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Research report

Intrinsic functional connectivity in social anxiety disorder with and without comorbid attention deficit hyperactivity disorder

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HIGHLIGHTS

- Fusiform cortex hypoconnectivity is unique for whole SAD group.
- Default mode network hypoconnectivity is related with pure SAD.
- Salience network hyperconnectivities are related with comorbid ADHD.

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ABSTRACT

Neuroimaging research about social anxiety disorder (SAD) points to hyperactivity in the fear circuit and altered connectivity between the fear circuit and the intrinsic connectivity networks that modulate it. We investigated intrinsic functional connectivity changes in SAD patients by taking into consideration the commonly overlooked comorbidity of attention deficit hyperactivity disorder (ADHD). We compared intrinsic functional connectivity alterations in 16 patients with pure SAD, 18 patients with SAD and comorbid ADHD and 21 healthy controls using seed-to-voxel functional connectivity analyses. Hypoconnectivity of the right fusiform gyrus with the left lingual gyrus was the unique difference between whole SAD group and healthy controls, while in the pure SAD group the fusiform gyrus displayed hypoconnectivity with the posterior default mode network (DMN) regions. In contrast, ADHD comorbidity was associated with hyperconnectivities of the salience network (SN) with the fusiform cortex and the posterior DMN regions, and hyperconnectivities of the posterior DMN with visual, somatosensory and motor cortices. The dichotomic dissociation of the SAD related functional connectivity changes into hypoconnectivities in the pure SAD group vs hyperconnectivities in the SAD-ADHD group leads also to the question, whether ADHD treatment can be considered an alternative for selected SAD cases.

1. Introduction

Social anxiety disorder (SAD) is a common disorder characterized by persistent and considerable distress in situations of social interaction or performance, in which one might face embarrassment or humiliation (American Psychiatric Association, 1994). A number of studies provided evidence for the genetic basis of the disorder (Hettema et al., 2001), and many others assessing the neuropsychological properties of SAD patients showed an attention bias toward fear inducing stimuli and increased self-focused attention (Becker et al., 2001; Andersson et al., 2006; Spector et al., 2003; Heinrichs and Hofmann, 2001). The neural basis of SAD has been investigated via structural and functional neuroimaging studies aiming to improve the understanding of the disorder's development. The majority of early neuroimaging research on SAD is focused on the activations in task-based functional magnetic resonance imaging (fMRI) studies by comparing negative emotional

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processing to baseline, neutral or positive emotion conditions. In their *meta*-analysis, Etkin and Wager (2007) found that the typical fear circuit (amygdala, insula, inferior frontal gyrus, fusiform gyrus, superior temporal gyrus) is hyperactive in SAD. In contrast to these studies the methods developed for the analysis of the resting state fMRI data allowed the decomposition of the blood oxygen level dependent (BOLD) signal into a set of large-scale functional connectivity networks with specific topologies that can be assigned to some meaningful functional anatomic constructs (Park and Friston, 2013). This paradigm shift based on intrinsic correlations of BOLD signal among various brain areas made it possible to extend the fMRI analyses beyond the limitations of activation analyses under specific task conditions and resulted into a wide range of studies that compared the changes in large-scale intrinsic connectivity networks (ICNs) in various brain disorders including the SAD. This led to new descriptions of the neural basis of SAD. In addition to hyperactivity in the fear circuit, altered connectivity between the fear circuit and large-scale ICNs that might have modulatory effects on it have been reported. Brühl and coworkers (2014a) performed a *meta*-analysis of neuroimaging studies on SAD published between 2007 and 2014 by including functional connectivity studies with task-based and resting state data. While the results supported hyperactivation of the fear circuit including amygdala, insula, anterior cingulate and prefrontal cortex, they further described components of an emotion regulation network comprising dynamic interactions among various nodes of the established ICNs.

Main ICNs investigated in relation with SAD have been default mode network (DMN), central executive network (CEN) and salience network (SN) (Peterson et al., 2014). Liao et al. (2010) reported increased connectivity in the anterior node (dorsomedial prefrontal cortex, dmPFC) but decreased connectivity in the posterior nodes (precuneus and posterior cingulate cortex) of the DMN in SAD patients pointing to the prominent cognitive behavioral role of the DMN in SAD. Decreased coherence in the bilateral angular gyri and the left medial prefrontal cortex reported by Qiu et al. (2011) suggests a functional impairment in self-related mental representations and provides additional support for the role of DMN in SAD pathophysiology. However, Pannekoek et al. (2013) reported no difference between healthy controls and patients with SAD in terms of DMN connectivity, but they reported an increased SN connectivity to the left precuneus and left lateral occipital cortex in SAD, indicating greater inter-network connectivities between DMN and SN. Additionally, Arnold Anteraper et al. (2014) detected increased connectivity between several subcortical regions and DMN nodes (e.g., between the caudate and the medial frontal regions; among the putamen, cingulate cortex and dorsomedial prefrontal cortex) in their study investigating the functional connectivity changes among subcortical seeds involved in emotion processing and ICNs.

The ICN perspective including the within and inter-network connectivity differences is an important one for understanding the pathophysiology of SAD. However, current ICN findings point to a range of inconsistencies among studies. Beyond the methodological differences, the inconsistencies might depend on the selection of patients, as comorbidities such as attention deficit hyperactivity disorder (ADHD) are rather common for SAD. ADHD is a brain disorder marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development (American Psychiatric Association, 1994). However, ADHD comorbidity in SAD has been mostly overlooked, because the majority of studies implemented the Structured Clinical Interview for DSM-IV (SCID), which does not include ADHD diagnostic criteria. On the other hand, studies using tools specific for diagnosing ADHD have yielded childhood ADHD comorbidity rates as high as 60–70% in adults with SAD (Koyuncu et al., 2015a,b). Koyuncu and colleagues (2016) proposed that in some patients, SAD may have developed secondary to childhood ADHD. According to their developmental hypothesis, ADHD symptoms such as inattention, disinhibition and impulsivity cause difficulties in social communication which lead to frequent criticism and warning from the social circle. As a result, feelings of inadequecy and chronic shame develop, and the patient accepts defeat lowering their self-esteem. These lead to the behavioral/cognitive inhibition typical in SAD, and patients begin to overvalue feedback and increase their self monitorization, which may in social settings trigger anxiety attacks (Koyuncu et al., 2016). Nevertheless, there is no clear evidence of a causal relationship between SAD and ADHD, and which one precedes the other.

Intrinsic functional connectivity studies on ADHD showed either hyperconnectivity within DMN (Sidlauskaite et al., 2016) or decreased coherence within the DMN and between the DMN and SN (Castellanos and Aoki, 2016; Posner et al., 2014). Zhao and coworkers (2017) reported a positive SN-DMN inter-connectivity in ADHD, in contrast to the negative correlation between these two networks usually observed in healthy subjects (Zhao et al., 2017). It has been suggested that the maturation of the functional connections between the anterior and posterior DMN and between SN and sensorimotor regions is delayed in ADHD (Choi et al., 2013).

In sum, within the framework of this literature, the DMN and SN seem to be key intrinsic connectivity networks for understanding the neural mechanism underlying SAD and its ADHD comorbidity. Therefore, to contribute to the current knowledge about the neurobiology of SAD, present study aims to develop a new perspective on ADHD comorbidity in SAD by exploring changes within and between two large-scale neurocognitive networks, the DMN and the SN. For this purpose, we studied patients with pure SAD and with comorbid ADHD in comparison to age, gender and education matched healthy controls. To our knowledge, this is the first study investigating the neurobiology of SAD-ADHD comorbidity.

2. Results

From the 34 SAD patients and 22 healthy controls (HC) recruited for the study, one subject from the HC group, for whom the fMRI data exceeded the threshold for mean framewise displacement (FD) of 0.5 mm, was excluded from the study. Hence, the SAD group divided into two sub-groups according to the ADHD module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) consisted of 16 pure SAD (pSAD) and 18 SAD-ADHD cases, and the HC group consisted of 21 subjects.

