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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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, Third, 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 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.
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, Luuken, & 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; Cauette & 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; Luuken 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](image-url)
| 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 | BDH-I | HAM-D | CDI | SCARED | Field strength (T) | Scanner | T1-w | DTI | fMRI | Material for genetics |
|----------|---------|-----------|--------|----------------|-------|------|-------------|-----|---------------------|-----------|---------------|----------|----------|-----------|---------|--------|-------|-------|------|-------|-------|-------|------|-------|-------|------|------|-------|---------------------|---------|-------|------|------|------------------|
| GAD_01   | BR      | INPD      | Brazilian | (Salum et al., 2015) | 101   | 668  | 5–15       | M&F | OTH                | 1         | 1              | 0        | 0       | 0         | 0       | 0      | 0     | 0     | 0    | 0     | 0     | 0     | 0    | 0     | 1     | 15   | 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        | 0       | 0         | 0       | 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 | CDI              | 1         | 1              | 0        | 1       | 0         | 0       | 0      | 0     | 0     | 0    | 1     | 0     | 1     | 0    | 0     | 0     | 3    | SIE   | 1     | 0    | 1    | 1    |                          |
| GAD_04   | DE      | University of Munich | Munich GAD | (Buff et al., 2016) | 25    | 29   | 19–56     | M&F | ?                | 0         | 0              | 0        | 1       | 1         | 0       | 0      | 0     | 0     | 0    | 1     | 0     | 0     | 0    | 0     | 0     | 3    | SIE   | 1     | 0    | 0    | 1    |                          |
| GAD_05   | DE      | University Medicine Göttingen | SHIP | (Wölke et al., 2011) | 12    | 24   | 41–70     | M&F | CDI              | 1         | 1              | 1        | 0       | 0         | 0       | 0      | 0     | 0     | 0    | 1     | 0     | 1     | 0    | 0     | 0     | 15   | SIE   | 1     | 0    | 0    | 1    |                          |
| GAD_06   | ES      | Universität Autonoma de Barcelona | Barcelona | (Porta et al., 2017) | 31    | 60   | 18–40     | M&F | MINI            | 1         | 1              | 0        | 1       | 1         | 1       | 1      | 0     | 0     | 0    | 1     | 1     | 0     | 1    | 0     | 0     | 15   | SIE   | 1     | 0    | 1    | 0    |                          |
| GAD_07   | IT      | University of Milan | Milan | (Milet et al., 2018) | 34    | 64   | 21–73     | M&F | SCID            | 1         | 1              | 1        | 0       | 0         | 0       | 0      | 1     | 0     | 0    | 0     | 1     | 0     | 1    | 0     | 0     | 3    | PHI   | 1     | 1    | 1    | 1    |                          |
| GAD_08   | IT      | University Vita-Salute San Raffaele | San Raffaele | (Cann et al., 2015) | 21    | 71   | 22–63     | M&F | SCID            | 1         | 1              | 1        | 0       | 0         | 0       | 0      | 0     | 1     | 0    | 1     | 1     | 0     | 0    | 0     | 0     | 15   | SIE   | 1     | 1    | 1    | 1    |                          |
