explore external and internal information and the environment with a reduced attentional-perception bias. Moreover, internally oriented rumination is at low levels. From a neurobiological standpoint, the DM network, and particularly the precuneus and the posterior cingulate, might be more 'available' to receive inputs from other brain regions and thus their activity may be less predictable. When trait social anxiety is high, the subject may be more self-focused, and outside stimuli can result in relatively less interference. Thus, the balance of attention between external and self-oriented processing is altered in favor of the latter (Clark and McManus,

2002). The reduction of externally oriented attention is also related to a reduced attention and awareness of external cues that might disconfirm the individual's judgments of her/her social skills in social situations. Moreover, internally directed rumination increases. On the neurobiological side, the spontaneous DMN activity could become less 'free', more predictable and 'rigid', as if the flow of information from other districts is reduced and less able to interfere with the system and make it less 'stable' and less 'predictable' (Fig. 1). Our interpretation of the HE as a measure of flexibility or rigidity is consistent with the conclusions drawn by Lei and colleagues (Lei et al., 2013). In particular, they suggested that in subjects low in Extraversion (and with a higher HE) the past dynamics and long-term memories have a stronger influence on future responses (Lei et al., 2013). Although the Extraversion-Introversion personality trait is not exactly the same construct of social anxiety, the two are generally highly correlated: namely, high social anxiety corresponds to low Extraversion (Rosellini and Brown, 2011). Lei and collegues, however, considered the whole DMN, while we were able to pinpoint specific subregions where HE is related to the degree of social anxiety. Although the DMN is a network of regions with coherent behaviour, the presence of regional segreation of functions is well documented. A better knowledge of the role of each single region would support a better knowledge of the network's functioning and dysfunctioning in pathological conditions.

Using a variety of distinct paradigms and approaches to data analysis, several independent studies have consistently suggested a role of DMN areas in emotional processing and regulation in normal and pathological conditions (Benelli et al., 2012; Freton et al., 2014). For instance, a role of the precuneus and the posterior cingulate cortex has been shown in emotional processing, especially when emotions are self-referred as compared with when they are referred to others (Schneider et al., 2008) and more in general with the experience of self (Brewer et al., 2013). Brain activity in these regions seems to be related to self-referential thoughts and attributions (Saxe et al., 2006). Consistently, abnormal activity and connectivity in these regions has been reported in several anxiety disorders, including social phobia (Zhao et al., 2007; Liao et al., 2010a; Pannekoek et al., 2013; Rogers et al., 2013). The posterior cingulate and precuneus displayed a weakened deactivation in social phobics as compared with findings in healthy controls when switching from resting state to a face perception task (Gentili et al., 2009). This lack of deactivation was interpreted as a biological counterpart of the trait characteristic of self-focused attention which is a type of rumination defined as "an awareness of self-referent, internally generated information" (Ingram, 1990) including wariness of physical states, thoughts and emotions. The posterior cingulate and the precuneus were also found to be involved in other forms of rumination (Berman et al., 2011). The BFNE scale we used specifically measures the fear related to the anticipation of negative cognitive appraisals, processes closely related to self-focused attention and ruminative thinking (Thomas and Hersen, 2009).

Bilateral parietal lobules showed increased HE with the increase of LSAS scores. Liao and colleagues (Liao et al., 2010a) showed that functional networks, particularly the DMN and the dorsal attention network including the inferior and superior parietal lobules were altered in SAD patients. The dorsal attentional network has been shown to play a role in goal-directed top-down processing (Corbetta and Shulman, 2002) and might be involved in emotional regulation and arousal.

In healthy volunteers, parahippocampal gyrus activity and its functional coupling with the DMN was linked to long-term memory processes. Its role in the abnormal response to social stimuli in social phobia was related to fear conditioning processes, recently considered a potential target for psychotherapy interventions (Straube et al., 2004; Wild and Clark, 2011).

Conjunction analysis provided further useful evidence in the interpretation of our results. From a psychological point of view, the LSAS is considered a more clinical scale, which measures several aspects and situations in which the individual may experience social anxiety. On the other hand, the BFNE is considered a more 'cognitive' scale, measuring thoughts and beliefs about social situations. Thus, the two scales measure similar, but not identical constructs. Conjunction analysis showed a significant overlap in the parahippocampal gyrus and in the posterior cingulate and the precuneus. This result reinforces the interpretation that these structures play an important role in the cognitive evaluation of social situations and suggests a neurobiological segregation among social anxiety components assessed by different psychological tools.

It is relevant to note that another measure of intrinsic brain activity (fALFF) produced consistent results with those obtained with HE. fALFF is a relative measure of LFO that seems to be less affected by physiological noise (Zou et al., 2008). LFO metrics can highlight resting state networks, including DMN, and represent a measure of intensity of neuronal activity both in healthy subjects and in pathological conditions, including depression, schizophrenia and cognitive alterations (Hoptman et al., 2010; Han et al., 2011; Wang et al., 2012). We estimated fALFF both regressing and not regressing out white matter and ventricle signals. A recent work highlighted differences in individual parameter estimation between the two approaches, although no significant differences were found at a group level comparison between patients and controls (Turner et al., 2013). This was ascribed to a similar regression effect across the subjects. In our study, the results with the two approaches differed. The whole brain analysis performed regressing out WM and CSF signals gave similar, though not identical, results to those obtained with HE, at least regarding LSAS. However, ROI analysis showed overlapping results among analyses. This consistency may help to provide a physiological meaning for HE, since the increase of HE and thus a more predictable neuronal discharge seems also to be related to increased neural discharge as measured by LFO.

As our results were not elicited by any socially relevant stimuli, they are indicative of trait social anxiety and in line with the hypothesis that trait characteristics affect spontaneous brain activity *at rest*. Such brain activity might account for the different brain (and behavioral) responses during social stimuli. The idea that the way in which we react to situations is strictly related to our "mind disposition" is an old one (Raichle and Snyder, 2007): it stretches from Plato to Immanuel Kant to William James. In this vein, the way in which we react to socially relevant situations is, at least in part, determined *a priori* and derives from our personality and psychological characteristics. According to cognitive models of SAD (Clark and Wells, 1995), the development of the disorder is not just related to emotional hyperactivity, but also to biased information, leading to abnormal and excessive responses (Morrison and Heimberg, 2013).

