Altered executive control network resting-state connectivity in social anxiety disorder

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ABSTRACT

Objectives: Research into the neural basis of social anxiety disorder (SAD) suggests alterations in prefrontal networks, which may in turn disrupt regulation of the limbic system. Better understanding of the disturbed interface between these networks may improve current pathogenic models of this disorder. Methods: Applying group independent component analysis (ICA) to recordings of fMRI resting-state, connectivity in the executive control network was studied in 18 patients with SAD and 15 age- and sex-matched healthy controls. Results: Results revealed a dissociation within the left executive control network, with SAD patients showing decreased connectivity of the orbitofrontal gyrus and increased connectivity of the middle frontal gyrus compared to healthy controls. In a subsequent seed-based functional connectivity analysis, patients with SAD displayed increased connectivity between the left orbitofrontal gyrus and the left amygdala. Conclusions: Findings suggest that hypo-connectivity in the executive control network and hyper-connectivity between the orbitofrontal cortex and the amygdala may reflect a disturbance in the balance between top-down and bottom-up control processes, potentially contributing to the development of SAD.

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Introduction

Individuals with social anxiety disorder (SAD) have a persistent fear or anxiety of social or performance situations in which negative evaluation may occur (APA 2013). They feel scrutinised by others and are concerned that they might embarrass themselves. Social situations are avoided or endured with intense and persistent fear. SAD leads to impairments in social and occupational functioning and patients are at increased risk for other psychiatric conditions (Stein and Stein 2008). With a lifetime prevalence of 6.1%, SAD is one of the most prevalent psychiatric disorders in both the developed and developing world (Stein et al. 2010).

Studies on the neural basis of SAD have identified altered activations in different limbic and cortical areas including amygdala, insula, anterior cingulate, prefrontal and parietal regions (for review see Freitas-Ferrari et al. 2010; Fouche et al. 2013; Bruhl et al. 2014). Hyperactivation in limbic areas of the so called “fear circuitry” has repeatedly been found in patients with SAD (Etkin and Wager 2007; Hattingh et al. 2012). For instance, compared to healthy controls (HC), patients with SAD showed increased activity in the amygdala during the presentation of neutral or angry faces (Birbaumer et al. 1998; Stein et al. 2002) or during fear learning (Pejic et al. 2013). These findings suggest that hyper-responsivity in limbic areas of the fear circuitry might be one key mechanism explaining why patients with SAD experience excessive fear in social situations.

Anxiety disorders have furthermore been associated with a general disturbance of higher cortical networks involved in attentional control. For example, individuals with high trait anxiety may have altered activations in prefrontal regions during situations requiring attentional control even in the absence of threatening stimuli (Bishop 2009; Basten et al. 2011). A similar pattern has been observed in SAD, in that patients displayed decreased recruitment of prefrontal regions when
processing emotional non fear-related stimuli and during a task requiring cognitive control (Bruhl et al. 2011, 2013).

Recent studies have employed a network approach in studying the neural basis of SAD. Using independent component analysis of fMRI resting-state data, activation differences (both increased and decreased connectivity) were found in the default mode, dorsal attention, central executive and the salience networks between patients with SAD and HC (Liao et al. 2010a). Other studies have found altered connectivity of frontal and occipital regions (Ding et al. 2011), the default mode network (Gentili et al. 2009), increased prefrontal-subcortical connectivity (Arnold et al. 2014) and increased resting perfusion in the frontal cortex and the cerebellum using single photon emission computed tomography (SPECT; Warwick et al. 2008). Furthermore, studies suggest that the temporal synchrony of activations in the dorsolateral prefrontal cortex and the inferior parietal gyrus might be reduced in SAD, potentially affecting cognitive control functioning (Qiu et al. 2011).

