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PII: S0149-7634(21)00300-6

DOI: https://doi.org/10.1016/j.neubiorev.2021.07.002

Reference: NBR 4256

To appear in: *Neuroscience and Biobehavioral Reviews*

Received Date: 25 January 2021

Revised Date: 6 June 2021

Accepted Date: 5 July 2021

Please cite this article as: Serra-Blasco M, Radua J, Soriano-Mas C, Gómez-Benlloch A, Porta-Casterà̀s D, Carulla-Roig M, Albajes-Eizagirre A, Arnone D, Klauser P, Canales-Rodríguez EJ, Hilbert K, Wise T, Cheng Y, Kandilarova S, Mataix-Cols D, Vieta E, Via E, Cardoner N, Structural Brain Correlates in Major Depression, Anxiety Disorders and Post-traumatic Stress Disorder: A Voxel-Based Morphometry Meta-analysis, *Neuroscience and Biobehavioral Reviews* (2021), doi: https://doi.org/10.1016/j.neubiorev.2021.07.002

Structural Brain Correlates in Major Depression, Anxiety Disorders and Post-traumatic Stress Disorder: A Voxel-Based Morphometry Meta-analysis

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Highlights

- MDD participants have smaller GMV than HC in cerebellum and the frontal operculum
- ANX participants have less GMV than HC in temporal gyrus and pars orbitalis
- PTSD participants have smaller GMV in lingual gyrus and superior frontal gyrus
- As patients age, GMV reductions are more pronounced in fronto-temporal regions
- Higher proportion of females are related with GMV diminutions in temporal areas

ABSTRACT

The high comorbidity of Major Depressive Disorder (MDD), Anxiety Disorders (ANX), and Posttraumatic Stress Disorder (PTSD) has hindered the study of their structural neural correlates. The authors analyzed specific and common grey matter volume (GMV) characteristics by comparing them with healthy controls (HC). The meta-analysis of voxel-based morphometry (VBM) studies showed unique GMV diminutions for each disorder ($p<0.05$, corrected) and less robust smaller GMV across diagnostics ($p<0.01$, uncorrected). Pairwise comparison between the disorders showed GMV differences in MDD versus ANX and in ANX versus PTSD. These results endorse the hypothesis that unique clinical features characterizing MDD, ANX, and PTSD are also reflected by disorder specific GMV correlates.

Keywords: Major depressive disorder, Anxiety disorders, Posttraumatic stress disorder, Comorbidities, Gray matter volume, Meta-analysis, Structural neuroimaging, Neuropsychiatry

1. Introduction

Major depressive disorder (MDD), anxiety disorders (ANX) and posttraumatic stress disorder (PTSD) display a range of both overlapping and distinctive epidemiological and clinical features. From an epidemiological perspective, MDD and ANX are the most frequent mental disorders, being highly prevalent in the general population, and with comorbidity levels higher than expected by chance (Kessler et al., 2008, 2005). Likewise, MDD is the psychiatric comorbidity most commonly associated with PTSD (Rytwinski et al., 2013), a diagnosis that has been moved from the anxiety disorders category to the stress-disorder group in current diagnostic manuals (Diagnostic and Statistical Manual of Mental Disorders 5th Edition; DSM-5).

Similarly, their phenotype is characterized by a high presence of negative emotional states (Eysenck and Fajkowska, 2018), distress, cognitive biases (Byllesby et al., 2016) and rumination. They also share prominent avoidance behaviors, which are linked with the development and maintenance of ANX and PTSD and also mediate subsequent progression to MDD (Struijs et al., 2018). Neurobiologically, they share a complex hereditary predisposition involving genes typically related to monoamine systems, neuropeptides and hypothalamus-pituitary-adrenal (HPA) axis, which in turn modify normal stress responses (Smoller, 2016).

