Therapy for Adult Social Anxiety Disorder:
A Meta-Analysis of Functional Neuroimaging Studies

Yuchen Li, MD[a,‡]; Yajing Meng, MD, PhD[a,b,‡]; Minlan Yuan, MD[a]; Ye Zhang, MD[a]; Zhengjia Ren, MD[a]; Yan Zhang, MD[a]; Hongru Zhu, MD, PhD[a]; Changjian Qiu, MD, PhD[a,*]; and Wei Zhang, MD[a]

ABSTRACT

Objective: We conducted a meta-analysis of the literature reporting neuroimaging in patients undergoing psychotherapy and pharmacotherapy for social anxiety disorder (SAD).

Data Sources: Using PubMed, MEDLINE, and Embase, we searched for English-language studies published between January 2000 and February 2015 with terms related to SAD, therapy, and neuroimaging.

Study Selection: Twelve studies were included with a total of 295 subjects with SAD before and after therapy from January 2000 to February 2015.

Data Extraction: We extracted peak coordinates of clusters of significant group differences and performed a meta-analysis using effect-size signed differential mapping to analyze the peak coordinates of clusters and thresholds.

Results: Therapy significantly reduced activity in the left inferior parietal gyrus ($Z = 1.441$; $P < .001$), right postcentral gyrus ($Z = 1.711$; $P < .001$), and right precuneus ($Z = 1.352$; $P < .01$) and increased activity in the left inferior frontal gyrus/insula ($Z = 1.939$; $P < .001$) and bilateral middle cingulate gyrus ($Z = 1.836$; $P < .001$). Psychotherapy significantly increased activity in the bilateral precuneus ($Z = 2.259$; $P < .001$) and left inferior parietal gyrus ($Z = 1.786$; $P < .001$) and decreased activity in the left anterior cingulate gyrus ($Z = 1.707$; $P < .001$), left middle frontal gyrus ($Z = 1.584$; $P < .001$), and right cerebellum ($Z = 1.424$; $P < .01$). Pharmacotherapy increased activity in the right postcentral gyrus ($Z = 1.215$; $P < .01$), left middle occipital gyrus ($Z = 1.269$; $P < .01$), and right medial orbital frontal gyrus ($Z = 1.250$; $P < .01$) and reduced activity in the bilateral insula ($Z = 2.172$; $P < .001$; $Z = 1.608$; $P < .01$) and left medial cingula ($Z = 1.479$; $P < .01$). The improvement in social anxiety symptoms was positively associated with hyperactivity of the bilateral precuneus, left inferior partial gyrus, right medial cingulate, and right postcentral gyrus but negatively associated with hypoactivity of the bilateral insula and right medial cingulate ($P < .01$). We did not find any difference of amygdala among these 3 groups.

Conclusions: Previous reports of brain imaging suggest that pharmacotherapy and psychotherapy impact different brain regions in adult patients with SAD.

J Clin Psychiatry 2016;77(11):e1429–e1438
dx.doi.org/10.4088/JCP.15r10226

[a]Mental Health Center, West China Hospital of Sichuan University, Chengdu, China
[b]Psychiatric Genetics Laboratory, Biotherapy State Key Laboratory, West China Hospital of Sichuan University, Chengdu, China
‡Drs Li and Meng contributed equally to this work.
*Corresponding author: Changjian Qiu, MD, PhD, Mental Health Center, West China Hospital of Sichuan University, Chengdu, China (qiuchangjian18@126.com).

Social anxiety disorder (SAD) is one of the most prevalent psychiatric disorders in the general population, affecting 12.1% of people at least once in a lifetime.[1] The core clinical features of SAD are fear and avoidance of social situations in which patients may be scrutinized by others.[2] Functional magnetic resonance imaging (MRI) studies of patients with SAD have implicated hyperactivity of the amygdala, prefrontal cortex and anterior cingulate cortex (ACC), and insula in SAD.[3–5] These regions of the brain compose the fear circuit and are involved in coordinating autonomic responses.[3] Moreover, these regions (ie, prefrontal cortex) act in concert with subcortical regions involved in emotional reactivity,[6] expression,[7] regulation,[8–10] learning,[11] and resolving emotional conflicts,[12] which may influence susceptibility to SAD. Social anxiety disorder has also been reported to involve diminished recruitment of brain networks implicated in attention regulation (posterior cingulate/precuneus, inferior parietal lobe, left middle occipital gyrus) and cognitive regulation (dorsolateral prefrontal and anterior cingulate cortex) during cognitive reappraisal of emotional reactivity to social threat[13] and negative self-beliefs.[14]

Despite the prevalence of SAD and availability of multiple pharmacologic and nonpharmacologic treatment options, only a minority of patients seek help for this condition or receive adequate treatment.[15] Psychotherapies including group or individual cognitive-behavioral therapy, exposure and social skills, mindfulness-based stress reduction,[16,17] psychodynamic psychotherapy, and psychological placebo can all play a therapeutic role in SAD to reduce anxiety symptoms. These techniques can modify negative beliefs and behaviors and change self-evaluation through social skills training, systematic desensitization, flooding, and anxiety management techniques.[18]

Psychotherapy was reported to reduce neural responses in the midline cortical regions, including ventromedial prefrontal cortex, dorsomedial prefrontal cortex, posterior cingulate/precuneus,[19] cerebellum,[20,21] caudate,[21] and left inferior parietal lobule,[21] and to increase activity in the precuneus,[20] middle temporal gyrus,[20] left postcentral gyrus,[21] and superior temporal gyrus.[21] Mayo-Wilson and colleagues[22] recommended individual cognitive-behavioral therapy as the most effective intervention for treatment of SAD.

Psychopharmacologic approaches, however, have also been reported to successfully improve SAD.[22–25] Patients with SAD were reported to have lower 5-HT_{1A} binding in the brain regions associated with anxiety, including the right medial orbital frontal gyrus, and lower dopamine D_2-receptor levels in

Clinical Points

- Adequate neuroimaging evidence to help select the method of therapy for social anxiety disorder is lacking.
- Pharmacotherapy and psychotherapy achieve results through different brain mechanisms.
- Our meta-analysis of the literature on patients with social anxiety disorder revealed that the left inferior parietal gyrus and precuneus were critical brain regions in psychotherapy while the left and right insulae were important brain regions in pharmacotherapy.

the brain were previously reported to cause social anxiety.[26] Pharmacologic treatment with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), anticonvulsants, benzodiazepines, monoamine oxidase inhibitors (MAOIs), and/or mirtazapine mainly functions by altering 5-HT and dopamine activity, restraining the ascending reticular activating system in the brainstem. Pharmaceutical intervention has been reported to reduce activity in the insula,[27] amygdala,[28] and precuneus[20] and to increase activity in the middle occipital gyrus,[20] superior frontal gyrus,[20] and ventromedial prefrontal cortex.[29]

In summary, the capacity of psychotherapy or pharmacotherapy to alter brain activity in patients with SAD remains to be determined. In assessment of the literature on this topic, we must acknowledge that small sample sizes and diverse populations and interventions may generate different results. Changes in brain activity measured before and after psychotherapy or psychopharmacologic intervention differ from one brain region to another.

In this study, we aimed to compare neurobiological changes associated with pharmacologic and nonpharmacologic interventions in adult patients with SAD. We conducted a meta-analysis of studies reporting neuroimaging of patients before and after interventions to further elucidate the potential mechanisms of action of these interventions on the activity of different brain regions. On the basis of the literature, we hypothesize that the brain regions affected by pharmacotherapy differ from those affected by psychotherapy.

