

Data supplement for Chavanne and Robinson, The Overlapping Neurobiology of Induced and Pathological Anxiety: A Meta-Analysis of Functional Neural Activation. *Am J Psychiatry* (doi: 10.1176/appi.ajp.2020.19111153)

Supplementary Methods

Literature search and inclusion

Database keywords for titles and abstracts included ‘major depression’, ‘major depressive’, ‘unipolar depression’, ‘traumatized’, ‘trauma’, ‘anxiety’, ‘anxious’, ‘phobia’, ‘phobic’, ‘phobics’, ‘post-traumatic stress disorder’, ‘posttraumatic stress disorder’, ‘panic’, ‘PTSD’ in conjunction with ‘fMRI’ or ‘functional magnetic resonance imaging’. Studies reporting null results for the whole-brain analysis were included.

Unpredictability of the threat relied on the time of delivery and/or the intensity of the stimulus, and nociceptive stimuli were not excluded provided they fit these criteria. Only potent aversive stimuli (ex: electrical shocks, thermal stimuli) were selected as unpredictable threats to avoid potential confusion with stimuli used in other included articles (ex: emotional faces). Classical fear-conditioning paradigms were excluded as they did not fit the unpredictability criteria.

Records were excluded if they were not experimental (and therefore did not include data to analyze), if they were not published in English (as we did not want to risk misunderstanding the reported information), if activation was only reported after treatment administration, and if they used a sample fully comorbid with any current medical or mental condition (other anxiety disorders and unipolar depression excepted), as both treatment and comorbidity could confound reported activations. Authors were contacted for unthresholded activation maps

Full-text articles were excluded if they did not report activation/deactivation coordinates (as they constituted the main analysis), or if thresholding was inhomogenous across the brain (Müller et al., 2018). Exceptions were made for the latter criteria if only *one* region of interest was thresholded differently (in all cases but one this was an amygdala region of interest– we assumed that it was too small to come up in most whole-brain analyses, hence the need for authors to threshold it differently), in which case articles were included but *only* the data using the whole-brain threshold was collected. Articles using fully duplicate samples were excluded where reported. Articles were also excluded if they reported incomplete post-hoc analyses for a whole-brain interaction analysis with more than two levels, as this meant it was impossible to determine which group/condition was driving effects. No additional judgments of study quality were made beyond the exclusions reported above. Authors were contacted for unthresholded activation maps.

For the PTSD category, only articles using healthy controls (and not traumatized controls) were used in the main analysis. Eligible PTSD articles with traumatized controls (22 for emotion tasks, 325 patients, 353 controls) were kept aside only to be compared with the PTSD healthy controls articles. See Table S7 for a whole-brain meta-analysis of PTSD patients vs. traumatized controls for emotion tasks.

Note that for each study we do not take the effect of task, but the effect of anxiety (either induced or pathological) *on* the task contrast of interest. Our analysis therefore makes the assumption that the average effect of anxiety across multiple tasks provides an estimate of the average impact of anxiety on emotional cognitive task processing *in general*. Notably, this does not mean, for example, that we are comparing the effect of specific tasks in patients to the overall effect of threat of shock. We are comparing the *average impact of patients vs. controls on tasks relative to the average impact of threat vs safe on tasks*. In an ideal world we would compare the exact same tasks across types of anxiety. However, as with any meta-analysis we need to trade precision (i.e. restricting it to the small number of identical tasks) and power (i.e., number of studies) against each other. Given that there simply aren't enough studies to solely examine a single task type, we believe that this analysis provides the best *current* approximation of the consistencies between induced and pathological anxiety. If anything, averaging across tasks increases the noise, making it harder to find consistent activations, thus the observed overlap is likely biased towards the lower end of true overlap (which in turn urges caution in interpretation of activation *differences*).

SDM meta-analysis procedure

Z-values, or uncorrected p-values were collected and converted to t-values via the SDM online converter. SDM-PSI also allows for absence of a statistical value, requiring only the direction of the analysis (activation or deactivation): this was used for articles reporting only corrected p-values, F-values not originating from a 2x2 design, or not reporting any statistical value. Atlas space (MNI, Talairach) for each article was also entered into SDM-PSI, which uses matrix transforms (Lancaster et al., 2007) to convert into consistent space. According to SDM recommendations, cluster-forming height thresholds were used instead of voxel thresholds for articles using cluster-based statistics. A conservative value of $p = 0.001$ (converted to t) was used as threshold for articles in which there was no uncorrected threshold reported or if the threshold was unclear

Articles were split by anxiety type (7 groups: Induced, post-traumatic stress disorder [PTSD], social anxiety disorder, generalized anxiety disorder, panic disorder, specific phobia, transdiagnostic [articles contrasting anxious subjects pooled across two or more of the 5 previous anxiety disorders, with the possible addition of separation anxiety disorder for pediatric samples, with healthy controls]).

Large clusters were also checked in a complementary FWHM 10mm analysis conducted with all other parameters identical. Meta-analytic maps were computed with the SDM mean analysis via permutation tests (Albajes-Eizagirre et al., 2019), thresholded with peak height 1, voxelwise $p \leq 0.0025$ (paired one-tailed tests, resulting in two-tailed $p \leq 0.005$), uncorrected and clusterwise $k \geq 10$ voxels as the classical balance between Type I and Type II errors (Lieberman & Cunningham, 2009). Pairwise convergence maps approximating significant commonalities and differences between two article groups were computed with the multimodal SDM tool by assuming error in p-values and adjusting to reduce false negative rates, and thresholded with a voxelwise uncorrected $p \leq 0.0025$ (four-tailed) and clusterwise $k \geq 10$ voxels, peak height 0.00025 (Radua et al., 2013).

Identified clusters were large and encompassed many areas. This meant automated approaches would miss relevant areas by focusing solely on peaks (or indeed erroneously identify out-of-cluster coordinates by triangulating between contributing clusters). As such, all clusters reported

were manually confirmed using the AAL atlas visualized on the MRICron software. All contributing brain regions within each cluster were listed. Additionally, the PAG (peri-aqueductal gray) and BNST (bed nucleus of the stria terminalis) regions were visually examined using MNI coordinates ($x=\pm 4$, $y=-29 (\pm 5)$, $z=-12 (\pm 7)$) (Linnman et al., 2012) and $x=\pm 8$, $y=0$, $z=5$ (Buff et al., 2017) respectively).