There were no significant differences between whole SAD and healthy control (HC) groups in terms of age, year of education and gender ratio (Table 1). The demographical characteristics were also analyzed among sub-groups of SAD and HCs. All three groups were found similar with respect to variables mentioned above (Table 2). No significant differences were found between sub-groups of SAD in terms of symptom severity and functioning (all $p > 0.05$) (Table 3). The mean Adult ADHD Self Report Scale (ASRS) score of the SAD-ADHD subgroup was 37.17 ± 8.69 (21–53).

2.1. MRI findings

Seed-to-voxel functional connectivity analyses conducted on the resting state functional MRI (rs-fMRI) data with 20 seeds revealed significant differences among the 3 groups for 6 of the seeds including

Table 1
Group comparisons of demographical data.

	Mean ± sd		Test	*p*
	SAD (N = 34)	HC (N = 21)		
Age	28.15 ± 6.28	27.24 ± 6.39	$t = 0.518$	0.607
Years of education	14.68 ± 2.37	14.90 ± 2.88	$t = -0.320$	0.751
Gender (F/M ratio)	10/24	8/13	$X^2 = 0.445$	0.563

F: female, M: male, sd: standard deviation.

Table 2
Subgroup comparisons of demographical data.

	Mean ± sd			Test	p
	pSAD (N = 16)	SAD-ADHD (N = 18)	HC (N = 21)		
Age	29.56 ± 6.53	26.89 ± 5.94	27.24 ± 6.39	F = 0.901	0.413
Year of education	15.31 ± 1.92	14.11 ± 2.63	14.90 ± 2.88	F = 0.989	0.379
Gender (F/M ratio)	5/11	5/13	8/13	X^2 = 0.491	0.782

F: female, M: male, sd: standard deviation.

Table 3
Subgroup comparisons of clinical data.

	Mean ± sd		Test	p
	pSAD (N = 16)	SAD-ADHD (N = 18)		
Age	29.56 ± 6.53	26.89 ± 5.94	t = 1.250	0.220
Years of education	15.31 ± 1.92	14.11 ± 2.63	t = 1.503	0.143
Gender (F/M ratio)	5/11	5/13	X^2 = 0.049	0.824
HAM-A	7.88 ± 4.26	8.50 ± 4.03	U = 122.5	0.456
HAM-D	4.25 ± 2.05	4.28 ± 1.96	U = 138.5	0.846
Q-LES-Q	50.6 ± 7.80	48.72 ± 7.89	U = 119.5	0.397
GAF	72.50 ± 6.33	75.83 ± 6.70	t = -1.487	0.147
CGI	3.50 ± 0.63	3.67 ± 0.69	U = 125.0	0.465
Sheehan work	5.19 ± 2.26	5.44 ± 2.66	U = 127.5	0.564
Sheehan social life	5.63 ± 2.03	6.00 ± 2.47	U = 126.0	0.530
Sheehan home	3.25 ± 1.84	3.50 ± 1.38	U = 126.5	0.538
LSAS	72.00 ± 15.17	75.11 ± 19.19	t = -0.520	0.607

the left retrosplenial cortex (RSC), left and right precunei, right ventral posterior cingulate cortex (vPCC), left amygdala, and right fusiform gyrus (Tables 4 and 5). In order to visualize the ICN involvement of these seeds, one sample t-tests were conducted on the seed-to-voxel functional connectivity maps of the whole subject group (N = 55). While the left RSC, left and right precunei, and right vPCC seeds produced the typical DMN pattern, the left amygdala seed derived a typical SN map (Fig. 1). As the right fusiform gyrus' functional connectivity map did not match any single resting state network, but a combination of visual networks and dorsal and ventral attention networks, the fusiform connectivity differences among the groups will be handled independent of its ICN involvement.

First of all, the comparison between whole SAD group and the HC revealed significant differences for two seed regions, which are the right fusiform gyrus and the left amygdala. The right fusiform gyrus revealed a significant hypoconnectivity in the whole SAD group compared to HCs with a cluster of 262 voxels mainly corresponding to left lingual gyrus ($p_{FWE\text{-}corr}$ = 0.047, Cohen's d = 0.9) (Fig. 2). The left amygdala seed of the SN displayed a significant hyperconnectivity with a cluster of 398 voxels corresponding to the right middle occipital gyrus ($p_{FWE\text{-}corr}$ = 0.007, Cohen's d = 0.9) (Fig. 5) (Table 4). In addition to these findings in the whole SAD group, comparisons among the SAD subgroups and HC revealed further connectivity differences for the left and right precunei and right vPCC seeds of the DMN and the left amygdala seed of the SN (Table 5).

Regarding the DMN, the left RSC seed displayed a significantly reduced functional connectivity with the right fusiform gyrus in the pSAD group compared with the HC ($p_{FWE\text{-}corr}$ = 0.042, Cohen's d = 1.15, cluster size: 239 voxels) (Fig. 3). In contrast, the left precuneus seed of the DMN revealed an increased connectivity with the left amygdala and hippocampus in SAD-ADHD compared with the HC group ($p_{FWE\text{-}corr}$ = 0.02, Cohen's d = 1.11, cluster size: 311 voxels). Three further DMN connectivity differences were observed between the SAD-ADHD and pSAD groups, which were increased connectivity of the left precuneus ($p_{FWE\text{-}corr}$ = 0.032, Cohen's d = 1.21, cluster size: 248 voxels) and the right vPCC ($p_{FWE\text{-}corr}$ = 0.013, Cohen's d = 1.21, cluster size: 303 voxels) with middle and inferior occipital gyri and increased connectivity of the right precuneus with a cluster containing both left pre- and postcentral gyri ($p_{FWE\text{-}corr}$ = 0.007, Cohen's d = 1.21, cluster size: 348 voxels) in the SAD-ADHD group (Fig. 4) (Table 5). While the FWE-corrected cluster-level statistics of the first 3 results, despite their large effect sizes, could not survive the Bonferroni correction for multiple group comparisons, the last two finding were highly significant. To further test the first 3 trend-level results, we computed mean connectivity value for each cluster and ran one-way ANOVAs among the three groups followed by pairwise post-hoc tests on these mean values. These supplementary analyses revealed significant main effects and significant Bonferroni corrected post-hoc results for all 3 between-group comparisons: Mean connectivity of the left RSC with the right fusiform gyrus decreased significantly in the pSAD (0.03 ± 0.14) compared with the HC group (0.24 ± 0.11) (p = 0.001); mean connectivity of the left precuneus with left amygdala and hippocampus revealed significant hyperconnectivity in the SAD-ADHD (0.16 ± 0.09) vs HC group (-0.03 ± 0.09) (p < 0.001); and mean connectivity of left precuneus with right middle occipital gyrus demonstrated significant hyperconnectivity in the SAD-ADHD (0.15 ± 0.16) vs pSAD comparison (-0.06 ± 0.12) (p = 0.001).

The SN revealed hyperconnectivities in the SAD-ADHD group compared with both the pSAD subgroup and HC. When the SAD-ADHD and HC groups were compared, the left amygdala seed that also revealed a significant hyperconnectivity in the whole SAD group, displayed further hyperconnectivities with two clusters. One of these clusters included the right fusiform cortex, bilateral middle and inferior occipital and lingual gyri and the posterior cerebellum ($p_{FWE\text{-}corr}$ < 0.001, Cohen's d = 1.11, cluster size: 3364 voxels) and the other included precuneus and precentral gyrus in the midline ($p_{FWE\text{-}corr}$ = 0.007, Cohen's d = 1.11, cluster size: 360 voxels). The same seed showed also greater connectivity with bilateral lingual gyri when the SAD-ADHD group was compared with the pSAD group ($p_{FWE\text{-}corr}$ = 0.001, Cohen's d = 1.21, cluster size: 564 voxels) (Fig. 5) (Table 5).