METHODS

Literature Collection

We searched MEDLINE (http://www.medline.com), PubMed (http://www.ncbi.nlm.nih.gov/pubmed), and Embase (http://www.elsevier.com/online-tools/embase) using the following keywords: *psychotherapy* (*exposure therapy* or *cognitive behavioral therapy* or *mindfulness-based stress reduction*) or *pharmacotherapy* (*SSRI* or *MAOI* or *SNRI* or *cannabidiol* or *tiagabine* or *benzodiazepine*) and *neuroimaging* (*magnetic resonance imaging* [*MRI*] or *single photon emission computed tomography* [*SPECT*] or *positron emission tomography* [*PET*] or *image*) and with the terms *social anxiety disorder* and *social phobia* (including *public speaking phobia*). Studies published between January 2000 and February 2015 were included. Each hit was cross-checked and evaluated. After elimination of duplicates and screening of titles and abstracts, 1,310 relevant articles were identified (see Figure 1).

Eligible studies were those that included a group of adult patients with SAD and examined changes in brain activity after intervention. The 4 main inclusion criteria were (1) inclusion of an adult SAD group based on *DSM-IV* and/or *DSM-III* and/or *ICD-10* diagnostic criteria, (2) functional MRI, (3) explicitly reported whole-brain analysis in stereotactic coordinates and threshold values, and (4) comparison of SAD patients before and after treatment. We further excluded (1) studies that included no treatment (26 articles); (2) studies without stereotactic coordinates (9 articles); (3) studies without threshold values (2 articles); (4) studies without comparison of SAD patients before and after treatment (5 articles); (5) studies without the report of whole-brain analysis, for example studies that reported region of interest analysis (40 articles); (6) studies without an adult SAD group based on *DSM-IV* and/or *DSM-III* and/or *ICD-10* diagnostic criteria (44 articles); (7) inaccessible full text, such as a conference paper (4 articles); (8) review studies (7 articles); (9) structural MRI (1 article); and (10) area under the concentration-time curve (1 article). Authors were contacted by email to confirm details. In total, 12 studies were included into our meta-analysis (Table 1).

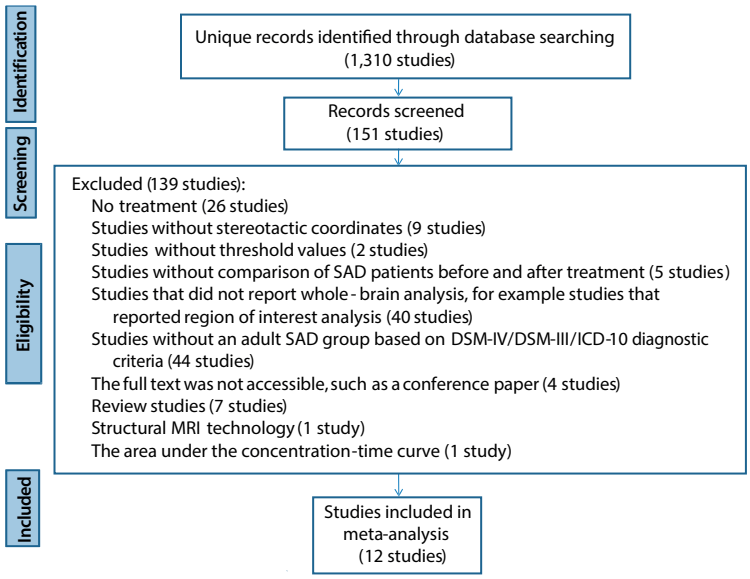
Analysis of Clinical Effect

We compared the Liebowitz Social Anxiety Scale (LSAS; http://www.socialanxietysupport.com/disorder/liebowitz/) scores before and after pharmacotherapy or psychotherapy. We also compared the pre-LSAS scores (LSAS before therapy), LSAS scores after therapy, decrease of LSAS scores, and decreased percentage of LSAS scores between pharmacotherapy and psychotherapy. We used the LSAS mean scores reported in selected studies and analysis by SPSS 20.0 (IBM Corp, Armonk, NY).

Meta-Analysis of Studies

We compared the brain activity reported in patients with SAD before and after pharmacotherapy or psychotherapy (SADpre and SADpost, respectively). We also compared the brain activity reported in patients with SAD before and after pharmacotherapy (SADpre-M and SADpost-M, respectively) and that reported in SAD patients before and after psychotherapy (SADpre-P and SADpost-P, respectively). Only 5 articles included healthy control patients, so healthy control patients were not included in this analysis. Regional differences in hyperactivities between patient groups were calculated using mean and threshold probability procedures with effect-size signed differential mapping (ES-SDM) software (http://www.sdmproject.com), which enables both peak coordinates and statistical parametric maps to be combined and uses standard effect size and variance-based meta-analytic calculations. The steps involved in this estimation are explained in detail in the ES-SDM Tutorial (http://www.sdmproject.com/sdmtools/).

Figure 1. Summary of Exclusion Criteria Used in Finding Suitable Studies to Be Included in the Meta-Analysis



Abbreviations: MRI = magnetic resonance imaging, SAD = social anxiety disorder.

The full width at half maximum (FWHM) in SDM was set at 8 mm, which is reported to provide an excellent control for false positives.[28,30] A systematic whole-brain voxel-based jackknife sensitivity analysis was performed to test the reliability of the results,[31] and subgroup and meta-regression analyses were applied to identify the contribution of confounding variables to the heterogeneity of the results[32] (ie, imaging technology and analysis method).

RESULTS

Included Studies and Sample Characteristics

A total of 12 high-quality studies met the inclusion criteria for the meta-analysis (Figure 1). These studies included a total of 295 patients with SAD (mean age = 33.8 years). Three included studies did not provide the gender of participants (Goldin et al,[31] Goldin et al,[33] and Faria et al[28]). In the studies reporting gender, 50.4% (83/165) of patients were female.

One hundred sixty-seven (56.6%) patients with SAD received pharmacotherapy (mean age = 34.2 years), and 128 (43.4%) received psychotherapy (mean age = 33.3 years). The mean LSAS score of the 269 patients in the SADpre group was 81.1 (except 1 nonreported study, Månsson et al[21]), which decreased to 26.8 for the 238 patients who experienced the second scanning in the SADpost group.

In the SADpost group, 167 patients (70.2%) in 7 studies received pharmacotherapy consisting of citalopram (16.0%; Warwick et al,[27] Faria et al,[28] and Furmark et al[26]), moclobemide (5.8%; Warwick et al[27]), paroxetine (16.4%; Schneier et al[30] and Faria et al[28]), tiagabine (5.0%; Evans et al[29]), nefazodone (4.6%; Kilts et al[34]), sertraline (8.8%; Phan et al[35]), or neurokinin-1 antagonist GR205171 (5.0%; Furmark et al[26]). Seventy-one patients (29.9%) in 5 studies received psychological treatment: mindfulness-based stress reduction (21.8%; Goldin et al,[31] Goldin et al,[33] and Goldin et al[36]), attention bias modification (4.6%; Månsson et al[21]), or cognitive-behavioral therapy (10.5%; Månsson et al[21] and Klummp et al[20]). No significant heterogeneity was found in any of the analyses (Table 1).