Our work provides direct evidence that the levels of social anxiety may also be related to intrinsic regional spontaneous brain activity and that this relationship is trait based, present even in the absence of social cues. These results are fully consistent with data obtained with different experimental designs (Gentili et al., 2008; Gentili et al., 2009; Liao et al., 2010a; Liao et al., 2010b) showed that social anxiety levels are related to the strength of connectivity between the amygdala and other brain regions involved in emotional modulation and perception during rest. In this sense, it is important to note that previous studies focused on functional relationship and connectivity among regions, while our study is the first one to consider also intrinsic segregated activity.

4.1 Limitations

As the meaning of the HE is not yet fully understood, it is difficult to provide a neurobiological interpretation for our findings. However, the evidence offered by convergent results of fALFF analysis, together along with the studies discussed above (Gentili et al., 2008; Liao et al., 2010a), supports the proposed interpretation of our data.

The aim of this study was to explore the social anxiety dimension as continuum in healthy volunteers. Similar studies in SAD patients are needed to determine whether this continuum extends to the pathological condition.

Another limitation of this study is the lack of control for heart rate and respiration as we decided to perform only head movement correction and linear detrending. fALFF is considered to be robust against physiological noise, was also computed regressing out movements, WM and CSF signals, and lead to consistent results with those obtained with the HE. Nevertheless, we cannot rule out that both measures might have been influenced by residual physiological confounds related to unobserved physiological signal changes. Several works highlighted how preprocessing steps significantly influence the results of HE estimation (Rubin et al., 2013) and of resting state analyisis in general (Murphy et al., 2013). On the other

hand, regressing out heart and respiration may occult neural activity of interest since these physiological measures may correlate with emotional or mood states.

Finally, we are aware that the HE cannot provide a complete understanding of the neurobiology of social anxiety and that we did not consider other measures of complexity (e.g., sample entropy) since they belong to different classes of models and measure different properties of complexity as compared with the HE (Takahashi, 2013). In this regards, future research should perform systematic comparisons among different metrics to define differences and commonalities.

4.2 Conclusions

This study is the first to demonstrate that spontaneous brain activity *at rest* is modulated by the degree of social anxiety across a wide range of intensities in healthy individuals, providing a neurobiological support for the dimensional continuity of social anxiety. This is in line with clinical psychology studies on social anxiety (Spurr and Stopa, 2002), but also with the recent views on psychiatric diagnosis arguing for a recovery of the dimensional assessment of psychopathology (Watson et al., 2013). Importantly, as the relationship between social anxiety and brain activity was found *at rest*, these findings suggest that social anxiety may reflect trait characteristics that shape brain activity and predispose to different reactions to social contexts. Moreover, our results confirm the potential of the HE in identifying brain regions related to psychological dimensions. As recently shown for other mental disorders (Wei et al., 2013), the use of this index could become a possible measure to aid psychiatric diagnosis.

Acknowledgments

This research was supported by Fondazione IRIS. The authors wish to dedicate the present paper to Prof. Mario Guazzelli (1948-2012), who inspired the study.

Ioana A. Cristea was supported by a Young Researcher Grant (GTC_34064/2013), awarded by the Babes-Bolyai University, Romania.

Author contributions

Conceived the idea of the experiment: CG, IC, NV, ER, PP; Data collection: CG, IC, ER; Data analysis: CG, NV, IC; Data interpretation: CG, IC, DD, PP; Manuscript draft: CG, NV, PP; Review of the manuscript: all.

Financial disclosures

All the authors reported no biomedical financial interests or potential conflicts of interest.

References

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. American Psychiatric Publishing, Washington, DC.

Amir, N., Klumpp, H., Elias, J., Bedwell, J.S., Yanasak, N., Miller, L.S., 2005. Increased activation of the anterior cingulate cortex during processing of disgust faces in individuals with social phobia. Biological Psychiatry 57, 975-981.

Azevedo, F.A.C., Carvalho, L.R.B., Grinberg, L.T., Farfel, J.M., Ferretti, R.E.L., Leite, R.E.P., Filho, W.J., Lent, R., Herculano-Houzel, S., 2009. Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. Journal of Comparative Neurology 513, 532-541.

Baranger, M., 2001. Chaos, complexity, and entropy: a physics talk for non-physicists. Center for Theoretical Physics, Laboratory for Nuclear Science and Department of Physics
Massachusetts Institute of Technology, Cambridge, MA 02139, USA.

Baria, A.T., Mansour, A., Huang, L., Baliki, M.N., Cecchi, G.A., Mesulam, M.M., Apkarian, A.V., 2013. Linking human brain local activity fluctuations to structural and functional network architectures. NeuroImage 73, 144-155.

Bassett, D.S., Gazzaniga, M.S., 2011. Understanding complexity in the human brain. Trends in Cognitive Sciences 15, 200-209.

Benelli, E., Mergenthaler, E., Walter, S., Messina, I., Sambin, M., Buchheim, A., Sim, E.J., Viviani, R., 2012. Emotional and cognitive processing of narratives and individual appraisal styles: recruitment of cognitive control networks vs. modulation of deactivations. Frontiers in Human Neuroscience 6, 239.

Berman, M.G., Peltier, S., Nee, D.E., Kross, E., Deldin, P.J., Jonides, J., 2011. Depression, rumination and the default network. Social Cognitive and Affective Neuroscience 6, 548-555.

Brewer, J.A., Garrison, K.A., Whitfield-Gabrieli, S., 2013. What about the "self" is processed in the posterior cingulate cortex? Frontiers in Human Neuroscience 7, 647.

Bullmore, E., Long, C., Suckling, J., Fadili, J., Calvert, G., Zelaya, F., Carpenter, T.A., Brammer, M., 2001. Colored noise and computational inference in neurophysiological (fMRI) time series analysis: resampling methods in time and wavelet domains. Human Brain Mapping 12, 61-78.

Clark, D.M., McManus, F., 2002. Information processing in social phobia. Biological Psychiatry 51, 92-100.

Clark, D.M., Wells, A., 1995. A cognitive model of social phobia. In: Heimberg, R., Liebowitz, M., Hope, D., Schneier, F. (Eds.), Social Phobia: Diagnosis, Assessment and Treatment. Guilford Press, New York, pp. 69-93.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews. Neuroscience 3, 201-215.

Costa, P.T., McCrae, R.R., 1992. Normal personality assessment in clinical practice: The NEO Personality Inventory. Psychological Assessment 4, 5-13.

Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Computers and Biomedical Research, An International Journal 29, 162-173.

