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Neurocircuitry of treatment in anxiety disorders

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ABSTRACT

Background: Understanding how treatments change neurobiology is critical to developing predictors of treatment response. This is especially true for anxiety disorders—the most common psychiatric disorders across the lifespan. With this in mind, we examined neurofunctional predictors of treatment response and neurofunctional changes associated with treatment across anxiety disorders.

Methods: PubMed/Medline was searched for prospective treatment studies that included parallel examinations of functional activation or connectivity (both task-based and resting state) in adults and youth with panic disorder and generalized, separation, and/or social anxiety disorders published before April 30, 2021. All studies examining baseline predictors or changes related to pharmacologic and psychotherapeutic treatment of *DSM-IV* and *DSM-5* anxiety disorders were included. Demographic, clinical, and treatment data as well as neurofunctional outcomes were extracted and summarized.

Results: Twenty-nine studies examined changes in functional activation and/or connectivity (56 treatment arms) related to treatment and twenty-three examined neurofunctional predictors of treatment response. Predictors of treatment response and treatment-related neurofunctional changes were frequently observed within amygdala-prefrontal circuits. However, immense heterogeneity and few replication studies preclude a cohesive neurofunctional treatment response model across anxiety disorders.

Conclusions: The extant literature describing neurofunctional aspects of treatment response in anxiety disorders is best viewed as a partially constructed scaffold on which to build a clinically translatable set of robust neuroimaging biomarkers that can be used to guide treatment and to select from available treatment. The construction of this understanding will require harmonization of analytic and task approaches, larger samples, and replication of component studies.

Introduction

Over the past decade, the prevalence of anxiety disorders and disability-adjusted life years attributed to anxiety disorders (particularly in adolescents and young adults) has increased (Abbafati et al., 2020). In fact, anxiety disorders are now the sixth leading cause of disability worldwide in individuals aged 10-24 and the 15th in those aged 25-50 (Abbafati et al., 2020). Currently, these disorders affect 7.3% of the global population and, in the United States, have a lifetime prevalence of almost 31% (Merikangas et al., 2010). Importantly, these conditions frequently respond to psychotherapy and pharmacotherapy, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitor (SNRIs) (Jakubovski et al., 2019; Strawn et al., 2020). For many patients, treatment effectively reduces anxiety, but studies of the neurobiological mechanisms of these interventions in anxiety are limited and have produced conflicting results. Understanding the neural mechanisms of anxiety treatments could inform treatment selection, treatment development, and allow clinicians to consider alternative or adjunctive treatments earlier.

Psychotherapy and SSRIs/SNRIs affect limbic, attentional, and executive control circuitry in regions including the amygdala, insula, dorsolateral prefrontal cortex (dlPFC), ventrolateral PFC (vlPFC),

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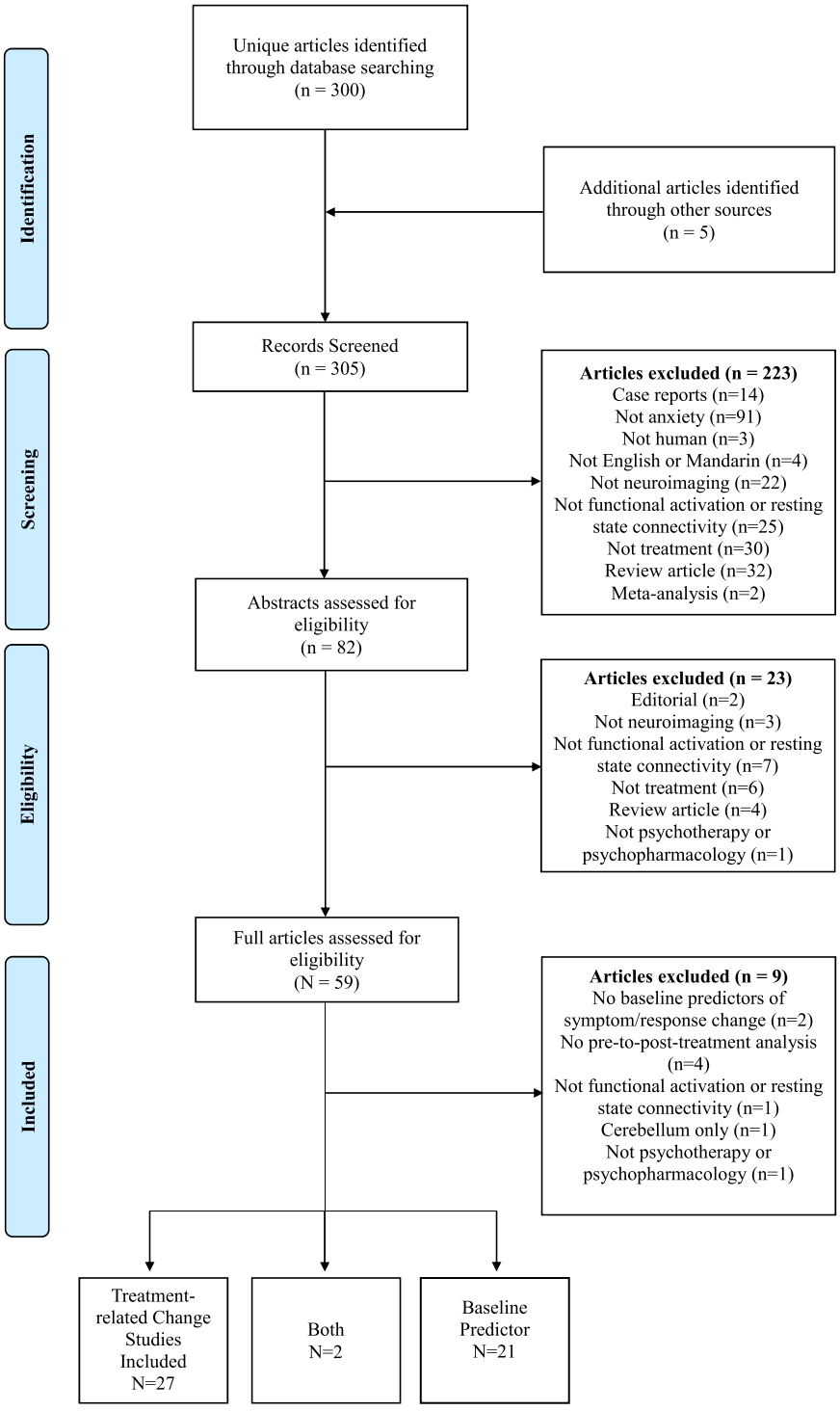

Fig. 1. Systematic Review Study Selection Inclusion and Exclusion.

medial PFC (mPFC), and dorsal anterior cingulate cortex (dACC) (Godlewska et al., 2016; Harmer et al., 2017; Ma, 2015; Strawn et al., 2020). These studies implicate the prefrontal-amygdala circuitry as a target of successful treatment whether psychotherapeutic or psychopharmacologic. Importantly, these circuits – particularly the amygdala, vlPFC, and ACC – show abnormal activity across numerous tasks designed to probe emotional reactivity and regulation as well as attention (Strawn et al., 2012). To date, one study has reviewed neurofunctional predictors of treatment response and our earlier work – from a decade ago – examined the neurofunctional basis of treatment in pediatric anxiety disorders (Lueken et al., 2016; Strawn et al., 2012). Previously, Lueken et al. systematically reviewed predictors of response to psychotherapy or psychopharmacologic treatment across anxiety disorders (Lueken et al., 2016) and included both genetic and neurofunctional markers (*e.g.*, electroencephalography, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI)). Also, we previously reviewed the neurofunctional effects of these treatments but restricted our efforts to pediatric patients and to generalized anxiety disorder (GAD) (Strawn et al., 2012).

The lack of comprehensive synthesis in the existing literature limits

Table 1
Characteristics of included studies.

