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REVIEW ARTICLE

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ENIGMA-anxiety working group: Rationale for and organization of large-scale neuroimaging studies of anxiety disorders

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Abstract

Anxiety disorders are highly prevalent and disabling but seem particularly tractable to investigation with translational neuroscience methodologies. Neuroimaging has

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informed our understanding of the neurobiology of anxiety disorders, but research has been limited by small sample sizes and low statistical power, as well as heterogeneous imaging methodology. The ENIGMA-Anxiety Working Group has brought together researchers from around the world, in a harmonized and coordinated effort to address these challenges and generate more robust and reproducible findings. This paper elaborates on the concepts and methods informing the work of the working group to date, and describes the initial approach of the four subgroups studying generalized anxiety disorder, panic disorder, social anxiety disorder, and specific phobia. At present, the ENIGMA-Anxiety database contains information about more than 100 unique samples, from 16 countries and 59 institutes. Future directions include examining additional imaging modalities, integrating imaging and genetic data, and collaborating with other ENIGMA working groups. The ENIGMA consortium creates synergy at the intersection of global mental health and clinical neuroscience, and the ENIGMA-Anxiety Working Group extends the promise of this approach to neuroimaging research on anxiety disorders.

KEYWORDS

amygdala, anxiety disorders, genetics, limbic system, magnetic resonance imaging, neuroimaging, prefrontal cortex

1 | INTRODUCTION

Although anxiety symptoms have long been described in literature on psychopathology, only more recent research emphasizes the construct of anxiety disorder diagnoses, including conditions such as generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), and specific phobia (SP). The third edition of the Diagnostic and Statistical Manual (DSM-III [1980]) and the 10th edition of the International Classification of Diseases (ICD-10 [1990]) stimulated research on these diagnostic categories by providing operational diagnostic guidelines and criteria for specific anxiety disorders. Based on subsequent research, nosological constructs were refined and the overarching conceptualization of anxiety disorders was altered in DSM-5 (2013) and ICD-11 (2019). For example, both classification systems, unlike earlier schemes, now distinguish obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) from anxiety disorders (Kogan et al., 2016).

Important insights on the DSM and ICD constructs defining anxiety disorders came from community surveys. Serious mental illnesses are relatively common in clinical settings, but there is a relative under-recognition of the symptomatology and need for treatment of anxiety disorders by clinicians (Aydin et al., 2020; Calleo et al., 2009; Chapdelaine, Carrier, Fournier, Duhoux, & Roberge, 2018; Edwards, Thind, Stranges, Chiu, & Anderson, 2019; Furmark, 2002; Ormel, Koeter, van den Brink, & van de Willige, 1991). However, research in community settings finds that anxiety disorders are the most prevalent group of mental disorders, with lifetime prevalence averaging

approximately 11% globally (Kessler et al., 2009), with even higher estimates in high-income countries (Wittchen et al., 2011). Anxiety disorders typically have an early age of onset and are accompanied by significant subsequent comorbidity of both physical and mental disorders, as well as by considerable burden for patients, relatives and society (Fineberg et al., 2013; Stein et al., 2017). The Global Burden of Disease Study found that, in high-income as well as low- and middle-income regions, anxiety disorders are the sixth leading cause of disability, in terms of years lived with disability (Baxter, Vos, Scott, Ferrari, & Whiteford, 2014).

Several factors support the need for more research on the neurobiology of anxiety disorders. First, the early onset of anxiety disorders, and their association with subsequent comorbidity (Beesdo et al., 2007; Beesdo-Baum & Knappe, 2012; Bulley, Miloyan, Brilot, Gullo, & Suddendorf, 2016; Kessler et al., 2005; Plana-Ripoll et al., 2019) raise the question of whether a better understanding of the relevant underlying mechanisms might ultimately be useful for preventive interventions. Second, although there is now a growing evidence-base of efficacious and cost-effective interventions for anxiety disorders, many individuals do not respond to first-line treatments, do respond but do not remit, or have relapse and recurrence of their illness (Fernandez, Salem, Swift, & Ramtahal, 2015; Loerinc et al., 2015; Taylor, Abramowitz, & McKay, 2012). Improvements in health-care delivery could lead to earlier diagnosis and scaling up of currently available, efficacious treatments that can close the treatment gap (Alonso et al., 2018). However, better delineation of specific underlying mechanisms might also lead to more personalized and

more effective interventions (Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008).

Anxiety disorders may be particularly tractable to translational neuroscience. First, similar forms of brain-behavior associations manifest in a range of mammalian species during encounters with threats (stimuli capable of harming the organisms), as demonstrated through research on fear conditioning and extinction (Kalin, 2017; Milad & Quirk, 2011). Second, vulnerability for anxiety disorders can be quantified using intermediate phenotypes such as corticolimbic reactivity, behavioral inhibition, anxious temperament, and increased startle response (Gottschalk & Domschke, 2016); the neural circuitry and molecular mechanisms of these intermediate phenotypes can be productively investigated in rodent, nonhuman primates, and human models (Fox and Kalin, 2014). Third, genetic studies of anxiety disorders show considerable heritability, with heritability estimates ranging between 30 and 67% (Bandelow et al., 2016; Levey et al., 2020; Meier & Deckert, 2019; Shimada-Sugimoto, Otowa, & Hettema, 2015), and recent genome-wide association studies (GWAS) reported on various single-nucleotide polymorphisms associated with anxiety (Levey et al., 2020; Meier et al., 2019; Purves et al., 2019). Thus, extending such genetic work through brain imaging could reveal molecular pathways associated with psychopathology through influences on brain structure and function.

Neuroimaging studies using magnetic resonance imaging (MRI) have begun to advance research into the neurobiology of anxiety

disorders. Early neuroimaging studies suggested that these conditions were characterized by structural and functional alterations, thereby stimulating the formulation of neurobiological models for anxiety disorders that focused on the frontolimbic system (Etkin & Wager, 2007). Subsequent MRI studies have led to more detailed neurocircuitry models of GAD, PD, SP, and SAD (Bandelow et al., 2016; Bas-Hoogendam, Roelofs, Westenberg, & van der Wee, 2020; Brühl, Delsignore, Komossa, & Weidt, 2014; Cremers & Roelofs, 2016; Duval, Javanbakht, & Liberzon, 2015; Goddard, 2017; Hilbert, Lueken, & Beesdo-Baum, 2014; Kolesar, Bilevicius, Wilson, & Kornelsen, 2019; Mochcovitch, da Rocha Freire, Garcia, & Nardi, 2014), and of anxiety in general (Grupe & Nitschke, 2013; Shin & Liberzon, 2010; Taylor & Whalen, 2015; VanElzakker, Kathryn Dahlgren, Caroline Davis, Dubois, & Shin, 2014), including its neurodevelopmental origins (Blackford & Pine, 2012; Caouette & Guyer, 2014) (we refer to Figure 1 for an overview of neurocircuitry involved in anxiety disorders). Finally, neuroimaging studies have identified putative neurobiological predictors for treatment response in, and also across, anxiety disorders (Klump & Fitzgerald, 2018; Lueken et al., 2016).

Despite several promising findings, neuroimaging research on anxiety disorders has had important limitations. Small sample sizes have entailed low statistical power and, together with differences in acquisition and analytic approaches, have likely contributed to inconsistent findings and limited reproducibility (Blackford, 2017). In SAD,

Neurocircuitry implicated in anxiety disorders

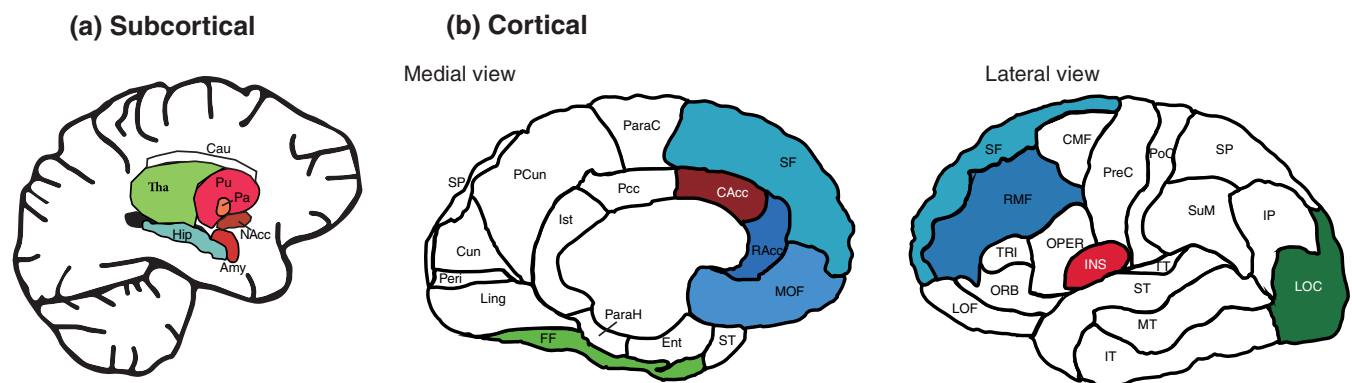


FIGURE 1 Overview of neurocircuitry involved in anxiety disorders. This schematic overview illustrates the subcortical (Figure 1a) and cortical (Figure 1b) regions that are part of the FreeSurfer pipeline (RRID:SCR_001847; <http://surfer.nmr.mgh.harvard.edu>). Regions involved in anxiety are colored based on the work on the neurocircuitry of anxiety disorders (Duval et al., 2015), implicating brain areas involved in sensory processing (occipital cortex, fusiform gyrus, thalamus; green), emotion generating and processing (striatum, amygdala, insula, dorsal anterior cingulate cortex; red) and emotion modulation regions (medial prefrontal cortex, hippocampus, dorsolateral prefrontal cortex, subgenual/rostral anterior cingulate cortex; blue). Note that other models of brain circuitry in anxiety, for example those described by (Brühl et al., 2014; Kolesar et al., 2019), are more extended and also involve other regions—most notably regions of the parietal cortex. Figure 1a (subcortical) Amy, Amygdala; Cau, Nucleus Caudatus; Hip, Hippocampus; NAcc, Nucleus Accumbens; Pa, Pallidum; Pu, Putamen; Tha, Thalamus. Figure 1b (cortical) CAcc, Caudal Anterior Cingulate Cortex; CMF, Caudal Middle Frontal; Cun, Cuneus; Ent, Entorhinal; FF, Fusiform; INS, Insula; IP, Inferior Parietal; Ist, Isthmus; IT, Inferior Temporal; Ling, Lingual; LOC, Lateral Occipital; LOF, Lateral Orbitofrontal; MOF, Medial Orbitofrontal; MT, Middle Temporal; OPER, Pars Opercularis; ORB, Pars Orbitalis; ParaC, Paracentral; ParaH, Parahippocampal; Pcc, Posterior Cingulate Cortex; PCun, precuneus; Peri, Pericalcarine; PoC, Postcentral; PreC, Precentral; RAcc, Rostral Anterior Cingulate Cortex; RMF, Rostral Middle Frontal; SF, Superior Frontal; SP, Superior Parietal; ST, Superior Temporal; SuM, Supramarginal; TRI, Pars Triangularis; TT, Transverse Temporal

TABLE 1 Anx_GAD (generalized anxiety disorder)

General sample information			Clinical information										Questionnaires				MRI and genetic information																	
Sample #	Country	Institute	Sample	Key-references	# GAD	# HC	Age-range(y)	Sex	Diagnostic interview	Anx comorb	Other comorb	Age onset	Psych trait	STAI-	Field strength	SCARED (T)	HAM_D	BDI-II	PSWQ	GAD_7	ACQ	PDSS	HAM_A	CDI	SCARED (T)	Scanner	MRI	DTI	FMRI	Material for genetics				
GAD_01	BR	INPD	Brazilian HRC study	(Salum et al., 2015)	101	668	5-15	M&F	OTH	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1.5	GE	1	1	1	1	1		
GAD_02	BR	Universidade Federal do Rio Grande do Sul	PROTAIMA	(Salum et al., 2011; Tozaza et al., 2016)	26	18	13-22	M&F	KSADS	1	1	0	1	0	0	0	0	1	1	0	0	0	0	1	1	3	?	1	?	0	1	1		
GAD_03	DE	Technische Universität Dresden	Dresden GAD	(Hilbert et al., 2015)	47	47	18-51	M&F	CIDI	1	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	3	SIE	1	0	0	1	1	1	
GAD_04	DE	University of muenster	Muenster GAD	(Buff et al., 2016)	25	29	19-56	M&F	?	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	3	SIE	1	0	0	1	0	0	
GAD_05	DE	University Medicine Greifswald	SHIP	(Völzke et al., 2011)	12	24	41-70	M&F	CIDI	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1.5	SIE	1	0	0	0	1	1	
GAD_06	ES	Universitat Autònoma de Barcelona	Barcelona	(Porta et al., 2017)	31	60	18-40	M&F	MINI	1	1	0	1	1	1	0	0	0	1	1	0	0	0	0	0	1.5	GE	1	0	0	1	0	0	
GAD_07	IT	University of Milan	Milan	(Molent et al., 2018)	34	64	21-73	M&F	SCID	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	3	PHI	1	1	1	1	1	1	
GAD_08	IT	University Vita-Salute San Raffaele	San Raffaele	(Canu et al., 2015)	21	71	22-63	M&F	SCID	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1.5	PHI	1	1	1	1	1	1	
GAD_09	UK	Sussex university/ Sapienza university of Rome	Sussex	(Makovac et al., 2016; Makovac et al., 2016)	19	21	18-55	M&F	SCID	1	Excl.	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1.5	SIE	1	0	0	1	0	0	
GAD_10	US	National Institute on Drug Abuse	ABCD study	(Casey et al., 2018; Volkow et al., 2018)	114	1,495	8-11	M&F	OTH	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	3	?	1	?	?	?	?	?	
GAD_11	US	Baylor College of Medicine	Baylor	(Curtis et al., 2019; Gosnell et al., 2020)	98	149	12-79	M&F	SCID	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	3	SIE	1	1	1	1	1	1	1
GAD_12	US	Boys Town National Research Hospital	Boystown	(Blair et al., 2019; Blair et al., 2019)	50	45	13-18	M&F	OTH	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	3	SIE	1	0	0	1	0	0	1

TABLE 1 (Continued)

General sample information			Clinical information										Questionnaires					MRI and genetic information																
Sample #	Country	Institute	Sample	Key-references	# GAD	Age-range (y)	Sex	Diagnostic interview	Anx comorb	Other comorb	Age onset	Psych med	STAI-trait	ASI	BAI	LSAS	PAS	ACQ	PDSS	HAM_A	PSWQ	GAD_7	BDI-II	HAM_D	CDI	SCARED (T)	Field strength	T1-w	Scanner	MRI	DTI	fMRI	Material for genetics	
GAD_13	US	University of Illinois at Chicago	Chicago-Phan	(Gorka et al., 2019; Klumpp et al., 2018)	104	18-60	M&F	?	1	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	0	?	?	1	?	?	?	?	?	?
GAD_14	US	University of Illinois at Chicago	Chicago-Milad		27	18-59	M&F	?	1	1	0	0	1	1	1	0	0	0	0	0	0	1	0	0	0	?	?	1	?	?	?	?	?	?
GAD_15	US	University of Cincinnati	Cincinnati	(Strawn et al., 2012)	10	12-18	M&F	KSADS	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	4	OTH	1	0	1	0	1	1	
GAD_16	US	Child Mind Institute	CMI	(Alexander et al., 2017)	121	5-21	M&F	KSADS	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	3	SIE	1	1	1	1	1	1
GAD_17	US	Duke University	Duke	(Carpenter et al., 2015)	26	6-10	M&F	OTH	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	GE	1	1	1	1	0	0	
GAD_18	US	Harvard Medical School	Harvard		203	18-40	M&F	SCID	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	3	SIE	1	1	1	1	1	1	1
GAD_19	US	UT Health	Houston_GAD		9	8-68	M&F	SCID	1	1	0	1	0	0	0	0	0	1	0	0	1	1	0	1	1.5	PHI	1	0	0	0	0	0	0	
GAD_20	US	University of Pittsburgh	PittsburghAndrescu	(Kairm et al., 2016)	38	19-90	M&F	SCID	1	1	1	1	0	0	0	0	0	1	1	0	0	1	1	0	3	SIE	1	1	1	1	1	0	0	
GAD_21	US	University of Pittsburgh	PittsburghPrice	(Price et al., in press; Price et al., 2018)	69	18-54	M&F	MINI	1	1	0	1	1	0	1	1	0	0	0	1	0	1	0	0	3	SIE	1	0	1	0	1	0	0	
GAD_22	US	National Institute of Mental Health	SDAN	(Gold et al., 2020; Gold et al., 2017)	243	8-51	M&F	SCID & KSADS	1	1	0	0	1	1	1	1	0	0	0	1	1	0	1	0	1	3	GE	1	1	1	1	1	1	1
GAD_23	US	National Institute of Mental Health	SNFA	(Balderston et al., 2017)	23	19-50	M&F	SCID	1	1	0	1	1	0	1	0	0	0	0	0	0	0	1	0	0	3	GE	1	0	0	0	0	0	0
GAD_24	US	Stony Brook University	Stony Brook	(Cha et al., 2016)	41	18-49	Only F	?	0	1	0	1	1	1	0	0	0	0	0	1	0	1	0	0	?	?	1	?	?	?	?	?	?	
GAD_25	US	University of California - San Diego	UCSD	(Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2013; Forzo et al., 2014)	46	17-53	M&F	MINI & SCID	1	1	0	1	1	1	0	0	0	0	0	1	0	1	0	0	3	GE	1	0	1	0	1	?	?	
GAD_26	US	University of Pennsylvania	PNC	(Calkins et al., 2015; Satterthwaite et al., 2014)	27	8-23	M&F	OTH	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	3	SIE	1	1	1	1	1	1	1	

(Continues)

TABLE 1 (Continued)

General sample information				Clinical Information										Questionnaires					MRI and genetic information														
Sample #	Country	Institute	Sample	Key-references	# GAD # HC	Age-range (y)	Sex	Diagnostic interview	Anx comorb	Other comorb	Age onset	Psych med	STAI-trait	ASI	BAI	LSAS	PAS	ACQ	PDSS	HAM_A	HAM_D	BDI-II	GAD_7	PSWQ	CDI	SCARED (T)	Field strength	T1-w Scanner	DTI	Material for fMRI genetics			
GAD_27	US	Washington University	Washington		32	8–12	M&F	KSADS	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	3	SIE	1	0	1	0
GAD_28	US	Institute of Living/Hartford Hospital	IOL	(Assaf et al., 2018; Diefenbach et al., 2016)	32	21–71	M&F	MINI	1	1	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	3	SIE	1	0	1	0

Note: Leaders of the Anx_GAD subgroup: Anderson M. Winkler and Daniel S. Pine.

for example, a review of samples included in a recent volumetric meta-analysis (Bas-Hoogendam, 2019; Wang, Cheng, Luo, Qiu, & Wang, 2018) and a recent paper on anatomical endophenotypes of SAD (Table 1 of (Bas-Hoogendam et al., 2018)), show that the numbers of patients included in individual studies are seldom higher than 30. In addition, common artifacts (for example, related to head motion, breathing effects), and important confounders (such as educational attainment and psychiatric comorbidity) may vary systematically between patient and control groups, leading some authors to conclude that study findings largely represent artifacts or false-positive results, so potentially misinforming practitioners and patients (Weinberger & Radulescu, 2015). Hence, there is a need for rigorous examination of the replicability of neuroimaging findings within and across anxiety disorders, and for closer investigation of clinical and methodological variables that contribute to heterogeneity in findings.

