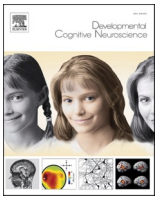
Developmental Cognitive Neuroscience 44 (2020) 100804

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: www.elsevier.com/locate/dcn



OFC and its connectivity with amygdala as predictors for future social anxiety in adolescents

Yu Mao [a,b], Xinian Zuo [c,**], Cody Ding [b,d,*], Jiang Qiu [a,b,*]

[a] Key Laboratory of Cognition and Personality (SWU), Ministry of Education, Chongqing, 400715, China
[b] Department of Psychology, Southwest University, Chongqing, 400715, China
[c] Institute of Psychology, CAS, Beijing, China
[d] Educational Psychology, University of Missouri-St. Louis, United States

ARTICLE INFO

Keywords:
Social anxiety
Attention bias
OFC
Amygdala

ABSTRACT

Social anxiety is a common problem that usually emerges at puberty, during which great developmental changes occur both in the brain and mental state. However, little is known about the influence of social anxiety on adolescents' brain and behavior. The present study investigated the neural basis of social anxiety using voxel-based morphometry (VBM) and functional connectivity analysis. Then we investigated whether social anxiety is associated with attention bias. Furthermore, we investigated the neural basis of this association. Finally, longitudinal data was used to test if these biomarkers could predict social anxiety. The results indicated that social anxiety is positively associated with the grey matter volume (GMV) of orbital-frontal cortex (OFC), and the functional connectivity (FC) of OFC-amygdala. Mediation analysis revealed that the relationship between social anxiety and attention avoidance is partly mediated by the FC of OFC-amygdala. Finally, the present study demonstrated a close relationship between FC of the OFC-amygdala, the GMV of the OFC and the individual's social anxiety one year later. The present study suggested the aberrant structure of OFC and its connectivity with amygdala as the neural underpinning of social anxiety, which might serve as a compensatory mechanism to decrease attention avoidance and promote effective emotion regulation.

1. Introduction

Social anxiety refers to feelings of discomfort in a wide variety of social situations, such as public speaking, interacting with an interviewer, or coping with strangers. Generally, individuals with high social anxiety exhibit exaggerated somatic symptoms, such as headaches, cold sweats and gastrointestinal discomfort, which may lead to social avoidance (March et al., 1997). Social anxiety is a common problem that usually emerges in the teenage years, during which great developmental changes occur both in the brain and mental state, and is often accompanied by a high risk of mental illness (Paus et al., 2008). Notably, the incidence rate of social anxiety disorder among adolescents has increased in recent years (Social and Threat, 2009). In sum, these studies support that early adolescence is a crucial time period for individuals with excessive social anxiety. However, little is known about the neural and cognitive basis of social anxiety in adolescents. The present study begins to resolve this issue by exploring the structural and functional basis of individual differences in social anxiety with a large group of adolescents.

Converging evidence supports the critical role of the amygdala in the perception of emotional stimuli, the processing of social signals, and the response to threats (LaBar and LeDoux, 1996; LeDoux et al., 1988; Phelps and LeDoux, 2005; Prater et al., 2013). For example, a patient with social anxiety disorder exhibited exaggerated amygdala reactivity to social cues of threat in an emotion perception task (Prater et al., 2013). In addition to the amygdala, irregular brain volume of the prefrontal cortex (including ACC, OFC, VMPFC) is also widely reported to be associated with social anxiety (Mueller et al., 2013; Shang et al., 2014; Talati et al., 2013). It is well confirmed that the prefrontal region, especially the OFC and the ventromedial prefrontal cortex (vmPFC), play crucial roles in the regulation of negative affect and fear response (Brust, 2007; Kalisch et al., 2006; Kringelbach and Rolls, 2004), considering the strong structural connections between the prefrontal cortex and the amygdala (Bechara et al., 2000; Phillips et al., 2008).

* Corresponding authors at: Department of Psychology, Southwest University, Chongqing, 400715, China.
** Corresponding author.
E-mail addresses: zuoxn@psych.ac.cn (X. Zuo), codydinge@foxmail.com (C. Ding), qiuj318@swu.edu.cn (J. Qiu).

https://doi.org/10.1016/j.dcn.2020.100804
Received 14 January 2020; Received in revised form 1 May 2020; Accepted 5 June 2020
Available online 8 June 2020

Neurocognitive models of fear modulation emphasize top-down regulation of prefrontal regions toward the amygdala (Phelps and LeDoux, 2005; Williams et al., 2006). Following this logic, aberrant structural or functional connectivity of amygdala-prefrontal may prompt the inefficient down-regulation of anxiety responses (Banks et al., 2007; Kim and Whalen, 2009; Phan et al., 2009). Consequently, a prominent hypothesis predicts social anxiety might associated with the abnormal structure or function of frontal-limbic system.

From the cognitive processing perspective, anxiety in individuals is characterized by the attention biases toward threat stimuli (Beck et al., 1985).The particular form of inappropriate processing has been confirmed to be crucial in the etiology and maintenance of emotional disorders (Roy et al., 2008). Numerous studies suggest that there is a robust association between social anxiety and attention bias, However, the relationship between social anxiety and attention bias still remains controversial (Phan et al., 2006; Sharpe et al., 2015; Vassilopoulos, 2005; Waters et al., 2004). Some studies have shown that anxious individuals pay more attention to negative stimuli (Roy et al., 2008; Telzer et al., 2008; Vassilopoulos, 2005), whereas other studies produce opposite results suggesting that anxious individuals exert attentional bias away from negative stimuli (Chen et al., 2002; Mansell et al., 1999). A study by Vassilopoulos indicated that anxious individual tends to direct attention toward threat stimuli at a 200 ms presentation duration and then away from these stimuli at 500 ms (Vassilopoulos, 2005). Cognitive neuroscience studies have shown that the amygdala is involved in attentional bias toward threat (Cisler and Koster, 2010; El Khoury-Malhame et al., 2011). For example, functional connectivity between the amygdala and ACC is negatively correlated with attention bias toward fearful faces (Carlson et al., 2013). Social anxiety is associated with attention bias, which relied on the amygdala's function. For some people, social anxiety improves as they get older, although for others it doesn't go away on its own. Thus far, plenty of studies have investigated the neural basis of social anxiety. Nonetheless, there remains a lack of research focused on social anxiety during the most crucial developmental period—adolescence. Therefore, it is of great significance to investigate the neural and psychological feature of social anxiety and integrate all of that information into a neurocognitive model of social anxiety. Firstly, the current study applied VBM and functional connectivity to investigate the neural basis of social anxiety in a large group of adolescents. Secondly, considering the controversial relationship between attention bias and anxiety, we adopted a dot probe task to explore whether social anxiety was associated with attention bias. Furthermore, we attempted to explore the neural basis of the connection between social anxiety and attention bias in order to obtain a deeper understanding of social anxiety and its underlying mechanisms. Finally, a longitudinal method was used in the present study to determine if the neural basis of social anxiety could predict the social anxiety of an individual one year later. Compared with cross-sectional studies, longitudinal studies increase statistical power, and can be used to predict behavior in the future. Drawing upon findings from previous neuroimaging studies, we hypothesized that social anxiety might be associated with the GMV of the brain regions involved in emotion regulation (e.g., especially the OFC) and the FC between these regions and the amygdala, as previous studies suggested the defect in frontal-limbic circuits in anxiety disorder (Krain et al., 2008). Based on the self-focused model of social anxiety (Clark and Wells, 1995; Mellings and Alden, 2000), we hypothesized that people with high social anxiety would demonstrate attention avoidance when shown images of angry faces.

