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Dorsal anterior cingulate cortex activity during cognitive challenge in social anxiety disorder

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ABSTRACT

Background: Social anxiety disorder (SAD) is associated with aberrant emotional information processing while little is known about non-emotional cognitive processing biases. The dorsal anterior cingulate cortex (dACC) has been implicated in SAD neuropathology and is activated both by emotional and non-affective cognitive challenges like the Multisource Interference Task (MSIT).
Methods: Here, we used fMRI to compare dACC activity and test performance during MSIT in 69 SAD patients and 38 healthy controls. In addition to patient-control comparisons, we examined whether neural activity in the dACC correlated with social anxiety, trait anxiety or depression levels.
Results: The MSIT activated the dACC as expected but with no differences in task performance or neural reactivity between SAD patients and controls. There were no significant correlations between dACC activity and social or trait anxiety symptom severity. In patients, there was a significant negative correlation between dACC activity and depressive symptoms.
Conclusions: In absence of affective challenge, we found no disorder-related cognitive profile in SAD patients since neither MSIT task performance nor dACC neural activity deviated in patients relative to controls.

1. Introduction

Social anxiety disorder (SAD) is characterized by an excessive fear of social situations in which the individual is exposed to possible scrutiny by others. Individuals with SAD tend to avoid these social situations or endure them with intense anxiety or fear [2]. SAD is one of the most common anxiety disorders with a life- time prevalence exceeding 10% [38]. First line treatments in adults consist of selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT) [52].

Neuroimaging methods such as functional magnetic resonance imaging (fMRI) can increase our understanding of the neural underpinnings of social anxiety. Differential neural reactivity in SAD

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patients compared with healthy controls has been demonstrated in several brain regions. In response to negative emotional stimuli such as emotional faces, criticism or anticipation of public speaking, some of the most consistently reported findings have been higher activity of the anterior cingulate cortex (ACC), amygdala, insula, medial and ventrolateral prefrontal cortices, parietal cortex, globus pallidus, and the parahippocampal, fusiform, inferior frontal and superior temporal gyri [7,9,17,39,63]. Thus, many of the brain regions showing increased activation in SAD are part of a proposed [9,17,48], but questioned [43] "fear circuit".

Previous research suggests that SAD is characterized by information processing biases in social situations, such as interpretation, attention and memory biases [11,12,36]. However, studies investigating cognitive function in SAD without using emotional or social stimuli are scarce. Some [30] but not all [14] neuropsychological studies have found lower executive function in SAD compared with healthy controls. Another study found that cognitive functioning in SAD was impaired only during social stress (videotaping) [33]. Neuroimaging studies using cognitive tasks in SAD are also scarce in comparison with those using emotional stimuli. One fMRI study found intact performance but differential brain reactivity during an implicit learning task [54] in SAD compared with healthy controls, suggesting differentiation at the neural, but not at the behavioral, level during cognitive testing.

In addition to fMRI patient-control comparisons, neural reactivity patterns predicting psychological and/or pharmacological treatment response in SAD have also been assessed. The ACC in particular has been the most consistently reported region in treatment prediction studies of anxiety disorders as well as depression [26,28,46]. More specifically, its dorsal subdivision (dACC) has emerged as an area of interest in predicting treatment response in SAD [26,27,40–42,51]. Studies using emotional stimuli, such as disgusted or harsh faces or anticipation of public speaking, have reported mixed results of dACC function in SAD, i.e. increased [3,5,53,58], decreased [6,19,44,58] or unchanged [55] dACC activity. Relative to healthy controls, patients with SAD have been reported to show decreased dACC activity during emotion regulation tasks specifically targeting cognitive reappraisal, indicating insufficient top-down control [62]. One PET study reported decreased resting glucose uptake in the dACC in SAD [18]. In a previous paper we showed that reactivity within the dACC during a cognitively demanding task outperformed genetic, demographic, and clinical variables with respect to treatment prediction success [26].