2 | EARLY MULTI-SITE COLLABORATION

Researchers on anxiety disorders have forged many collaborations in recent decades. Regular conferences (such as that of the Anxiety Disorders Association of America) as well as specially convened meetings (such as those convened by the Dutch Royal Academy of Sciences) have provided opportunities for interaction, and funding mechanisms for network science have been useful in initiating and promoting collaborative research. The “European South-African Research Network in Anxiety Disorders” (EUSARNAD), for example, was funded by the EU (Baldwin & Stein, 2012); one aim was to conduct a multi-center voxel-based morphological mega-analysis of SAD. In this early initiative, research centers from five different countries participated, and T1-weighted 3 Tesla brain MRI scans of 174 SAD patients and 213 healthy controls were included in the analysis (Bas-Hoogendam et al., 2017b). A hypothesis-driven region of interest (ROI) approach was used and found that patients with SAD had, on average, larger gray matter volume in the dorsal striatum than healthy controls, after adjusting for gender, age, scan center, and total gray matter volume. Notably, this increase correlated positively with the severity of self-reported social anxiety symptoms (Bas-Hoogendam et al., 2017b). This mega-analysis, however, did not replicate gray matter changes in amygdala, hippocampus, precuneus, prefrontal cortex and parietal regions, which had previously been reported in small-sample case-control studies. Taken together, the findings of this study emphasize the importance of standardized meta-analytic and mega-analytic approaches for SAD in particular, and the anxiety disorders in general (Bas-Hoogendam et al., 2017a).

During the data collection for the EURSANAD project and the subsequent steps for the mega-analysis, the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) initiative, launched in 2009, gained momentum. As described extensively elsewhere, ENIGMA has developed a well-supported and robust platform to perform novel meta-analyses on data derived from harmonized and locally applied data-processing pipelines (Bearden & Thompson, 2017; Thompson et al., 2014; Thompson et al., 2020), publicly available at

<http://enigma.ini.usc.edu/protocols/imaging-protocols/>. Considering the advantages of this approach, the quality of support provided by the ENIGMA core, the expanding reach and resources of the ENIGMA consortium, and the clear need to facilitate large-scale analyses of anxiety disorders and across disorders, the EUSARNAD-SAD consortium decided to join the ENIGMA initiative and to launch the ENIGMA-Anxiety Working Group.

3 | THE START AND STRUCTURE OF THE ENIGMA-ANXIETY WORKING GROUP

When the ENIGMA-Anxiety Working Group was initiated in 2016, we immediately noted that most ENIGMA working groups devoted to psychiatric disorders focused on just one condition, such as schizophrenia (van Erp et al., 2016), major depressive disorder (MDD) (Schmaal et al., 2016; Schmaal et al., 2017), or OCD (Boedhoe et al., 2017). The anxiety disorders comprise a number of disparate conditions with disorder-specific clinical presentations (American Psychiatric Association, 2013). Nevertheless, the class of anxiety disorders involves very high rates of comorbidity between the disorders, and few studies link individual anxiety disorders to unique neurobiological alterations, suggesting that there (partly) are shared neurobiological characteristics (Fonzo et al., 2015; Kim & Yoon, 2018; Pannekoek et al., 2015; Rabany et al., 2017). We therefore set up three subgroups under the umbrella of ENIGMA-Anxiety (focused on SAD, PD with and without agoraphobia, and GAD) and later also added a fourth group (focused on SP). Our initial focus was on case-control comparisons per subgroup, as this was expected to be sensitive to relatively small effect sizes, would allow for comparisons with findings from other ENIGMA working groups, and help to gain a critical mass (as illustrated by the addition of the SP subgroup). We envisaged that this sort of collaboration would facilitate progress in each disorder, and also provide a foundation for subsequent cross-disorder collaborations.

The leaders of each subgroup reached out to research sites across the world, explaining the aim and methods of the ENIGMA approach, and asking principal investigators whether they were willing to contribute data to the initiative. Potential sites were identified via personal contacts of the coordinators and literature searches, as well as by carefully screening abstracts submitted for scientific meetings (for example, the annual OHBM meeting (2016) and the annual meeting of the Society of Biological Psychiatry (2017)). In addition, when the initiative became more known, several sites contacted the ENIGMA-Anxiety Working Group themselves and expressed their interest to contribute data. For each contributing site, the principal investigator(s) signed the Memorandum of Understanding (MOU), describing the policies of the working group with respect to authorship, publications, secondary proposals, and an opt-in approach to project participation. Next, members provided information on data availability for their samples; this material was used to construct the ENIGMA-Anxiety database and, subsequently, to allocate research samples to the appropriate subgroup. We want to stress that the Working Group

continues to welcome new contributors. Interested researchers are encouraged to contact the Working Group leaders and coordinators to discuss their participation (<http://enigma.ini.usc.edu/ongoing/enigma-anxiety/>). Importantly, the availability of genotyping data is not a prerequisite for joining. However, samples do need to be phenotyped with regard to anxiety disorders or symptoms, and structural MRI data need to be available (T1-weighted scans; diffusion tensor imaging [DTI] and functional MRI data are optional).

To facilitate future cross-disorder comparisons between anxiety disorders as well as across ENIGMA working groups, and building on the experience of already existing working groups, we aimed for a detailed characterization of samples when constructing the ENIGMA-Anxiety database. Thus, in addition to details about the MRI data, we inquired for each sample whether the researchers collected information on the presence of psychiatric diagnoses (derived from clinical interviews), severity of anxiety and depressive symptoms (derived from self-report questionnaires), imaging parameters, and demographic characteristics of the samples; we strove to collect this information in a standardized way across the four subgroups. This collation of information subsequently aided us with study design; it was particularly important for deciding which variables to include in plans for analysis and to assess the feasibility of secondary proposals (for a recent paper illustrating the effect of accounting for psychiatric comorbidity while investigating biomarkers in psychiatry, we refer to (Gosnell et al., 2020)). Data availability is summarized in Table 1 (Anx_GAD), Table 2 (Anx_PD), Table 3 (Anx_SAD) and Table 4 (Anx_SP).

In addition to the samples that could be allocated to the four subgroups, the ENIGMA-Anxiety database contains information on samples with anxiety disorder diagnoses that are not an immediate focus of investigation; these samples concern, for example, children with separation anxiety (Calkins et al., 2015; Salum et al., 2011; Salum et al., 2015; Satterthwaite et al., 2014), children at risk for developing an anxiety disorder (Battaglia et al., 2012; Fu, Taber-Thomas, & Pérez-Edgar, 2017; Taber-Thomas, Morales, Hillary, & Pérez-Edgar, 2016), participants with anxiety-related traits and at risk phenotypes (Campbell-Sills et al., 2011; Dannlowski et al., 2015; Dannlowski et al., 2016; Mujica-Parodi et al., 2009; Thompson et al., 2019; Tolkunov, Rubin, & Mujica-Parodi, 2010), participants with behavioral inhibition (Blackford, Allen, Cowan, & Avery, 2013; Blackford, Avery, Cowan, Shelton, & Zald, 2011), as well as participants with hypochondriasis (van den Heuvel et al., 2011) and twin-pairs with and without a diagnosis of an anxiety disorder (Córdova-Palomera et al., 2015). As discussed in the section on future research directions, analyses of these data may in due time shed light on the developmental timeline of anxiety-related alterations in the brain, across the full spectrum of subclinical and clinical anxiety phenotypes.

Within each subgroup, data availability was highest for T1-weighted anatomical MRI scans. Therefore, and following the usual ENIGMA procedures, the first projects within each subgroup were devoted to investigation of subcortical volumes (initiated in 2017) and cortical morphology (initiated in 2019). Secondary projects that have been recently proposed will examine anxiety-related

TABLE 2 Anx_PD (panic disorder)

General sample information			Clinical information					Questionnaires										MRI and genetic information														
Sample #	Country	Institute	Sample	Key-references	# PD	HC (y)	Age-range (y)	Sex	Diagnostic interview	Anx comorb	Other comorb	Age onset	Psych med	STAI-trait	ASI	BAI	LSAS	PAS ACQ	PDSS HAM_A	PSWQ	GAD_7	BDI/II	HAM_D	CDI	SCZARED	Field strength (T)	Scanner	T1-w MRI	DTI	fMRI	Material for genetics	
PD_01	DE	Max Planck Institute of Psychiatry	MARS anxiety (RUD controls)	(Erhardt et al., 2012)	20	212	19–79	M&F	SCID	1	1	1	1	1	0	0	0	1	0	0	1	0	0	1	0	0	1.5	GE	1	0	1	1
PD_02	DE	Philipps-University Marburg	Panic-net	(Kircner et al., 2013; Yang et al., 2019)	159	182	19–67	M&F	SCID	1	1	0	Excl	0	1	0	0	1	0	0	1	0	0	0	0	3	SIE	1	0	1	1	
PD_03	DE	University Medicine Greifswald	SHIP	(Pané-Farré et al., 2014; Völzke et al., 2011)	27	699	31–90	M&F	CIDI	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1.5	SIE	1	0	0	1		
PD_04	DE	University of Marburg	FOR2107 MR	(Kircner et al., 2019; Vogelbacher et al., 2018)	35	471	18–65	M&F	SCID	1	1	0	1	1	0	0	0	0	0	0	1	0	0	0	3	SIE	1	1	1	1	1	
PD_05	DE	University of Wuerzburg	DOM-PANTHER	(Gotschalk et al., 2019; Neufang et al., 2019)	33	45	21–55	M&F	SCID	1	1	1	1	1	1	0	0	1	0	0	1	0	0	0	3	SIE	1	1	1	1	1	
PD_06	DE	University of Muenster	IMPS	(Feldler et al., 2016)	40	41	18–46	M&F	SCID	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	3	SIE	1	0	1	0	0	
PD_07	DE	University of Muenster	Münster neuroimaging cohort and panic emotion processing	(Ohmann et al., 2010; Opel et al., 2019)	71	735	15–65	M&F	SCID	1	1	0	1	1	0	0	0	0	0	0	1	0	0	0	3	PHI	1	1	1	1	1	
PD_08	DE	University of Muenster	FOR2107 MS	(Repple et al., 2020)	29	233	18–65	M&F	SCID	1	1	0	1	1	0	0	0	0	0	0	1	0	0	0	3	SIE	1	1	1	1	1	
PD_09	DE	University Hospital Wuerzburg	Wuerzburg	(Dresler et al., 2011; Dresler et al., 2012)	18	27	21–59	M&F	OTH	1	1	0	1	1	1	0	0	1	0	0	0	0	0	1.5	SIE	1	0	0	0	?		
PD_10	DE	University Hospital Wuerzburg, Department of systems neuroscience Hamburg	Hamburg	(Dresler et al., 2012)	20	23	19–49	M&F	SCID	1	1	0	1	1	1	0	0	1	0	0	0	0	0	3	SIE	1	0	0	0	?		
PD_11	IT	University Vita-Salute San Raffaele	Milan_OS	(Poletti et al., 2015)	21	196	18–65	M&F	OTH	Excl	1	1	1	1	1	0	0	0	0	0	0	0	0	0	3	PHI	1	0	1	0		
PD_12	IT	University of Milan	Milan_1.5 T	(Maggioli et al., 2019)	11	21	18–66	M&F	SCID	1	1	1	1	0	0	0	0	0	0	0	1	0	0	1.5	SIE	1	1	1	1	1		
PD_13	IT	University of Milan	Milan_3T	(Molent et al., 2018)	12	64	19–65	M&F	SCID	1	1	1	1	0	0	0	0	0	0	0	0	0	0	3	PHI	1	1	1	1	1		

TABLE 2 (Continued)

General sample information			Clinical information										Questionnaires										MRI and genetic information												
Sample #	Country	Institute	Sample	Key-references	# PD	# HC	Age-range (y)	Sex	Diagnostic interview	Anx	Other comorb	Age onset	Psych med	STAI-trait	ASI	BAI	LSAS	PAS	ACQ	PDSS	HAMA	A	PSWQ	GAD_7	BDI-II	HAM_D	CDI	SCZARED	Field strength (T)	Scanner	T1-w MRI	DTI	fMRI	Material for genetics	
PD_14	JP	Yokohama City University	YCU	(Asami et al., 2018)	38	68	19-58	M&F	SCID	1	Excl	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PD_15	KR	CHA Bundang Medical Center	Cortical morphology	(Kang, Lee, & Lee, 2017; Kim et al., 2014)	43	2	17-62	M&F	SCID	1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	1	1	0	0	3	GE	1	1	1	1	1
PD_16	NL	Amsterdam, Groningen, Leiden University Medical Centers	NESDA	(Penninx et al., 2008; van Toi et al., 2010)	44	65	18-65	M&F	CIDI	1	1	1	1	1	0	1	0	0	0	0	1	0	0	1	1	0	0	3	PHI	1	0	1	1	1	
PD_17	NL	Amsterdam UMC, Vrije Universiteit Amsterdam	Vumc	(van den Heuvel et al., 2005)	15	23	18-58	M&F	SCID	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.5	SIE	1	0	1	0	1	0
PD_18	UK	Oxford university		(Reinecke et al., 2015; Reinecke, Thilo, Croft, & Harmer, 2018)	68	20	18-65	M&F	SCID	1	1	1	1	1	0	0	0	0	1	1	1	0	0	0	1	0	0	3	SIE	1	0	1	0	1	1
PD_19	US	Boys Town National Research Hospital	Boystown	(Blair, Aloi, et al., 2019)	50	56	1-18	M&F	OTH	1	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	1	3	SIE	1	0	1	0	1	1
PD_20	US	University of Pennsylvania	PNC	(Calkins et al., 2015; Satterthwaite et al., 2014)	14	428	8-23	M&F	OTH	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	3	SIE	1	1	1	1	1	0
PD_21	US	Harvard Medical School	RDoc		24	57	18-40	M&F	CIDI	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	3	SIE	1	?	?	?	?	?
PD_22	US	UT Health	Houston_PD	(Wu et al., 2015)	15	34	08-62	M&F	SCID	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1.5	PHI	1	0	0	0	0	0	0
PD_23	US	Columbia University & New York State psychiatric institute		(Talati, Pantazatos, Schneider, Weissman, & Hirsch, 2013)	17	19	18-65	M&F	OTH	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1.5	PHI	1	0	0	0	0	0	1
PD_24	US	University of California -San Diego	INSULA, DV, SDSU	(Ball et al., 2013; Fonzo et al., 2015)	45	45	20-49	M&F	OTH	1	1	0	1	1	1	0	0	0	0	0	0	0	1	0	1	0	3	GE	1	0	1	0	1	1	1
PD_25	US	Weill Cornell Medical College and University of Pennsylvania		(Milrod et al., 2016)	24	0	18-70	M&F	OTH	1	1	1	1	0	1	0	0	0	0	0	1	1	0	0	0	1	3	GE	1	0	1	0	1	0	0

Note: Leaders of the Anx_PD subgroup: Moji Aghajani and Dick J. Veltman.

TABLE 4 Anx_SP (specific phobia)

General sample information			Clinical information					Questionnaires					MRI and genetic information																				
Sample #	Country	Institute	Sample	Key-references	# SP # HC (y)	Age-range	Sex	Diagnostic interview	Anx comorb	Other comorb	Age onset	Psych STAI-trait	ASI	BAI	LSAS	PAS	ACQ	PDS5	HAM_A	PSWQ	GAD_7	BDI-II	HAM_D	CDI	SCARED	Specific phobia questionnaires (T)	Field strength	T1-w MRI	Material for DTI	fMRI genetics			
SP_01	AT	University of Graz	Graz dental phobia	(Wabnegger, Scharmüller, & Schiene, 2014)	36	36	20–56	M&F	OTH	1	1	1	Excl	0	0	0	0	0	0	0	0	0	0	0	0	0	DAS, FDP	3	SIE	1	0	0	0
SP_02	AT	University of Graz	Graz dental phobia II	(Schiene, Scharmüller, Leutgeb, Schäfer, & Stark, 2013)	45	41	19–62	M&F	SCID	1	1	1	Excl	0	0	0	0	0	0	0	0	0	0	0	0	0	DAS	1.5	SIE	1	0	0	0
SP_03	BR	INPD	Brazilian HRC study	(Salum et al., 2015)	89	516	5–15	M&F	OTH	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	DAWBA	1.5	GE	1	1	1	1
SP_04	DE	Ruhr-Universität Bochum	Dresden specific phobia subtypes	(Hilbert, Evens, Isabel Maslowski, Wittchen, & Lueken, 2015)	18	0	27–60	M&F	OTH	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	DAS	1.5	SIE	1	0	1	1	
SP_05	DE	Technische Universität Dresden	Dresden specific phobia subtypes	(Hilbert, Evens, Isabel Maslowski, Wittchen, & Lueken, 2015)	59	37	18–46	M&F	CIDI	1	1	0	Excl	0	1	0	0	0	0	0	0	0	1	0	0	SNAQ, DFS	3	SIE	1	0	1	0	
SP_06	DE	Technische Universität Dresden	CRC940C5	None	100	82	18–49	M&F	CIDI	1	1	1	Excl	1	0	0	0	0	0	0	0	1	0	0	0	FSQ	3	SIE	1	0	1	0	
SP_07	DE	University of Gießen	BION_SP	(Schweckendiek et al., 2011)	15	14	18–31	M&F	OTH	Excl	Excl	0	Excl	1	0	0	0	0	0	0	0	0	0	0	0	SPQ	1.5	SIE	1	0	0	0	
SP_08	DE	University of Greifswald	Greifswald spider/Snake phobia	(Wendt, Schmidt, Lotze, & Hamm, 2012)	20	25	18–29	Only F	OTH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	SPQ, SNAQ	1.5	SIE	1	0	1	0	
SP_09	DE	University Medicine Greifswald	SHIP	(Völzke et al., 2011)	148	699	31–90	M&F	CIDI	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.5	SIE	1	0	0	1
SP_10	DE	Friedrich-Schiller-Universität Jena	Jena spider phobia	(Lipka, Miltner, & Straube, 2011)	14	15	19–49	Only F	SCID	Excl	Excl	0	Excl	1	0	0	0	0	0	0	0	0	0	0	0	SPQ	3	SIE	1	0	1	0	
SP_11	DE	University of Marburg	FOR2107MR	(Kircher et al., 2019; Vogelbacher et al., 2018)	16	516	18–65	M&F	SCID	1	1	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	3	SIE	1	1	1	1
SP_12	DE	University of Muenster	FOR2107MS	(Repple et al., 2020)	28	247	18–65	M&F	SCID	1	1	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	3	SIE	1	1	1	1
SP_13	DE	University of muenster	Muenster dental phobia	(Feldker et al., 2017)	19	19	18–60	M&F	SCID	Excl	Excl	0	Excl	1	1	0	0	0	0	0	0	0	0	0	0	DAS	3	SIE	1	0	1	0	
SP_14	DE	University of Muenster	Muenster spider phobia	(Münsterkötter et al., 2015)	29	478	18–59	M&F	SCID	1	1	0	Excl	0	0	0	0	0	0	0	0	0	0	0	0	0	SPQ, FSQ	3	PHI	1	1	1	1
SP_15	DE	University of Muenster	SFBTRR-58 project C09 (SpiderVR)	(Schwarzmeier et al., 2019)	87	0	18–56	M&F	SCID	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	3	SIE	1	0	1	1
SP_16	DE	University of Wuerzburg	Wuerzburg spider phobia	(Wiemer et al., 2014)	18	18	18–37	Only F	SCID	Excl	Excl	0	Excl	1	0	0	0	0	0	0	0	0	0	0	0	0	SPQ, FSQ	1.5	SIE	1	0	0	0

(Continues)

TABLE 4 (Continued)