Danti, S., Ricciardi, E., Gentili, C., Gobbini, M.I., Pietrini, P., Guazzelli, M., 2010. Is social phobia a "mis-communication" disorder? Brain functional connectivity during face perception differs between patients with social phobia and healthy control subjects. Frontiers in Systems Neuroscience 4, 152.

Ding, J.R., Liao, W., Zhang, Z., Mantini, D., Xu, Q., Wu, G.R., Lu, G., Chen, H., 2011. Topological fractionation of resting-state networks. PLoS One 6.

Freitas-Ferrari, M.C., Hallak, J.E., Trzesniak, C., Filho, A.S., Machado-de-Sousa, J.P., Chagas, M.H., Nardi, A.E., Crippa, J.A., 2010. Neuroimaging in social anxiety disorder: a systematic review of the literature. Progress in Neuropsychopharmacology and Biological Psychiatry 34, 565-580.

Fresco, D.M., Coles, M.E., Heimberg, R.G., Liebowitz, M.R., Hami, S., Stein, M.B., Goetz, D., 2001. The Liebowitz Social Anxiety Scale: a comparison of the psychometric properties of self-report and clinician-administered formats. Psychological Medicine 31, 1025-1035.

Freton, M., Lemogne, C., Bergouignan, L., Delaveau, P., Lehéricy, S., Fossati, P., 2014. The eye of the self: precuneus volume and visual perspective during autobiographical memory retrieval. Brain Structure & Function 219 (3), 959-968.

Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S., Turner, R., 1996. Movement-related effects in fMRI time-series. Magnetic Resonance in Medicine 35, 346-355.

Gentili, C., Gobbini, M.I., Ricciardi, E., Vanello, N., Pietrini, P., Haxby, J.V., Guazzelli, M., 2008. Differential modulation of neural activity throughout the distributed neural system for face perception in patients with Social Phobia and healthy subjects. Brain Research Bulletin 77, 286-292.

Gentili, C., Ricciardi, E., Gobbini, M.I., Santarelli, M.F., Haxby, J.V., Pietrini, P., Guazzelli, M., 2009. Beyond amygdala: Default Mode Network activity differs between patients with social phobia and healthy controls. Brain Research Bulletin 79, 409-413.

Hahn, T., Dresler, T., Ehlis, A.-C., Pyka, M., Dieler, A.C., Saathoff, C., Jakob, P.M., Lesch, K.-P., Fallgatter, A.J., 2012. Randomness of resting-state brain oscillations encodes Gray's personality trait. NeuroImage 59, 1842-1845.

Han, Y., Wang, J., Zhao, Z., Min, B., Lu, J., Li, K., He, Y., Jia, J., 2011. Frequency-dependent changes in the amplitude of low-frequency fluctuations in amnestic mild cognitive impairment: a resting-state fMRI study. Neuroimage 55, 287-295.

Hattingh, C.J., Ipser, J., Tromp, S.A., Syal, S., Lochner, C., Brooks, S.J., Stein, D.J., 2012. Functional magnetic resonance imaging during emotion recognition in social anxiety disorder: an activation likelihood meta-analysis. Frontiers in Human Neuroscience 6, 347.

He, B.J., 2011. Scale-free properties of the functional magnetic resonance imaging signal during rest and task. The Journal of Neuroscience 31, 13786-13795.

Hoptman, M.J., Zuo, X.N., Butler, P.D., Javitt, D.C., D'Angelo, D., Mauro, C.J., Milham, M.P., 2010. Amplitude of low-frequency oscillations in schizophrenia: a resting state fMRI study. Schizophrenia Research 117, 13-20.

Ignaccolo, M., Latka, M., Jernajczyk, W., Grigolini, P., West, B.J., 2010. The dynamics of EEG entropy. Journal of Biological Physics 36 (2), 185-196.

Ingram, R.E., 1990. Self-focused attention in clinical disorders: review and a conceptual model. Psychological Bulletin 107, 156-176.

Istas, J., Lang, G., 1997. Quadratic variations and estimation of the local Hölder index of a Gaussian process. Annales de l'institut Henri Poincare (B) Probability and Statistics 33, 407-436.

Killgore, W.D.S., Yurgelun-Todd, D.A., 2005. Social anxiety predicts amygdala activation in adolescents viewing fearful faces. Neuroreport 16, 1671-1675.

Kiviniemi, V., Remes, J., Starck, T., Nikkinen, J., Haapea, M., Silven, O., Tervonen, O., 2009. Mapping transient hyperventilation induced alterations with estimates of the multi-scale dynamics of BOLD signal. Frontiers in Neuroinformatics 3, 18.

Ladyman, J., Lambert, J., Wiesner, K., 2013. What is a complex system? European Journal for Philosophy of Science 3, -67.

Lai, M.-C., Lombardo, M.V., Chakrabarti, B., Sadek, S.A., Pasco, G., Wheelwright, S.J., Bullmore, E.T., Baron-Cohen, S., Suckling, J., 2010. A shift to randomness of brain oscillations in people with autism. Biological Psychiatry 68, 1092-1099.

Leary, M., 1983. Social anxiousness: the construct and its measurement, Journal of Personalality Assessment 47 (1), 66-75.