2. Method

2.1. Participants

This study was conducted as part of the Chinese Color Nest Project (Chinese Color Nest Project: Growing up in China). In total, we collected structural and functional MRI scans of 192 healthy right-handed adolescents who were recruited from Chao Yang primary school and Chao Yang middle school. Subjects with a history of neurological or psychiatric diseases or substance abuse were excluded at the beginning. 148 participants completed the behavioral measures (44 participants were excluded for missing one or more answers of the questionnaire). One year later, 66 participants completed the behavior measures. The investigation was conducted in accordance with Helsinki Declaration. All of the subjects completed the MRI scan. Before the MRI scanning, they were informed of the procedure of the experiment, and signed a consent form. The present study was approved by the Research Project Ethical Review Application Form, Faculty of Psychology. Written informed consent was obtained from teachers (rate 100 %), parents (rate 100 %), and participants (rate 100 %).

2.2. MRI data acquisition

The magnetic resonance imaging (MRI) scans were obtained by a 3-T Siemens Magnetom Trio scanner (Siemens Medical, Erlangen, Germany). High-resolutionT1-weighted anatomical images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time =1900 ms, echo time =3.02 ms, inversion time =900 ms, flip angle = 8°; slices = 176; slice thickness = 1.0 mm; resolution matrix = 256 × 256; voxel size = 1 × 1×1 mm^3). The scanning time of a resting state MRI was 7 min 45 s, using gradient-echoplanar imaging (EPI) sequence with the following parameters: slice = 38, repetition time (TR)/echo time (TE) = 2500/30 ms, flip angle = 80°, field of view (FOV) = 216 mm × 216 mm, and thickness/slice gap = 3/0.33 mm, voxel size 3 × 3 × 3 mm^3.

2.3. Dot probe task

Participants completed the experiment outside of the MRI scanner. Eprime 2.0 software (https://pstnet.com/products/e-prime/) was used to control the presentation of stimuli and to record response accuracy and response time. The dot probe task was designed according to MacLeod (MacLeod et al., 1986). At the beginning of the task, there was a fixation cross presented for 500 ms on the screen, followed by a pair of faces for 500 ms, after which the dots appeared, then the dots disappeared. The participants were then asked to identify whether the small dots were arranged horizontally or vertically by pressing the associated key (see Fig. 1). Before the real experiment started, participants were given five practice trials to familiarize themselves with the procedure. The task contained 6 conditions: 3 emotion face pairs (neutral and happy, NH, neutral and sad, NS, neutral and angry, NA) x 2 probe locations (in the location of the emotional face or the neutral face) and was comprised of 2blocks of 130 trails (NH 44 trails, NS 44 trails, NA 42 trails), with a short break between the blocks. Attention bias scores were calculated as follows:

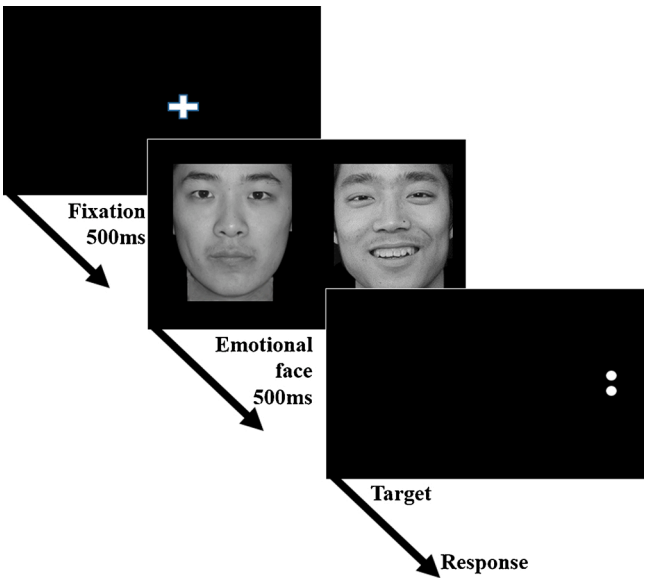


Fig. 1. Illustration of the Dot probe task. At the begging of the task, there was a fixation cross presented for 500 ms in the screen, then followed by a pair of emotional faces for 500 ms, after which the target appeared, then the participants need to identify whether the dots were arranged horizontal or vertical by pressing the particular key.

Attentional bias score = 1/2[(RpLe - RpRe) + (LpRe - LpLe)]

R = right positon; L = left position; p = probe; e = emotional face. In this equation, RpLe represents the mean reaction time when the probe is in the right position and the emotional face is in the left position, and so on. This equation calculates the "attention capturing" quality of emotional faces by subtracting the mean probe detection times for probes appearing in the same position as the emotional face from the mean probe detection times for probes appearing in a different position than the emotional face (Gotlib et al., 2004). Positive bias scores represent the allocation of attention toward the emotional face relative to matched neutral faces, and negative bias scores represent the allocation of attention away from emotional face relative to matched neutral faces, that is attention avoidance.