It should be noted that effect sizes for non-significant results are unknown and conservatively assumed to be 0 by SDM-PSI unless unthresholded maps were used ($N=17$ of 138), making the Egger's test exploratory only.

Supplementary Results

Other tasks

We investigated brain activation patterns across anxiety studies for attention, decision and memory tasks as well, although they included an order of magnitude less papers than emotion tasks.

Briefly, anxious patients ($N=396$) vs. controls ($N=324$) during attention tasks did not show any significant activation or deactivation. During decision tasks (222 patients vs. 218 controls), they showed reduced activation in bilateral middle frontal gyri and right putamen. During the memory tasks, anxious patients ($N=217$) compared to controls ($N=216$) showed increased activation in left hippocampus and right inferior frontal gyrus (IFG) opercular, but reduced activation in anterior cingulate cortex (ACC), midcingulate cortex (MCC) and left insula. (See Table S8 for additional clusters description and peak information).

PTSD controls vs trauma

No convergence was found between studies contrasting PTSD patients with healthy controls and studies contrasting PTSD patients with non-PTSD traumatized controls for emotion tasks.

Supplementary Discussion

Induced anxiety as a model for pathological anxiety

Our findings of bilateral BNST activation in induced anxiety is in line with recent literature, which reports that the BNST plays a key role in generating anxious feeling and is engaged when faced with uncertain threat, both in humans and rodents (Davis et al., 2010; LeDoux & Pine, 2016). Interestingly, consistent with older meta-analyses (Etkin & Wager, 2007), BNST activations were not consistently seen in pathological anxiety (although this may depend on medication status; see below), which suggests that this might be an activation that is specific to imminent state anxiety, which may be less present at any given time in anxious patients than someone undergoing direct threat manipulation (Gungor & Paré, 2016). This is in contrast with the amygdala which was observed in the pathological – but not induced – anxiety group, perhaps indicating more of a role in dispositional anxiety (Hur et al., 2019). Animal work nevertheless demonstrates that uncertain threat response in the BNST usually travels through the amygdala (Gungor & Paré, 2016; Hur et al., 2019) so it may actually be that this dissociation is an artefact

of confounds/power issues inherent in meta-analyses. Interestingly, of prior anxiety-linked subcortical regions it was the PAG that was consistent across both groups, perhaps indicating a more general role in anxiety/negative affect. These patterns should of course be treated with caution until replicated in well-controlled direct test across anxiety groups, but they do highlight interesting predictions for future research.

It is worth noting that medication status may be an important factor modulating the role of the BNST in pathological anxiety as excluding medicated patients led to BNST activations in the pathological anxiety group (consistent with the induced anxiety group). It is important therefore to test the effects of medication on BNST activation in future studies.

Our findings indicate a globally satisfactory functional overlap between induced anxiety and anxiety disorders, although some differences were also found, including the absence of amygdala activation in induced anxiety. We however advise caution in overinterpreting apparent differences, particularly for the amygdala and other small regions, and elaborate further on this in the limitations section.

Specificity across disorders

One reason for the apparent differences between diagnostic groups might be that the cingulate cortex is an architecturally complex structure, with anterior regions thought to be involved in social and emotional processing, while medial regions are involved in goal-directed behavior (Apps, 2018). Thus, increased activation in MCC and ACC may reflect an increase in goal-directed behavior in response to emotional stimuli, corresponding to the high state-anxiety following exposure to phobic stimuli in specific phobia patients. By contrast, *reduced* activation in generalized anxiety disorder could perhaps reflect a difficulty engaging in such behavior perhaps as illustrated by housebound avoidance behavior during more continuous trait-like anxiety. In other words, subtleties in symptoms may emerge from (or drive) activation patterns in adjacent medial prefrontal regions with dissociable roles.

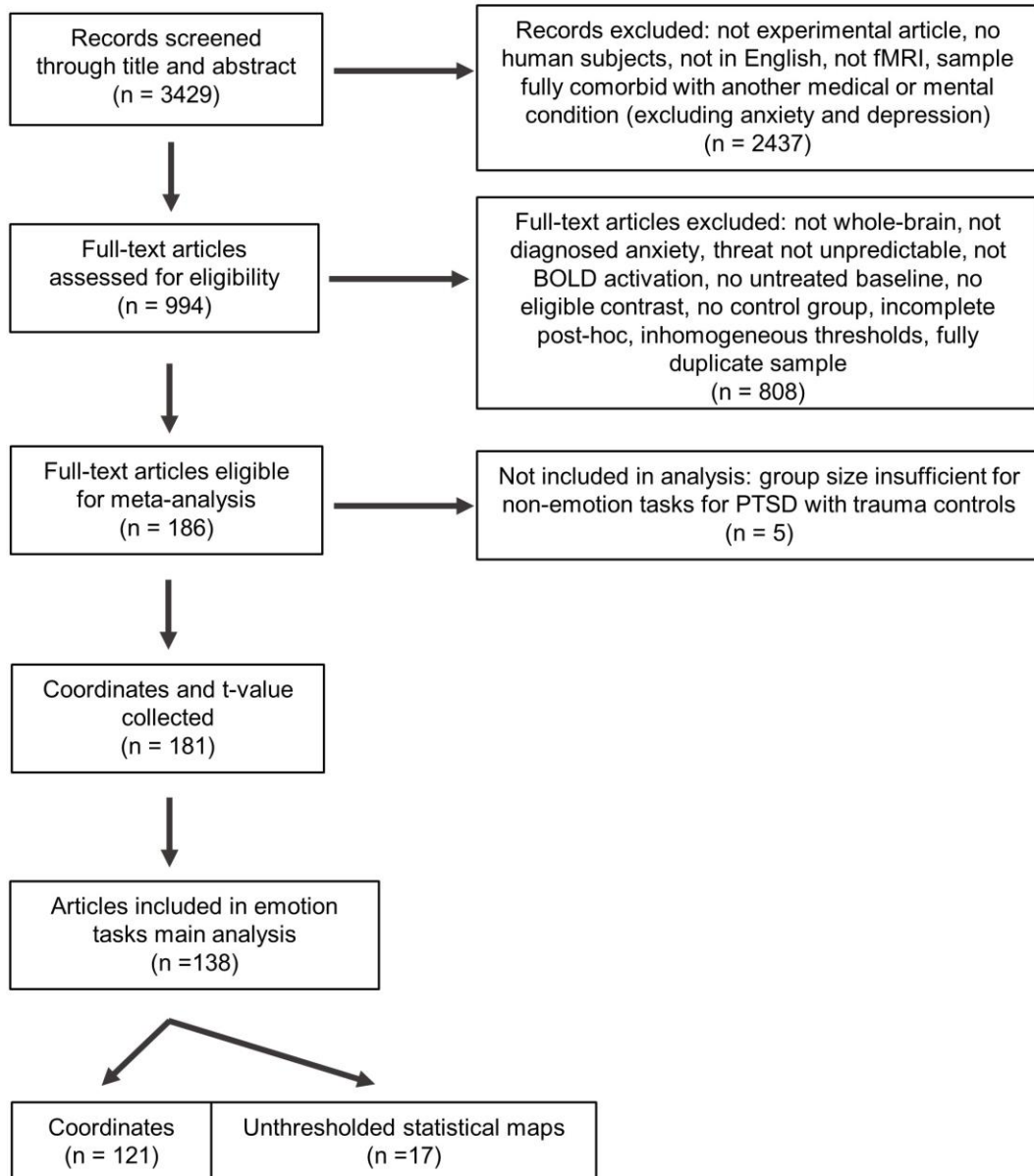
The insula is also a complex brain structure receiving numerous sensory inputs and believed to play a key role in interoceptive perception and the integration of bodily sensations (Gogolla, 2017; Paulus & Stein, 2006). Our findings point to hyperactivation of the insula in specific phobia, panic disorder, PTSD and possibly social anxiety disorder, but potential deactivation in generalized anxiety disorder. This could be in line with the difference between defining symptoms of these disorders, some – like specific phobia or panic disorder – are more centred on bodily sensations, whereas generalized anxiety disorder is associated with general feelings of worry, often about external environmental factors. Thus, involvement of this region in anxiety disorders may be specific to symptoms involving interoception. Alternatively, since both cingulate and insula are also part of a hypothetical salience network as defined by Yeo (2011) (Yeo et al., 2011) deactivation in both regions in generalized anxiety disorder might be because it is characterized by more general apprehension and hypervigilance rather than targeted responses to specific salient (e.g. phobic) stimuli.