Neurocognitive models of anxiety have therefore proposed a shift in attentional network function in patients with anxiety disorders, with decreased function of the fronto-parietal executive control system reflecting disturbed top-down control of the limbic system, and increased function of the cingulo-opercular and the right ventral attention system, systems associated with the bottom-up influence of salient stimuli (Sylvester et al. 2012). In trying to understand the role of top-down and bottom-up processes in the pathogenesis of anxiety disorders, the connection between the amygdala and the prefrontal cortex has received particular interest (Bishop 2007). In SAD, some studies suggest that functional connectivity between the prefrontal cortex and the amygdala is reduced (Hahn et al. 2011), while others found increased connectivity between the amygdala and parts of the frontal cortex (Liao et al. 2010b). Thus, it remains to be elucidated whether SAD is associated with a diminished functional link between the amygdala and the frontal cortex, presumably mirroring disturbed top-down processes, or rather with a hypersensitive cortico-limbic interaction leading to hyper-responsivity of the frontal cortex to bottom-up signals from the amygdala.

Against this background, in the present study the function of the executive control network in SAD was studied in a two-step design for the first time combining singular approaches used in previous studies: first, it was investigated which parts of the executive control network show differences in connectivity between patients with SAD and HC by applying group independent component analysis to resting-state fMRI data. Previous resting-state fMRI studies and studies comparing task-based fMRI data on executive control and resting-state data confirmed that the executive control network can reliably be detected in the resting-state (Damoiseaux et al. 2006; Smith et al. 2009; Shirer et al. 2012). In a second step, results from the group independent component analysis were complemented with a seed-based functional connectivity approach to explore the identified alterations in the executive control network in SAD and their possibly disturbed link with the limbic system, particularly the amygdala. We hypothesised that patients with SAD would show altered functional connectivity in different parts of the executive control network depending on the connectivity of the respective part of the network with the limbic system.

Methods
Participants
All patients (n = 18) met DSM-IV-TR criteria for a primary diagnosis of SAD (APA 2000) on the Structured Clinical Interview for the Diagnosis of Axis I Disorders – Patient Version (SCID-I/P; First et al. 1998). Patients were required to have no history of psychosis or other significant psychiatric comorbidity, and to be free of psychotropic medication. Not being right-handed, inadequate understanding of the goals and implications of study participation and unwillingness to provide consent after being presented with the study information, were exclusion criteria for all participants. Healthy control research participants (n = 18) were recruited from university campuses and the community, and were age- and sex-matched to the patients. A psychologist or psychiatrist interviewed the participants. Symptoms related to SAD were assessed with the Liebowitz Social Anxiety Scale (LSAS; Liebowitz 1987) and the Blushing Propensity Scale (BPS; Leary and Meadows 1991) (see Table I for demographic and clinical data).

The study protocol and patient information and consent forms were approved by the Institutional Review Boards of the Faculty of Medicine and Health Sciences, University of Stellenbosch, and by the Human Research Ethics Committee of the University of Cape Town, and were carried out in accordance with the Declaration of Helsinki Principles. All participants gave informed written consent to participate after risks and benefits of participation had been fully explained.

Data acquisition
Five minutes of fMRI data was acquired on a 3T Siemens Allegra MRI brain scanner (Siemens, Erlangen, Germany) at the Cape Universities Brain Imaging Centre (CUBIC).
Table I. Demographic and clinical variables.

| Group          | Total sample | SAD        | HC        | Statistical comparisons |
|----------------|--------------|------------|-----------|-------------------------|
| N              | 33           | 18         | 15        | 10                      |
| Sex (male/female) | 14/19        | 7/11       | 7/7       | 2           |
| Age, mean (SD)  | 29.06 (8.49) | 29.56 (8.97) | 28.47 (8.15) | t(31) = 0.36 |
| LSAS, mean (SD) | 62.08 (40.53)| 88.6 (24.82)| 22.3 (22.18) | t(23) = 6.82* |
| BPS, mean (SD)  | 43.86 (14.79)| 53 (9.4)   | 30.67 (10.51) | t(20) = 5.23* |
| Duration of illness, mean years (SD) | na | 20.5 (14.86) | na | na |

This table depicts demographics of participants included in the final analysis; SAD, social anxiety disorder; HC, healthy controls; SD, standard deviation; LSAS, Liebowitz Social Anxiety Scale; BPS, Blushing Propensity Scale; LSAS and BPS clinical measures not available for all participants (LSAS SAD = 15 and HC = 10; BPS SAD = 13 and HC = 9); na, not applicable.