The dACC has a key role in many functions that are thought to be affected in SAD, partly due to its involvement in both cognitive and emotional processing. It has been proposed that the dACC has an evaluative function and findings indicate that it has a key role in conflict monitoring [8], target detection [10,59], response selection [4], and appraisal and expression of negative emotion [16], as well as monitoring of emotion and gating its access into conscious awareness [15]. Other functions include conscious threat appraisal, worrying and catastrophizing, all of which are important features of anxiety disorders [37,47].

In light of cognitive biases in SAD, and since previous fMRI research has been dominated by socio-affective paradigms, we aimed to study whether performance and dACC activity during a cognitive challenge differs between patients and healthy controls when the emotional load is low. For this purpose we used the Multisource Interference Task; MSIT [10], i.e., a cognitive interference task designed to specifically activate the dACC. We hypothesized that patients with SAD would show differential dACC reactivity to the MSIT compared with healthy controls. We also examined whether performance measures as well as anxiety and depression severity scores correlated with dACC activity.

2. Materials and methods

The current study sample combines samples of patients with SAD from two randomized controlled trials (RCTs) and two groups of healthy controls included in parallel with the RCTs. All data were collected by our group at Uppsala University. Behavioral and neural treatment effects from the RCTs have been reported elsewhere [21,32], albeit for a different fMRI paradigm involving emotional faces.

2.1. Recruitment procedure

Participants aged 18–65 years were recruited through newspaper advertisements and public billboards. During the initial screening, the Social Phobia Screening Questionnaire (SPSQ) [31] and the Montgomery-Åsberg Depression Rating Scale - self-rating version (MADRS-S) [50] were administered online. One of the healthy control groups did not fill out the MADRS-S questionnaire. Participants passing initial screening were interviewed using the Mini International Neuropsychiatric Interview (MINI) [57], the SAD section of the Structured Clinical Interview for DSM-IV (SCID-I) [23] and underwent a medical check-up. All patients had to meet the DSM-IV [1] criteria for SAD as the primary diagnosis; healthy controls could not meet criteria for any psychiatric diagnosis. Exclusion criteria for all participants were contraindications for MR, presence of severe somatic disease or serious additional psychiatric disorder such as psychosis or severe major depression, treatment for any psychiatric disorder (ongoing or terminated within three months), drug abuse or dependency, pregnancy and menopause.

2.2. Study procedure

Study design, study procedure and treatments for the randomized controlled trials involving patients but not healthy controls have been reported elsewhere [21,32]. Briefly, patients (before randomization) and healthy controls underwent fMRI scanning. Social anxiety symptom severity and trait anxiety were assessed using the self-report version of the Liebowitz Social Anxiety Scale (LSAS-SR) [25], administered online, and the Spielberger State-Trait Anxiety Inventory – Trait version (STAI-T) [60], respectively.

2.3. fMRI Image acquisition

MRI scanning was performed using a Philips Achieva 3.0 T whole body MR scanner (Philips Medical Systems, Best, the Netherlands) equipped with an 8-channel head-coil. An anatomical T1-weighted image (echo time (TE) = 15 ms; repetition time (TR) = 5700 ms; inversion time = 400 ms; field of view = 230x230mm^2; voxel size = 0.8 × 1.0 × 2.0 mm^2; 60 contiguous slices) and a blood oxygenation level-dependent (BOLD) echo planar imaging (EPI) sequence were acquired (TE = 35 ms; TR = 3000 ms; flip angle = 90 degree, acquisition matrix = 76 ×77, voxel size = 3.0 ×3.0 ×3.0 mm^3, gap = 1 mm, 30 axial slices). Visual stimuli were presented through goggles (Visual System, Nordic-NeuroLab, Bergen, Norway) using E-prime (Psychology Software Tools, Sharpsburg, Pennsylvania, USA) and answers were provided with a button-press.