2.4. Assessment of individual social anxiety

Social anxiety was assessed by the multidimensional anxiety scale for children (MASC), which was designed by March in 1997 (March et al., 1997) and has been widely used in childhood anxiety research. MASC is a useful adjunct to the diagnosis of anxiety disorders. The whole scale contains 39 items and measures four main parts of children's anxiety (Physical symptoms, Harm avoidance, Social anxiety, and Separation anxiety). Self-reporting measures consisted of a 4-item Likert-type scale to describe the degree of each item, with responses ranging from "almost never" to "often". The Cronbach's alpha of the scale was 0.905 in this sample.

2.5. Preprocessing of MRI data

The structural MRI data were processed using Statistical Parametric Mapping software (SPM8;Wellcome Department of Cognitive Neurology, London, UK (www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB 7.8 (Math Works Inc., Natick, MA, USA). MRI scans were displayed in SPM8 to screen for artifacts or gross anatomical abnormalities. The reorientation of the images was manually set to the posterior commissure for better registration. Then, a new segment was implied to segment the images into grey matter, white matter, and cerebrospinal fluid in SPM8. We then performed Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) in SPM8 for registration, normalization, and modulation (Ashburner, 2007). To ensure that regional differences in the absolute amount of grey matter were conserved, the image intensity of each voxel was modulated by the Jacobian determinants. Then, the registered images were transformed to the Montreal Neurological Institute (MNI) space. Finally, the normalized modulated images (grey and white matter images) were smoothed with an 8 mm full-width at half-maximum (FWHM) Gaussian kernel to increase the signal-to-noise ratio.

Resting-state fMRI data was preprocessed by data processing assistant for resting-state fMRI (DPARSF) software (http://www.restfmri.net/forum/DPARSF) (Yan and Zang, 2010). The first 10 volumes of the functional images were excluded to ensure signal equilibrium and participants' adaptation to their immediate environment. Thus, the remaining 174 images were included for further analysis. The preprocessing procedure was as follows: slice timing, head motion correction, and spatial normalization to a standard template. Then all the nuisance variables (global mean signal, white matter, cerebrospinal fluid, and 24 motion parameters for head movement) were regressed out to avoid the potential impact of physiological artifacts. All images were spatially normalized to the MNI template and resampled into 3-mm cubic voxels, followed by spatial smoothing (6 mm FWHM). Subsequently, the smoothed data were filtered by a band pass filter (0.01–0.1 Hz). 24 subjects were excluded maximal motion between volumes in each direction >3 mm, and rotation about each axis >3°, or displaced frames >20 % in the scrubbing procedure.

2.6. Voxel-based morphometry analysis

Statistical analyses of grey matter volume (GMV) data were performed using SPM8. In the whole-brain analyses, multiple linear regression was used to identify regions where the GMV was associated with individual differences in social anxiety. The social anxiety scores were used as the variable of interest in these analyses. Age, sex, and whole brain volume were included as covariates in the regression model to control for possible confounding variables. We also applied explicit masking using the population-specific masking toolbox in SPM8 to restrict the search volume within grey matter (http://www.cs.ucl.ac.uk/staff/g.ridgway/masking/). This approach was used instead of absolute or relative threshold masking so as to reduce the risk of false negatives caused by overly restrictive masking, in which potentially interesting voxels are excluded from the statistical analysis (Ridgway et al., 2009). The results were corrected by family-wise error (FWE) correction ($p < 0.05$).

2.7. Functional connectivity analysis

Functional connectivity was investigated using a region of interest (ROI) based method performed in the Resting-State fMRI Data Analysis Toolkit (REST) software package (Song et al., 2011). The VBM results were used as ROI in the present analysis (center at -13.5, 58.5, -19.5). The functional connectivity map was computed through correlating the average time series of the seed region and the time series of other voxels in the whole brain. The resulting correlation coefficient map was then converted into a z-map by Fisher's r-to-z transformation to improve the normality. Subsequently, multiple regression analysis was performed to examine whether there was a correlation between individual social anxiety and resting state functional connectivity (RSFC) of the OFC. Age and sex were included as regressors of no interest. Previous studies suggested the OFC and amygdala were structural connected through the uncinate fasciculus (Von Der Heide et al., 2013), and the abnormal modulation of OFC on amygdala was reported to be associated with anxiety related symptom (Gold et al., 2015; Hahn et al., 2011), which

was involved in regulating anxiety during threat exposure (Diekhof et al., 2011). Thus, the connectivity between OFC and amygdala is of particular interest in this study. We conduct small volume correction (SVC) on the FC results ($P < 0.05$). The masks of amygdala were generated based on the AAL template (Tzourio-Mazoyer et al., 2002)

2.8. Mediation analysis

To test whether the FC of the OFC-amygdala could explain the relationship between attention bias and social anxiety, we performed a mediation analysis. A mediating variable (M) is a variable that is part of the causal pathway by which an independent variable (X) affects a dependent variable (Y). Mediation analyses were conducted using the indirect macro designed for SPSS (Preacher and Hayes, 2008). In the current study, X is the social anxiety, Y is the attention bias, and M is the FC of the OFC-amygdala. Age and sex were used as covariates in the model. This macro uses bootstrapped sampling to estimate the indirect mediation effect. In this analysis, 2000 bootstrapped samples were drawn, and bias corrected 95 % bootstrap confidence intervals (CIs) were reported. CIs that do not include zero indicate a significant indirect effect of the independent variable on the dependent variable through the mediators (Preacher and Hayes, 2008).

2.9. Prediction analysis

To test the robustness of the brain-behavior relationship, we performed a machine-learning method named linear support vector regression (SVR) and leave one out cross-validation procedure (Supekar et al., 2013). Social anxiety was taken as the dependent variable and the GMV of OFC and the FC between OFC and amygdala were taken as independent variables in the linear regression algorithm. The $r_{(predicted, observed)}$ was estimated by leave one out cross-validation, and represent the prediction accuracy of the independent variable.

