Corticolimbic Brain Reactivity to Social Signals of Threat Before and After Sertraline Treatment in Generalized Social Phobia

Supplemental Information

Supplemental Methods

None of the generalized social phobia (gSP) subjects had a current/recent depressive episode or alcohol/substance abuse (within 12 months of study entry), or another anxiety disorder that was more clinically salient or preceded the generalized social anxiety symptoms. gSP subjects were excluded if they had: 1) a history of posttraumatic stress disorder, bipolar disorder, psychotic disorder, mental retardation, or developmental disorders; 2) Hamilton Depression Rating Scale (HAM-D) score > 17; 3) Liebowitz Social Anxiety Scale (LSAS) score < 60; 4) ongoing psychotherapy treatment of any kind; 5) intolerance or contraindication to taking sertraline or another selective serotonin reuptake inhibitor (SSRI); and 6) prior failure of response to sertraline or another SSRI for social anxiety disorder, as defined by adequate duration to achieve a clinical response (equivalent to fluoxetine 20-40 mg/d for 5 months) or who had received sertraline for any other indication but had not responded. Healthy control subjects were excluded if they had a history of any Axis I psychiatric disorder. None of the subjects had a history of a major medical or neurological illness. All subjects were right-handed and free of psychoactive/psychotropic medications (for at least 8 weeks) at the time of study entry, and had negative urine drug screen at time of functional magnetic resonance imaging (fMRI) scanning session.

Six gSP subjects had some form of past history (>12 months) of substance abuse or dependence, all of whom were in full remission at the time of study entry; of these, two had past alcohol dependence (one of whom also had past cannabis abuse) and four had past alcohol abuse (2 of whom also had cannabis abuse/dependence). Several participants had at least one secondary Axis I psychiatric comorbidity and/or past diagnosis: (n = 2, generalized anxiety disorder; n = 6, major depressive episode; n = 4, alcohol abuse; n = 3,

specific phobia; $n = 2$, adjustment disorder; $n = 1$, dysthymia; $n = 1$, somatoform disorder; $n = 1$, obsessive-compulsive disorder).

Supplemental Results

fMRI Activation Results

We conducted a *post hoc* analysis separating treatment 'Responders' and 'Non-Responders', which showed that the attenuation from pre-treatment (PreTx) to post-treatment (PostTx) in amygdala reactivity to fearful faces was observed to be significant in Responders ($p = 0.01$) but not in Non-Responders ($p = 0.22$); of note, there was a difference in sample size between Responders and Non-Responders ($n = 14$ and $n = 7$, respectively).

A *post hoc* analysis separating treatment 'Responders' and 'Non-Responders' showed that the attenuation from PreTx to PostTx in ventral medial prefrontal cortex (vmPFC) response to angry faces was observed to be significant in Responders ($p = 0.02$) but not in Non-Responders ($p = 0.29$).

A *post hoc* correlational analysis between vmPFC response to angry faces and amygdala reactivity to fearful faces in the gSP group at PostTx revealed a negative correlation ($r = -0.47$, $p = 0.03$).

Contrary to our hypotheses, significant Group x Time interactions were not observed in the insula or anterior cingulate cortex (ACC). To address the possibility that failure of the Emotional Face Matching Task to activate these regions at 'baseline'/PreTx obviated an effect by treatment, we examined activation/deactivation of insula and ACC to fearful (vs. happy) and angry (vs. happy) faces within the gSP group. In the gSP group, angry (vs. happy) and fearful (vs. happy) faces activated bilateral insula at PreTx but the extent of this activation was no different than that of controls and there was not a significant PreTx vs. PostTx effect (data not shown). Similarly, in the gSP group, angry (vs. happy) and fearful (vs. happy) faces activated dorsal ACC at PreTx, but the extent of this activation was no different than that of controls and there was not a significant PreTx vs. PostTx effect (data not shown). These data confirm that the task was effective at evoking enhanced activation to angry and fearful faces (vs. happy) in both insula and ACC.