2.4. fMRI paradigm

During fMRI image acquisition, participants underwent the cognitive interference task MSIT [10] (Fig. 1). In each trial, a set of three digits (0, 1, 2, or 3) was presented in the center of the display. One digit (target) was always different from the other two digits (distractors) in the set. In the control condition, the target digit and its position matched (target digit and position were congruent). In the interference condition, target digit and position were incongruent, i.e. did not match. The participants were asked to indicate the value of the target digit ('1', '2' or '3') by pressing the corresponding response button. Due to programming error, response times and errors were recorded for interference trials but not for control trials.

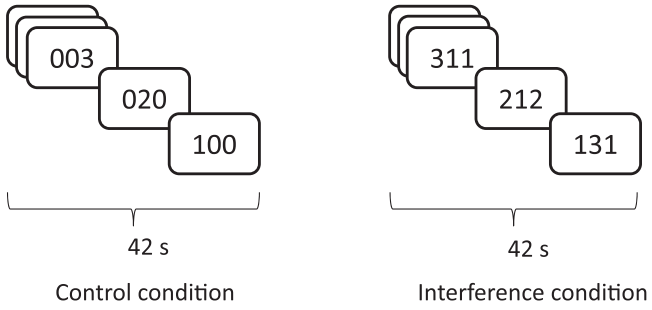

Fig. 1. The modified Multi-Source Interference Task. Four blocks each of the control and of the interference conditions were presented to the participants in a fixed sequential order with the control condition always presented first. Each block had a duration of 42 s and consisted of 24 trials (1750 ms per trial) in pseudo-randomized order. Fixation crosses were presented for the first and last 30 s of image acquisition, for a total length of 6 min and 36 s. Each trial consisted of a set of three digits, one target and two distractor digits. In the control condition (left), the distractors were always '0' and the target digit corresponded to its position (i.e. '1' was always in the first (leftmost) position; '2' in the second (middle) position; and '3' in the third (rightmost) position. Thus, target digit and position were congruent. In the interference condition (right), distractors were either '1', '2' or '3' and the target digit and its position were incongruent. The participants indicated the value of the target digit ('1', '2' or '3') by pressing the corresponding response button ('1': left thumb, '2': left index finger, '3': right index finger)". The figure above shows three trials each of the control and interference condition. In this example, the correct answers would be (left to right): '3', '2' and '1' for the control condition and '3', '1' and '3' for the interference condition.

2.5. Analyses of imaging data

The fMRI-data were analyzed in MATLAB (MathWorks, Natick, MA, USA) using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) for preprocessing and SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12) for later analyses, since these were performed at a later time-point. Each participant's BOLD EPI images were realigned to the mean image of each time series, slice timing corrected to the middle slice of each volume, co-registered with the anatomical scan and normalized to Montreal Neurological Institute (MNI) standard space using parameters obtained from unified segmentation of the anatomical image. Finally, smoothing was performed using an 8 mm Gaussian kernel (full width, half maximum). The BOLD signal in each voxel was high-pass filtered with 128 s, regressed on the stimulus function (onsets and durations of control and interference blocks), six movement parameters obtained from the realignment step, and convolved with the canonical hemodynamic response function provided by SPM.

Participants with head movement exceeding 3 mm or 1 degree of rotation were excluded, as were participants with head movement below 3 mm or 1 degree of rotation if the movement coincided with the onset of a stimulus block.

2.6. Statistical analysis

Demographic, clinical and behavioral data were compared between groups by two-tailed independent samples t-tests or chi-squared tests using MATLAB R2018b. Missing clinical data (i.e. participants had not answered the whole questionnaire) were excluded from the analyses.