A: Characteristics of studies based on imaging approach									
	Treatment Related Changes				Baseline Predictor				
	Region of Interest (*n*=13)	Whole Brain (*n*=17)	Functional Connectivity (*n*=15)	Total Change Studies (*n*=29)	Region of Interest (*n*=11)	Whole Brain (*n*=9)	Functional Connectivity (*n*=3)	Machine Learning (*n*=5)	Total Predictor Studies (*n*=23)
N	20.4 ± 11.4	20.6 ± 10.0	21.5 ± 8.8	20.3 ± 10.8	21.6 ± 12.1	21.7 ± 6.5	21.8 ± 7.1	37.0 ± 11.8	24.2 ± 11.6
Age	29.9 ± 7.4	29.7 ± 7.6	32.2 ± 10.2	29.9 ± 9.7	24.5 ± 8.7	23.8 ± 8.5	26.7 ± 1.2	32.1 ± 2.2	25.9 ± 7.7
Sex (% Female)	64.6 ± 14.2	63.9 ± 12.3	60.3 ± 18.6	61.9 ± 14.7	65.4 ± 12.4	64.9 ± 7.7	63.35 ± 9.9	64.0 ± 20.5	64.7 ± 12.5
Pharmaco-therapy	4 / 13	6/ 17	4 / 15	10 / 29	8 / 11	8 / 9	3 / 3	5 / 5	4 / 23
Psycho-therapy	11 / 13	13 / 17	11 / 15	22 / 29	3 / 11	2 / 9	0 / 3	0 / 5	19 / 23
Mixed Treatment	0 / 13	0 / 17	0 / 15	0 / 29	1 / 11	1 / 9	0 / 3	0 / 5	2/ 23
Duration (weeks)	8.9 ± 3.1	10.4 ± 3.3	9.6 ± 2.9	9.5 ± 2.9	9.8 ± 2.5	10.5 ± 3.3	12.0 ± 0.0	10.0 ± 2.7	10.5 ± 2.6

B: Characteristics of pharmacotherapy and psychotherapy studies		
	Pharmacotherapy Studies (*n*=16)	Psychotherapy Studies (*n*=38)
N	17.1 ± 6.4	23.3 ± 11.6
Age	26.3 ± 13.2	29.1 ± 6.7
Sex (% Female)	65.4 ± 11.1	61.9 ± 14.7
Duration (weeks)	8.9 ± 2.0	10.3 ± 3.0
Primary GAD (%)	9 (56%)	7 (18%)
Primary Social AD (%)	5 (31%)	21 (55%)
Primary PD (%)	2 (13%)	10 (26%)

Characteristics of studies based on imaging approach are shown in A.
Characteristics of pharmacotherapy and psychotherapy studies are shown in B.

current understanding of treatment-related neurofunctional changes in anxiety disorders, or the effect of treatments on brain functions. Current knowledge is limited to individual studies with relatively small sample sizes that often have conflicting results and varying levels of stringent procedures. Contextualization of the findings is difficult given sample heterogeneity (*e.g.*, diagnosis), variation in study implementation and analysis (*e.g.*, search space, correction for head motion artifacts). Additionally, there is heterogeneity of task design for task-based fMRI studies that can be broadly described as measuring brain activation during emotional-processing.

With these considerations in mind, we reviewed brain imaging studies conducted within treatment trials in children, adolescents, and adults with *DSM-IV or DSM-5* anxiety disorders. Here, we sought to build upon the current literature by (1) providing an updated review of neurofunctional predictors of treatment response across anxiety disorders, and (2) reviewing treatment effects on neurocircuitry across anxiety disorders and the lifespan.

Specifically, we extracted data from task- and resting state-based fMRI studies published before April 30, 2021, to review the literature with regard to treatment-related changes in functional activation and functional connectivity, and with regard to baseline imaging predictors of treatment response. From this we sought to summarize (1) cumulative evidence to clarify the neural substrates of pharmacological and psychotherapeutic treatment response, (2) baseline predictors of pharmacological and psychotherapeutic treatment response across anxiety disorders, and (3) neural treatment response between pharmacological and psychotherapy treatments (primarily SSRI and cognitive behavioral therapy (CBT)). While heterogeneity adds complexity to examining the neurofunctional aspects of treatment across anxiety disorders, we predicted – based on prior studies – that psychopharmacologic and psychotherapeutic treatment impact unique neurophysiological targets and pathways within prefrontal-amygdala circuitry. We aimed to identify and assess consistent, replicated biomarkers across trials.

Methods

Literature search

We conducted a literature search with the PubMed database from inception to April 30, 2021 using the following terms: (generalized anxiety disorder OR separation anxiety disorder OR social anxiety disorder OR panic disorder OR social phobia OR agoraphobia OR generalized social anxiety disorder OR generalized social phobia) AND (fMRI OR functional magnetic resonance imaging OR functional connectivity OR resting state OR rsfMRI) AND ((SSRI OR selective serotonin reuptake inhibitor OR fluoxetine OR paroxetine OR escitalopram OR fluvoxamine OR citalopram OR vortioxetine OR vilazodone OR sertraline OR SNRI* OR serotonin norepinephrine reuptake inhibitor OR duloxetine OR venlafaxine OR desvenlafaxine OR levomilnacipran OR bupropion OR mirtazapine) OR (CBT OR MBCT OR cognitive behavioral therapy OR cognitive therapy OR IPT OR interpersonal therapy OR ACT OR acceptance commitment therapy OR DBT OR dialectical behavioral therapy)) for neuroimaging studies of treatment-related neurophysiologic changes in anxiety disorders. Of note, papers were included only if response to controlled therapeutic intervention was examined. Then, the reference lists and tables of relevant meta-analysis and review articles were examined to identify any studies that may been missed in the original search (Fig. 1).

Table 2
Demographic and study design characteristics of included studies of baseline neurofunctional predictiors of treatment response.

Studies of baseline predictors of treatment response

Study	N	Primary Diagnosis†	Age ± SD	% Female	Treatment Type	Treatment‡	Duration	Dosage	Anxiety Scale§	Change in Symptoms¶ Pre, Post	Search Space∂	Task$^{\Omega}$
Whole brain												
Frick et al. 2018 &	24	SoAD	32 ±9	50	Mix	CBT + placebo	9 weeks	1 session/wk	LSAS	NR, NR	WB	Emotional face shifting of attention task
Frick et al. 2020	24	SoAD	35 ±10	50	Mix	CBT + escitalopram	9 weeks	1 session/wk, 20 mg/day	LSAS	NR, NR	Machine learning based on Frick et al. 2018 finding	
Klumpp et al. 2013	14	SoAD	28±9	64	Therapy	CBT	12 weeks	1 hr/wk	LSAS	71,50	WB	Emotional face matching task
Klumpp et al. 2014	21	SoAD	25±6	71	Therapy	CBT	12 weeks	1 hr/wk	LSAS	73, 50	WB	Emotional face matching task
Klumpp et al. 2016	32	SoAD	25±5	75	Therapy	CBT	12 weeks	1 hr/wk	LSAS	74, 48	WB	Discriminate letters displayed on an emotional face under high and low perceptual loads
Klumpp et al. 2017	34	SoAD	25±5	65	Therapy	CBT	12 weeks	1 hr/wk	LSAS	78, 47	WB	Reappraise or maintain with emotional images
Grambal et al. 2015	22	PD	32 ±12	68	Mix	CBT adjunct added to long-term antidepressant (n=18)	6 weeks	25 sessions	BAI	NR, NR	WB	Response to Threat Words
Reinecke et al. 2014	14	PD	37 ±11	71	Therapy	CBT	4 weeks	unspecified	PDSS	11, 4	WB	Maintain or reappraise while viewing panic scenes
Kujawa et al. 2016	20	GAD 33%, SepA 8%, SoAD 58%	14±3	63	Med	sertraline	12 weeks	25-200 mg/d	PARS	23, 11	WB	Emotional face shifting of attention task
	21	GAD 41%, SepA 6%, SoAD 53%	13±3	65	Therapy	CBT	16 weeks	1 hr/wk	PARS	23, 12		
Burkhouse et al. 2017	16	GAD 57%, SoAD 43%	15±3	69	Therapy	CBT	10 weeks	1 hr/wk	PARS	22, 9	WB	Emotional face shifting of attention task
	21	GAD 57%, SoAD 43%	14±3	52	Med	sertraline	10 weeks	12.5 or 25 mg/d	PARS	24, 10		
Region of interest												
Klumpp et al. 2014	21	SoAD	25±6	71	Therapy	CBT	12 weeks	1 hr/wk	LSAS	73, 50	ACC, amyg, aInsula	Emotional face matching task
Klumpp et al. 2017	38	SoAD	25±6	63	Therapy	CBT	12 weeks	1 hr/wk	LSAS	78, 49	rACC, dACC, amyg	React vs reappraise emotional face under high and low perceptual loads
Klumpp et al. 2017	34	SoAD	25±5	65	Therapy	CBT	12 weeks	1 hr/wk	LSAS	78, 47	dmPFC, dlPFC	Reappraise or maintain with emotional images
Burklund et al. 2017	17	SoAD	28±8	49	Therapy	CBT	12 weeks	1 hr/wk	LSAS	82, 53	Amyg, insula, ACC	Viewing rejecting vs neutral images and verbal sentences
	19	SoAD	28±8	49	Therapy	ACT	12 weeks	1 hr/wk	LSAS	2, 53		
Reinecke et al. 2014	14	PD	37 ±11	71	Therapy	CBT	4 weeks	unspecified	PDSS	11, 4	Amyg	Maintain or reappraise while viewing panic scenes
Wittmann et al. 2018	51	PD	36 ±11	67	Therapy	CBT	8 weeks	12 sessions	HAMA	24, 12	Ventral striatum, insula, amygdala	Viewing neutral or panic related photos after a cue or no cue
McClure et al. 2007	12	GAD	12±2	50	Therapy or Med	CBT or fluoxetine	8 weeks	5-40 mg/day or 1-1.5 hr/wk	CGI-S	4, 2	Amyg	Viewing faces and making judgements
Whalen et al. 2008	15	GAD	27± 7	80	Med	venlafaxine	8 weeks	37.5-225 mg/d	HAMA	19, 7	rACC, amygdala	Viewing fearful, happy, and neutral faces
Nitschke 2009	14	GAD	33 ±NR	86	Med	venlafaxine	8 weeks	37.5 mg/d to 225 mg/d	HAMA	20, 8	Amyg, Insula, ACC, PFC, hippo	Aversive scenes preceded by cues