Clinical Effects

In patients who received pharmacotherapy or psychotherapy, there was a significant difference in LSAS scores before and after therapy ($P < .000$). Between SADpost-P patients and SADpost-M patients, there was no significant difference in LSAS scores ($P = .240$), LSAS scores after therapy ($P = .202$), decrease of LSAS scores ($P = .079$), and decreased percentage of LSAS scores ($P = .073$) (see Supplementary eTable 1).

Regional Differences in Activity and Meta-Regression

Activity in the left inferior parietal gyrus ($P < .000$), right postcentral gyrus ($P < .000$), and right precuneus ($P < .01$) was observed to be significantly higher in the SADpre group than in the SADpost group. Conversely, activity in the left inferior frontal gyrus/insula ($P < .000$) and bilateral middle cingulate gyrus ($P < .000$) was observed to be significantly lower in the SADpost group than in the SADpre group.

Activity in the right postcentral gyrus ($P < .01$), left middle occipital gyrus ($P < .01$), and right medial orbital frontal gyrus ($P < .01$) was observed to be significantly higher in the SADpost-M group than in the SADpre-M group. Conversely, activity in the left insula ($P < .000$), left medial cingulate gyrus ($P < .01$), and right insula ($P < .01$) was observed to be significantly lower in the SADpost-M group than in the SADpre-M group.

Table 1. Characteristics of the Included Studies

Characteristic	Goldin 2009[31]	Warwick 2006[27]	Goldin 2012[33]	Schneier 2011[30]	Faria 2012[28]	Goldin 2010[36]	Evans 2008[29]	Kilts 2006[34]	Furmark 2005[26]	Månsson 2013[21]	Phan 2013[35]	Klumpp 2013[20]
Type	GSAD	GSAD	GSAD	GSAD	SAD	SAD	GSAD	GSAD	GSAD	SAD	SAD	SAD
Comorbid	5	5	24	3	14	7	3	…	8	5 (SSRI treatment)	…	…
Sample/female												
SADpre	16/9	31/10	56/29	16/10	36/…	16/9	15/6	12/5	36/19	26/22	21/13	14/9
SADpost	14/…	31/10	24/…	16/10	35/22	14/8	12/…	11/5	24/…	22/19	21/13	14/9
Age, mean, y	35.2	33.0	34.0	29.8	44.6	35	31.6	38	31.6	32.5	25.9	28.07
Duration, mean, y	…	…	…	…	…	…	16.6	…	…	…	…	…
Treatment duration, mean, wk	8	8	8	8	6–8	8	6	8	6	4	12	12
LSAS score of SADpre, mean	68.7	100.8	88.6	81.4	68.1	68.7	79.6	85.8	71.3	…	82.3	71.2
Change in LSAS score from SADpre to SADpost, mean	19.4	27.7	29.8	35.5	22.6	19.4	35.7	40.0	18.0	22.8	37.6	21.3
Percent of LSAS change	28.24	27.48	35.65	43.61	33.19	28.24	44.85	53.38	25.25	30.20	45.69	29.92
Treatment												
Psychotherapy	MBSR	…	MBSR	…	…	MBSR	…	…	…	iCBT/ABM	…	CBT
Drug	…	Citalopram/ moclobemide	…	Paroxetine	Citalopram/ paroxetine	…	Tiagabine	Nefazodone	NK_1/ citalopram	…	Sertraline	…
State	Self-referential encoding task	Resting-state	Self-referential encoding task	Eye contact	Public speaking task	Breath-focused attention task	Resting-state	Resting state, following a mental arithmetic task	Public speaking task	Affective face processing task	Threat social signals	Threat against positive social signals
Imaging technology	fMRI	SPECT	fMRI	fMRI	PET	fMRI	PET	PET	PET	fMRI	fMRI	fMRI
Imaging size	3.0T	…	3.0T	1.5T	…	3.0T	1.5T	…	…	3.0T	3.0T	3.0T
Analysis method	AFNI	SPM99	AFNI	SPM5	SPM2	AFNI	SPM5	SPM99	SPM99	SPM	SPM5	SPM8
Full width at half maximum (mm^3)	4	12	4	8	8	4	12	9	12	8	8	8

Symbol: … = not given.

Abbreviations: ABM = attention bias modification, AFNI = Analysis of Functional Neuroimages, CBT = cognitive-behavioral therapy, fMRI = functional magnetic resonance imaging, GSAD = generalized social anxiety disorder, iCBT = internet cognitive-behavioral therapy, LSAS = Liebowitz Social Anxiety Scale, MBSR = mindfulness-based stress reduction, NK_1 = neurokinin-1 antagonist GR205171, PET = positron emission tomography, SAD = social anxiety disorder, SADpost = patients with SAD after treatment, SADpre = patients with SAD before treatment, SPECT = single photon emission computed tomography, SPM = statistical parametric mapping, SSRI = selective serotonin reuptake inhibitor.

It is illegal to post this copyrighted PDF on any website.

Table 2. Regional Changes in Gray Matter Function Between Individuals With SADpre and SADpost

Region	MNI (X,Y,Z)	*Z* Value	*P* Value	Voxel Number	Description	Brodmann Area
SADpre vs SADpost						
Increased clusters	–44,–56,52	1.441	.000790120	108	Left inferior parietal gyrus	40
	50,–24,48	1.711	.000115344	641	Right postcentral gyrus	3
	10,–62,42	1.352	.001365809	116	Right precuneus	…
Decreased clusters	–50,12,4	1.939	.000239204	1,180	Left inferior frontal gyrus, opercular part/insula	48
	4,28,32	1.836	.000451571	866	Bilateral middle cingulate gyrus	24
SADpre-M vs SADpost-M						
Increased clusters	50,–24,50	1.215	.002705555	47	Right postcentral gyrus	3
	–16,94,–2	1.269	.001535341	87	Left middle occipital gyrus	18
	8,52,–6	1.250	.001912855	325	Right medial orbital frontal gyrus	11
Decreased clusters	–40,–2,–4	2.172	.000051092	2,552	Left insula	48
	–8,–28,40	1.479	.003048491	26	Left medial cingulate gyrus	…
	48,8,–6	1.608	.001451736	144	Right insula	48
SADpre-P vs SADpost-P						
Increased clusters	2,–62,44	2.259	.000084379	622	Bilateral precuneus	17
	–44,–54,56	1.786	.000919398	98	Left inferior parietal gyrus	40
Decreased clusters	2,38,14	1.707	.000232753	895	Left anterior cingulate gyrus	24
	–26,34,38	1.584	.000425767	328	Left middle frontal gyrus	9
	26,–70,–42	1.424	.002790709	22	Right cerebellum (crus II)	…
Whole-Brain Regression With Different Neuroimaging Changes in LSAS Scores						
SADpre vs SADpost						
Increased clusters					None	
Decreased clusters						
SADpre-M vs SADpost-M						
Increased clusters	56,–18,50	1.753	.000540337	189	Right postcentral gyrus	4
Decreased clusters	–50,–16,12	1.897	.000989844	680	Left insula	48
SADpre-P vs SADpost-P						
Increased clusters	2,–60,32	2.695	.000524080	199	Bilateral precuneus	…
	–46,–60,54	2.777	.000318680	31	Left inferior parietal gyri	39
Decreased Clusters					None	

Abbreviations: LSAS = Liebowitz Social Anxiety Scale, MNI = Montreal Neurological Institute, SADpost = patients with social anxiety disorder after treatment, SADpre = patients with social anxiety disorder before treatment, SADpre-M = patients with SAD before pharmacotherapy, SADpre-P = patients with SAD before psychotherapy, SADpost = patients with SAD after treatment, SADpost-M = patients with SAD after pharmacotherapy, SADpost-P = patients with SAD after psychotherapy.
Symbol: … = none.