Analysis of imaging data was performed with focus on the dorsal ACC through a region of interest (ROI) analysis. The dorsal ACC ROI was defined as the portion of the cingulate cortex between Y= 0 and Y= 30 mm and superior to Z = 0 mm (Talairach coordinates) [10,26]. The lateral borders of the ROI included voxels between x = −12 and x = 15. The size of the ROI was 526 voxels. Interference trials were contrasted against control trials for voxels within the dACC ROI (left and right dACC combined) and the resulting differences in neural reactivity in the dACC was further analysed in SPM12, both in the sample as a whole using a one-sample t-test and in a between-group t-test comparing patients and controls. For both analyses, the significance level was set to $p_{FWE} < 0.05$.

The one- sample t-test performed within this dACC ROI rendered, at $p_{FWE} < 0.05$, a cluster of 293 voxels from which individual values of mean neural reactivity in the 'Interference > Control' contrast were extracted and used in Pearson's correlation tests with behavioral and clinical data. Correlation analyses were performed across groups as well as in the patient and control group, respectively. The significance threshold was set at $p < 0.05$.

In addition to the ROI analysis, an exploratory whole-brain analysis was performed using between-group t-tests to investigate whether neural activity in the 'Interference > Control' contrast differed between subject groups in any other brain region (significance set at $p_{FWE}<0.05$). Spatial localizations are reported in MNI coordinates.

2.7. Ethical statements

The Regional Ethical Review Board in Uppsala approved the studies which complied with the standards established by the Declaration of Helsinki. All participants gave written informed consent prior to inclusion.

3. Results

3.1. Participants

We included 89 patients and 50 healthy controls that were all scanned using the same MR scanner. Of these, 20 patients and 12 controls were excluded due to excessive head movement during the task. Thus, a total of 69 patients (mean ± SD age 31.9 ± 9.0 years, 31 women) and 38 healthy controls (mean ± SD age 28.6 ± 10.6 years, 22 women) were included in the final sample.

Descriptive characteristics are provided in Table 1. Patients with SAD did not differ significantly from healthy controls on sociodemographic variables (age, gender and educational level). Confirming group designation, patients scored significantly higher on measures of anxiety and depression (LSAS-SR, MADRS-S and STAI-T) compared with the healthy controls. No participants had any ongoing psychiatric pharmacological or psychological treatment. Patients' treatment history are provided in Appendix A1.

3.2. Behavioral results

Table 2 illustrates group-averaged reaction times and accuracy data during interference trials in the MSIT. There were no statistically

Table 1
Participant Characteristics.

Measure	Patients (n = 69)		Controls (n = 38)			
					Statistic	***p***
Age; mean, SD	31.9	9.0	28.6	10.6	t = −1.71	n.s.
Women; n, %	31	45	22	58	$\chi2 = 1.65$	n.s.
Educational level; n,	1	2	1	3	$\chi2 = 0.42$	n.s.
%	29	42	14	37		
≥ 9 years	39	56	23	60		
High school						
University						
LSAS-SR; mean, SD	78.7	22.1	8.6	7.0	t = −24.15	< 0.001
MADRS-S; mean, SD	15.6	7.9	2.8	4.0	t = −9.49	< 0.001
STAI-T; mean, SD	50.0	11.5	30.2	6.0	t = −11.40	< 0.001

LSAS-SR, Liebowitz Social Anxiety Scale- self-report version; MADRS-S, Montgomery- Åsberg Depression Rating Scale- self-rating version; STAI-T, Spielberger State-Trait Anxiety Inventory – Trait version.

Table 2
Group-averaged reaction time and accuracy data during interference trials.

Measure	Patients (n = 69)		Controls (n = 38)			
					Statistic	*p*
Reaction time (ms); mean, SD	937	88	927	98	t = −0.52	0.60
Accuracy (percent correct); mean, SD	35.3	4.0	35.4	7.1	t = 0.14	0.89

significant results between the two groups regarding mean reaction time or accuracy.