3. Results

3.1. Descriptive statistics

The demographic data and behavioral results are shown in Table 1 and Fig. 2. Social anxiety was significantly correlated with age ($r = 0.295$, $p = 0.001$), and no gender difference of social anxiety was found in the present study ($t = 0.166$, $p = 0.462$). There were significant positive relationship between social anxiety and somatic symptoms ($r = 0.555$, $p < 0.001$). We also found that social anxiety was negatively correlated with attention bias ($r = -0.239$, $p = 0.03$), indicating that adolescents with higher social anxiety showed increased attention avoidance to an angry face. In the next section of the paper, the attention bias is equal to the attention score of angry face. In addition, there were significant association between social anxiety of Time 1 and Time 2 ($r = 0.288$ $p = 0.02$).

3.2. Correlations between GMV and social anxiety

After correcting for age, sex, and global grey matter volumes, social anxiety was correlated with the GMV of the OFC (MNI coordinate: -13.5, 58.5, -19.5; $t = 4.7$; Cluster size = 621; $p < 0.001$) and corrected for multiple comparisons at the cluster-level of $p < 0.05$ with Family Wise Error correction (See Fig. 3). Considering the age span (7–18 years) of the sample, we divided the sample into 2 groups to test if social anxiety was still correlated with the GMV of the OFC. The results indicated that there were significant correlations between social anxiety and the GMV of the OFC in these 2 groups. (see supplementary information, Fig S1)

Table 1
Demographic data.

	Time 1 (n = 148)			Time 2 (n = 66)		
Measure	Mean	SD	Range	Mean	SD	Range
Social anxiety	8.73	6.61	0–26	7.94	7.12	0–23
Physical symptom	6.62	6.03	0–21	4.73	5.72	0–25
Harm avoidance	14.41	4.75	3–25	13.88	5.26	0–26
Separation anxiety	6.11	4.60	0–18	5.80	4.32	0–23

Note: SD = standard deviation.

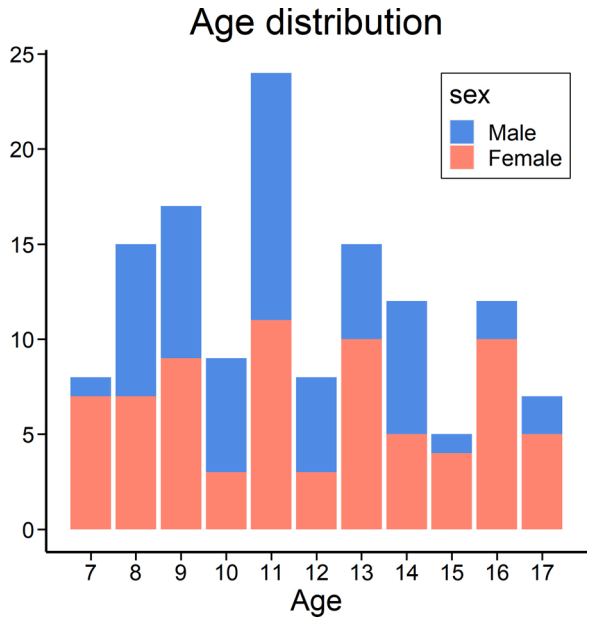


Fig. 2. The distribution of the age.

3.3. Correlations between RSFC and social anxiety

We examined brain regions that showed significant correlations between the social anxiety and the strength of FC with the OFC. The results supported previous hypotheses that social anxiety is positively correlated with the FC between the OFC and the amygdala (MNI coordinate: 21, 6, -18; $t = 4.9$; Cluster size = 11; $p < 0.001$) and corrected for multiple comparisons at the cluster-level of $p < 0.05$ with SVC (See Fig. 4). Considering the age span (7–18 years) of the sample, we divided the sample into 2 groups to test if social anxiety is still correlated with the FC between the OFC and the amygdala. The results indicated that there were significant correlations between social anxiety and the FC between OFC and amygdala in 2 groups. (see supplementary information Fig S2)

3.4. Mediation results

Indirect mediation effects can be interpreted as the strength of the relationship between social anxiety and attention bias when accounting for mediating pathways. Social anxiety is negatively associated with attention bias. FC of the OFC-amygdala was positively correlated with social anxiety ($r = 0.364$, $p = 0.002$) and attention bias ($r = 0.269$, $p = 0.02$). Further mediation analysis indicated that FC between the OFC and the amygdala mediate the relationship between social anxiety and attention bias. The results showed a significant and indirect effect between social anxiety and attention bias, CI [2.7074, 3.951], through the FC of the OFC-amygdala (see Fig. 5)

3.5. Prediction of future social anxiety

The regression model was applied to investigate whether the structural and functional results could predict future social anxiety. The results indicated a close relationship between future social anxiety and the FC between the OFC-amygdala and the GMV of OFC ($r_{(predicted,}$

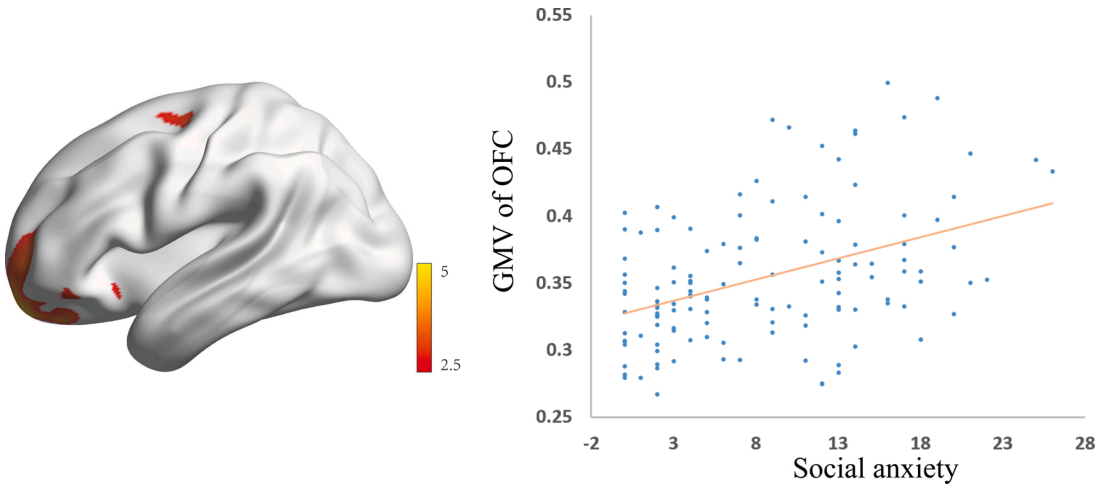


Fig. 3. The GMV of OFC is positively correlated with social anxiety and the scatterplot in the right depicted the relationship between social anxiety and mean GMV of OFC. For visualization purposes, we used a relatively less stringent yet accepted thresholding criteria, with a height threshold of $p < 0.005$.