*P < 0.05.

with a four-channel head coil using a gradient echo planar imaging (EPI) T2*-weighted sequence recording 150 volumes consisting of 34 slices (210 × 210 matrix, 210 cm field of view, voxel size 3.3 × 3.3 × 3.0 ms, TR = 2000 ms, TE = 30 ms, flip angle = 90°). Additionally, a high resolution T1*-weighted structural image was acquired from each participant. During the fMRI resting-state recordings participants were asked to lay restful, stay awake and keep their eyes open. Resting-state recordings of two healthy participants could not be completed due to delays during the measurements and thus did not enter further analyses.

**Data preprocessing**

fMRI data preprocessing was performed in a SPM12b (Wellcome Department of Imaging Neuroscience, London, UK) pipeline. Data were slice time corrected, realigned to the first volume and unwarped. Motion parameter files displaying the rotation and translation of the participants head in the scanner were screened for extreme outliers. One healthy participant had to be excluded at this step from the rest of the analysis because of excessive head movement (>2 mm per TR). Images were spatially normalised to the Montreal Neurological Institute (MNI) template brain, resampled to isotropic 2 mm³ voxel and spatially smoothed with an 8-mm full-width at half-maximum Gaussian kernel. ArtRepair-toolbox (Mazaika et al. 2007) was used to correct spiking and motion outliers.

**Statistical analysis**

In order to identify potential aberrant patterns of functional connectivity in the executive control network, functional connectivity resting-state MRI (fcrsMRI) recordings were analysed applying group independent component analysis (ICA) in GIFT toolbox (Calhoun et al. 2001). Independent component analysis is a blind source separation method requiring no explicit model. The median number of components was estimated as 23 using the minimum description length (MDL) algorithm over all subjects. A brain-only mask was built using AFNI 3dAutomask based on the mean functional images (Cox 1996). Independent component estimation was performed using the infomax algorithm, after reduction with principal component analysis. Single-subject individual spatial maps and time courses maps were then GICA type back-reconstructed for all participants and converted to z-scores. Using the ICASSO toolbox, the stability index of the estimated components was validated running the ICA algorithm 15 times. Results were scaled in time courses. For the ICA, the patient and healthy participant groups were merged into one analysis, thus yielding the same component structure for both groups.

In order to distinguish functionally relevant independent components from noise, the independent components were firstly explored by visual inspection. The 23 components (mean components, averaged over all subjects) were displayed in GIFT on a T1 structural template brain, showing positive and negative values, with a threshold of Z > 3. Selection was based on inspection of spatial maps and average power spectra (cf. Allen et al. 2011), whereas criteria included overlap with grey matter, high power in a low frequency range and low power in a high frequency range (>0.1 Hz) and similarity with canonical resting-state networks (Biswal et al. 2010; Allen et al. 2011; Shirer et al. 2012). As a second step, congruence with previously published resting-state network was examined using the AFNI 3dMatch toolbox (Taylor and Saad 2013). For this purpose, correlations were calculated with the resolution matched (AFNI 3dResample) group images of 20 resting-state networks acquired in a multicentre study with 1441 participants (Biswal et al. 2010).

For group comparison of the connectivity in the identified networks between patients with SAD and HC, individual spatial maps were entered into a full factorial second level model with the factor group (SAD and HC) and condition (all selected components) in SPM12b. The interaction “group × condition” revealed regions that showed differences over all selected components between patients with SAD and HC. To verify which
component explained the interaction, a two-sample t-test masked by a thresholded map of the interaction “group × condition” was computed. Group differences in executive control network connectivity were tested using a one-sample t-test between the respective component and baseline ($P < 0.05$, FWE, extent cluster threshold $k = 20$).

To determine whether aberrant patterns of functional executive control network connectivity were associated with disturbances in connections to parts of the limbic system, specifically the amygdala, independent component analysis was complemented by a univariate seed-based functional connectivity analysis. ICA is generally useful at parcelling out functional brain networks without any a priori assumptions about locations of these networks (Beckmann et al. 2005). However, to study a hypothesis of functional connectivity of a specific region with other regions, a seed-based approach is more suitable (Margulies et al. 2010). Generally both analyses should yield similar results (Joel et al. 2011): however, the advantage of a hybrid approach is that general group differences between patients with SAD and HC in the executive control network can be discerned in the initial ICA without any a priori anatomical hypothesis about a specific seed region in this network. In a second step, the identified differences and their potential implication for a disturbed top-down control of the limbic system, specifically the amygdala, can be studied more in a more targeted way applying a seed-based approach.

