Received: 2 March 2020 | Revised: 9 May 2020 | Accepted: 8 June 2020

DOI: 10.1002/hbm.25100

REVIEW ARTICLE

WILEY

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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Funding information
Anxiety Disorders Research Network European College of Neuropsychopharmacology; Claude Leon Postdoctoral Fellowship; Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), Grant/Award Number: 44541416 - TRR 58; EU7th Frame Work Marie Curie Actions International Staff Exchange Scheme grant 'European and South African Research Network in Anxiety Disorders' (EUSARNAD); Geestkracht programme of the Netherlands Organization for Health Research and Development (ZonMw), Grant/Award Number: 10-000-1002; Intramural Research Training Award (IRTA) program within the National Institute of Mental Health under the Intramural Research Program (NIMH-IRP), Grant/Award Number: MH002781; National Institute of Mental Health under the Intramural Research Program (NIMH-IRP), Grant/Award Number: ZIA-MH-002782; SA Medical Research Council; U.S. National Institutes of Health grants, Grant/Award Numbers: P01 AG026572, P01 AG055367, P41 EB015922, R01 AG060610, R56 AG058854, RF1 AG051710, U54 EB020403

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 heterogenous 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 underrecognition 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 (Klumpp & 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,

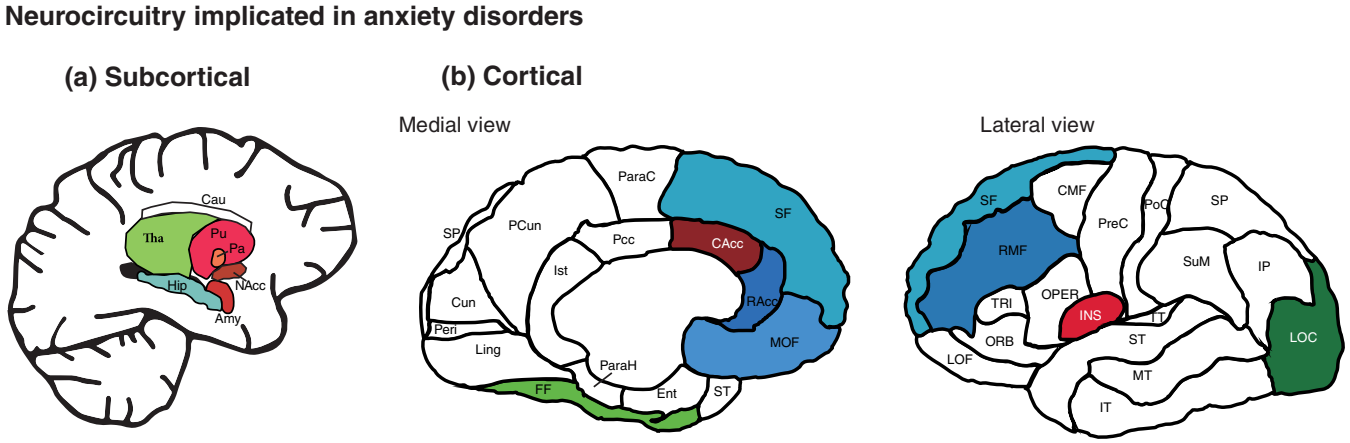

FIGURE 1 Overview of neurocircuitry involved in anxiety disorders. This schematic overview illustrates the subcortical (Figure 1a) and cortical (Figure 1b) regions that are part of the FreeSurfer pipeline (RRID:SCR_001847; http://surfer.nmr.mgh.harvard.edu). Regions involved in anxiety are colored based 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 med	STAI-trait	ASI	BAI	LSAS	PAS	ACQ	PDSS	HAM_A	PSWQ	GAD_7	BDI-II	HAM_D	CDI	SCARED	Field strength (T)	Scanner	T1-w 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	0	0	1	1.5	GE	1	1	1	1
GAD_02	BR	Universidade Federal do Rio Grande do Sul	PROTAIA	(Salum et al., 2011; Toazza et al., 2016)	26	18	13–22	M&F	KSADS	1	1	0	1	0	0	0	1	0	0	0	0	0	1	1	0	1	1	3	?	1	?	0	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	1	0	0	0	0	1	0	1	0	0	0	3	SIE	1	0	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	1	0	0	0	0	0	0	1	0	0	0	0	0	3	SIE	1	0	1	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	1	0	0	0	1.5	SIE	1	0	0	1
GAD_06	ES	Universitat Autonoma de Barcelona	Barcelona	(Porta et al., 2017)	31	60	18–40	M&F	MINI	1	1	0	1	1	1	1	1	0	0	0	1	1	0	1	0	0	0	1.5	GE	1	0	1	0