We also conducted *post hoc* Pearson correlational analyses of treatment change ($\Delta_{PostTx\ -\ PreTx}$) in depression symptom severity (BDI$\Delta_{PostTx-PreTx}$ and HAM-D$\Delta_{PostTx-PreTx}$) – as we had done with LSAS social anxiety severity scores – blood oxygen-level dependent signal treatment change ($\Delta_{PostTx-PreTx}$); this did not reveal any significant correlations with in amygdala activity to fearful faces and in vmPFC response to angry faces ($p_s > 0.05$). Tables S1 and S2 show findings from an exploratory whole-brain voxel-wise regression analysis between change in depression symptom severity (BDI$\Delta_{PostTx-PreTx}$ and HAM-D$\Delta_{PostTx-PreTx}$) and brain activation change (FvH$\Delta_{PostTx-PreTx}$; AvH$\Delta_{PostTx-PreTx}$).

Table S1. Pre-Treatment to Post-Treatment Decrease Beck Depression Inventory and Change in Brain Activation: Whole-brain Voxel-wise Regression[a]

		MNI Coordinates			Volume	
	Region	**x**	**y**	**z**	**(mm³)**	**Z**
Fearful > Happy						
Positive Correlation	Putamen	-28	6	-8	392	3.14
(decreasing activation)		34	12	-10	296	2.80
	Middle Temporal Gyrus	-60	-20	-8	416	3.04
Negative Correlation	No significant regions					
(increasing activation)						
Angry > Happy						
Positive Correlation	Postcentral Gyrus	34	-20	56	8696	5.31
(decreasing activation)	Postcentral Gyrus	-50	-10	50	360	3.14
	Parahippocampal Gyrus	-24	-26	-20	800	3.35
	Superior Frontal Gyrus	-14	16	46	1280	3.30
	Superior Occipital Gyrus	24	-86	12	288	3.25
	Precentral Gyrus	-30	-14	52	400	3.08
	Middle Frontal Gyrus	32	20	44	248	2.98
	Anterior Cingulate	12	34	2	280	2.93
	Paracentral Lobule	-10	-26	64	296	2.93
Negative Correlation	No significant regions					
(increasing activation)						

[a] All listed clusters significant at $p < 0.005$ (uncorrected) with a cluster extent threshold of greater than 20 contiguous voxels. MNI, Montreal Neurological Institute; Z, Z-score.

Table S2. Pre-Treatment to Post-Treatment Decrease Hamilton Depression Rating Scale and Change in Brain Activation: Whole-brain Voxel-wise Regression[a]

		MNI Coordinates			Volume	
	Region	**x**	**y**	**z**	**(mm^3)**	**Z**
Fearful > Happy						
Positive Correlation	Middle Temporal Gyrus	72	-38	-16	3992	4.51
(decreasing activation)		62	2	-32	648	3.32
		-64	-44	8	248	3.03
		-66	-34	-16	192	2.95
		-54	-4	-32	200	2.72
	Fusiform Gyrus	-34	-32	-24	800	4.16
		38	-34	-28	216	3.10
	Precentral Gyrus	-36	-44	54	14344	4.14
		36	-32	64	6464	3.61
	Inferior Frontal Gyrus	-24	36	-22	2816	4.03
		34	32	-12	1544	3.78
	Middle Frontal Gyrus	54	52	-2	1136	3.84
		-42	56	-2	728	3.41
	Inferior Temporal Gyrus	36	8	-50	528	3.68
	Cerebellum	48	-50	-46	344	3.41
	Mid Cingulate	16	-16	46	480	3.38
	Supplementary Motor Area	-8	-18	56	760	3.29
		6	4	62	280	2.78
	Paracentral Lobule	-6	-24	76	1168	3.26
		12	-22	72	880	3.21
	Inferior Parietal Gyrus	36	-40	40	728	3.20
	Superior Frontal Gyrus	-10	62	34	512	3.08
		-12	26	54	360	2.89
Negative Correlation	Cerebellum	-42	-84	-26	784	3.63
(increasing activation)		-36	-62	-42	808	3.20
		0	-48	6	368	3.02
	Caudate	12	12	-12	720	3.47
	Cuneus	18	-84	8	984	3.35
Angry > Happy						
Positive Correlation	Middle Temporal Gyrus	30	6	-36	2656	4.88
(decreasing activation)		-32	24	-38	432	4.11
	Fusiform Gyrus	36	-24	-26	1536	3.63
	Amygdala	22	-2	-16	1160	3.46
	Precuneus	-10	-46	78	704	3.43
	Postcentral Gyrus	14	-40	78	888	3.26
	Middle Frontal Gyrus	-22	38	-20	552	3.09