Limitations

Finally, it is important to recognize some limitations with the meta-analytic approach specifically. SDM only allows one to prioritize maps that were corrected for multiple

comparisons and does not filter studies by the p- or z-value threshold they use. There is also a potential publication bias towards activation in the patient vs. control contrast, as many eligible articles do not clearly state whether the opposite (controls vs. patients) contrast had null results meaning it was not possible to know if this evoked significant but unreported activations. The use of unthresholded maps in place of coordinates allows us to avoid those biases, but we were only able to collect 17 maps out of 138 articles. Unfortunately, even the raw data cannot fully circumvent the differences between MRI scanners and pre-processing strategies across all eligible studies. Nevertheless, the Egger's test indicated no significant publication bias for any of the clusters in the primary analyses of interest.

FIGURE S1. Flowchart of article selection



N represents the number of articles.

TABLE S1. Demographic sample description for all 181 articles meeting criteria

	Induced anxiety	PTSD	PTSD HC	SAD	SAD HC	GAD	GAD HC	PD	PD HC	SpP	SpP HC	Tdiag	Tdiag HC	PTSD ^a	PTSD TC ^a
Articles (studies)	18 (19)	34		41		17		14		21 (23)		14		22	
Sample	693	576	539	830 ^b	766 ^c	289	260	310	323	414	373	492	424	325	353 ^d
Mean Age	25.15	32.48	31.38	28.70	28.83	34.79	35.01	33.04	32.32	25.53	22.66	21.13	21.58	34.88	35.13
Mean Male %	53.67	31.32	31.54	37.52	39.58	36.70	41.93	34.52	35.60	12.03	10.92	30.29	35.59	44.93	43.60

a: articles not using emotion tasks were not included in analysis because there were too few; b: including 33 comorbidly depressed SAD patients; c: including 27 depressed non-SAD controls; d: including 16 depressed non-PTSD patients; HC: healthy controls; TC: trauma-exposed controls; SAD: social anxiety disorder; GAD: generalized anxiety disorder; PD: panic disorder; SpP: specific phobia; Tdiag: transdiagnostic anxiety category, where each article reports two or more anxiety disorders in one pooled group of patient

TABLE S2. Comprehensive list of the 181 articles meeting inclusion criteria

Eligible articles	Anxiety type	Task category
Sakamoto et al. (2005)	PTSD	Emotion, Attention
Williams et al. (2006)	PTSD	Emotion
Strigo et al. (2010)	PTSD	Emotion
Zweerings et al. (2018)	PTSD	Emotion, Attention
Elman et al. (2018)	PTSD	Emotion
Dégeilh et al. (2017)	PTSD	Emotion
Brinkmann et al. (2017)	PTSD	Emotion
Aupperle et al. (2016)	PTSD	Attention
M. J. Kim et al. (2008)	PTSD	Emotion
Rabellino et al. (2016)	PTSD	Emotion
Werner et al. (2009)	PTSD	Memory
Moore et al. (2008)	PTSD	Attention
Simmons et al. (2008)	PTSD	Emotion
Xiong et al. (2013)	PTSD	Emotion
van Rooij et al. (2015)	PTSD	Emotion
Bryant et al. (2005)	PTSD	Attention
Thomaes et al. (2012)	PTSD	Emotion, Attention
Landré et al. (2012)	PTSD	Emotion, Memory
Fonzo et al. (2010)	PTSD	Emotion
Sailer et al. (2008)	PTSD	Decision
Cisler et al. (2015)	PTSD	Decision
Steiger et al. (2015)	PTSD	Emotion
van Rooij et al. (2014)	PTSD	Attention
Aupperle et al. (2012)	PTSD	Emotion
St Jacques et al. (2011)	PTSD	Emotion, Memory
Elman et al. (2009)	PTSD	Emotion
New et al. (2009)	PTSD, PTSD trauma	Emotion
Falconer et al. (2008)	PTSD	Attention
Astur et al. (2006)	PTSD	Memory
Mazza et al. (2012)	PTSD	Emotion
Zhang et al. (2013)	PTSD	Emotion, Memory
Garrett et al. (2019)	PTSD	Emotion
Steuwe et al. (2014)	PTSD	Emotion
Simmons et al. (2011)	PTSD	Emotion
Stevens et al. (2013)	PTSD trauma	Emotion
Naegeli et al. (2018)	PTSD trauma	Emotion
Ke et al. (2016)	PTSD trauma	Emotion
Mazza et al. (2013)	PTSD trauma	Emotion
Mazza et al. (2015)	PTSD trauma	Emotion
Mueller-Pfeiffer et al. (2013)	PTSD trauma	Emotion
Hou et al. (2007)	PTSD trauma	Emotion
Lanius et al. (2002)	PTSD trauma	Emotion
Shin et al. (2001)	PTSD trauma	Emotion
Whalley et al. (2009)	PTSD trauma	Emotion
Whalley et al. (2013)	PTSD trauma	Emotion
Cortese et al. (2018)	PTSD trauma	Emotion
Linnman et al. (2011)	PTSD trauma	Emotion
Rabinak et al. (2014)	PTSD trauma	Emotion
Simmons et al. (2013)	PTSD trauma	Emotion
Fani et al. (2012)	PTSD trauma	Emotion