| GAD_09   | UK      | Sussex university/ Sheffield university | Sussex | (Makovic et al., 2016; Makovic et al., 2016) | 19    | 21   | 18–35     | M&F | SCID            | 1         | Excl           | 1         | 1       | 1         | 0       | 0      | 0     | 0     | 0    | 1     | 0     | 1     | 0    | 0     | 0     | 15   | SIE   | 1     | 1    | 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     | 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    | 1     | 0     | 0     | 0    | 0     | 0     | 3    | SIE   | 1     | 1    | 1    | 1    |                          |
| GAD_12   | US      | Boys Town National Research Hospital | Boys Town | (Blair et al., 2019; Blair et al., 2019) | 50    | 45   | 13–38     | M&F | OTH            | 1         | 1              | 0        | 1       | 0         | 0       | 0      | 0     | 0     | 0    | 0     | 0     | 0     | 0    | 0     | 0     | 3    | SIE   | 1     | 0    | 1    | 1    |                          |
| Sample # | Country | Institute | Sample Key-References | Sample Type | Age-Range (y) | Sex | Diagnostic Interview | Other Psych. Stds. | Comorb Diagnoses | MRI & Scan Information | Genetic Information | Score Information | Qscore Information | Note Information |
|----------|---------|-----------|-----------------------|-------------|---------------|-----|----------------------|-----------------|-------------------|---------------------|---------------------|------------------|------------------|------------------|
| GAD_13   | US      | University of Illinois at Chicago | Chicago-Phan (Gorka et al., 2019; Klumpp et al., 2018) | 27 - 30 | 26.18-39 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_14   | US      | University of Illinois at Chicago | Chicago-Milad | 27 - 30 | 26.18-39 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_15   | US      | University of Cincinnati | Cincinnati (Strawn et al., 2012) | 10 - 18 | 10.12-18 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_16   | US      | Child Mind Institute | CMI (Alexander et al., 2017) | 121 - 170 | 120.170-120 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_17   | US      | Duke University | Duke | 26 - 39 | 39.6-39 | M&F | 1 1 1 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_18   | US      | University of Cincinnati | Cincinnati (Strawn et al., 2012) | 10 - 18 | 10.12-18 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_19   | US      | University of Pittsburgh | PittsburghAndreescu (Karim et al., 2016) | 69 - 0 | 0-18 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_20   | US      | National Institute of Mental Health | SDAN (Gold et al., 2020; Gold et al., 2017) | 89 - 0 | 0-18 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_21   | US      | National Institute of Mental Health | University of Michigan | 100 - 0 | 0-18 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_22   | US      | Stony Brook University | Stony Brook (Cha et al., 2016) | 41 - 20 | 20.41-20 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_23   | US      | University of California - San Diego | UCSD (Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2013; Fonzo et al., 2014) | 23 - 57 | 57.23-35 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_24   | US      | University of California - San Diego | UCSD (Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2013; Fonzo et al., 2014) | 23 - 57 | 57.23-35 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_25   | US      | University of Pennsylvania | PNH | 46 - 30 | 30.46-30 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| GAD_26   | US      | University of Pennsylvania | PNH | 46 - 30 | 30.46-30 | M&F | 01 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |

(Continued)
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
| 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 | MRI | DTI | T1-w | 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        | 0         | 0   | 0   | 1    | 0   | 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 | 39–67        | M&F | SCID               | 1          | 1          | 0          | Excl     | 0         | 1   | 0   | 1    | 0   | 0   | 1    | 0     | 0     | 0     | 3    | SIE  | 1     | 0     | 1     | 1     |