GAD_07	IT	University of Milan	Milan	(Molent et al., 2018)	34	64	21–73	M&F	SCID	1	1	1	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	3	PHI	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	1	0	0	0	0	0	0	0	1	0	0	1	1	0	0	1.5	PHI	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	1	0	0	0	0	0	1	0	1	0	0	0	1.5	SIE	1	0	1	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	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	1	0	0	0	0	3	SIE	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	1	0	0	0	0	0	0	0	0	0	1	3	SIE	1	0	1	1

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	PSWQ	GAD_7	BDI-II	HAM_D	CDI	SCARED	Field strength (T)	Scanner	T1-w 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	43	18–60	M&F	?	1	1	0	1	1	0	1	1	0	0	1	1	1	0	1	1	0	0	?	?	1	?	?	?
GAD_14	US	University of Illinois at Chicago	Chicago-Milad		27	16	18–59	M&F	?	1	1	0	0	1	1	1	0	0	0	0	0	0	0	1	0	0	0	?	?	1	?	?	?
GAD_15	US	University of Cincinnati	Cincinnati	(Strawn et al., 2012)	10	11	12–18	M&F	KSADS	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	OTH	1	0	1	1
GAD_16	US	Child Mind Institute	CMI	(Alexander et al., 2017)	121	170	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
GAD_17	US	Duke University	Duke	(Carpenter et al., 2015)	26	19	6–10	M&F	OTH	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	GE	1	1	1	0
GAD_18	US	Harvard Medical School	Harvard		203	57	18–40	M&F	SCID	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	3	SIE	1	1	1	1
GAD_19	US	UT Health	Houston_GAD		9	264	8–68	M&F	SCID	1	1	0	1	0	0	0	0	0	0	0	1	0	0	1	1	0	1	1.5	PHI	1	0	0	0
GAD_20	US	University of Pittsburgh	PittsburghAndreescu	(Karim et al., 2016)	38	741	19–90	M&F	SCID	1	1	1	1	0	0	0	0	0	0	0	1	1	0	0	1	0	0	3	SIE	1	1	1	0
GAD_21	US	University of Pittsburgh	PittsburghPrice	[Price et al., in press; Price et al., 2018]	69	0	18–54	M&F	MINI	1	1	0	1	1	0	1	1	0	0	0	0	1	0	1	0	0	0	3	SIE	1	0	1	0
GAD_22	US	National Institute of Mental Health	SDAN	(Gold et al., 2020; Gold et al., 2017)	243	166	8–51	M&F	SCID & KSADS	1	1	0	0	1	1	1	1	0	0	0	1	1	0	1	0	1	1	3	GE	1	1	1	1
GAD_23	US	National Institute of Mental Health	SNFA	(Balderston et al., 2017)	23	40	19–50	M&F	SCID	1	1	0	1	1	0	1	0	0	0	0	0	0	0	1	0	0	0	3	GE	1	0	0	0
GAD_24	US	Stony Brook University	Stony Brook	(Cha et al., 2016)	41	20	18–49	Only F	?	0	1	0	1	1	1	0	0	0	0	0	0	1	0	1	0	0	0	?	?	1	?	?	?
GAD_25	US	University of California - San Diego	UCSD	(Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2013; Fonzo et al., 2014)	46	50	17–53	M&F	MINI & SCID	1	1	0	1	1	1	0	0	0	0	0	0	0	1	0	1	0	0	0	3	GE	1	0	1	?
GAD_26	US	University of Pennsylvania	PNC	(Calkins et al., 2015; Satterthwaite et al., 2014)	27	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