Using MarsBaR (Brett et al. 2002), region of interest (ROIs) spheres (radius: 4 mm) were built around peak activations in regions that showed aberrant executive control network connectivity in patients with SAD compared to HC. Seed-based functional connectivity analysis was performed in the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon 2012). The CONN toolbox extracted the mean BOLD signal time course of the individual ROIs and corrected for confounding effects of signal in the white matter and in cerebrospinal fluid. A temporal band filter was applied to reduce effects of low frequency drift and high frequency noise (0.008 Hz < band-pass filter < 0.02 Hz). Pearson correlations between the mean time courses of all ROIs were calculated for each ROI and then converted to z-scores using Fisher’s transformation. Differences in ROI to voxel connectivity between patients with SAD and HC were studied in a general linear model with “group” as between subject factor. To study the association between functional connectivity and dimensional scores of SAD, a linear regression model of connectivity and LSAS scores was computed across patients and controls (LSAS scores available for $N = 25$). The main steps of the analysis pipeline are summarised in Figure 1.

If not otherwise specified, results are reported at a significance threshold of $P < 0.05$ (FWE (family-wise error))
corrected). For the left and right amygdala, a small volume correction for the bilateral amygdala was applied based on the mask for this region provided as part of the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al. 2002), given an a priori hypothesis regarding this region.

**Results**

**Estimation of resting-state networks by group independent component analysis**

To identify the executive control network, the whole brain signal was decomposed into 23 components using group independent component analysis. The quality index of all 23 components as examined with the ICASSO algorithm was above 0.95. Out of the 23 components, ten could be classified as intrinsic resting-state networks, 13 did not meet the above defined criteria and were classified as noise. As specified above, correlations with the 23 networks and canonical resting-state networks (Biswal et al. 2010) were computed. This analysis revealed correlation coefficients between $r = 0.3$ and $r = 0.72$ (mean $r = 0.53$) with the components identified as representing intrinsic networks, whereas components classified as noise showed only small correlations (mean $r = 0.08$). Apart from the left and right executive control network, several other independent components such as the dorsal and ventral default model network, the dorsal and ventral salience network, the visuospatial network, the sensorimotor network, the primary visual network and the auditory network were identified. For an overview of the peak activations and surface maps of the respective independent components see Supplementary Table S1 and Figure S1 (available online).

The left executive control network comprised the left inferior parietal gyrus, the left and right middle frontal gyrus as well as medial and orbital parts of the left prefrontal cortex and the cerebellum (Supplementary Figure S1, IC 01, available online). The right part of the executive control network comprised right fronto-parietal regions, the right middle temporal gyrus, the right insula, the cingulate gyrus, the cerebellum and the right inferior parietal lobe.

**Group differences in left executive control network functional connectivity**

The interaction “group × component” at a threshold of $P < 0.001$ (uncorrected) yielded differences between patients with SAD and HC in left fronto-parietal and visual regions, i.e., in the occipital, angular and fusiform gyrus, the cerebellum and left fronto-parietal regions overlapping with what had previously been classified as the left part of the executive control network (Table II). As noted earlier, verification was done computing post-hoc two-sample t-tests for all components masked by the interaction “group × component”. This calculation confirmed group differences in the left executive control network and furthermore suggested effects in the right executive control network, the ventral default mode network and the auditory network (Table III).

A two-sample t-test revealed that within the left executive control network patients with SAD displayed decreased connectivity of the orbitofrontal gyrus, i.e., the orbital part of the left superior frontal gyrus, and increased connectivity of the left middle frontal gyrus (Table IV, Figure 2).

**Seed-based functional connectivity analysis of the left executive control network**

To assess whether the shift in intra-network connectivity found in the left executive control network was associated with disturbed top-down control of limbic structures, the connectivity of the orbitofrontal gyrus (orbital part of the left superior frontal gyrus) and the left middle frontal gyrus was analysed applying a seed-based connectivity approach. Seed-to-voxel analysis revealed increased connectivity between the seed region in the orbitofrontal gyrus (orbital part of the left superior frontal gyrus) and the left amygdala in
patients with SAD (Table V, Figure 3), while decreased connectivity of the seed region in the left middle frontal gyrus with the angular gyrus was found in SAD compared to HC.