| PD_03    | DE      | University Medicine Greifswald | SHP | (Pané-Faré et al., 2014; Völkle et al., 2011) | 27   | 699 | 31–90        | M&F | CIDI               | 1          | 1          | 1          | 1        | 0         | 0   | 0   | 0    | 0   | 0   | 0    | 0     | 1     | 0     | 0    | 1.5  | SIE  | 1     | 0     | 0     | 1     |
| PD_04    | DE      | University of Marburg | FOR2107 MR | (Kircher et al., 2019; Vogt et al., 2018) | 35   | 471 | 38–65        | M&F | SCID               | 1          | 1          | 0          | 1        | 0         | 0   | 0   | 0    | 1   | 0   | 1    | 0     | 1     | 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   | 0   | 1    | 1     | 0     | 1     | 0    | 3    | SIE  | 1     | 1     | 1     | 1     |
| PD_06    | DE      | University of Muenster | IMPS | (Fedorner et al., 2016) | 40   | 41  | 38–46        | M&F | SCID               | 1          | 1          | 0          | 1        | 1         | 0   | 0   | 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 | (Oehmann et al., 2010; Opel et al., 2019) | 71   | 735 | 15–65        | M&F | SCID               | 1          | 1          | 0          | 1        | 0         | 0   | 0   | 0    | 0   | 0   | 0    | 1     | 0     | 1     | 0    | 3    | PHI  | 1     | 1     | 1     | 1     |
| PD_08    | DE      | University of Muenster | FOR2107 MS | (Bupp et al., 2020) | 29   | 233 | 38–65        | M&F | SCID               | 1          | 1          | 0          | 1        | 0         | 0   | 0   | 0    | 0   | 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         | 0   | 0   | 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  | 39–49        | M&F | SCID               | 1          | 1          | 0          | 1        | 1         | 0   | 0   | 0    | 0   | 1   | 0    | 0     | 0     | 0     | 3    | SIE  | 1     | 0     | 0     | ?     |
| PD_11    | IT      | University Vita-Salute San Raffaele | Milan_CSR | (Poletti et al., 2015) | 21   | 196 | 38–65        | M&F | OTH               | Excl       | 1          | 1          | 1        | 1         | 0   | 0   | 0    | 0   | 0   | 0    | 1     | 0     | 1     | 0    | 3    | PHI  | 1     | 0     | 1     | 0     |
| PD_12    | IT      | University of Milan | Milan_1.5 T | (Maggioni et al., 2019) | 11   | 21  | 38–66        | M&F | SCID               | 1          | 1          | 1          | 1        | 0         | 0   | 0   | 0    | 0   | 0   | 0    | 1     | 0     | 0     | 0    | 1.5  | SIE  | 1     | 1     | 1     | 1     |
| PD_13    | IT      | University of Milan | Milan_3T | (Molent et al., 2018) | 12   | 64  | 39–65        | M&F | SCID               | 1          | 1          | 1          | 1        | 0         | 0   | 0   | 0    | 0   | 1   | 0    | 0     | 1     | 0     | 0    | 3    | PHI  | 1     | 1     | 1     | 1     |
| 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 | SCARED | MRI | DWI | DTI | T1-w | Material for genetics |
|----------|---------|-----------|--------|---------------|------|------|--------------|-----|---------------------|-----|--------|-------------|----------|---------|-----------|-----|-----|------|-----|-----|------|------|------|-------|-------|-----|-------|-----|-----|------------------|
| PO_14    | JP      | Yokohama City University | YCU | (Asami et al., 2018) | 38   | 68   | 19–58       | MF | SCID               | 1   | 1      | 1           | 0        | 0       | 0         | 0   | 0   | 0    | 0   | 0   | 0    | 0    | 0    | 0     | 0     | 0   |      | 1.5 | 1    | 1      | 0     | 0     |