(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	PSWQ	GAD_7	BDI-II	HAM_D	CDI	SCARED	Field strength (T)	Scanner	T1-w MRI	DTI	fMRI	Material for genetics
GAD_27	US	Washington University	Washington		32	31	8–12	M&F	KSADS	1	1	1	1	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	21–71	M&F	MINI	1	1	0	1	0	0	0	1	0	0	0	1	1	0	0	1	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	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	SC2ARED	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	1	0	0	1.5	GE	1	0	1	1
PD_02	DE	Philipps-University Marburg	Panic-net	(Kircher et al., 2013; Yang et al., 2019)	159	182	19–67	M&F	SCID	1	1	0	*Excl*	0	1	0	0	1	1	0	1	0	0	1	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	1	0	0	0	1.5	SIE	1	0	0	1
PD_04	DE	University of Marburg	FOR2107 MR	(Kircher 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	1	1	0	0	3	SIE	1	1	1	1
PD_05	DE	University of Wuerzburg	DOM-PANTHER	(Gottschalk et al., 2019; Neufang et al., 2019)	33	45	21–55	M&F	SCID	1	1	1	1	1	1	1	0	0	1	0	1	1	0	1	0	0	0	3	SIE	1	1	1	1
PD_06	DE	University of Muenster	IMPS	(Feldker et al., 2016)	40	41	18–46	M&F	SCID	1	1	0	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	3	SIE	1	0	1	0
PD_07	DE	University of Muenster	Münster neuroimaging cohort and panic emotion processing	(Ohrmann 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	1	1	0	0	3	PHI	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	1	1	0	0	3	SIE	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	1	0	0	0	0	1	0	0	0	1.5	SIE	1	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	1	0	0	0	0	1	0	0	0	3	SIE	1	0	0	?
PD_11	IT	University Vita-Salute San Raffaele	Milan_OSR	(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	1	0	0	0	3	PHI	1	0	1	0
PD_12	IT	University of Milan	Milan_1.5 T	(Maggioni et al., 2019)	11	21	18–66	M&F	SCID	1	1	1	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	1.5	SIE	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	1	0	0	0	1	0	0	3	PHI	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 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	SC2ARED	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	0	0	0	0	0	1	0	0	0	0	0	0	0	1.5	SIE	1	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	0	0	3	GE	1	1	1	1
PD_16	NL	Amsterdam, Groningen, Leiden University Medical Centers	NESDA	(Penninx et al., 2008; van Tol 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
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
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	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	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	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	1	0	1	0	0	1.5	PHI	1	0	0	0
PD_23	US	Columbia University & New York State psychiatric institute		(Talati, Pantazatos, Schneier, 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	0	1.5	PHI	1	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	1	0	1	0	0	0	3	GE	1	0	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	1	1	0	0	0	1	0	0	3	GE	1	0	1	0

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

TABLE 3 Anx_SAD (social anxiety disorder)

