

**SUPPLEMENTAL TABLE 1: Reported maxima of clusters reported in experiments that have investigated surrogates of neural activity in SAD**

**participants compared to healthy controls.**

Paradigm/ Study	Technique	Participants	Analysis details	↑/↓	Reported maxima*			Location
					x	y	z	
<b><u>Rest</u></b>								
Warwick et al	<sup>99m</sup> Tc HMPAO SPECT	SAD:28 HC: 19	<i>Search volume:</i> whole brain <i>Statistical threshold:</i> voxel-level p<0.001 (uncorr)	↑	-36	36	40	L frontal
				↑	20	52	36	R anterior frontal
				↑	52	28	8	R lateral frontal
				↑	40	-76	-28	R cerebellum
				↓	-12	-28	-32	Pons
				↓	-8	-36	-8	L cerebellum
				↓	16	-48	36	R precuneus
Evans et al	<sup>18</sup> F-FDG PET	SAD:15 HC:10	<i>Search volume:</i> a priori regions <i>Statistical threshold:</i> voxel-level p<0.001 (uncorr); cluster level extent >15 voxels	↓	-4	20	-18	Subcallosal cortex
				↓	-8	31	9	Dorsal anterior cingulate cortex
Doruyter et al	<sup>18</sup> F-FDG PET	SAD:15 HC:15	<i>Search volume:</i> a priori regions <i>Statistical threshold:</i> voxel-level p<0.001 (uncorr) combined with cluster level p<0.05(FWE)	Nil	-	-	-	
				↑	-34	-46	-22	L fusiform gyrus
				↑	36	16	-34	R temporal pole (mid)

combined with cluster level  
extent >15 voxels

**Rest (functional connectivity)**

Doruyter et al <sup>99m</sup>Tc-HMPAO SPECT  
SAD:23  
HC:15

*Search volume:* whole brain  
*Statistical threshold:* voxel-  
level p<0.001 (uncorr)  
combined with cluster level  
p<0.05(FWE)

*R thalamus seed*

↑ 26 42 0 R middle frontal gyrus

*L amygdala seed*

↓ 20 28 36 R superior frontal  
gyrus/anterior cingulate  
cortex

*Posterior cingulate  
cortex/precuneus seed*

↓ -48 -78 -44 L cerebellar crus

**Provocation**

Tillfors et al <sup>15</sup>O-water PET  
SAD:18  
HC:6

*Search volume:* a priori regions  
*Statistical threshold:* voxel-  
level p<0.005 (uncorr)

↑ 14 -9 -23 R amygdalar complex  
↓ -40 -6 0 L insula  
↓ 3 -45 20 Bilateral retrosplenial cortex  
↓ 52 -65 5 R parietal cortex  
↓ 48 -68 6 Right secondary visual cortex  
↓ -39 -42 -24 L perirhinal cortex  
↓ 45 11 -19 R temporal pole

Kilts et al <sup>15</sup>O-water PET  
SAD:12  
HC:6

*Search volume:* whole brain  
*Statistical threshold:* voxel-  
level p<0.001 (uncorr)

↑ -55 -7 55 L postcentral gyrus  
↑ 49 17 3 R inferior frontal gyrus  
↑ 56 -12 -17 R middle temporal gyrus  
↑ -23 -11 -1 L lenticulate  
↓ 47 -67 31 R middle temporal gyrus  
↓ -26 -56 44 L precuneus

				↓	-5	-59	10	Posterior cingulate gyrus
				↓	-38	-34	-11	L hippocampus
				↓	10	4	7	R caudate
				↓	27	-1	-22	R amygdala
Furmark et al	<sup>15</sup> O-water PET	SAD:34 HC:18	<i>Search volume:</i> a priori region (amygdala) <i>Statistical threshold:</i> voxel level p<0.05 (FWE) combined with cluster level extent > 10 voxels	Nil	-	-	-	

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\*All coordinates reported in MNI space. Where applicable, coordinates were converted from Talairach to MNI space to using the Lancaster transform in BrainMap GingerALE 2.3 (Research Imaging Institute UT Health Science Centre San Antonio, <http://www.brainmap.org>).

*Abbreviations:* SAD: social anxiety disorder; <sup>99m</sup>Tc: technetium-99m; HMPAO: hexamethyl propylene amine oxime; SPECT: single photon emission tomography; HC: healthy controls; uncorr: uncorrected (for multiple comparisons); L/R: left/right; <sup>18</sup>F: fluorine-18; FDG: fluorodeoxyglucose; PET: positron emission; FWE: family-wise error corrected; <sup>15</sup>O: oxygen-15; tomography; MNI: Montreal Neurological Institute.