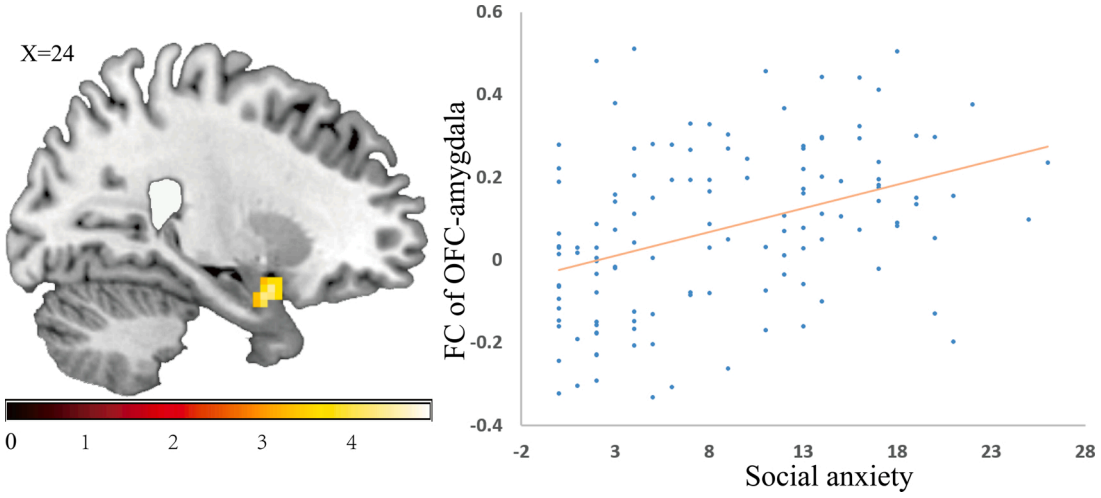


Fig. 4. The FC of OFC-Amygdala is positively correlated with social anxiety and the scatterplot in the right depicted the relationship between social anxiety and the FC of OFC-Amygdala. For visualization purposes, we used a relatively less stringent yet accepted thresholding criteria, with a height threshold of $p < 0.005$.

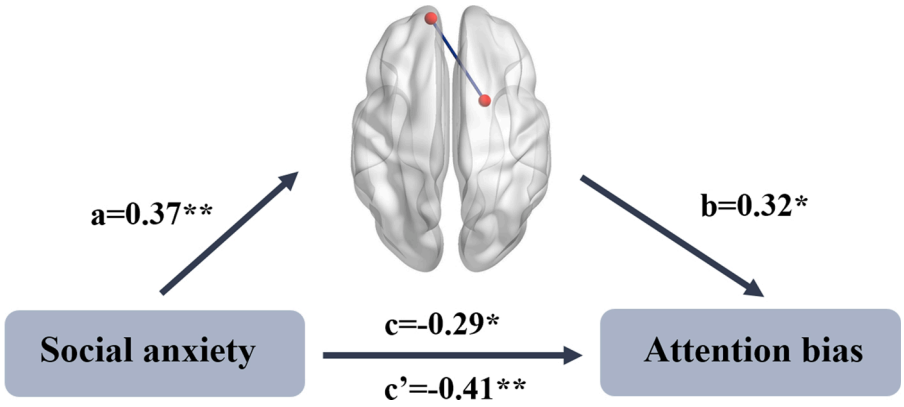


Fig. 5. The mediation resultsshowed that the FC of OFC-Amygdala partly mediated the association between social anxiety and attention avoidance. * $p < 0.05$; ** $p < 0.01$.

$_{observed)} = 0.301$, $p = 0.02$, see Fig. 6).

4. Discussion

Behavior results indicated that social anxiety is associated with physical symptoms (such as trembling, tachycardia, etc). MRI results indicated that social anxiety is positively correlated with GMV of the left OFC. This is supported by previous studies that found anxiety is associated with disrupted functioning of the OFC (Grachev and Apkarian, 2000; Phan et al., 2009; Roppongi et al., 2010). The OFC is widely

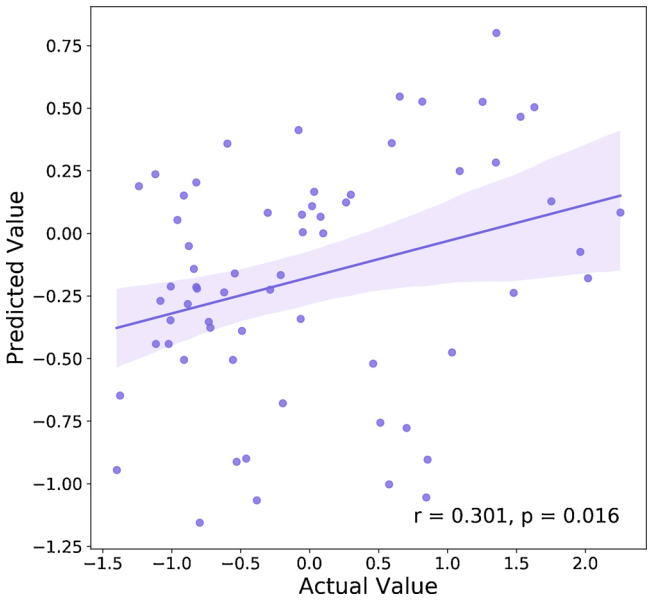


Fig. 6. The correlation between the actual value and predicted value of social anxiety.