Lei, X., Zhao, Z., Chen, H., 2013. Extraversion is encoded by scale-free dynamics of default mode network. NeuroImage 74, 52-57.
Liao, W., Chen, H., Feng, Y., Mantini, D., Gentili, C., Pan, Z., Ding, J., Duan, X., Qiu, C., Lui, S., Gong, Q., Zhang, W., 2010a. Selective aberrant functional connectivity of resting state networks in social anxiety disorder. NeuroImage 52, 1549-1558.
Liao, W., Qiu, C., Gentili, C., Walter, M., Pan, Z., Ding, J., Zhang, W., Gong, Q., Chen, H., 2010b. Altered effective connectivity network of the amygdala in social anxiety disorder: a resting-state fMRI study. PloS One 5, e15238.
Liebowitz, M.R., 1993. Pharmacotherapy of social phobia. The Journal of Clinical Psychiatry 54 (Suppl), 31-35.
Mandelbrot, B.B., 1971. A fast fractional Gaussian noise generator. Water Resources Research 7, 543–553.
Mandelbrot, B.B., Van Ness, J.W., 1968. Fractional Brownian motions, fractional noises and applications. SIAM Review 10, 422-437.
Maxim, V., Sendur, L., Fadili, J., Suckling, J., Gould, R., Howard, R., Bullmore, E., 2005. Fractional Gaussian noise, functional MRI and Alzheimer's disease. NeuroImage 25, 141-158.
Morrison, A.S., Heimberg, R.G., 2013. Social anxiety and social anxiety disorder. Annual Review of Clinical Psychology 9, 249-274.
Murphy, K., Birn, R.M., Bandettini, P.A., 2013. Resting-state fMRI confounds and cleanup. NeuroImage 80, 349-359.
Pannekoek, J.N., Veer, I.M., van Tol, M.-J., van der Werff, S.J.A., Demenescu, L.R., Aleman, A., Veltman, D.J., Zitman, F.G., Rombouts, S.A.R.B., van der Wee, N.J.A., 2013. Resting-state functional connectivity abnormalities in limbic and salience networks in social anxiety disorder without comorbidity. European Neuropsychopharmacology 23, 186-195.
Phan, K.L., Fitzgerald, D.A., Nathan, P.J., Tancer, M.E., 2006. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. Biological Psychiatry 59, 424-429.
Raichle, M.E., Snyder, A.Z., 2007. A default mode of brain function: a brief history of an evolving idea. NeuroImage 37, 1083-1090; discussion 1097-1099.
Rodebaugh, T.L., Heimberg, R.G., Brown, P.J., Fernandez, K.C., Blanco, C., Schneier, F.R., Liebowitz, M.R., 2011. More reasons to be straightforward: findings and norms for two scales relevant to social anxiety. Journal of Anxiety Disorders 25, 623-630.
Rogers, J., Raveendran, M., Fawcett, G.L., Fox, A.S., Shelton, S.E., Oler, J.A., Cheverud, J., Muzny, D.M., Gibbs, R.A., Davidson, R.J., Kalin, N.H., 2013. CRHR1 genotypes, neural circuits and the diathesis for anxiety and depression. Molecular Psychiatry 18, 700-707.
Rosellini, A.J., Brown, T.A., 2011. The NEO Five-Factor Inventory: latent structure and relationships with dimensions of anxiety and depressive disorders in a large clinical sample. Assessment 18, 27-38.
Rubin, D., Fekete, T., Mujica-Parodi, L.R., 2013. Optimizing complexity measures for FMRI data: algorithm, artifact, and sensitivity. PloS One 8, e63448.
Rytwinski, N.K., Fresco, D.M., Heimberg, R.G., Coles, M.E., Liebowitz, M.R., Cissell, S., Stein, M.B., Hofmann, S.G., 2009. Screening for social anxiety disorder with the self-report version of the Liebowitz Social Anxiety Scale. Depression and Anxiety 26, 34-38.
Saxe, R., Moran, J.M., Scholz, J., Gabrieli, J., 2006. Overlapping and non-overlapping brain regions for theory of mind and self reflection in individual subjects. Social Cognitive and Affective Neuroscience 1, 229-234.
Schneider, F., Bermpohl, F., Heinzel, A., Rotte, M., Walter, M., Tempelmann, C., Wiebking, C., Dobrowolny, H., Heinze, H.J., Northoff, G., 2008. The resting brain and our self: self-relatedness modulates resting state neural activity in cortical midline structures. Neuroscience 157, 120-131.

Shimizu, Y., Barth, M., Windischberger, C., Moser, E., Thurner, S., 2004. Wavelet-based multifractal analysis of fMRI time series. NeuroImage 22, 1195-1202.
Sokunbi, M.O., Gradin, V.B., Waiter, G.D., Cameron, G.G., Ahearn, T.S., Murray, A.D., Steele, D.J., Staff, R.T., 2014. Nonlinear complexity analysis of brain fMRI signals in schizophrenia. PLoS One 9, e95146.
Spielberg, C.D., 1989. State–Trait Anxiety Inventory: A Comprehensive Bibliography. Consulting Psychologists Press, Palo Ato, CA.
Spurr, J.M., Stopa, L., 2002. Self-focused attention in social phobia and social anxiety. Clinical Psychology Review 22, 947-975.
Stein, M.B., Goldin, P.R., Sareen, J., Zorrilla, L.T.E., Brown, G.G., 2002. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. Archives of General Psychiatry 59, 1027-1034.
Steinke, G.K., Galán, R.F., 2011. Brain rhythms reveal a hierarchical network organization. PLoS Computational Biology 7.
Straube, T., Kolassa, I.-T., Glauer, M., Mentzel, H.-J., Miltner, W.H.R., 2004. Effect of task conditions on brain responses to threatening faces in social phobics: an event-related functional magnetic resonance imaging study. Biological Psychiatry 56, 921-930.
Takahashi, T., 2013. Complexity of spontaneous brain activity in mental disorders. Progress in Neuropsychopharmacology and Biological Psychiatry 45, 258-266.
Talairach, J., Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain: Three-Dimensional Proportional System: An Approach to Cerebral Imaging. Thieme, Stuttgart.
Thomas, J.C., Hersen, M., 2009. Handbook of Clinical Psychology Competencies. Springer, Berlin.
Tomasi, D., Volkow, N.D., 2011. Association between functional connectivity hubs and brain networks. Cerebral Cortex 21, 2003-2013.
Turner, J.A., Damaraju, E., Van Erp, T.G.M., Mathalon, D.H., Ford, J.M., Voyvodic, J., Mueller, B.A., Belger, A., Bustillo, J., McEwen, S., Potkin, S.G., Calhoun, V.D., 2013. A multi-site resting state fMRI study on the amplitude of low frequency fluctuations in schizophrenia. Frontiers in Neuroscience 7, 137.
Wang, L., Dai, W., Su, Y., Wang, G., Tan, Y., Jin, Z., Zeng, Y., Yu, X., Chen, W., Wang, X., Si, T., 2012. Amplitude of low-frequency oscillations in first-episode, treatment-naive patients with major depressive disorder: a resting-state functional MRI study. PLoS One 7, e48658.
Watson, D., Stasik, S.M., Ro, E., Clark, L.A., 2013. Integrating normal and pathological personality: relating the DSM-5 trait-dimensional model to general traits of personality. Assessment 20, 312-326.
Wei, M., Qin, J., Yan, R., Li, H., Yao, Z., Lu, Q., 2013. Identifying major depressive disorder using Hurst exponent of resting-state brain networks. Psychiatry Research: Neuroimaging 214, 306-312.
Wild, J., Clark, D.M., 2011. Imagery rescripting of early traumatic memories in social phobia. Cognitive and Behavioral Practice 18, 433-443.
Wink, A.M., Bernard, F., Salvador, R., Bullmore, E., Suckling, J., 2006. Age and cholinergic effects on hemodynamics and functional coherence of human hippocampus. Neurobiology of Aging 27, 1395-1404.
Zarahn, E., Aguirre, G.K., D'Esposito, M., 1997. Empirical analyses of BOLD fMRI statistics. I. Spatially unsmoothed data collected under null-hypothesis conditions. NeuroImage 5, 179-197.
Zhao, X.-H., Wang, P.-J., Li, C.-B., Hu, Z.-H., Xi, Q., Wu, W.-Y., Tang, X.-W., 2007. Altered default mode network activity in patient with anxiety disorders: an fMRI study. European Journal of Radiology 63, 373-378.
Zou, Q.H., Zhu, C.Z., Yang, Y., Zuo, X.N., Long, X.Y., Cao, Q.J., Wang, Y.F., Zang, Y.F., 2008. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. Journal of Neuroscience Methods 172, 137-141.