Eligible articles	Anxiety type	Task category
Hayes et al. (2011)	PTSD trauma	Emotion
Lanius et al. (2007)	PTSD trauma	Emotion
Lanius et al. (2003)	PTSD trauma	Emotion
Yang et al. (2004)	PTSD trauma	Emotion
Fani et al. (2019)	PTSD trauma	Emotion
Patel et al. (2016)	PTSD trauma	Emotion
Stein et al. (2002)	Social anxiety disorder	Emotion
Månsson et al. (2016)	Social anxiety disorder	Emotion
Richey et al. (2014)	Social anxiety disorder	Emotion, Decision
Heeren et al. (2017)	Social anxiety disorder	Emotion, Decision
Kim et al. (2016)	Social anxiety disorder	Emotion
Richey et al. (2017)	Social anxiety disorder	Emotion, Decision
Frick et al. (2013)	Social anxiety disorder	Emotion
Prater et al. (2013)	Social anxiety disorder	Emotion
Giménez et al. (2012)	Social anxiety disorder	Emotion, Attention
Brown et al. (2019)	Social anxiety disorder	Emotion
Goldin et al. (2009a)	Social anxiety disorder	Emotion
Goldin et al. (2009b)	Social anxiety disorder	Emotion
Boehme et al. (2014)	Social anxiety disorder	Emotion
Gaebler et al. (2014)	Social anxiety disorder	Emotion
Ziv et al. (2013)	Social anxiety disorder	Emotion
Pujol et al. (2013)	Social anxiety disorder	Emotion, Memory
Schneier et al. (2011)	Social anxiety disorder	Emotion
Klumpp et al. (2012)	Social anxiety disorder	Emotion
Koric et al. (2012)	Social anxiety disorder	Decision
Blair et al. (2011a)	Social anxiety disorder	Emotion
Blair et al. (2011b)	Social anxiety disorder	Emotion
Brühl et al. (2011)	Social anxiety disorder	Emotion
Nakao et al. (2011)	Social anxiety disorder	Emotion
Klumpp et al. (2010)	Social anxiety disorder	Emotion
Sripada et al. (2009)	Social anxiety disorder	Emotion
Yoon et al. (2007)	Social anxiety disorder	Emotion
Yoon et al. (2016)	Social anxiety disorder	Memory
Sareen et al. (2007)	Social anxiety disorder	Attention, Memory
Phan et al. (2006)	Social anxiety disorder	Emotion
Amir et al. (2005)	Social anxiety disorder	Emotion
Evans et al. (2008)	Social anxiety disorder	Emotion
Heitmann et al. (2017)	Social anxiety disorder	Emotion
Heitmann et al. (2016)	Social anxiety disorder	Emotion
Blair et al. (2016)	Social anxiety disorder	Emotion
Binelli et al. (2016)	Social anxiety disorder	Emotion
Blair et al. (2010)	Social anxiety disorder	Emotion
Gentili et al. (2008)	Social anxiety disorder	Emotion
Schmidt et al. (2010)	Social anxiety disorder	Emotion
Stoddard et al. (2017)	Social anxiety disorder	Emotion
Waugh et al. (2012)	Social anxiety disorder	Emotion
Hamilton et al. (2015)	Social anxiety disorder	Emotion
Yin et al. (2017)	Generalized anxiety disorder	Emotion
Diwadkar et al. (2017)	Generalized anxiety disorder	Memory
Moon et al. (2016)	Generalized anxiety disorder	Emotion, Memory
Moon & Jeong (2017)	Generalized anxiety disorder	Emotion, Memory
Moon et al. (2017)	Generalized anxiety disorder	Emotion, Memory