(*continued on next page*)

Table 2 (*continued*)

Studies of baseline predictors of treatment response												
Study	N	Primary Diagnosis†	Age ± SD	% Female	Treatment Type	Treatment‡	Duration	Dosage	Anxiety Scale§	Change in Symptoms¶ Pre, Post	Search Space∂	Task$^{\Omega}$
Strawn et al. 2016	9	GAD, SoAD, SepA	13± 2	78	Therapy	MBCT	12 weeks	NR	PARS	11, NR	aInsula, L ACC, (significant WB regions)	Continuous Processing Task with Emotional and Neutral Distractors
Burkhouse et al. 2017	16	GAD 57%, SoAD 43%	15±3	69	Therapy	CBT	10 weeks	1 hr/wk	PARS	22, 9	Amyg, dlPFC, vlPFC, rACC	Emotional face shifting of attention task
	21	GAD 57%, SoAD 43%	14±3	52	Med	sertraline	10 weeks	12.5 or 25 mg/d	PARS	24, 10		
Functional connectivity												
Klumpp et al. 2014	21	SoAD	28±9	67	Therapy	CBT	12 weeks	1 hr/wk	LSAS	72, 52	Amyg-PFC, WB	rs-fcMRI w/ crosshair
Klumpp et al. 2016	32	SoAD	25±5	75	Therapy	CBT	12 weeks	1 hr/wk	LSAS	74, 48	Significant dACC region from WB analysis-WB	Discriminate letters displayed on an emotional face under high and low perceptual loads
Young et al. 2019	17	SoAD	26±6	53	Therapy	CBT	12 weeks	1 hr/wk	LSAS	80, 52	Seed-seed: amyg, vmPFC, vlPFC,	Implicit emotional regulation with match and label faces and shapes and explicit emotional regulation with watching actors say emotional phrases with maintain and reappraise
	17	SoAD	27±5	59	Therapy	ACT	12 weeks	1 hr/wk	LSAS	85, 51		
Support vector modeling & machine learning												
Månsson et al., 2015	26	SoAD	32 ±10	85	Therapy	iCBT (w. adjunctive ABM)	9 weeks CBT + 4 weeks ABM	NR	LSAS	75, 45	vACC, dACC, amyg, hippo, insula, dlPFC, vmPFC	Reading self vs other referential criticism sentences
Whitfield-Gabrieli et al. 2016	38	SoAD	29 ±NR	37	Therapy	CBT	12 weeks	1 hr/wk	LSAS	>60, NR	Amyg-WB	rs-fcMRI
Hahn et al. 2015	49	PD	35 ±NR	67	Therapy	CBT	6 weeks	2 sessions/wk	HAMA	25, NR	WB	classical conditioning
Ball et al. 2014	48	GAD 25, PD 23,	31 ±10	81	Therapy	CBT	10 weeks	1 session/wk	PSWQ	25, 24	70 ROIs	maintain or reappraise emotional response to negative images

† SoAD = social anxiety disorder, PD = panic disorder, GAD, generalized anxiety disorder, SepA = separation anxiety disorder

‡ CBT = Cognitive Behavioral Therapy, iCBT = internet-based CBT, ABM = Attention Bias Modification, ACT = Acceptance and Commitment Therapy, MBCT = Mindfulness Based Cognitive Therapy

§ LSAS = Liebowitz Social Anxiety Scale, PDSS = Panic Disorder Severity Scale, HAMA = Hamilton Anxiety Rating Scale, BAI = Beck Anxiety Inventory, PSWQ = Penn State Worry Questionnaire, CGI-S = Clinical Global Impressions-Severity, PARS = Pediatric Anxiety Rating Scale

¶ Change in anxiety symptomology as expressed by anxiety scale scores before and after treatment, NR = not reported

∂ WB= whole brain, ACC = anterior cingulate cortex, amyg = amygdala, aInsula = anterior insula, rACC = rostral ACC, dACC = dorsal ACC, dmPFC = dorsal medial prefrontal cortex, dlPFC = dorsal lateral PFC, hippo = hippocampus, L ACC = left ACC, vlPFC = ventral lateral PFC, vACC = ventral ACC, vmPFC, ventral medial PFC, ROI = region of interest

Ω = rsfc-MRI = resting state functional connectivity magnetic resonance imaging

Table 3
Demographic and study design characteristics of included studies of treatment-related neurofunctional effects.

Studies of treatment-related effects

Study	N	Primary Diagnosis[†]	Age ± SD	% Female	Treatment Type	Treatment[‡]	Duration	Dosage/ Frequency	Anxiety Scale[§]	Change in Symptoms[¶] Pre, Post	Search Space[∂]	Neuroimaging Task[Ω]
Whole brain												
Schneier et al. 2011	16	SoAD	30±9	63	Med	paroxetine	8 weeks	34±8.3 mg/d	LSAS	81, 45	WB	Eye gaze
Giménez et al. 2014	17	SoAD	24 ±NR	82	Med	paroxetine	8 weeks	20 mg/d	LSAS	80, 72	WB	Emotional Faces
Phan et al. 2013	21	SoAD	26±6	62	Med	sertraline	12 weeks	100 mg/d/8wk 150 mg/d/4wk	LSAS	82, 45	WB	Emotional Faces
Goldin & Gross 2010	14	SoAD	35 ±12	50	Therapy	MBSR	8 weeks	2.5 hr/wk + 0.5 day retreat	LSAS	69, 49	WB	React vs. Mindful Breathing to Self-Criticism Sentences
Klumpp et al. 2013	14	SoAD	28±8	64	Therapy	CBT	12 weeks	1 hr/wk	LSAS	71, NR	WB	Emotional Faces
Månsson et al., 2013	13	SoAD	33±9	85	Therapy	iCBT	9 weeks	Weekly + modules	LSAS	76, 50	WB	Emotional Face Matching
Goldin et al. 2013	31	SoAD	33±8	47	Therapy	CBT	16 weeks	16 sessions	LSAS	88, 49	WB	Emotional Beliefs
Goldin et al. 2014	31	SoAD	34±8	47	Therapy	CBT	16 weeks	1 session/wk	LSAS	88, 49	WB	React vs Reappraise to Verbal v Visual Criticism
Brown et al. 2019	17	SoAD	27±6	47	Therapy	CBT	12 weeks	1 hr/wk	LSAS	82, 62	WB	Watch Self v. Other Speech
	20	SoAD			Therapy	ACT	12 weeks	1 hr/wk	LSAS	91, 67		
Kircher et al. 2013	42	PD	35 ±NR	69	Therapy	CBT	8 weeks	2 session/wk	HAMA	24, 12	WB	Classical Conditioning
Straube et al. 2014	22	PD	37 ±10	64	Therapy	CBT	8 weeks	12 sessions	HAMA	25, 14	WB	Early Acquisition of Classical Conditioning
Reinecke et al. 2018	14	PD	35 ±15	NR	Therapy	CBT	4 weeks	4 sessions/wk	HADS	14, NR	WB	React vs Reappraise Emotional Images
Yang et al. 2020	42	PD	32 ±11	60	Therapy	CBT	6 or 12 weeks	Twice weekly	PAS	22, 12	WB	Emotional Words
Hoehn-Saric et al. 2004	6	GAD	36 ±NR	50	Med	citalopram	7 weeks	10-40 mg.d	HAMA	10, 3	WB	Emotional Auditory Statements
Fonzo et al. 2014	21	GAD	34 ±11	76	Therapy	CBT	12 weeks	10 sessions	PSWQ	18, 17	WB	Emotional Faces
Strawn et al. 2016	9	GAD, SoAD, SepA	13±2	78	Therapy	MBCT	12 weeks	NR	PARS	11, NR	WB	Continuous Processing Task with Emotional and Neutral Distractors
Burkhouse et al. 2018	6	GAD	15±3	78	Therapy	CBT	14-16 weeks	1 hr/wk	PARS	22, 10	WB	Emotional Faces
	3	SoAD										
	7	GAD	16±3	56	Med	Sertraline	12 weeks	25-200 mg/d	PARS	23, 10		
	8	SoAD										
	1	SepA										
Region of interest												
Phan et al. 2013	21	SoAD	26±6	62	Med	sertraline	12 weeks	100 mg/d/8wk 150 mg/d/4wk	LSAS	82, 45	Amyg, insula, ACC, mPFC	Emotional Faces
Giménez et al. 2014	17	SoAD	24 ±NR	82	Med	paroxetine	8 weeks	20 mg/d	LSAS	80, 72	Amyg, insula, hippo, thal, vmPFC	Emotional Faces
Goldin et al. 2013	31	SoAD	33±8	47	Therapy	CBT	16 weeks	16 sessions	LSAS	88, 49	Amyg, dmPFC, dACC, maPFC, dlPFC, vlPFC	Reappraise vs. React to Negative Self-Beliefs

(*continued on next page*)

Table 3 (*continued*)