| PO_15    | KR      | CHA Bundang Medical Center | Cortical morphology | (Kang, Lee, & Lee, 2017; Kim et al., 2014) | 43   | 2    | 57–62       | MF | SCID               | 1   | 1      | 1           | 1        | 1        | 0         | 1   | 1   | 1    | 1   | 0    | 0    | 0    | 0    | 0     | 0     | 0   |      | 3   | 1    | 1      | 1     | 1     |
| PO_16    | NL      | Amsterdam, Groningen, Leiden University Medical Centers | NESDA | (Penninx et al., 2008; van Tol et al., 2010) | 44   | 65   | 18–65       | MF | CIDI               | 1   | 1      | 1           | 0        | 1        | 0         | 0   | 1   | 1    | 0   | 0    | 0    | 0    | 0    | 0     | 0     | 0   |      | 3   | PHI  | 1      | 1     | 1     |
| PO_17    | NL      | Amsterdam UMC, Vrije Universiteit Amsterdam | Vumc | (van den Heuvel et al., 2005) | 15   | 23   | 18–58       | MF | SCID               | 1   | 1      | 0           | 1        | 0        | 0         | 0   | 0   | 0    | 0   | 0    | 0    | 0    | 0    | 0     | 0     | 0   |      | 1.5 | SIE   | 1      | 0     | 1     |
| PO_18    | UK      | Oxford University |  | (Reinecke et al., 2015; Reinecke, THiQ, Croft, & Hamer, 2018) | 68   | 20   | 18–65       | MF | SCID               | 1   | 1      | 1           | 1        | 0        | 0         | 1   | 1   | 0    | 0   | 0    | 0    | 0    | 0    | 0     | 0     | 1   |      | 3   | SIE   | 1      | 0     | 1     |
| PO_19    | US      | Boys Town National Research Hospital | Boystown | (Blair, Aloi et al., 2019) | 50   | 56   | 1–18        | MF | OTH               | 1   | 1      | 0           | 1        | 0        | 0         | 0   | 0   | 0    | 0   | 0    | 0    | 0    | 0    | 0     | 1     | 0   |      | 3   | SIE   | 1      | 0     | 1     |
| PO_20    | US      | University of Pennsylvania | Penn | (Calhoun et al., 2015; Satterthwaite et al., 2014) | 14   | 428  | 8–23        | MF | OTH               | 1   | 1      | 0           | 1        | 0        | 0         | 0   | 0   | 0    | 0   | 0    | 0    | 0    | 0    | 0     | 0     | 0   |      | 3   | SIE   | 1      | 1     | 1     |
| PO_21    | US      | Harvard Medical School | RDoC |  | 24   | 57   | 38–40       | MF | CIDI               | 1   | 1      | 1           | 1        | 0        | 0         | 0   | 0   | 0    | 0   | 0    | 0    | 0    | 0    | 0     | 0     | 0   |      | 3   | SIE   | 1      | ?     | ?     |
| PO_22    | US      | UT Health | Houston_PD | (Wu et al., 2015) | 15   | 34   | 8–62        | MF | SCID               | 1   | 1      | 1           | 0        | 0        | 0         | 0   | 1   | 0    | 0   | 0    | 0    | 0    | 0    | 0     | 0     | 0   |      | 1.5 | PHI   | 1      | 0     | 0     |
| PO_23    | US      | Columbia University & New York State psychiatric institute |  | (Talati, Pantazis, Schweier, Weissman, & Hinch, 2013) | 17   | 19   | 18–65       | MF | OTH               | 1   | 1      | 1           | 1        | 0        | 0         | 0   | 0   | 0    | 0   | 0    | 0    | 0    | 0    | 0     | 0     | 0   |      | 1.5 | PHI   | 1      | 0     | 0     |
| PO_24    | US      | University of California - San Diego | INSULA, DV, SDSU | (Ball et al., 2013; Fonzo et al., 2015) | 45   | 45   | 20–49       | MF | OTH               | 1   | 1      | 0           | 1        | 1        | 0         | 0   | 0   | 1    | 0   | 1    | 0    | 0    | 0    | 0     | 0     | 0   |      | 3   | GE    | 1      | 0     | 1     |
| PO_25    | US      | Weill Cornell Medical College and University of Pennsylvania |  | (Milrod et al., 2016) | 24   | 0    | 18–70       | MF | OTH               | 1   | 1      | 1           | 1        | 0        | 0         | 0   | 1   | 0    | 0   | 0    | 0    | 0    | 0    | 0     | 0     | 0   |      | 3   | GE    | 1      | 0     | 1     |

Note: Leaders of the Anx_PD subgroup: Moji Aghajani and Dick J. Veltman.