In an additional regression analysis across patients and controls ($N = 25$), we tested whether the connectivity between the orbital part of the left superior frontal gyrus and other regions of the brain was related to LSAS scores. Results were not significant, though there was a slight trend for the regression model of functional connectivity between the orbital part of the left superior frontal gyrus and the left amygdala ($-30 \leq x \leq -18$) and LSAS score ($t = 2.08$, $p < 0.05$ (uncorrected); $R = 0.398$, $P < 0.05$; see Supplementary Figure S2 available online). Please note that LSAS scores were not available for all patients and participants (see Table I).

**Discussion**

In the current study, group independent component analysis was applied to resting-state fMRI recordings to study functional connectivity within the executive control network in patients with SAD compared to HC. Patients with SAD showed a dissociation of functional connectivity in the left executive control network with decreased connectivity of the orbitofrontal gyrus and increased connectivity of the middle temporal gyrus. Furthermore, the part of the orbitofrontal gyrus that was less connected within the left executive control network showed increased connectivity with the left amygdala in the patient group.

It is increasingly clear that in anxiety disorders there are not only alterations in networks supporting emotion processing but also in networks supporting higher cognition (Sylvester et al. 2012). These latter networks are anatomically linked to regions of the fear circuitry; however, their function is classically dedicated to higher cognitive processes such as attention, perception or language. Hypoactivation of the medial part of the orbitofrontal cortex with its projections to the amygdala, the hypothalamus, the periaqueductal grey and the hippocampus has been associated with insufficient inhibition of anxiety responses in patients with anxiety disorders (Milad and Rauch 2007). The present finding of diminished connectivity of the orbitofrontal cortex within the executive control network may indicate that dysfunction of this network is related to difficulties in top-down regulation of fear and anxiety in SAD. At the same time, the results indicate a dorsal shift of connectivity in the executive control network towards an increase in connectivity with the middle frontal gyrus in SAD, a region associated with processing of evaluative statements in this disorder (Blair et al. 2008), and is consistent with a previous rs-fMRI work. Increased activation in this part of the attention system might reflect increased attentiveness to salient threatening stimuli (Schwarz et al. 2013) potentially at the expense of disturbed top-down control.

**Table III.** Differences in connectivity in independent components (IC) between patients with SAD and healthy controls (post-hoc tests).

| IC | Network                          | x   | y   | z   | Peak t value | x   | y   | z   | Peak t value |
|----|----------------------------------|-----|-----|-----|--------------|-----|-----|-----|--------------|
| 01 | Left executive control           | -20 | 50  | 2   | 4.73         | -40 | 16  | 46  | 5.66         |
| 02 | Right executive control          | 50  | -60 | 50  | 3.68         | -   | -   | -   | -            |
| 03 | Dorsal default mode              | 0   | -62 | 18  | 4.41         | -   | -   | -   | -            |
| 04 | Ventral default mode             | -   | -   | -   | -            | -   | -   | -   | -            |
| 05 | Dorsal salience                  | -   | -   | -   | -            | -   | -   | -   | -            |
| 06 | Ventral salience                 | -   | -   | -   | -            | -   | -   | -   | -            |
| 07 | Visuospatial                     | -   | -   | -   | -            | -   | -   | -   | -            |
| 08 | Sensorimotor                     | -   | -   | -   | -            | -   | -   | -   | -            |
| 09 | Primary visual                   | -   | -   | -   | -            | -   | -   | -   | -            |
| 10 | Auditory                         | -   | 62  | -38 | 4.76         | -   | 40  | -   | 4.76         |

SAD, social anxiety disorder; HC, healthy controls; Results are reported for $p < 0.001$ (uncorrected, cluster threshold $k = 20$). Post-hoc two-sample $t$-tests were masked by the interaction group x component. Coordinates are reported in Montreal Neurological Institute (MNI) space.