Eligible articles	Anxiety type	Task category
Moon et al., 2015)	Generalized anxiety disorder	Emotion, Memory
Moon & Jeong (2015)	Generalized anxiety disorder	Emotion, Memory
Monk et al. (2008)	Generalized anxiety disorder	Emotion
Ottaviani et al. (2016)	Generalized anxiety disorder	Emotion, Attention
Fonzo et al. (2014)	Generalized anxiety disorder	Emotion
Price et al. (2011)	Generalized anxiety disorder	Emotion
Schlund et al. (2012)	Generalized anxiety disorder	Emotion
White et al. (2017)	Generalized anxiety disorder	Decision
Karim et al. (2016)	Generalized anxiety disorder	Emotion
Strawn et al. (2012)	Generalized anxiety disorder	Emotion
Paulesu et al. (2010)	Generalized anxiety disorder	Emotion
Palm et al. (2011)	Generalized anxiety disorder	Emotion
Robinson et al. (2013)	Induced – unpredictable shock	Emotion (due to threat)
Balderston et al. (2017a)	Induced – unpredictable shock	Emotion (due to threat)
Balderston e al. (2017b)	Induced – unpredictable shock	Emotion (due to threat)
Kirlic et al. (2017)	Induced – unpredictable shock	Emotion (due to threat)
Klumpers et al. (2017) – 2 studies	Induced – unpredictable shock	Emotion (due to threat)
Torrise et al. (2016)	Induced – unpredictable shock	Emotion (due to threat)
Gold et al. (2015)	Induced – unpredictable shock	Emotion (due to threat)
Choi et al. (2012)	Induced – unpredictable shock	Emotion (due to threat)
Alvarez et al. (2015)	Induced – unpredictable shock	Emotion (due to threat)
Clarke & Johnstone (2013)	Induced – unpredictable shock	Emotion (due to threat)
Holtz et al. (2012)	Induced – unpredictable hyperventilation	Emotion (due to threat)
Drabant et al. (2011)	Induced – unpredictable shock	Emotion (due to threat)
Klumpers et al. (2010)	Induced – unpredictable shock	Emotion (due to threat)
Reichert et al. (2017)	Induced – unpredictable thermal painful stimuli	Emotion (due to threat)
Yoshimura et al. (2014)	Induced – unpredictable shock	Emotion (due to threat)
Eser et al. (2009)	Induced – unpredictable CCK4-induced panic-like symptoms	Emotion (due to threat)
Yang et al. (2012)	Induced – unpredictable thermal painful stimuli	Emotion (due to threat)
Kalisch et al., 2006)	Induced – unpredictable shock	Emotion (due to threat)
Wittmann et al. (2018)	Panic disorder	Emotion
Feldker et al. (2018)	Panic disorder	Emotion
Held-Poschardt et al. (2018)	Panic disorder	Emotion, Decision
Reinecke et al. (2015)	Panic disorder	Emotion
Feldker et al. (2016)	Panic disorder	Emotion
Schwarzmeier et al. (2019)	Panic disorder	Emotion
Engel et al. (2016)	Panic disorder	Emotion
Petrowski et al. (2014)	Panic disorder	Emotion
Lueken et al. (2014)	Panic disorder	Emotion
Dresler et al. (2012)	Panic disorder	Emotion, Attention
van den Heuvel et al. (2011)	Panic disorder	Decision
Maddock et al. (2003)	Panic disorder	Emotion, Attention
Wintermann et tal. (2013)	Panic disorder	Attention
Pfleiderer et al. (2010)	Panic disorder	Attention
Caseras et al. (2010a) – 2 studies	Specific phobia	Emotion
Caseras et al. (2010b) – 2 studies	Specific phobia	Emotion
Rivero et al. (2017)	Specific phobia	Emotion
Wiemer et al. (2015)	Specific phobia	Emotion
Scharmüller et al. (2014)	Specific phobia	Emotion

Eligible articles	Anxiety type	Task category
Lipka et al. (2014)	Specific phobia	Emotion
Schienle et al. (2013)	Specific phobia	Emotion
Schienle et al. (2007)	Specific phobia	Emotion
Straube et al. (2007)	Specific phobia	Emotion
Goossens et al. (2007)	Specific phobia	Emotion
Schienle et al. (2005)	Specific phobia	Emotion
Dilger et al. (2003)	Specific phobia	Emotion
Aue et al. (2019)	Specific phobia	Emotion
Hilbert et al. (2014)	Specific phobia	Emotion
Zilverstand et al. (2017)	Specific phobia	Emotion
Aue et al. (2015)	Specific phobia	Emotion
Barke et al. (2012)	Specific phobia	Emotion
Straube et al. (2011)	Specific phobia	Emotion, Attention
Schweckendiek et al. (2011)	Specific phobia	Emotion
Hermann et al. (2007)	Specific phobia	Emotion
Lange et al. (2019)	Specific phobia	Emotion
Feldker et al. (2017)	Transdiagnostic anxiety	Emotion
Neumeister et al. (2018)	Transdiagnostic anxiety	Emotion
Williams et al. (2015)	Transdiagnostic anxiety	Emotion
Price et al. (2014)	Transdiagnostic anxiety	Emotion, Attention
Demenescu et al. (2011)	Transdiagnostic anxiety	Emotion
Carlisi et al. (2017)	Transdiagnostic anxiety	Emotion
Galván & Peris (2014)	Transdiagnostic anxiety	Decision
Smith et al. (2018)	Transdiagnostic anxiety	Emotion
Smith et al. (2019)	Transdiagnostic anxiety	Attention
Swartz et al. (2014a)	Transdiagnostic anxiety	Emotion
Swartz et al. (2014b)	Transdiagnostic anxiety	Emotion
Benson et al. (2015)	Transdiagnostic anxiety	Decision
Krain et al. (2008)	Transdiagnostic anxiety	Decision
Campbell-Sills et al. (2011)	Transdiagnostic anxiety	Emotion

TABLE S3. Whole-brain meta-analysis of the anxiety disorders diagnostic groups in emotion tasks

MNI coordinates	Voxels	Z value	Description	Egger's Intercept	Egger's p value
Social anxiety disorder					
-38,-80,26	1422	3.714	L. MOG, Angular g., MTG	0.01	0.996
42,20,-4	634	4.054	R. Insula, IFG all, STG pole	-0.04	0.971
4,-90,12	564	4.222	Bilateral Calcarine, cuneus	1.09	0.309
-20,0,-12	354	3.251	L. Amygdala, Hippocampus, Parahippocampal g., Olfactive b., Pallidum	0.60	0.614
58,-54,6	192	2.947	R. MTG	1.00	0.415
14,-60,-4	90	2.629	R. Lingual g.	-0.02	0.987
-40,26,-12	61	2.635	L. IFG orbital, triangular	-0.07	0.949
24,62,24	32	2.847	R. SFG, MFG	0.42	0.715
-8,-4,2	33	2.358	L. Thalamus	-0.07	0.956
14,-54,60	12	2.288	R. SPG, Precuneus	-0.32	0.784
-8,34,-8	12	2.170	L. MedFG orb., ACC	0.34	0.774
-12,-2,14	11	2.372	L. Caudate	0.09	0.936
Panic disorder					
-56,-6,-12	536	3.129	L. MTG, STG, ITG, STG pole, Insula	0.04	0.972
34,6,-6	204	3.089	R. Putamen, Insula	-0.10	0.937
-48,36,28	188	3.680	L. IFG triangular, MidFG	-0.45	0.709
26,-36,-16	82	2.245	R. Fusiform g.	0.22	0.863
-10,-32,-10	39	3.166	L. Cerebellum 4/5	1.05	0.413
-34,18,-14	20	2.373	L. Insula	0.60	0.684
44,-12,16	14	2.191	R. Rolandic operculum	1.46	0.253
34,14,26	12	2.325	R. IFG triangular, opercular	0.51	0.687
Generalized anxiety disorder					
58,-28,38	477	3.841	R. Supramarginal g., Postcentral g.	1.09	0.744
42,-28,-18	488	3.537	R. Parahippocampal, Angular g., Hippocampus	0.29	0.926
40,-68,14	241	3.416	R. MTG	0.71	0.837
48,-8,-12	209	3.095	R. MTG, STG, ITG	0.35	0.913
-26,-40,8	175	3.569	L. Hippocampus, Parahippocampal g., Lingual g.	0.25	0.941
44,-74,-2	180	3.107	R. MOG, IOG, ITG	0.49	0.880
-18,-76,-10	161	2.943	L. Lingual g.	1.21	0.688
-64,-14,-6	128	3.131	L. MTG, STG	0.36	0.912
-14,-26,16	101	2.740	L. Thalamus	0.61	0.846
54,10,40	90	2.712	R. Precentral g.	0.14	0.965
-26,-96,6	76	2.651	L. MOG	0.84	0.791
-2,-64,-28	74	2.575	Vermis 8	1.23	0.693
16,-92,-6	54	2.521	R. Calcarine, Lingual g.	0.27	0.936
-4,-50,-12	42	2.559	L. Cerebellum 4/5	0.18	0.957
30,-44,0	38	2.865	R. Hippocampus	0.18	0.957
6,-68,16	37	2.832	Calcarine	0.41	0.899
-60,-30,38	29	2.672	L. Supramarginal g.	0.58	0.856
2,-82,4	30	2.384	Calcarine	-0.31	0.921
-22,30,44	24	2.633	L. MidFG, SFG	-0.23	0.941
-18,-48,-14	15	2.252	L. Cerebellum 4/5, Fusiform g.	-0.32	0.925