General sample information									Clinical information					Questionnaires															MRI and genetic information					
Sample #	Country	Institute	Sample	Key-references	# SAD	# 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	Field strength (T)	Scanner	T1-w MRI	DTI	fMRI	Material for genetics
SAD_01	BE	Université Catholique de Louvain	Louvain	(Heeren et al., 2017)	23	23	18–38	Only F	MINI	*Excl*	*Excl*	0	*Excl*	1	0	0	1	0	0	0	0	0	0	1	0	0	0	3	PHI	1	0	0	0
SAD_02	BR	INPD	Brazilian HRC study	(Salum et al., 2015)	8	668	5–15	M&F	OTH	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1.5	GE	1	1	1	1
SAD_03	CN	West China Hospital of Sichuan University	HMRRC	(Qiu et al., 2015)	19	20	18–32	M&F	SCID	*Excl*	*Excl*	1	*Excl*	0	0	0	1	0	0	0	1	0	0	0	1	0	0	3	GE	1	1	1	0
SAD_04	DE	Technische Universität Dresden	Dresden SAD		20	21	18–40	M&F	CIDI	1	1	1	*Excl*	1	0	0	1	0	0	0	0	1	0	1	0	0	0	3	SIE	1	0	1	1
SAD_05	DE	University of Marburg	FOR2107 MR	(Kircher et al., 2019; Vogelbacher et al., 2018)	29	370	18–65	M&F	SCID	1	1	0	1	1	0	0	0	0	0	0	1	0	0	1	1	0	0	3	SIE	1	1	1	1
SAD_06	DE	University of Muenster	FOR2107 MS	(Repple et al., 2020)	27	238	18–65	M&F	SCID	1	1	0	1	1	0	0	0	0	0	0	1	0	0	1	1	0	0	3	SIE	1	1	1	1
SAD_07	DE	University of Tübingen	Fortuene	(Kreifelts et al., 2017)	12	14	19–30	M&F	SCID	1	1	0	*Excl*	1	0	0	1	0	0	0	0	0	0	1	0	0	0	3	SIE	1	1	1	0
SAD_08	DE	University of Muenster	Muenster PACK	(Heitmann et al., 2016)	45	46	19–57	M&F	SCID	1	1	0	1	1	1	0	1	0	0	0	0	0	0	1	1	0	0	3	SIE	1	1	1	1
SAD_09	DE	University Medicine Greifswald	SHIP	(Völzke et al., 2011)	32	699	31–90	M&F	CIDI	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1.5	SIE	1	0	0	1
SAD_10	DE	University of Muenster	SP_Münster	(Laeger et al., 2014; Laeger et al., 2014)	67	490	17–59	M&F	SCID	1	1	1	1	1	0	0	1	0	0	0	0	0	0	1	1	0	0	3	PHI	1	1	1	1
SAD_11	DE	University of Muenster	TIP		27	38	18–53	M&F	SCID	*Excl*	1	1	1	1	1	0	1	0	0	0	0	0	0	1	0	0	0	3	SIE	1	1	1	1
SAD_12	DE	University of Muenster	Muenster SAD	(Boehme et al., 2014; Boehme, Mohr, Becker, Miltner, & Straube, 2014)	19	22	19–56	M&F	SCID	1	1	0	*Excl*	0	0	0	1	0	0	0	0	0	0	1	0	0	0	3	SIE	1	0	0	0
SAD_13	ES	Hospital del Mar Barcelona	DelMar		63	99	18–61	M&F	OTH	*Excl*	*Excl*	0	*Excl*	1	0	0	1	0	0	0	0	0	0	0	1	0	0	1.5	GE	1	0	1	0
SAD_14	NL		DCCN		23	24	19–57	M&F	MINI	1	1	0	*Excl*	0	0	0	1	0	0	0	0	0	0	1	0	0	0	1.5	SIE	1	0	1	0

TABLE 3 (Continued)

General sample information										Clinical information					Questionnaires															MRI and genetic information					
Sample #	Country	Institute	Sample	Key-references	# SAD	# 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	Field strength (T)	Scanner	T1-w MRI	DTI	fMRI	Material for genetics
		Donders Institute Nijmegen																																
SAD_15	NL	Leiden University Medical Center, Leiden University	LFLSAD	(Bas-Hoogendam et al., 2018; Bas-Hoogendam, van Steenbergen, et al., 2018)	11	11	18–61	M&F	MINI	1	1	1	1	1	0	0	1	0	0	0	0	0	0	1	0	0	0	3	PHI	1	1	1	1
SAD_16	NL	Leiden University Medical Center	LUMC	(Cremers et al., 2014; Cremers, Veer, Spinhoven, Rombouts, & Roelofs, 2015)	20	20	20–45	M&F	MINI	1	1	0	1	0	0	0	1	0	0	0	0	0	0	1	0	0	0	3	PHI	1	0	1	0
SAD_17	NL	Amsterdam, Groningen, Leiden University Medical Centers	NESDA	(Penninx et al., 2008; van Tol et al., 2010)	102	64	19–56	M&F	CIDI	1	1	1	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	3	PHI	1	0	1	1
SAD_18	SA	SU/UCT MRC Unit on Anxiety & Stress Disorders	SU_MRC	(Doruyter et al., 2016)	11	11	21–46	M&F	SCID	*Excl*	*Excl*	1	*Excl*	1	0	0	1	0	0	0	0	0	0	1	0	0	0	1.5	SIE	1	0	0	1
SAD_19	SA	SU/UCT MRC Unit on Anxiety & Stress Disorders	UCT_MRC	(Howells et al., 2015; Syal et al., 2012)	11	11	18–45	M&F	SCID	1	1	1	*Excl*	0	0	0	1	0	0	0	0	0	0	0	0	0	0	3	SIE	1	0	1	1
SAD_20	SE	Umea University	Umea_Vox	(Månsson et al., 2019)	46	42	18–52	M&F	MINI & SCID	1	1	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	3	GE	1	0	1	1
SAD_21	SE	Umea University	Umea_Sofie	(Månsson et al., 2013; Månsson et al., 2015)	26	23	18–57	M&F	SCID	1	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	3	GE	1	0	1	1
SAD_22	TR	Istanbul University	Istanbul	(Tükel et al., 2015)	34	22	23–45	M&F	SCID	1	1	0	*Excl*	0	0	0	1	0	0	0	1	0	0	0	1	0	0	1.5	PHI	1	1	1	0
SAD_23	US	Baylor College of Medicine	Baylor	(Curtis et al., 2019; Gosnell et al., 2020)	72	149	12–79	M&F	SCID	1	1	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	3	SIE	1	1	1	1
SAD_24	US	Boys Town National Research Hospital	Boystown	(Blair, Aloi, et al., 2019; Blair, White, et al., 2019)	50	44	11–18	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	1
SAD_25	US	Columbia University & New York State Psych. Institute	Columbia_SAD	(Talati et al., 2013; Talati, Pantazatos, Hirsch, & Schneier, 2015)	16	16	19–53	M&F	OTH	1	1	0	*Excl*	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1.5	GE	1	0	1	0