| Sample # | Country | Institute | Sample | Key-references | Age-range (y) | Sex | # SAD # | MCI | Age | Anxiety comorb | Other comorb | Age onset med | Psych | STAI-trait | ASI | BAI | LSAS | PAS | ACQ | PDSS | HAM_A | PSWQ | GAD_7 | BDI-II | HAM_D | CDI | SCARED | MCI | Field | T1-w | Material for genetics |
|----------|---------|-----------|--------|---------------|--------------|-----|--------|------|------|-------------|-------------|-------------|-------|------------|-----|-----|------|-----|-----|------|-------|------|-------|--------|------|-----|-------|-----|------|
| SAD_01   | BE      | Université Catholique de Louvain | Louvain | (Heenan et al., 2017) | 23 | 23 | 18-38 | Only F | MNI | Excl | Excl | 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 | 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 | (Qu et al., 2015) | 19 | 20 | 18-32 | M&F | SCID | Excl | Excl | 1 | Excl | 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 | Excl | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 3 | SIE | 1 | 0 | 1 | 1 |
| SAD_05   | DE      | University of Marburg | FOR2107 MR | (Kirsch et al., 2019; Vogelbacher et al., 2018) | 29 | 370 | 18-65 | M&F | SCID | 1 | 1 | 0 | 1 | 1 | 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 | (Rappl et al., 2020) | 27 | 238 | 18-65 | M&F | SCID | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 3 | SIE | 1 | 1 | 1 | 1 |
| SAD_07   | DE      | University of Tubingen | Fortune | (Kreifelts et al., 2017) | 12 | 14 | 19-30 | M&F | SCID | 1 | 1 | 0 | Excl | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 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 | 1 | 1 | 0 | 0 | 3 | SIE | 1 | 1 | 1 | 1 |
| SAD_09   | DE      | University of Muenster | SHP | (Wilke et al., 2011) | 32 | 699 | 31-90 | M&F | CIDI | 1 | 1 | 1 | 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_Muenster | (Larger et al., 2014; Larger et al., 2016) | 67 | 490 | 17-39 | M&F | SCID | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 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 | 1 | 0 | 0 | 0 | 3 | SIE | 1 | 1 | 1 | 1 |
| SAD_12   | DE      | University of Muenster | Muenster SAD | (Boehme et al., 2014; Boehme, Mahr, Becker, Matthor, & Straube, 2016) | 19 | 22 | 19-56 | M&F | SCID | 1 | 1 | 0 | Excl | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 3 | SIE | 1 | 0 | 0 | 0 |
| SAD_13   | ES      | Hospital del Mar Barcelona | DeMar | | 63 | 99 | 18-61 | M&F | OTH | Excl | Excl | 0 | Excl | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1.5 | GE | 1 | 0 | 1 | 0 |
| SAD_14   | NL      | DCON      | | | 23 | 24 | 19-57 | M&F | MINI | 1 | 1 | 0 | Excl | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1.5 | SIE | 1 | 0 | 1 | 0 |
| Sample # | Country | Institute | Sample | Key-references | General sample information | Clinical information | Questionnaires | MRI and genetic information |
|----------|---------|-----------|--------|---------------|---------------------------|----------------------|---------------|-----------------------------|
|          |         |           |        |               | Age-range (y) | Sex | Diagnostic interview | Anx comorbs | Other comorb onset med | Age onset | Psych STAI-ttrait | ASI BAI LSAS PAS ACQ PDSS HAM_A PSWQ GAD_7 BDI-II HAM_D CDI SCARED strength (T) Scammer MRI T1-w | Field | Material for gen |
| 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 | MNI | 1 1 1 1 0 0 0 0 0 1 0 0 0 0 3 | PHI | 1 1 1 1 |
| SAD_16   | NL      | Leiden University Medical Center | LUMC | (Greven et al., 2014; Groen, Veer, Sankhyan, Rembold, & Rooda, 2015) | 20 20 20–45 M & F | MNI | 1 1 0 1 0 0 0 1 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 | (Remijn et al., 2008; van Tol et al., 2010) | 102 64 19–56 M & F | CIDI | 1 1 1 1 1 0 0 0 0 1 0 0 0 0 3 | PHI | 1 0 1 1 |
