Minireview

Beyond emotions: A meta-analysis of neural response within face processing system in social anxiety

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Abstract

Patients with social anxiety disorder (SAD) experience anxiety and avoidance in face-to-face interactions. We performed a meta-analysis of functional magnetic resonance imaging (fMRI) studies in SAD to provide a comprehensive understanding of the neural underpinnings of face perception in this disorder. To this purpose, we adopted an innovative approach, asking authors for unpublished data. This is a common procedure for behavioral meta-analyses, which, however has never been used in neuroimaging studies. We searched Pubmed with the key words ''Social Anxiety AND faces'' and ''Social Phobia AND faces.'' Then, we selected those fMRI studies for which we were able to obtain data for the comparison between SAD and healthy controls (HC) in a face perception task, either from the published papers or from the authors themselves. In this way, we obtained 23 studies (totaling 449 SAD and 424 HC individuals). We identified significant clusters in which faces evoked a higher response in SAD in bilateral amygdala, globus pallidus, superior temporal sulcus, visual cortex, and prefrontal cortex. We also found a higher activity for HC in the lingual gyrus and in the posterior cingulate. Our findings show that altered neural response to face in SAD is not limited to emotional structures but involves a complex network. These results may have implications for the understanding of SAD pathophysiology, as they suggest that a dysfunctional face perception process may bias patient person-to-person interactions.

Keywords: Face perception, social phobia, functional magnetic resonance imaging, meta-analysis, amygdala, anxiety

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Introduction

Social anxiety disorder (SAD)—also known as social phobia—is a relatively common anxiety disorder in which patients experience high levels of anxiety during social situations, which are consequently avoided.[1] Typically, patients experience an excessive wariness of others' judgment and are afraid to appear socially inadequate or awkward. Among the most frequent clinical features observed in patients with SAD are increased anxiety and avoidance behaviors in social face-to-face interactions. SAD patients are mostly afraid of finding negative expressions on the faces of their interlocutors. Moreover, behavioral results highlight an increased bias toward negative expressions in SAD patients,[2–4] as well as biased memory encoding and recall of negative expressions.[5]

Face perception is a highly complex and sophisticated process underpinned by a distributed neural system that comprises several brain areas, including the fusiform gyrus, superior temporal sulcus (STS), insula, amygdala, and temporal poles.[6,7] Behavioral and neurobiological studies consistently suggest that such a system may be affected in SAD.[8–10]

While a hyperreactivity in the amygdala has been a consistent finding across most studies on face perception in SAD (e.g. in the literature[8,11–14]), results diverged regarding the potential role of other structures that are involved in face perception (e.g. in the literature[8,12,15]). As a matter of fact, a possible explanation for these partially discrepant results can be ascribed to the fact that most brain imaging studies, with only a few exceptions (e.g. in the literature[8,12]), used faces as a major and powerful tool to elicit an emotional response in SAD patients, in the same way one would use spiders to trigger a response in arachnophobias. In this sense, the goal was not to understand brain correlates of

face (or spider) processing but simply of their emotional effects. Thus, experimental paradigms in SAD were designed to detect the dysfunctional response within the emotional brain rather than to map neural processing in the face perception network.

This very same ''emotional brain dysfunction'' line of research was the focus of a recent meta-analysis by Hattingh *et al.* on differential brain activity in SAD patients as compared to healthy controls (HCs) in response to emotionally relevant stimuli (either faces or statements).[16] In their analysis, the authors did not just look at faces, but at all socially relevant stimuli that may trigger an altered response in SAD. The strength of this analysis resides in the fact that a consistent pattern of brain response emerged irrespectively of the kind of paradigms utilized, either faces or statements. The meta-analysis highlighted activations, in particular, in the bilateral amygdala, parahippocampus, and ventral anterior cingulate cortex, strengthening the idea of the pivotal role of the amygdala in fear conditioning and, more generally, of the role of the limbic system in anxiety disorders.

Another recent meta-analytic review of neurobiological studies in SAD tried to cover all the studies on SAD including functional connectivity, activation, response to treatment, and structural ones.[17] The purpose was to provide further evidence for the neurobiological model of phobias and anxiety disorders developed by Etkin and Wager.[18] The results confirmed the hyperrecruitment of fear circuits, as well as the involvement of medial parietal and occipital regions and the disconnection among parietal, limbic, and executive network.[17]

Aim of the present study

Although these meta-analyses investigated the topic of emotional reactivity in SAD, they did not provide any information about the functional neuroanatomy of face perception processes in this disorder, in spite of the potential role that this phenomenon likely plays in the psychopathology of SAD. To fill this gap, we aimed to find a pattern of neural alterations that may be specifically related to disrupted face processing in SAD. We investigated the hypothesis that an abnormal neural response in SAD patients may not be limited to the amygdala but rather may affect the extended cortical system for face perception as well. Specifically, alterations within social cognition and theory of mind areas, as well as in areas related to empathy, may represent the neurobiological correlates of the abnormal features typically observed in clinical and experimental studies in SAD patients. To this purpose, we conducted a meta-analysis taking into account all the functional magnetic resonance imaging (fMRI) studies on face perception in which a direct comparison between SAD patients and HCs had been carried out, regardless of the emotional characteristics of faces used in the experimental tasks and the contrasts chosen for the analysis and also including unpublished data, a strategy commonly used in behavioral meta-analysis.