(Continues)

TABLE 3 (Continued)

General sample information									Clinical information					Questionnaires																MRI and genetic information					
Sample #	Country	Institute	Sample	Key-references	# SAD	# 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	Field strength (T)	Scanner	T1-w MRI	DTI	fMRI	Material for genetics
SAD_26	US	Columbia University & New York State Psychiatric Institute	Columbia_SPP	(Pantazatos, Talati, Schneier, & Hirsch, 2014; Talati et al., 2013)	16	19	21–53	M&F	SCID	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1.5	GE	1	0	1	0
SAD_27	US	UT Health	Houston_SAD		34	34	8–61	M&F	SCID	1	1	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1.5	PHI	1	0	0	0
SAD_28	US	University of Pennsylvania	PNC	(Calkins et al., 2015; Satterthwaite et al., 2014)	328	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	0
SAD_29	US	National Institute of Mental Health	SDAN	(Gold et al., 2020; Gold et al., 2017)	80	95	8–22	M&F	SCID & KSADS	1	1	0	Excl	1	0	0	1	0	0	0	0	0	0	1	0	1	1	3	GE	1	1	1	1
SAD_30	US	University of California-San Diego	UCSD_Ball_SDSU	(Campbell-Sills et al., 2011)	17	19	17–33	M&F	SCID	1	1	0	*Excl*	1	1	0	1	0	0	0	0	1	0	1	0	0	0	3	GE	1	0	1	0
SAD_31	US	University of California - San Diego	UCSD_Sapient_INSULA	(Fonzo et al., 2015)	44	26	18–53	M&F	MINI	1	1	0	*Excl*	1	1	0	0	0	0	0	0	1	0	1	0	0	0	3	GE	1	0	1	1
SAD_32	US	Vanderbilt University	Vanderbilt	(Clauss et al., 2014; Clauss et al., 2014)	10	15	19–26	M&F	SCID	1	1	0	*Excl*	1	1	0	0	0	0	0	0	0	0	1	0	0	0	3	PHI	1	1	1	1
SAD_33	US	Washington University	Washington		19	30	8–12	M&F	KSADS	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	3	SIE	1	0	1	0
SAD_34	US	University of Illinois at Chicago	UIC	(Phan et al., 2013)	12	11	22–50	M&F	SCID	1	1	1	*Excl*	1	0	0	1	0	0	0	0	0	0	1	0	0	0	3	GE	1	1	0	1
SAD_35	US	Institute of Living/Hartford hospital	IOL	(Rabany et al., 2017)	11	21	21–71	M&F	MINI	1	1	0	1	0	0	0	1	0	0	0	1	1	0	0	1	0	0	3	SIE	1	0	1	0

Note: Leaders of the Anx_SAD subgroup: Janna Marie Bas-Hoogendam, Nynke A. Groenewold, Dan J. Stein, Nic J. A. van der Wee.