Figure and table legends

Table 1. Significant clusters for the linear regression in which LSAS and BFNE were the independent variable and the HE the dependent one, respectively ($p < 0.01$; cluster size > 180 µl). The *r* values (Pearson *r*) refer to the peak correlation of the cluster. Alpha refers to the type I error probability for each cluster as estimated by the program alphasym of the AFNI distribution.

LSAS: Liebowitz Social Anxiety Scale; BFNE: Brief Fear of Negative Evaluation; PCUN: precuneus; PCC/PCUN: Posterior cingulate/precuneus; IPS: inferior parietal lobule; PHyp: parahippocampal gyrus. fALFF refers to correlation (Pearson *r*) between fALFF values and LSAS/BFNE scores, respectively; *: $p < 0.05$; **: $p < 0.01$.

Table 2. Significant clusters for the linear regression in which LSAS and BFNE were the independent variables and the fALFF the dependent variable, respectively ($p < 0.01$; cluster size > 180 µl). The *r* values (Pearson *r*) refer to the peak correlation of the cluster. Alpha refers to the type I error probability for each cluster as estimated by the program alphasym of the AFNI distribution.

LSAS: Liebowitz Social Anxiety Scale; BFNE: Brief Fear of Negative Evaluation; PCUN: precuneus; PCC/PCUN: posterior cingulate/precuneus; IPS: inferior parietal lobule; PHyp: parahippocampal gyrus; **: $p < 0.01$.

Fig. 1. Exemplificative illustrations of time-series with different HE. Lower panel: time series with an HE of 0.97 (peak value in the precuneus of a subject with high LSAS scores); Upper panel: time-series with an HE of 0.58 (lower value in the precuneus of a subject with low LSAS scores).

Fig. 2. Significant cluster for the linear regression in which BFNE (upper panel) and LSAS (lower panel) were the independent variable and the HE the dependent one ($p < 0.01$; cluster size > 180 µl). Warm colors indicate positive correlations. PCUN: precuneus; PCC/PCUN: posterior cingulate/precuneus; IPS: inferior parietal lobule; PHyp: parahippocampal gyrus.

Fig. 3. Scatter plots for the significant clusters showed in Table 1 and in Fig. 2. PCUN: precuneus; PCC/PCUN: posterior cingulate/precuneus, IPS: inferior pariteal sulcus, PHyp: parahypocamapal gyrus. *X*-axis: mean HE in the cluster. *Y*-axis: LSAS or BFNE score. The plots are for illustrative purposes only; the *r* values for each correlation are presented in Table 1.

Fig. 4. Conjunction analysis showing significant overlap between the linear regression for BFNE and LSAS. Yellow: areas in which LSAS predicts HE; Blue: areas in which BFNE predicts HE; Green: areas of overlap ($p < 0.01$; cluster size > 180 µl).

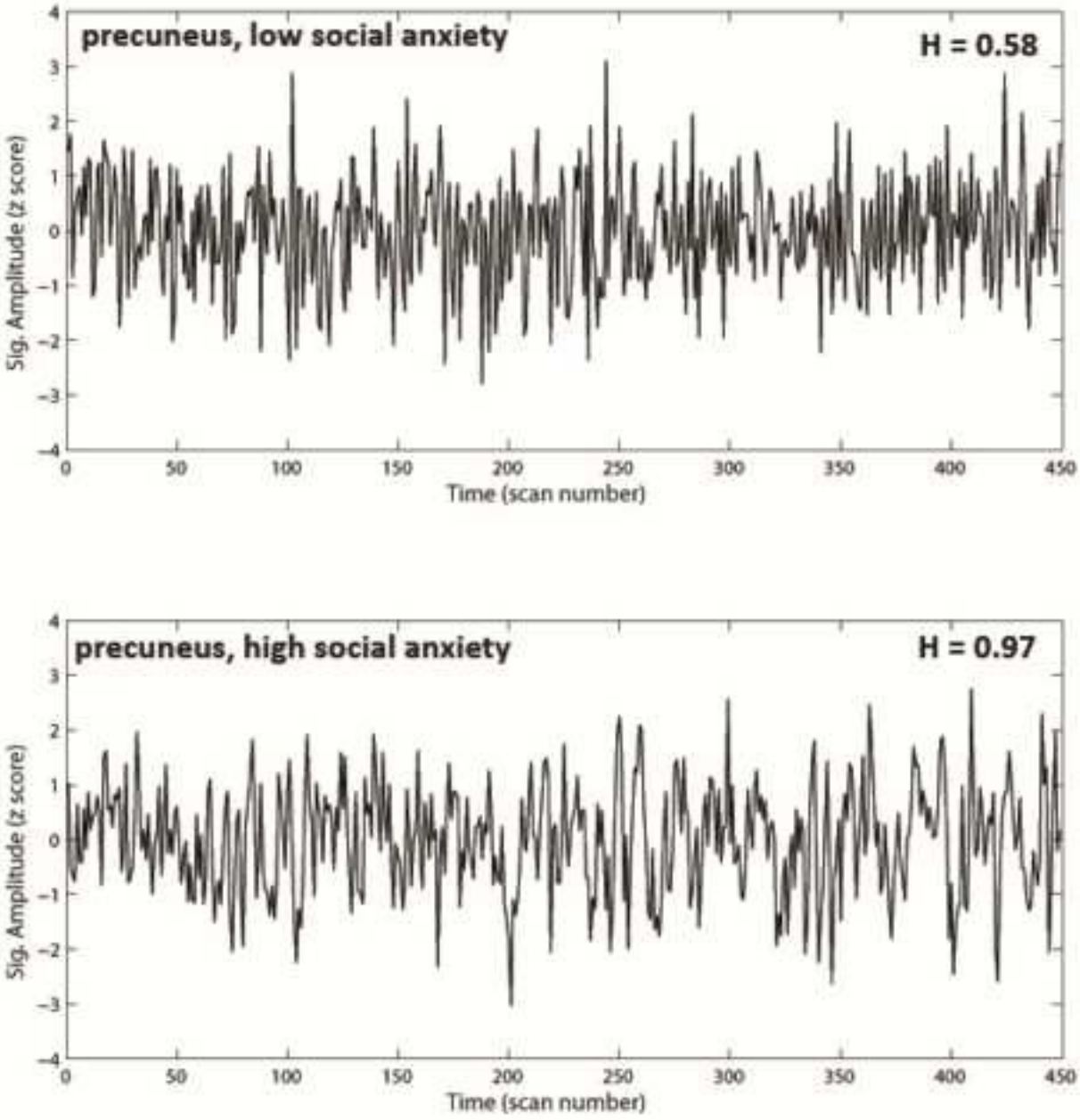
Fig. 5. Significant cluster for the linear regression in which LSAS were the independent variable and the fALFF values the dependent one ($p < 0.01$; cluster size > 180 µl). Warm colors indicate positive correlations. PCC/PCUN: posterior cingulate/precuneus; PHyp: parahippocampal gyrus.