reported to be involved in controlling emotional responses (Izquierdo et al., 2004; Kringelbach and Rolls, 2004; O'Doherty et al., 2003), including evaluating the negative emotion state and mediating the response toward negative stimuli (Elliott et al., 2000; O'Doherty et al., 2001). For example, when faced with a stressful situation, such as public speaking, patients with social anxiety disorder show higher OFC activation compared with the healthy controls. This confirmed that the perspective of patients with social anxiety disorder needs more involvement of the OFC to regulate fear response (Lorberbaum et al., 2004; Simpson et al., 2001; Tillfors et al., 2002). Additionally, social anxiety is significantly associated with FC of the OFC-amygdala. Aberrant FC of the OFC-amygdala is reported both in rest and task fMRI studies (Liao et al., 2010; Sladky et al., 2013). As the most critical node of the limbic system, the amygdala is crucial for imbuing percepts with affective significance, especially for frightening or dangerous environmental stimuli (Amaral and Price, 1984; LeDoux, 2000). Regulation of the amygdala has been shown to be essential for emotional processing in the extended limbic system. A growing body of fundamental studies indicated that there are strong anatomical connections between the OFC and the amygdala (Ghashghaei and Barbas, 2002; Stein et al., 2007), which supports the top-down modulation of prefrontal regions toward the amygdala during fear regulation (Phelps and LeDoux, 2005). In sum, social anxiety is characterized by hyperactivity of fear-processing circuits toward negative or threat cues (Labuschagne et al., 2012; Phan et al., 2006). On the basis of the structural and functional results, social anxiety is positively correlated with the GMV of the OFC, and the FC of the OFC-amygdala, which aligns with the fact that individuals with higher levels of social anxiety may experience more pressure, embarrassment, and frustration, thus they might more frequently invoke the OFC to regulate the amygdala's response toward negative emotion. The prediction analysis supports the key role of the OFC and its connectivity with the amygdala in social anxiety.

The results showed that social anxiety is negatively correlated with the attention bias score of an angry face, which was in accordance with previous studies in which people with mild social anxiety tend to avoid negative faces in dot probe tasks (Mansell et al., 1999; Pishyar et al., 2004; Watkins, 1997). It is well documented that compared with an external stimulus, people with social phobia might attribute more attention to themselves. This self-focused processing style allows them to selectively allocate attention away from potential stressors, which gradually develops into a coping strategy for constant anxiety (Wells and Matthews, 1994).With respect to recent studies linking attentional avoidance to emotional regulation strategies (Koole, 2009; Werner et al., 2011), we investigated the relationship between attentional avoidance and coping style in a sample of adults. The results indicated that attentional avoidance is positively associated with avoidant coping (This result came from another study of the lab. The paper is still in preparation). Thus, the present study might indicate that people with high social anxiety may not be able to regulate negative affect due to an unavailability of other cognitive coping resources (Bar-Haim et al., 2007; Mogg and Bradley, 1998; van der Doef, 1992).

In the present study, higher FC of the OFC-amygdala is associated with lower attention avoidance of threat stimuli. Further analysis indicated that the relationship between social anxiety and attention avoidance is partly mediated by the FC of the OFC-amygdala. Considering the role of the OFC-amygdala in threat processing and emotion regulation, it's reasonable to infer that stronger FC of the OFC-amygdala could decrease the tendency of attention avoidance when facing negative stimuli, thus facilitating effective emotion regulation. Together, all of the above results provide evidence for the idea that during the time of growth, adolescents with higher social anxiety develop a compensatory neuro-mechanism (higher FC of the OFC-amygdala) to cope with anxiety-arousing stimuli. Stronger FC of the OFC-amygdala can slightly decrease the tendency of attention avoidance when faced with negative stimuli, thus facilitating effective emotion regulation.

5. Conclusion

Humans are social beings and regular socializing is needed to keep ourselves healthy and lively. Thus, it is necessary to focus on the neural and cognitive mechanism of adolescents' social anxiety and explore potential interventions to alleviate it. Since there is significant association between social anxiety and attention bias, we can infer that attention bias modification (ABM) might be an effective intervention to alleviate adolescents' social anxiety. The present study also indicated the OFC and its connection with amygdala as the vital neural underpinnings for social anxiety. Considering the mediation role for the FC of OFC-amygdala in the relationship between social anxiety and attention bias, it might be used as a target in neurobiological training for social anxiety.

Declaration of Competing Interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Acknowledgements

This study funded by the Innovative Research Project for Postgraduate Student of Chongqing (CYB19102). National Natural Science Foundation of China (31800947; 31470981; 31571137; 31500885; 31600878; 31771231), Project of the National Defense Science and Technology Innovation Special Zone, Chang Jiang Scholars Program, National Outstanding Young People Plan, the Program for the Top Young Talents by Chongqing, the Fundamental Research Funds for the Central Universities (SWU1609177), Natural Science Foundation of Chongqing (cstc2015jcyjA10106), Fok Ying Tung Education Foundation (151023), the Research Program Funds of the Collaborative Innovation Center of Assessment toward Basic Education Quality at Beijing Normal University.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2020.100804.

References

Amaral, D.G., Price, J., 1984. Amygdalo-cortical projections in the monkey (Macaca fascicularis). J. Comp. Neurol. 230 (4), 465–496.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. Neuroimage 38 (1), 95–113.

Banks, S.J., Eddy, K.T., Angstadt, M., Nathan, P.J., Phan, K.L., 2007. Amygdala–frontal connectivity during emotion regulation. Soc. Cogn. Affect. Neurosci. 2 (4), 303–312.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M.J., Van Ijzendoorn, M. H., 2007. Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. Psychol. Bull. 133 (1), 1.

Bechara, A., Damasio, H., Damasio, A.R., 2000. Emotion, decision making and the orbitofrontal cortex. Cereb. Cortex 10 (3), 295–307.

Beck, A., Emery, G., Greenberg, R., 1985. Anxiety and Phobias: A Cognitive Approach. Basic Books, New York.

Brust, J.C., 2007. The human frontal lobes: functions and disorders. LWW.

Carlson, J.M., Cha, J., Mujica-Parodi, L.R., 2013. Functional and structural amygdala–anterior cingulate connectivity correlates with attentional bias to masked fearful faces. Cortex 49 (9), 2595–2600.

Chen, Y., Ehlers, A., Clark, D., Mansell, W., 2002. Patients with generalized social phobia direct their attention away from faces. Behav. Res. Ther. 40 (6), 677–687.

Cisler, J.M., Koster, E.H., 2010. Mechanisms of attentional biases towards threat in anxiety disorders: an integrative review. Clin. Psychol. Rev. 30 (2), 203–216.

Clark, D.M., Wells, A., 1995. A cognitive model of social phobia. Social phobia: Diagnosis, assessment, and treatment 41 (68), 00022–00023.