Recently, another meta-analysis, published by Binelli *et al.* in 2014, has assessed this topic comparing face perception in SAD patients versus controls and in patients with William's syndrome versus controls.[19] Although the methodology for the inclusion criteria of this meta-analysis is similar to the present work, there are also fundamental differences. In particular, to our knowledge, ours is the first study in which authors of individual papers were asked to provide unpublished data for the meta-analysis. Specifically, we asked authors of studies that used faces as stimuli, but in which a direct comparison between SAD versus HCs had not been reported in the original paper, to provide us with the coordinates for this contrast. This strategy has potentially important consequences for the results. Asking for unpublished coordinates allowed us to increase the number of studies entered into the meta-analysis and to reduce publication bias. Publication bias is the tendency to avoid publishing negative results, which indeed may play quite a relevant role in neuroimaging studies. Furthermore, the meta-analysis by Binelli *et al.* also used data from ROI-based studies. This choice could also introduce a bias in the results since the meta-analysis approach in neuroimaging calculates some parameters (including smoothing and suggested cluster size), assuming that whole brain is considered. For this reason we excluded ROI studies, unless authors could provide also results for the whole brain analysis.

Methods

The selection process took place in three stages. In the first stage, two independent investigators searched Pubmed (www.pubmed.gov) with the key words ''social anxiety'' AND ''faces'' and ''social phobia'' AND ''faces'' for the time frame up to January 2015. In the second step, we refined the search assessing from the title and abstract whether the studies: (1) were fMRI studies; (2) used faces for the experimental paradigm; (3) included both a group of patients with social phobia and a control group. In this phase, we also excluded narrative reviews on the topic. Following this selection, we obtained 43 studies, for which we recovered the full texts. Out of these, in a third step, we further excluded those papers that used particular type of patients (e.g. autism patients with social anxiety;[20] subclinical social anxiety[21]) or particular type of faces (e.g. own-face perception[22]) and we included only those papers in which the results of the comparison between SAD and HC in a face perception task were reported. For those studies in which the basic contrast was not reported in the paper, we asked the authors to provide it, if possible with the same statistical level used in each original paper. For the studies that only considered the SAD > HC contrast, we also requested the contrast HC > SAD if available. For studies based on ROI analysis, we also requested the author to provide whole brain results if available. In case of absence of response or impossibility to provide data for a whole brain analysis, we excluded the paper from the analysis (Table 2). Finally, we excluded any study that explicitly reported having used, even partially, data from another published study already included in our meta-analysis.

Thus, ultimately we included 23 fMRI studies with a total of 873 subjects 449 with SAD and 424 HCs in our meta-analysis (Table 1). For 16 studies, we used published

Table 1 Characteristics of the papers entered the meta-analysis

	SAD				HC							
	N.	M/F	Age (mean ± SD)	SAD severity* (mean ± SD)	N.	M/F	Age (mean ± SD)	SAD severity* (mean ± SD)	Type of faces	Type of contrast†	Table number	Notes
Fonzo *et al.*[23]	14	4/10	25.4 ± 8.5	Not evaluated	15	6/9	30.0 ± 10.2	Not evaluated	H, F, A	F > HF > A	Data provided by authors	
Wheaton *et al.*[24]	23	16/7	26.1 ± 6.7	70.7 ± 15.1	24	11/13	25.0 ± 5.6	6.8 ± 5.6	N, F, A	F > NA > N	Data provided by authors	Each of the contrast was considered for the two conditions of the original experiment. High and low cognitive load.
Ziv *et al.*[25]	67	35/32	33.0 ± 8.8	84.1 ± 17.5	28	15/13	32.6 ± 9.5	15.3 ± 9.1	A, C	Faces > fixation asterisks	3	The whole group analysis was conducted on 27 SAD patients (with highest scores at LSAS) and 27 HC
Klumpp *et al.*[26]	29	11/18	24.9 ± 6.3	77.3 ± 15.4	27	12/15	24.9 ± 5.9	24.9 ± 5.9	H, F, A	H > shF > shA > sh	Data provided by authors	
Phan *et al.*[27]	21	8/13	25.9 ± 5.5	82.29 ± 13.02	19	10/9	26.9 ± 8.1	9.17 ± 7.40	H, F, A	F > H A > H	Data provided by authors	
Prater *et al.*[27]	20	9/11	25.9 ± 5.3	79.35 ± 15.41	17	7/10	25.7 ± 7.1	7.94 ± 7.05	H, F, A	F > H A > H	Data provided by authors	
Pantazatos *et al.*[28,‡]	16	2/14	33.6 ± 7.1	Not provided	19	11/8	31.7 ± 8	Not provided	F, N, MF, MN	All faces versus baseline	S4	
Pantazatos *et al.*[28]	14	4/10	27.3 ± 7.5	86.7 ± 18.1	17	7/10	31 ± 10.7	7.8 ± 5.3	A, H, N	All faces versus baseline	S4	
Frick *et al.*[29]	14	Not provided	32.4 ± 8.8	72.1 ± 25.7	12	Not provided	28.0 ± 8.2	Not provided	F,N	F > N	2	
Labuschagne *et al.*[30]	18	18/0	29.4 ± 9.0	>70	18	18/0	29.9 ± 10.2	Not provided	S, H, N	S > N H > N	2	Contrast obtained for the placebo condition. No significant regions for H > N were found
Klumpp *et al.*[31]	29	12/17	24.7 ± 5.9	81.0 ± 15.2	26	10/16	26.2 ± 6.3	8.2 ± 7.7	F,H	F > H	2	
Hahn *et al.*[32]	10	9/1	28.6 ± 4.3	Not evaluated	27	11/16	27.7 ± 7.2	Not evaluated	A, F, D, S, Su, H, N	Emotional faces > baseline	Data in the text and provided by authors	Contrast obtained for the nine men with SAD compared with 11 HC
Blair *et al.*[33,§]	25	10/15	32.2 ± 9.1	73.2 ± 20.4	25	13/10	29.7 ± 8.3	Not provided	A, F, H	A, F > H	2	Main effect of diagnosis and diagnosis X emotion interaction were considered
Blair *et al.*[33,**]	14	7/7	13.3 ± 3.4	21.7 ± 4.8	14	9/7	14.9 ± 2	Not provided	A, F, H	A, F > H	2	Main effect of diagnosis and diagnosis X emotion interaction were considered