3.3. Neural activity in the dorsal anterior cingulate cortex (dACC)

Across groups, neural activity in the dorsal ACC (peak voxel: x, y, z = 3, 14, 44; cluster size = 293 voxels; t = 12.98; $p_{FWE} < 0.001$) was increased during interference as compared to control trials, see Fig. 2. There were no statistically significant differences between patients and controls in dorsal ACC activity, see Fig. 3.

3.4. Exploratory whole-brain analysis

The exploratory whole-brain analysis revealed no brain regions where neural activity differed patients from controls in any direction during the 'Interference > Control' contrast (all voxels $p_{FWE} > 0.05$).

3.5. Correlations between dACC activity, behavioral and clinical data

There were no statistically significant correlations between dACC activity in the 'Interference > Control' contrast and behavioral data (mean reaction time and accuracy in the interference task) or clinical data (social anxiety symptoms, trait anxiety and depressive symptoms) neither in the groups combined, nor in the two separate groups, except for a small but significant negative correlation between dACC activity and MADRS-S score in patients, see Table 3 and Appendix A2.

4. Discussion

In this neuroimaging study, we applied a cognitive interference task (MSIT) designed to activate the dACC [10] to study neural activity in parallel with cognitive function in SAD patients and healthy controls. Contrary to our hypothesis, we did not observe any group differences in dACC activation. Also, dACC activity did not correlate with clinical measures except for a weak negative correlation with depression scores in the SAD group.

The dACC has been implicated in SAD neuropathology and we previously reported that individual differences in dACC activity was predictive of treatment outcome in this group [26,51]. The dACC has been suggested to influence general brain functioning and has an important role in both cognitive and emotional processing [61]. Although previous functional neuroimaging studies using emotional stimuli have reported aberrant dACC-reactivity in SAD, results have been inconsistent [3,5,6,19,44,53,55,58]. The dACC is a functionally heterogeneous region and it is probable that emotional and cognitive tasks activate different subregions within the dACC [10].

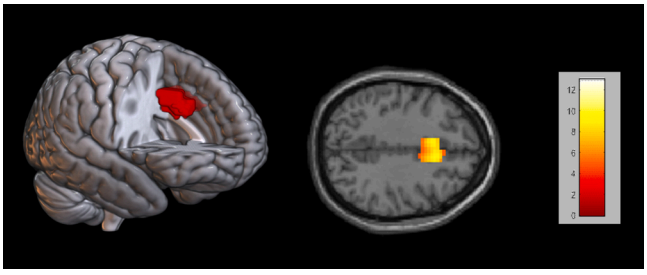

Fig. 2. Cluster in dorsal anterior cingulate cortex (dACC) with greater neural reactivity to the MSIT cognitive interference task ('Interference > Control') in the whole sample. Peak voxel at Montreal Neurological Institute (MNI) coordinate x, y, z = 3, 14, 44. The cluster is thresholded at $P_{FWE} < 0.05$, cluster size = 293 voxels, t = 12.98. Three- dimensional image created using MRIcroGL from http://www.nitrc.org/.

It has been suggested that social anxiety is characterized by information processing biases such as excessively negative interpretation of external social events, an imbalance of attention between self-focus and external information, and exaggerated recall of negative information [11,12,36]. As noted, very few studies have investigated cognitive function in SAD without at the same time adapting emotional stimuli or challenges. Reduced executive function, measured by the Wisconsin card sorting test, has been reported in SAD patients, and has been found to correlate with LSAS scores [30], while another study found that patients with SAD showed impairments in executive function on self-report ratings only, while their objective performance was intact, suggesting that impairments in SAD likely relate to negative self-monitoring [14]. Partly in line with this finding, Sareen and colleagues [54] found that patients with generalized SAD did not differ from healthy controls in behavioral performance of an implicit sequence learning task; however, patients did show reduced neural activation in the left caudate head, left inferior parietal lobe, and bilateral insula, suggesting a striatal dysfunction. Another study [33] found that individuals with generalized SAD performed equally to healthy controls in neuropsychological tests in a low-stress environment, but that the patient group exhibited declining spatial attention and complex problem solving during a psychosocial stress condition (videotaping). Our findings of intact performance during a situation characterized by cognitive load without an emotional component, combined with similar brain activation patterns as in healthy controls, indicate that information processing deficiencies in SAD are circumscribed to emotionally challenging social situations. Error-processing might be an interesting target for further analyses to assess whether individuals with SAD differ from controls in neural reactivity to the cognitive task. However, in the present study, the lack of behavioral data for the control condition prevents such an analysis.