Diekhof, E.K., Geier, K., Falkai, P., Gruber, O.J.N., 2011. Fear is only as deep as the mind allows: a coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect. Neuroimage 58 (1), 275–285.

El Khoury-Malhame, M., Reynaud, E., Soriano, A., Michael, K., Salgado-Pineda, P., Zendjidjian, X., et al., 2011. Amygdala activity correlates with attentional bias in PTSD. Neuropsychologia 49 (7), 1969–1973.

Elliott, R., Dolan, R.J., Frith, C.D., 2000. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cereb. Cortex 10 (3), 308–317.

Ghashghaei, H.T., Barbas, H., 2002. Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. Neuroscience 115 (4), 1261–1279.

Gold, A.L., Morey, R.A., McCarthy, G.J.Bp., 2015. Amygdala–prefrontal cortex functional connectivity during threat-induced anxiety and goal distraction. Biol. Psychiatry 77 (4), 394–403.

Gotlib, I.H., Krasnoperova, E., Yue, D.N., Joormann, J., 2004. Attentional biases for negative interpersonal stimuli in clinical depression. J. Abnorm. Psychol. 113 (1), 127.

Grachev, I., Apkarian, A., 2000. Anxiety in healthy humans is associated with orbital frontal chemistry. Mol. Psychiatry 5 (5), 482.

Hahn, A., Stein, P., Windischberger, C., Weissenbacher, A., Spindelegger, C., Moser, E., et al., 2011. Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. Neuroimage 56 (3), 881–889.

Izquierdo, A., Suda, R.K., Murray, E.A., 2004. Bilateral orbital prefrontal cortex lesions in rhesus monkeys disrupt choices guided by both reward value and reward contingency. J. Neurosci. 24 (34), 7540–7548.

Kalisch, R., Korenfeld, E., Stephan, K.E., Weiskopf, N., Seymour, B., Dolan, R.J., 2006. Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. J. Neurosci. 26 (37), 9503–9511.

Kim, M.J., Whalen, P.J., 2009. The structural integrity of an amygdala–prefrontal pathway predicts trait anxiety. J. Neurosci. 29 (37), 11614–11618.

Koole, S.L., 2009. The psychology of emotion regulation: an integrative review. Cogn. Emot. 23 (1), 4–41.

Krain, A.L., Gotimer, K., Hefton, S., Ernst, M., Castellanos, F.X., Pine, D.S., Milham, M.P. J.Bp., 2008. A functional magnetic resonance imaging investigation of uncertainty in adolescents with anxiety disorders. Biol. Psychiatry 63 (6), 563–568.

Kringelbach, M.L., Rolls, E.T., 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog. Neurobiol. 72 (5), 341–372.

LaBar, K.S., LeDoux, J.E., 1996. Partial disruption of fear conditioning in rats with unilateral amygdala damage: correspondence with unilateral temporal lobectomy in humans. Behav. Neurosci. 110 (5), 991.

Labuschagne, I., Phan, K.L., Wood, A., Angstadt, M., Chua, P., Heinrichs, M., et al., 2012. Medial frontal hyperactivity to sad faces in generalized social anxiety disorder and modulation by oxytocin. Int. J. Neuropsychopharmacol. 15 (7), 883–896. https://doi.org/10.1017/S1461145711001489.

LeDoux, J.E., 2000. Emotion circuits in the brain. Annu. Rev. Neurosci. 23 (1), 155–184.

LeDoux, J.E., Iwata, J., Cicchetti, P., Reis, D.J., 1988. Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. J. Neurosci. 8 (7), 2517–2529.

Liao, W., Qiu, C., Gentili, C., Walter, M., Pan, Z., Ding, J., et al., 2010. Altered effective connectivity network of the amygdala in social anxiety disorder: a resting-state FMRI study. PLoS One 5 (12), e15238.

Lorberbaum, J.P., Kose, S., Johnson, M.R., Arana, G.W., Sullivan, L.K., Hamner, M.B., et al., 2004. Neural correlates of speech anticipatory anxiety in generalized social phobia. Neuroreport 15 (18), 2701–2705.

MacLeod, C., Mathews, A., Tata, P., 1986. Attentional bias in emotional disorders. J. Abnorm. Psychol. 95 (1), 15.

Mansell, W., Clark, D.M., Ehlers, A., Chen, Y.-P., 1999. Social anxiety and attention away from emotional faces. Cogn. Emot. 13 (6), 673–690.

March, J.S., Parker, J.D., Sullivan, K., Stallings, P., Conners, C.K., 1997. The Multidimensional Anxiety Scale for Children (MASC): factor structure, reliability, and validity. J. Am. Acad. Child Adolesc. Psychiatry 36 (4), 554–565.

Mellings, T.M., Alden, L.E., 2000. Cognitive processes in social anxiety: the effects of self-focus, rumination and anticipatory processing. Behav. Res. Ther. 38 (3), 243–257.

Mogg, K., Bradley, B.P., 1998. A cognitive-motivational analysis of anxiety. Behav. Res. Ther. 36 (9), 809–848.

Mueller, S.C., Aouidad, A., Gorodetsky, E., Goldman, D., Pine, D.S., Ernst, M., 2013. Gray matter volume in adolescent anxiety: an impact of the brain-derived neurotrophic factor Val66Met polymorphism? J. Am. Acad. Child Adolesc. Psychiatry 52 (2), 184–195.

O'Doherty, J., Kringelbach, M.L., Rolls, E.T., Hornak, J., Andrews, C., 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat. Neurosci. 4 (1), 95.

O'Doherty, J., Winston, J., Critchley, H., Perrett, D., Burt, D.M., Dolan, R.J., 2003. Beauty in a smile: the role of medial orbitofrontal cortex in facial attractiveness. Neuropsychologia 41 (2), 147–155.

Paus, T., Keshavan, M., Giedd, J.N., 2008. Why do many psychiatric disorders emerge during adolescence? Nat. Rev. Neurosci. 9 (12), 947.

Phan, K.L., Orlichenko, A., Boyd, E., Angstadt, M., Coccaro, E.F., Liberzon, I., Arfanakis, K., 2009. Preliminary evidence of white matter abnormality in the uncinate fasciculus in generalized social anxiety disorder. Biol. Psychiatry 66 (7), 691–694.