Activity in the bilateral precuneus ($P < .000$) and left inferior parietal gyrus ($P < .000$) was observed to be significantly higher in the SADpost-P group than in the SADpre-P group. Conversely, activity in the left anterior cingulate ($P < .000$), left middle frontal gyrus ($P < .000$), and right cerebellum (crus II) ($P < .01$) was observed to be significantly lower in the SADpost-P group than in the SADpre-P group (Table 2 and Figure 2).

Regression analyses indicated that changes in the LSAS scores before and after pharmacotherapy were associated with increased activity in the right postcentral gyrus and decreased activity in the left insula. Regression analysis also indicated that the LSAS scores before pharmacotherapy were associated with decreased activity in the bilateral insulae and right medial cingulate, while LSAS scores before psychotherapy were associated with increased activity in the left precuneus and left inferior parietal gyrus. Moreover, regression analyses indicated that percentage changes in LSAS scores after pharmacotherapy were associated with increased activity in the right postcentral gyrus and decreased activity in left insula, while percentage changes in LSAS scores after psychotherapy were associated with increased activity in the left precuneus and left inferior parietal gyrus. (Table 3, Figure 2)

Sensitivity Analysis

In comparison to SADpre patients, SADpost patients exhibited increased activity in the right postcentral gyrus in 12 studies, the left inferior parietal gyrus in 10 studies, and the right precuneus in 9 studies. SADpost patients also exhibited decreased activity in the middle cingulate gyrus in 12 studies and the left inferior frontal gyrus/insula in 11 studies.

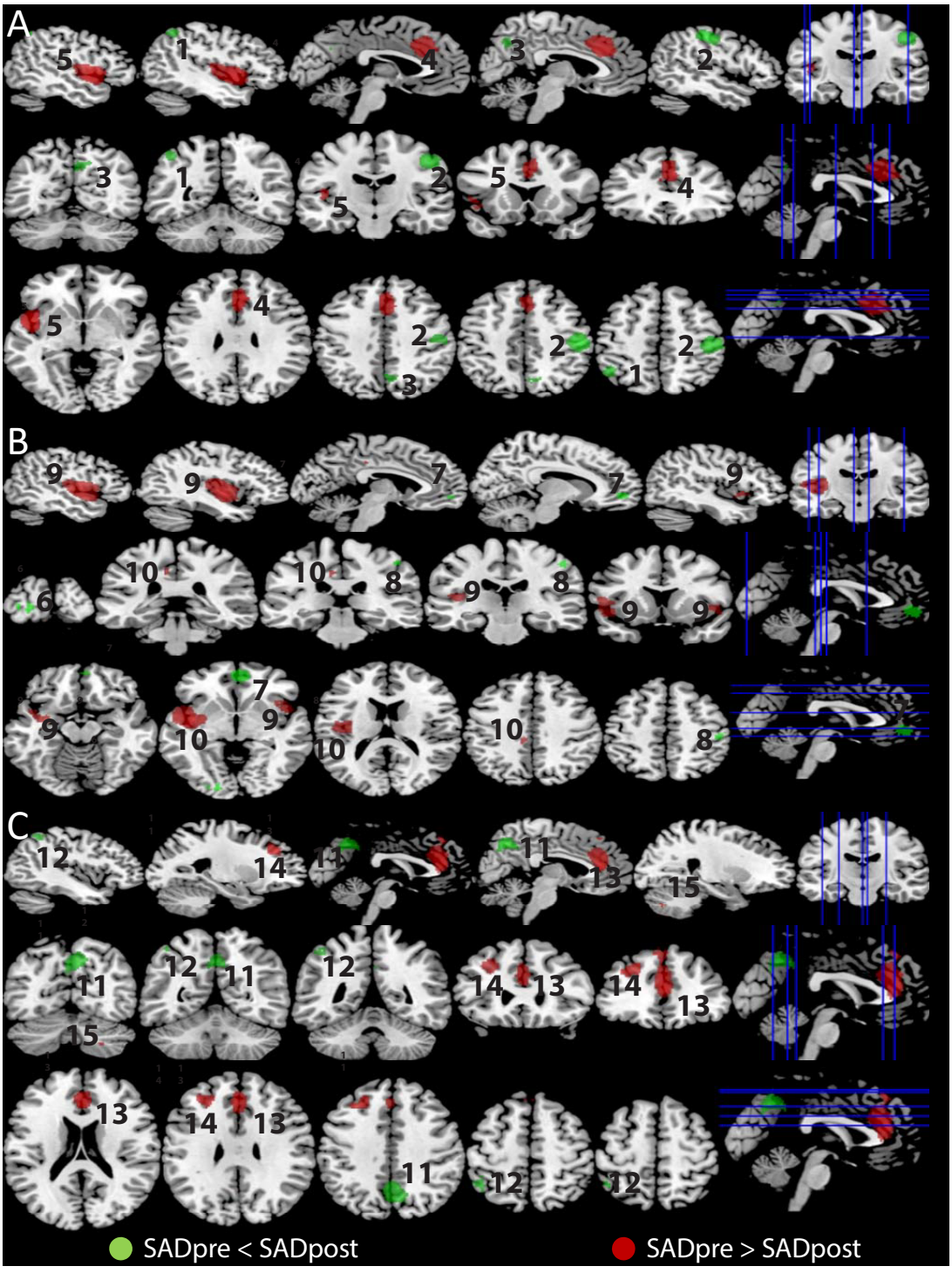
In patients who received pharmacotherapy, activity was decreased in the left insula in 6 of 7 studies, the right insula in 5 of 7 studies, and the left medial cingulate in 5 of 7 studies. In contrast, activity increased in the right medial orbital frontal gyrus in 6 of 7 studies, the left middle occipital gyrus in 3 of 7 studies, and the right postcentral gyrus in 4 of 7 studies.

Moreover, in patients who received psychotherapy, activity was decreased in the left middle frontal gyrus in 5 of 5 studies and in the ACC and cerebellum in 4 of 5 studies and was increased in the precuneus in 5 of 5 studies and the left inferior parietal gyrus in 4 of 5 studies (Table 4, Supplementary eTable 2).