**Table IV.** Differences in functional connectivity in the left executive control network between patients with SAD and healthy controls.

| Region                              | L/R | x   | y   | z   | Cluster size | Peak t-value |
|-------------------------------------|-----|-----|-----|-----|--------------|--------------|
| Orbitofrontal gyrus (superior frontal gyrus, orbital part) | L   | -22 | 48  | 0   | 31           | 5.25         |
| Middle frontal gyrus                | L   | -40 | 16  | 46  | 56           | 5.66         |

SAD, social anxiety disorder; HC, healthy controls. Results are reported for $P < 0.001$ (uncorrected), peak activation are significant for $P < 0.05$ (FWE corrected, cluster threshold $k = 20$), two-sample $t$-tests are masked by the left executive control network as specified in the method section.
It was furthermore observed that the region in the left orbitofrontal cortex that was less connected in patients with SAD showed an increase in connectivity with the left orbitofrontal gyrus compared to healthy controls (HC) ($P < 0.001$, uncorrected, for illustration purposes). Statistics are reported in Table IV. Bar plots represent parameter estimates (beta values) with 95% confidence intervals for the differences in connectivity. * $P < 0.05$ (FWE corrected).

**Table V. Results of seed-based functional connectivity analysis.**

| Region | L/R | $x$ | $y$ | $z$ | Cluster size | Peak $t$ value |
|--------|-----|-----|-----|-----|--------------|----------------|
| Seed region: left orbitofrontal gyrus (superior frontal gyrus, orbital part) | | | | | | |
| Amygdala | L | -24 | 4 | -18 | 21 | 3.89* |
| SAD < HC | | | | | | |
| No cluster surviving threshold | | | | | | |
| Seed region: left middle frontal gyrus | | | | | | |
| SAD > HC | R | 42 | -54 | 24 | 173 | 5.04 |
| No cluster surviving threshold | | | | | | |
| SAD < HC | | | | | | |
| Angular gyrus | | | | | | |

SAD, social anxiety disorder; HC, healthy controls. If not otherwise specified, results are reported at $P < 0.001$ (uncorrected), peak activations are significant at $P < 0.05$ (FWE corrected).

* $P < 0.05$ (FWE small volume corrected for bilateral amygdala).
uncinate fasciculus (Phan et al. 2009) in SAD. However, connectivity studies have so far revealed no consistent pattern, with some reporting reduced connectivity between the amygdala and the prefrontal cortex (Hahn et al. 2011; Prater et al. 2013) and others showing increased functional connectivity (Blair et al. 2008; Danti et al. 2010; Liao et al. 2010a). This inconsistency may reflect different methodological approaches used in these studies (effective connectivity and functional connectivity studies) and the different localisation of regions of interests. An important issue here may be the known functional heterogeneity of the orbitofrontal cortex with unequal connectivity between different parts of the orbitofrontal cortex and the amygdala (Carmichael and Price 1995). In the current study, independent component analysis was used as an initial step to restrict the seed-based connectivity analysis with the amygdala to parts of the orbitofrontal cortex that showed less connectivity within the executive control network and thus are presumably disturbed in their functional integration. Higher connectivity of the amygdala with the orbitofrontal cortex in SAD, as observed here, might reflect stronger bottom-up influences emerging from the amygdala to this part of the orbitofrontal cortex. This finding is underscored by a trend-wise positive correlation of functional connectivity between the orbital part of the left superior frontal gyrus and the left amygdala with dimensional social anxiety scores (LSAS) across patients and controls. This excessive bottom-up influence could be facilitated by reduced integration of the orbitofrontal cortex in the executive control network. Alternatively, the observed increased connectivity between the orbitofrontal cortex and the amygdala might reflect an excessive driving input of this particular part of the orbitofrontal cortex on the activity of the amygdala. This latter notion is supported by a recent study applying dynamic causal modelling during a face processing task, in which a fully functional top-down regulation of the amygdala by the orbitofrontal cortex was observed in healthy participants, while in patients with SAD activity of the amygdala was found to be up-regulated by the orbitofrontal gyrus (Sladky et al. 2013). Higher coupling between the amygdala and the executive control has also been observed in patients with general anxiety disorder (Etkin et al. 2009). Thus, even though in the present study differences in the executive control network were identified in a SAD population only, we would expect that a disturbed link between the executive control network and the amygdala is rather a general marker of anxiety than specific to SAD, which remains to be elucidated in future studies on dimensional markers of anxiety (e.g., trait anxiety) or across different anxiety disorders.