When focusing on the brain, neural correlates in structural magnetic resonance imaging (sMRI) have been regularly found in the three disorders, including lower grey matter volume (GMV) in the anterior cingulate (ACC)(Emre Bora et al., 2012; O'Doherty et al., 2015; Radua et al., 2010) and insular cortices (Bromis et al., 2018; Radua et al., 2010; Sprengelmeyer et al., 2011). Indeed, the most recent meta-analysis of functional neuroimaging in mood and anxiety disorders described differences versus healthy controls in brain activity -located in negative valence systems- shared across these disorders (Janiri et al., 2020a). However, each of them has specific and predominant symptom expressions, like sadness and apathy in MDD, worry and fear in ANX and intrusive thoughts and avoidance in PTSD, as well as particular neural correlates. Yet, the

identification of such disorder-specific correlates is particularly difficult as sMRI studies rarely exclude comorbidities and lower GMV in key regions such as ACC and insula appear to be a general marker of psychopathology (Goodkind et al., 2015). The few sMRI studies comparing MDD and ANX have pointed to potential differences in fronto-temporal regions (Lai and Wu, 2015; van Tol et al., 2010; Zhao et al., 2017), which have also demonstrated higher accuracy than clinical questionnaires distinguishing generalized anxiety disorder (GAD) from MDD using machine learning approaches (Hilbert et al., 2017).

Given the above notions, the considerable amount of literature studying brain structure in these disorders and the necessity to measure their reproducibility, it is suitable to perform a meta-analysis of grey matter VBM (Ashburner and Friston, 2000) studies of MDD, ANX and PTSD. Samples will include non or minimal percentages of comorbidities in order to delineate their common and specific neural underpinnings. Specific neural correlates were studied looking at these disorders independently versus healthy controls (HC) and trough their direct comparison

We hypothesized that common GMV reductions would overlap across disorders in key cognitive and emotional brain networks including cortical areas such as insula and cingulate gyrus, and also subcortical limbic structures such as hippocampus and amygdala (Janiri et al., 2020b; Logue et al., 2018; Sha et al., 2019). We also expected to find more prominent GMV reductions in prefrontal cortices (i.e. dorsolateral, orbitofrontal or ventromedial) in MDD (Bora et al., 2012; Wise et al., 2016; Wu et al., 2019). Regarding ANX disorders, PTSD has been included in the analyses until a few years ago, and there are no studies analyzing ANX disorders as they are conceptualized today in the DSM-5. However, based on proposed brain networks and recent studies on specific anxiety disorders, we expected to find GMV differences versus HC in regions included in fronto-parietal or/and ventral attention networks (i.e. ventrolateral PFC and temporo-parietal junction, Sylvester et al., 2012). Finally, based on a recent review of MRI findings in PTSD and a study using machine learning classification methods (Kunimatsu et al., 2020; Zilcha-Mano et al., 2020), we expected participants with PTSD diagnosis to display greater GMV reductions in fronto-occipital networks and

putatively in the basal ganglia, as the structures with a greater amount of evidence potentially overlap across disorders (i.e. prefrontal cortices, hippocampus, amygdala, anterior cingulate or insula).

2. Methods and materials

2.1. Literature Search

An extensive search of structural VBM studies comparing subjects with MDD, ANX and PTSD disorders with HC was conducted in PubMed, Web of Knowledge, Science Direct and Scopus databases (**Figure 1**). The search keywords were [Title/Abstract]: morphometry OR voxel-based OR voxel-wise AND depression OR anxiety disorder OR panic disorder OR agoraphobia OR phobia OR stress disorder OR posttraumatic stress disorder AND "1998"[Date - Publication]: "2020/01/17"[Date - Publication]. Studies were included if: 1) performed whole-brain analysis, 2) included a comparison between patients with MDD/ANX/PTSD disorders and HC, 3) participants' age was above 18 and below 65, 4) provided the t-map or coordinates in Montreal Neurological Institute [MNI] or Talairach space, 5) samples were free of any comorbid neurological conditions and 6) samples of patients had no or minimal current comorbid psychiatric disorders. In order to find the most optimal balance between excluding samples with any comorbidity (as they may be then non representative) and including highly comorbid samples, the maximum rate of current comorbidity with MDD/ANX/PTSD diagnosis was set at 25%. The percentage of studies not reporting comorbidities was 18.7 (18% for MDD, 8% for ANX and 30% for PTSD. If a sample was used in several studies, only the larger one was included. Similarly, only baseline data of longitudinal studies was incorporated. Manuscripts were included from 1998 for MDD (first VBM study in MDD, (Shah et al., 1998)) and from 2003 for anxiety disorders(Massana et al., 2003) and PTSD(Yamasue et al., 2003) until 17th January 2020. See **Table 1**.