DISCUSSION

In this meta-analysis, we integrated the findings of 12 neuroimaging studies of adult patients with SAD. We found that after treatment, patients exhibited reduced activity in the left inferior frontal gyrus, insulae, and bilateral middle cingulate gyrus but exhibited increased activity in the left inferior parietal gyrus, right postcentral gyrus, and right precuneus. Improvement in symptoms was positively correlated with increased activity in the bilateral precuneus in

Figure 2. Regional Changes in Gray Matter Function Between Individuals With SADpre and SADpost



A. Difference between patients with SAD before pharmacotherapy or psychotherapy and patients with SAD after pharmacotherapy or psychotherapy
SADpre < SADpost: 1. left inferior parietal gyrus, 2. right postcentral gyrus, 3. right precuneus.
SADpre > SADpost: 4. bilateral middle cingulate gyrus, 5. left inferior frontal gyrus, opercular part/insula.
B. Difference between patients with SAD before pharmacotherapy and patients with SAD after pharmacotherapy
SADpre < SADpost: 6. left middle occipital gyrus, 7. right postcentral gyrus, 8. right medial orbital frontal gyrus.
SADpre > SADpost: 9. bilateral insula, 10. left medial cingulate gyrus.
C. Difference between patients with SAD before psychotherapy and patients with SAD after psychotherapy
SADpre < SADpost: 11. bilateral precuneus, 12. left inferior parietal gyrus.
SADpre > SADpost: 13. left anterior cingulate, 14, left middle frontal gyrus, 15. right cerebellum (crus II).
Abbreviations: SAD = social anxiety disorder, SADpost = patients with SAD after treatment, SADpre = patients with SAD before treatment.

Table 3. Whole Brain Level Regressions in Activities Between Individuals With SADpre and SADpost

Region	MNI (X,Y,Z)	*Z* Value	*P* Value	Voxel Numbers	Description	Brodmann Area
Decrease of LSAS scores						
SADpre-M vs SADpost-M						
Increased clusters	56,–18,50	1.753	.000540337	189	Right postcentral gyrus	4
Decreased clusters	–50,–16,12	1.897	.000989844	680	Left insula	48
SADpre-P vs SADpost-P						
Increased clusters	2,–60,32	2.695	.000524080	199	Bilateral precuneus	…
	–46,–60,54	2.777	.000318680	31	Left inferior parietal gyrus	39
Decreased clusters	None					
LSAS scores before therapy						
SADpre-M vs SADpost-M						
Increased clusters	None					
Decreased clusters	–46,2,0	4.076	.000019095	761	Left insula	48
	40,14,–10	4.064	.000021675	382	Right insula	48
	6,18,44	3.788	.000135213	303	Right medial cingulate	32
SADpre-P vs SADpost-P						
Increased clusters	–46,–60,54	2.696	.000303198	35	Left inferior parietal gyrus	40
	2,–60,30	2.631	.000449249	202	Left precuneus	…
Decreased clusters	None					
Percent changes of LSAS scores						
SADpre-M vs SADpost-M						
Increased clusters	52,–22,50	2.057	.000427315	366	Right postcentral gyrus	3
	–44,–86,16	1.763	.001278333	34	Left middle occipital gyrus	…
Decreased clusters	–48,–18,12	2.144	.000918366	845	Left insula	48
	50,12,6	1.770	.003306273	64	Right insula	48
SADpre-P vs SADpost-P						
Increased clusters	2,–58,32	2.570	.000673486	169	Left precuneus	…
Decreased clusters	–46,–60,54	2.663	.000376739	25	Left inferior parietal gyrus	40

Abbreviations: LSAS = Liebowitz Social Anxiety Scale, MNI = Montreal Neurological Institute, SADpost = patients with social anxiety disorder after treatment, SADpre = patients with social anxiety disorder before treatment, SADpre-M = patients with SAD before pharmacotherapy, SADpre-P = patients with SAD before psychotherapy, SADpost = patients with SAD after treatment, SADpost-M = patients with SAD after pharmacotherapy, SADpost-P = patients with SAD after psychotherapy.
Symbol: … = none.

Table 4. Regional Decreases in Gray Matter Function Between Individuals With SADpre and SADpost by Jackknife Analysis

	Right		Left		Middle
Analysis	Postcentral Gyrus	Precuneus	IPG	IFG/ Insula	Cingulate Gyrus
Jackknife analysis					
All studies but Goldin[31]	Yes	No	Yes	Yes	Yes
All studies but Schneier[30]	Yes	Yes	Yes	Yes	Yes
All studies but Goldin[33]	Yes	No	No	Yes	Yes
All studies but Faria[28]	Yes	Yes	Yes	Yes	Yes
All studies but Goldin[36]	Yes	No	No	Yes	Yes
All studies but Evans[29]	Yes	Yes	Yes	Yes	Yes
All studies but Kilts[34]	Yes	Yes	Yes	Yes	Yes
All studies but Furmark[26]	Yes	Yes	Yes	Yes	Yes
All studies but Månsson[21]	Yes	Yes	Yes	Yes	Yes
All studies but Warwick[27]	Yes	Yes	No	No	Yes
All studies but Phan[35]	Yes	Yes	Yes	Yes	Yes
All studies but Klumpp[20]	Yes	Yes	Yes	Yes	Yes
	12 of 12	9 of 12	10 of 12	11 of 12	12 of 12
Subgroup analyses					
Studies using medicine (n = 7, 58.3%)	Yes	No	No	Yes	Yes
Studies using psychotherapy (n = 5, 41.7%)	No	Yes	Yes	No	Yes
Studies using 3.0T scanners (n = 6, 50%)	Yes	Yes	Yes	No	Yes
Studies using SPM (n = 9, 75%)	Yes	Yes	No	Yes	Yes
Studies using task (n = 9, 75%)	Yes	Yes	No	No	No
Studies applying ≤ 8 mm FWHM (n = 7, 58.3%)	Yes	Yes	Yes	No	No
Studies with a corrected *P* value	No	Yes	Yes	No	Yes

Abbreviations: FWHM = full width at half maximum, IFG = inferior frontal gyrus, IPG = inferior parietal gyrus, LSAS = Liebowitz Social Anxiety Scale, SPM = statistical parametric mapping.

patients who received psychotherapy and in the left insula in patients who received pharmacotherapy, which implicates the precuneus and insular cortex in the efficacy of treatment for SAD. Different regions of the brain were altered in different ways by pharmacotherapy and psychotherapy, suggesting that these therapies achieve results through different mechanisms.

Psychotherapy

Increased activity in the inferior parietal gyrus and posterior cingulate cortex (PCC)/precuneus has previously been associated with symptom reduction in patients with SAD following psychotherapy.[37] The PCC/precuneus can make an enormous impact on the development of socioemotional skills and self-concept because this brain region is implicated in multiple higher-order cognitive functions.[38,40,41] In our meta-analysis, SADpost-P exhibited significantly higher activity in the left inferior parietal gyrus, as previously reported.[33,34] Increases in PCC/precuneus activity during negative self-referential processing in SADpost-P have also been previously reported.[31] The patients with SAD exhibited increased neural responses during negative self-referential processing in brain regions including the left inferior parietal lobule and precuneus, which are implicated in attentional allocation,[39] although they endorsed fewer negative social traits. It is interesting that not only the pre-LSAS scores, but also the changed LSAS scores following psychotherapy, were correlated positively with increased activity in the left inferior parietal lobule and precuneus. This correlation indicates that the left inferior parietal lobule and precuneus are critical brain regions in psychotherapy effects, especially in the relief of symptoms in patients with severe social anxiety. Clinically, successful pharmacologic therapy[37] and psychotherapy for depression[42] have been associated with concomitant increases in the left inferior parietal lobule and PCC. For social anxiety disorder, psychotherapy increased activity in the inferior parietal lobule and precuneus implicated in attention regulation, which reduced habitual automatic emotional and behavioral patterns.[33,35,41,45] Furthermore, increased activity in these 2 brain regions enhanced attention control in SAD patients during negative self-referential processing, perhaps allowing patients with SAD to allocate attention away from negative self-concepts. This mechanism would suggest that these 2 brain regions are crucial in predicting the efficacy of psychotherapy for SAD. Therefore, we could focus on altering the attention regulation of patients with SAD during psychotherapy to promote the therapy effect in further studies. These findings were consistent with previous studies suggesting that activity in regions involved in response to threat signals may predict clinical improvement or be altered by treatment.[20,41,45]

In line with previous reports,[21] our results provided further evidence to support the hypothesis that ACC activity in patients with SAD is reduced by psychotherapy. Exaggerated activity has been observed in the ACC in generalized social anxiety disorder.[13,36,43,44] Compared with healthy controls, patients with SAD were less likely to recruit dorsolateral prefrontal cortex and dorsal ACC, and these brain regions were involved in cognitive reappraisal during threatening social situations.[44] The anterior cingulate has been associated with unpleasant feelings and selective attention, which are underlying contributors to fear conditioning models,[6] while psychotherapy can affect ACC by modulating the cognitive reappraisal and the attention of SAD patients.