General sample information			Clinical information										Questionnaires					MRI and genetic information																		
Sample #	Country	Institute	Sample	Key-references	# SP	# HC	Age-range (y)	Sex	Diagnostic interview	Anx comorb	Other comorb	Age onset	Psych med	STAI-trait	ASI	BAI	LSAS	PAS	ACQ	PDSS	HAM_A	PSWQ	GAD_7	BDI-II	HAM_D	CDI	SCARED	questionnaires (T)	Field strength	Specific phobia	Scanner	T1-w MRI	DTI	Material for fMRI		
SP_17	DE	University of Wuerzburg	Wuerzburg spider phobia II		13	12	19-42	M&F	SCID	0	0	0	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	FSQ, FEAS	1.5	SIE	1	0	1	0	
SP_18	DE	University of Wuerzburg	Wuerzburg spider phobia III		10	6	18+	?	SCID	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.5	SIE	1	0	1	0	0	
SP_19	DE	University Hospital of Wuerzburg	SFBTRR-56 project C09 (SpiderVR)	(Schwarzmeier et al., 2019)	87	0	18-65	M&F	SCID	1	1	1	1	1	1	0	1	0	0	0	0	1	0	1	0	0	0	0	SPQ	3	SIE	1	0	1	1	0
SP_20	DE	Multicenter study (University of Marburg)	PROTECT-AD: Specific phobia sample	(Heinig et al., 2017)	57	0	18-67	M&F	CIDI	1	1	1	Excl	0	1	0	1	1	0	0	0	0	1	1	0	0	0	0	DSM-5-SP	3	SIE	1	0	1	1	0
SP_21	ES	Universidad de La Laguna	Tenerifa animals phobia	(Rivero, Herrero, Vña, Álvarez-Pérez, & Peñate, 2017)	37	41	18-60	M&F	OTH	Excl	Excl	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	S-R/IA	3	GE	1	0	1	0	
SP_22	NL	University of Amsterdam	RepSpi	(Visser, Haver, Zwiitser, Scholte, & Kindt, 2016)	18	20	18-43	M&F	OTH	0	0	0	Excl	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	SPQ	3	PHI	1	0	1	0	0
SP_23	NL	Maastricht University	SPIN	(Zilverstand, Sorger, Kaemingk, & Goebel, 2017)	7	7	18-29	?	MINI	Excl	Excl	1	Excl	?	?	?	?	?	?	?	?	?	?	?	?	?	?	SPQ, FSQ	3	SIE	1	0	1	0	0	
SP_24	NL	Maastricht University	SPIN NF	(Zilverstand et al., 2017)	18	0	19-26	?	MINI	Excl	Excl	1	Excl	?	?	?	?	?	?	?	?	?	?	?	?	?	?	SPQ, FSQ	3	SIE	1	0	1	0	0	
SP_25	NL	Maastricht University	SMARTSCAN PHOBIA	(Lange et al., 2019)	46	47	16-25	?	MINI	1	1	0	Excl	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	FSQ	3	SIE	1	1	1	1	0
SP_26	NL	Maastricht University, Katholieke Universiteit Leuven	PHOBIA exposure	(Lange et al., 2016)	20	0	19-29	Only F	MINI	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	SPQ	3	PHI	1	1	0	0	0
SP_27	PL	SWPS University of Social Sciences and Humanities	Czuwaj	(Michalowski et al., 2017)	25	11	19-36	M&F	OTH	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	FSS	3	SIE	1	1	1	0	0
SP_28	SE	Uppsala University	Uppsala spider phobia	(Björkstrand et al., 2016)	47	0	20-55	M&F	OTH	0	0	1	Excl	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	SPQ	3	PHI	1	1	1	0	0
SP_29	UK	COMIC Research/ LYPTF	Spider phobia	(Wright et al., 2013; Wright et al., 2015)	12	0	17-42	M&F	OTH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	FSQ	3	GE	1	0	0	0	0
SP_30	US	National Institute of Mental Health	SDAN	(Gold et al., 2020; Gold et al., 2017)	125	225	10-51	M&F	SCID & KSADS	1	1	0	Excl	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	None	3	GE	1	0	?	0	0

TABLE 4 (Continued)

General sample information			Clinical information										Questionnaires				MRI and genetic information														
Sample #	Country	Institute	Key-references	# SP	# HC	Age-range (y)	Sex	Diagnostic interview	Anx comorb	Other comorb	Age onset	Psych trait	ASI	BAI	PAS	ACQ	PDSS	HAM_A	PSWQ	GAD_7	BDI-II	HAM_D	CDI	SCARED	Specific phobia questionnaires (T)	Field strength (T)	TI-w Scanner	Material for DTI fMRI genetics			
SP_31	US	University of Pennsylvania	(Calkins et al., 2015; Satterthwaite et al., 2014)	426	428	8-23	M&F	OTH	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	3	SIE	1	1	1	0
SP_32	US	Vanderbilt University	(Claus, Avery, et al., 2014; Claus, Seay, et al., 2014)	9	9	10-25	M&F	SCID	1	1	0	Excl	1	1	0	0	0	0	0	0	0	1	0	0	0	3	PHI	1	0	1	1

Note: Leaders of the Anx_SP subgroup: Kevin Hilbert and Ulrike Lueken.

alterations in the microstructure of white matter tracts based on DTI data (Kochunov et al., 2015), in the connectivity of brain functional networks utilizing resting-state functional (f)MRI (Adhikari et al., 2018), and in the responsivity of brain regions to anxiety-related cues utilizing task-related functional (f)MRI paradigms (under development). Then, ENIGMA approaches that assess more subtle variations in brain morphology including investigation of regional subfields (e.g., of hippocampus and amygdala (Salminen et al., 2019; Saygin et al., 2017)), subcortical shape (Ching et al., 2020; Gutman et al., 2015; Gutman, Wang, Rajagopalan, Toga, & Thompson, 2012; Ho et al., 2019), and brain asymmetry (Kong et al., 2018), can be key next steps.

4 | DATA AVAILABILITY WITHIN THE ENIGMA-ANXIETY WORKING GROUP

At present, more than 180 researchers from 80 research groups based within 59 institutes around the world (16 countries—see Figure 2) are members of the ENIGMA-Anxiety Working Group. In Tables 1–4, details on the MRI samples and data-collection within the participating cohorts within the four ENIGMA-Anxiety subgroups are summarized. It should be noted that the numbers of subjects in these tables represent initial sample sizes, before exclusion of data due to, for example, comorbidity with other severe psychopathology (e.g., bipolar disorder), and that data from individual subjects can be included in several subgroups due to comorbidity; in addition, healthy control participants from samples included in multiple subgroups are nonunique. Here, we wish to highlight several interesting and valuable features of the available neuroimaging data that may well be unique to the ENIGMA-Anxiety Working Group.

First, to our best knowledge, the ENIGMA-Anxiety Working Group is the largest neuroimaging (MRI) collaboration (with respect to sample size and number of collaborators) to date focusing on anxiety disorders, encompassing a broad range of studies varying in geographic location, clinical setting, and disease stage. The individual subgroups each include over 800 (Anx_PD) or even over 1,000 (Anx_GAD, Anx_SAD, Anx_SP) anxiety patients and as such the total sample size is substantial, even when considering anticipated data loss due to, for example, insufficient scan quality and segmentation failures.

Second, there is considerable overlap in recorded clinical characteristics such as age of onset and symptom severity measures within and across subgroups, and data are available for a range of possible confounders (for example, medication-use at the time of scan). At the same time, there are several limitations regarding the availability of more detailed clinical characteristics (for example, treatment use during the lifetime, adverse life-events, level of depressive symptoms).

Importantly, the majority of samples within ENIGMA-Anxiety collected information about comorbidity with other anxiety disorders, as well as with nonanxiety disorders. As to be expected, this comorbidity is considerable, and most prominent in the Anx_GAD subgroup. In a first exploration of data in 910 GAD patients, 299 met criteria for

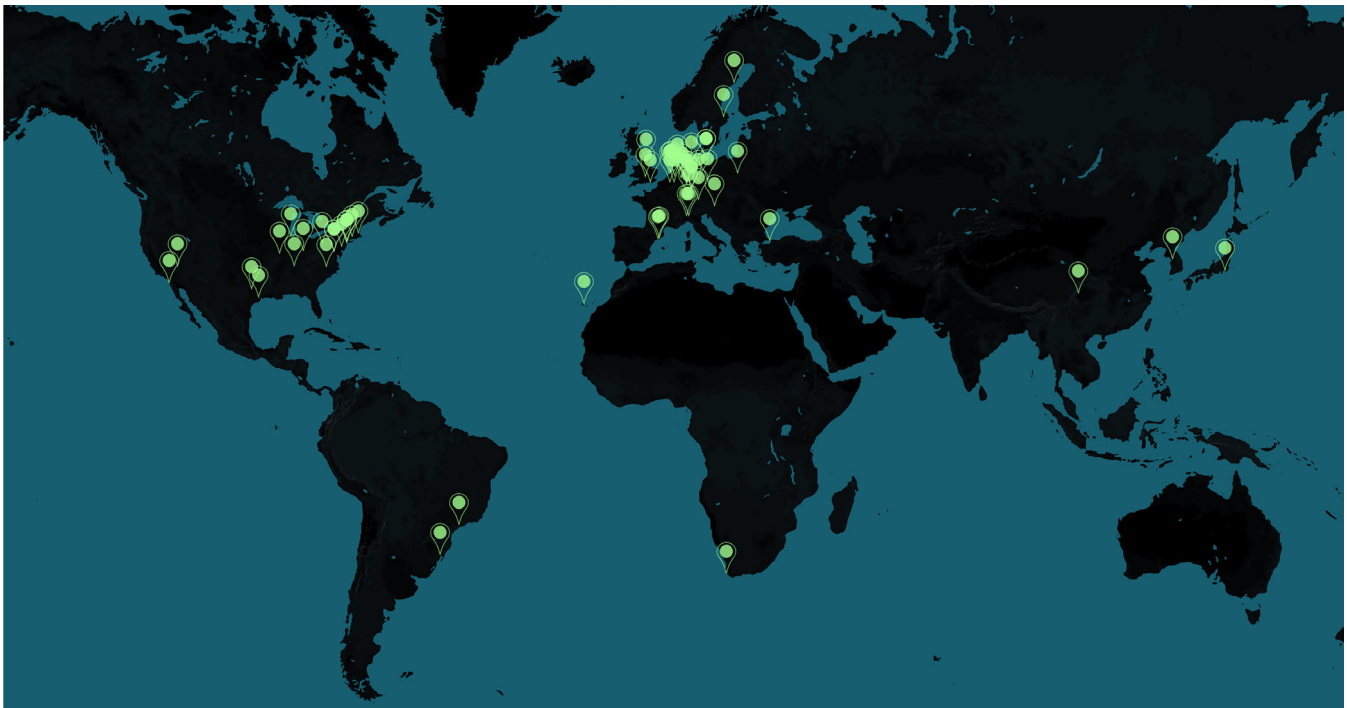


FIGURE 2 Institutes participating in ENIGMA-Anxiety—world map

concurrent SAD, 164 met criteria for concurrent MDD, and 132 met criteria for concurrent SP. Comorbidity rates vary considerably across samples as a function of recruitment setting and inclusion strategy, introducing heterogeneity. Importantly, comorbidity is inherent to the clinical anxiety phenotype. Therefore, the inclusion of patients with comorbidity improves the generalizability of findings while allowing exploration of moderating effects of comorbid diagnoses.

5 | WORK IN PROGRESS

Projects examining subcortical volumes and cortical thickness and cortical surface area are currently being performed within all four subgroups of ENIGMA-Anxiety. These studies are based on individual-participant data (IPD), meaning that anonymized summary statistics at the level of individual output are shared (Anx_PD, Anx_SAD, Anx_SP), or on raw imaging data (Anx_GAD) (cf. discussion provided in (Thompson et al., 2020)). For the Anx_PD, Anx_SAD, and Anx_SP subgroups, detailed protocols enabling harmonized data processing have been distributed to individual sites, and these local analyses are currently being performed or have been completed.

With respect to the Anx_SAD subgroup, preliminary results on SAD-related differences in subcortical volumes have been presented at the SOBP and OHBM 2018 meetings (Groenewold et al., 2018). The analyses, which involved only a subset of the present data set (SOBP 2018 meeting: $n = 404$ patients with SAD and 775 healthy controls, from 14 adult cohorts; OHBM 2018 meeting: additional $n = 98$ patients with SAD and 106 healthy controls, from two pediatric cohorts) used a meta-analytic approach to pool effect sizes across

samples. The analyses revealed subtle alterations in the left thalamus (patients < controls), and the right amygdala and right hippocampus, with smaller volumes for patients with higher severity of SAD symptoms (Groenewold et al., 2018). Results from these preliminary analyses were not significant after correction for multiple comparisons. Since then, data availability has more than doubled, as IPD has been submitted for 16 additional cohorts. Presently, one site is continuing to work to provide IPD data, which will allow for mega-analysis without bias related to attrition. Final analyses for the Anx_SAD subcortical and cortical projects are scheduled for later in 2020.

For the Anx_PD and Anx_SP subgroups, it was not yet possible to conduct preliminary analyses, but analyses for these subgroups are scheduled for 2020. The first set of analyses within Anx_PD will simultaneously probe cortical and subcortical morphology in PD with and without agoraphobia, using a mega-analytical approach. The ANX_SP project will investigate differences between patients and healthy controls, but will also include analyses examining potential differences between specific phobia subtypes. Prior research indicated a distinct psychophysiological response pattern for blood-injection-injury phobia compared to more prototypical animal phobias (McTeague, Lang, Wangelin, Laplante, & Bradley, 2012; Thyer & Curtis, 1985). Similarly, there were at least partly different neural correlates between these subtypes, but sample sizes were small (Hilbert, Evens, et al., 2015; Lueken et al., 2011). The ENIGMA-Anxiety SP project presents a rare opportunity to examine the replicability of these findings with considerably increased statistical power.

An innovative approach of the Anx_GAD subgroup involved pre-registration of the data-analytic plan (publicly available at osf.io/yxajs); furthermore, the group adopted a comprehensive approach to address

potential sources of heterogeneity in effects. This plan included 12 statistical contrasts involving 16 subcortical regions, as well as vertex-wise cortical thickness and surface area as dependent variables, a random intercept per scanner, and random slopes per site for two sets of variables. The first set of analyses included GAD, sex, age, age-squared (age^2) and their interactions, IQ, years of education, medication use at time of the scan, comorbidity, and scanner. The second set also included total surface area, mean thickness and total intracranial volume as covariates. Permutation tests controlled for multiple testing across all factors (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Similarly to Anx_SAD, preliminary analyses of the Anx_GAD subgroup using subcortical regions, as well as thickness and surface area in 68 cortical regions as dependent variables, have so far revealed no significant associations between GAD and brain structure when correcting for multiple comparisons (Harrewijn et al., 2020), despite the presence of effect sizes of comparable magnitude seen in ENIGMA research on other mental disorders, including MDD and OCD. Importantly, these findings are based on a mega-analytic approach. The Anx_GAD subgroup chose this approach to address the high comorbidity between GAD and other disorders (Beesdo, Knappe, & Pine, 2009), as comorbidity hinders attempts to differentiate associations that brain structure shows with GAD as opposed to associated disorders (Pine, Cohen, Gurley, Brook, & Ma, 1998). Random-effects models can assess cross-site heterogeneity both in GAD-related findings and in effects of comorbidity, as well as other site-specific differences. These models were immediately feasible: 25 sites provided raw data, and in addition structural MRI data from three publicly available imaging repositories were downloaded (Adolescent Brain Cognitive Development Study (Casey et al., 2018; Volkow et al., 2018), Child Mind Institute Healthy Brain Network (Alexander et al., 2017), and Duke Preschool Anxiety Study (Carpenter et al., 2015)). The analytic approach of the Anx_GAD group is outlined elsewhere in more detail (Zugman et al., 2020, this issue). Analyses on subcortical and cortical characteristics are currently being finalized.

We welcome sharing data with researchers, requiring only that they submit an analysis plan for a secondary project to the leading team of the Working Group (<http://enigma.ini.usc.edu/ongoing/enigma-anxiety/>). Once this analysis plan is approved, access to the relevant data will be provided contingent on data availability and local PI approval. Where applicable, distribution of analysis protocols to sites will be facilitated.

6 | SOME RECOMMENDATIONS FOR THE FIELD AND PERSPECTIVES FOR THE FUTURE OF ENIGMA-ANXIETY

Once these ongoing projects are completed, we foresee several future research directions. First, the ENIGMA-Anxiety Working Group is well placed to conduct rigorous comparisons of data both across anxiety disorders, and with other neuropsychiatric conditions (cf. information in Tables 1–4). ENIGMA has already initiated such work in comparing

OCD, ADHD, and ASD (Boedhoe et al., 2019), and a cross-disorder or transdiagnostic approach is particularly relevant to anxiety disorders given their high comorbidity rates (Janiri et al., 2019; Kunas et al., 2019). Notably, an early meta-analysis found that patients with anxiety disorders (including OCD and PTSD) showed decreased bilateral gray matter volumes in dorsomedial frontal/anterior cingulate gyri, but that individuals with OCD had increased bilateral gray matter volumes in the lenticular/caudate nuclei (Radua, van den Heuvel, Surguladze, & Mataix-Cols, 2010). It would be timely to return to such work; we are particularly interested in comparisons of anxiety disorders with OCD and PTSD, as well as with MDD (cf. (Gong et al., 2019)).

Second, we are enthusiastic about extending our analyses to include genetic data (also see (Mufford et al., 2017)), a key goal of the ENIGMA Consortium. In proof of principle work, we have explored the overlap between genes contributing to anxiety disorders and genes contributing to brain structure (van der Merwe et al., 2019). We obtained summary statistics of GWAS of anxiety disorders, PTSD, and of subcortical brain volumes, and conducted SNP effect concordance analysis (SECA) and linkage disequilibrium (LD) analyses. Significant concordance was observed between variants associated with increased anxiety risk and variants associated with smaller amygdala volume, consistent with a range of translational neuroscience research focused on the role of this structure in anxiety disorders. However, these findings need to be interpreted with caution, given heterogeneity and limited power in the input GWAS (for recent work, see: (Satizabal et al., 2019); PGC-Anxiety GWAS underway). These genetic overlap analyses could be extended to involve cortical structure, for example with summary statistics derived from ENIGMA's recent large-scale GWAS of cortical structure (Grasby et al., 2020). Any regions of genetic overlap can be queried for alterations in gene expression, and the aberrant genes can be categorized by cell type or function (an approach called virtual histology; (Patel et al., 2020)). In addition, we will plan analyses of polygenic risk scores for anxiety, building on GWAS summary statistics and odds ratios for the disorders, to compute individual measures of risk based on a person's genome. In the case of Alzheimer's disease, we know that the major risk haplotypes (such as APOE4) and measures of overall polygenic risk are robustly associated with net shifts in volumes of key brain structures implicated in the disease, and the timing of these shifts across the lifespan can be identified with great power using genetic analysis of neuroimaging data (Brouwer et al., 2020). As the PGC-Anxiety GWAS increases in power and discovers more genome-wide significant loci, we will be able to see which phenotypes are shifted in people at high polygenic risk, and when these shifts occur.

Third, in alignment with the focus on translational neuroscience exemplified by the Research Domain Criteria (RDoC; (Insel, 2014)), it would be useful to move beyond work that is framed using traditional diagnostic boundaries, and toward research that addresses trans-species and trans-diagnostic behavioral dimensions underpinned by specific neuronal circuitry and molecular mechanisms (Grillon, Robinson, Cornwell, & Ernst, 2019). In line with this, neurobiological candidate endophenotypes of anxiety disorders, to be assessed by family-

genetic studies, may inform about the stability of observed alterations and could potentially serve as risk signatures (Bas-Hoogendam et al., 2016; Bas-Hoogendam et al., 2019; Bas-Hoogendam, Harrewijn, et al., 2018; Bas-Hoogendam, van Steenbergen, et al., 2018; Bas-Hoogendam, van Steenbergen, Tissier, van der Wee, & Westenberg, 2019; Bas-Hoogendam, van Steenbergen, van der Wee, & Westenberg, 2020; Bearden & Freimer, 2006; Beauchaine & Constantino, 2017; Glahn et al., 2012; Glahn, Thompson, & Blangero, 2007; Hasler, Drevets, Gould, Gottesman, & Manji, 2006; Lenzenweger, 2013; Miller & Rockstroh, 2013). Furthermore, behavioral innate trait characteristics, such as behavioral inhibition, may help to predict the development of anxiety disorders, and may involve mechanisms that can be investigated in nonhuman experimental models, in healthy individuals, and in a range of mental disorders (Auday & Pérez-Edgar, 2019; Blackford, Clauss, & Benningfield, 2018; Clauss & Blackford, 2012; Henderson, Pine, & Fox, 2015; Muris, van Brakel, Arntz, & Schouten, 2011).