Table 4
Seed-to-voxel results at height threshold p < 0.001 (uncorrected) combined with cluster level threshold $p_{FWE\text{-}corr}$ < 0.05 for the whole SAD vs. HC group comparison.

Seed Region	Regions showing altered connectivity	Group Contrast	Peak Coordinate	Cluster Size	T	$p_{FWE\text{-}corr}$	Effect Size (d)
R Fusiform gyrus	L Lingual gyrus	SAD < HC	−16–42 −08	262	4.93	0.047	0.9
SN - L Amygdala	L Middle occipital gyrus	SAD > HC	−14–98 −04	398	4.16	0.006	0.9

L: left, R: right.

Table 5
Seed-to-voxel results at height threshold $p < 0.001$ (uncorrected) combined with cluster level threshold $p_{FWE\text{-}corr} < 0.05$ for pSAD vs. HC, SAD-ADHD vs. HC, SAD-ADHD vs. pSAD pairwise comparisons. The Bonferroni corrected results with $p_{FWE\text{-}corr} < 0.017$ for 3 pairwise comparisons are marked in bold.

Seed Region	Regions showing altered connectivity	Group Contrast	Peak Coordinate	Cluster Size	T	$p_{FWE\text{-}corr}$	Effect Size (d)
DMN – L RSC	R fusiform gyrus and posterior cerebellum	pSAD < HC	44 -64 -22	239	4.82	0.042	1.15
DMN – L Precuneus	L amygdala and hippocampus	SAD-ADHD > HC	-28 -8 -12	311	4.80	0.020	1.11
DMN – L Precuneus	R middle and inferior occipital gyri	SAD-ADHD > pSAD	32 -96 2	248	4.37	0.032	1.21
DMN – R Precuneus	L postcentral and precentral gyri	SAD-ADHD > pSAD	-28 -40 70	348	4.33	**0.007**	1.21
DMN – R vPCC	L middle and inferior occipital gyri	SAD-ADHD > pSAD	34 -96 0	303	5.52	**0.013**	1.21
SN – L Amygdala	Bilateral middle, inferior occipital and lingual gyri, R fusiform gyrus and posterior cerebellum	SAD-ADHD > HC	46 -56 -26	3364	5.53	**< 0.001**	1.11
	Midline precuneus and precentral gyrus		0 -28 72	360	5.00	**0.007**	1.11
	Bilateral lingual gyri	SAD-ADHD > pSAD	4 -84 -6	564	5.77	**< 0.001**	1.21

L: left, R: right.

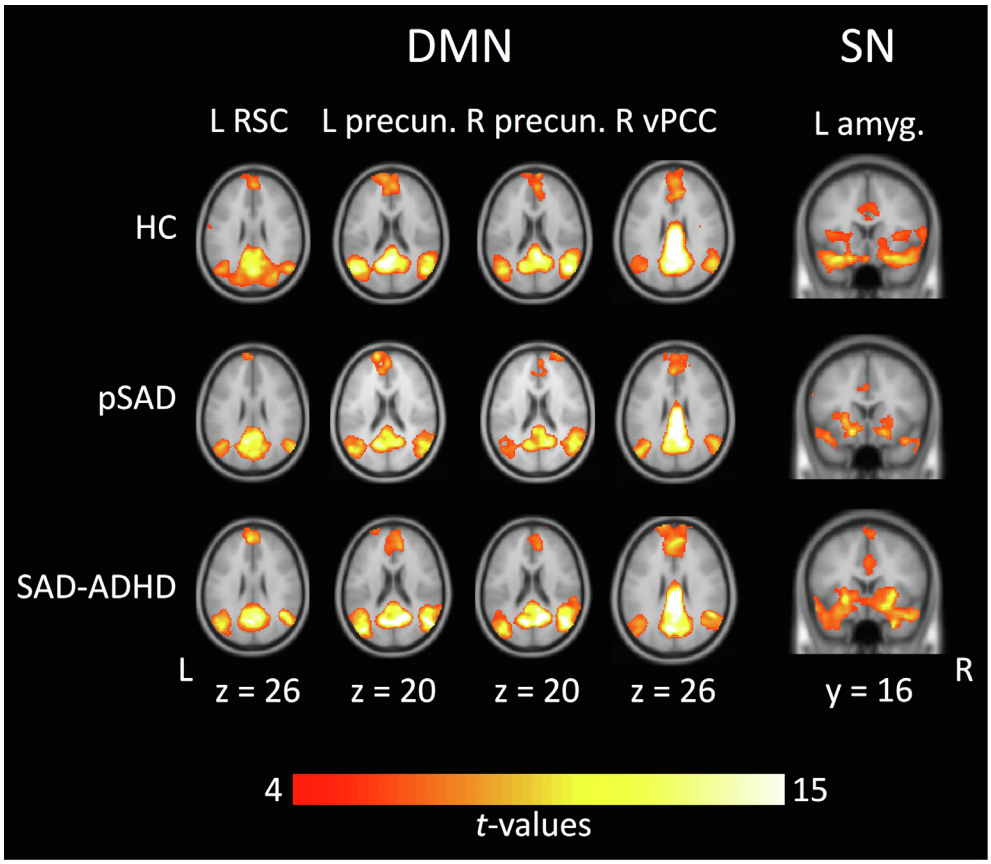


Fig. 1. Functional connectivity maps for DMN and SN. DMN functional connectivity maps obtained separately for the left retrosplenial cortex and left and right precunei seeds for HCs and 2 sub-groups of SAD. SN functional connectivity map obtained by using the left amygdala seed for the three groups.

2.2. Functional connectivity correlations with the clinical scores

Both DMN and SN connectivities displayed a number of significant correlations with clinical symptoms in the whole SAD group. First, DMN (left RSC) connectivity to right fusiform gyrus, which displayed an attenuation in the pSAD subgroup compared to the HC group, was negatively correlated with Liebowitz Social Anxiety Scale (LSAS) (Spearman's rho = -0.560, p = 0.001) (Fig. 6A) and positively correlated with Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Spearman's rho = 0.426, p = 0.012) (Fig. 6B). DMN (left precuneus) connectivity to the left amygdala and hippocampus, which increased in the SAD-ADHD subgroup compared to the HC group, was negatively correlated with LSAS (Spearman's rho = -0.396, p = 0.02) (Fig. 6C). Fusiform connectivity to left lingual gyrus, which displayed an attenuation in the whole SAD group compared to the HCs, displayed a negative correlation with Q-LES-Q (Spearman's rho = -0.341, p = 0.049) (Fig. 6D).

3. Discussion

The aim of this study was to investigate brain's intrinsic connectivity network alterations in SAD patients with and without ADHD comorbidity. Based on previous fMRI findings we carried out seed-based connectivity analyses that include amygdala, insula and fusiform gyrus as the central nodes of the fear circuit (Brühl et al., 2014a) in addition to important nodes of the salience and default mode networks as two large-scale ICNs often reported to be affected in anxiety disorders (Liao et al., 2010; Pannekoek et al., 2013). While precuneus and dorsal, ventral and retrosplenial parts of the PCC were included in the analyses to probe the DMN, the SN was probed by ventral, dorsal and