Pharmacotherapy

We also observed increased activity in the right medial orbital frontal gyrus after pharmacotherapy, which is also consistent with previous studies.[20,33] And in our meta-analysis, the percentage changes of LSAS scores were positively correlated with increased activity of the medial orbital part of the right frontal gyrus. Increased activities in the right medial orbital frontal gyrus may reduce negative self-focused thoughts, a core symptom of SAD. It also showed that relief of social anxiety was primarily associated with increases in the postcentral and midcingulate gyrus response, which is also consistent with previous studies.[34] Furthermore, pharmacotherapy was associated with reduced activity in the insula, in line with previous studies.[34,36] It was previously reported that the insula can activate amygdalo-hippocampal complexes, while a conditioned response is evoked or when the patients were evaluated during anticipation of an unpleasant task.[46] Social activity might be easier for patients with SAD after pharmacotherapy as anticipatory anxiety is lessened and the basal activity of the insula is decreased. After successful pharmacotherapy, social stimuli were less likely to be experienced as unpleasant, and decreased baseline activity in this region was reported.[35] In our meta-analysis, the LSAS scores before therapy and change of LSAS scores were positively correlated with reduced activity of the left insula. Thus, deactivation of the insula might not merely reflect treatment with medication, but might be directly related to effective pharmacotherapy. Patients with SAD were previously reported to have lower 5-HT_{1A} binding in brain regions including the amygdala and insula.[47] The fact that symptom improvement achieved by SSRIs is reversible by serotonin depletion[48] also highlights the key role of this transmitter in SAD.

Our meta-analysis concludes that psychotherapy and pharmacotherapy affect different brain regions in patients with SAD. Psychotherapy reduced anxiety symptoms through modification of negative beliefs and behavior[18] by cognitive restructuring, more exposure to fears, developing attention regulation, more sensitive body awareness, enhancing emotion regulation, and improving self-view.[38,49,50] Emotional perception (involving the left medial frontal gyrus and left anterior cingulate gyrus) and threat signal responses (involving the inferior parietal lobule and precuneus) may be altered by treatment.[20,41,45] Pharmacotherapy altered the activity of brain regions by increasing the concentration of dopamine and 5-HT to relieve SAD symptoms. Previous reports have also implicated specific neurotransmitter (dopaminergic and serotonergic) systems in SAD.[4,51,52] The receptor-binding affinity of 5-HT_{1A} in brain regions including dorsal/medial prefrontal cortex, anterior cingulate, parietal

cortex, and occipital cortex was negatively associated with the degree of anxiety.[53] Moreover, patients with SAD had lower 5-HT_{1A} receptor–binding rates in brain regions including the insula, amygdala, and ACC than did healthy controls. Another neurotransmitter, γ-aminobutyric acid (GABA), which is proposed to serve as the primary neurotransmitter within the corticolimbic circuitry that mediates fear extinction,[54,55] may also affect symptoms of SAD. Moreover, in a region-by-region analysis, negative correlations between changes in D_2-receptor–binding potential and LSAS were found in the brain regions including the medial prefrontal cortex and hippocampus after therapy.[56] In conclusion, psychotherapy encouraged appropriate attention distribution and reduced negative self-concept, altering activity in brain regions responsible for executive function and attention allocation, thus reducing avoidance and anxiety. However, pharmacotherapy altered neurotransmitter availability, and thus reduced anxiety, modifying activity and improving symptoms of avoidance.

However, our conclusions are limited by the content of the studies we analyzed and the small number of studies included. First, small sample sizes resulted in wide standard errors and inaccurate results. Second, clinical characteristics and symptom severity and duration differed between studies, or, in some cases, were not reported. In the future, more studies of drug and psychological therapy of SAD may further elucidate the mechanisms by which these therapies improve symptoms. Such findings would facilitate evaluation of interventions and may highlight prognostic markers for treatment efficacy.

Amygdala

We did not find any difference of amygdala among these 3 groups, which is the most consistent finding in neuroimaging studies of SAD.[57] The amygdala is associated with the fear circuit involved in detecting threat signals and coordinating autonomic responses.[58] In the total 12 studies included into our meta-analysis, only 1 study referred amygdala. Faria et al[28] observed activity in the left lateral amygdala to be significantly ($P < .05$) lower in the SADpre group than in the SADpost group. It might be the small sample of the study (n = 14), so there is no positive result about amygdala in the meta-analysis. One possible reason is that the amygdala is too small to be significant in the whole brain analysis. Another possible reason is that the amygdala, which is usually treated as a single structure in neuroimaging studies, is functionally and anatomically heterogeneous as extensively demonstrated in animal studies.[5] It is possible that different therapies engage different subregions of the amygdala and/or different modulatory cortical activity patterns; therefore, the null amygdala result may be due to the mixed amygdala findings. Moreover, the different tasks may engage different regions of brain in different ways. Happy faces can elicit amygdala reactivity in social anxiety,[29,59] potentially due to negative interpretations of the expression.[60,61] Individual differences in the interpretation of happy may have reduced our ability to find significant amygdala effects.

Limitation

In our meta-analysis, some of the studies were done with functional MRI, some with SPECT, and some with PET. Although the 3 methods (SPECT, functional MRI, and PET) focus on different parts of brain function, all of them can reflect the activity of brain regions by indirect ways. The key point of our meta-analysis was comparing the difference of brain function before and after therapy. Unfortunately, the research on the differences in radiologic technology is limited at present. Because of the limited number of selected studies, we had to combine the studies that used the 3 methods. In the future, we hope to observe the brain changes before and after treatment under different technological conditions with the accumulation of literature.

Taken together, our meta-analysis illuminated evidence to support the hypothesis that pharmacotherapy and psychotherapy impact different brain regions. The insula, left inferior parietal lobule, and precuneus were associated with improvement in symptoms after therapy.

Submitted: July 9, 2015; accepted March 9, 2016.

Online first: September 27, 2016.

Drug names: citalopram (Celexa and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), tiagabine (Gabitril and others).

Potential conflicts of interest: None.

Funding/support: This study was supported by the National Natural Science Foundation of China (grant nos. 81371484, 81000605), National Key Technologies R&D Program of China (program no. 2012BAI01B03), the Support Plan of Sichuan (grant no. 2011SZ0292), and Natural Science Foundation of Guangdong (grant no. S20120200-10867). Qiyong Gong, MD, PhD, chief of the project, acknowledges the support from his American CMB Distinguished Professorship Award (award no. F510000/G16916411) administered by the Institute of International Education, USA.