Fourth, ENIGMA has a growing interest in using multivariate pattern recognition and machine learning to explore neuroimaging data in search of individual-level inferences (cf. (Poldrack, Huckins, & Varoquaux, 2019)). ENIGMA-OCD has, for example, performed multivariate analysis of structural neuroimaging data on 46 data sets using machine learning methods for group classification. Classification performance for OCD versus controls was poor, but good classification performance was achieved within subgroups of patients, split according to their medication status (Bruin, Denys, & van Wingen, 2019). However, with sufficiently large and detailed data sets, future work may ultimately open new avenues for generating predictive markers that can be applied to individual patients, to inform clinical decision-making regarding diagnosis and treatment (Durstewitz, Koppe, & Meyer-Lindenberg, 2019; Lueken & Hahn, 2016; Woo, Chang, Lindquist, & Wager, 2017).

Fifth, it would be ideal if prospective neuroimaging data on anxiety disorders could be collected at a range of sites, using similar protocols, and in alignment with clinical interventions over time. Until that, research within the ENIGMA-Anxiety Working Group will suffer from several limitations of current neurobiological and neuroimaging research, including relatively sparse clinical data on participating individuals (Etkin, 2019). Prospectively planned research would ensure that clinical data as well as confounding variables are carefully collocated, and longitudinal designs would allow more detailed investigation of the mechanisms underlying anxiety disorders as well as of the impact of interventions (Gloster et al., 2009; Heinig et al., 2017; Månsson et al., 2016; Phan et al., 2013; Schwarzmeier et al., 2019; Steiger et al., 2017; Talati et al., 2015; Yang et al., 2019); cf. the accomplishments by the Alzheimer's Disease Neuroimaging Initiative (ADNI), an ongoing, longitudinal, multicenter study aimed at developing clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease using standardized methods (Mueller et al., 2005; Weiner et al., 2013). There is a need to integrate the concerns of global mental health (which have focused on the importance of implementing treatments in real-world contexts) with those of translational neuroscience (which have focused on the

potential value of discovery research on the neurobiology of mental disorders) (Stein et al., 2015; Stein & Wegener, 2017).

Despite these promising future research directions, several limitations of the large-scale approach taken by ENIGMA need to be emphasized. Although it can be considered good practice to re-utilize valuable imaging data from vulnerable patient groups, analyses of aggregated data sets are limited by variations in data acquisition and phenotyping of the samples. The resulting noise may decrease sensitivity to detect effects. To improve the comparability of samples, the ENIGMA-Anxiety Working Group plans (sub-)analyses using DSM diagnoses established with validated clinical interviews, which can be supplemented with sensitivity analyses to account for variations in data availability across sites. Furthermore, the use of harmonized processing protocols executed locally by participating sites offers some protection against the selection bias that can arise from data sharing restrictions. Nonetheless, local processing makes it more challenging to perform fine-grained analyses and limits model complexity, especially in the context of interaction effects and restricted ranges within sites. This limitation can be addressed by planning mega-analyses on individual participant (imaging) data in addition to meta-analyses. Moreover, an improved spatial resolution can be achieved with vertex-wise structural analyses (cf. ongoing work by the GAD subgroup) or seed-based functional connectivity analyses. Finally, although large-scale analyses come with an increase in power to detect small effect sizes, it is important to bear in mind that any statistically significant findings are not necessarily clinically significant and may not apply to individual patients. Hence, we intend to interpret our results with appropriate caution.

7 | CONCLUSION

Research on anxiety disorders has greatly advanced in recent decades: we have a much better appreciation of their early onset, high prevalence, and significant morbidity and comorbidity; we have developed models of their underlying neurocircuitry and obtained insights into their significant heritability and polygenic architecture; and we have introduced a range of evidence-based interventions encompassing both pharmacotherapy and psychotherapy. At the same time, much remains to be accomplished: there is a large treatment gap for anxiety disorders and our models require much greater depth. Importantly, our findings require much more replicability if they are to form the basis of a personalized medicine approach to intervention. Such an approach seems crucial, as many individuals with anxiety disorders do not respond or remit to first-line intervention.

Against this context, the ENIGMA Consortium in general, and the ENIGMA-Anxiety Working Group in particular, are exciting collaborations with much potential. First, they exemplify how cross-national collaboration can be useful in obtaining data sets with sufficient statistical power to obtain robust and replicable results even when effect sizes are small. Second, they illustrate how access to big data (brain imaging, genetics) together with sophisticated analytic approaches can yield novel and significant findings. Although based firmly within

the conceptual framework of translational neuroscience, many of the concerns and methods of ENIGMA (e.g., ensuring diverse samples, scaling up methods) are redolent of the best features of global mental health. Taken together, ENIGMA-Anxiety exemplifies the synergy found at the intersection of global mental health and clinical neuroscience, and promises to further contribute to advancing the field of anxiety disorders in particular.

Tables Information box belonging to the tables

Tables 1–4 summarize samples that have been submitted to the ENIGMA-Anxiety Working Group (either individual patient data (IPD) or raw scans), or that are in the process of submission. The tables list for each sample whether certain information was collected in the original study. Importantly, the numbers of subjects in these tables represent initial sample sizes, before exclusion of data due to, for example, comorbidity with other severe psychopathology (e.g., bipolar disorder); furthermore, data from individual subjects can be included in several subgroups due to anxiety disorder comorbidity, and healthy control participants from samples included in multiple subgroups can be nonunique.

List of abbreviations used in tables

General

- 0 No, not investigated/information not collected.
- 1 Yes, information was collected.
- ? No information available yet.

General sample information

- GAD Patients with a diagnosis of generalized anxiety disorder.
- PD Patients with a diagnosis of panic disorder.
- SAD Patients with a diagnosis of social anxiety disorder.
- SP Patients with a diagnosis of specific phobia.
- HC Healthy control participants.
- M&F Males and females were included in the study.
- Only F Only females were included in the study.

Clinical information

- Excl This was an exclusion criterion for this sample.
- CIDI Composite Interview Diagnostic Instrument version (Kessler & Üstün, 2004).
- KSADS Schedule for Affective Disorders and Schizophrenia for School-Age Children (Ambrosini, 2000).
- MINI Mini-International Neuropsychiatric Interview (Sheehan et al., 1997)
- OTH Other diagnostic interview.

SCID Structured Clinical Interview for DSM-IV disorders (First, Spitzer, Gibbon, Williams, & Benjamin, 1998)

Anx comorb Comorbidity with other anxiety disorders.

Other comorb Comorbidity with psychopathology other than anxiety (major depressive disorder, obsessive–compulsive disorder, post-traumatic stress disorder, substance use dependence, other DSM diagnoses).

Psych med Psychotropic medication.

Questionnaires

General anxiety

STAI-trait State Trait Anxiety Inventory (Spielberger & Vagg, 1984).

ASI Anxiety Sensitivity Index (Reiss, Peterson, Gursky, & McNally, 1986)

BAI Beck Anxiety Inventory (Steer & Beck, 1997).

Social anxiety

LSAS Liebowitz Social Anxiety Scale (Heimberg et al., 1999)

Panic disorder and agoraphobia

PAS Panic and Agoraphobia Scale (Bandelow, 1995).

ACQ Agoraphobic Cognitions Questionnaire (Chambless, Caputo, Bright, & Gallagher, 1984)

PDSS Panic Disorder Severity Scale (Shear et al., 1997)

Generalized anxiety

HAM_A Hamilton Anxiety Rating Scale (Hamilton, 1959).

PSWQ Penn State Worry Questionnaire (Molina & Borkovec, 1994).

GAD_7 Generalized Anxiety Disorder 7 item scale (Spitzer, Kroenke, Williams, & Löwe, 2006)

Depression

BDI-II Beck Depression Inventory (second edition) (Beck, Steer, & Carbin, 1988)

HAM_D Hamilton Depression Rating Scale (Hamilton, 1960).

CDI Child Depression Inventory (Kovacs, 1985).

Pediatric anxiety

SCARED Screen for Child Anxiety Related Emotional Disorders (Muris et al., 1998)

Specific phobia questionnaires

Only in Table 4

DAS Dental Anxiety Scale (Corah, 1969).

DAWBA Development and Well-Being Assessment (Goodman, Ford, Richards, Gatward, & Meltzer, 2000)

DFS Dental Fear Survey (Kleinknecht, Klepac, & Alexander, 1973; Tönnies, Mehrstedt, & Eisentraut, 2002)

DSM-5-SP Dimensional Specific Phobia Scale for DSM-5 (Lebeau et al., 2012)

FDP Fear of Dental Pain Questionnaire (Van Wijk & Hoogstraten, 2003).

FEAS Fragebogen zu Ekel und Angst vor Spinnen [Anxiety and disgust towards Spiders Questionnaire] (Schaller, Gerdes, & Alpers, 2006)

FSS Fear Survey Schedule.

SNAQ Snake Phobia Questionnaire (Klorman, Weerts, Hastings, Melamed, & Lang, 1974)

SPQ Spider Phobia Questionnaire (Klorman et al., 1974)

S-RIA S-R Inventory of Anxiousness (Endler, Hunt, & Rosenstein, 1962)

MRI and genetic information

T Tesla.

T1-w-MRI T1-weighted structural MRI scan.

DTI Diffusion tensor imaging scan.

fMRI functional MRI scan (during rest or related to a task).

GE General Electric scanner.

PHI Philips scanner.

OTH Other scanner.

SIE Siemens scanner.

Material for genetics Blood or saliva collected for genetic analyses, or GWAS data available.

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CONFLICT OF INTEREST

N. J. received a research grant from Biogen, Inc., for work unrelated to this manuscript. P. M. T received a research grant from Biogen, Inc., for work unrelated to this manuscript. N. J. A. W. has received consultancy honoraria from Wyeth, Pfizer, Eli Lilly and Servier, for work unrelated to this manuscript. D. J. S. has received research grants and/or consultancy honoraria from Lundbeck, ORION Pharma and Sun, for work unrelated to this manuscript. All other authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

- Adhikari, B. M., Jahanshad, N., Shukla, D., Turner, J., Grotegerd, D., Dannlowski, U., ... Kochunov, P. (2018). A resting state fMRI analysis pipeline for pooling inference across diverse cohorts: An ENIGMA rs-fMRI protocol. *Brain Imaging and Behavior*, 13, 1453–1467. <https://doi.org/10.1007/s11682-018-9941-x>
- Alexander, L. M., Escalera, J., Ai, L., Andreotti, C., Febre, K., Mangone, A., ... Milham, M. P. (2017). An open resource for transdiagnostic research in pediatric mental health and learning disorders. *Science Data*, 4, 170181. <https://doi.org/10.1038/sdata.2017.181>
- Alonso, J., Liu, Z., Evans-Lacko, S., Sadikova, E., Sampson, N., Chatterji, S., ... Thornicroft, G. (2018). Treatment gap for anxiety disorders is global: Results of the world mental health surveys in 21 countries. *Depression and Anxiety*, 35, 195–208.
- Ambrosini, P. J. (2000). Historical development and present status of the schedule for affective disorders and schizophrenia for school-age children (K-SADS). *Journal of the American Academy of Child & Adolescent Psychiatry*, 39, 49–58.
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (Vol. DSM-5, 4th ed.). Washington, DC: American Psychiatric Association Publishing.
- Asami, T., Takaishi, M., Nakamura, R., Yoshida, H., Yoshimi, A., Whitford, T. J., ... Hirayasu, Y. (2018). Cortical thickness reductions in the middle frontal cortex in patients with panic disorder. *Journal of Affective Disorders*, 240, 199–202. <http://www.sciencedirect.com/science/article/pii/S0165032718300296>
- Assaf, M., Rabany, L., Zertuche, L., Bragdon, L., Tolin, D., Goethe, J., & Diefenbach, G. (2018). Neural functional architecture and modulation during decision making under uncertainty in individuals with generalized anxiety disorder. *Brain and Behavior: A Cognitive Neuroscience Perspective*, 8, e01015. <https://doi.org/10.1002/brb3.1015>
- Auday, E. S., & Pérez-Edgar, K. E. (2019). Limbic and prefrontal neural volume modulate social anxiety in children at temperamental risk. *Depression and Anxiety*, 36, 690–700. <https://doi.org/10.1002/da.22941>
- Aydin, S., Crone, M. R., Siebelink, B. M., Vermeiren, R. R. J. M., Numans, M. E., & Westenberg, P. M. (2020). Recognition of anxiety

- disorders in children: A cross-sectional vignette-based survey among general practitioners. *BMJ Open*, 10, e035799. <http://bmjopen.bmj.com/content/10/4/e035799.abstract>
- Balderston, N. L., Vytal, K. E., O'Connell, K., Torrisi, S., Letkiewicz, A., Ernst, M., & Grillon, C. (2017). Anxiety patients show reduced working memory related dlPFC activation during safety and threat. *Depression and Anxiety*, 34, 25–36. <http://www.ncbi.nlm.nih.gov/pubmed/27110997>
- Baldwin, D. S., & Stein, D. J. (2012). A joint European and south African research network in anxiety disorders. *Human Psychopharmacology*, 27, 4–5. <http://www.ncbi.nlm.nih.gov/pubmed/22278972>
- Ball, T. M., Ramsawh, H. J., Campbell-Sills, L., Paulus, M. P., & Stein, M. B. (2013). Prefrontal dysfunction during emotion regulation in generalized anxiety and panic disorders. *Psychological Medicine*, 43, 1475–1486. <https://www.cambridge.org/core/article/prefrontal-dysfunction-during-emotion-regulation-in-generalized-anxiety-and-panic-disorders/C34E4C308DB3F6B1BF0338EBC3AD528E>
- Bandelow, B. (1995). *Assessing the efficacy of treatments for panic disorder and agoraphobia: II. The panic and agoraphobia scale. International clinical psychopharmacology*. US: Lippincott Williams & Wilkins.
- Bandelow, B., Baldwin, D., Abelli, M., Altamura, C., Dell'Osso, B., Domschke, K., ... Riederer, P. (2016). Biological markers for anxiety disorders, OCD and PTSD – A consensus statement. Part I: Neuroimaging and genetics. *The World Journal of Biological Psychiatry*, 17, 321–365.
- Bas-Hoogendam, J. M. (2019). Commentary: Gray matter structural alterations in social anxiety disorder: A voxel-based Meta-analysis. *Frontiers in Psychiatry*, 10, 1–3. <https://www.frontiersin.org/article/10.3389/fpsy.2019.00001>
- Bas-Hoogendam, J. M., Blackford, J. U., Brühl, A. B., Blair, K. S., van der Wee, N. J. A., & Westenberg, P. M. (2016). Neurobiological candidate endophenotypes of social anxiety disorder. *Neuroscience and Biobehavioral Reviews*, 71, 362–378. <http://www.sciencedirect.com/science/article/pii/S0149763416302639>
- Bas-Hoogendam, J. M., Harrewijn, A., Tissier, R. L. M., van der Molen, M. J. W., van Steenbergen, H., van Vliet, I. M., ... Westenberg, P. M. (2018). The Leiden family lab study on social anxiety disorder: A multiplex, multigenerational family study on neurocognitive endophenotypes. *International Journal of Methods in Psychiatric Research*, 27, e1616. <https://onlinelibrary.wiley.com/doi/abs/10.1002/mpr.1616>
- Bas-Hoogendam, J. M., Roelofs, E. F., Westenberg, P. M., & van der Wee, N. J. A. (2020). Pathogenesis of SAD. In N. M. Simon, E. Hollander, B. O. Rothbaum, & D. J. Stein (Eds.), *Textbook of anxiety, trauma and OCD-related disorders* (3rd ed., pp. 429–444). Washington DC: The American Psychiatric Association Publishing.
- Bas-Hoogendam, J. M., van Steenbergen, H., Blackford, J. U., Tissier, R. L. M., van der Wee, N. J. A., & Westenberg, P. M. (2019). Impaired neural habituation to neutral faces in families genetically enriched for social anxiety disorder. *Depression and Anxiety*, 36, 1143–1153. <https://doi.org/10.1002/da.22962>
- Bas-Hoogendam, J. M., van Steenbergen, H., Pannekoek, J. N., Fouche, J.-P., Lochner, C., Hattinck, C. J., ... van der Wee, N. J. A. (2017b). Voxel-based morphometry multi-center mega-analysis of brain structure in social anxiety disorder. *NeuroImage: Clinical*, 16, 678–688. <http://www.sciencedirect.com/science/article/pii/S2213158217301912>
- Bas-Hoogendam, J. M., van Steenbergen, H., Pannekoek, J. N., Fouche, J.-P., Lochner, C., Hattinck, C. J., ... van der Wee, N. J. A. (2017a). 16 – Sample size matters: A voxel-based morphometry multi-center mega-analysis of gray matter volume in social anxiety disorder. *Biological Psychiatry*, 81, S7–S8. http://www.sciencedirect.com/science/article/pii/S0006322317301476?dgcid=raven_sd_via_email
- Bas-Hoogendam, J. M., van Steenbergen, H., Tissier, R. L. M., Houwing-Duistermaat, J. J., Westenberg, P. M., & van der Wee, N. J. A. (2018). Subcortical brain volumes, cortical thickness and cortical surface area in families genetically enriched for social anxiety disorder - a multiplex multigenerational neuroimaging study. *eBioMedicine*, 36, 410–428. <https://doi.org/10.1016/j.ebiom.2018.08.048>
- Bas-Hoogendam, J. M., van Steenbergen, H., Tissier, R. L. M., van der Wee, N. J. A., & Westenberg, P. M. (2019, in press). Altered neurobiological processing of unintentional social norm violations: A multiplex, multigenerational fMRI study on social anxiety endophenotypes. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. <https://doi.org/10.1016/j.bpsc.2019.03.003>
- Bas-Hoogendam, J. M., van Steenbergen, H., van der Wee, N. J. A., & Westenberg, P. M. (2020). Amygdala hyperreactivity to faces conditioned with a social-evaluative meaning - a multiplex, multigenerational fMRI study on social anxiety endophenotypes. *NeuroImage: Clinical*, 26, 102247.
- Battaglia, M., Zanoni, A., Taddei, M., Giorda, R., Bertoletti, E., Lampis, V., ... Tettamanti, M. (2012). Cerebral responses to emotional expressions and the development of social anxiety disorder: A preliminary longitudinal study. *Depression and Anxiety*, 29, 54–61. <http://www.ncbi.nlm.nih.gov/pubmed/21898716>
- Baxter, A. J., Vos, T., Scott, K. M., Ferrari, A. J., & Whiteford, H. A. (2014). The global burden of anxiety disorders in 2010. *Psychological Medicine*, 44, 1–12. http://journals.cambridge.org/abstract_S0033291713003243
- Bearden, C. E., & Freimer, N. B. (2006). Endophenotypes for psychiatric disorders: Ready for primetime? *Trends in Genetics*, 22, 306–313. <http://www.ncbi.nlm.nih.gov/pubmed/16697071>
- Bearden, C. E., & Thompson, P. M. (2017). Emerging global initiatives in Neurogenetics: The enhancing neuroimaging genetics through Meta-analysis (ENIGMA) consortium. *Neuron*, 94, 232–236. <http://www.sciencedirect.com.ezproxy.leidenuniv.nl:2048/science/article/pii/S0896627317302453>
- Beauchaine, T. P., & Constantino, J. N. (2017). Redefining the endophenotype concept to accommodate transdiagnostic vulnerabilities and etiological complexity. *Biomarkers in Medicine*, 11, 769–780. <https://www.futuremedicine.com/doi/10.2217/bmm-2017-0002>
- Beauchaine, T. P., Neuhaus, E., Brenner, S. L., & Gatzke-Kopp, L. (2008). Ten good reasons to consider biological processes in prevention and intervention research. *Development and Psychopathology*, 20, 745–774. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2690981&tool=pmcentrez&rendertype=abstract>
- Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck depression inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, 8, 77–100. <http://www.sciencedirect.com/science/article/pii/0272735888900505>
- Beesdo, K., Bittner, A., Pine, D. S., Stein, M. B., Höfler, M., Lieb, R., & Wittchen, H.-U. (2007). Incidence of social anxiety disorder and the consistent risk for secondary depression in the first three decades of life. *Archives of General Psychiatry*, 64, 903–912. <http://archpsyc.jamanetwork.com/article.aspx?articleid=482391>
- Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and anxiety disorders in children and adolescents: Developmental issues and implications for DSM-V. *Psychiatra Clinica*, 32, 483–524. <https://doi.org/10.1016/j.psc.2009.06.002>
- Beesdo-Baum, K., & Knappe, S. (2012). Developmental epidemiology of anxiety disorders. *Child and Adolescent Psychiatric Clinics of North America*, 21, 457–478. <http://www.ncbi.nlm.nih.gov/pubmed/22800989>
- Björkstrand, J., Agren, T., Åhs, F., Frick, A., Larsson, E.-M., Hjorth, O., ... Fredrikson, M. (2016). Disrupting reconsolidation attenuates long-term fear memory in the human amygdala and facilitates approach behavior. *Current Biology*, 26, 2690–2695. <https://doi.org/10.1016/j.cub.2016.08.022>
- Blackford, J. U. (2017). Leveraging statistical methods to improve validity and reproducibility of research findings. *JAMA Psychiatry*, 74, 119–120. <http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/jamapsychiatry.2016.3730>
- Blackford, J. U., Allen, A. H., Cowan, R. L., & Avery, S. N. (2013). Amygdala and hippocampus fail to habituate to faces in individuals with an