MNI coordinates	Voxels	Z value	Description	Egger's Intercept	Egger's p value
22,-78,-10	10	2.244	L. Lingual g., Fusiform g.	0.86	0.785
2,6,46	282	-2.843	MCC, SMA	-0.98	0.762
10,52,6	156	-3.273	R. MedFG orbital, ACC	1.07	0.750
-8,-34,54	165	-2.984	L. Precuneus, MCC	-0.59	0.861
26,54,0	145	-3.397	R. SFG orb., MidFG orb., SFG, MidFG	0.26	0.938
40,16,-14	105	-2.910	R. Insula, STG pole	-0.47	0.885
44,-60,-20	81	-3.526	R. Fusiform g., Cerebellum 1	0.55	0.875
16,-24,-22	66	-3.100	R. Cerebellum 3, possible Parahippocampal g.	-1.40	0.675
12,12,-10	63	-2.509	R. Caudate	-0.29	0.932
12,16,2	61	-2.896	R. Caudate	0.24	0.944
-10,-70,54	59	-2.991	L. Precuneus	-0.54	0.862
-32,-38,66	40	-2.395	L. Postcentral g.	0.19	0.955
-28,-44,52	38	-2.394	L. IPG, Postcentral g.	-0.20	0.952
2,-12,2	21	-2.438	Bilateral thalamus	-0.49	0.889
36,-16,6	18	-2.540	L. Insula	-3.62	0.185
34,46,30	15	-2.400	R. MidFG	-1.37	0.686
PTSD					
50,4,-6	1671	5.105	R. STG, STG pole, Insula, Heschl's g., Rolandic operculum, IFG opercular, MTG, MTG pole	1.35	0.319
-42,-8,6	283	3.059	L. Insula, STG pole, STG, Heschl's g., Rolandic operculum,	-0.39	0.805
-52,4,34	39	2.567	L. Precentral g.	-0.41	0.805
-44,-60,36	18	-2.285	L. Angular g.	-0.24	0.905
-62,-54,32	11	-2.269	L. Supramarginal g.	-0.15	0.937
Specific phobia					
-4,28,36	4369	4.906	MCC, ACC, MedFG sup., SMA	0.62	0.590
-6,-70,-12	2357	3.651	Cerebellum 6, 3-5, 1, Vermis 6, Lingual g.	0.79	0.523
-44,16,-2	2073	3.825	L. Insula, IFG all, STG, STG pole, Heschl's g., Rolandic operculum, Amygdala, Hippocampus, Putamen	1.09	0.382
14,8,14	1177	3.475	Bilateral Caudate	0.80	0.492
38,20,-8	658	3.237	R. Insula, IFG all	1.32	0.329
36,-76,-14	628	2.902	R. Cerebellum 6, 1, Fusiform g., IOG	0.17	0.883
36,-54,54	174	2.832	R. IPG, Angular g.	-0.41	0.760
12,-14,-24	172	2.714	R. Parahippocampal g., Hippocampus	0.61	0.675
-48,-46,46	138	2.735	L. IPG	0.01	0.993
-18,-90,-8	115	2.723	L. Lingual g., IOG	0.90	0.461
24,-36,-34	86	2.641	R. Cerebellum 4/5	0.91	0.437
56,-50,6	80	2.684	R. MTG	-0.10	0.931
-60,-34,8	50	2.535	L. MTG	0.24	0.841
-44,-64,-16	39	2.358	L. Fusiform g.	-0.31	0.806
-20,30,42	30	2.673	L. MidFG/SFG	-0.31	0.797
-36,-64,42	31	2.275	L. Angular g., IPG	0.02	0.988
44,10,-22	30	2.412	R. STG, MTG pole	0.64	0.633
42,38,20	26	2.361	R. MidFG	0.76	0.514
-32,2,48	24	2.287	L. Precentral g./MidFG	0.33	0.770

MNI coordinates	Voxels	Z value	Description	Egger's Intercept	Egger's p value
-6,48,38	18	2.271	L. MedFG	0.25	0.834
48,-12,50	15	2.231	R. Precentral g.	0.15	0.899
-6,-32,-30	13	2.264	Undefined – L. Pons suggested	0.68	0.583
40,-38,48	10	2.090	R. IPG	-0.60	0.612
Transdiagnostic anxiety					
-34,6,-10	224	2.837	L. Insula, Putamen	0.31	0.838
10,-66,18	184	2.996	R. Calcarine, Cuneus, Lingual g., Precuneus	0.69	0.681
2,20,40	132	2.651	MCC, MedFG	1.03	0.504
12,-36,-24	52	2.409	R. Cerebellum 3, 4/5	1.44	0.325
-4,22,54	42	2.389	R. SMA, MedFG	0.57	0.711
-16,-28,-28	21	2.350	L. Cerebellum 4/5	0.24	0.885
-30,24,38	18	2.355	L. MidFG	0.84	0.608

$p \leq 0.005$, $k \geq 10$. Exploratory Egger's tests are reported for meta-analytic clusters.