Role of the sponsor: None.

Supplementary material: See accompanying pages.

REFERENCES

1. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of *DSM-IV* disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593–602.
2. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
3. Brühl AB, Herwig U, Delsignore A, et al. General emotion processing in social anxiety disorder: neural issues of cognitive control. *Psychiatry Res*. 2013;212(2):108–115.
4. Stein MB, Goldin PR, Sareen J, et al. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Arch Gen Psychiatry*. 2002;59(11):1027–1034.
5. LeDoux J. The amygdala. *Curr Biol*. 2007;17(20):R868–R874.
6. Büchel C, Dolan RJ. Classical fear conditioning in functional neuroimaging. *Curr Opin Neurobiol*. 2000;10(2):219–223.
7. Barbas H, Saha S, Rempel-Clower N, et al. Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. *BMC Neurosci*. 2003;4(1):25.
8. Hartley CA, Phelps EA. Changing fear: the neurocircuitry of emotion regulation. *Neuropsychopharmacology*. 2010;35(1):136–146.
9. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci*. 2012;1251(1):E1–E24.
10. Kohn N, Eickhoff SB, Scheller M, et al. Neural network of cognitive emotion regulation—an ALE meta-analysis and MACM analysis. *Neuroimage*. 2014;87:345–355.
11. Phelps EA, Delgado MR, Nearing KI, et al. Extinction learning in humans: role of the amygdala and vmPFC. *Neuron*. 2004;43(6):897–905.
12. Etkin A, Egner T, Peraza DM, et al. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron*. 2006;51(6):871–882.
13. Goldin PR, Manber T, Hakimi S, et al. Neural

bases of social anxiety disorder: emotional reactivity and cognitive regulation during social and physical threat. *Arch Gen Psychiatry*. 2009;66(2):170–180.
14. Goldin PR, Manber-Ball T, Werner K, et al. Neural mechanisms of cognitive reappraisal of negative self-beliefs in social anxiety disorder. *Biol Psychiatry*. 2009;66(12):1091–1099.
15. Gross R, Olfson M, Gameroff MJ, et al. Social anxiety disorder in primary care. *Gen Hosp Psychiatry*. 2005;27(3):161–168.
16. Kabat-Zinn JTN. *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness*. New York, NY: Dell Publishing; 1990.
17. Bishop SR. What do we really know about mindfulness-based stress reduction? *Psychosom Med*. 2002;64(1):71–83.
18. Beck AT, Emery G, Greenberg RL. *Anxiety Disorders and Phobias: A Cognitive Perspective*. New York, NY: Basic Books; 2005.
19. Northoff G, Heinzel A, de Greck M, et al. Self-referential processing in our brain—a meta-analysis of imaging studies on the self. *Neuroimage*. 2006;31(1):440–457.
20. Klumpp H, Fitzgerald DA, Phan KL. Neural predictors and mechanisms of cognitive behavioral therapy on threat processing in social anxiety disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;45:83–91.
21. Månsson KN, Carlbring P, Frick A, et al. Altered neural correlates of affective processing after internet-delivered cognitive behavior therapy for social anxiety disorder. *Psychiatry Res*. 2013;214(3):229–237.
22. Mayo-Wilson E, Dias S, Mavranezouli I, et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2014;1(5):368–376.
23. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol*. 1999;19(4):341–348.
24. Munjack DJ, Baltazar PL, Bohn PB, et al. Clonazepam in the treatment of social phobia: a pilot study. *J Clin Psychiatry*. 1990;51(suppl):35–40, discussion 50–53.
25. Muehlbacher M, Nickel MK, Nickel C, et al. Mirtazapine treatment of social phobia in women: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2005;25(6):580–583.
26. Furmark T, Appel L, Michelgård A, et al. Cerebral blood flow changes after treatment of social phobia with the neurokinin-1 antagonist GR205171, citalopram, or placebo. *Biol Psychiatry*. 2005;58(2):132–142.
27. Warwick JM, Carey P, Van der Linden G, et al. A comparison of the effects of citalopram and moclobemide on resting brain perfusion in social anxiety disorder. *Metab Brain Dis*. 2006;21(2–3):241–252.
28. Faria V, Appel L, Åhs F, et al. Amygdala subregions tied to SSRI and placebo response in patients with social anxiety disorder. *Neuropsychopharmacology*. 2012;37(10):2222–2232.
29. Evans KC, Simon NM, Dougherty DD, et al. A PET study of tiagabine treatment implicates ventral medial prefrontal cortex in generalized social anxiety disorder. *Neuropsychopharmacology*. 2009;34(2):390–398.
30. Schneier FR, Pomplun M, Sy M, et al. Neural response to eye contact and paroxetine treatment in generalized social anxiety disorder. *Psychiatry Res*. 2011;194(3):271–278.
31. Goldin P, Ramel W, Gross J. Mindfulness meditation training and self-referential processing in social anxiety disorder: behavioral and neural effects. *J Cogn Psychother*. 2009;23(3):242–257.
32. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *Br J Psychiatry*. 2009;195(5):393–402.
33. Goldin P, Ziv M, Jazaieri H, et al. Randomized controlled trial of mindfulness-based stress reduction versus aerobic exercise: effects on the self-referential brain network in social anxiety disorder. *Front Hum Neurosci*. 2012;6:295.
34. Kilts CD, Kelsey JE, Knight B, et al. The neural correlates of social anxiety disorder and response to pharmacotherapy. *Neuropsychopharmacology*. 2006;31(10):2243–2253.
35. Phan KL, Coccaro EF, Angstadt M, et al. Corticolimbic brain reactivity to social signals of threat before and after sertraline treatment in generalized social phobia. *Biol Psychiatry*. 2013;73(4):329–336.
6. Goldin PR, Gross JJ. Effects of mindfulness-based stress reduction (MBSR) on emotion regulation in social anxiety disorder. *Emotion*. 2010;10(1):83–91.
37. Samson AC, Meisenzahl E, Scheuerecker J, et al. Brain activation predicts treatment improvement in patients with major depressive disorder. *J Psychiatr Res*. 2011;45(9):1214–1222.
38. Pfeifer JH, Peake SJ. Self-development: integrating cognitive, socioemotional, and neuroimaging perspectives. *Dev Cogn Neurosci*. 2012;2(1):55–69.
39. Fan J, McCandliss BD, Fossella J, et al. The activation of attentional networks. *Neuroimage*. 2005;26(2):471–479.
40. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*. 2006;129(pt 3):564–583.
41. Hölzel BK, Lazar SW, Gard T, et al. How does mindfulness meditation work? proposing mechanisms of action from a conceptual and neural perspective. *Perspect Psychol Sci*. 2011;6(6):537–559.
42. Martin SD, Martin E, Rai SS, et al. Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride: preliminary findings. *Arch Gen Psychiatry*. 2001;58(7):641–648.
43. Blair K, Shaywitz J, Smith BW, et al. Response to emotional expressions in generalized social phobia and generalized anxiety disorder: evidence for separate disorders. *Am J Psychiatry*. 2008;165(9):1193–1202.
44. Amir N, Klumpp H, Elias J, et al. Increased activation of the anterior cingulate cortex during processing of disgust faces in individuals with social phobia. *Biol Psychiatry*. 2005;57(9):975–981.
45. Farb NA, Segal ZV, Mayberg H, et al. Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. *Soc Cogn Affect Neurosci*. 2007;2(4):313–322.
46. Veit R, Singh V, Sitaram R, et al. Using real-time fMRI to learn voluntary regulation of the anterior insula in the presence of threat-related stimuli. *Soc Cogn Affect Neurosci*. 2012;7(6):623–634.
47. Lanzenberger R, Wadsak W, Spindelegger C, et al. Cortisol plasma levels in social anxiety disorder patients correlate with serotonin-1A receptor binding in limbic brain regions. *Int J Neuropsychopharmacol*. 2010;13(9):1129–1143.
48. Argyropoulos SV, Hood SD, Adrover M, et al. Tryptophan depletion reverses the therapeutic effect of selective serotonin reuptake inhibitors in social anxiety disorder. *Biol Psychiatry*. 2004;56(7):503–509.
49. Mattia JI, Heimberg RG, Hope DA. The revised Stroop color-naming task in social phobics. *Behav Res Ther*. 1993;31(3):305–313.
50. Pishyar R, Harris LM, Menzies RG. Responsiveness of measures of attentional bias to clinical change in social phobia. *Cogn Emotion*. 2008;22(7):1209–1227.
51. Harmer CJ. Have no fear: the neural basis of anxiolytic drug action in generalized social phobia. *Biol Psychiatry*. 2013;73(4):300–301.
52. Varnäs K, Halldin C, Hall H. Autoradiographic distribution of serotonin transporters and receptor subtypes in human brain. *Hum Brain Mapp*. 2004;22(3):246–260.
53. Tauscher J, Bagby RM, Javanmard M, et al. Inverse relationship between serotonin 5-HT(1A) receptor binding and anxiety: a [(11) C]WAY-100635 PET investigation in healthy volunteers. *Am J Psychiatry*. 2001;158(8):1326–1328.
54. Quirk GJ, Garcia R, González-Lima F. Prefrontal mechanisms in extinction of conditioned fear. *Biol Psychiatry*. 2006;60(4):337–343.
55. Akirav I, Maroun M. The role of the medial prefrontal cortex-amygdala circuit in stress effects on the extinction of fear. *Neural Plast*. 2007;2007:30873.
56. Cervenka S, Hedman E, Ikoma Y, et al. Changes in dopamine D2-receptor binding are associated to symptom reduction after psychotherapy in social anxiety disorder. *Transl Psychiatr*. 2012;2(5):e120.
57. Freitas-Ferrari MC, Hallak JEC, Trzesniak C, et al. Neuroimaging in social anxiety disorder: a systematic review of the literature. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(4):565–580.
58. Amorapanth P, LeDoux JE, Nader K. Different lateral amygdala outputs mediate reactions and actions elicited by a fear-arousing stimulus. *Nat Neurosci*. 2000;3(1):74–79.
59. Straube T, Kolassa IT, Glauer M, et al. Effect of task conditions on brain responses to threatening faces in social phobics: an event-related functional magnetic resonance imaging study. *Biol Psychiatry*. 2004;56(12):921–930.
60. Campbell DW, Sareen J, Paulus MP, et al. Time-varying amygdala response to emotional faces in generalized social phobia. *Biol Psychiatry*. 2007;62(5):455–463.
61. Coles ME, Heimberg RG. Recognition bias for critical faces in social phobia: a replication and extension. *Behav Res Ther*. 2005;43(1):109–120.