- inhibited temperament. *Social Cognitive and Affective Neuroscience*, 8, 143–150. <http://scan.oxfordjournals.org/content/8/2/143.abstract>
- Blackford, J. U., Avery, S. N., Cowan, R. L., Shelton, R. C., & Zald, D. H. (2011). Sustained amygdala response to both novel and newly familiar faces characterizes inhibited temperament. *Social Cognitive and Affective Neuroscience*, 6, 621–629. <http://scan.oxfordjournals.org/content/6/5/621.short>
- Blackford, J. U., Clauss, J. A., & Benningfield, M. M. (2018). The neurobiology of behavioral inhibition as a developmental mechanism BT - behavioral inhibition: Integrating theory, research, and clinical perspectives. In K. Pérez-Edgar & N. A. Fox (Eds.), *Behavioral inhibition* (pp. 113–134). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-98077-5_6
- Blackford, J. U., & Pine, D. S. (2012). Neural substrates of childhood anxiety disorders: A review of neuroimaging findings. *Child and Adolescent Psychiatric Clinics of North America*, 21, 501–525. <http://www.sciencedirect.com/science/article/pii/S1056499312000375>
- Blair, K. S., Aloï, J., Crum, K., Meffert, H., White, S. F., Taylor, B. K., ... Blair, R. J. (2019). Association of Different Types of childhood maltreatment with emotional responding and response control among youths. *JAMA Network Open*, 2, e194604–e194604. <https://doi.org/10.1001/jamanetworkopen.2019.4604>
- Blair, R. J. R., White, S. F., Tyler, P. M., Johnson, K., Lukoff, J., Thornton, L. C., ... Blair, K. S. (2019). Threat responsiveness as a function of Cannabis and alcohol use disorder severity. *Journal of Child and Adolescent Psychopharmacology*, 29, 526–534. <https://doi.org/10.1089/cap.2019.0004>
- Boedhoe, P. S. W., Schmaal, L., Abe, Y., Ameis, S. H., Arnold, P. D., Batistuzzo, M. C., ... van den Heuvel, O. A. (2017). Distinct subcortical volume alterations in pediatric and adult OCD: A worldwide Meta- and mega-analysis. *The American Journal of Psychiatry*, 174, 60–69. <http://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2016.16020201>
- Boedhoe, P. S. W., van Rooij, D., Hoogman, M., Twisk, J. W. R., Schmaal, L., Abe, Y., ... van den Heuvel, O. A. (2019). Subcortical brain volume, regional cortical thickness and cortical surface area across attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD). *bioRxiv*, 673012. <http://biorxiv.org/content/early/2019/06/18/673012.abstract>
- Boehme, S., Mohr, A., Becker, M. P., Miltner, W. H., & Straube, T. (2014). Area-dependent time courses of brain activation during video-induced symptom provocation in social anxiety disorder. *Biology of Mood & Anxiety Disorders*, 4, 6. <http://www.biolmoodanxietydisord.com/content/4/1/6/abstract>
- Boehme, S., Ritter, V., Tefikow, S., Stangier, U., Strauss, B., Miltner, W. H. R., & Straube, T. (2014). Brain activation during anticipatory anxiety in social anxiety disorder. *Social Cognitive and Affective Neuroscience*, 9, 1413–1418. <http://scan.oxfordjournals.org/content/early/2013/09/11/scan.nst129.abstract.html?papetoc>
- Brouwer, R. M., Klein, M., Grasby, K. L., Schnack, H. G., Jahanshad, N., Teeuw, J., ... Pol, H.E.H. (2020). Dynamics of Brain Structure and its Genetic Architecture over the Lifespan. *bioRxiv*. <https://doi.org/10.1101/2020.04.24.031138>
- Brühl, A. B., Delsignore, A., Komossa, K., & Weidt, S. (2014). Neuroimaging in social anxiety disorder—a meta-analytic review resulting in a new neuro-functional model. *Neuroscience and Biobehavioral Reviews*, 47, 260–280. <http://www.sciencedirect.com/science/article/pii/S0149763414002012>
- Bruin, W., Denys, D., & van Wingen, G. (2019). Diagnostic neuroimaging markers of obsessive-compulsive disorder: Initial evidence from structural and functional MRI studies. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 91, 49–59. <http://www.sciencedirect.com/science/article/pii/S0278584618303105>
- Buff, C., Brinkmann, L., Neumeister, P., Feldker, K., Heitmann, C., Gathmann, B., ... Straube, T. (2016). Specifically altered brain responses to threat in generalized anxiety disorder relative to social anxiety disorder and panic disorder. *NeuroImage: Clinical*, 12, 698–706. <http://www.sciencedirect.com/science/article/pii/S221315821630184X>
- Bulley, A., Miloyan, B., Brilot, B., Gullo, M. J., & Suddendorf, T. (2016). An evolutionary perspective on the co-occurrence of social anxiety disorder and alcohol use disorder. *Journal of Affective Disorders*, 196, 62–70. <http://www.sciencedirect.com/science/article/pii/S0165032715309630>
- Calkins, M. E., Merikangas, K. R., Moore, T. M., Burstein, M., Behr, M. A., Satterthwaite, T. D., ... Gur, R. E. (2015). The Philadelphia neurodevelopmental cohort: Constructing a deep phenotyping collaborative. *Journal of Child Psychology and Psychiatry*, 56, 1356–1369. <https://doi.org/10.1111/jcpp.12416>
- Calleo, J., Stanley, M. A., Greisinger, A., Wehmanen, O., Johnson, M., Novy, D., ... Kunik, M. (2009). Generalized anxiety disorder in older medical patients: Diagnostic recognition, mental health management and service utilization. *Journal of Clinical Psychology in Medical Settings*, 16, 178–185. <https://doi.org/10.1007/s10880-008-9144-5>
- Campbell-Sills, L., Simmons, A. N., Lovero, K. L., Rochlin, A. A., Paulus, M. P., & Stein, M. B. (2011). Functioning of neural systems supporting emotion regulation in anxiety-prone individuals. *NeuroImage*, 54, 689–696. <https://doi.org/10.1016/j.neuroimage.2010.07.041>
- Canu, E., Kostić, M., Agosta, F., Munjiza, A., Ferraro, P. M., Pesic, D., ... Filippi, M. (2015). Brain structural abnormalities in patients with major depression with or without generalized anxiety disorder comorbidity. *Journal of Neurology*, 262, 1255–1265. <https://doi.org/10.1007/s00415-015-7701-z>
- Caouette, J. D., & Guyer, A. E. (2014). Gaining insight into adolescent vulnerability for social anxiety from developmental cognitive neuroscience. *Developmental Cognitive Neuroscience*, 8, 65–76. <http://www.sciencedirect.com/science/article/pii/S1878929313000625>
- Carpenter, K. L. H., Angold, A., Chen, N.-K., Copeland, W. E., Gaur, P., Pelphrey, K., ... Egger, H. L. (2015). Preschool anxiety disorders predict different patterns of amygdala-prefrontal connectivity at school-age. *PLoS ONE*, 10, e0116854. <https://doi.org/10.1371/journal.pone.0116854>
- Casey, B. J., Cannonier, T., Conley, M. I., Cohen, A. O., Barch, D. M., Heitzeg, M. M., ... Dale, A. M. (2018). The adolescent brain cognitive development (ABCD) study: Imaging acquisition across 21 sites. *Developmental Cognitive Neuroscience*, 32, 43–54. <http://www.sciencedirect.com/science/article/pii/S1878929317301214>
- Cha, J., Greenberg, T., Song, I., Blair Simpson, H., Posner, J., & Mujica-Parodi, L. R. (2016). Abnormal hippocampal structure and function in clinical anxiety and comorbid depression. *Hippocampus*, 26, 545–553. <https://doi.org/10.1002/hipo.22566>
- Chambless, D. L., Caputo, G. C., Bright, P., & Gallagher, R. (1984). Assessment of fear of fear in agoraphobics: The body sensations questionnaire and the agoraphobic cognitions questionnaire. *Journal of Consulting and Clinical Psychology*, 52, 1090–1097.
- Chapdelaine, A., Carrier, J.-D., Fournier, L., Duhoux, A., & Roberge, P. (2018). Treatment adequacy for social anxiety disorder in primary care patients. *PLoS ONE*, 13, e0206357. <https://doi.org/10.1371/journal.pone.0206357>
- Ching, C. R. K., Gutman, B. A., Sun, D., Villalon Reina, J., Ragothaman, A., Isaev, D., ... Bearden, C. E. (2020). Mapping subcortical brain alterations in 22q11.2 deletion syndrome: Effects of deletion size and convergence with idiopathic neuropsychiatric illness. *The American Journal of Psychiatry*. <https://doi.org/10.1176/appi.ajp.2019.19060583>
- Clauss, J. A., Avery, S. N., Vanderklok, R. M., Rogers, B. P., Cowan, R. L., Benningfield, M. M., & Blackford, J. U. (2014). Neurocircuitry underlying risk and resilience to social anxiety disorder. *Depression and Anxiety*, 31, 822–833. <http://www.ncbi.nlm.nih.gov/pubmed/24753211>
- Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 51, 1066–1075. <http://www.sciencedirect.com/science/article/pii/S0890856712005928>

- Clauss, J. A., Seay, A. L., Vanderklok, R. M., Avery, S., Cao, A., Cowan, R. L., ... Blackford, J. U. (2014). Structural and functional bases of inhibited temperament. *Social Cognitive and Affective Neuroscience*, 9, 2049–2058. <http://scan.oxfordjournals.org/content/early/2014/01/19/scan.nsu019.abstract>
- Corah, N. L. (1969). Development of a dental anxiety scale. *Journal of Dental Research*, 48, 596. <https://doi.org/10.1177/00220345690480041801>
- Córdova-Palomera, A., Fatjó-Vilas, M., Falcón, C., Bargalló, N., Alemany, S., Crespo-Facorro, B., ... Fañanás, L. (2015). Birth weight and adult IQ, but not anxious-depressive psychopathology, are associated with cortical surface area: A study in twins. *PLoS ONE*, 10, e0129616. <https://doi.org/10.1371/journal.pone.0129616>
- Cremers, H. R., & Roelofs, K. (2016). Social anxiety disorder: A critical overview of neurocognitive research. *Wiley Interdisciplinary Reviews: Cognitive Science*, 7, 218–232. <http://www.ncbi.nlm.nih.gov/pubmed/27240280>
- Cremers, H. R., Veer, I. M., Spinhoven, P., Rombouts, S. A. R. B., & Roelofs, K. (2015). Neural sensitivity to social reward and punishment anticipation in social anxiety disorder. *Frontiers in Behavioral Neuroscience*, 8, 1–9. <http://journal.frontiersin.org/article/10.3389/fnbeh.2014.00439/abstract>
- Cremers, H. R., Veer, I. M., Spinhoven, P., Rombouts, S. A. R. B., Yarkoni, T., Wager, T. D., & Roelofs, K. (2014). Altered cortical-amygdala coupling in social anxiety disorder during the anticipation of giving a public speech. *Psychological Medicine*, 45, 1521–1549. http://journals.cambridge.org/abstract_S0033291714002657
- Curtis, K., Stewart, C. J., Robinson, M., Molfese, D. L., Gosnell, S. N., Kosten, T. R., ... Salas, R. (2019). Insular resting state functional connectivity is associated with gut microbiota diversity. *The European Journal of Neuroscience*, 50, 2446–2452. <https://doi.org/10.1111/ejn.14305>
- Dannlowski, U., Grabe, H. J., Wittfeld, K., Klaus, J., Konrad, C., Grotegerd, D., ... Baune, B. T. (2015). Multimodal imaging of a tescalcin (TESC)-regulating polymorphism (rs7294919)-specific effects on hippocampal gray matter structure. *Molecular Psychiatry*, 20, 398–404. <https://doi.org/10.1038/mp.2014.39>
- Dannlowski, U., Kugel, H., Grotegerd, D., Redlich, R., Opel, N., Dohm, K., ... Baune, B. T. (2016). Disadvantage of social sensitivity: Interaction of oxytocin receptor genotype and child maltreatment on brain structure. *Biological Psychiatry*, 80, 398–405. <https://doi.org/10.1016/j.biopsych.2015.12.010>
- Diefenbach, G. J., Bragdon, L. B., Zertuche, L., Hyatt, C. J., Hallion, L. S., Tolin, D. F., ... Assaf, M. (2016). Repetitive transcranial magnetic stimulation for generalised anxiety disorder: A pilot randomised, double-blind, sham-controlled trial. *The British Journal of Psychiatry*, 209, 222–228. <https://www.cambridge.org/core/article/repetitive-transcranial-magnetic-stimulation-for-generalised-anxiety-disorder-a-pilot-randomised-double-blind-shamcontrolled-trial/03731E1D35DE6F96EA42B97B56C40F85>
- Doruyter, A., Lochner, C., Jordaan, G. P., Stein, D. J., Dupont, P., & Warwick, J. M. (2016). Resting functional connectivity in social anxiety disorder and the effect of pharmacotherapy. *Psychiatry Research: Neuroimaging*, 251, 34–44. <http://linkinghub.elsevier.com/retrieve/pii/S0925492715301517>
- Dresler, T., Attar, C. H., Spitzer, C., Löwe, B., Deckert, J., Büchel, C., ... Fallgatter, A. J. (2012). Neural correlates of the emotional Stroop task in panic disorder patients: An event-related fMRI study. *Journal of Psychiatric Research*, 46, 1627–1634. <http://www.sciencedirect.com/science/article/pii/S0022395612002749>
- Dresler, T., Ehlis, A.-C., Hindi Attar, C., Ernst, L. H., Tupak, S. V., Hahn, T., ... Fallgatter, A. J. (2012). Reliability of the emotional Stroop task: An investigation of patients with panic disorder. *Journal of Psychiatric Research*, 46, 1243–1248. <http://www.sciencedirect.com/science/article/pii/S0022395612001884>
- Dresler, T., Hahn, T., Plichta, M. M., Ernst, L. H., Tupak, S. V., Ehlis, A.-C., ... Fallgatter, A. J. (2011). Neural correlates of spontaneous panic attacks. *Journal of Neural Transmission*, 118, 263–269. <https://doi.org/10.1007/s00702-010-0540-2>
- Durstewitz, D., Koppe, G., & Meyer-Lindenberg, A. (2019). Deep neural networks in psychiatry. *Molecular Psychiatry*, 24, 1583–1598. <https://doi.org/10.1038/s41380-019-0365-9>
- Duval, E., Javanbakht, A., & Liberzon, I. (2015). Neural circuits in anxiety and stress disorders: A focused review. *Therapeutics and Clinical Risk Management*, 11, 115–126.
- Edwards, J., Thind, A., Stranges, S., Chiu, M., & Anderson, K. K. (2019). Concordance between health administrative data and survey-derived diagnoses for mood and anxiety disorders. *Acta Psychiatrica Scandinavica*, 141, 385–395. <https://doi.org/10.1111/acps.13143>
- Endler, N. S., Hunt, J. M., & Rosenstein, A. J. (1962). An S-R inventory of anxiousness. *Psychological Monographs: General and Applied*, 76, 1–33.
- Erhardt, A., Akula, N., Schumacher, J., Czamara, D., Karbalai, N., Müller-Myhok, B., ... Binder, E. B. (2012). Replication and meta-analysis of TMEM132D gene variants in panic disorder. *Translational Psychiatry*, 2, e156–e156. <https://doi.org/10.1038/tp.2012.85>
- Etkin, A. (2019). A reckoning and research agenda for neuroimaging in psychiatry. *The American Journal of Psychiatry*, 176, 507–511. <https://doi.org/10.1176/appi.ajp.2019.19050521>
- Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *The American Journal of Psychiatry*, 164, 1476–1488. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3318959&tool=pmcentrez&rendertype=abstract>
- Feldker, K., Heitmann, C. Y., Neumeister, P., Bruchmann, M., Vibrans, L., Zwitterlood, P., & Straube, T. (2016). Brain responses to disorder-related visual threat in panic disorder. *Human Brain Mapping*, 37, 4439–4453. <https://doi.org/10.1002/hbm.23320>
- Feldker, K., Heitmann, C. Y., Neumeister, P., Tupak, S. V., Schrammen, E., Moeck, R., ... Straube, T. (2017). Transdiagnostic brain responses to disorder-related threat across four psychiatric disorders. *Psychological Medicine*, 47, 730–743. <https://www.cambridge.org/core/article/transdiagnostic-brain-responses-to-disorder-related-threat-across-four-psychiatric-disorders/B53A02647B8258019725E4E569086B83>
- Fernandez, E., Salem, D., Swift, J. K., & Ramtahal, N. (2015). Meta-analysis of dropout from cognitive behavioral therapy: Magnitude, timing, and moderators. *Journal of Consulting and Clinical Psychology*, 83, 1108–1122.
- Fineberg, N. A., Haddad, P. M., Carpenter, L., Gannon, B., Sharpe, R., Young, A. H., ... Sahakian, B. J. (2013). The size, burden and cost of disorders of the brain in the UK. *Journal of Psychopharmacology*, 27, 761–770. <http://jop.sagepub.com/content/27/9/761>
- First, M., Spitzer, R., Gibbon, M., Williams, J., & Benjamin, L. (1998). *Structured clinical interview for DSM-IV axis I disorders (SCID) version 2.0*. New York, NY: Biometrics Research Department, New York State Psychiatric Institute.
- Fonzo, G. A., Ramsawh, H. J., Flagan, T. M., Sullivan, S. G., Letamendi, A., Simmons, A. N., ... Stein, M. B. (2015). Common and disorder-specific neural responses to emotional faces in generalised anxiety, social anxiety and panic disorders. *The British Journal of Psychiatry*, 206, 206–215. <http://bjp.rcpsych.org/content/early/2015/01/02/bjp.bp.114.149880.abstract>
- Fonzo, G. A., Ramsawh, H. J., Flagan, T. M., Sullivan, S. G., Simmons, A. N., Paulus, M. P., & Stein, M. B. (2014). Cognitive-behavioral therapy for generalized anxiety disorder is associated with attenuation of limbic activation to threat-related facial emotions. *Journal of Affective Disorders*, 169, 76–85. <http://www.sciencedirect.com/science/article/pii/S0165032714004698>
- Fox, A. S., & Kalin, N. H. (2014). A translational neuroscience approach to understanding the development of social anxiety disorder and its pathophysiology. *The American Journal of Psychiatry*, 171, 1162–1173. <http://www.ncbi.nlm.nih.gov/pubmed/25157566>