TABLE 4 Anx_SP (specific phobia)

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	Specific phobia questionnaires	Field strength (T)	Scanner	T1-w MRI	DTI	fMRI	Material for genetics
SP_01	AT	University of Graz	Graz dental phobia	(Wabnegger, Scharmüller, & Schienle, 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	0	DAS, FDP	3	SIE	1	0	0	0
SP_02	AT	University of Graz	Graz dental phobia II	(Schienle, 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	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	1	DAWBA	1.5	GE	1	1	1	1
SP_04	DE	Ruhr-Universität Bochum	Bochum dental phobia		18	0	27–60	M&F	OTH	1	1	0	1	0	0	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	0	1	0	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	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	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	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	1	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	0	0	SPQ	3	SIE	1	0	1	0
SP_11	DE	University of Marburg	FOR2107 MR	(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	1	0	0	1	1	0	0	0	3	SIE	1	1	1	1
SP_12	DE	University of Muenster	FOR2107 MS	(Repple et al., 2020)	28	247	18–65	M&F	SCID	1	1	0	1	1	0	0	0	0	0	0	1	0	0	1	1	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	1	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	1	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	1	1	0	1	0	0	1	0	1	0	0	0	SPQ	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	1	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	Specific phobia questionnaires	Field strength (T)	Scanner	T1-w MRI	DTI	fMRI	Material for genetics
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	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
SP_19	DE	University Hospital of Wuerzburg	SFBTRR-58 project C09 (SpiderVR)	(Schwarzmeier et al., 2019)	87	0	18–65	M&F	SCID	1	1	1	1	1	1	1	1	0	1	0	0	1	0	1	0	0	0	SPQ	3	SIE	1	0	1	1
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	1	0	1	0	1	1	0	0	0	DSM-5-SP	3	SIE	1	0	1	1
SP_21	ES	Universidad de La Laguna	Teneriffa animals phobia	(Rivero, Herrero, Viña, 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	S-R IA	3	GE	1	0	1	0
SP_22	NL	University of Amsterdam	RepSpi	(Visser, Haver, Zwitser, 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	SPQ	3	PHI	1	0	1	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
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
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	FSQ	3	SIE	1	1	1	1
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	SPQ	3	PHI	1	1	0	0
SP_27	PL	SWPS University of Social Sciences and Humanities	Czuwaj	(Michałowski 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	FSS	3	SIE	1	1	1	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	SPQ	3	PHI	1	1	1	0
SP_29	UK	COMIC Research/ LYPFT	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	FSQ	3	GE	1	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	None	3	GE	1	0	?	0

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	Specific phobia questionnaires	Field strength (T)	Scanner	T1-w MRI	DTI	fMRI	Material for genetics
SP_31	US	University of Pennsylvania	PNC	(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	0	0	3	SIE	1	1	1	0
SP_32	US	Vanderbilt University	Vanderbilt phobia sample	(Clauss, Avery, et al., 2014; Clauss, 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	None	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