Studies of treatment-related effects

Study	N	Primary Diagnosis[†]	Age ± SD	% Female	Treatment Type	Treatment[‡]	Duration	Dosage/ Frequency	Anxiety Scale[§]	Change in Symptoms[¶] Pre, Post	Search Space[∂]	Neuroimaging Task[Ω]
Månsson et al., 2013	13	SoAD	32±9	85	Therapy	iCBT	9 weeks	Weekly + modules	LSAS	76, 50	Amyg	Emotional Face Matching
Månsson et al. 2016	13	SoAD	32 ±10	85	Therapy	iCBT	9 weeks	Weekly + modules	LSAS	76, NR	Amyg, ACC, insula, hippo	Emotional Reading
Young et al. 2017	13	SoAD	27±7	46	Therapy	CBT	12 weeks	1 hr/wk	LSAS	80, 56	Amyg	Emotional Faces
	16	SoAD	27±5	44	Therapy	ACT	12 weeks	1 hr/wk	LSAS	88, 59		
Liebscher et al. 2016	28	PD	36 ±12	64	Med	escitalopram 21; venlafaxine 4; citalopram 2; sertraline 1	8 weeks	10-20 mg/d; 75-225 mg/d; 20-40 mg/d; 50-100 mg/d	HAMA	22, 11	Amyg	Emotional Images
	29	PD	37 ±10	62	Therapy	CBT	8 weeks	12 session	HAMA	22, 13		
	22	PD	36 ±13	73	Therapy	iCBT	8 weeks	12 sessions	HAMA	21, 11		
Reinecke et al. 2018	14	PD	35 ±15	NR	Therapy	CBT	4 weeks	4 session/wk	HADS	14, NR	Amyg	React vs Reappraise Emotional Images
Wittmann et al. 2018	51	PD	37 ±11	67	Therapy	CBT	8 weeks	12 sessions	HAMA	24, 12	Amyg, insula, vStriatum	Emotional Images
Neufang et al. 2019	34	PD	34 ±10	73	Therapy	CBT	6 weeks	1 session/wk	ASI	29, 17	R MFG, R SFG, R SPL, R IPL, brainstem	Flanker Task
Beutel et al. 2010	9	PD	32 ±NR	67	Therapy	Psycho-dynamic	4 weeks	NR	STAI	49, 35	vlPFC, dlPFC, mOFC, lOFC, SMA, vACC, dACC, aInsula, caudate, putamen, amyg, hippo, and parahippo	Emotional words go-nogo
Maslowsky et al. 2010	7	GAD	13±2	57	Med	fluoxetine	8 weeks	5-40 mg/d	PARS	15, 9	R vlPFC, amyg	Dot Probe Task
	7	GAD	13±3	43	Therapy	CBT	8 weeks	1 hr/wk	PARS	16, 5		
Fonzo et al. 2014	21	GAD	34 ±11	76	Therapy	CBT	12 weeks	10 sessions	PSWQ	18, 17	Insula, amyg, ACC/mPFC	Emotional Faces
Functional connectivity												
Giménez et al. 2014	17	SoAD	24 ±NR	82	Med	paroxetine	8 weeks	20 mg/d	LSAS	80, 72	Default Mode, Posterior Insula, Anterior Paralimbic, Fronto-Parietal components	rsfc-MRI
Pantazatos et al. 2014	12	SoAD	28±8	66	Med	paroxetine	8 weeks	10-60 mg/d	LSAS	86, 45	248 nodes from 124 brain regions	Judging Emotions of Faces
Månsson et al., 2013	13	SoAD	33±9	85	Therapy	iCBT	9 weeks	Weekly + modules	LSAS	76, 50	L amyg-WB	Emotional Face Matching
Goldin et al. 2013	31	SoAD	33±8	47	Therapy	CBT	16 weeks	16 sessions	LSAS	88, 49	dmPFC-WB & PFC-amyg	Reappraise vs. React to Negative Self-Beliefs
Yuan et al. 2016	15	SoAD	27±8	33	Therapy	CBT	8 weeks	2.5 hr/wk	LSAS	79, 51	Amyg-WB	rsfc-MRI
Young et al. 2017	13	SoAD	27±7	46	Therapy	CBT	12 weeks	1 hr/wk	LSAS	80, 56	Amyg-WB	Emotional Faces
	16	SoAD	27±5	44	Therapy	ACT	12 weeks	1 hr/wk	LSAS	88, 59		
Brown et al. 2019	17	SoAD	27±6	47	Therapy	CBT	12 weeks	1 hr/wk	LSAS	82, 62	R Amyg-WB	Watch Self v. Other Speech
	20	SoAD			Therapy	ACT	12 weeks	1 hr/wk	LSAS	91, 6		
Kircher et al. 2013	42	PD	35 ±NR	69	Therapy	CBT	8 weeks	2 session/wk	HAMA	24, 12	IFG-WB	Classical Conditioning
Reinecke et al. 2018	14	PD	35 ±15	NR	Therapy	CBT	4 weeks	4 session/wk	HADS	14, NR	Amyg-WB	React vs Reappraise Emotional Images

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Table 3 (*continued*)

Studies of treatment-related effects

Study	N	Primary Diagnosis†	Age ± SD	% Female	Treatment Type	Treatment‡	Duration	Dosage/ Frequency	Anxiety Scale§	Change in Symptoms¶ Pre, Post	Search Space∂	Neuroimaging TaskΩ
Straube et al. 2014	22	PD	37 ±10	64	Therapy	CBT	8 weeks	12 sessions	HAMA	25, 14	IFG-hippo, L occipito-temporal cluster	Early Acquisition of Classical Conditioning
Neufang et al. 2019	34	PD	34 ±10	73	Therapy	CBT	6 weeks	1 session/wk	ASI	29, 17	Seed-seed: SPL, MFG, locus coeruleus, SFG	Flanker Task
Fonzo et al. 2014	21	GAD	34 ±11	76	Therapy	CBT	12 weeks	10 sessions	PSWQ	18, 17	WB & Amyg, insula, ACC/mPFC-WB	Emotional Faces
Andreescu et al. 2015	28	GAD	64±7	68	Med	citalopram	12 weeks	20 mg/d	HAMA	19, NR	L aInsula, L dlPFC, BNST, PVN-WB	rsfc-MRI and Listening to Worry Statements
Lu et al. 2021	21	GAD	15±2	76	Med	escitalopram	8 weeks	5-20 mg/d	PARS	17, 7	Amyg, amygdalostriatal transition amyg, basolateral amyg, centralmedial amyg, superficial amyg-WB	rsfc-MRI
Zhao et al. 2019	32	GAD	34±8	25	Therapy	MBCT	8 weeks	2 hr/wk	HAMA	19, 15	PCC-WB	rsfc-MRI

† SoAD = social anxiety disorder, PD = panic disorder, GAD, generalized anxiety disorder, SepA = separation anxiety disorder

‡ CBT = Cognitive Behavioral Therapy, iCBT = internet-based Cognitive Behavioral therapy, MBSR = Mindfulness Based Stress Reduction, ACT = Acceptance and Commitment Therapy, MBCT = Mindfulness Based Cognitive Therapy

§ LSAS = Liebowitz Social Anxiety Scale, HAMA = Hamilton Anxiety Rating Scale, HADS = Hospital Anxiety and Depression Scale, ASI = Anxiety Severity Inventory, STAI = State Trait Anxiety Inventory, PARS = Pediatric Anxiety Rating Scale, PSWQ = Penn State Worry Questionnaire, PAS = Panic and Agoraphobia Scale

¶ Change in anxiety symptomology as expressed by anxiety scale scores before and after treatment

∂ WB = whole brain, amyg = amygdala, ACC = anterior cingulate cortex, mPFC = medial prefrontal cortex, hippo = hippocampus, thal = thalamus, vmPFC= ventral medial prefrontal cortex, dmPFC = dorsal medial PFC, dACC = dorsal ACC, maPFC = medial anterior PFC, dlPFC= dorsal lateral PFC, vlPFC = ventral lateral PFC, vStriatum = ventral striatum, mOFC = medial orbital frontal cortex, lOFC = lateral OFC, SMA = supplementary motor area, vACC = ventral ACC, aInsula = anterior insula, parahippo = parahippocampus, R MFG = right middle frontal gyrus, R SFG = right superior frontal gyrus, R SPL = right superior parietal lobule, R IPL = right inferior parietal lobule, L = left, IFG = inferior frontal gyrus, BNST = bed nucleus of the stria terminalis, PVN = paraventricular nucleus, PCC = posterior cingulate cortex

Ω rsfc-MRI = resting state functional connectivity magnetic resonance imaging

Inclusion criteria were as follows: (1) included patients with anxiety disorders; (2) employed task-based or resting-state fMRI, (3) reported region of interest (ROI), whole-brain, or functional connectivity analyses, (4) treated individuals with anxiety disorders with pharmacotherapy and/or psychotherapy, and (5) performed activation or connectivity-based predictor and/or pre-to-post treatment-related change analyses. Studies were excluded if they: (1) did not include patients with an anxiety disorder (as described above); (2) focused on subclinical anxiety; (3) did not perform whole-brain, ROI, functional connectivity analyses or machine learning approaches (*e.g.*, using multivoxel pattern analysis) (4) included co-morbid neurological diseases (*e.g.*, Parkinson's disease); (5) did not report brain regions that differed between groups or predicted treatment outcome. Given the systematic nature of this review, when publications reported overlapping samples, we treated each publication as an independent sample as they often probed related, but different cognitive processes. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the study selection procedures are summarized in Fig. 1.