The fact that we did not find statistically significant differences in dACC activity between patients and controls is noteworthy as the dACC has been the most commonly implicated brain region in prediction of treatment response in SAD [26,27,41,42,51]. For example, Frick and colleagues reported that increased dACC activity at pretreatment predicted response to CBT and CBT+SSRI combined treatment [26]. However, consistent with the notion that separate brain regions are implicated in treatment mechanisms and prediction [45], they did not observe a relationship between reduced dACC activity and clinical response [26]. Our results extend this notion in the case of SAD by suggesting that while initial dACC activity is predictive of treatment success, it may not differ patients with SAD from healthy controls. We can suggest that although dACC activity seems to be a promising neural biomarker for treatment prediction, its usability may not reflect pre-treatment differences between patients with SAD and healthy controls, but rather some more general capacity related to treatment responsivity. Interestingly, dACC activity has been shown to predict treatment response in other anxiety disorders like obsessive compulsive disorder (OCD) [35], post-traumatic stress disorder (PTSD) [24], and depression [29]. It might therefore be of interest to study if patients with these disorders differ from healthy controls in dACC activity or whether this predictive power is independent of group differences in neural activity.

Consistent with the non-significant group differences, we did not find any correlations between neural dACC activity and anxiety symptoms. This is partly in line with previous research, e.g., Savage and colleagues found no correlations between the magnitude of dACC activation during a threat reversal learning task and LSAS scores in patients with SAD, patients with major depressive disorder or healthy controls [55].

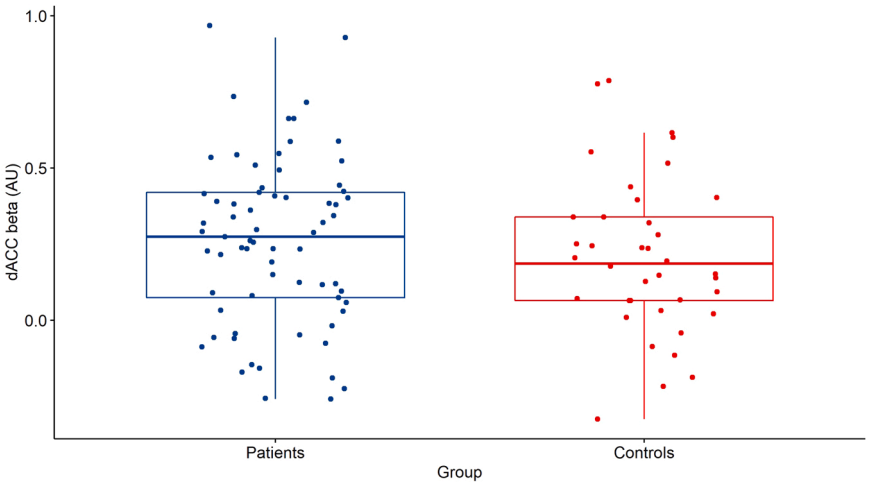

Fig. 3. Boxplot depicting mean neural activity within the dorsal anterior cingulate cortex cluster where all participants showed higher reactivity to the MSIT cognitive interference task ('Interference > Control'). The figure shows extracted beta weights (AU; arbitrary units) for patients (blue) and healthy controls (red).