Scale	Region	Hemisphere	BA	Center of mass			Peak			Volume (microliters)	R (peak value)	Strength of correlation	alpha
BFNE				**x**	**y**	**z**	**x**	**y**	**z**				
	PCC/PCUN	L	23/30	-7.1	-56	14	-8	-58	9	252	0.53619026	high	0.008
LSAS													
	PCC	R	7	12.9	-73	37	14	-76	41	533	0.56524331	high	> 0.0005
	IPS	L	40	-51.2	-38	45	-53	-40	44	238	0.55127126	high	0.014
	IPS	R	7	25.3	-53	46	26	-52	45	235	0.58025856	high	0.014
	PHyp	R	30	22.3	-51	7.9	24	-51	8	229	0.56471232	high	0.018
	PCUN	L	7	-15	-66	41	-12	-66	40	212	0.52896125	high	0.046

Scale	Region	Hemisphere	BA	Center of mass			Peak			Volume (microliters)	R (peak value)	Strenght of correlation	alpha
LSAS				**x**	**y**	**z**	**x**	**y**	**z**				
	PCC/PCUN	R	7	15.8	-68	32	12	-76	43	312	0.66**	high	0.001
	PHyp	L	30	21.3	-49	9.5	20	-54	12	240	0.60**	high	0.013

1. **We want to** test the hypothesis that brain spontaneous activity at rest is modulated by trait social anxiety in healthy individuals
2. We evaluate whether the Hurst Exponent (HE), an index of complexity of time series, is modulated by Social Anxiety as measured by Liebowitz Social Anxiety Scale (LSAS) and of Brief Fear of Negative Evaluation (BFNE).
3. We use fractional Amplitude of Low Frequency Fluctuations (fALFF) as an independent measure of resting state activity to have an independent validation of our data
4. LSAS and BFNE linearly predict the HE value in the precuneus and in posterior cingulate regions which are relevant in emotional processing, and are affected in anxiety disorders. fALFF analysis produces consistent results.
5. Since this relationship is obtained at rest we suggest that social anxiety is a trait psychological condition that shapes the brain even in absence of any social exposure.

Figure 1



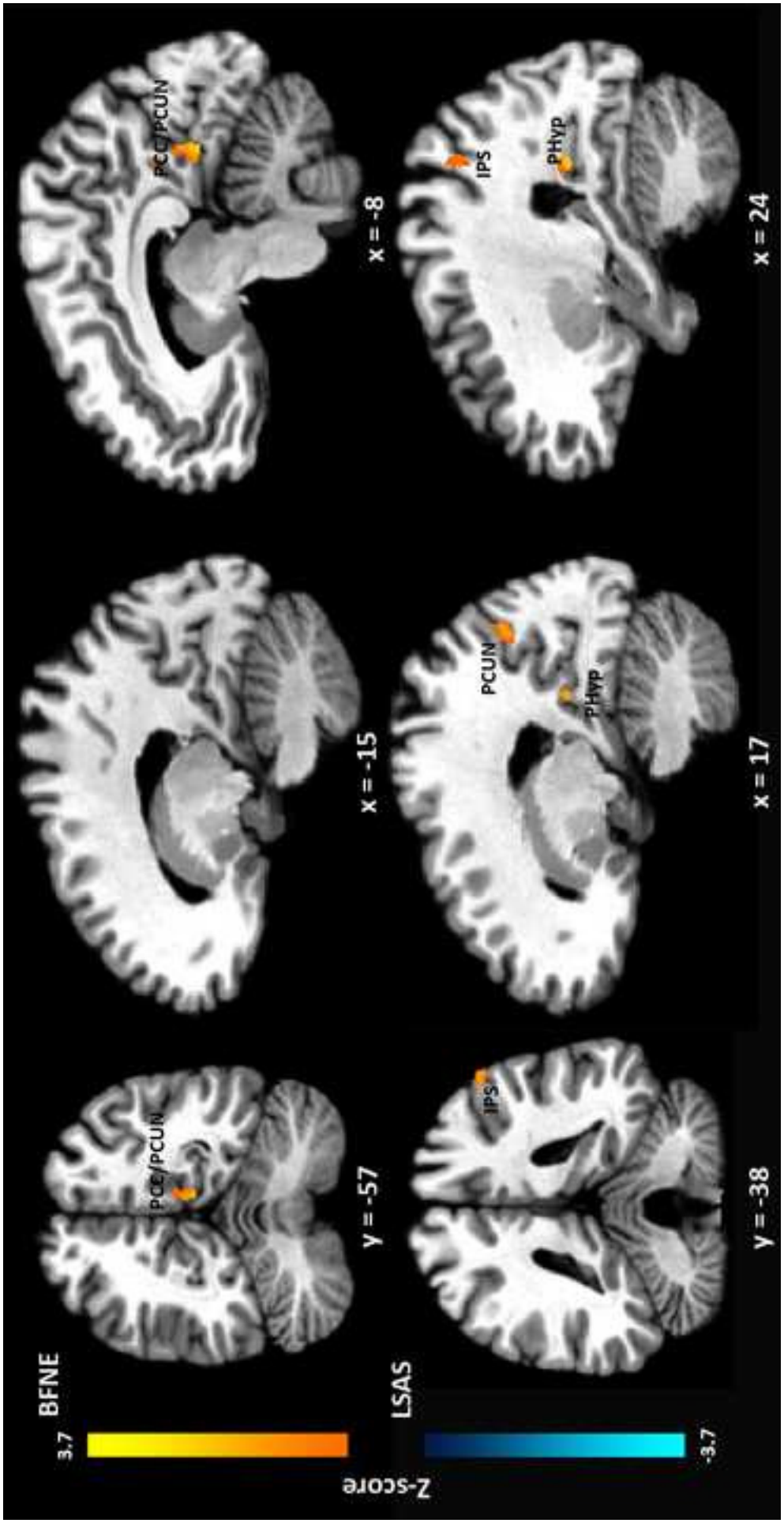
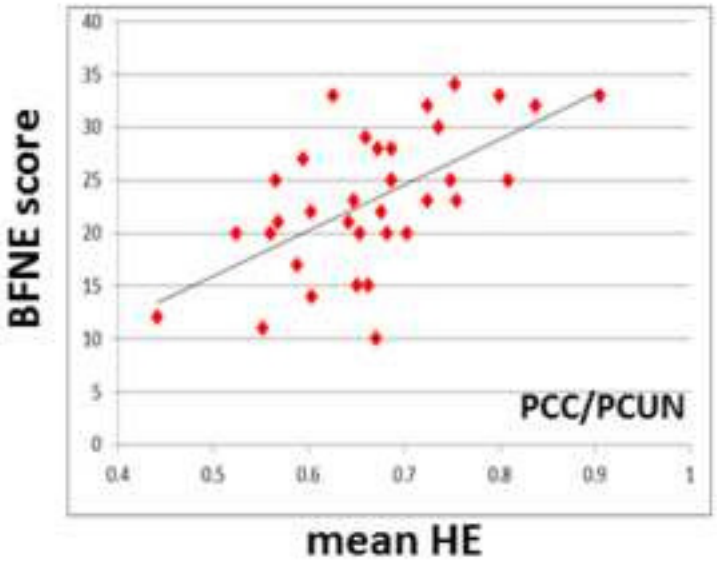