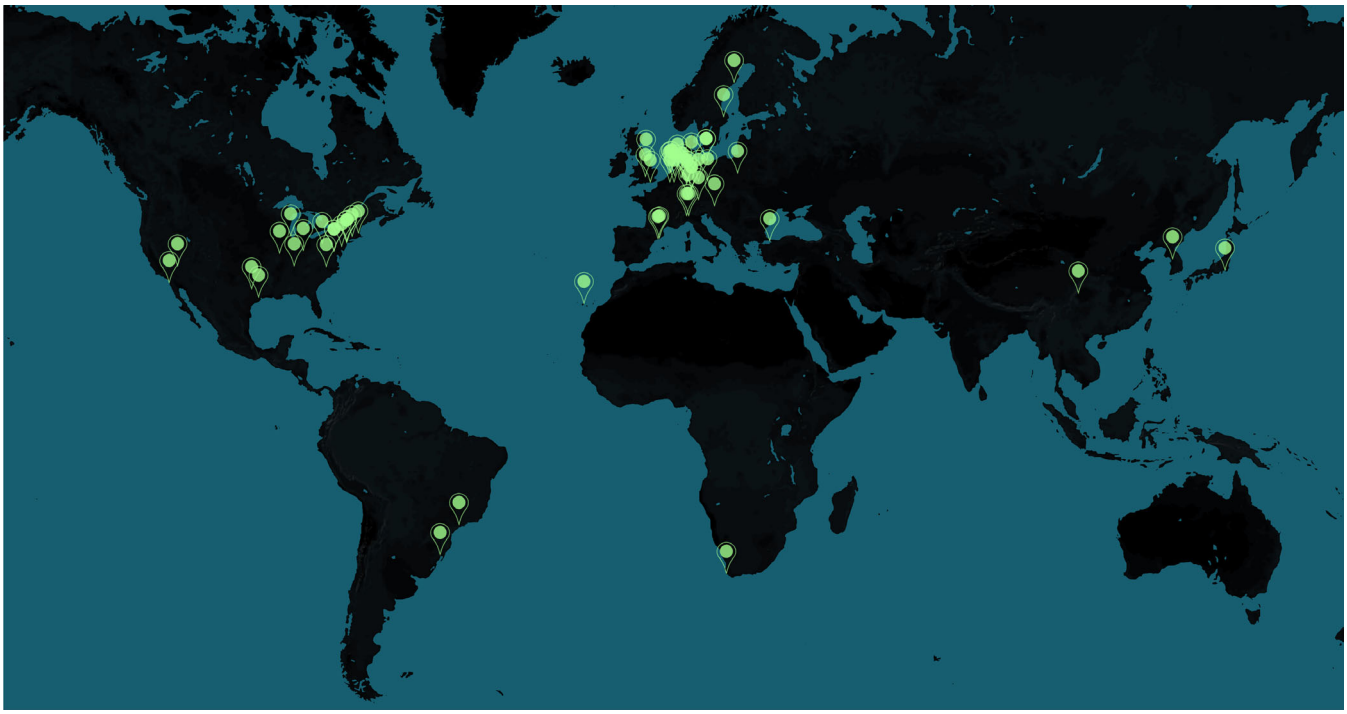

FIGURE 2 Institutes participating in ENIGMA-Anxiety—world map

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 preregistration 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 collated, 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 & Ustün, 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.

ACKNOWLEDGMENTS

J. M. B. H. none. N. A. G was supported by a Claude Leon Postdoctoral Fellowship. M. A. none. G. F. F. is supported by the Intramural Research Training Award (IRTA) program within the National Institute of Mental Health under the Intramural Research Program (NIMH-IRP) through project MH002781. A. H., A. M. W. and D. S. P. are supported by the National Institute of Mental Health under the Intramural Research Program (NIMH-IRP) through project ZIA-MH-002782. K. H. none. N. J., S. I. T., and P. M. T. were supported by U.S. National Institutes of Health grants U54 EB020403, P41 EB015922, P01 AG026572, P01 AG055367, RF1 AG051710, R01 AG060610, and R56 AG058854 to the ENIGMA World Aging Center. D. J. V. none. UL was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Projektnummer 44541416—TRR 58. N. J. A. W. EU7th Frame Work Marie Curie Actions International Staff Exchange Scheme grant “European and South African Research Network in Anxiety Disorders” (EUSARNAD), Anxiety Disorders Research Network European College of Neuropsychopharmacology; the infrastructure for the Netherlands Study of Depression and Anxiety (NESDA) was funded through the Geestkracht programme of the Netherlands Organization for Health Research and Development (ZonMw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations. D. J. S. is supported by the SA Medical Research Council. EU7th Frame Work Marie Curie Actions International Staff Exchange Scheme grant 'European and South African Research Network in Anxiety Disorders' (EUSARNAD).

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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How to cite this article: Bas-Hoogendam JM, Groenewold NA, Aghajani M, et al. ENIGMA-anxiety working group: Rationale for and organization of large-scale neuroimaging studies of anxiety disorders. *Hum Brain Mapp*. 2022;43:83–112. https://doi.org/10.1002/hbm.25100