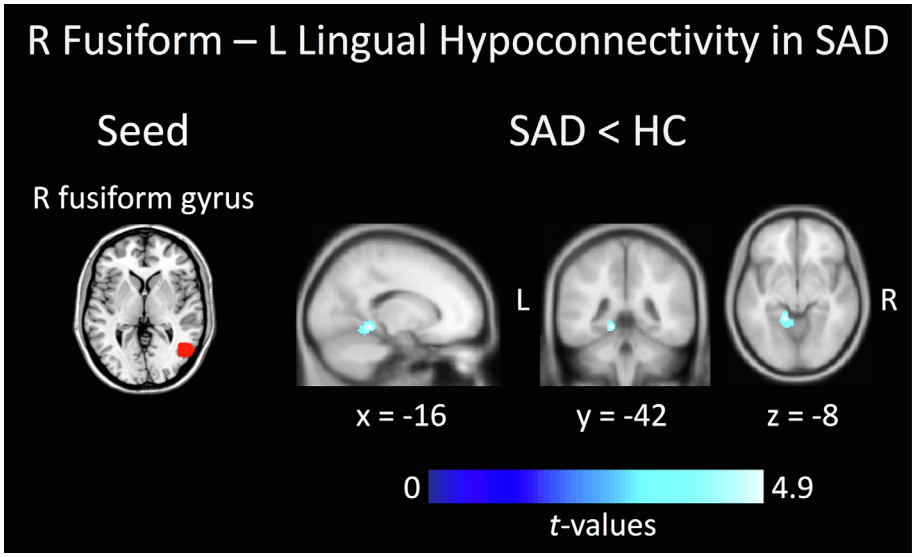


Fig. 2. Reduced right fusiform functional connectivity in SAD. The SAD < HC contrast revealed a hypoconnectivity with the left lingual gyrus (cluster size: 262 voxels). Between-group height threshold uncorrected $p < 0.001$, cluster-level $p_{FWE\text{-}corr} < 0.05$.

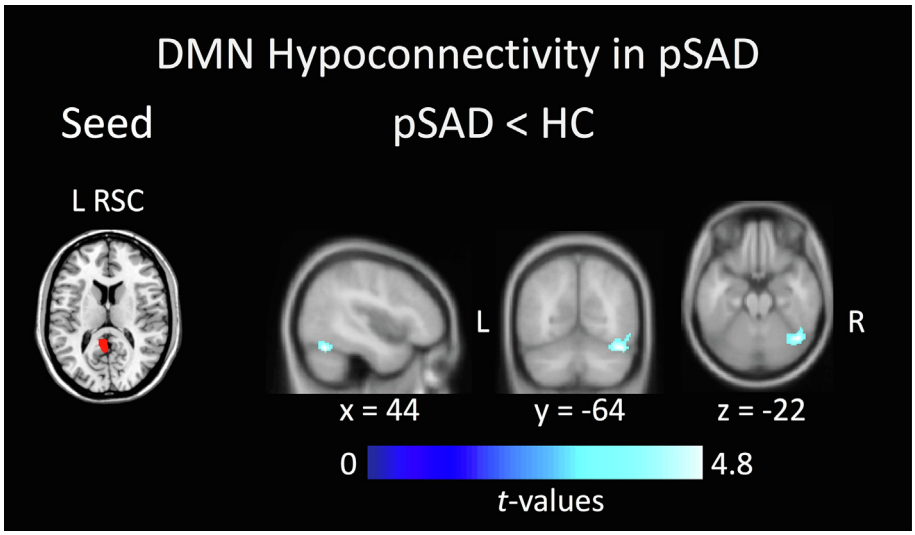


Fig. 3. Posterior DMN hypoconnectivity with visual areas in pSAD. The pSAD < HC contrast revealed a hypoconnectivity between the left RSC seed and the right fusiform gyrus (cluster size: 239 voxels). Height threshold uncorrected $p < 0.001$, cluster-level $p_{FWE\text{-}corr} = 0.042$.

pregenual parts of the ACC in addition to the amygdala and insula that are also part of the fear circuit. The connectivity maps of these seeds resulted in typical DMN and SN patterns across all subjects (Fig. 1), which were then statistically tested between pairs of groups.

Among all seeds used to probe the DMN, the precuneus, vPCC and RSC seeds revealed functional connectivity alterations, whereas dPCC did not reveal any significant group difference. On the other side, neither subfields of the anterior cingulate cortex (ACC) nor the insula probing the SN revealed any significant connectivity difference among the groups, while left amygdala as the subcortical component of SN did. In addition to these ICN effects, the fusiform gyrus revealed a significant functional connectivity difference.

While the fusiform gyrus hypoconnectivity with secondary visual areas was a unique feature for the whole SAD group, the ICN connectivities revealed a significant hyperconnectivity between the left amygdala of the SN and the middle occipital gyrus. Further comparisons between the SAD subgroups with and without ADHD comorbidity and HCs and between the two subgroups resulted in a specific pattern of reduced DMN connectivities associated with pSAD but increased DMN and SN connectivities related with the ADHD comorbidity in SAD. As the social anxiety scores did not differ between the pure SAD and SAD-ADHD subgroups, these functional connectivity differences can reliably be assigned to underlying neural processes of the ADHD comorbidity.

Since the critical contribution of the present study is related with the ADHD comorbidity in SAD, we will first discuss the specific functional connectivity changes in SAD-ADHD subgroup, which will be followed by findings specific to pure SAD subgroup and a short evaluation of a fusiform cortex hypoconnectivity unique for the whole SAD group.

3.1. DMN hyperconnectivities related with the comorbid ADHD in SAD

In contrast to the reduced posterior DMN connectivities observed in the pSAD group, two DMN nodes, the precuneus and vPCC displayed increased functional connectivity in the SAD-ADHD compared with the pSAD subgroup. In the SAD-ADHD subgroup, left precuneus and vPCC displayed higher functional connectivity with middle and inferior occipital gyri and right precuneus with left postcentral and precentral gyri. The precuneus and the PCC as important parts of the DMN (Raichle and Snyder, 2007) together take role in processing self-