- Fu, X., Taber-Thomas, B. C., & Pérez-Edgar, K. (2017). Frontolimbic functioning during threat-related attention: Relations to early behavioral inhibition and anxiety in children. *Biological Psychology*, 122, 98–109. <http://www.sciencedirect.com/science/article/pii/S0301051115300491>
- Furmark, T. (2002). Social phobia: Overview of community surveys. *Acta Psychiatrica Scandinavica*, 105, 84–93. <https://www.ncbi.nlm.nih.gov/pubmed/11939957>
- Glahn, D. C., Curran, J. E., Winkler, A. M., Carless, M. A., Kent, J. W., Charlesworth, J. C., ... Blangero, J. (2012). High dimensional endophenotype ranking in the search for major depression risk genes. *Biological Psychiatry*, 71, 6–14. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3230692&tool=pmcentrez&rendertype=abstract>
- Glahn, D. C., Thompson, P. M., & Blangero, J. (2007). Neuroimaging endophenotypes: Strategies for finding genes influencing brain structure and function. *Human Brain Mapping*, 28, 488–501. <http://www.ncbi.nlm.nih.gov/pubmed/17440953>
- Gloster, A. T., Wittchen, H. U., Einsle, F., Höfler, M., Lang, T., Helbig-Lang, S., ... Arolt, V. (2009). Mechanism of action in CBT (MAC): Methods of a multi-center randomized controlled trial in 369 patients with panic disorder and agoraphobia. *European Archives of Psychiatry and Clinical Neuroscience*, 259, 155–166. <https://doi.org/10.1007/s00406-009-0065-6>
- Goddard, A. W. (2017). The neurobiology of panic: A chronic stress disorder. *Chronic Stress*, 1, 2470547017736038. <https://doi.org/10.1177/2470547017736038>
- Gold, A. L., Abend, R., Britton, J. C., Behrens, B., Farber, M. J., Ronkin, E. G., ... Pine, D. S. (2020). Age differences in the neural correlates of anxiety disorders: An fMRI study of response to learned threat. *The American Journal of Psychiatry*, 177, 454–463.
- Gold, A. L., Steuber, E. R., White, L. K., Pacheco, J., Sachs, J. F., Pagliaccio, D., ... Pine, D. S. (2017). Cortical thickness and subcortical gray matter volume in pediatric anxiety disorders. *Neuropsychopharmacology*, 42, 2423–2433. <http://www.ncbi.nlm.nih.gov/pubmed/28436445>
- Gong, Q., Scarpazza, C., Dai, J., He, M., Xu, X., Shi, Y., ... Mechelli, A. (2019). A transdiagnostic neuroanatomical signature of psychiatric illness. *Neuropsychopharmacology*, 44, 869–875. <https://doi.org/10.1038/s41386-018-0175-9>
- Goodman, R., Ford, T., Richards, H., Gatward, R., & Meltzer, H. (2000). The development and well-being assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. *Journal of Child Psychology and Psychiatry*, 41, 645–655. <https://doi.org/10.1111/j.1469-7610.2000.tb02345.x>
- Gorka, S. M., Young, C. B., Klumpp, H., Kennedy, A. E., Francis, J., Ajilore, O., ... Phan, K. L. (2019). Emotion-based brain mechanisms and predictors for SSRI and CBT treatment of anxiety and depression: A randomized trial. *Neuropsychopharmacology*, 44, 1639–1648. <https://doi.org/10.1038/s41386-019-0407-7>
- Gosnell, S. N., Meyer, M. J., Jennings, C., Ramirez, D., Schmidt, J., Oldham, J., & Salas, R. (2020). Hippocampal volume in psychiatric diagnoses: Should psychiatry biomarker research account for comorbidities? *Chronic Stress*, 4, 1–10.
- Gottschalk, M. G., & Domschke, K. (2016). Novel developments in genetic and epigenetic mechanisms of anxiety. *Current Opinion in Psychiatry*, 29(1), 32–38. <http://ovidsp.tx.ovid.com/sp-3.18.0b/ovidweb.cgi?Q52=434f4e1a73d37e8cff7fb618affc25b161f76a9259dddab0c7659c5f36a932289521dd5b6485f86e8dcb2c80338aba14fbd25fbc9b450edde6cae6c665a0b3bad4371069cf20f055f40f009670b538f390b368090ec81cf66a3bd8665d0346a7de0803b23e>
- Gottschalk, M. G., Richter, J., Ziegler, C., Schiele, M. A., Mann, J., Geiger, M. J., ... Domschke, K. (2019). Orexin in the anxiety spectrum: Association of a HCRTR1 polymorphism with panic disorder/agoraphobia, CBT treatment response and fear-related intermediate phenotypes. *Translational Psychiatry*, 9, 75. <https://doi.org/10.1038/s41398-019-0415-8>
- Grasby, K. L., Jahanshad, N., Painter, J. N., Colodro-Conde, L., Bralten, J., Hibar, D. P., ... Medland, S. E. (2020). The genetic architecture of the human cerebral cortex. *Science* (80-), 367, eaay6690. <http://science.sciencemag.org/content/367/6484/eaay6690.abstract>
- Grillon, C., Robinson, O. J., Cornwell, B., & Ernst, M. (2019). Modeling anxiety in healthy humans: A key intermediate bridge between basic and clinical sciences. *Neuropsychopharmacology*, 44, 1999–2010. <https://doi.org/10.1038/s41386-019-0445-1>
- Groenewold, N., Bas-Hoogendam, J. M., Amod, A. R., van Velzen, L., Aghajani, M., Filippi, C., ... van der Wee, N. J. A. (2018). F27. Subcortical volumes in social anxiety disorder: Preliminary results from enigma-anxiety. *Biological Psychiatry*, 83, S247–S248. <http://www.sciencedirect.com/science/article/pii/S000632231830742X>
- Grupe, D. W., & Nitschke, J. B. (2013). Uncertainty and anticipation in anxiety: An integrated neurobiological and psychological perspective. *Nature Reviews. Neuroscience*, 14, 488–501. <https://doi.org/10.1038/nrn3524>
- Gutman BA, Jahanshad N, Ching CRK, Wang Y, Kochunov P V, Nichols TE, Thompson PM (2015): Medial demons registration localizes the degree of genetic influence over subcortical shape variability: An N= 1480 meta-analysis. Paper presented at 2015 IEEE 12th International Symposium on Biomedical Imaging (ISBI) pp 1402–1406.
- Gutman BA, Wang Y, Rajagopalan P, Toga AW, Thompson PM (2012): Shape matching with medial curves and 1-D group-wise registration. Paper presented at 2012 9th IEEE International Symposium on Biomedical Imaging (ISBI) pp 716–719.
- Hamilton, M. (1959). The assessment of anxiety states by rating. *The British Journal of Medical Psychology*, 32, 50–55. <https://doi.org/10.1111/j.2044-8341.1959.tb00467.x>
- Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, 23, 56–62. <https://www.ncbi.nlm.nih.gov/pubmed/14399272>
- Harrewijn A, Cardinale EM, Groenewold N, Bas-Hoogendam JM, Aghajani M, ENIGMA-GAD WG, Veltman DJ, Thompson PM, Steinh DJ, Wee NJA van der, Winkler AM, Pine DS (2020);ENIGMA Mega-Analysis of Brain Structure in Generalized Anxiety Disorder. In: 2020 SOBP Annual Meeting.
- Hasler, G., Drevets, W. C., Gould, T. D., Gottesman, I. I., & Manji, H. K. (2006). Toward constructing an endophenotype strategy for bipolar disorders. *Biological Psychiatry*, 60, 93–105. <http://www.sciencedirect.com/science/article/pii/S0006322305013934>
- Heeren, A., Dricot, L., Billieux, J., Philippot, P., Grynberg, D., de Timary, P., & Muraige, P. (2017). Correlates of social exclusion in social anxiety disorder: An fMRI study. *Scientific Reports*, 7, 260. <http://www.ncbi.nlm.nih.gov/pubmed/28325901>
- Heimberg, R. G., Horner, K. J., Juster, H. R., Safren, S. A., Brown, E. J., Schneier, F. R., & Liebowitz, M. R. (1999). Psychometric properties of the Liebowitz social anxiety scale. *Psychological Medicine*, 29, 199–212. http://journals.cambridge.org/abstract_S0033291798007879
- Heinig, I., Pittig, A., Richter, J., Hummel, K., Alt, I., Dickhöver, K., ... Wittchen, H.-U. (2017). Optimizing exposure-based CBT for anxiety disorders via enhanced extinction: Design and methods of a multi-centre randomized clinical trial. *International Journal of Methods in Psychiatric Research*, 26, e1560. <https://doi.org/10.1002/mpr.1560>
- Heitmann, C. Y., Feldker, K., Neumeister, P., Zepp, B. M., Peterburs, J., Zwitterlood, P., & Straube, T. (2016). Abnormal brain activation and connectivity to standardized disorder-related visual scenes in social anxiety disorder. *Human Brain Mapping*, 37, 1559–1572. <http://www.ncbi.nlm.nih.gov/pubmed/26806013>
- Henderson, H. A., Pine, D. S., & Fox, N. A. (2015). Behavioral inhibition and developmental risk: A dual-processing perspective. *Neuropsychopharmacology*, 40, 207–224. <https://doi.org/10.1038/npp.2014.189>
- Hilbert, K., Evens, R., Isabel Maslowski, N., Wittchen, H.-U., & Lueken, U. (2015). Neurostructural correlates of two subtypes of specific phobia: A voxel-based morphometry study. *Psychiatry Research: Neuroimaging*,

- 231, 168–175. <http://www.sciencedirect.com/science/article/pii/S0925492714003308>
- Hilbert, K., Lueken, U., & Beesdo-Baum, K. (2014). Neural structures, functioning and connectivity in generalized anxiety disorder and interaction with neuroendocrine systems: A systematic review. *Journal of Affective Disorders*, 158, 114–126. <http://www.sciencedirect.com/science/article/pii/S0165032714000500>
- Hilbert, K., Pine, D. S., Muehlhan, M., Lueken, U., Steudte-Schmiedgen, S., & Beesdo-Baum, K. (2015). Gray and white matter volume abnormalities in generalized anxiety disorder by categorical and dimensional characterization. *Psychiatry Research*, 234, 314–320. <http://www.sciencedirect.com/science/article/pii/S0925492715301244>
- Ho, T. C., Gutman, B., Pozzi, E., Grabe, H. J., Hosten, N., Wittfeld, K., ... Schmaal, L. (2019). Subcortical shape alterations in major depressive disorder: Findings from the ENIGMA major depressive disorder working group. *bioRxiv*, 534370. <http://biorxiv.org/content/early/2019/02/01/534370.abstract>
- Howells, F. M., Hattingh, C. J., Syal, S., Breet, E., Stein, D. J., & Lochner, C. (2015). H-magnetic resonance spectroscopy in social anxiety disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 58, 97–104. <http://www.sciencedirect.com/science/article/pii/S0278584614002450>
- Insel, T. R. (2014). The NIMH research domain criteria (RDoC) project: Precision medicine for psychiatry. *The American Journal of Psychiatry*, 171, 395–397. <http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2014.14020138>
- Janiri, D., Moser, D. A., Doucet, G. E., Luber, M. J., Rasgon, A., Lee, W. H., ... Frangou, S. (2019). Shared neural phenotypes for mood and anxiety disorders: A Meta-analysis of 226 task-related functional imaging studies. *JAMA Psychiatry*, 77, 1–8. <https://doi.org/10.1001/jamapsychiatry.2019.3351>
- Kalin, N. H. (2017). Mechanisms underlying the early risk to develop anxiety and depression: A translational approach. *European Neuropsychopharmacology*, 27, 543–553. <http://www.sciencedirect.com.ezproxy.leidenuniv.nl:2048/science/article/pii/S0924977X17301864>
- Kang, E.-K., Lee, K. S., & Lee, S.-H. (2017). Reduced cortical thickness in the temporal pole, insula, and pars triangularis in patients with panic disorder. *Yonsei Medical Journal*, 58, 1018–1024. <http://synapse.koreamed.org/DOIx.php?id=10.3349%2Fymj.2017.58.5.1018>
- Karim, H., Tudorascu, D. L., Aizenstein, H., Walker, S., Good, R., & Andreescu, C. (2016). Emotion reactivity and cerebrovascular burden in late-life GAD: A neuroimaging study. *The American Journal of Geriatric Psychiatry*, 24, 1040–1050. <http://www.sciencedirect.com/science/article/pii/S106474811630183X>
- Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J., Chatterji, S., Lee, S., Ormel, J., ... Wang, P. S. (2009). The global burden of mental disorders: An update from the WHO world mental health (WMH) surveys. *Epidemiologia e Psichiatria Sociale*, 18, 23–33. <https://www.cambridge.org/core/article/global-burden-of-mental-disorders-an-update-from-the-who-world-mental-health-wmh-surveys/FCE4DE10C9FB1A9FFDDBA3C5264F445>
- Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, 62, 593–602. <http://archpsyc.jamanetwork.com/article.aspx?articleid=208678>
- Kessler, R. C., & Üstün, T. B. (2004). The world mental health (WMH) survey initiative version of the World Health Organization (WHO) composite international diagnostic interview (CIDI). *International Journal of Methods in Psychiatric Research*, 13, 93–121. <http://www.ncbi.nlm.nih.gov/pubmed/15297906>
- Kim, B., Kim, J. H., Kim, M.-K., Lee, K. S., Kim, Y., Choi, T. K., ... Lee, S.-H. (2014). Frontal white matter alterations in short-term medicated panic disorder patients without comorbid conditions: A diffusion tensor imaging study. *PLoS ONE*, 9, e95279. <https://doi.org/10.1371/journal.pone.0095279>
- Kim, Y. K., & Yoon, H. K. (2018). Common and distinct brain networks underlying panic and social anxiety disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 80, 115–122. <https://doi.org/10.1016/j.pnpbp.2017.06.017>
- Kircher, T., Arolt, V., Jansen, A., Pyka, M., Reinhardt, I., Kellermann, T., ... Straube, B. (2013). Effect of cognitive-behavioral therapy on neural correlates of fear conditioning in panic disorder. *Biological Psychiatry*, 73, 93–101. <http://www.sciencedirect.com/science/article/pii/S0006322312006701>
- Kircher, T., Wöhr, M., Nenadic, I., Schwarting, R., Schrott, G., Alferink, J., ... Dannlowski, U. (2019). Neurobiology of the major psychoses: A translational perspective on brain structure and function—The FOR2107 consortium. *European Archives of Psychiatry and Clinical Neuroscience*, 269, 949–962. <https://doi.org/10.1007/s00406-018-0943-x>
- Kleinknecht, R. A., Klepac, R. K., & Alexander, L. D. (1973). Origins and characteristics of fear of dentistry. *Journal of the American Dental Association* (1939), 86, 842–848. <https://doi.org/10.14219/jada.archive.1973.0165>
- Klorman, R., Weerts, T. C., Hastings, J. E., Melamed, B. G., & Lang, P. J. (1974). Psychometric description of some specific-fear questionnaires. *Behavior Therapy*, 5, 401–409. <http://www.sciencedirect.com/science/article/pii/S0005789474800080>
- Klumpp, H., & Fitzgerald, J. M. (2018). Neuroimaging predictors and mechanisms of treatment response in social anxiety disorder: An overview of the amygdala. *Current Psychiatry Reports*, 20, 89. <https://doi.org/10.1007/s11920-018-0948-1>
- Klumpp, H., Kinney, K. L., Kennedy, A. E., Shankman, S. A., Langenecker, S. A., Kumar, A., & Phan, K. L. (2018). Trait attentional control modulates neurofunctional response to threat distractors in anxiety and depression. *Journal of Psychiatric Research*, 102, 87–95. <http://www.sciencedirect.com/science/article/pii/S0022395617307720>
- Kochunov, P., Jahanshad, N., Marcus, D., Winkler, A., Sprooten, E., Nichols, T. E., ... Van Essen, D. C. (2015). Heritability of fractional anisotropy in human white matter: A comparison of human connectome project and ENIGMA-DTI data. *NeuroImage*, 111, 300–311. <https://www.sciencedirect.com/science/article/pii/S1053811915001512>
- Kogan, C. S., Stein, D. J., Maj, M., First, M. B., Emmelkamp, P. M. G., & Reed, G. M. (2016). The classification of anxiety and fear-related disorders in the ICD-11. *Depress Anxiety*, 33, 1141–1154.
- Kolesar, T. A., Bilevicius, E., Wilson, A. D., & Kornelsen, J. (2019). Systematic review and Meta-analyses of neural structural and functional differences in generalized anxiety disorder and healthy controls using magnetic resonance imaging. *NeuroImage: Clinical*, 24, 102016. <http://www.sciencedirect.com/science/article/pii/S2213158219303663>
- Kong, X.-Z., Mathias, S. R., Guadalupe, T., Glahn, D. C., Franke, B., Crivello, F., ... Francks, C. (2018). Mapping cortical brain asymmetry in 17,141 healthy individuals worldwide via the ENIGMA consortium. *Proceedings of the National Academy of Sciences*, 115, E5154–E5163. <http://www.pnas.org/content/115/22/E5154.abstract>
- Kovacs, M. (1985). The Children's depression inventory (CDI). *Psychopharmacology Bulletin*, 21, 995–998.
- Kreifelts, B., Brück, C., Ethofer, T., Ritter, J., Weigel, L., Erb, M., & Wildgruber, D. (2017). Prefrontal mediation of emotion regulation in social anxiety disorder during laughter perception. *Neuropsychologia*, 96, 175–183. <http://www.sciencedirect.com/science/article/pii/S0028393217300222>
- Kunas, S. L., Yang, Y., Straube, B., Kircher, T., Gerlach, A. L., Pfeleiderer, B., ... Lueken, U. (2019). The impact of depressive comorbidity on neural plasticity following cognitive-behavioral therapy in panic disorder with agoraphobia. *Journal of Affective Disorders*, 245, 451–460. <http://www.sciencedirect.com/science/article/pii/S0165032718314253>
- Laeger, I., Döbel, C., Radenz, B., Kugel, H., Keuper, K., Eden, A., ... Zwanzger, P. (2014). Of 'disgrace' and 'pain' – Corticolimbic interaction patterns for disorder-relevant and emotional words in social phobia. *PLoS ONE*, 9, e109949. <https://doi.org/10.1371/journal.pone.0109949>