A limitation of this study is that the function of the identified executive control network was not validated in a task-based approach activating regions of the

Figure 3. Amygdala–orbitofrontal gyrus connectivity in patients versus healthy controls. Patients with social anxiety disorder (SAD) showed an increased connectivity between the seed region of interest (ROI) in the left orbitofrontal gyrus (OFG) and the left amygdala (Amy) compared to healthy controls (HC). Statistics are reported in Table V ($P < 0.001$, uncorrected, for illustration purposes). Bar plots represent parameter estimates (beta values) with 95% confidence intervals for the differences in connectivity. * $P < 0.05$ (FWE small volume corrected).
executive control network directly, but was estimated via comparisons with canonical resting-state networks. Furthermore, the independent component analysis was based on a relatively low model order. It is possible that a finer segregation of brain activity into more networks could have provided a more detailed distinction of the executive control network. Also, altered connectivity was only found in the left, but not in the right executive control network. This latter system, comprising right fronto-parietal regions, has primarily been associated with the detection of salient stimuli and potentially noradrenergically controlled alerting function (Corbetta and Shulman 2002) and might thus be overactive in anxiety disorders related to a dysfunction in these dimensions such as panic disorder or posttraumatic stress disorder rather than in SAD (Sylvester et al. 2012). The present sample size is relatively small, though within the range of comparable studies on functional resting-state connectivity in SAD (Liao et al. 2010a, 2010b; Hahn et al. 2011; e.g., Ding et al. 2011; Qiu et al. 2011; Pannekoek et al. 2013; Prater et al. 2013). Due to a lack of statistical power, additional smaller group effects in other networks than the presently evaluated executive control network could thus have remained undetected. Strengths of the current study include using a cohort of SAD patients who were without any clinically significant psychiatric comorbidity and who were not medicated at the time of the scan, given that selective serotonergic reuptake inhibitors (SSRIs), widely prescribed first-line pharmacotherapeutic agents in SAD, have been shown to exert distributed and pervasive effects on functional connectivity in several brain networks (McCabe et al. 2011; Schaefer et al. 2014; Gimenez et al. 2014). Another point to be considered is that resting-state by nature is a relatively uncontrolled experimental approach, and whether participants are asked to keep their eyes open or closed may confound the results. Since some studies on connectivity in SAD instructed participants to keep their eyes open during the recordings as done in our study (Hahn et al. 2011; Arnold et al. 2014), while other studies asked for closed eyes (Liao et al. 2010a; Ding et al. 2011), the comparability of the present study to the latter studies is limited. Studies explicitly investigating the influence of the eyes-open or eyes-closed instruction in a resting-state paradigm, however, identified effects on some networks, but not on the executive control network targeted in the present study (Patriat et al. 2013).

It is uncertain whether deficits in cognitive control are a cause or a consequence of anxiety disorders. However, even if deficits in cognitive control mechanism may not be causal in anxiety disorders, these conditions may be “ameliorated or even prevented” with effective functioning of the executive control system (Cole et al. 2014). There is a clear need for more task-based and resting-state fMRI studies investigating the role of the executive control system in the pathogenesis of anxiety disorders (see Geiger et al. 2014) and its potential malleability in the course of psychotherapy, e.g., by interventions specifically targeting the attentional network (e.g., Hakamata et al. 2010). Further work is needed to understand the genetic and environmental factors associated with alterations in connectivity, and the effects of pharmacological and psychological intervention on connectivity (Dodhia et al. 2014).

In summary, the results of the current study support a model of SAD in which hyper-responsiveness of limbic regions of the fear circuitry, particularly the amygdala, is accompanied by a dysfunction of higher cortical attentional systems as indicated by aberrant patterns of connectivity within the executive control network. The present study adds to the growing number of findings suggesting a key role for disturbed top-down and bottom-up regulation of anxiety in the pathogenesis of SAD.

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Statement of interest

None to declare.

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