**SUPPLEMENTAL TABLE 2: Reported maxima of clusters reported in experiments that have investigated surrogates of neural activity in SAD**

**patients post-therapy compared to baseline.**

Paradigm/ Study	Technique	Participants	Analysis details	↑/↓	Reported maxima*			Location
					x	y	z	
<b><i>Rest</i></b>								
Warwick et al	<sup>99m</sup> Tc HMPAO SPECT	Citalopram:17 Moclobemide:14 (pooled)	<i>Search volume:</i> whole brain <i>Statistical threshold:</i> voxel- level p<0.001 (uncorr) combined with cluster-level extent > 10 voxels	↓	36	12	-4	R insula
				↓	-44	4	4	L insula
Evans et al	<sup>18</sup> F-FDG PET	Tiagibine:12	<i>Search volume:</i> a priori regions <i>Statistical threshold:</i> voxel- level p<0.001 (uncorr) combined with cluster level extent >15 voxels	↑	4	51	-18	Ventral medial prefrontal cortex
Crippa et al	<sup>99m</sup> Tc ECD SPECT	Cannabidiol vs. placebo: 10	<i>Search volume:</i> a priori regions <i>Statistical threshold:</i> voxel- level p<0.001 (one-tailed, uncorr) combined with cluster level extent >20 voxels	↑	10	-23	32	Posterior cingulate gyrus
				↓	-36	-14	-23	Parahippocampal gyrus
Doruyter et al	<sup>18</sup> F FDG PET	Moclobemide:11	<i>Search volume:</i> a priori regions <i>Statistical threshold:</i> voxel- level p<0.001 (uncorr) combined with cluster level p<0.05(FWE)	Nil	-	-	-	

<i>Search volume:</i> whole brain	↑	46	16	-6	R Insula
<i>Statistical threshold:</i> voxel-level p<0.001 (uncorr)	↑	-58	-6	22	L postcentral
combined with cluster level extent >15 voxels	↑	10	12	6	R Caudate
	↑	12	2	6	R Caudate
	↓	-16	62	30	L frontal superior
	↓	-2	38	54	L frontal superior medial
	↓	-12	28	60	L frontal superior medial
	↓	-6	24	56	L frontal superior medial /supplementary motor area
	↓	10	70	18	R frontal superior medial
	↓	8	56	42	R frontal superior medial

**Resting functional connectivity**

Doruyter et al	<sup>99m</sup> Tc HMPAO SPECT	Citalopram:11 Moclobemide:7 (pooled)	<i>Search volume:</i> whole brain <i>Statistical threshold:</i> voxel-level p<0.001 (uncorr) combined with cluster level p<0.05(FWE)	<i>R fusiform gyrus seed</i>	
				↑	-6 44 30 Bilateral anterior-dorsal anterior cingulate cortex (superior frontal gyrus, medial segment)
					<i>Anterior-dorsal anterior cingulate cortex seed</i>
				↑	14 -62 42 R precuneus
				↑	36 -74 4 R middle occipital gyrus

**Provocation**

Furmark et al	<sup>15</sup> O water PET	CGBT:6 Citalopram: 6	<i>Search volume:</i> a priori regions <i>Statistical threshold:</i> voxel-level not specified; cluster level p<0.005 (uncorr)	<i>CGBT</i>	
				↓	22 -2 -23 R amygdala
				<i>Citalopram</i>	
				↓	-28 -23 -16 L hippocampus

*Search volume: whole brain*  
*Statistical threshold: voxel-level not specified; cluster level p<0.01 (corrected: method not specified)*

↓	-16	-7	-17	L amygdala
↓	-26	-25	-12	L hippocampus
↓	24	-29	-13	R hippocampus
↓	-19	-1	-13	L temporal cortex
↓	20	-34	-13	R temporal cortex

*Citalopram*

↓	-20	-5	-23	L amygdala
	21	-4	-24	R amygdala
	19	-11	-23	R hippocampus
	-59	-27	-26	L temporal cortex
	16	-7	-23	R temporal cortex

Furmark et al <sup>15</sup>O water PET

GR205171:12  
 Citalopram:12  
 Placebo:12

*Search volume: a priori region (medial temporal lobe)*  
*Statistical threshold: voxel-level p<0.05 (corrected: method not specified)*

*GR2015171 vs Placebo*

↓	-19	-9	-39	L inferior temporal cortex (BA36)
↓	-21	-13	-37	BA28
↓	-19	-13	-31	BA35
↓	-17	-8	-28	BA34
↓	-23	4	-40	BA38
↓	-19	-6	-28	L amygdala

*Citalopram vs Placebo*

↓	-21	-9	-39	L inferior temporal cortex (BA36)
↓	-21	-14	-38	BA28
↓	-23	-13	-31	BA35
↓	-25	-13	-26	L hippocampus