Phelps, E.A., LeDoux, J.E., 2005. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 48 (2), 175–187.

Phillips, M.L., Ladouceur, C.D., Drevets, W.C., 2008. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol. Psychiatry 13 (9), 833.

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. Biol. Psychiatry 59 (5), 424–429.

Pishyar, R., Harris, L.M., Menzies, R.G., 2004. Attentional bias for words and faces in social anxiety. Anxiety Stress Coping 17 (1), 23–36.

Prater, K.E., Hosanagar, A., Klumpp, H., Angstadt, M., Luan Phan, K., 2013. Aberrant amygdala–frontal cortex connectivity during perception of fearful faces and at rest in generalized social anxiety disorder. Depress. Anxiety 30 (3), 234–241.

Preacher, K.J., Hayes, A.F., 2008. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav. Res. Methods 40 (3), 879–891.

Ridgway, G.R., Omar, R., Ourselin, S., Hill, D.L., Warren, J.D., Fox, N.C., 2009. Issues with threshold masking in voxel-based morphometry of atrophied brains. Neuroimage 44 (1), 99–111.

Roppongi, T., Nakamura, M., Asami, T., Hayano, F., Otsuka, T., Uehara, K., et al., 2010. Posterior orbitofrontal sulcogyral pattern associated with orbitofrontal cortex volume reduction and anxiety trait in panic disorder. Psychiatry Clin. Neurosci. 64 (3), 318–326.

Roy, A.K., Vasa, R.A., Bruck, M., Mogg, K., Bradley, B.P., Sweeney, M., et al., 2008. Attention bias toward threat in pediatric anxiety disorders. J. Am. Acad. Child Adolesc. Psychiatry 47 (10), 1189–1196.

Shang, J., Fu, Y., Ren, Z., Zhang, T., Du, M., Gong, Q., et al., 2014. The common traits of the ACC and PFC in anxiety disorders in the DSM-5: meta-analysis of voxel-based morphometry studies. PLoS One 9 (3), e93432.

Sharpe, L., Dudeney, J., Sharpe, L., Hunt, C., 2015. Attentional bias towards threatening stimuli in children with anxiety : a Clinical Psychology Review Attentional bias towards threatening stimuli in children with anxiety : a meta-analysis. Clin. Psychol. Rev. 40 (October), 66–75. https://doi.org/10.1016/j.cpr.2015.05.007.

Simpson, J.R., Drevets, W.C., Snyder, A.Z., Gusnard, D.A., Raichle, M.E., 2001. Emotion-induced changes in human medial prefrontal cortex: II. During anticipatory anxiety. Proc. Natl. Acad. Sci. 98 (2), 688–693.

Sladky, R., Höflich, A., Küblböck, M., Kraus, C., Baldinger, P., Moser, E., et al., 2013. Disrupted effective connectivity between the amygdala and orbitofrontal cortex in social anxiety disorder during emotion discrimination revealed by dynamic causal modeling for fMRI. Cereb. Cortex 25 (4), 895–903.

Social, C.R.D., Threat, P., 2009. Neural bases of social anxiety disorder. Arch. Gen. Psychiatry 66 (2), 170–180.

Song, X.-W., Dong, Z.-Y., Long, X.-Y., Li, S.-F., Zuo, X.-N., Zhu, C.-Z., et al., 2011. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PLoS One 6 (9), e25031.

Stein, J.L., Wiedholz, L.M., Bassett, D.S., Weinberger, D.R., Zink, C.F., Mattay, V.S., Meyer-Lindenberg, A., 2007. A validated network of effective amygdala connectivity. Neuroimage 36 (3), 736–745.

Supekar, K., Swigart, A.G., Tenison, C., Jolles, D.D., Rosenberg-Lee, M., Fuchs, L., Menon, V., 2013. Neural predictors of individual differences in response to math tutoring in primary-grade school children. Proc. Natl. Acad. Sci. 110 (20), 8230–8235.

Talati, A., Pantazatos, S.P., Schneier, F.R., Weissman, M.M., Hirsch, J., 2013. Gray matter abnormalities in social anxiety disorder: primary, replication, and specificity studies. Biol. Psychiatry 73 (1), 75–84.

Tillfors, M., Furmark, T., Marteinsdottir, I., Fredrikson, M., 2002. Cerebral blood flow during anticipation of public speaking in social phobia: a PET study. Biol. Psychiatry 52 (11), 1113–1119.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15 (1), 273–289.

van der Doef, P., 1992. Cognitive psychology and emotional disorders. Kind en Adolesc. 13 (4), 166.
Vassilopoulos, S.P., 2005. Social anxiety and the vigilance-avoidance pattern of attentional processing. Behav. Cognit. Psychotherapy 33 (1), 13–24. https://doi.org/10.1017/S1352465804001730.
Von Der Heide, R.J., Skipper, L.M., Klobusicky, E., Olson, I.R., 2013. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain 136 (6), 1692–1707.
Watkins, E., 1997. Attention and emotion: a clinical perspective. Behav. Res. Ther. 3 (35), 277–278.
Waters, A.M., Lipp, O.V., Spence, S.H., 2004. Attentional bias toward fear-related stimuli: an investigation with nonselected children and adults and children with anxiety disorders. J. Exp. Child Psychol. 89, 320–337. https://doi.org/10.1016/j.jecp.2004.06.003.
Wells, A., Matthews, G., 1994. Self-consciousness and cognitive failures as predictors of coping in stressful episodes. Cogn. Emot. 8 (3), 279–295. https://doi.org/10.1080/02699939408408942.
Werner, K.H., Goldin, P.R., Ball, T.M., Heimberg, R.G., Gross, J.J., 2011. Assessing emotion regulation in social anxiety disorder: the emotion regulation interview. J. Psychopathol. Behav. Assess. 33 (3), 346–354.
Williams, L.M., Kemp, A.H., Felmingham, K., Barton, M., Olivieri, G., Peduto, A., et al., 2006. Trauma modulates amygdala and medial prefrontal responses to consciously attended fear. Neuroimage 29 (2), 347–357.
Yan, C., Zang, Y., 2010. DPARSF: a MATLAB toolbox for" pipeline" data analysis of resting-state fMRI. Front. Syst. Neurosci. 4, 13.