(continued)

Table 1 Continued

	SAD				HC							
	N.	M/F	Age (mean ± SD)	SAD severity* (mean ± SD)	N.	M/F	Age (mean ± SD)	SAD severity* (mean ± SD)	Type of faces	Type of contrast†	Table number	Notes
Schneier *et al.*[34]	16	6/10	29.8 ± 9.0	81.4 ± 15.6	16	6/10	30.3 ± 9.7	8.2 ± 5.4	N	Direct > averted gaze	3	
Klumpp *et al.*[35]	12	Not provided	28.2 ± 8.6	Not provided	12	Not provided	33.6 ± 9.6	Not provided	A,F,D	A,F,D > baseline	1	Data from amygdala obtained by ROI analysis
Goldin *et al.*[36]	15	6/9	31.6 ± 9.7	67.6 ± 21.1	17	8/9	32.1 ± 9.3	29.3 ± 20.9	HA, NS	HA > NS	2	
Evans *et al.*[37]	11	4/7	29 ± 7.5	82.4 ± 21.5	11	4/7	27.9 ± 10.6	Not provided	A,H,N	A > N	2,3	Schematic faces
Gentili *et al.*[8]	8	4/4	39 ± 7	69.6 ± 1.01	7	4/3	30 ± 7	24.7 ± 1.25	N,H,D,F,A	All faces > scrambled	1	
Blair *et al.*[13]	17	9/8	29 ± 8.7	68.3 ± 20.7	17	9/8	31.2 ± 9.1	57.2 ± 26.7	A,F,H	A, F > H	Data provided by the authors	Main effect of diagnosis and diagnosis X emotion interaction were considered
Yoon *et al.*[38]	11	5/6	27 ± 6	70.91 ± 19.98	11	5/6	26.9 ± 6.1	9.64 ± 8.42	A,F,D,H**	High > low††	Data in the text	Data from amygdala obtained by ROI analysis
Phan *et al.*[14]	10	5/5	26.7 ± 6.8	72.1 ± 20.6	10	5/5	26.6 ± 6.8	9.8 ± 8.9	A, F, D, S, H, N	A,F,D, S > H	Data in the text	
Amir *et al.*[15]	11	3/8	24.1 ± 5.2	Not provided	11	3/8	23.9 ± 5.7	Not provided	D, N	D > N	2	
Straube *et al.*[39]	9	4/5	25.7 8 3.4	Not provided	9	4/5	22.7 8 2.6	Not provided	A, F, H, N	A, F, H, N > fixation cross	1	Data from ROIAuthors reported no other clusters outside the ROI
Stein *et al.*[11]	15	10/5	39.1 ± 14.3	87.7 ± 25.7	15	10/5	39.3 ± 12.3	15.5 ± 13.4	A,F,H,C	A,F,C > H	2	

A: angry faces; C: contemptuous faces; D: disgusted faces; F: fearful faces; H: happy faces; HC: healthy controls; MF: masked fearful faces; MN: masked neutral faces; N: neutral faces; S: sad faces; SAD: patients with social anxiety disorders; Sh: shapes; Su: surprised faces; LSAS: Liebowitz Social Anxiety Scale.

*SAD severity was evaluated with the Liebowitz Social Anxiety Scale in all the study but in the adolescent group of the study by Blair *et al.*[33] where the Pediatric Anxiety Rating Scale was used: all the values are mean ± SD with the exclusion of Labuschagne *et al.*[30] who reported only that all SAD patients score over 70 at the LSAS.

†Type of contrast used for the comparison between SAD and HC.

‡Two independent groups with two different tasks were used in the study. The analysis assessed the main effect of diagnosis (SAD versus HC) on all faces perception.

§Demographic data for the adult groups.

**Demographic data for the adolescent groups.

††Faces were presented with a low and a high degree of emotional intensity.

Table 2 List of the papers excluded at the third step of selection and principal reason for exclusion