| SAD_18   | SA      | SU/UCT MRC Unit on Anxiety & Stress Disorders | SU_MRC | (Duyker et al., 2016) | 11 11 21–46 M & F | SCID | Excl | Excl | 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; Syed 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 3 | SIE | 1 0 1 1 |
| SAD_20   | SE      | Umea University | Umea_Vox | (Mansson et al., 2019) | 46 42 18–52 M & F | MINI & SCID | 1 1 1 1 1 0 1 0 0 0 0 0 0 0 0 3 | GE | 1 0 1 1 |
| SAD_21   | SE      | Umea University | Umea_Soffe | (Mansson et al., 2013; Mansson et al., 2015) | 26 23 18–57 M & F | SCID | 1 1 1 1 1 0 0 1 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 0 0 1.5 | PHI | 1 1 1 0 |
| SAD_23   | US      | Baylor College of Medicine | Baylor | (Gur et al., 2019; Good et al., 2020) | 72 149 12–79 M & F | SCID | 1 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 3 | SIE | 1 1 1 1 |
| SAD_24   | US      | Boys Town National Research Hospital | Boys Town | (Blair, Aki, et al., 2019; Blair, White, et al., 2019) | 50 44 11–38 M & F | OTH | 1 1 0 1 0 0 0 1 0 0 0 0 0 0 0 1 0 0 3 | SIE | 1 0 1 1 |
| SAD_25   | US      | Columbia University & New York State Psych Institute | Columbia_SAD | (Talati et al., 2013; Talati, Pantazatos, Hirsh, & Schmeir, 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 0 0 1 5 | GE | 1 0 1 0 |

(Continues)
| Sample # | Country | Institute | Sample | Key references | Age range # SAD # HC (y) | Sex | Diagnostic interview | Anxiety comorb | Other comorb | Age onset med | Psych STAI- trait | ADI EA LSAS PAS ACQ PDSS HAM_A PSWQ GAD_7 BDI-II HAM_D CDI SCARED | Field | T1-w | MRI | DTI | fMRI | Material for genetics |
|----------|---------|-----------|--------|----------------|--------------------------|-----|----------------------|---------------|-------------|--------------|----------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| SAD_26   | US      | Columbia University & New York State Psychiatric Institute | Columbia_SAD | Pantazatos, Talati, Schneier, & Hirsch, 2014; Talati et al., 2013 | 16 | 19 | 21-53 M&F | SCID | 1 | 1 | 1 | 0 | 0 | 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 | Columbia_SAD | Pantazatos, Talati, Schneier, & Hirsch, 2014; Talati et al., 2013 | 34 | 34 | 8-60 M&F | SCID | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1.5 | GE | 1 | 0 | 0 | 0 |
| SAD_28   | US      | University of Pennsylvania PNC | Columbia_SAD | Pantazatos, Talati, Schneier, & Hirsch, 2014; Talati et al., 2013 | 328 | 428 | 8-23 M&F | OTH | 1 | 1 | 0 | 1 | 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 | Columbia_SAD | Pantazatos, Talati, Schneier, & Hirsch, 2014; Talati et al., 2013 | 80 | 95 | 8-22 M&F | SDD & 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 | Columbia_SAD | Pantazatos, Talati, Schneier, & Hirsch, 2014; Talati et al., 2013 | 44 | 26 | 18-53 M&F | MINI | 1 | 1 | Excl | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | GE | 1 | 0 | 1 | 1 |
| SAD_31   | US      | University of California - San Diego UCSD_Sapient_INSULA | Columbia_SAD | Pantazatos, Talati, Schneier, & Hirsch, 2014; Talati et al., 2013 | 10 | 15 | 19-26 M&F | MINI | 1 | 1 | Excl | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | GE | 1 | 1 | 1 | 1 |
| SAD_32   | US      | Vanderbilt University Vanderbilt | Columbia_SAD | Pantazatos, Talati, Schneier, & Hirsch, 2014; Talati et al., 2013 | 19 | 30 | 8-12 M&F | KSADS | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 3 | SIE | 1 | 0 | 1 | 0 |
| SAD_33   | US      | Washington University Washington | Columbia_SAD | Pantazatos, Talati, Schneier, & Hirsch, 2014; Talati et al., 2013 | 12 | 11 | 22-50 M&F | KSADS | 1 | 1 | Excl | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 | GE | 1 | 1 | 0 | 1 |