ACC: anterior cingulate cortex; MCC: midcingulate cortex; MidFG: middle frontal gyrus; MedFG: Medial frontal gyrus; SMA: Supplementary motor area; STG: superior temporal gyrus; MTG: Middle temporal gyrus; ITG: inferior temporal gyrus; SPG: superior parietal gyrus; IPG: inferior parietal gyrus; SOG: superior occipital gyrus; MOG: middle occipital gyrus; IOG: inferior occipital gyrus

TABLE S4. Whole-brain meta-analysis of anxiety induced by threat-of-shock only

MNI coordinates	Voxels	Z value	Description	Egger's Intercept	Egger's p value
42,16,8	8111	6.145	Bilateral Insula, IFG all, STG pole, Putamen, Rolandic operculum, Caudate, Pallidum, Thalamus, Vermis 3, R Lingual g., L.STG	0.84	0.466
2,-4,48	7499	6.011	MCC, SMA, MedFG, ACC, R. SFG	0.06	0.960
58,-44,36	2081	6.505	R. Supramarginal g., Angular g., IPG, STG, MTG, Rolandic operculum	0.75	0.500
32,42,18	888	3.967	R. MidFG, SFG	0.48	0.738
-60,-38,26	743	4.986	L. Supramarginal g., STG	0.69	0.516
18,-62,34	378	4.276	R. Precuneus, Cuneus, SOG	-0.07	0.956
-38,44,26	265	3.598	L. MidFG	1.08	0.333
-42,-52,-30	161	2.758	L. Cerebellum 6, Cerebellum crus 1	0.61	0.624
-34,-54,-48	76	2.794	Cerebellum 8	0.59	0.605
0,-50,-26	65	2.749	Vermis 9, Vermis 4-5	1.08	0.391
54,-30,-10	30	2.643	R. MTG	0.13	0.918
-10,-34,-48	24	2.749	Undefined – Cerebellum 9 suggested	0.58	0.630
28,-48,70	22	2.443	R. SPG	-0.23	0.855
-10,-70,46	17	2.465	L. Precuneus	0.83	0.493
54,-60,-8	2227	-4.151	R. ITG, MTG, MOG, SOG, IOG	-0.60	0.616
-48,-70,0	2130	-4.123	L. IOG, ITG, MTG, MOG, SOG, IPG, SPG, Angular g.	-0.76	0.496
-56,-22,48	1101	-4.630	L. Postcentral g., Precentral g., IPG	-0.76	0.506
-8,50,-22	1074	-4.518	Rectus g., Bilateral SFG orb	-0.15	0.906
-22,-16,-22	899	-4.237	L. Hippocampus, Parahippocampal g., Fusiform g, Lingual g, Calcarine	-0.61	0.605
-42,-10,16	295	-3.506	L. Insula, Heschl's g., Rolandic operculum	-0.37	0.747
52,-2,24	285	-3.829	R. Postcentral, Precentral	-0.67	0.549
26,-6,-28	276	-3.600	R. Parahippocampal g. Hippocampus	-0.40	0.731
-12,-54,18	195	-3.150	L. Calcarine, Cuneus, Precuneus	0.02	0.987
12,-54,12	179	-3.127	R. Calcarine, Cuneus, Precuneus	0.01	0.994
-4,-32,66	109	-2.287	Paracentral lobule	-0.23	0.907
26,-62,-6	101	-2.735	R. Fusiform g., Lingual g.	-0.58	0.620
-22,32,40	33	-2.336	L. MidFG	0.24	0.889
28,-56,10	15	-2.311	R. Calcarine	-0.41	0.747
30,-76,14	13	-2.160	R. MOG	-0.45	0.697

$p \leq 0.005$, $k \geq 10$. Exploratory Egger's tests are reported for meta-analytic clusters.

ACC: anterior cingulate cortex; MCC: midcingulate cortex; MidFG: middle frontal gyrus; MedFG: Medial frontal gyrus; SMA: Supplementary motor area; STG: superior temporal gyrus; MTG: Middle temporal gyrus; ITG: inferior temporal gyrus; SPG: superior parietal gyrus; IPG: inferior parietal gyrus; SOG: superior occipital gyrus; MOG: middle occipital gyrus; IOG: inferior occipital gyrus

TABLE S5. Whole-brain pairwise analysis of convergence between induced anxiety and pathological anxiety with exclusions

MNI coordinates	Voxels	Description
Induced vs. Pathological anxiety (youth patient sample excluded)		
-10,-4,68	2442	SMA, MCC, MedFG sup., ACC
46,14,-14	2150	R. Insula, IFG all, Rolandic operculum, STG pole, STG
-40,20,-10	1009	L. Insula, IFG all, Putamen, Rolandic operculum, STG pole
-4,-22,-10	615	R. Thalamus, Lingual g., Vermis 3
50,4,46	183	R. Precentral g., MidFG
12,-26,40	49	R. MCC
Induced vs. Pathological anxiety (medicated patient sample excluded)		
-2,0,40	2778	MCC, MedFG sup., ACC, SMA
44,20,-2	1720	R. Insula, IFG all, Rolandic operculum, STG pole, STG, Putamen
-48,16,2	1362	L. Insula, IFG all, Rolandic operculum, STG pole, Putamen, Pallidum
-2,-22,-10	517	R. Thalamus, Lingual g., Vermis 3
-6,6,2	192	L. Caudate, Pallidum
-10,-4,68	172	L. SMA

$p \leq 0.005$, $k \geq 10$.