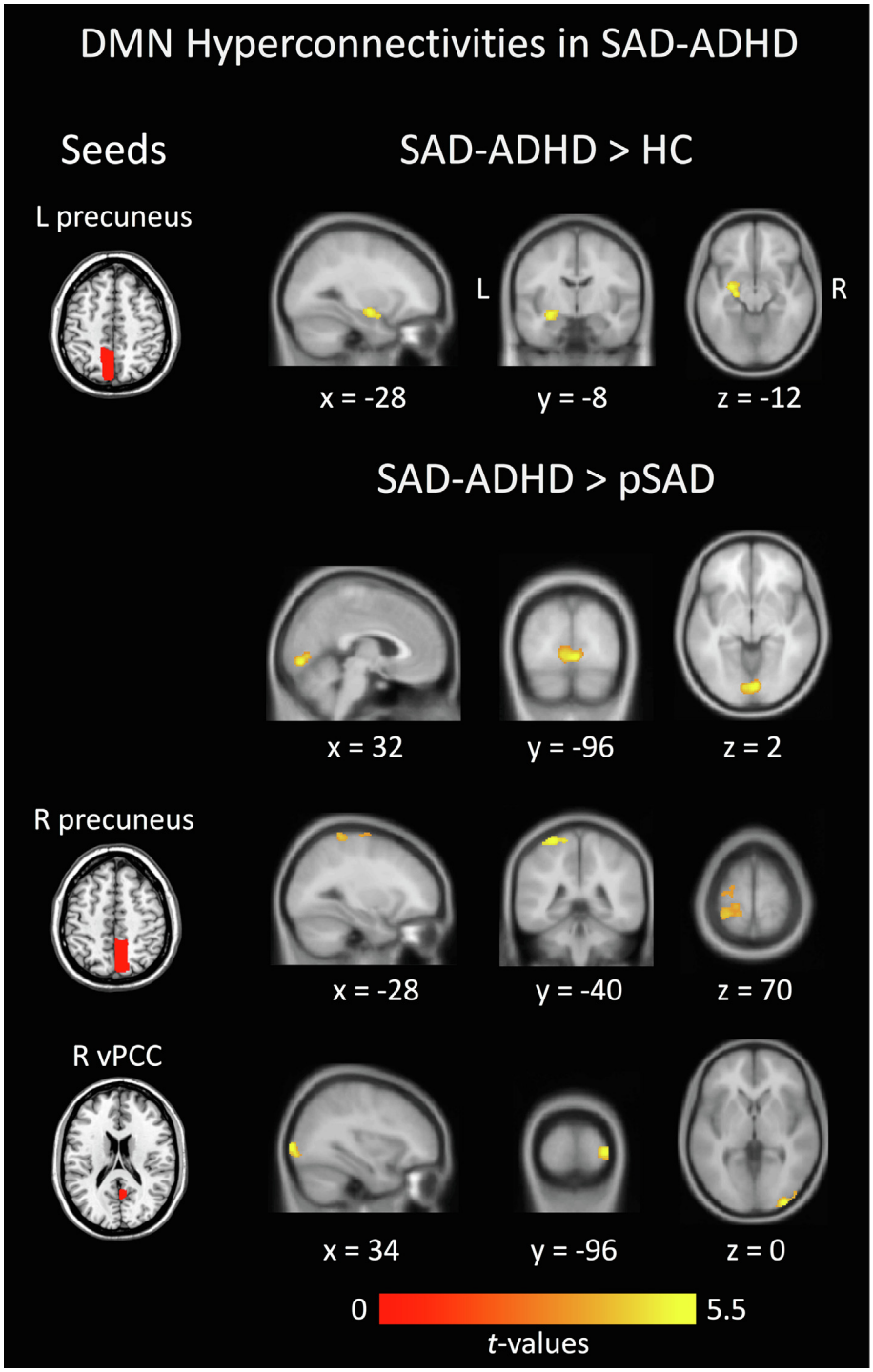


Fig. 4. Posterior DMN hyperconnectivities with visual, sensorimotor and SN regions in comorbid ADHD in SAD. Functional connectivity differences of the left and right precunei and right vPCC in SAD-ADHD group compared with the HC and pSAD groups (height threshold uncorrected $p < 0.001$). SAD-ADHD > HC: left precuneus hyperconnectivity with the left amygdala and hippocampus (cluster size: 311 voxels; $p_{FWE\text{-}corr} = 0.02$); SAD-ADHD > pSAD: left precuneus hyperconnectivity with middle and inferior occipital gyri (cluster size: 248 voxels; $p_{FWE\text{-}corr} = 0.032$), right precuneus hyperconnectivity with left postcentral and precentral gyri (cluster size: 348 voxels; $p_{FWE\text{-}corr} = 0.007$). Right vPCC hyperconnectivity with the right middle and inferior occipital gyri (cluster size: 303 voxels; $p_{FWE\text{-}corr} = 0.013$).

referred emotions (Schneider et al., 2008) and self-referential thoughts and attributions (Saxe et al., 2006). In task-related functional studies on SAD patients, hyperactivation of precuneus/PCC is a common finding (Brühl et al., 2014a) suggesting an increased attention towards self. Additionally, the precuneus and the PCC showed a lower deactivation in SAD patients in a face perception task, and this impairment in deactivation was interpreted as the biological counterpart of self-focused attention (Gentili et al., 2009). In addition to these functional connectivity results, greater gray matter volume and cortical thickness in precuneus were reported in previous SAD studies (Tukel et al., 2015; Irle et al., 2014; Brühl, et al., 2014b), which point to the significant role of these structures in SAD pathophysiology. These hyperactivations, reduced deactivations under task conditions and increased gray matter volumes can generally be interpreted to reflect the adaptation to abnormal perception of self in social and performance situations in patients with SAD.

On the other hand, the review by Brühl et al. (2014a) on a wide range of task-based and resting state fMRI data reports consistent reductions in the functional connectivity of precuneus/PCC with occipital areas, which are actually hyperactive in SAD. Our results dissociate the PCC connectivities with the occipital areas into two distinct patterns, where the RSC, most caudo-ventral subdivision of the PCC, displays a reduced functional connectivity with the fusiform gyrus in pure SAD patients, whereas the vPCC and left precuneus show hyperconnectivity

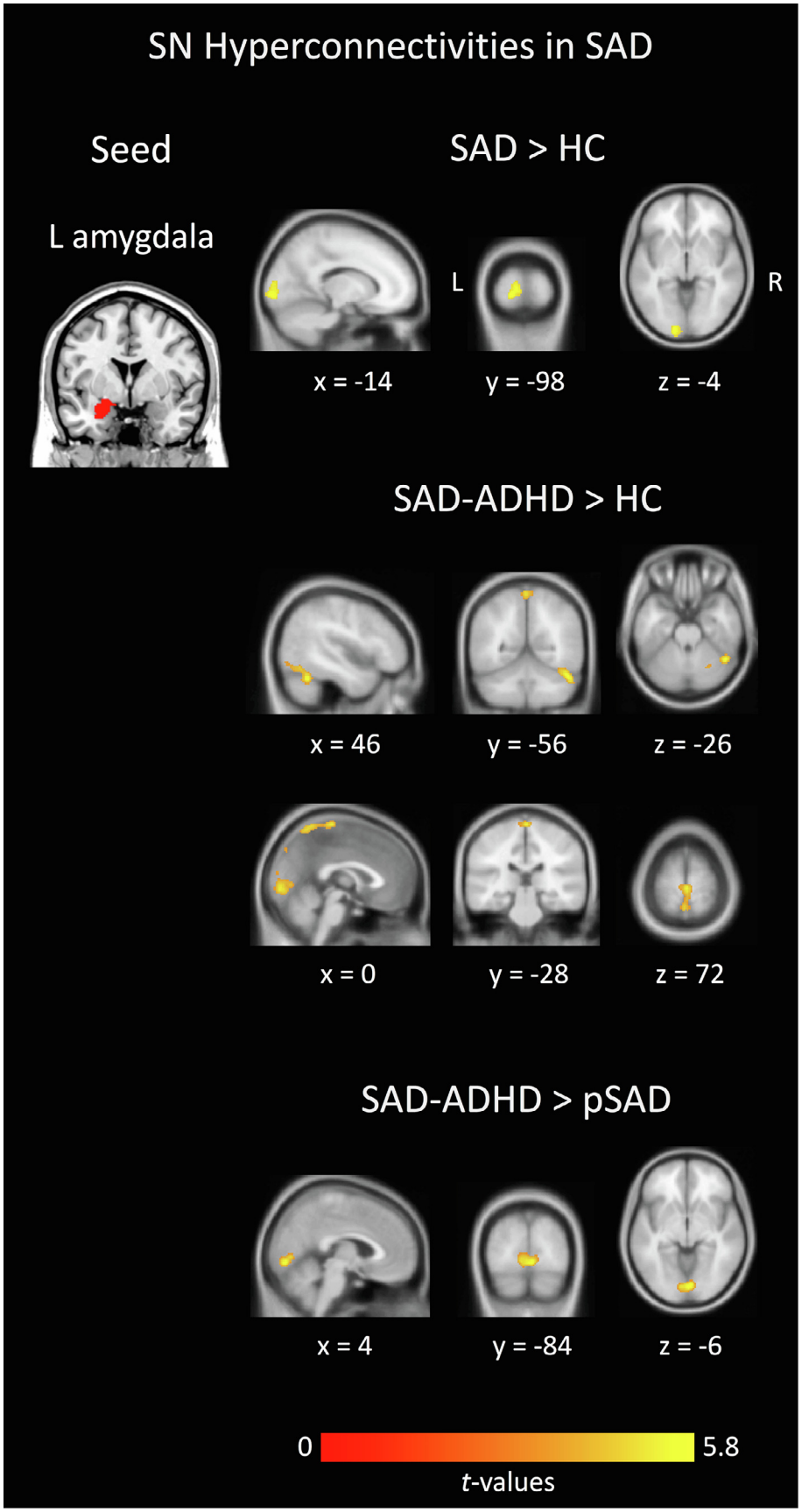


Fig. 5. SN hyperconnectivities with visual areas and DMN regions in SAD. Functional connectivity differences of the left amygdala seed (height threshold uncorrected $p < 0.001$). SAD > HC: hyperconnectivity with right middle occipital gyrus (cluster size: 398 voxels; $p_{FWE\text{-}corr} = 0.006$). SAD-ADHD > HC: hyperconnectivity with bilateral middle, inferior occipital and lingual gyri, right fusiform gyrus and posterior cerebellum (cluster size: 3364 voxels; $p_{FWE\text{-}corr} < 0.001$); with midline precuneus and precentral gyrus (cluster size: 360 voxels; $p_{FWE\text{-}corr} = 0.007$). SAD-ADHD > pSAD: increased functional connectivity with bilateral lingual gyri (cluster size: 564 voxels; $p_{FWE\text{-}corr} < 0.001$).