Title	First Author	Date	Reason for exclusion
fMRI reveals amygdala activation to human faces in social phobics	Birbaumer N	1998	No direct comparison between phobics and controls in a face perception study
Brain circuits involved in emotional learning in antisocial behavior and social phobia in humans	Veit R.	2002	No direct comparison between phobics and controls in a face perception study
Effect of task conditions on brain responses to threatening faces in social phobics: an event-related functional magnetic resonance imaging study	Straube T.	2004	ROI study—not full brain cover
Amygdala activation in the processing of neutral faces in social anxiety disorder: is neutral really neutral?	Cooney RE	2006	ROI study
Time-varying amygdala response to emotional faces in generalized social phobia	Campbell DW	2007	ROI study—analysis on temporal dynamics and not on magnitude of response
Activity in medial prefrontal cortex during cognitive evaluation of threatening stimuli as a function of personality style	Rubino V.	2007	Target population is phobic prone subjects which cannot be considered as patients with social phobia
Common and distinct amygdala-function perturbations in depressed vs anxious adolescents	Beesdo K	2009	Anxiety adolescents group is heterogeneous
Beyond amygdala: Default mode network activity differs between patients with social phobia and healthy controls	Gentili C.	2009	Same data-set used for another paper already in the meta-analysis
Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder	Labuschagne I.	2010	No direct comparison between phobics and healthy controls but just drug*group interactions Same data-set used for another paper already in the meta-analysis
Is social phobia a ''mis-communication'' disorder? Brain functional connectivity during face perception differs between patients with social phobia and healthy control subjects	Danti S.	2010	Same data-set already entered the meta-analysis
Association between amygdala response to emotional faces and social anxiety in autism spectrum disorders	Kleinhans NM	2010	Target population is autistic patients with or without social anxiety
Neural correlates of perception of emotional facial expressions in out-patients with mild-to-moderate depression and anxiety. A multicenter fMRI study	Demenescu LR	2011	Anxiety patients group is heterogeneous
Amygdala and hippocampus fail to habituate to faces in individuals with an inhibited temperament	Blackford JU	2013	Target population is inhibited temperament subjects which cannot be considered as patients with social phobia
Neural response to the observable self in social anxiety disorder	Pujol J.	2013	Task involved own-face perception
Disrupted effective connectivity between the amygdala and orbitofrontal cortex in social anxiety disorder during emotion discrimination revealed by dynamic causal modeling for fMRI	Sladky R.	2013	Contrast for SAD versus HC not available neither in the manuscript nor from the authors
Self-referential and anxiety-relevant information processing in subclinical social anxiety: an fMRI study	Abraham A.	2013	Subjects with subclinical social anxiety
Amygdala activation and its functional connectivity during perception of emotional faces in social phobia and panic disorder	Demenescu L.R.	2013	No main effect for the diagnosis of SAD (only for the diagnosis of panic disorder)
Neural predictors and mechanisms of cognitive behavioral therapy on threat processing in social anxiety disorder	Klumpp H.	2013	Same data-set used for another paper already in the meta-analysis
Serotonin transporter gene alters insula activity to threat in social anxiety disorder	Klumpp H.	2014	Same data-set used for another paper already in the meta-analysis
Classifying social anxiety disorder using multivoxel pattern analyses of brain function and structure	Frick A.	2014	Same data-set used for another paper already in the meta-analysis

data, while for seven studies we used, partially or totally, the unpublished analysis provided by the authors.[13,23,24,27,31,32,40] Table 1 reports the characteristics of each study of the present meta-analysis including type of faces, type of contrasts, and type of task used.[8,11,13–15,23–27,29–41] Table 2 reports the 20 studies excluded in the second step of the selection and the main reason why they were not included in the final analysis.

Activation likelihood estimation (ALE) meta-analysis was conducted using the GingerALE software (version 2.3 http://www.brainmap.org/ale/).

ALE meta-analysis is a coordinate-based meta-analysis approach, which is widely adopted in neuroimaging. ALE has been typically used to identify concordance across studies or to compare results across distinct tasks or groups of subjects. ALE models the probability of localizing active foci with Gaussian probability density distributions. Distributions map are derived by each data-set entering in the meta-analysis. The ALE value, generated by the union of each distribution at a voxel level, is an estimate of the likelihood that at least one of the foci in a data-set was truly located at a given voxel of the final ALE map (for a more detailed description of the method refer to Turkeltaub *et al.*[42] and Eickhoff *et al.*[43]).

We considered the foci from the contrasts in SAD versus HC during face perception. We were able to obtain the contrast SAD > HC for all the 23 studies. As far as the HC > SAD, 12 out of the 23 included studies explicitly stated that they had performed the comparison HC > SAD. Among these studies the comparison yielded significant differences in only six studies[8,28,33,35–37] and non-significant results in the other six. For the studies that did not explicitly report the contrast, we asked authors for the results of the contrast. We obtained a response for each of the remaining 11 papers: three had obtained non-significant results for the comparison HC > SAD[13,23,39]; for additional three papers, it was not possible to recover the original data to run the new analysis[15,34,38]; for the remaining five papers, we recovered original unpublished data for the comparison HC > SAD.

Finally, 11 out of the 23 papers used in this meta-analysis are from previous publications of the authors of the present paper. More in particular, regarding the seven studies for which we used unpublished data provided under request, four of them are studies from the authors of the present paper, while three were provided by independent researchers (see ''Acknowledgment'' section). The meta-analysis was run by one author who was not involved in the analysis for the original papers (see ''Acknowledgment'' section).

We used Talairach coordinates for the meta-analysis and accordingly converted coordinates from papers using MNI with the GingerALE foci converter tool. We calculated the Random Effects Model according to Turkeltaub *et al.*[42] and the p values according to Eickhoff *et al.*[43] We used an False Discovery Rate (FDR)-corrected p value of 0.01 to compute ALE maps and we also considered a minimum cluster size of 32 mm^3 in order to minimize type I and II errors. The cluster size was chosen according to the simulations provided by the GingerALE software. Specifically, the cluster volume was determined through a Monte Carlo simulation performed by the software on simulated data created from the results data-set. The obtained cluster size was calculated to allow only a 5% of false positive at the given statistical threshold of FDR 0.01.

AFNI toolbox[44] was used to display the results.

Results

The meta-analysis highlighted clusters in which SAD patients showed a higher activation for face perception as compared to HC. Namely, significant clusters were located in the two amygdalae, in the STS, in the prefrontal cortex (inferior frontal gyrus, medial frontal gyrus, superior frontal gyrus, and in the subgenual cingulate), and in the visual cortex (lingual gyrus, middle occipital, and middle temporal gyrus) (Figure 1 and Table 3). Of note, the right amygdala cluster extended to the region of the globus pallidus.

We also identified two significant clusters for the contrast HC > SAD in the precuneus and in the lingual gyrus.