ACC: anterior cingulate cortex; MCC: midcingulate cortex; MidFG: middle frontal gyrus; MedFG: Medial frontal gyrus; SMA: Supplementary motor area; STG: superior temporal gyrus; ITG: inferior temporal gyrus

TABLE S6. Whole-brain pairwise analyses of convergence between induced anxiety and anxiety disorders diagnostic groups in emotion tasks

MNI coordinates	Voxels	Description
Induced vs. Specific phobia		
2,28,16	5043	MCC, MedFG sup., ACC, SMA
38,20,-8	1274	R. Insula, IFG all, STG pole, STG, Putamen
2,-20,-8	997	Bilateral Thalamus, Caudate, L. Pallidum
-42,18,-4	846	L. Insula, IFG all, Putamen, Rolandic operculum, STG pole
-38,4,-14	51	L. Putamen, Insula
Induced vs. Panic disorder		
34,6,-6	490	R. Insula, Putamen, STG pole
-34,18,-14	131	L. Insula, IFG orbital, STG pole
Induced vs Generalized anxiety disorder		
58,-30,34	205	R. Supramarginal g.
Induced vs. PTSD		
52,8,-6	689	R. Rolandic operculum, Insula, IFG opercular, STG pole, STG
-50,8,2	36	L. Rolandic operculum, Insula, IFG opercular, STG pole
Induced vs. Social anxiety disorder		
48,18,-12	954	R. IFG all, Insula, STG pole
-56,-46,32	225	L. Supramarginal g., STG, MTG
-42,26,-10	82	L. IFG orbital
-8,-2,64	34	L. SMA
Induced vs. Transdiagnostic anxiety		
2,20,40	621	SMA, MCC, MedFG
-26,10,-2	193	L. Insula, putamen, STG pole

$p \leq 0.005$, $k \geq 10$.

ACC: anterior cingulate cortex; MCC: midcingulate cortex; MidFG: middle frontal gyrus; MedFG: Medial frontal gyrus; SMA: Supplementary motor area; STG: superior temporal gyrus; MTG: Middle temporal gyrus; ITG: inferior temporal gyrus; SPG: superior parietal gyrus; IPG: inferior parietal gyrus; SOG: superior occipital gyrus; MOG: middle occipital gyrus; IOG: inferior occipital gyrus

TABLE S7. Whole-brain meta-analysis of PTSD contrasting patients vs. traumatized controls in emotion tasks

MNI coordinates	Voxels	Z value	Description	Egger's Intercept	Egger's p value
-2,-30,48	193	2.745	MCC, Precuneus, PCC	0.57	0.663
-48,-68,14	42	2.519	L. MTG, MOG	1.19	0.389
-16,-64,54	38	2.654	L. SPG, Precuneus	1.12	0.398
-26,-70,50	32	2.429	L. SPG	1.08	0.420
-14,46,4	28	2.684	L. ACC, MedFG orb.	0.64	0.622
10,-24,44	28	2.447	R. MCC	0.68	0.597
-14,-74,14	21	2.460	L. Calcarine	1.16	0.355
6,-80,20	21	2.396	Cuneus, Calcarine	1.91	0.113
48,26,28	16	2.535	R. IFG triangular	0.36	0.770
44,-18,50	16	2.281	R. Postcentral g., Precentral g.	-0.73	0.586
32,42,14	14	2.596	R. MidFG	1.27	0.288
0,-68,12	11	2.191	Calcarine	1.59	0.203
4,34,0	197	-3.948	ACC (pregenual), MedFG orb.	-1.13	0.371
56,-30,16	11	-2.529	R. STG	-0.90	0.462

$p \leq 0.005$, $k \geq 10$. Exploratory Egger's tests are reported for meta-analytic clusters.

ACC: anterior cingulate cortex; MCC: midcingulate cortex; PCC: posterior cingulate cortex; MidFG: middle frontal gyrus; MedFG: Medial frontal gyrus; STG: superior temporal gyrus; MTG: Middle temporal gyrus; SPG: superior parietal gyrus; MOG: middle occipital gyrus

TABLE S8. Whole-brain meta-analysis of pathological anxiety across disorders for non-emotion tasks

MNI coordinates	Voxels	Z value	Description	Egger's Intercept	Egger's p value
Attention					
<i>No peaks</i>					
Decision					
20,10,-10	69	-2.636	R. Olfactory c., Putamen	0.98	0.743
26,48,20	45	-2.594	R. MidFG	-1.01	0.730
-24,46,30	13	-2.327	L. MidFG, SFG	-0.31	0.891
Memory					
-28,-40,-2	98	3.298	L. Hippocampus, Parahippocampal g.	0.15	0.962
58,12,30	94	2.984	R. IFG opercular, Precentral g.	0.68	0.840
2,4,40	647	-4.344	Bilateral MCC, SMA, ACC	-0.61	0.846
-20,-90,22	459	-4.712	L. SOG, MOG, Cuneus	-1.61	0.584
12,-44,40	363	-3.048	R. Precuneus, MCC, PCC	-1.90	0.526
14,18,4	287	-4.135	R. Caudate	-2.50	0.373
48,42,4	250	-3.690	R. MidFG, IFG orbital, triangular	0.23	0.945
26,-86,32	233	-3.169	R. SOG, Cuneus, MOG	-2.19	0.506
-32,46,32	197	-3.032	L. MidFG, IFG triangular	0.05	0.988
34,-4,16	167	-3.066	L. Insula, Rolandic operculum, Putamen, Heschl's g.	-1.72	0.576
-44,-56,20	153	-3.357	L. MTG, Angular g.	-0.79	0.773
6,36,32	124	-2.890	L. ACC, MCC, MedFG sup.	2.08	0.578
14,10,-10	106	-2.986	R. Caudate, Putamen, Olfactory c., Rectus	-0.46	0.888
-40,44,8	104	-3.165	L. MidFG, IFG triangular, MidFG orbital	-0.42	0.882
16,-78,48	91	-2.854	R. Cuneus, Precuneus, SPG	-0.01	0.996
-28,-14,-20	63	-2.778	L. Hippocampus	-0.47	0.888
-10,-74,56	55	-3.151	L. Precuneus	-0.81	0.791
40,34,30	54	-2.727	R. MidFG, IFG triangular	0.11	0.973
46,30,10	37	-2.659	R. IFG triangular	1.35	0.720
52,-2,8	19	-2.470	R. Rolandic operculum	-1.17	0.699
10,-14,70	13	-2.372	R. SMA	-0.65	0.842

$p \leq 0.005$, $k \geq 10$. Exploratory Egger's tests are reported for meta-analytic clusters.

ACC: anterior cingulate cortex; MCC: midcingulate cortex; MidFG: middle frontal gyrus; MedFG: Medial frontal gyrus; SMA: Supplementary motor area; STG: superior temporal gyrus; MTG: Middle temporal gyrus; ITG: inferior temporal gyrus; SPG: superior parietal gyrus; IPG: inferior parietal gyrus; SOG: superior occipital gyrus; MOG: middle occipital gyrus; IOG: inferior occipital gyrus

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