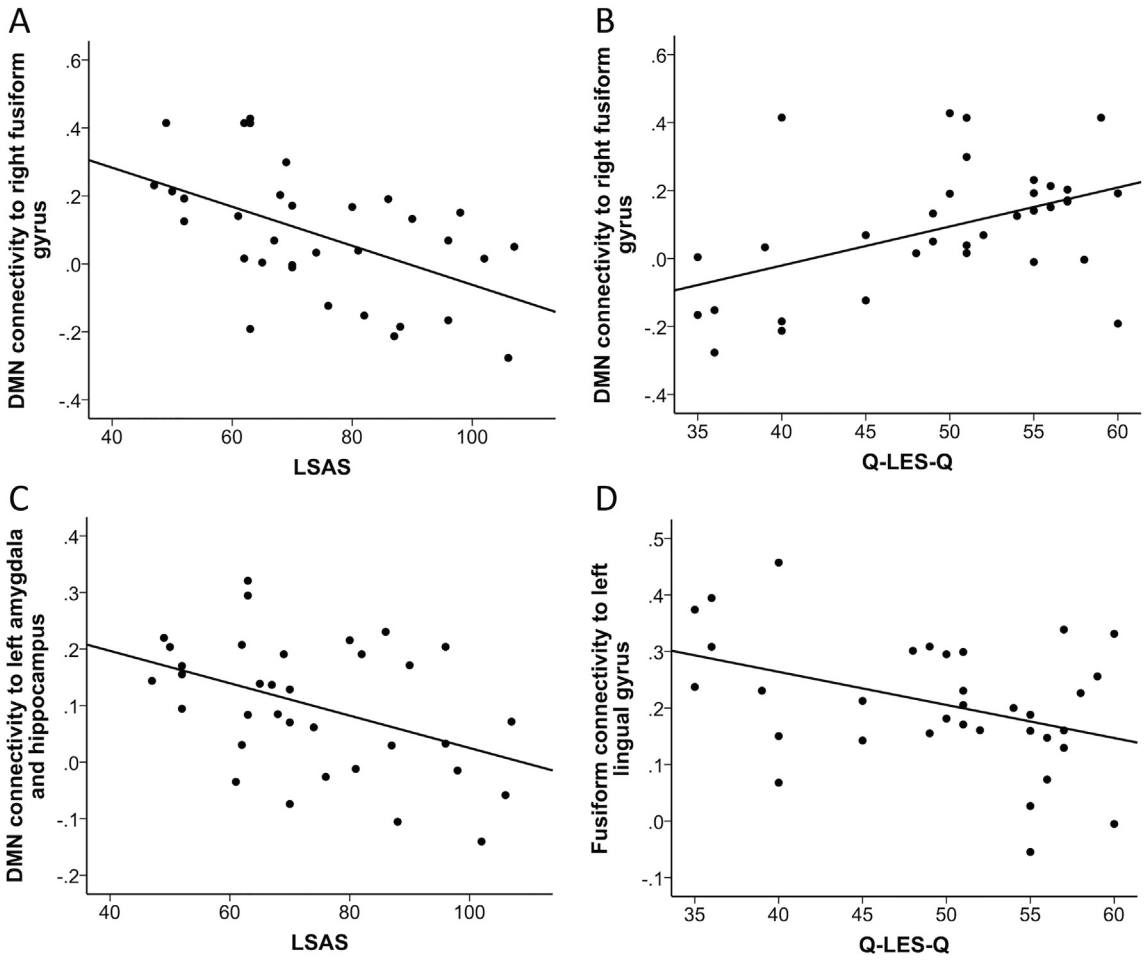


Fig. 6. Correlations between the functional connectivities and clinical scales of SAD patients. DMN (left RSC) connectivity to right fusiform gyrus (A) displayed negative correlation with LSAS (Spearman's rho = -0.560, p = 0.001) and (B) positive correlation with Q-LES-Q (Spearman's rho = 0.426, p = 0.012). (C) DMN (left precuneus) connectivity to the left amygdala and hippocampus displayed negative correlation with Q-LES-Q (Spearman's rho = -0.396, p = 0.02). (D) Negative correlation between fusiform cortex connectivity to left lingual gyrus and Q-LES-Q (Spearman's rho = -0.341, p = 0.049).

with the middle and inferior occipital gyri in SAD patients with ADHD comorbidity. While the hypoconnectivity of PCC with the fusiform gyrus might be associated with a difficulty in face memory and recognition in pure SAD (Geiger et al., 2016), the increased connectivity of the vPCC and left precuneus to middle and inferior occipital gyri in addition to the increased connectivity of the right precuneus with the precentral and postcentral gyri should be further elucidated in terms of the association with ADHD symptoms. Under normal conditions, the increased connectivity of the DMN with sensory cortices accompanies increased task-based connectivity between the executive control network and sensory areas, which leads to enhancement of task relevant sensory input supporting the top-down processes through inhibition of the distractors (Chadick and Gazzaley, 2011). Within this context, our finding of increased resting-state functional connectivity between the DMN and both the visual and somato-motor cortices in SAD-ADHD but not in pure SAD patients may correspond to decreased sensitivity to external events and to worse attentional performance previously reported in ADHD patients (Barber et al., 2015).

3.2. SN hyperconnectivities related with the comorbid ADHD in SAD

In addition to DMN, SN also displayed significant hyperconnectivities in SAD-ADHD patients. The left amygdala as a central node of the SN created the typical SN map when used as a seed in our seed-to-voxel functional connectivity analyses. It further displayed significant hyperconnectivities with the right fusiform cortex, which is mainly responsible for face processing (Kanwisher et al., 1997), bilateral middle and inferior occipital and lingual gyri and the posterior cerebellum in the in the SAD-ADHD group, whereas none of these differences were present in the pure SAD group. Amygdala is claimed to play an important role in anxiety disorders since it is a part of the 'fear circuit' and increase in amygdala volume and activity have been reported in a number of SAD studies (Hahn et al., 2011; Machado-de-Sousa et al., 2014; Tillfors et al., 2001; Tillfors et al., 2002). Furthermore, functional connectivity changes of amygdala were associated with SAD symptoms, because it is involved in the processing of negative facial expressions (Iidaka et al., 2001). Our results extend and complement these previous findings mainly in terms of SN to fusiform connectivity changes specific for ADHD comorbidity in SAD.

Increased activity of the fusiform gyrus in SAD patients' responses to emotional facial expressions has been reported in a previous study by Pujol et al. (2009) in addition to the two large *meta*-analytic studies by Etkin and Wager (2007) and by Brühl et al. (2014a) that discussed the participation of the fusiform gyrus in the fear circuit. Several other studies about emotional face processing in SAD also showed changes in the connectivity between the fusiform gyrus and the amygdala and its correlation with the severity of SAD (Frick et al., 2013; Danti et al., 2010; Gentili et al., 2009). Additionally, the fusiform gyrus has been reported to display bilateral thinning in SAD patients (Syal et al., 2012), while the contradictory finding of a significantly greater gray matter volume in the right fusiform area is reported in patients with SAD (Tukel et al., 2015). Although in contrary direction, these findings also

suggest a possible role of this area in the pathogenesis of SAD.