Discussion

The aim of the present meta-analysis was to evaluate the presumed altered recruitment of the extended face perception system in SAD patients. Specifically, we intended to verify whether neural abnormalities would occur beyond those attributed to ''emotional'' and/or ''threat'' processing in prior published narrative and meta-analytic reviews[17,19] and would extend to the perceptive, attentive, and cognitive systems involved in face perception.[6] To this purpose, we considered all the fMRI studies that conducted a direct comparison between SAD and HC using a face perception task, regardless of the face emotional expressions and task used. Our study highlighted a higher activation of SAD patients in regions related to emotional recognition and processing (STS), related to attention (superior frontal gyrus) and emotional regulation (subgenual anterior cingulate and medial frontal gyrus). We also found an abnormally higher response to faces in the visual cortex. Of note, our meta-analysis highlighted for the first time also areas that are more active in HC as compared to SAD during face perception, namely in a cluster of the occipital visual cortex (lingual gyrus) and in the posterior cingulate, Finally, consistently with the other available meta-analyses and with the vast majority of functional brain imaging studies, we identified an abnormal activation in the amygdalae of SAD patients as compared to HCs in response to face stimuli (e.g. in the literature [8,11,12,14,35,45]).

Specifically, as expected, we found that bilateral amygdala was more active in SAD patients as compared to HCs. An altered amygdala response has been consistently reported by brain imaging studies in SAD patients, as well as in subjects with other anxiety disorders, both by ROI[12,39] and whole brain studies.[16] Although amygdala alterations are almost always present in SAD studies involving faces, it is possible to underline different patterns of altered brain activity. For instance, some studies highlighted bilateral amygdala hyperactivity in SAD (e.g. in the literature[11,13,14,31,33,35,37,38]), while others found a

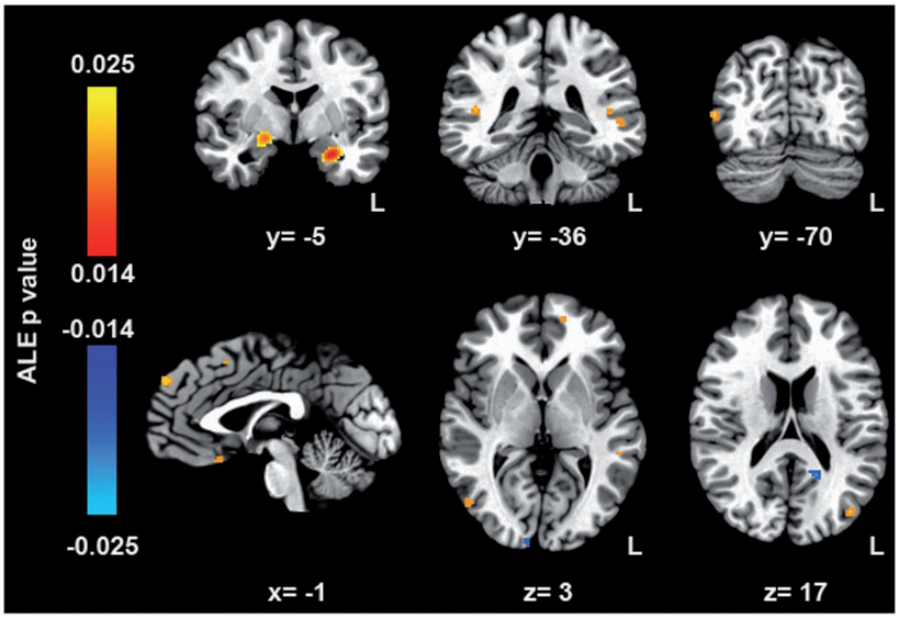

Figure 1 ALE map of the significant cluster for face perception in SAD patients versus HC. All the clusters were significant at a p value of 0.01 (FDR corrected) and of $> 35\,mm^3$ volume. Warm colors indicate higher activity in SAD while cold ones indicate higher activity in HC. Higher ALE probability values are related to more significant clusters, while lower ALE probability values are related to less significant clusters. (A color version of this figure is available in the online journal.)

Table 3 Significant ALE clusters for face perception in SAD patients versus HC. All the clusters were significant at a p value of 0.01 (FDR corrected) and of $> 35\,mm^3$ volume

	Hemi-sphere	Region	BA	Center of mass			Peak			Peak ALE p-value	Volume (mm3)
				x	y	z	x	y	z		
SAD > HC											
	R	IFG	47	29.21	14.43	−14	30	16	−14	0.014	40
	L	MedFG	9	.45	53.79	36.26	0	54	36	0.02	240
	L	SFG	8	−2.53	15.47	48.12	−2	16	48	0.017	120
	R	MedFG	10	6.99	43.03	−7.98	6	44	−8	0.016	96
	L	MedFG	10	−13	51.03	3	−14	52	2	0.015	64
	L	SubACC	25	−2.19	17.76	−14.25	−2	18	−14	0.017	200
		SubACC	25				−2	14	−12	0.015	
	R	GP/amygdala		20.72	−4.76	−8.05	18	−2	−8	0.021	952
	L	amygdala		−23.65	−3.84	−18.04	−24	−4	−18	0.025	760
	L	MTG	19	−38.13	−74.38	18	−38	−74	18	0.017	128
	R	MTG/MOG	19	49.41	−68.67	6.02	50	−68	6	0.017	192
	R	STS	41	43.57	−36.87	9.76	44	−36	10	0.016	144
	L	STS	22	−50.36	−35.5	1.66	−50	−36	2	0.016	96
	L	STS	41	−42.86	−35.15	8.85	−44	−36	8	0.014	56
	R	Lingual gyrus	18	22.78	−86.82	−6.38	22	−86	−6	0.014	40
HC > SAD											
	L	Precuneus	30	−15.21	−49.04	16.33	−16	−50	16	0.013	216
	R	Lingual gyrus	17	11.56	−92.7	1.64	10	−94	2	0.012	184

BA: Broadmann areas; GP: globus pallidus; IFG: inferior frontal gyrus; MedFG: medial frontal gyrus; MOG: middle occipital gyrus; MTG: middle temporal gyrus; SFG: superior frontal gyrus; SubACC: subgenual anterior cingulate cortex.

lateralized greater amygdala response. For instance, several works identified an altered response in the right amygdala only,[13,14,31,37] while others reported an opposite pattern (e.g. Gentili *et al.*[8]).