BFNE
LSAS
Z-score
3.7
-3.7
PCC/PCUN
IPS
PCUN
PHyp
x = -8
x = -15
x = 17
x = 24
y = -57
y = -38

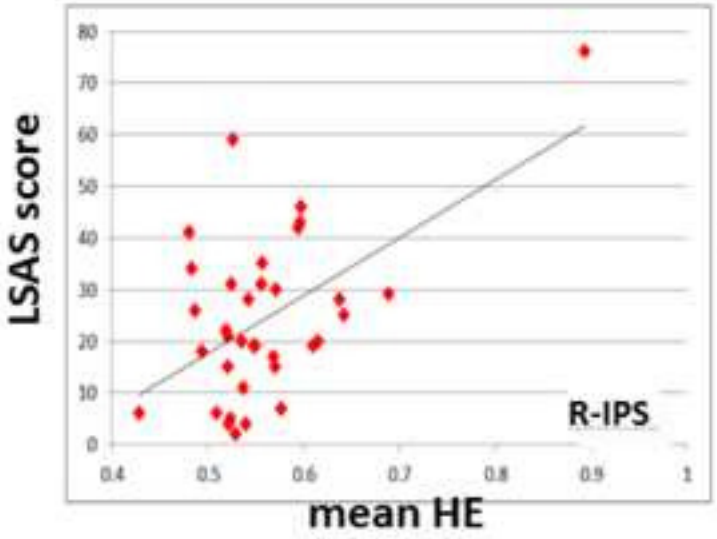
Figure 2

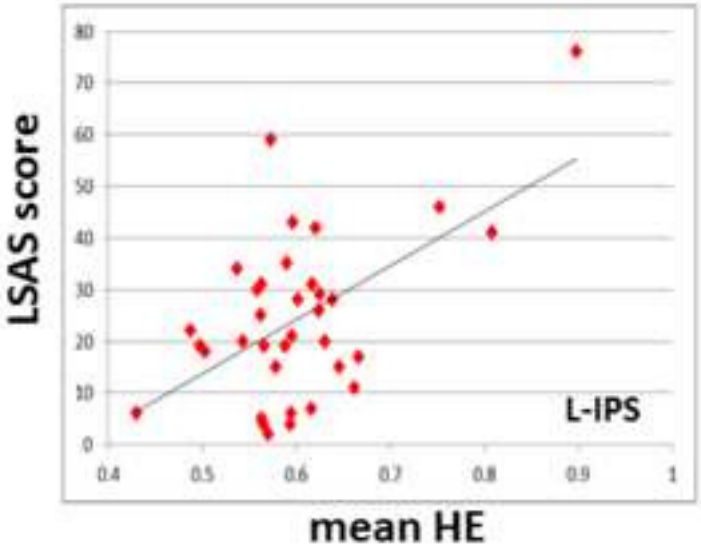
Figure 3