- Laeger, I., Keuper, K., Heitmann, C. Y., Kugel, H., Dobel, C., Eden, A., ... Zwanzger, P. (2014). Have we met before? Neural correlates of emotional learning in women with social phobia. *Journal of Psychiatry & Neuroscience*, 39, E14–E23. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3997608&tool=pmcentrez&rendertype=abstract>
- Lange, I., Goossens, L., Bakker, J., Michielse, S., Marcelis, M., Wichers, M., ... Schruers, K. (2019). Functional neuroimaging of associative learning and generalization in specific phobia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 89, 275–285. <http://www.sciencedirect.com/science/article/pii/S0278584618302598>
- Lange, I., Goossens, L., Leibold, N., Vervliet, B., Sunaert, S., Peeters, R., ... Schruers, K. (2016). Brain and behavior changes following exposure therapy predict outcome at 8-year follow-up. *Psychotherapy and Psychosomatics*, 85, 238–240. <https://www.karger.com/DOI/10.1159/000442292>
- Lebeau, R. T., Glenn, D. E., Hanover, L. N., Beesdo-Baum, K., Wittchen, H.-U., & Craske, M. G. (2012). A dimensional approach to measuring anxiety for DSM-5. *International Journal of Methods in Psychiatric Research*, 21, 258–272. <https://doi.org/10.1002/mp.1369>
- Lenzenweger, M. F. (2013). Thinking clearly about the endophenotype-intermediate phenotype-biomarker distinctions in developmental psychopathology research. *Development and Psychopathology*, 25, 1347–1357. <http://www.ncbi.nlm.nih.gov/pubmed/24342844>
- Levey, D. F., Gelernter, J., Polimanti, R., Zhou, H., Cheng, Z., Aslan, M., ... Stein, M. B. (2020). Reproducible genetic risk loci for anxiety: Results from ~200,000 participants in the million veteran program. *The American Journal of Psychiatry*, 177, 223–232. <https://doi.org/10.1176/appi.ajp.2019.19030256>
- Lipka, J., Miltner, W. H. R., & Straube, T. (2011). Vigilance for threat interacts with amygdala responses to subliminal threat cues in specific phobia. *Biological Psychiatry*, 70, 472–478. <https://doi.org/10.1016/j.biopsych.2011.04.005>
- Loerinc, A. G., Meuret, A. E., Twohig, M. P., Rosenfield, D., Bluett, E. J., & Craske, M. G. (2015). Response rates for CBT for anxiety disorders: Need for standardized criteria. *Clinical Psychology Review*, 42, 72–82. <http://www.sciencedirect.com/science/article/pii/S0272735815001178>
- Lueken, U., & Hahn, T. (2016). Functional neuroimaging of psychotherapeutic processes in anxiety and depression: From mechanisms to predictions. *Current Opinion in Psychiatry*, 29, 25–31. <https://doi.org/10.1097/YCO.0000000000000218>
- Lueken, U., Kruschwitz, J. D., Muehlhan, M., Siegert, J., Hoyer, J., & Wittchen, H.-U. (2011). How specific is specific phobia? Different neural response patterns in two subtypes of specific phobia. *NeuroImage*, 56, 363–372. <http://www.sciencedirect.com/science/article/pii/S1053811911001546>
- Lueken, U., Zierhut, K. C., Hahn, T., Straube, B., Kircher, T., Reif, A., ... Domschke, K. (2016). Neurobiological markers predicting treatment response in anxiety disorders: A systematic review and implications for clinical application. *Neuroscience and Biobehavioral Reviews*, 66, 143–162. <http://www.sciencedirect.com/science/article/pii/S0149763416300227>
- Maggioni, E., Delvecchio, G., Grottaroli, M., Garzitto, M., Piccin, S., Bonivento, C., ... Brambilla, P. (2019). Common and different neural markers in major depression and anxiety disorders: A pilot structural magnetic resonance imaging study. *Psychiatry Research: Neuroimaging*, 290, 42–50. <http://www.sciencedirect.com/science/article/pii/S0925492718303329>
- Makovac, E., Meeten, F., Watson, D. R., Herman, A., Garfinkel, S. N. D., Critchley, H., & Ottaviani, C. (2016). Alterations in amygdala-prefrontal functional connectivity account for excessive worry and autonomic dysregulation in generalized anxiety disorder. *Biological Psychiatry*, 80, 786–795.
- Makovac, E., Watson, D. R., Meeten, F., Garfinkel, S. N., Cercignani, M., Critchley, H. D., & Ottaviani, C. (2016). Amygdala functional connectivity as a longitudinal biomarker of symptom changes in generalized anxiety. *Social Cognitive and Affective Neuroscience*, 11, 1719–1728. <https://academic.oup.com/scan/article-lookup/doi/10.1093/scan/nsw091>
- Månsson, K. N. T., Carlbring, P., Frick, A., Engman, J., Olsson, C.-J., Bodlund, O., ... Andersson, G. (2013). Altered neural correlates of affective processing after internet-delivered cognitive behavior therapy for social anxiety disorder. *Psychiatry Research*, 214, 229–237. <http://www.sciencedirect.com/science/article/pii/S0925492713002412>
- Månsson, K. N. T., Frick, A., Boraxbekk, C.-J., Marquand, A. F., Williams, S. C. R., Carlbring, P., ... Furmark, T. (2015). Predicting long-term outcome of internet-delivered cognitive behavior therapy for social anxiety disorder using fMRI and support vector machine learning. *Translational Psychiatry*, 5, e530. <https://doi.org/10.1038/tp.2015.22>
- Månsson, K. N. T., Lindqvist, D., Yang, L. L., Svanborg, C., Isung, J., Nilsson, G., ... Furmark, T. (2019). Improvement in indices of cellular protection after psychological treatment for social anxiety disorder. *Translational Psychiatry*, 9, 340. <https://doi.org/10.1038/s41398-019-0668-2>
- Månsson, K. N. T., Salami, A., Frick, A., Carlbring, P., Andersson, G., Furmark, T., & Boraxbekk, C. J. (2016). Neuroplasticity in response to cognitive behavior therapy for social anxiety disorder. *Translational Psychiatry*, 6, e727. <https://doi.org/10.1038/tp.2015.218>
- McTeague, L. M., Lang, P. J., Wangelin, B. C., Laplante, M.-C., & Bradley, M. M. (2012). Defensive mobilization in specific phobia: Fear specificity, negative affectivity, and diagnostic prominence. *Biological Psychiatry*, 72, 8–18. <http://www.sciencedirect.com/science/article/pii/S0006322312000510>
- Meier, S. M., & Deckert, J. (2019). Genetics of anxiety disorders. *Current Psychiatry Reports*, 21, 16. <https://doi.org/10.1007/s11920-019-1002-7>
- Meier, S. M., Trontti, K., Purves, K. L., Als, T. D., Grove, J., Laine, M., ... Mors, O. (2019). Genetic variants associated with anxiety and stress-related disorders: A genome-wide association study and mouse-model study. *JAMA Psychiatry*, 76, 924–932. <https://doi.org/10.1001/jamapsychiatry.2019.1119>
- Michałowski, J. M., Matuszewski, J., Drożdżel, D., Koziejowski, W., Rynkiewicz, A., Jednoróg, K., & Marchewka, A. (2017). Neural response patterns in spider, blood-injection-injury and social fearful individuals: New insights from a simultaneous EEG/ECG-fMRI study. *Brain Imaging and Behavior*, 11, 829–845. <https://doi.org/10.1007/s11682-016-9557-y>
- Milad, M. R., & Quirk, G. J. (2011). Fear extinction as a model for translational neuroscience: Ten years of Progress. *Annual Review of Psychology*, 63, 129–151. <https://doi.org/10.1146/annurev.psych.121208.131631>
- Miller, G. A., & Rockstroh, B. (2013). Endophenotypes in psychopathology research: Where do we stand? *Annual Review of Clinical Psychology*, 9, 177–213. <http://www.ncbi.nlm.nih.gov/pubmed/23297790>
- Milrod, B., Chambless, D. L., Gallop, R., Busch, F. N., Schwalberg, M., McCarthy, K. S., ... Barber, J. P. (2016). Psychotherapies for panic disorder: A tale of two sites. *The Journal of Clinical Psychiatry*, 77, 927–935. <http://europepmc.org/abstract/MED/27464313>
- Mochcovitch, M. D., da Rocha Freire, R. C., Garcia, R. F., & Nardi, A. E. (2014). A systematic review of fMRI studies in generalized anxiety disorder: Evaluating its neural and cognitive basis. *Journal of Affective Disorders*, 167, 336–342. <http://www.sciencedirect.com/science/article/pii/S0165032714004091>
- Molent, C., Maggioni, E., Cecchetto, F., Garzitto, M., Piccin, S., Bonivento, C., ... Brambilla, P. (2018). Reduced cortical thickness and increased gyrification in generalized anxiety disorder: A 3 T MRI study. *Psychological Medicine*, 48, 2001–2010. <https://www.cambridge.org/core/article/reduced-cortical-thickness-and-increased-gyrification-in-generalized-anxiety-disorder-a-3-t-mri-study/FC704464772ECF396DDF24CC5D5C0853>
- Molina, S., & Borkovec, T. D. (1994). The Penn State worry questionnaire: Psychometric properties and associated characteristics. In *Worrying: Perspectives on theory, assessment and treatment* (pp. 265–283). Oxford, England: John Wiley & Sons. Wiley series in clinical psychology.

- Mueller, S. G., Weiner, M. W., Thal, L. J., Petersen, R. C., Jack, C., Jagust, W., ... Beckett, L. (2005). The Alzheimer's Disease Neuroimaging Initiative. *NeuroImage: Clinical*, *15*, 869–877. <https://doi.org/10.1016/j.nic.2005.09.008>
- Mufford, M. S., Stein, D. J., Dalvie, S., Groenewold, N. A., Thompson, P. M., & Jahanshad, N. (2017). Neuroimaging genomics in psychiatry—A translational approach. *Genome Medicine*, *9*, 102. <https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-017-0496-z>
- Mujica-Parodi, L. R., Korgaonkar, M., Ravindranath, B., Greenberg, T., Tomasi, D., Wagshul, M., ... Malaspina, D. (2009). Limbic dysregulation is associated with lowered heart rate variability and increased trait anxiety in healthy adults. *Human Brain Mapping*, *30*, 47–58. <https://doi.org/10.1002/hbm.20483>
- Münsterkötter, A. L., Notzon, S., Redlich, R., Grotegerd, D., Dohm, K., Arolt, V., ... Dannlowski, U. (2015). Spider or no spider? Neural correlates of SUSTAINED and phasic fear in spider phobia. *Depression and Anxiety*, *32*, 656–663. <https://doi.org/10.1002/da.22382>
- Muris, P., Merckelbach, H., Mayer, B., van Brakel, A., Thissen, S., Moulart, V., & Gadet, B. (1998). The screen for child anxiety related emotional disorders (SCARED) and traditional childhood anxiety measures. *Journal of Behavior Therapy and Experimental Psychiatry*, *29*, 327–339. <http://www.sciencedirect.com/science/article/pii/S0005791698000238>
- Muris, P., van Brakel, A. M. L., Arntz, A., & Schouten, E. (2011). Behavioral inhibition as a risk factor for the development of childhood anxiety disorders: A longitudinal study. *Journal of Child and Family Studies*, *20*, 157–170. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3048305&tool=pmcentrez&rendertype=abstract>
- Neufang, S., Geiger, M. J., Homola, G. A., Mahr, M., Schiele, M. A., Gehrmann, A., ... Domschke, K. (2019). Cognitive-behavioral therapy effects on alerting network activity and effective connectivity in panic disorder. *European Archives of Psychiatry and Clinical Neuroscience*, *269*, 587–598. <https://doi.org/10.1007/s00406-018-0945-8>
- Ohrmann, P., Pedersen, A., Braun, M., Bauer, J., Kugel, H., Kersting, A., ... Suslow, T. (2010). Effect of gender on processing threat-related stimuli in patients with panic disorder: Sex does matter. *Depression and Anxiety*, *27*, 1034–1043. <https://doi.org/10.1002/da.20721>
- Opel, N., Redlich, R., Dohm, K., Zaremba, D., Goltermann, J., Repple, J., ... Dannlowski, U. (2019). Mediation of the influence of childhood maltreatment on depression relapse by cortical structure: A 2-year longitudinal observational study. *The Lancet Psychiatry*, *6*, 318–326. <http://www.sciencedirect.com/science/article/pii/S2215036619300446>
- Ormel, J., Koeter, M. W. J., van den Brink, W., & van de Willige, G. (1991). Recognition, management, and course of anxiety and depression in general practice. *Archives of General Psychiatry*, *48*, 700–706. <https://doi.org/10.1001/archpsyc.1991.01810320024004>
- Pané-Farré, C. A., Stender, J. P., Fenske, K., Deckert, J., Reif, A., John, U., ... Hamm, A. O. (2014). The phenomenology of the first panic attack in clinical and community-based samples. *Journal of Anxiety Disorders*, *28*, 522–529. <http://www.sciencedirect.com/science/article/pii/S0887618514000711>
- Pannekoek, J. N., van der Werff, S. J. A., van Tol, M. J., Veltman, D. J., Aleman, A., Zitman, F. G., ... van der Wee, N. J. A. (2015). Investigating distinct and common abnormalities of resting-state functional connectivity in depression, anxiety, and their comorbid states. *European Neuropsychopharmacology*, *25*, 1933–1942. <http://www.sciencedirect.com/science/article/pii/S0924977X15002473>
- Pantazatos, S. P., Talati, A., Schneier, F. R., & Hirsch, J. (2014). Reduced anterior temporal and hippocampal functional connectivity during face processing discriminates individuals with social anxiety disorder from healthy controls and panic disorder, and increases following treatment. *Neuropsychopharmacology*, *39*, 425–434. <https://doi.org/10.1038/npp.2013.211>
- Patel, Y., Parker, N., Shin, J., Howard, D., French, L., Thomopoulos, S. I., ... ENIGMA OCD ESGW (2020): Virtual histology of cortical thickness reveals shared neurobiology across six psychiatric disorders. In: Abstract at the 75th Society of Biological Psychiatry Annual Meeting, April 30–May 2, 2020, New York, USA.
- Penninx, B. W. J. H., Beekman, A. T. F., Smit, J. H., Zitman, F. G., Nolen, W. A., Spinhoven, P., ... Van Dyck, R. (2008). The Netherlands study of depression and anxiety (NESDA): Rationale, objectives and methods. *International Journal of Methods in Psychiatric Research*, *17*, 121–140. <http://doi.wiley.com/10.1002/mpr.256>
- Phan, K. L., Coccaro, E. F., Angstadt, M., Kreger, K. J., Mayberg, H. S., Liberzon, I., & Stein, M. B. (2013). Corticolimbic brain reactivity to social signals of threat before and after sertraline treatment in generalized social phobia. *Biological Psychiatry*, *73*, 329–336. <http://www.sciencedirect.com/science/article/pii/S000632231200858X>
- Pine, D. S., Cohen, P., Gurley, D., Brook, J., & Ma, Y. (1998). The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of General Psychiatry*, *55*, 56–64. <https://doi.org/10.1001/archpsyc.55.1.56>
- Plana-Ripoll, O., Pedersen, C. B., Holtz, Y., Benros, M. E., Dalsgaard, S., de Jonge, P., ... McGrath, J. J. (2019). Exploring comorbidity within mental disorders among a Danish National Population. *JAMA Psychiatry*, *76*, 259–270. <https://dx.doi.org/10.1001/jamapsychiatry.2018.3658>
- Poldrack, R. A., Huckins, G., & Varoquaux, G. (2019). Establishment of best practices for evidence for prediction: A review. *JAMA Psychiatry*, *77*, 534. <https://doi.org/10.1001/jamapsychiatry.2019.3671>
- Poletti, S., Radaelli, D., Cucchi, M., Ricci, L., Vai, B., Smeraldi, E., & Benedetti, F. (2015). Neural correlates of anxiety sensitivity in panic disorder: A functional magnetic resonance imaging study. *Psychiatry Research: Neuroimaging*, *233*, 95–101. <http://www.sciencedirect.com/science/article/pii/S0925492715300020>
- Porta, D., Goldberg, X., Martínez-Zalacain, I., González, I., Fullana, M. A., Harrison, B. J., ... Via, E. (2017). 121. From healthy to pathological anxiety: Testing the Prefronto-subcortical circuit in high anxiety-trait and generalized anxiety disorder. *Biological Psychiatry*, *81*, S51. <https://doi.org/10.1016/j.biopsych.2017.02.133>
- Price, R. B., Beltz, A. M., Woody, M. L., Cummings, L., Gilchrist, D., & Siegle, G. J. (in press). Neural connectivity subtypes predict discrete attentional bias profiles among heterogeneous anxiety patients. *Clinical Psychological Science: A Journal of the Association for Psychological Science*, *8*, 491–505.
- Price, R. B., Cummings, L., Gilchrist, D., Graur, S., Banihashemi, L., Kuo, S. S., & Siegle, G. J. (2018). Towards personalized, brain-based behavioral intervention for transdiagnostic anxiety: Transient neural responses to negative images predict outcomes following a targeted computer-based intervention. *Journal of Consulting and Clinical Psychology*, *86*, 1031–1045.
- Purves, K. L., Coleman, J. R. I., Meier, S. M., Rayner, C., Davis, K. A. S., Cheesman, R., ... Eley, T. C. (2019). A major role for common genetic variation in anxiety disorders. *Molecular Psychiatry*. <https://doi.org/10.1038/s41380-019-0559-1>
- Qiu, C., Feng, Y., Meng, Y., Liao, W., Huang, X., Lui, S., ... Zhang, W. (2015). Analysis of altered baseline brain activity in drug-naive adult patients with social anxiety disorder using resting-state functional MRI. *Psychiatry Investigation*, *12*, 372–380. <https://doi.org/10.4306/pi.2015.12.3.372>
- Rabany, L., Diefenbach, G. J., Bragdon, L. B., Pittman, B. P., Zertuche, L., Tolin, D. F., ... Assaf, M. (2017). Resting-state functional connectivity in generalized anxiety disorder and social anxiety disorder: Evidence for a dimensional approach. *Brain Connectivity*, *7*, 289–298. <http://online.liebertpub.com.ezproxy.leidenuniv.nl:2048/doi/pdf/10.1089/brain.2017.0497>
- Radua, J., van den Heuvel, O. A., Surguladze, S., & Mataix-Cols, D. (2010). Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. *Archives of*