As a matter of fact, it is well established that the two amygdalae have different functions. For instance, Zalla *et al.*[46] showed a differential amygdala response in healthy individuals while they were performing a competitive

computer game: neural activity in the left amygdala became progressively greater in a parametrically increasing winning condition while the opposite behavior was shown by the right one. Other studies reported that the two amygdalae reacted differently to diverse types of mood induction, suggesting a different role in emotional processing.[47] Finally, a differential effect of gender on amygdala-lateralized discharge during face perception has been shown.[48] Thus, it is possible that differences in experimental designs may account for differences in amygdala activations. It is also possible that the two amygdalae may play different roles in face perception in SAD. However, the meta-analytic approach cannot directly support this hypothesis, because it evaluates common patterns among studies and does not single out particularities from individual studies.

It is worth noting that the right amygdala cluster also included the globus pallidus. Interestingly, the globus pallidus was found to be altered also in a previous meta-analysis on the neurobiological dysfunctions of emotional processing in SAD,[16] as well as in a meta-analysis of specific phobias.[49] Although globus pallidus is primarily related to motor control, it has been linked also to emotional regulation.[50,51] Recently, neural activity in the right globus pallidus was found to correlate with a better short-term memory for faces portraying negative emotions (namely anger).[52] The recruitment of this area may be related to the involvement of the salience circuit, which is more prominent for faces conveying information about a potential threat.[52,53] Thus, the increased discharge in the globus pallidus and amygdala in SAD patients may be related to an increased salience attribution to faces and to the worry of a potential threat.

Contrary to the findings from the other meta-analysis on the topic,[19] we identified several clusters in the prefrontal cortex that are more active in patients as compared to HC. The inferior frontal gyrus (IFG) is a region that has been linked to regulation and modulation of emotions both in social[54] and non-social contexts[55] and which mediates aspects of empathy.[56] A similar role has been postulated for the subgenual anterior cingulate.[57] It has been suggested that this region gathers information about pain, threat, punishment and, more in general, negative feedback, triggering fear and anxiety, influencing goal-directed behaviors, and biasing the balance between self-focused and other-focused attention in favor of the first.[55] For this reason, it is not surprising that the cingulate cortex activity has been found altered in several psychiatric disorders, including not only SAD,[58,59] but also other anxiety and mood disorders.[57,60] Moreover, medial prefrontal cortex clusters, including medial frontal gyrus and superior frontal gyrus, were hyperrecruited in SAD as compared to HC. These regions are typically involved not only in emotional modulation but also in cognitive and attentive processes including decision-making and autobiographical memory[61,62] and seem to contribute to neuro-vegetative control and to the sympathovagal balance.[63] Moreover, several studies highlighted their recruitment (together with the subgenual cingulate) while subjects practiced cognitive strategies of emotional modulation.[64–66] Finally, their abnormal activity seems to be specifically involved in SAD given its role in fear conditioning and extinction in phobias.[67] These frontal areas also seem to modulate self-focused attention—the attention to inner sensations and thoughts, which typically is abnormally increased in anxiety disorders.[68,69] The higher response in these areas in SAD may be interpreted as the neurobiological counterpart of altered emotional regulation processing while patients are exposed to socially anxious stimuli. It is interesting to note that a recent meta-analysis in healthy individuals also found bilateral amygdala, globus pallidus, and areas belonging to the IFG and the ventral prefrontal cortex to be more activated during negative social evaluation of faces.[70] We suggest that such an overlap may be related to the increased proneness to rate faces as negative, which is typical behavioral feature in SAD patients.[71,72] Moreover, these results are also in line with the cortico-limbic dysfunction hypothesis of SAD.[73]

Concerning the extended network for face perception, we also identified significant clusters in the bilateral STS in which response for faces was higher in SAD as compared to HC. STS plays a fundamental role in several components of the face perception process,[6] including gaze perception,[10,74] emotion recognition,[75,76] and mental state attribution.[75] The existing evidence consistently points to the role of the STS in linking variant face characteristics (expression, gaze, etc.) to their social and communicative meanings.[77] Thus, it is not surprising that STS was also found to be hyperactive in studies on social phobia. Straube *et al.*, for instance, showed a significantly greater activity in STS in SAD patients as compared to HCs in a wide range of conditions and independently from the type of face image (schematic draw or picture) and task (explicit or implicit face perception task) used.[39,78] Gentili *et al.*[8] found an hyperactivation of bilateral STS for face perception as compared to scrambled images in SAD versus HC. A significantly stronger activation in STS in SAD patients than in healthy matched controls also was found by Amir *et al.*[15] in a study focused on the role of cingulate cortex during the perception of disgusted/contemptuous faces. Overall, hyperactivation in STS is thought to reflect an increased wariness to socially relevant stimuli. This increased wariness may be related to the perceptual bias toward negative emotions, a seemingly core characteristic of SAD.[8,79]