2.2. Data Extraction

Relevant data for the studies were retrieved by six authors -all investigators- (MSB, EV, AG, DPC and MC) and then compared by MSB, EV, AG and DPC in order to minimize interpretation and data entry errors. PRISMA guidelines were followed as recommended in the study of Moher and colleagues(Moher et al., 2009).

The corresponding authors (or the principal in case of no response) of all studies meeting inclusion criteria were contacted via e-mail and asked for their original (t-maps) and/or relevant missing data of the manuscript.

2.3. Differences in Demographic Variables

We combined the age means and standard deviations and the proportion of males of the samples and applied ANOVA/□2 tests on the resulting statistics to explore potential demographic differences between MDD, ANX, and PTSD patients (R Stats Package version 4.0, https://www.r-project.org/). Please see the Supplement methods for details on the specific formulas used.

2.4. Differences in Grey Matter Volume

2.4.1. Global Differences

We assessed the differences in global GMV using the function "Globals" from SDM-*PSI* (see below), which conducts a random-effects meta-analysis.

2.4.2. Regional Differences

To investigate grey matter volume regional differences we used the Signed Differential Mapping with Permutation of Subject Images (SDM-PSI, https://www.sdmproject.com/) version 6.21 (Albajes-Eizagirre, 2019; Radua et al., 2014, 2012), the newest version of a meta-analytical neuroimaging method successfully used in many published meta-analyses. Some new features in SDM-PSI include a familywise correction for multiple comparisons using the Freedman-Lane procedure for its optimal statistical properties, and threshold-free cluster enhancement (TFCE, (Smith and Nichols, 2009)) statistics. SDM-PSI also includes an almost unbiased estimation of effect sizes based on MetaNSUE algorithms, which use maximum likelihood estimation and conduct repeated leave-one-out jackknife procedures to avoid the possibility that a single or few studies drive the results.

2.5. Meta-analyses

We conducted seven main meta-analyses, namely 1) all patients versus HC, 2) patients with MDD versus patients with ANX, 3) patients with MDD versus patients with PTSD, 4) patients with ANX versus patients with PTSD, 5) patients with MDD versus HC, 6) patients with ANX versus HC, and 7) patients with PTSD versus HC. All meta-analyses were run combining peak coordinates of each sample or original t-maps if provided. The MDD vs HC meta-analysis was replicated I) without including the 6 MDD t-maps to explore the effect of raw and unbiased data inclusion (rather than solely using the coordinates provided by the authors) in neuroimaging meta-analyses and ii) without including remitted patients in order to explore potential effects of having an active MDD episode. Finally, we used meta-regression to understand the potential contribution of age and sex to all patients' neural correlates altogether. Psychotropic medication was meta-regressed in all patients as well as for each psychiatric condition separately. For the MDD samples, meta-regressions were used to explore the effects of illness duration (in years) and depression severity in GMV. Depression severity was mostly measured through the Hamilton Depression Rating Scale 17. For studies reporting Montgomery-Åsberg Depressing Rating Scale (MADRS) scores, we converted them to HDRS-17 equivalents (HDRS-17=-1.58+0.86*MADRS, 33). We explored potential publication bias of each cluster peak of statistically significant clusters via funnel plots and Egger's test.