Negative Correlation	Cerebellum	36	-58	-40	3040	3.91
(increasing activation)		-22	-90	-38	2064	3.59
		18	-50	-50	376	3.29
		-2	-54	4	528	3.11
	Superior Frontal Gyrus	16	58	12	808	3.43
	Parahippocampal Gyrus	-32	-38	-8	1384	3.43
	Middle Frontal Gyrus	38	52	4	504	3.19
	Angular Gyrus	-38	-62	30	272	3.01

[a] All listed clusters significant at $p < 0.005$ (uncorrected) with a cluster extent threshold of greater than 20 contiguous voxels. MNI, Montreal Neurological Institute; Z, Z-score.

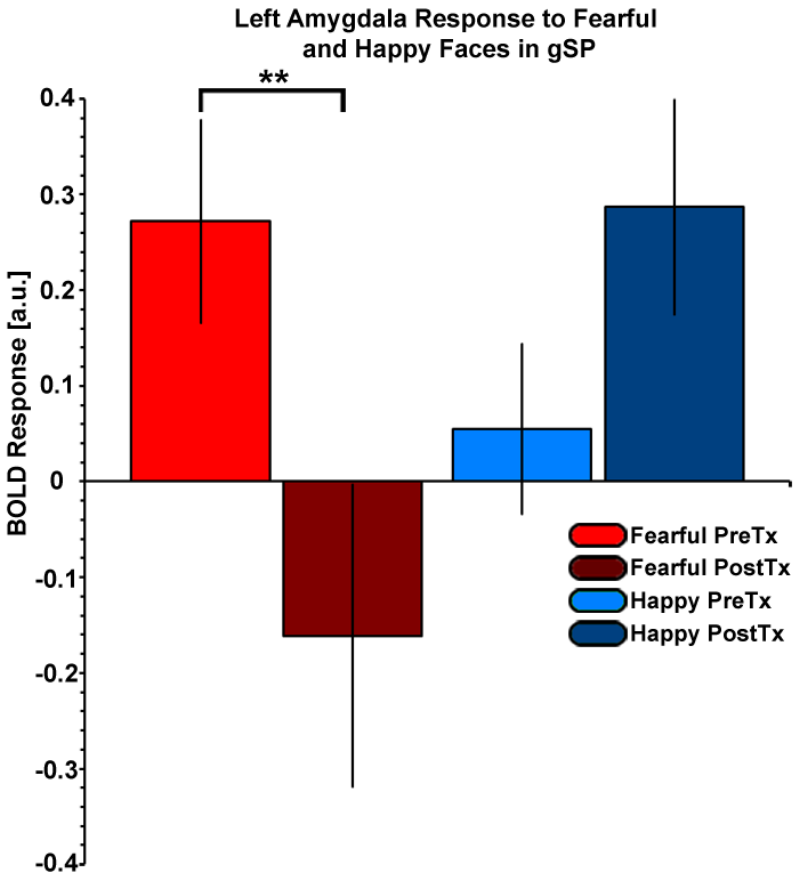

Figure S1. Brain changes after 12 weeks of sertraline treatment in patients with generalized social phobia (gSP) showing treatment effect shown in Figure 1 is driven by significant and specific attenuation to fearful faces. Bar graphs depict extracted blood oxygen-level dependent (BOLD) signal change from amygdala in response to fearful (vs. shapes) and happy (vs. shapes) faces. Treatment significantly attenuates amygdala reactivity to fearful faces ($gSP_{PreTx} > gSP_{PostTx}$, $^{**}p = 0.04$) and non-significantly enhances amygdala reactivity to happy faces ($gSP_{PreTx} < gSP_{PostTx}$ $p = 0.12$). PreTx, pre-treatment; PostTx, post-treatment.