Our results also showed significant differences in brain activity within the visual cortex. Namely, clusters in the lingual gyrus and in the temporal cortex were more active in SAD while another cluster, again in the lingual gyrus, was more active in HC. We believe that this complex pattern of altered response to faces in the visual cortex is related to the dysfunctional perceptive process in SAD. In this sense, it is interesting to note that Giménez *et al.* found an increased activation of visual areas in social phobics while they were under scrutiny by others.[80] Pujol *et al.* reported an increased activation in the primary visual cortex during a self-recognition task in SAD patients,[22] which was interpreted as an increased arousal due to negative self-judgment, typically present in these patients. Given the importance of early visual areas in face processing (particularly in the case of aversive emotions),[81] it is possible that this cluster of activation may also be related to the increased arousal and wariness toward faces. An alternative

interpretation for this finding implies that altered face processing in SAD could also involve early visual processing areas. Some studies suggested that activity in the fusiform face area is disrupted in SAD.[8,20] Consequently, this alteration may represent the neurobiological counterpart of the altered scan path usually detected in SAD patients while exploring faces.[9] We can hypothesize that because of the altered functionality in the fusiform gyrus, face recognition processes would rely on a partially different path within the distributed ventro-temporal cortex.[6]

Apart from the above-mentioned cluster in the lingual gyrus, we also found another region, the precuneus, in which HC showed a higher response to faces as compared to SAD. Precuneus activity seems to be related to the sense of self[82] and the self-attribution of emotions, as compared to when emotions are attributed to others.[83] Moreover, abnormal activity and connectivity in precuneus has been reported in anxiety disorders, including SAD.[84–88] Studying the switch between rest and a face perception task, Gentili *et al.* reported a weakened deactivation in SAD as compared to HC.[89] This lack of deactivation was considered a possible neurobiological correlate of self-focused attention. Finally, resting state activity in this region as measured by means of fALFF and Hurst exponent seems to be modulated by social anxiety severity in a group of healthy volunteers.[90]

Methodological considerations and comparison with other published meta-analyses

Emotional processing in SAD is a very relevant topic in social neuroscience. In the last few years, a narrative review[91] and three meta-analyses[16,17,19] have focused on this topic. Hattingh and coworkers investigated brain responses to socially relevant stimuli and compared emotional faces and statements to neutral ones.[16] In this way, the emotional dysregulation in SAD was assessed in a consistent and coherent way, independently from the characteristics of the specific stimuli. Brühl *et al.*, in the same framework, tried to be as inclusive as possible and create an inclusive network-based model of brain abnormal responses in SAD.[17] On the other hand, we decided to focus on the functional neuroanatomy of face perception and not to include studies with other stimuli, as we predicted that face perception in SAD would be a unique phenomenon with distinctive abnormalities.

As expected, some of the regions we identified in our meta-analysis (for instance the bilateral amygdala and the globus pallidus) are consistent with Hattinigh *et al.*'s and Brühl *et al.*'s results.[16,17] These areas may be related to the altered emotional regulation process, which is a relevant core aspect in SAD and is evoked whenever patients cope with any socially relevant stimuli. Interestingly, as hypothesized, we found altered neural activity in additional regions, including STS, and prefrontal cortical areas, which are more active in SAD, as well as a reduced activation in the precuneus and lingual gyrus. We argued these regions could be more strictly related to the specific alteration in the face perception process rather than to emotional dysregulation, because while we found significant differences here, these were absent in the two above-mentioned meta-analyses. However, we acknowledge that the attempt to disentangle the dysfunctions in face perception processes from those associated with emotional regulation is rather speculative, as the two are intrinsically intertwined.[55] It may be that face perception in SAD induces specific increases in arousal and alterations in emotional regulation regions, while, in turn, alterations in these regions may interfere with the normal exploration of faces.

The third recent meta-analysis tackles a very similar research question to our present work.[19] Binelli *et al.* were interested in evaluating face processing in SAD and William's syndrome patients, in order to explore the complete spectrum of emotional reactivity to faces. As expected, results partially overlapped with our own (specifically, in the bilateral amygdalae), but they also differed from the present study for several aspects. First of all, they found a greater recruitment in the insula for the contrast SAD versus HC, possibly driven by ROI-based studies. On the other hand, we found higher activation in bilateral STS, in the superior frontal gyrus and in the IFG which were not found by Binelli *et al.* Moreover, we identified clusters in medial frontal gyrus, anterior cingulate, and visual cortex that, although similar to those found by Binelli *et al.*, were not overlapping. Finally and, in our opinion, most relevantly, we also found areas in which SAD patients had a significantly lower response as compared to HC, namely the precuneus and lingual gyrus.

We believe that discrepancy in results is mostly due to the different research questions investigated by the two papers. The work by Binelli *et al.*[19] was interested in assessing face perception process in two distinct disorders, which are at the opposite extremes of the continuum of social fear, SAD, and William's syndrome. As in other studies in the literature, the Binelli's review seems specifically interested in assessing emotional response to faces. On the other hand, we were more interested in assessing the whole face perception process in SAD. These differences are not trivial as for instance, for our purposes we were also very interested in the contrast HC > SAD, as differences in this direction may also indicate a face perception dysfunction in SAD. However, several studies did not report such a contrast, with the consequence that the Binelli's meta-analysis found no significant clusters. We believe that these two different approaches did play an effect on inclusion/exclusions criteria for individual studies and search methodology, producing two very relevant differences between the two meta-analyses:

1. The meta-analysis by Binelli *et al.*[19] considered also ROI studies in which the whole brain was not covered, as well as *a priori* regions (with *a priori* significant thresholds) were considered. For instance, the study by Straube *et al.*,[12] which considered ROIs in the insula, amygdala, and fusiform gyrus, was conducted without a complete brain coverage.
2. We had the opportunity to use unpublished contrasts for some papers available in the literature leading to an increase of the number of studies and to a better control of publication bias, while also allowing us to

focus on the comparison HC > SAD which is typically less evaluated and often considered less important.