| SAD_34   | US      | University of Illinois at Chicago UC | Columbia_SAD | Pantazatos, Talati, Schneier, & Hirsch, 2014; Talati et al., 2013 | 11 | 21 | 21-71 M&F | MINI | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 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)

| Sample # | Country | Institute | Sample | Key-references | Age-range | Sex | Diagnostic interview | Anx | Other comorb | Age-onset | Psych med | STAI-trait | ASB | BAI | LSAS | PAS | ACQ | PDSS | HAM_A | PASIQ | GAD_7 | BDI-II | HAM_D | CDI | SCARED | Field strength | T1-w | MRI | DTI | FMRI | Material for genetics |
|----------|---------|-----------|--------|---------------|-----------|-----|----------------------|-----|--------------|-----------|----------|----------|-----|-----|------|-----|-----|------|-------|-------|-------|-------|-----|------|-------------------|-----|-----|-----|-----|-------------------|
| SP_01    | AT      | University of Graz | Graz dental phobia | (Wabnegger, Schämmler, & 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 | SE | 1 | 0 | 0 | 0 |
| SP_02    | AT      | University of Graz | Graz dental phobia | (Schienle, Schämmler, 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 | SE | 1 | 0 | 0 | 0 |
| SP_03    | BR      | INPD | Brazilian HRC study | (Salum et al., 2015) | 89 516 5-15 | M&F | OTH | 1 1 1 | Excl | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | DAS, FDP | 3 | SE | 1 | 0 | 0 | 0 |
| SP_04    | DE      | Ruhr-Universität Bochum | Bochum dental phobia | | 18 0 27-60 | M&F | OTH | 1 1 1 | Excl | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | DAS | 1.5 | SE | 1 | 0 | 1 | 1 |
| SP_05    | DE      | Technische Universität Dresden | Dresden specific phobia subtypes | (Hilbert, Evers, Isabel Malskavi, Witschen, & Lueken, 2015) | 59 37 18-46 | M&F | IDIDI | 1 1 0 | Excl | 0 1 0 0 0 0 0 0 0 1 0 0 0 | SNAQ, DFS | 3 | SE | 1 | 0 | 1 | 0 |
| SP_06    | DE      | Technische Universität Dresden | CRC94C3 | | 100 82 18-49 | M&F | IDIDI | 1 1 1 | Excl | 1 0 0 0 0 0 0 0 0 1 0 0 0 | FSQ | 3 | SE | 1 | 0 | 1 | 0 |
| SP_07    | DE      | University of Gießen | BION.SP | (Schwecaert 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 | SE | 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 | SPQ, SNAQ | 1.5 | SE | 1 | 0 | 1 | 0 |
| SP_09    | DE      | University Medicine Greifswald | SHIP | (Wdle et al., 2015) | 148 699 31-90 | M&F | IDIDI | 1 1 1 1 | 0 0 0 0 0 0 0 0 0 1 0 0 0 0 | SNAQ, DFS | 3 | SE | 1 | 0 | 1 | 1 |
| SP_10    | DE      | Friedrich-Schiller-Universität Jena | Jenna spider phobia | (Lüppke, Milner, & Strobe, 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 | SE | 1 | 0 | 1 | 0 |
| SP_11    | DE      | University of Marburg | FORZ107 MR | (Kicher et al., 2019; Vogebacher et al., 2018) | 16 516 18-65 | M&F | SCID | 1 1 0 1 | 1 0 0 0 0 0 1 0 0 1 1 0 0 0 | 3 | SE | 1 | 1 | 1 | 1 |
| SP_12    | DE      | University of Muenster | FORZ107 MS | (Repple et al., 2020) | 28 247 18-65 | M&F | SCID | 1 1 0 1 1 0 0 0 0 1 0 0 1 1 0 0 0 | 3 | SE | 1 | 1 | 1 | 1 |
| SP_13    | DE      | University of Muenster | Munich 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 1 0 0 0 | DAS | 3 | SE | 1 | 0 | 1 | 0 |
| SP_14    | DE      | University of Muenster | Munich spider phobia | (Münstrongchter et al., 2013) | 29 478 18-59 | M&F | SCID | 1 1 0 | Excl | 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 | SPQ, FSQ | 3 | PH | 1 | 1 | 1 | 1 |
| SP_15    | DE      | University of Muenster | SFBTRR-58 project COV (SpiderVR) | (Schwarzmeier et al., 2019) | 87 0 18-56 | M&F | SCID | 1 1 1 | 1 1 1 1 0 1 0 0 1 0 1 0 0 0 | SPQ | 3 | SE | 1 | 0 | 1 | 1 |
| SP_16    | DE      | University of Wuerzburg | Wuerzburg spider phobia | (Wiener et al., 2004) | 18 18 18-37 | Only F | SCID | Excl | Excl | 0 | Excl | 1 0 0 0 0 0 0 0 0 1 0 0 0 | SPQ, FSQ | 1.5 | SE | 1 | 0 | 0 | 0 |

(Continues)
TABLE 4 (Continued)