*Search volume: whole brain* Nil - - -

*Statistical threshold: voxel-level p<0.05 (corrected: method not specified)*

Kilts et al	<sup>15</sup> O water PET	Nefazodone:12	<i>Search volume: whole brain</i>	↑	-44	-86	16	L middle occipital gyrus
				↑	-12	-58	0	L lingual gyrus
				↑	61	-18	53	R postcentral gyrus
				↑	-6	20	-32	L gyrus rectus
				↑	29	-76	-4	R lingual gyrus
				↑	36	-17	-16	R hippocampus
				↓	-54	-11	11	L precentral gyrus
				↓	47	18	6	R insula
				↓	12	-19	-4	R midbrain/hypothalamus
				↓	-56	39	14	L middle frontal gyrus
			↓	-5	38	21	L dorsal anterior cingulate gyrus	

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*Abbreviations:* SAD: social anxiety disorder; <sup>99m</sup>Tc: technetium-99m; HMPAO: hexamethyl propylene amine oxime; SPECT: single photon emission tomography; uncorr: uncorrected (for multiple comparisons); R/L: right/left; <sup>18</sup>F: fluorine-18; FDG: fluorodeoxyglucose; PET: positron emission tomography; ECD: ethyl cysteinate dimer; FWE: family-wise error corrected; <sup>15</sup>O: oxygen-15; BA: Brodmann area; CGBT: cognitive behavioural therapy; GR205171: (2S,3S)-N-[[2-[<sup>11</sup>C]methoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl]methyl]-2-phenyl-piperidin-3-amine; MNI: Montreal Neurological Institute.

**SUPPLEMENTAL TABLE 3:** Selected (patho-) physiological processes that have been studied in SAD with nuclear imaging.

<b>(Patho-) physiological process</b>	<b>Molecular target</b>	<b>Radiotracer</b>	<b>Imaging modality</b>
<i>Proxies of regional neuronal activity</i>			
Blood flow	N/A	<sup>15</sup> O-water	PET
Regional perfusion (no temporal component)	Lipid cell membrane	<sup>99m</sup> Tc-HMPAO	SPECT
		<sup>99m</sup> Tc-ECD	SPECT
Glucose metabolism	Hexokinase	<sup>18</sup> F-FDG	PET
<i>Neurotransmitter systems</i>			
Dopaminergic	DAT	<sup>123</sup> I-ioflupane	SPECT
		<sup>123</sup> I β-CIT	SPECT
		<sup>99m</sup> Tc-TRODAT	SPECT
	D2/3	<sup>123</sup> I-IBZM	SPECT
		<sup>11</sup> C-raclopride	PET
		<sup>11</sup> C-FLB457	PET
Serotonergic	TPH2	<sup>11</sup> C-HTP	PET
	5-HT <sub>1A</sub>	<sup>11</sup> C-WAY-100635	PET
	SERT	<sup>11</sup> C-DASB	PET
		<sup>11</sup> C-McN5652	PET
Neuropeptide substance P	NK <sub>1</sub>	<sup>11</sup> C-GR205171	PET

*Abbreviations:* SAD: social anxiety disorder; <sup>15</sup>O: oxygen-15; PET: positron emission tomography; <sup>99m</sup>Tc: technetium-99m; HMPAO:

hexamethyl propylene amine oxime; SPECT: single photon emission tomography; ECD: ethyl cysteinate dimer; <sup>18</sup>F: fluorine-18; FDG:



fluorodeoxyglucose; DAT: dopamine transporter; <sup>123</sup>I: iodine-123; β-CIT: methyl 3β-(4-iodophenyl) tropane-2b-carboxylate; TRODAT-1: 2-[2-[[[(1S,3S,4R,5R)-3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octan-4-yl]methyl-(2-sulfanylethyl)amino]ethylamino]ethanethiol; D<sub>2/3</sub>: dopamine receptor types 2 and 3; IBZM: iodobenzamide ; <sup>11</sup>C: carbon-11; FLB457: (S)-(-)-5-bromo-N-((1-ethyl-2pyrrolidinyl)methyl)-2,3-dimethoxybenzamide; TPH2: tryptophan hydroxylase-2; HTP: hydroxytryptophan; 5-HT<sub>1A</sub>: serotonin receptor type 1A; WAY-100635: N-[2-[4-(2-ethoxyphenyl)piperazin-1-yl]ethyl]-N-pyridin-2-ylcyclohexanecarboxamide; SERT: serotonin transporter; DASB:3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile; McN5652:(6R,10bS)-6-(4-methylsulfanylphenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline; NK<sub>1</sub>: neurokinin receptor 1; GR205171: (2S,3S)-N-[[2-[<sup>11</sup>C]methoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl]methyl]-2-phenyl-piperidin-3-amine.