Our fusiform cortex findings point to a differential position of the right fusiform gyrus in SAD patients in terms of its hyperconnectivity to amygdala in SAD-ADHD group in contrast to its hypoconnectivity with the posterior DMN in the pure SAD group. While the latter finding suggests a general deficit in face recognition and memory in SAD patients, the hyperconnectivity to amygdala in the SAD-ADHD but not in the pSAD subgroup suggest that this pattern, which has often been associated with a dysfunctional processing of facial expressions in the SAD literature, actually depends on the confounding effect of the ADHD comorbidity in SAD. Overlooking an important comorbidity in SAD and the natural tendency to assign the findings related with the amygdala to the anxiety disorder itself may have resulted to miss the link between the SN-fusiform cortex connectivity and ADHD, although the deficient facial emotion detection in ADHD is well documented in a number of studies (Borhani and Nejati, 2018; Romani et al., 2018). Additionally, fMRI studies with facial expression recognition tasks carried out with ADHD patients revealed increased activation of both amygdala and fusiform cortex (Malisza et al., 2011), which may be considered as a reflection of the resting state hyperconnectivity of the SN with the fusiform cortex as reported in the present study.

3.3. Increased SN-DMN inter-network connectivity in comorbid ADHD in SAD

In addition to the above results, the left amygdala seed of the SN displayed increased functional connectivity with precuneus and the left precuneus seed of the DMN an increased connectivity with the left amygdala. This finding suggests a greater inter-network connectivity between the SN and the DMN in comorbid ADHD in SAD. Additionally, the functional connectivity between the left precuneus seed of the DMN and left amygdala of the SN was negatively correlated with LSAS, revealing that increased SN-DMN inter-connectivity is associated with decreasing social anxiety in SAD patients. Previous resting state functional connectivity studies on SAD patients reported increased amygdala connectivity to PCC, a posterior DMN node near precuneus (Arnold Anteraper et al., 2014) and reduced negative connectivity between the left amygdala and the precuneus (Blackford et al., 2014). Additionally, a recent study by Gotting et al. (2017) elegantly depicts the interaction between SN and DMN at rest in susceptibility to distraction. The authors reported that subjects more susceptible to task-irrelevant external information of high salience showed increased ACC resting state functional connectivity to precuneus. This report fits nicely to our SN-DMN finding in SAD patients with ADHD comorbidity and may be associated with the higher distractibility of the subjects with ADHD symptoms.

3.4. DMN hypoconnectivity related with pure SAD

Left RSC of the DMN displayed a reduced connectivity with the occipitotemporal portion of the right fusiform gyrus in the pure SAD subgroup compared with the HCs, while this effect was absent in the SAD-ADHD group. This exclusively significant finding in the pure SAD subgroup suggests that the hypoconnectivity of the posterior DMN with the right fusiform gyrus is the typical pattern due to SAD. This finding is further supported by the correlations with clinical scales that revealed a negative correlation of the LSAS scores and positive correlation of the Q-LES-Q scores with the RSC connectivity to fusiform gyrus, suggesting that decreased posterior DMN-fusiform cortex connectivity is associated with higher social anxiety and worse quality of life in SAD patients.

The RSC (Broadmann areas 29 and 30), the most caudal subdivision of the cingulate cortex (Vogt and Peters, 1981), has been identified as a main and mostly replicated component of the DMN (Buckner et al., 2008; Greicius et al., 2009; Vann et al., 2009). While the function of the RSC within the DMN remains elusive, it is suggested to play an important role in retrieving episodic memories (Vogt et al., 2006), hence is compromised in most common neurological disorders that impair memory (Vann et al., 2009). The reduced functional connectivity of the RSC with the occipitotemporal fusiform cortex observed in the present study might therefore be interpreted to reflect a problem in retrieving episodic memories of faces leading to a difficulty in face recognition in SAD as discussed in previous research (Geiger et al., 2016). Furthermore, the findings of Frick et al. (2014) on enlargement of visual processing areas in lateral occipital cortex and lingual gyri and on positive correlation between symptom severity in SAD and regional gray matter volume in the RSC show a strikingly similar pattern to the functional connectivity changes of the RSC in the pure SAD group. In the light of the our functional connectivity results, the increased gray matter volumes reported by Frick et al. (2014) might be the result of a compensation for dysfunctional connections among the posterior DMN and visual fields.

3.5. Unique fusiform cortex hypoconnectivity in the whole SAD group

The unique functional connectivity difference of the whole SAD group in comparison to HC that could not be replicated in both SAD sub-groups was the hypoconnectivity of the right fusiform gyrus with the left lingual gyrus. The absence of this effect in the SAD subgroups plausibly depends on the weakness of the effect that makes it disappear in between-group comparisons with smaller number of subjects. On the other hand, as a general feature for SAD independent of comorbid disturbances, it may represent a basic process for SAD. While the two large *meta*-analytic studies by Etkin and Wager (2007) and by Brühl et al. (2014a) discussed the participation of the fusiform gyrus in the fear circuit, our finding on a decreased functional connectivity with a secondary visual area rather suggests a defect in relatively earlier processes related with face recognition (Bruhl et al., 2014a,b; Etkin and Wager, 2007). A study by Davis et al. (2011) on a healthy population revealed that the recognition of face identity showed a small but significant association with social anxiety but not general anxiety, pointing to a correlation between face recognition and successful social interactions.

3.6. Overall interpretation of the results

In summary, the evaluation of ADHD symptoms in SAD patients and classification of the SAD patients based on the presence of significant comorbid ADHD symptoms revealed that an important part of the functional connectivity alterations previously reported as SAD-dependent features may actually rely on comorbid ADHD symptoms. While interestingly only the hypoconnectivities of the fusiform and posterior DMN regions with visual areas were specific to SAD, a large set of hyperconnectivities of the SN with the fusiform gyrus and with the posterior DMN nodes in addition to hyperconnectivities of the posterior DMN with sensory and motor areas were related with ADHD symptoms. While the hyperactivity and hyperconnectivity among the fear circuit components is reported in many previous SAD studies, our results suggest that these hyperconnectivities depend on the ADHD comorbidity. This leads to the question, whether ADHD treatment can be considered an alternative for selected SAD cases, which is also congruent with the findings of other studies that suggest different treatment priorities for the SAD patients with comorbid ADHD. For example, atomoxetine was shown to be effective in the treatment of SAD with comorbid ADHD (Adler et al., 2009) but not effective in the treatment of pure SAD (Ravindran et al., 2009).

The strengths of our study were that all patients had generalized SAD, and they were not using any medications. They also did not have any comorbid psychiatric disorders except for specific phobias according to the Structured Clinical Interview for DSM-IV/Clinical Version (SCID-I/CV). We implemented a specific tool to diagnose ADHD as it is not included in the SCID, and to our knowledge this is the first study examining the neurobiology of ADHD comorbidity in SAD. On the other hand, the basic limitation of the present study is the relatively

small number of patients, hence the need for replication studies with similar dissociation of ADHD symptoms in SAD groups.

3.7. Conclusion

In conclusion, our pSAD and SAD-ADHD groups revealed clearly distinct patterns of altered DMN and SN connectivities, indicating a dichotomic disassociation between pure SAD and ADHD comorbidity in SAD. The findings reported here, together with those related with developmental hypothesis, suggest that such neurobiological differences between pure SAD and SAD with comorbid ADHD necessitate scrutinizing these clinical groups as distinct entities. Our findings in general support the 'developmental hypothesis', and a new treatment algorithm for patients with SAD with comorbid ADHD might be developed in case these results can be replicated on larger patient groups. Further neuroimaging studies comparing pure SAD and pure ADHD as two separate clinical entities with relevant study design and selection of the subjects could also be beneficial for understanding the commonalities and contrasts in the neurocognitive network alteration patterns of both disorders and yield further information about the neurobiological bases of their comorbidity.