| Sample # | Country | Institute | Sample Key-references | Age-range (y) | Sex | Diagnostic interview | Other | Age onset | Psych med | STAI-trait | ASI | BAI | LSAS | PAS | ACQ | PASS | BPS | GAD_7 | BDI-II | HAM_A | PSWQ | GAD_7 | BDI-II | Material \( T \) | Scanner | T1-w | Field strength (T) | MRI and genetic information |
|----------|---------|-----------|------------------------|--------------|-----|----------------------|-------|-----------|-----------|------------|-----|-----|------|-----|-----|------|-----|------|-------|------|------|------|-------|----------------|--------|------|----------------|---------------------------|
| SP_17    | DE      | University of Wuerzburg | Wuerzburg spider phobia II | 13 12 | 19–42 | MF | SCID | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | FSQ, FEAS | 1.5 | SE | 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 | 1.5 | SE | 1 | 0 | 1 | 0 |
| SP_19    | DE      | University Hospital of Wuerzburg | SFBTRR-M 15 project COV (SpiderVR) | 87 0 | 18–65 | MF | SCID | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | FSQ, FEAS | 1.5 | SE | 1 | 0 | 1 | 0 |
| SP_20    | DE      | Multicenter study (University of Marburg) | PROTECT-AD: Specific phobia sample | 57 0 | 18–67 | MF | ODI | 1 | 1 | 1 | Excl | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | DSM-5-SP | 3 | SE | 1 | 0 | 1 | 0 |
| SP_21    | ES      | Universidad de La Laguna | Tenefta animals phobia | 37 41 | 18–60 | MF | OTH | Excl | Excl | 1 | 1 | 0 | 0 | 1 | 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 | Reephi | 18 20 | 18–43 | MF | OTH | 0 | 0 | 0 | Excl | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | SPQ | 3 | PHI | 1 | 0 | 1 | 0 |
| SP_23    | NL      | Maastricht University | SPIN | 7 7 | 18–29 | ? | MINI | Excl | Excl | 1 | Excl | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | SPQ, FSQ | 3 | SE | 1 | 0 | 1 | 0 |
| SP_24    | NL      | Maastricht University | SPIN NF | 18 0 | 19–26 | ? | MINI | Excl | Excl | 1 | Excl | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | SPQ, FSQ | 3 | SE | 1 | 0 | 1 | 0 |
| SP_25    | NL      | Maastricht University | SMARTSCAN PHOBIA | 46 47 | 16–25 | ? | MINI | 1 | 1 | 0 | Excl | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | FSQ | 3 | SE | 1 | 1 | 1 | 0 |
| SP_26    | NL      | Maastricht University | PHOBIA exposure | 20 0 | 19–29 | Only F | MINI | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | SPQ | 3 | PHI | 1 | 0 | 1 | 0 |
| SP_27    | PL      | SWPS University of Social Sciences and Humanities | Czuwaj | 25 11 | 19–36 | MF | OTH | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | FSS | 3 | SE | 1 | 1 | 1 | 0 |
| SP_28    | SE      | Uppsala University | Uppsala spider phobia | 47 0 | 20–55 | MF | OTH | 0 | 0 | 1 | Excl | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | SPQ | 3 | PHI | 1 | 1 | 1 | 0 |
| SP_29    | UK      | COMIC Research/ LYPET | Spider phobia | 12 0 | 17–42 | MF | OTH | 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 | MF | SCID & KSAADS | 1 | 1 | 0 | Excl | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | None | 3 | GE | 1 | 0 | ? | 0 |
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
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 gyrus, 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, Amtz, & 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 differences (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; Luken & 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)

Anxiety sensitivity

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)

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, & Eisenbraut, 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

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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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