- General Psychiatry*, 67, 701–711. <https://doi.org/10.1001/archgenpsychiatry.2010.70>
- Reinecke, A., Filippini, N., Berna, C., Western, D. G., Hanson, B., Cooper, M. J., ... Harmer, C. J. (2015). Effective emotion regulation strategies improve fMRI and ECG markers of psychopathology in panic disorder: Implications for psychological treatment action. *Translational Psychiatry*, 5, e673–e673. <https://doi.org/10.1038/tp.2015.160>
- Reinecke, A., Thilo, K. V., Croft, A., & Harmer, C. J. (2018). Early effects of exposure-based cognitive behaviour therapy on the neural correlates of anxiety. *Translational Psychiatry*, 8, 225. <https://doi.org/10.1038/s41398-018-0277-5>
- Reiss, S., Peterson, R. A., Gursky, D. M., & McNally, R. J. (1986). Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behaviour Research and Therapy*, 24, 1–8. <http://www.sciencedirect.com/science/article/pii/0005796786901439>
- Repple, J., Mauritz, M., Meinert, S., de Lange, S. C., Grotegerd, D., Opel, N., ... van den Heuvel, M. P. (2020). Severity of current depression and remission status are associated with structural connectome alterations in major depressive disorder. *Molecular Psychiatry*, 25, 1550–1558. <https://doi.org/10.1038/s41380-019-0603-1>
- Rivero, F., Herrero, M., Viña, C., Álvarez-Pérez, Y., & Peñate, W. (2017). Neuroimaging in cockroach phobia: An experimental study. *International Journal of Clinical and Health Psychology*, 17, 207–215. <http://www.sciencedirect.com/science/article/pii/S1697260017300376>
- Salminen, L. E., Sämann, P. G., Zheng, Y., Dennis, E. L., Clarke-Rubright, E. K., Jahanshad, N., ... Logue, M. W. (2019). Hippocampal subfield volumes are uniquely affected in PTSD and depression: International analysis of 31 cohorts from the PGC-ENIGMA PTSD Working Group. *bioRxiv*, 739094. <http://biorxiv.org/content/early/2019/08/21/739094.abstract>
- Salum, G. A., Gadelha, A., Pan, P. M., Moriyama, T. S., Graeff-Martins, A. S., Tamanaha, A. C., ... Rohde, L. A. (2015). High risk cohort study for psychiatric disorders in childhood: Rationale, design, methods and preliminary results. *International Journal of Methods in Psychiatric Research*, 24, 58–73. <http://www.ncbi.nlm.nih.gov/pubmed/25469819>
- Salum, G. A., Isolan, L. R., Bosa, V. L., Tocchetto, A. G., Teche, S. P., Schuch, I., ... Manfro, G. G. (2011). The multidimensional evaluation and treatment of anxiety in children and adolescents: Rationale, design, methods and preliminary findings. *Brazilian Journal of Psychiatry*, 33, 181–195.
- Satizabal, C. L., Adams, H. H. H., Hibar, D. P., White, C. C., Knol, M. J., Stein, J. L., ... Ikram, M. A. (2019). Genetic architecture of subcortical brain structures in 38,851 individuals. *Nature Genetics*, 51, 1624–1636. <https://doi.org/10.1038/s41588-019-0511-y>
- Satterthwaite, T. D., Elliott, M. A., Ruparel, K., Loughhead, J., Prabhakaran, K., Calkins, M. E., ... Gur, R. E. (2014). Neuroimaging of the Philadelphia neurodevelopmental cohort. *NeuroImage*, 86, 544–553.
- Saygin, Z. M., Kliemann, D., Iglesias, J. E., van der Kouwe, A. J. W., Boyd, E., Reuter, M., ... Augustinack, J. C. (2017). High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: Manual segmentation to automatic atlas. *NeuroImage*, 155, 370–382. <http://linkinghub.elsevier.com/retrieve/pii/S1053811917303427>
- Schaller E, Gerdes A, Alpers GW (2006): Fragebogen zu Ekel und Angst vor Spinnen [Anxiety and disgust towards Spiders Questionnaire]. In: Wissenschaftliche Beiträge zum 24. Symposium der Fachgruppe Klinische Psychologie und Psychotherapie (Vol. 105).
- Schienle, A., Scharmüller, W., Leutgeb, V., Schäfer, A., & Stark, R. (2013). Sex differences in the functional and structural neuroanatomy of dental phobia. *Brain Structure & Function*, 218, 779–787. <https://doi.org/10.1007/s00429-012-0428-z>
- Schmaal, L., Hibar, D. P., Sämann, P. G., Hall, G. B., Baune, B. T., Jahanshad, N., ... Veltman, D. J. (2017). Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA major depressive disorder working group. *Molecular Psychiatry*, 22, 900–909. <https://doi.org/10.1038/mp.2016.60>
- Schmaal, L., Veltman, D. J., van Erp, T. G. M., Sämann, P. G., Frodl, T., Jahanshad, N., ... Hibar, D. P. (2016). Subcortical brain alterations in major depressive disorder: Findings from the ENIGMA major depressive disorder working group. *Molecular Psychiatry*, 21, 806–812. <https://doi.org/10.1038/mp.2015.69>
- Schwarzmeier, H., Leehr, E. J., Böhnlein, J., Seeger, F. R., Roesmann, K., Gathmann, B., ... Dannlowski, U. (2019). Theranostic markers for personalized therapy of spider phobia: Methods of a bicentric external cross-validation machine learning approach. *International Journal of Methods in Psychiatric Research*, 29, 1–14. e1812. <https://doi.org/10.1002/mpr.1812>
- Schweckendiek, J., Klucken, T., Merz, C. J., Tabbert, K., Walter, B., Ambach, W., ... Stark, R. (2011). Weaving the (neuronal) web: Fear learning in spider phobia. *NeuroImage*, 54, 681–688. <http://www.sciencedirect.com/science/article/pii/S1053811910010220>
- Shear, M. K., Brown, T. A., Barlow, D. H., Money, R., Sholomskas, D. E., Woods, S. W., ... Papp, L. A. (1997). Multicenter collaborative panic disorder severity scale. *The American Journal of Psychiatry*, 154, 1571–1575. <https://doi.org/10.1176/ajp.154.11.1571>
- Sheehan, D. V., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., ... Dunbar, G. (1997). The validity of the MINI international neuropsychiatric interview (MINI) according to the SCID-P and its reliability. *European Psychiatry*, 12, 232–241.
- Shimada-Sugimoto, M., Otowa, T., & Hettema, J. M. (2015). Genetics of anxiety disorders: Genetic epidemiological and molecular studies in humans. *Psychiatry and Clinical Neurosciences*, 69, 388–401. <http://www.ncbi.nlm.nih.gov/pubmed/25762210>
- Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*, 35, 169–191. <https://doi.org/10.1038/npp.2009.83>
- Spielberger, C. D., & Vagg, P. R. (1984). Psychometric properties of the STAI: A reply to Ramanaiah, Franzen, and Schill. *Journal of Personality Assessment*, 48, 95–97. <http://www.ncbi.nlm.nih.gov/pubmed/6707862>
- Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine*, 166, 1092–1097. <https://doi.org/10.1001/archinte.166.10.1092>
- Steer, R. A., & Beck, A. T. (1997). *Beck anxiety inventory. Evaluating stress: A book of resources*. Lanham, MD, US: Scarecrow Education.
- Steiger, V. R., Brühl, A. B., Weidt, S., Delsignore, A., Rufer, M., Jäncke, L., ... Hänggi, J. (2017). Pattern of structural brain changes in social anxiety disorder after cognitive behavioral group therapy: A longitudinal multimodal MRI study. *Molecular Psychiatry*, 22, 1164–1171. <http://www.nature.com/doi/10.1038/mp.2016.217>
- Stein, D. J., He, Y., Phillips, A., Sahakian, B. J., Williams, J., & Patel, V. (2015). Global mental health and neuroscience: Potential synergies. *The Lancet Psychiatry*, 2, 178–185. <http://www.sciencedirect.com/science/article/pii/S2215036615000140>
- Stein, D. J., Lim, C. C. W., Roest, A. M., de Jonge, P., Aguilar-Gaxiola, S., Al-Hamzawi, A., ... Scott, K. M. (2017). The cross-national epidemiology of social anxiety disorder: Data from the world mental health survey initiative. *BMC Medicine*, 15, 143. <https://doi.org/10.1186/s12916-017-0889-2>
- Stein, D. J., & Wegener, G. (2017). Discovery versus implementation research on mental disorders in low- and middle-income countries. *Acta Neuropsychiatrica*, 29, 191–192. <https://www.cambridge.org/core/article/discovery-versus-implementation-research-on-mental-disorders-in-low-and-middle-income-countries/3CC0EDCB756B44301CF66E1638918534>
- Strawn, J. R., Bitter, S. M., Weber, W. A., Chu, W.-J., Whitsel, R. M., Adler, C., ... DelBello, M. P. (2012). NEUROCIRCUITRY of generalized anxiety disorder in adolescents: A pilot functional neuroimaging and

- functional connectivity study. *Depression and Anxiety*, 29, 939–947. <https://doi.org/10.1002/da.21961>
- Syal, S., Hattingh, C. J., Fouché, J.-P., Spottiswoode, B., Carey, P. D., Lochner, C., & Stein, D. J. (2012). Grey matter abnormalities in social anxiety disorder: A pilot study. *Metabolic Brain Disease*, 27, 299–309. <http://www.ncbi.nlm.nih.gov/pubmed/22527992>
- Taber-Thomas, B. C., Morales, S., Hillary, F. G., & Pérez-Edgar, K. E. (2016). Altered topography of intrinsic functional connectivity in childhood risk for social anxiety. *Depression and Anxiety*, 33, 995–1004. <http://www.ncbi.nlm.nih.gov/pubmed/27093074>
- Talati, A., Pantazatos, S. P., Hirsch, J., & Schneier, F. (2015). A pilot study of gray matter volume changes associated with paroxetine treatment and response in social anxiety disorder. *Psychiatry Research*, 231, 279–285. <http://www.sciencedirect.com/science/article/pii/S0925492715000098>
- Talati, A., Pantazatos, S. P., Schneier, F. R., Weissman, M. M., & Hirsch, J. (2013). Gray matter abnormalities in social anxiety disorder: Primary, replication, and specificity studies. *Biological Psychiatry*, 73, 75–84. <https://doi.org/10.1016/j.biopsych.2012.05.022>
- Taylor, J. M., & Whalen, P. J. (2015). Neuroimaging and anxiety: The neural substrates of pathological and non-pathological anxiety. *Current Psychiatry Reports*, 17, 49. <http://www.ncbi.nlm.nih.gov/pubmed/25957101>
- Taylor, S., Abramowitz, J. S., & McKay, D. (2012). Non-adherence and non-response in the treatment of anxiety disorders. *Journal of Anxiety Disorders*, 26, 583–589. <http://www.sciencedirect.com/science/article/pii/S0887618512000333>
- Thompson, K., King, K., Nahmias, E., Fani, N., Kvaran, T., Tone, E. B., & Turner, J. A. (2019). Social feedback modulates neural response associated with cognitive Bias in individuals expressing anxious symptoms. *Chronic Stress*, 3, 2470547019848648. <https://doi.org/10.1177/2470547019848648>
- Thompson, P., Jahanshad, N., Ching, C. R. K., Salminen, L., Thomopoulos, S. I., Bright, J., ... Zelman, V. (2020). ENIGMA and global neuroscience: A decade of large-scale studies of the brain in health and disease across more than 40 countries. *Translational Psychiatry*, 10, 100. <https://doi.org/10.1038/s41398-020-0705-1>
- Thompson, P. M., Stein, J. L., Medland, S. E., Hibar, D. P., Vasquez, A. A., Renteria, M. E., ... Drevets, W. (2014). The ENIGMA consortium: Large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging and Behavior*, 8, 153–182. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4008818&tool=pmcentrez&rendertype=abstract>
- Thyer, B. A., & Curtis, G. C. (1985). On the diphasic nature of vasovagal fainting associated with blood-injury-illness phobia. *Pavlov J Biol Sci off J Pavlov*, 20, 84–87. <https://doi.org/10.1007/BF03003257>
- Toazza, R., Franco, A. R., Buchweitz, A., Molle, R. D., Rodrigues, D. M., Reis, R. S., ... Manfro, G. G. (2016). Amygdala-based intrinsic functional connectivity and anxiety disorders in adolescents and young adults. *Psychiatry Research: Neuroimaging*, 257, 11–16. <http://www.sciencedirect.com/science/article/pii/S0925492716300944>
- Tolkunov, D., Rubin, D., & Mujica-Parodi, L. R. (2010). Power spectrum scale invariance quantifies limbic dysregulation in trait anxious adults using fMRI: Adapting methods optimized for characterizing autonomic dysregulation to neural dynamic time series. *NeuroImage*, 50, 72–80. <http://www.sciencedirect.com/science/article/pii/S1053811909013093>
- Tönnies, S., Mehrstedt, M., & Eisentraut, I. (2002). Die Dental Anxiety Scale (DAS) und das Dental Fear Survey (DFS) Zwei Messinstrumente zur Erfassung von Zahnbehandlungsängsten. *Zeitschrift für Medizinische Psychologie*, 11, 63–72.
- Tükel, R., Aydın, K., Yüksel, Ç., Ertekin, E., Koyuncu, A., & Taş, C. (2015). Gray matter abnormalities in patients with social anxiety disorder: A voxel-based morphometry study. *Psychiatry Research*, 234, 106–112. <http://www.sciencedirect.com/science/article/pii/S0925492715300755>
- van den Heuvel, O. A., Mataix-Cols, D., Zwieter, G., Cath, D. C., van der Werf, Y. D., Groenewegen, H. J., ... Veltman, D. J. (2011). Common limbic and frontal-striatal disturbances in patients with obsessive compulsive disorder, panic disorder and hypochondriasis. *Psychological Medicine*, 41, 2399–2410. <https://www.cambridge.org/core/article/common-limbic-and-frontal-striatal-disturbances-in-patients-with-obsessive-compulsive-disorder-panic-disorder-and-hypochondriasis/B7AAFF7F4E4F21A98F2198B6953570A5>
- van den Heuvel, O. A., Veltman, D. J., Groenewegen, H. J., Witter, M. P., Merkelbach, J., Cath, D. C., ... van Dyck, R. (2005). Disorder-specific neuroanatomical correlates of attentional Bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. *Archives of General Psychiatry*, 62, 922–933. <https://doi.org/10.1001/archpsyc.62.8.922>
- van der Merwe, C., Jahanshad, N., Cheung, J. W., Mufford, M., Groenewold, N., Koen, N., ... Stein, D. J. (2019). Concordance of genetic variation that increases risk for anxiety disorders and posttraumatic stress disorders and that influences their underlying Neurocircuitry. *Journal of Affective Disorders*, 245, 885–896. <http://www.sciencedirect.com/science/article/pii/S0165032718311789>
- van Erp, T. G. M., Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, G. D., Andreassen, O. A., ... Turner, J. A. (2016). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry*, 21, 547–553. <https://doi.org/10.1038/mp.2015.63>
- van Tol, M. J., van der Wee, N. J. A., van den Heuvel, O. A., Nielen, M. M. A., Demenescu, L. R., Aleman, A., ... Veltman, D. J. (2010). Regional brain volume in depression and anxiety disorders. *Archives of General Psychiatry*, 67, 1002–1011. <http://archpsyc.jamanetwork.com/article.aspx?articleid=210895>
- Van Wijk, A. J., & Hoogstraten, J. (2003). The fear of dental pain questionnaire: Construction and validity. *European Journal of Oral Sciences*, 111, 12–18. <https://doi.org/10.1034/j.1600-0722.2003.00005.x>
- VanElzakker, M. B., Kathryn Dahlgren, M., Caroline Davis, F., Dubois, S., & Shin, L. M. (2014). From Pavlov to PTSD: The extinction of conditioned fear in rodents, humans, and anxiety disorders. *Neurobiology of Learning and Memory*, 113, 3–18. <http://www.sciencedirect.com/science/article/pii/S1074742713002426>
- Visser, R. M., Haver, P., Zwieter, R. J., Scholte, H. S., & Kindt, M. (2016). First steps in using multi-voxel pattern analysis to disentangle neural processes underlying generalization of spider fear. *Frontiers in Human Neuroscience*, 10, 1–13. <https://www.frontiersin.org/article/10.3389/fnhum.2016.00222>
- Vogelbacher, C., Möbius, T. W. D., Sommer, J., Schuster, V., Dannowski, U., Kircher, T., ... Bopp, M. H. A. (2018). The Marburg-Münster affective disorders cohort study (MACS): A quality assurance protocol for MR neuroimaging data. *NeuroImage*, 172, 450–460. <http://www.sciencedirect.com/science/article/pii/S105381191830079X>
- Volkow, N. D., Koob, G. F., Croyle, R. T., Bianchi, D. W., Gordon, J. A., Koroshetz, W. J., ... Weiss, S. R. B. (2018). The conception of the ABCD study: From substance use to a broad NIH collaboration. *Developmental Cognitive Neuroscience*, 32, 4–7. <http://www.sciencedirect.com/science/article/pii/S1878929317300725>
- Völzke, H., Alte, D., Schmidt, C. O., Radke, D., Lorbeer, R., Friedrich, N., ... Hoffmann, W. (2011). Cohort profile: The study of health in Pomerania. *International Journal of Epidemiology*, 40, 294–307. <https://doi.org/10.1093/ije/dyp394>
- Wabnegger, A., Scharmüller, W., & Schienle, A. (2014). Sex-specific associations between grey matter volume and phobic symptoms in dental phobia. *Neuroscience Letters*, 580, 83–87. <http://www.sciencedirect.com/science/article/pii/S0304394014006351>
- Wang, X., Cheng, B., Luo, Q., Qiu, L., & Wang, S. (2018). Gray matter structural alterations in social anxiety disorder: A voxel-based Meta-analysis. *Frontiers in Psychiatry*, 9, 1–13. <https://www.frontiersin.org/article/10.3389/fpsy.2018.00449>

- Weinberger, D. R., & Radulescu, E. (2015). Finding the elusive psychiatric "lesion" with 21st-century neuroanatomy: A note of caution. *The American Journal of Psychiatry*, *173*, 27–33. <http://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2015.15060753>
- Weiner, M. W., Veitch, D. P., Aisen, P. S., Beckett, L. A., Cairns, N. J., Green, R. C., ... Trojanowski, J. Q. (2013). The Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception. *Alzheimer's & Dementia*, *9*, e111–e194. <http://www.sciencedirect.com/science/article/pii/S1552526013024291>
- Wendt, J., Schmidt, L. E., Lotze, M., & Hamm, A. O. (2012). Mechanisms of change: Effects of repetitive exposure to feared stimuli on the brain's fear network. *Psychophysiology*, *49*, 1319–1329. <https://doi.org/10.1111/j.1469-8986.2012.01451.x>
- Wiemer, J., Schulz, S. M., Reicherts, P., Glotzbach-Schoon, E., Andreatta, M., & Pauli, P. (2014). Brain activity associated with illusory correlations in animal phobia. *Social Cognitive and Affective Neuroscience*, *10*, 969–977. <https://doi.org/10.1093/scan/nsu142>
- Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage*, *92*, 381–397. <http://www.sciencedirect.com/science/article/pii/S1053811914000913>
- Wittchen, H.-U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., ... Steinhausen, H.-C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, *21*, 655–679. <http://www.sciencedirect.com/science/article/pii/S0924977X11001726>
- Woo, C.-W., Chang, L. J., Lindquist, M. A., & Wager, T. D. (2017). Building better biomarkers: Brain models in translational neuroimaging. *Nature Neuroscience*, *20*, 365–377. <http://www.nature.com/doi/10.1038/nn.4478>
- Wright, B., Alderson-Day, B., Prendergast, G., Kennedy, J., Bennett, S., Docherty, M., ... Green, G. (2013). Neural correlation of successful cognitive behaviour therapy for spider phobia: A magnetoencephalography study. *Psychiatry Research: Neuroimaging*, *214*, 444–451. <http://www.sciencedirect.com/science/article/pii/S0925492713002679>
- Wright, B. J. D., Kennedy, J., Bennett, S., Manea, L. E., Tomlinson, H., & Tindall, L. (2015). What can comprehensive cognitive Behavioural therapy achieve in people with spider phobia? – A case series. *Jacobs Journal of Clinical Case Reports*.
- Wu, M.-J., Wu, H. E., Mwangi, B., Sanches, M., Selvaraj, S., Zunta-Soares, G. B., & Soares, J. C. (2015). Prediction of pediatric unipolar depression using multiple neuromorphometric measurements: A pattern classification approach. *Journal of Psychiatric Research*, *62*, 84–91. <http://www.sciencedirect.com/science/article/pii/S002239561500028X>
- Yang, Y., Lueken, U., Richter, J., Hamm, A., Wittmann, A., Konrad, C., ... Kircher, T. (2019). Effect of CBT on biased semantic network in panic disorder: A multicenter fMRI study using semantic priming. *The American Journal of Psychiatry*, *177*, 254–264. <https://doi.org/10.1176/appi.ajp.2019.19020202>
- Zilverstand, A., Sorger, B., Kaemingk, A., & Goebel, R. (2017). Quantitative representations of an exaggerated anxiety response in the brain of female spider phobics—A parametric fMRI study. *Human Brain Mapping*, *38*, 3025–3038. <https://doi.org/10.1002/hbm.23571>
- Zilverstand, A., Sorger, B., Slaats-Willemse, D., Kan, C. C., Goebel, R., & Buitelaar, J. K. (2017). fMRI neurofeedback training for increasing anterior cingulate cortex activation in adult attention deficit hyperactivity disorder. An exploratory randomized, single-blinded study. *PLoS ONE*, *12*, e0170795. <https://doi.org/10.1371/journal.pone.0170795>
- Zugman, A., Harrewijn, A., Cardinale, E. M., Zwiebel, H., Freitag, G. F., Werwath, K. E., ... Winkler A. M. (2020). Mega-Analysis Methods in ENIGMA: The Experience of the Generalized Anxiety Disorder Working Group. *PsyArXiv:preprint*. <https://psyarxiv.com/n62vc/>.

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