4. Experimental procedure

A total of 34 consecutive patients with SAD who were seen in or referred to the outpatient clinic of the Psychiatry Department of Istanbul Faculty of Medicine between January 2015 and September 2016 were included in the study. Inclusion criteria were being diagnosed with SAD using the SCID-I/CV (First et al., 1997), being 18–50 years of age, being non-medicated for the last 6 weeks (8 weeks for fluoxetine) and being right handed. A subgroup of SAD patients with comorbid ADHD were diagnosed using the ADHD module of the K-SADS-PL (Kaufman et al., 1997). Exclusion criteria were having any current psychiatric disorder other than SAD according to SCID-I/CV, any serious concomitant general medical condition or neurological disorder, a history of alcohol or drug abuse/dependence, a history of medical disorders that may have a causal relationship with SAD, a contraindication for MRI, pregnancy or lactation.

Of the total 34 patients included in the study, 16 had pure SAD (pSAD sub-group), whereas 18 had comorbid ADHD (SAD-ADHD sub-group). All patients had generalized SAD. We also included two patients who had specific phobias according to SCID-I/CV. Seven patients had used selective serotonin reuptake inhibitors for short periods of time. Two patients were treated with cognitive behavioral therapy for several sessions.

Twenty-two right-handed healthy control subjects (HC group) who were screened for psychiatric disorders and any family history of psychiatric disorders were recruited on a voluntary basis and matched to the patients for gender, age, and years of education.

4.1. Clinical assessment

A semi-structured interview form prepared by the authors was used to evaluate the demographic features of the participants. All participants were assessed using the Turkish versions of SCID-I/CV (Çorapçıoğlu et al., 1999; First et al., 1997), the ADHD module of the K-SADS-PL (Kaufman et al., 1997), Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959; Yazici et al., 1998) and Hamilton Depression Rating Scale (HAM-D) (Akdemir et al., 1996; Hamilton, 1967), Q-LES-Q Short Form (Endicott et al., 1993), and General Assessment of Functioning Scale (Puls et al., 2001) that measures the general social, occupational and psychological functioning. The patients were also evaluated using Clinical Global Impression (CGI) Scale (Guy, 1976), Sheehan Disability Scale (Sheehan, 1986) and LSAS (Liebowitz, 1987; Soykan et al., 2003). Only the SAD-ADHD subgroup was given The World Health Organisation ASRS to measure their ADHD symptom severity (Doğan et al., 2009; Kessler et al., 2005).

4.2. MRI data acquisition

Structural and echo planar imaging (EPI) images were acquired on a Philips 3 Tesla magnetic resonance imaging system equipped with a SENSE-32 channel head coil (Philips Achieva, Best, The Netherlands). High resolution T1-weighted structural 3D images were collected with 250 × 250 mm field of view (FOV), 160 slices, 1 mm slice thickness, 0 mm gap.

Rs-fMRI data were obtained using an EPI sequence with the repetition time [TR] = 2 s, echo time [TE] = 30 ms, flip angle = 90°, FOV = 224 mm × 240 mm, acquisition matrix size = 112 × 117, voxel size = 2 × 2 × 4 mm^3 in-plane resolution. Following 10 dummy volumes, 214 volumes each containing 36 axial slices covering the whole brain, were obtained with a total scan time of 451 s. All participants were instructed simply to rest with their eyes closed, not to think of anything in particular, and not to fall asleep during the scan.

4.3. fMRI data preprocessing

The image preprocessing was performed using the SPM8 (Statistical Parametric Mapping software, www.fil.ion.ucl.ac.uk). For each participant, functional images were first realigned to the first scan to correct head motion. Movements and rotation in x, y and z axes were calculated, which were also used for computing the framewise displacement (FD) between consecutive scans according to the method described by Power et al. (2012). All subjects, who exceeded the movement threshold of 3 mm in x, y, or z directions or the rotation threshold of 3° in each axis in any single scan or mean FD value of 0.5 mm were excluded from further analyses. After coregistration to mean functional image, the anatomic image was segmented and normalized to the Montreal Neurological Institute (MNI) standard space. Then, the realigned functional images were spatially normalized using the resulting transformation matrix and resampled to 2 mm^3 voxels. Finally, the functional images were spatially smoothed by convolution with an isotropic Gaussian kernel (full width half maximum = 8 mm).

4.4. Connectivity analyses

Seed-to-voxel functional connectivity analysis was performed using the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). A total of 20 sources including regions within DMN and SN in addition to fear circuit for seed-based analysis were defined corresponding to the Brodmann Areas (BA) atlas and Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) as provided in the CONN toolbox. While right and left insular cortices (BA 13), vPCC (BA 23), vACC (BA 24), dPCC (BA 31), dACC (BA 32), RSC (part of cingulate cortex, BA 30), pgACC (part of anterior cingulate cortex, BA 33) and fusiform gyri (BA 37) were created based on BA atlas; right and left amygdalae and precuneus were chosen from AAL atlas.

In order to remove potential sources of noise, BOLD signal was band pass filtered between 0.01 and 0.1 Hz. In addition, the effects of the rest condition, white matter and cerebrospinal fluid components and the six head motion parameters obtained from spatial motion correction were used as confounds in the preprocessing step of the CONN toolbox.

Correlation coefficients were calculated between the average time course for each seed region with the time courses of all other voxels in the brain. Fisher transformation was used to convert the resulting correlation coefficients into Z-scores which were then used in second-level analyses. Mean FD values were added as a second-level covariate of no interest in the between-group comparisons. A height threshold of uncorrected $p < 0.001$ was used to identify areas of significant functional connectivity differences among the groups.

The group comparisons were initially performed between whole SAD group and HCs. Cluster-level significance was set at family-wise

error (FWE) corrected $p < 0.05$. Then, three pairwise comparisons were conducted among the pSAD, SAD-ADHD and HC groups, where cluster-level FWE-corrected results were further corrected by Bonferroni method for multiple group comparisons ($p < 0.05/3 = 0.017$). While the Bonferroni corrected results were reported as significant findings, those results that did not survive the Bonferroni correction were reported as trends. These pairwise trend-level differences were further tested by computing the mean connectivity values for each of these clusters and running one-way ANOVA test on these values followed by post-hoc pairwise comparisons with Bonferroni correction using the SPSS statistics software (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

All seed to voxel results were overlaid on the MNI avg152T1 template image from SPM8 for display purposes.

4.5. Correlations of the functional connectivities with clinical scales

In order to investigate the relation of the resting state functional connectivities with clinical measures, Spearman's correlation coefficients were calculated between the mean Fisher's z-transformed connectivity values in specific regions of interests (ROIs) and the clinical scores across the whole SAD group. To obtain reliable correlation results on a relatively large group of subjects, only clinical scores that were available for all SAD patients were included in the correlation analyses, which were LSAS, HAM-A and HAM-D, Q-LES-Q, three subscales of the Sheehan Disability Scale, the General Assessment of Functioning and CGI rating scale. The ROIs were defined as significant clusters observed in the seed to voxel whole brain connectivity comparison between the whole SAD vs HC groups as well as in sub-groups comparisons among pSAD, SAD-ADHD and HC groups. The connectivity values within these ROIs were extracted for each individual SAD patient by using the ROI extraction tool (REX) of the CONN toolbox.

4.6. Clinical data analyses

SPSS package (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) was used for statistical analyses. Chi-square test was used for comparing categorical variables. The *t* test was used to compare normally distributed continuous variables, while Mann–Whitney *U* test was used for variables not normally distributed. Differences at $p < 0.05$ were reported.

Ethical Standards

Written informed consent was obtained from all participants. The study was approved by the ethical committee of Istanbul Faculty of Medicine, Istanbul University and adhered to the Declaration of Helsinki.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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