Data extraction

The literature search and data extraction were conducted independently by one investigator (WTB) and reviewed by a second investigator (JRS). Study data and characteristics (*e.g.*, year of publication, sample size, age, percent female, anxiety scale, anxiety severity before treatment, anxiety severity after treatment, primary diagnosis, comorbidities, medication or psychotherapy, treatment duration, treatment dose, task, region of interest (ROI) or whole-brain or functional connectivity analyses, brain regions implicated, direction of effect) were extracted from primary articles, supplementary materials, and/or review articles into a database (Microsoft Excel). When data were missing, the corresponding author was contacted.

Task-based brain activation and task-based and resting-state connectivity results were all pooled. Additionally, given that task and measure heterogeneity can complicate synthesis of findings, care was taken to extract the task type (*e.g.*, classical conditioning, response to written fear words, response to emotional faces, resting state, etc.; see Table 2 and Table 3). To attend to this heterogeneity, task-based activation (*e.g.*, ROI, whole brain) and all connectivity studies were considered separately, including resting state and task-based connectivity.

Results

Study characteristics – Pharmacotherapy and psychotherapy

In total, 50 studies were identified. 16 included pharmacotherapy (2 studies utilized combined SSRI + CBT treatment and were included in this group) and 38 examined psychotherapy (Frick et al. 2018 and Frick et al. 2020 use the same sample and were counted as one study for the purposes of comparing pharmacotherapy versus psychotherapy studies) (Table 1). Pharmacotherapy – compared to psychotherapy – studies had fewer patients per treatment arm ($p = 0.011$) but were similar in female percentage ($p = 0.340$), age ($p = 0.435$), and duration ($p = 0.053$). Diagnostic characteristics of patients in all studies are shown in Table 1.

Within the 16 pharmacotherapy studies, 2 examined the combined effect of SSRI + CBT, 11 included SSRIs ($k_{\text{paroxetine}} = 3$, $k_{\text{sertraline}} = 4$, $k_{\text{es/citalopram}} = 3$, $k_{\text{fluoxetine}} = 1$), 2 examined an SNRI (venlafaxine), and 1 included SSRIs and SNRI (*i.e.*, escitalopram, citalopram, sertraline, and venlafaxine). Of the 38 psychotherapy studies, 31 examined CBT, 4 examined acceptance and commitment therapy (ACT) and CBT, 3 included mindfulness-based therapy (*i.e.*, mindfulness based cognitive therapy (MBCT) or mindfulness-based stress reduction (MBSR)), and 1 utilized a psychodynamic therapy arm.

Summary of functional neuroimaging approaches utilized

Of the 50 total studies, 27 examined treatment-related changes in neurophysiology (change studies), 21 examined baseline neurofunctional predictors of treatment outcomes (predictor studies), and 2 examined both. Of the 29 studies that examined treatment-related changes, 15 used functional connectivity analyses ($k_{\text{task-based}} = 10$, $k_{\text{resting-state}} = 4$, $k_{\text{both}} = 1$), 13 conducted ROI task-based functional activation analyses, and 17 used whole brain task-based analyses.

Twenty-three studies examined the baseline neurofunctional predictors of treatment outcome (Table 1). Of these 23 studies, 3 utilized functional connectivity analyses, 11 performed ROI task-based analyses, 9 conducted whole brain task-based analysis, and 5 employed machine learning. Children and adolescents were evaluated in 7 (14%) studies (3 predictor studies, 3 change studies, and 1 study that examined both).

Studies examining treatment-related change and predictor studies had similar sample sizes ($p = 0.185$), average ages ($p = 0.078$), female percentages ($p = 0.430$), and treatment durations ($p = 0.201$). Psychotherapy was the most common treatment in both predictor studies (82.6%) and change studies (75.8%). Pharmacotherapy was examined in 34.4% of change studies and in 17.4% of predictor studies.

Summary of tasks utilized

Among studies using baseline functional activation as predictors of treatment response, 11 employed a task based upon viewing emotional faces (*i.e.*, view faces, match faces, make judgements on faces, discriminate letters projected on faces), 5 employed a task that asked patients to respond normally to emotional stimuli vs. utilize therapeutic skills (*e.g.*, reappraisal), 4 employed viewing of non-face emotional stimuli (*e.g.*, scenes, written/spoken words), and 1 used a Continuous Processing Task with Emotional and Neutral Distractors (CPT-END) (See Table 2).

Baseline functional connectivity predictors of treatment response were explored by 1 study using resting-state data, 2 studies using emotional faces (specifically, discriminate letters projected on emotional faces and match/label faces), and 1 study using an additional task that asked patients to respond normally to emotional stimuli (actors speaking emotional sentences) vs. utilize therapeutic skills (*e.g.*, reappraisal) (See Table 2).

Among studies of treatment-related changes in functional activation, 12 used emotional faces (*i.e.*, viewing, matching, judgements, eye gaze direction), 5 asked patients to respond normally to emotional stimuli (emotional images, self-/verbal criticism) vs. utilize therapeutic skills (*e.g.*, reappraisal, mindful breathing), 6 used non-face emotional stimuli (beliefs, speech performance, spoken/written words, images, go-nogo task), 1 used a Flanker task, 1 used a Dot Probe Task, 1 used a CPT-END task, and 2 used a classical conditioning task (See Table 3).

Treatment-related changes in functional connectivity were examined in 5 studies using resting state data, 4 studies using tasks with emotional faces, 2 studies using tasks that asked patients to respond normally to emotional stimuli (emotional images, beliefs) vs. utilize therapeutic skills (*e.g.*, reappraisal), 2 studies using classical conditioning, 1 study using a Flanker Task, and 1 study using non-face emotional stimuli (self vs other giving a speech) (See Table 3).

Primary results

The subsequent sections summarize the primary results of each study (grouped by baseline predictor vs. treatment-related change, anxiety diagnosis, and analytic approach). Each study provides valuable insight toward identifying neurophysiologic predictors of treatment response and biomarkers of treatment change. However, the extant literature is extremely heterogeneous in study designs, samples, and tasks. Despite this heterogeneity, we attempted to synthesize and combine overlapping findings across studies.

Neurofunctional predictors of improvement in social anxiety disorder

In a prospective study of adults with social anxiety disorder, whole brain analyses revealed patients with greater pre-treatment dACC reactivity to faces vs. shapes had greater responses to CBT + escitalopram while patients with less pre-treatment dACC reactivity to faces vs. shapes had greater responses to CBT alone (*i.e.*, without escitalopram) (Frick et al., 2018). Additionally, a machine learning approach to predicting responders and non-responders in the same sample revealed that baseline dACC reactivity differentiated treatment responders vs. non-responders (Frick et al., 2020).

Several studies examined neurofunctional predictors of CBT response in adults with social anxiety disorder. Using whole brain analysis in adults with social anxiety disorder ($N = 14$), Klumpp found that patients with greater superior temporal gyrus and medial orbitofrontal gyri activation in response to fearful faces during an emotional face matching task had greater reductions in anxiety symptoms following 12 weeks of CBT (Klumpp *et al.,* 2013). In a subsequent (and larger, N=21) study, using the same fMRI emotional face matching task, whole brain analysis showed increased right medial orbitofrontal gyrus and decreased superior medial frontal gyrus, superior temporal pole, precentral gyrus, pallidum, inferior temporal gyrus, caudate and supplementary motor cortex activation prior to treatment predicted greater CBT-related improvement over 12 weeks. In this sample, ROI analysis showed patients with decreased right dACC and left amygdala activation prior to treatment had significant reduction in anxiety severity following CBT (Klumpp *et al.,* 2014). A third study by Klumpp and colleagues, which used resting state functional connectivity (right and left amygdala to whole brain voxel-wise resting state) in adults with social anxiety disorder, found that, prior to treatment, baseline connectivity predicted response to CBT. Specifically, greater baseline right amygdala-pregenual ACC (pgACC) connectivity and left amygdala- pgACC/mPFC connectivity predicted CBT related improvement. Further, beyond *a priori* regions, the magnitude of CBT-related improvement was predicted by greater pre-treatment right amygdala to bilateral insula connectivity (Klumpp *et al.,* 2014). In a fourth study of adults with social anxiety disorder, Klumpp and colleagues used an emotional processing task that varied perceptual load. In this study, whole brain analysis showed greater activity in diverse regions within the prefrontal and parietal cortices predicted response to CBT (*e.g.*, dACC, anterior insula and precentral gyrus) during high perceptual loads, while less dlPFC activity at baseline predicted more CBT-related improvement (Klumpp et al., 2016). Using the resultant dACC region as a seed, seed to whole brain analysis of functional connectivity during high perceptual load and threatening (*i.e.*, fearful or angry) faces revealed increased dACC-insula, and decreased dACC-precuneus and dACC to multiple frontal cortex regions (*e.g.*, dlPFC, precentral gyrus, dlPFC, superior frontal medial gyrus, SFG) connectivity predicted decreased symptom severity following CBT (Klumpp et al., 2016). Using a different task, whole brain analysis indicated patients with lower left dlPFC activation, at baseline, while reappraising vs. maintaining emotional responses (Klumpp et al., 2017) had greater CBT-related improvement, while another study using ROI analysis, showed those with increased rostral ACC (rACC) and amygdala activity in response to threatening faces under low perceptual load were more likely to be responders (compared to non-response) (Klumpp et al., 2017).