Supplementary material follows this article.

THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Therapy for Adult Social Anxiety Disorder: A Meta-Analysis of Functional Neuroimaging Studies

Author(s): Yuchen Li, MD; Yajing Meng, MD, PhD; Minlan Yuan, MD; Ye Zhang, MD; Zhengjia Ren, MD; Yan Zhang, MD; Hongru Zhu, MD, PhD; Changjian Qiu, MD, PhD; and Wei Zhang, MD

DOI Number: 10.4088/JCP.15r10226

List of Supplementary Material for the article

1. **eTable 1** (A) Clinic Effects of SAD P Post Patients and SAD M Post Patients (B) The Different Clinic Effects of SAD P Post Patients and SAD M Post Patients

2. **eTable 2** (A) Regional Decreases in Grey Matter Function Between Individuals With SAD M Pre and SAD M Post by Jackknife (B) Regional Decreases in Grey Matter Function Between Individuals With SAD P Pre and SAD P Post by Jackknife

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1

A Clinic effects of SAD P post. patients and SAD M post. patients

	LSAS pre.	LSAS post.	T value	P value
SAD P	74.31	51.60	10.94	0.000
SAD M	81.33	49.49	8.80	0.000

B The different clinic effects of SAD P post. patients and SAD M post. patients

	LSAS pre.	LSAS post.	Decrease of LSAS scores	Decrease percentage of LSAS scores（%）
SAD P	74.31±7.80	51.60±3.20	22.70±4.64	30.33±2.79
SAD M	81.33±10.63	49.49±11.14	31.84±9.58	39.06±10.51
T value	-1.249	-*	-1.956	-2.098
P value	0.240	0.202	0.079	0.073

LSAS pre. : LSAS scores before therapy, LSAS post. : LSAS scores after therapy; we used paired-samples t-test;

The decrease of LSAS scores and decrease percentage of LSAS scores follow a standard normal distribution，so we used independent-samples t test . LSAS scores after therapy do not follow a standard normal distribution，so we used Mann-Whitney U test *.

Supplementary eTable 2

A Regional decreases in grey matter function between individuals with SAD M pre and SAD M post by jackknife

	Right			Left		
	SFG(medial orbital)	insula	Postcentral gyrus	Insula	median cingulate gyrus	Middle occipital gyrus
Jackknife analysis						
All studies but Schneier	Yes	Yes	No	Yes	No	No
All studies but Faria	Yes	Yes	Yes	Yes	Yes	Yes
All studies but Evans	No	Yes	Yes	Yes	Yes	No
All studies but Kilts	Yes	No	No	Yes	Yes	No
All studies but Furmark	Yes	Yes	Yes	Yes	No	No
All studies but Warwick	Yes	No	Yes	No	Yes	Yes

All studies but Luan	Yes	Yes	No	Yes	Yes	Yes
	6 out of 7	5 out of 7	4 out of 7	6 out of 7	5 out of 7	3 out of 7
Whole-brain regression analyses with different neuroimaging changes in LSAS scores	No	No	Yes	Yes	No	Yes

superior frontal gyrus: SFG ; Liebowitz Social Anxiety Scale:LSAS

B Regional decreases in grey matter function between individuals with SAD P pre and SAD P post by jackknife

	right		left		
	cerebellum, crus I	MFG	IPG	anterior cingulate	precuneus
Jackknife analysis					
All studies but Klummp	Yes	Yes	Yes	Yes	Yes
All studies but Krist	No	Yes	Yes	No	Yes
All studies but Gross	Yes	Yes	Yes	Yes	Yes
All studies but Goldin	Yes	Yes	Yes	Yes	Yes
All studies but Phillipe	Yes	Yes	No	Yes	Yes
	4 out of 5	5 out of 5	4 out of 5	4 out of 5	5 out of 5

Whole-brain regression analyses with different neuroimaging changes in LSAS scores	No	No	Yes	No	Yes

inferior parietal gyri: IPG; middle frontal gyrus:MFG, Liebowitz Social Anxiety Scale:LSAS