Table 3
Correlations Between dACC Activity, Behavioral and Clinical Data.

		dACC activity	
Measure	**Group**	***r***	***p***
LSAS-SR (n = 106)	Whole sample	-0.02	0.84
MADRS-S (n = 86)	Whole sample	-0.11	0.32
STAI-T (n = 103)	Whole sample	-0.01	0.96
Reaction time (n = 107)	Whole sample	0.17	0.08
Accuracy (n = 107)	Whole sample	0.09	0.36
LSAS-SR (n = 69)	Patients	-0.22	0.07
MADRS-S (n = 69)	Patients	-0.26	0.03
STAI-T (n = 65)	Patients	-0.10	0.43
Reaction time (n = 69)	Patients	0.17	0.17
Accuracy (n = 69)	Patients	0.22	0.07
LSAS-SR (n = 37)	HC	-0.02	0.92
MADRS-S (n = 17)	HC	-0.04	0.88
STAI-T (n = 38)	HC	-0.04	0.80
Reaction time (n = 38)	HC	0.16	0.34
Accuracy (n = 38)	HC	-0.04	0.80

r: Pearson's correlation coefficient; LSAS-SR, Liebowitz Social Anxiety Scale-self-report version; MADRS-S, Montgomery-Åsberg Depression Rating Scale-self-rating version; STAI-T, Spielberger State-Trait Anxiety Inventory – Trait version; HC, Healthy Controls.

However, we found a small but significant inverse correlation between MADRS-S scores (scores of depressive symptoms) and dACC activity in patients. One may speculate whether affected cognitive function/ dorsal ACC activity in non- social settings is related to overall symptoms of depression/ illness rather than related to social phobia per se. This might further explain our lack of findings of differential dACC activity in SAD, where not all individuals might suffer from these symptoms. A negative correlation between depression severity and dACC activity is generally consistent with findings from Halari and colleagues [34] who reported that adolescents with MDD displayed reduced ACC activity when compared to healthy controls during cognitive challenges similar to the one used in this study.

Our study is not without limitations. Firstly, participants were recruited through newspaper advertisements and public billboards and it is possible that individuals with SAD who apply to these studies might be less affected than patients in a psychiatric setting. However, mean LSAS-SR scores in our patient group indicated a generalized SAD with fears related to most social situations [49]. Still, since large phenotypic variability has been reported in SAD [13] it is possible that robust cognitive biases exist only in patients with severe disorder, in certain subgroups, or when there is an overlap with neuropsychiatric conditions like autism or ADHD. Secondly, we included patients with some psychiatric comorbidities (generalized anxiety disorder, specific phobias, obsessive- compulsive disorder, panic disorder/ agoraphobia, current depressive episode and alcohol abuse [21,32]). Patients with these comorbidities might show different patterns of brain activation than patients with SAD only. One benefit of including patients with SAD and comorbid psychiatric disorders is that our results might be more clinically relevant and generalizable to patients with SAD in the population, where high lifetime comorbidity rates have been reported [20,22,56]. Thirdly, due to programming error, response times and accuracy rates were not recorded for the control condition, so we could not compare these with the interference condition. We would expect response rates to be lower, and accuracy rates to be higher, in the control compared with the interference condition.

5. Conclusion

In conclusion, while investigating cognitive function in parallel with dACC activity during a cognitive interference task in a large sample of SAD patients as compared to healthy controls, no group differences, nor any correlations between dACC reactivity and social or trait anxiety symptoms were observed. In patients, there was a significant negative correlation between dACC activity and depressive symptoms. Our results suggest that there are no differences in task performance and brain activation in SAD when a cognitive task is performed in absence of affective challenge. While we previously reported that dACC activity was predictive of treatment outcome in this population, the results here indicate that the neural mechanism of treatment prediction does not reflect a purely cognitively induced disorder-related activation profile within this brain region.

Funding

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Declarations of interest

None.

Data availability

As this study contains patient data the data set can not be made

publicly available. Requests for access to data could be made by personal communication with the research team.

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