In adults with social anxiety disorder, whole brain analysis of brain activity in response to rejecting images and verbal sentences was examined as a predictor of response to CBT ($n = 17$) and acceptance and commitment therapy ($n = 19$). Increased activity in the ACC, ventral medial PFC (vmPFC), left amygdala, and bilateral parietal/occipital regions predicted CBT-related improvement, while patients with greater posterior insula activation had greater ACT-related improvement (Burklund *et al.,* 2017). Further, following a priori seed-seed connectivity analyses between the amygdala, vmPFC, and vlPFC, the magnitude of negative connectivity between the right vlPFC-amygdala predicted response to both CBT and ACT (Young et al., 2019).

Recently, several studies have leveraged machine learning to predict response to CBT in adults with social anxiety disorder. In the first of these, Månsson et al., 2015, using support vector modeling, found pre-treatment dACC and amygdala activation – in response to self-referential criticism—predicted whether patients would be responders or non-responders (Clinical Global Impressions Scale–Severity [CGI-S]) (Månsson et al., 2015). A subsequent machine learning study, using resting state multi-voxel pattern analysis (MVPA), examined pre-treatment bilateral amygdala to whole brain resting state functional connectivity. In this sample, greater amygdala to subgenual ACC (sgACC) connectivity and decreased amygdala-bilateral central sulcus and amygdala-temporal occipital clusters connectivity, at baseline, predicted CBT-related improvement (Whitfield-Gabrieli et al., 2016).

Neurofunctional predictors of improvement in panic disorder

In antidepressant-treated adults with panic disorder (PD) ($n = 22$), adjunctive CBT ($n = 18$) responders vs. non-responders (as measured by Beck Anxiety Inventory (BAI) score change) were differentiated in pre-treatment whole brain analysis. Baseline increased non-responder and decreased responder activation of the bilateral dlPFC, bilateral inferior frontal gyrus, left orbitofrontal cortex, left frontal eye field, right superior parietal lobule, and intraparietal sulcus during response to threat words discriminated groups (Grambal et al., 2015).

Analyzing whole brain data in adults with PD, increased baseline activity to panic-related images in the insula bilaterally and left dlPFC predicted decreases in panic and agoraphobic symptoms at week 4 of treatment with CBT. No effects were found in the right or left amygdala ROI (Reinecke *et al.,* 2014). In adults with PD, ROI analysis of the amygdala, ventral striatum, and insula showed increased pre-treatment left insula and left ventral striatum activation in response to anticipation of emotional stimuli predicted CBT-related improvement (*i.e.*, Hamilton Anxiety Rating Scale (HAM-A) score) (Wittmann et al., 2018).

Hahn et al. (2015), using a machine learning approach (*e.g.*, development of regional and whole brain gaussian classifiers with cross validation), used the precentral gyrus, occipital fusiform gyrus, frontal orbital cortex, postcentral gyrus, inferior frontal gyrus pars triangularis, middle temporal gyrus, putamen, paracingulate gyrus, supramarginal gyrus, frontal pole, and occipital pole activity during classical conditioning to predict treatment response at 6 weeks in adults with PD (Hahn et al., 2015). In adults with either GAD ($n = 25$) or PD ($n = 23$), a machine learning approach (*i.e.*, random forest classification) predicted responders vs. non-responders following CBT by sampling 70 ROIs during a classical conditioning task and constructing best fit models off of the data. From this analysis, selecting pre-treatment activation to aversive images in the right hippocampus and left uncus, and pre-treatment activation to reappraisal in the left transverse temporal gyrus, left anterior insula, bilateral superior temporal gyri, left supramarginal gyrus, left superior temporal gyrus, left precentral gyrus, left superior frontal gyrus, and right substantia nigra (Ball *et al.,* 2014).

Neurofunctional predictors of improvement in GAD

In two studies of adults with generalized anxiety disorder (GAD), using an ROI-based approach, baseline ACC (either rACC or pgACC) activity in response to emotional cues predicted venlafaxine-related improvement (Nitschke, 2009), while in one of these studies, baseline amygdala activity in response to emotional faces also predicted greater improvement (Whalen et al., 2008).

Several pediatric studies – largely in youth with GAD – have examined neurofunctional predictors of treatment response (psychotherapy, psychotherapy + SSRI or SSRI) (Burkhouse et al., 2017; Kujawa et al., 2016). These studies, in general, included post-pubertal studies and patients with anxiety comorbidity in terms of social and separation anxiety disorder. In adolescents with GAD ($N = 12$), ROI analysis of

each amygdala showed lower left amygdala activation to emotional faces, at baseline, predicted CBT and fluoxetine-related improvement (McClure et al., 2007).

In adolescents with GAD (92%) using ROIs from whole-brain MBCT-related changes in functional activation, we observed increased baseline left anterior cingulate and right anterior insula activation in response to emotional images predicted MBCT-related improvement (Strawn et al., 2016). In adolescents with predominantly generalized and social anxiety disorders, higher dlPFC, vlPFC, precentral gyrus, and postcentral gyrus activation to threatening faces (whole brain analysis) predicted greater improvement to open-label CBT ($n = 21$) or sertraline ($n = 20$) (Kujawa et al., 2016). In adolescents with GAD (56%) of whom 44% also had social anxiety disorder ($n = 37$), decreased dACC and dorsal medial PFC (dmPFC) response to implicit threat processing (ROI-based) at baseline, predicted both sertraline and CBT-related improvement in anxiety. Treatment type (*i.e.*, CBT or SSRI) and primary diagnosis did not influence results (Burkhouse et al., 2017).

Neurofunctional effects of treatment in social anxiety disorder – Whole brain

Three studies have examined pharmacologic effects in adults with social anxiety disorder. In the first, sertraline decreased left amygdala activation to emotional stimuli to levels of healthy individuals and increased vmPFC activation to emotional stimuli to levels of healthy individuals (Phan et al., 2013). In the second, paroxetine decreased activation to direct – as opposed to averted – gaze in the left insula, right middle temporal gyrus, right precentral gyrus, right posterior cingulate cortex (PCC)/precuneus, and left occipital gyrus (Schneier *et al.,* 2011). However, in the third study ($N = 17$), paroxetine was not associated with treatment-related functional activation changes in an emotional face matching task (Giménez et al., 2014).

To date, a half dozen studies have evaluated the neurophysiology of psychotherapy in adults with social anxiety disorder (CBT $\kappa = 4$; MBSR $\kappa = 1$, ACT $\kappa = 1$). One study examined MBSR. Using a task that compared responses to self-criticism during mindful breathing or normal breathing, MBSR increased activation in the inferior parietal lobule, superior parietal lobule, cuneus, precuneus, middle occipital gyrus (Goldin and Gross, 2010). In a second study, twelve weeks of CBT decreased right insula, right medial orbitofrontal and right dmPFC activation to threatening faces toward levels of healthy individuals compared to baseline (Klumpp et al., 2013). Conversely, in a third study, sixteen weeks of CBT increased mPFC activation in response to emotional images and increased dlPFC activation when using cognitive reappraisal (Goldin et al., 2013). Another study of CBT, delivered using an internet-based platform, revealed decreased activation in the caudate, cerebellum, dlPFC, putamen, and rACC in response to emotional stimuli (Månsson et al., 2013). In a fourth study, CBT increased activation in the right superior frontal gyrus, inferior parietal lobule, and middle occipital gyrus to social praise; increased activation in the right superior frontal gyrus and inferior parietal lobule to social criticism; decreased activation in the left posterior superior temporal gyrus to social criticism, increased activation in the right superior frontal gyrus, and medial occipital gyrus when using cognitive reappraisal, and decreased activation in the left posterior superior temporal gyrus using cognitive reappraisal (Goldin et al., 2014). Finally, one study examined both CBT and acceptance and commitment therapy (ACT) and found that both treatments decreased activation in the left insula, ACC, left inferior parietal lobule, right inferior parietal lobule, right middle frontal gyrus, and visual cortex when participants watched videos of themselves as compared to videos of others (Brown et al., 2019).

Neurofunctional effects of treatment in panic disorder – Whole brain

CBT decreased left inferior frontal gyrus and anterior insula activation to conditioned responses using a classical conditioning paradigm (Kircher et al., 2013) and in a second study in the hippocampus to conditioned stimuli during the acquisition phase of classical conditioning (Straube et al., 2014). Also using panic-related images, CBT reduced activation in the dmPFC and left dlPFC compared to a waitlist (Reinecke *et al.,* 2018). Finally, using a task in which patients were presented panic words, CBT decreased ACC, PCC/precuneus, right middle frontal gyrus, and right inferior frontal gyrus activation (Yang et al., 2020).