As a result, our present work includes 23 studies, of which only 15 are in common with those reported by Binelli *et al*.[19]

Study limitations

Out of the 23 papers included in this meta-analysis, 11 are co-authored by at least one of the authors of the present paper. Thus, a potential critical issue is that we could be biased toward the confirmation of our own findings. This phenomenon, known as ''allegiance'' is well known in clinical research, especially when psychotherapies are compared, and may constitute an important source of bias.[92–94] In neuroimaging meta-analyses this problem has not yet been raised. However, it is less likely for neuroimaging data to be affected by this type of bias, given that the type of measures (discrete, as spatial coordinates are) is different as compared to those used in behavioral meta-analysis (continuous, as psychological scales are). In our specific case, moreover, the inclusion also of unpublished data from studies that were not conducted with the aim of comparing faces in SAD versus HC minimizes this potential bias even further. Finally, as far as the unpublished contrasts are concerned, it is relevant to underline that the authors who performed these new analyses are not those who performed the GingerALE meta-analytic one, as indicated in the ''Acknowledgment'' section.

A limitation of our study, as well as of the other recent meta-analyses, is that we did not calculate ALE maps for face perception separately for HC and SAD patients prior to performing a contrast meta-analysis. Although this is a more robust way to conduct this type of meta-analysis, neither any of the previous meta-analyses,[16,17,19] nor the present one were able to perform this type of analysis, as all the published papers just presented results for the comparison between the two groups. Further meta-analyses requesting this type of results from the authors may help to confirm the findings obtained in the present work. Moreover, in our meta-analysis we did not consider single typology of contrasts between faces (for instance negative versus neutral faces). On the one hand, this provides a pattern of activation that may be considered specifically related to general face processing in SAD; on the other hand, this makes it impossible to evaluate subtle differences.[11,16] However, our statement should be weighted also considering that dissecting the emotional component of face perception from the strictly sensory-perceptive one is obviously difficult (if not impossible), given the intertwined relation between these two aspects. One can speculate that an experimental approach using only neutral faces could allow to identify more specifically the sensory-perceptive component. However, that neutral faces are truly neutral, meaning without any emotional content, especially when SAD patients are concerned, is debated.[95]

Another possible methodological limitation is that the heterogeneity of the contrasts is a hard to control condition. Particularly, some contrasts are more frequently used than others across the studies we considered (e.g. the fearful versus neutral contrast is more present and therefore would weight more in the results as compared to the happy versus neutral faces). This may have biased the meta-analysis. Nevertheless, these limits do not reduce the general meaning of our results, indicating an alteration within the face perception neural pathway that can be highlighted despite differences across specific experimental designs.

Finally, our meta-analysis suffers from the limitations intrinsic to the ALE meta-analysis methods. For instance, data were collected and provided with different threshold and different corrections for multiple comparisons (and sometimes included no correction at all). Indeed, a unique approach to meta-analysis for fMRI data is still missing and methodological studies should look into the effects of using ROI studies and results from different thresholds, in order to produce a consensus methodological agreement. However, we believe that our innovative approach, derived from meta-analyses of behavioral data, could be extended to control for these issues, by asking authors for original data at a given pre-set threshold, and not limited to ROIs.

Conclusions

Our work expanded the available neurobiological models of SAD.[17,73,91] Recently, it has been underlined how the neural abnormalities in SAD may involve a wider network that still remains to be characterized.[73] To address this need, here we have examined the neurobiological alterations in SAD related to face perception processing.

In this meta-analysis, we used comparisons between SAD patients and HCs for all types of face perception contrasts reported in the fMRI studies published to date. Thus, we believe that the brain areas that emerged are consistently related to face perception and provide a comprehensive knowledge of face perception alterations in SAD patients. As a matter of fact, meta-analytic approach in neuroimaging allows to ''average'' brain activations which are consistent among studies.[43] For this reason, we think that gathering together different contrasts would dilute the activations due to specific contrasts and strengths into those related to the common face perception neural pathway.

In this meta-analysis, as compared to other similar ones, we adopted an innovative approach, which is widely used in behavioral meta-analyses. Considering the relevant differences that emerged in this work, using unpublished data, as compared to the commonly used approach with only published data[19] we believe that requesting supplementary results from authors should become a routine in fMRI meta-analyses. Specifically, we had the opportunity to increase the number of studies included into the meta-analysis and to minimize potential publication biases.

In line with recent positions on meta-analyses, we believe that the results of this meta-analysis would be a valid tool to define ROIs for functional connectivity studies.[96,97] In particular, ROI selection is a relevant issue in SAD since this approach is widely used in the study of this psychopathological condition (e.g. Straube *et al*.[12] and Straube *et al*.[39]). Our results found a significant cluster at

a meta-analytic level in the bilateral amygdala and STS, which are often used in ROI studies. However, we failed to detect significant clusters in other ROIs, such as the fusiform gyrus, which are often used as well.

To conclude, the foci identified in our meta-analysis support the idea that a complex network belonging to the extended neural system for face perception is altered in SAD.[6] Thus, while our results also provide additional support to the hypothesis that amygdala hyperactivity is a consistent marker of SAD patient response to faces, they clearly indicate that alterations of face perception in this disorder are more than just a dysfunction in amygdala discharge, in line with previous original reports, including those from our own lab.[8,89] These findings may have potential implications at a clinical level, both for a wider understanding of the pathogenesis of SAD and for the development of novel psychotherapeutic approaches, as they suggest that person-to-person contact in SAD patients may be biased by a dysfunctional perception of faces and reflect a broader alteration in social cognition.

AUTHORS' CONTRIBUTION

Paper conception: CG, IAC, PP
Article search: CG, LT
Data analysis for meta-analysis: CG
Original data-set re-analysis: LT, MA, HK, KLP
Manuscript writing: CG, IAC, PP
Manuscript reviewing: All

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DECLARATION OF CONFLICTING INTEREST

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