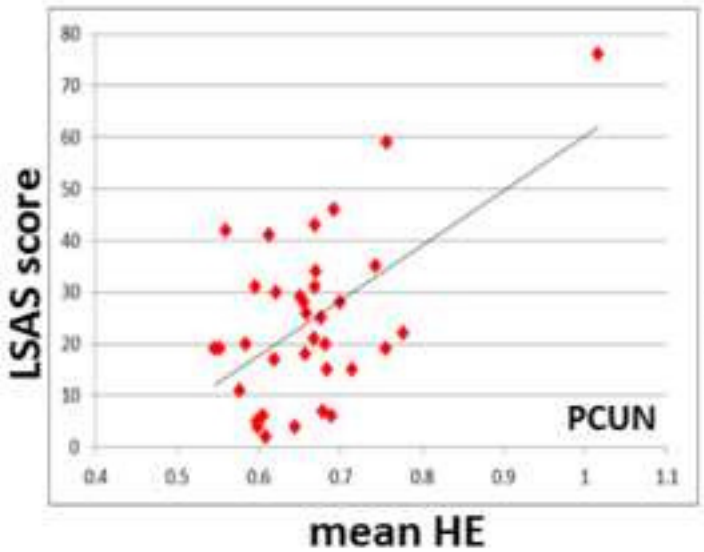
BFNE

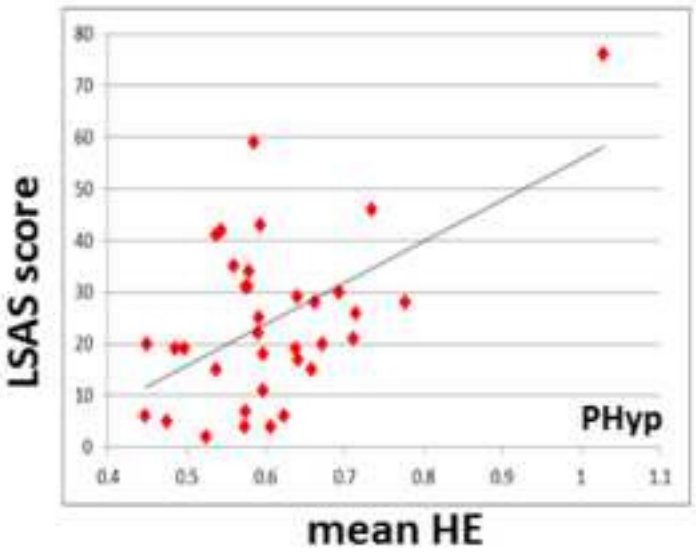


LSAS









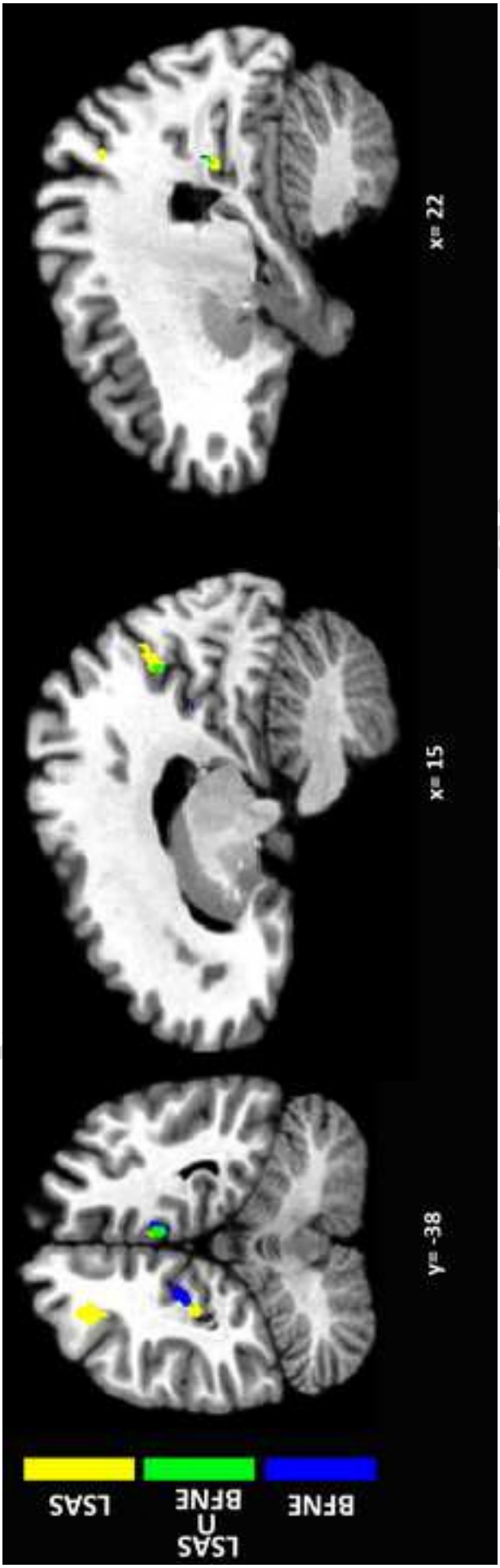


Figure 4

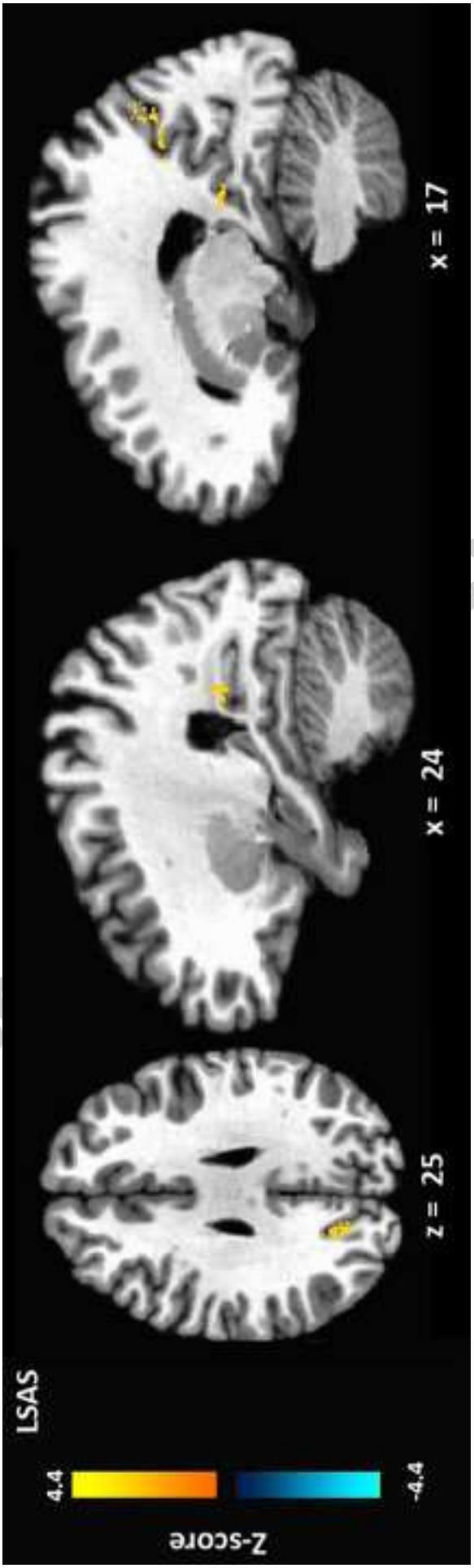


Figure 5