Neurofunctional effects of treatment in generalized anxiety disorder – Whole brain

In a very small pilot study ($N = 6$), seven weeks of citalopram treatment decreased activation across multiple structures throughout frontal regions, insula, cingulate, as well as temporal and parietal gyri and subcortical structures (*e.g.*, thalamic nuclei) to emotional images (Hoehn-Saric *et al.,* 2004). Also, twelve weeks of CBT attenuated right dlPFC activation in response to emotional faces (Fonzo et al., 2014).

Two studies have evaluated neurofunctional effects of psychotherapy and/or psychopharmacology in pediatric patients with GAD. In adolescents with predominantly GAD (some of whom had co-occurring social and/or separation anxiety disorders), whole brain analysis revealed increased activation of bilateral insula, lentiform nucleus, thalamus, and left ACC in response to emotional stimuli following treatment with MBCT (Strawn et al., 2016). In adolescents with GAD ($N = 25$), whole brain analyses revealed both sertraline and CBT-related differences within the rACC during an implicit threat task, with rACC activity levels in both increasing with treatment toward activity level of the healthy control group (Burkhouse et al., 2018).

Neurofunctional effects of treatment in social anxiety disorder – Region of interest studies

Region-of-interest (ROI) studies of the neurofunctional effect of treatment in social anxiety disorder, frequently employed tasks with a social/social evaluative component. When watching videos of themselves presenting compared to others presenting, paroxetine-treated patients with social anxiety disorder ($N = 17$) had decreased activation in the thalamus, left extended PFC/ACC, and right amygdala compared to those who received placebo (Giménez et al., 2014). Similarly, in sertraline-treated patients, decreased activation in the amygdala was seen with fearful faces, in addition to increased activation in the orbitofrontal cortex (OFC) (Phan et al., 2013).

In adults with social anxiety disorder, MBSR and internet-based CBT (iCBT) – across two trials – decreased amygdala activation (Månsson et al., 2013, 2016). CBT also decreased activation in multiple prefrontal regions (*e.g.*, mPFC, dmPFC and left dlPFC) when individuals reacted to negative self-beliefs (Goldin et al., 2013). Finally, CBT or ACT decreased emotional-face-related bilateral amygdala activation (Young et al., 2017).

Neurofunctional effects of treatment panic disorder – Region of interest studies

In adults with panic disorder, SSRIs and SNRIs were not associated with changes in amygdala activation in response to emotional images (Liebscher et al., 2016). However, psychodynamic psychotherapy decreased hippocampal activation and increased vlPFC activity (Beutel *et al.,* 2010). Additionally, CBT decreased emotional image-related amygdala activation in two studies (Liebscher et al., 2016; Reinecke et al., 2018), although this effect was not observed in a third CBT study (Wittmann et al., 2018). In addition, CBT decreased insular activation to emotional images (Wittmann et al., 2018) and increased middle frontal gyrus and superior parietal lobule activation during a Flanker task (Neufang et al., 2019).

Neurofunctional effects of treatment in generalized anxiety disorder – Region of interest studies

In adolescents with GAD, fluoxetine monotherapy and CBT monotherapy increased vlPFC activation in response to angry faces (Maslowsky et al., 2010). In young adults with GAD, post-hoc analysis of significant regions of a group (patient vs. control) × time (pre vs post) interaction revealed decreased anterior insula, sgACC, amygdala, and posterior insula activation to threatening faces following CBT (Fonzo et al., 2014).

Treatment-related functional connectivity changes in social anxiety disorder

With regard to pharmacotherapy Gimenez et al. (2014), using independent component analysis, open-label, fixed-dose paroxetine decreased connectivity within the default mode and fronto-parietal networks (Giménez et al., 2014). Additionally, paroxetine increased hippocampus-left temporal pole connectivity while viewing emotional faces (Pantazatos *et al.,* 2014).

CBT enhanced negative functional connectivity between the (i) left amygdala-right medial OFC (mOFC) and positive connectivity between the (ii) left amygdala-right dlPFC/right vlPFC (Månsson et al., 2013). Similarly, CBT (relative to waitlist) increased negative connectivity between the (i) dmPFC-left amygdala and (ii) dmPFC-right hippocampus, and found increased positive connectivity between the (iii) dmPFC-mPFC, and (iv) dmPFC-right dlPFC (Goldin et al., 2013). Additionally, CBT decreased connectivity between left amygdala-right putamen/left dmPFC/right dACC, during resting state, to levels of healthy adults (Yuan et al., 2016). CBT – but not ACT – reversed, from negative to positive, functional connectivity between right amygdala-vmPFC while watching videos of themselves in social situation, and attenuated positive connectivity between these regions while watching others in social situations (Brown et al., 2019). In a grouped analysis of amygdala to whole brain functional connectivity, CBT and ACT enhanced connectivity between right amygdala-visual cortex/-angular gyrus/primary motor cortex/parietal cortex (Young et al., 2017).

Treatment-related functional connectivity changes in panic disorder

In studies of adults with panic disorder, CBT decreased inferior frontal gyrus (IFG)-left hippocampus connectivity (Straube et al., 2014), increased right middle frontal gyrus (MFG)-right superior parietal lobule connectivity (Neufang et al., 2019), and flipped, from positive to negative, right amygdala-precuneus/ventral PCC connectivity (Reinecke et al., 2018). However, not all CBT studies have demonstrated schanges in connectivity. When exploring IFG to whole brain connectivity during classical conditioning, no CBT-related changes in functional connectivity were observed (Kircher et al., 2013).

Treatment-related functional connectivity changes in generalized anxiety disorder

In older adults with GAD (mean age: 64 ± 6.8 years), citalopram decreased connectivity between left anterior insula-left precentral gyrus/left MFG/left sgACC, left dlPFC-left inferior frontal gyrus/right OFC, and bed nucleus of the stria terminalis (BNST)-left insula/right supramarginal gyrus, and increased connectivity between BNST-left frontal middle gyrus/superior frontal gyrus - left lingual gyrus (Andreescu et al., 2015). In young adults with GAD, amygdala connectivity during viewing of emotional faces did not change following CBT (Fonzo et al., 2014). In adults with GAD, MBCT increased resting state connectivity between PCC-bilateral middle occipital gyrus/right ACC/bilateral insula (Zhao et al., 2019).

One study has examined treatment-related changes in functional connectivity in adolescents with GAD ($N = 41$, mean age: 15 ± 1.7 years) (Lu et al., 2021). In the study, adolescents were randomized to escitalopram or placebo. Resting-state functional MRI were acquired before and after 2 weeks of treatment. During the first 2 weeks of treatment, escitalopram – but not placebo – increased amygdala-vlPFC connectivity. This early functional connectivity change predicted symptom improvement over the subsequent 6 weeks of treatment in youth who received escitalopram, but not in those who received placebo (Lu et al., 2021).

Discussion

The extant literature reveals a surfeit of neurofunctional predictors of treatment response and neurofunctional effects of treatment in anxiety disorders. Taken together, these findings present a challenge and an opportunity. Why, despite dozens of treatment studies in hundreds of patients cumulatively, are we, as a field, only slightly closer to the goal of predictive, personalized psychiatric treatment for anxiety disorders? Here, we outline a pipeline that may help generate clinically useful neuroimaging-based treatment predictors. This corpus of experiments reveals regions, connections, and networks that might serve as biomarkers of treatment response or might predict treatment outcomes. Importantly, our synthesis illustrates how approach-, population-, and disorder-related heterogeneity precludes more traditional synthesis. That said, this review creates an opportunity to discuss how future studies could be refined to more conclusively identify biomarkers of treatment response and prediction.

The findings summarized herein have important implications for our traditional psychotherapeutic and pharmacological approaches to treating anxiety disorders. Current recommendations emphasize “one size fits all” approaches with regard to SSRIs and CBT; however, studies in children, adolescents and adults reveal substantial heterogeneity in treatment response with up to 40% of individuals failing to substantially improve with first line interventions (Walkup et al., 2008). This heterogeneity in treatment response could relate to neurophysiologic differences in individual patients. And, importantly, such differences could be leveraged to optimize treatment selection based on the likelihood that it would normalize a specific pattern of activation or activity that is altered in a particular patient. This also suggests that there are meaningful patterns of heterogeneity in the neurobiology of anxiety disorder, which is itself another important line of research for future studies in parallel with clinical trials. While our focus was on brain features, such data might be usefully combined with psychological characteristics and/or demographic features to create a fingerprint that would best guide a clinician toward a certain treatment approach. It is noteworthy that such approaches are already common in other areas of medicine (*e.g.*, Framingham score in coronary artery disease risk, CHADS2 in for stroke risk in patients with atrial fibrillation, APACHE2 for mortality benefit of ICU admission).

The majority of neurofunctional baseline predictor and treatment-related effect studies disproportionally examined psychotherapy, with almost all of these studies examining CBT. Future research would benefit from expanded insight into other psychotherapy modalities used for anxiety disorders such as ACT, MBCT, and DBT as well as addressing the sparsity of data examining the potentially different neurofunctional effects of SSRI and SNRI treatment. Additionally, despite anxiety disorders often manifesting in the first decades of life (Merikangas et al., 2010), few studies have examined the neuroactivational and functional connectivity changes associated with pharmacologic or psychotherapeutic treatment in pediatric and adolescent patients. Research has also focused on limited networks and brain circuits, mostly focusing on amygdala-PFC circuitry with sparse examination of other implicated regions such as ACC, precuneus, and insula. Last, mediators and modulators of treatment effects on brain function should be explored. This information could guide treatment choice that is patient-specific and based on personality, cognitive, and genetic characteristics.

However, the heterogeneity in the current literature precludes more complex conclusions beyond these admittedly superficial syntheses. Take the case example of synthesizing treatment-related effects on amygdala to whole brain functional connectivity. We choose this for a case example as amygdala connectivity has been widely implicated and well-characterized across anxiety disorders (McTeague et al., 2020; Sylvester et al., 2020). Seven studies have examined the treatment-related effects on amygdala to whole brain functional connectivity (Brown et al., 2019; Fonzo et al., 2014; Lu et al., 2021; Månsson et al., 2013; Reinecke et al., 2018; Young et al., 2017; Yuan et al., 2016). Of these, three use a sample of patients with social anxiety disorder, one uses a sample of patients with panic disorder, and two use a sample of patients with generalized anxiety disorder, one of which utilized a pediatric population and is the only pharmacotherapy study.

Synthesizing the six psychotherapy studies (and collapsing across anxiety disorders), the therapeutic approach, duration, and dose results in profuse heterogeneity that precludes reasonable, confident synthesis. Three different forms of psychotherapy were employed: iCBT, CBT, and ACT. In terms of duration and dose of psychotherapy, three studies provided treatment for 12 weeks (two for 1 hour/week and one 10 sessions across 12 weeks), one study for 9 weeks (weekly session plus online modules), one study for 8 weeks (2.5 hours/week), and one study for 4 weeks with four sessions per week. And, all treatment arms contained fewer than 21 patients. The task-based analysis is not consistent across studies as well. Only one of the psychotherapy studies utilized resting state functional connectivity, while the other five employed task-based functional connectivity. Of these task-based approaches, three used functional connectivity during matching of emotional faces, one used functional connectivity comparing watching yourself vs someone else give a speech, and one utilized a react to verses utilize cognitive reappraisal toward emotional images.

Synthesizing the three experiments that employed emotional face matching tasks (2 social anxiety disorder, 1 panic disorder [$n = 13$, 13, and 21]), one showed null results with CBT. The two studies with positive results had no overlapping findings with one showing treatment-related connectivity changes between the amygdala and PFC regions and the other showing treatment-related connectivity changes between the amygdala and occipital, parietal, and motor cortex regions (Fonzo et al., 2014; Månsson et al., 2013; Young et al., 2017). Such a case example could be made for any *a priori* functional activation or functional connectivity analysis. This case serves as a convincing example given the well-characterized contribution of aberrant amygdala functional connectivity to the pathophysiology of anxiety disorders (McTeague et al., 2020; Sylvester et al., 2020). Such marked heterogeneity impedes more nuanced synthesis of the existing literature, and, in turn, precludes translation of clinical research to clinical practice. We view this as an impetus for a call to action, and we provide outlined next steps toward more conclusively identifying biomarkers in treatment response and prediction.

Finally, while we have attempted to synthesize the literature – and distill the heterogeneity in an approachable fashion – there are inherent limitations to our analysis and approach. First, we did not pre-register the trial. However, before undertaking this systematic review, we specified our meta-analytic and systematic review methods and descriptive analysis (though heterogeneity ultimately precluded metanalysis). Second, our review was restricted to fMRI (both activation and functional connectivity) and therefore does not include PET or single-photon emission computed tomography (SPECT) studies as well as structural studies of prediction of treatment response or treatment-related effects. The inclusion of these studies would have accentuated an already substantial heterogeneity. Third, the heterogeneity that is extensively discussed above precluded a meta-analytic examination of the neurofunctional changes associated with treatment and treatment response prediction.

Conclusions

The extant literature describing neurofunctional aspects of treatment response in anxiety disorders is best viewed as a partially constructed scaffold on which to build a clinically translatable set of robust neuroimaging biomarkers that can guide treatment selection. Constructing this understanding will require harmonizing analytic and task approaches, larger samples, and replication of component studies.

A more-solid foundation for this understanding requires larger samples sizes and standardized methods to identify biomarkers most likely to be useful for clinical application (Stancil *et al.,* 2021). As the functional neuroimaging field has developed over the past decades, it has become clear that smaller datasets lead to insufficient reproducibility in complex psychological processes. Larger studies on the order of 100s of patients are needed to identify candidate fMRI treatment predictors. Related to this point, heterogeneity of experimental design contributes to slowing translational progress. If two studies differ both in neuroimaging task/target and clinical intervention, it is impossible to discern if differential patterns of neural activation reflect differences in the treatment, the experiment itself, or both. While flexible experimental design can be a powerful research tool, it presents an inherent challenge when comparing results between studies. It also directly hinders the synthesis of results towards a greater clinical translational goal. It is only possible to draw conclusions about differences in biomarkers between treatments when they are studied under the same conditions.

Once we have identified potential targets in large treatment studies, it is necessary to demonstrate that the targets can be reliably measured (Stancil et al., 2021). Within the resting state realm, numerous studies have shown that individual differences are reliable and discernable only with increased scan time (Gordon et al., 2017; Sylvester et al., 2020) or with new methods that potentially improve signal over shorter timeframes (Lynch et al., 2020). As one example, fMRI moment-to moment variability – often thought to be undesirable noise – may serve as a reliable and, as of yet, unharnessed, predictor of CBT response (Månsson et al., 2022). Reliable measures are a necessity for the development of useful biomarkers. ROIs or other *a priori* neuroimaging targets should be defined based only on the most reliable studies utilizing state-of-the-art standards in sample size and data collection.

Following the identification of potential biomarkers that can be reliably measured, it is necessary to pursue prospective studies in which all predictors and data analysis plans are delineated *a priori*. These prospective studies are required to determine the true (uninflated) effect size of the predictors in a manner that could be clinically useful. Retrospective analyses of neural treatment response predictors or simple neural associations with treatment assignment will inherently reveal association rather than causality. Treatment predictors should be tested prospectively to establish their utility.

Once reliable, prospectively tested neuroimaging-based treatment targets are identified, treatments could be individually selected or tailored based on relevant neural changes occurring on a much quicker timescale than clinical improvement. If successful, treatment then could be adapted based on individual neurofunctional changes during the course of treatment (Newbold et al., 2020). Such approaches would differ from the current treatment paradigm by directly exploring the interaction between a patient, his or her symptoms, and the intervention. This notion has led to efforts by the NIMH to establish correlates of measurable dimensional processes (*e.g.*, Research Domain Criteria) and clearly-defined biological targets (*e.g.*, the NIMH FAST-FAIL initiative and "Target Engagement" studies) in clinical trials for mental health (Grabb et al., 2020; Insel et al., 2010; Krystal et al., 2018; Pizzagalli et al., 2020; Stefaniak and Huber, 2020). With each of these novel approaches, replication in different populations would be vital in establishing generalizability.

We consider the studies summarized herein as a call to arms that should compel researchers to improve the reliability of neuroimaging

Table 4
Sources of Heterogeneity Across Treatment Studies in Anxiety Disorders Across Neuroimaging Studies of Treatment.

Source of heterogeneity	Impact
Disorder	• Multiple DSM anxiety disorders are frequently included; however, these disorders may have dissimilar neurobiology and treatment response
Sample	• Sample sizes and characteristics vary greatly. • Age and sex differences may confound treatment effects. • Baseline symptom severity varies greatly across studies and potentially compromises the ability to identify a treatment-related changes (*e.g.*, floor effects)
Anxiety Measures	• Symptom rating scales vary in their dimensionality. • Scales which measure multiple symptom dimensions may complicate interpretation of outcomes in that improvement in some symptoms may be important for overall improvement whereas other symptoms measured by the scale may have minimal functional impact. • Variation in symptoms assessed may relate to different underlying neurofunctional processes.
Treatment, Psychotherapy	• Psychotherapeutic modality and intensity (*e.g.*, frequency) vary considerably creating differences in "psychotherapy dose" across trials. • Delivery of psychotherapy varies in terms of clinician experience and format which may influence treatment response or target engagement.
Treatment, Psychopharmacology	• Psychopharmacologic treatment involves multiple medication classes. • No studies examined differences in medication exposure or sources of variable medication exposure (*e.g.*, cytochrome p450 variation, adherence)
Treatment Duration	• Treatment duration may impact response and tolerability, introducing additional outcome variation
fMRI Task	• Differential activation of specific structures by the task may not probe some regions.
Resting State MRI	• Resting state data are often gathered with either eyes open or eyes closed, which impacts connectivity measures. • Duration of data acquisition impacts resolution

approaches across studies, to compare treatments using common methods, and to establish generalizability through replication in appropriate populations. As a field, answering this charge, we should overcome the current issues in design and analytic approach to bridge the translational gap and bring neuroimaging-based biomarkers to the clinic (Table 4).

Conflicts of interest

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Data sharing statement

Data sharing not applicable; no datasets were generated or analyzed.

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