We first set the statistical threshold at $p<0.05$ TFCE corrected with a minimum cluster size of 10 voxels. Later, we explored a more relaxed one ($p<0.01$, uncorrected), choosing only those clusters exceeding 50 voxels. In the case of the meta-analysis including all patients vs. all controls, smaller clusters were accepted giving the probable high levels of heterogeneity. In order to ease future replication analyses, we have generated an online database (available upon request) with all the clinical and methodological data from every study included in this meta-analysis.

3. RESULTS

3.1. Included Studies

The search retrieved 3482 studies potentially suitable (**Figure 1**), from which finally 73 met all the inclusion criteria. The highest proportion of reported anxiety comorbidity in an MDD sample was 14.8% (Klauser et al.

2015) and the anxiety sample with highest reported MDD comorbidity was 24% (Irle et al. 2014). For PTSD, the proportion of comorbid cases was zero or not reported in three studies. All studies used parametric approaches, except for Koolscijn et al., 2010, Tavanti and colleagues (2012), Lai et al., (2012 and 2015), Rodriguez et al., 2014 and Lai et al. (2014 and 2015). A total of 7 original t-maps were achieved (MDD=6, ANX=1). See **Table 1** for more detailed information.

3.2. Sample Characteristics

MDD meta-analysis included 45 studies with 53 MDD independent datasets. When the MRI was performed, 145 patients (7.77%) were in remission and 1721 (92.23%) had an acute MDD episode. The mean score of the HDRS-17 was 2.07 for those patients in remission and 20.62 for those in an acute episode. Of the studies reporting psychotropic medication use, 47.21% of patients were taking at least one or more antidepressants at the time of the scanning. ANX meta-analysis included a total of 20 studies with 22 independent datasets. Of the 617 participants, 237 were diagnosed with panic disorder (PD, 38.4%), 234 with social anxiety disorder (SAD, 37.9%), 59 with GAD (9.6%), 59 with specific phobia (SP, 9.6%), 10 with panic disorder with agoraphobia (PDA, 1.6%) and 23 with comorbid anxiety disorders (2.76%). Of the studies reporting medication use, 9.6% were taking antidepressants or/and anxiolytics. For more detailed information of the studies included see **Table 1**).

3.3. Age and gender differences

3.3.1 Major Depression Versus Anxiety Disorders: patients with ANX diagnosis (age=33.09+/-11.02; 41.7% males) were younger (d=0.39, t=8.47, p<0.001) than those with MDD (age=38.04+/-13.07; 38.1% males) but had a similar proportion of men and women (X^2=2.38, p=0.123,). Age was then included in the MDD vs ANX meta-analysis as covariate.

3.3.2. Major Depression Versus Post-Traumatic Stress Disorder: There were no differences regarding age (d=0.13, t=1.69, p=0.09). However, participants with PTSD (age=36.44+/-10.41; 54.7% males) had higher

proportion of males (X^2=20.47, p<0.001) than those with MDD. Sex was then included in the MDD vs PTSD meta-analysis as covariate.

3.3.3. Anxiety Disorders Versus Post-Traumatic Stress Disorder: There were significant differences regarding age (d=-0.31, t=-3.80, p<0.001) and sex proportion (X^2=9.96, p=0.002), so both were included in the ANX vs PTSD meta-analysis as covariates.

3.4. Differences in Grey Matter Volume

3.4.1. Global Differences in Grey Matter Volume

A total of 22 samples reported global GMV (13 MDD; 5 ANX and 4 PTSD). Individuals with MDD had lower global GMV compared to HC (Hedges g=-0.174, SE=0.059; z=-2.966; p=0.003, CI=-0.289—0.059) with low heterogeneity (τ<0.001; Q=10.590; df=12 and p=0.564). There were no global GMV differences between ANX and HC (Hedges g=0.092, SE=0.116; z=0.795; p=0.426, CI=-0.135—0.320) with no heterogeneity (τ<0.001; Q=4.540; df=4 and p=0.338), or between PTSD and HC (Hedges g=-1.226, SE=0.964; z=-1.271; p=0.203, CI=-3.116—0.664) with significant levels of heterogeneity (τ<3.540; Q=47.725; df=3 and p<0.001).

After performing a sensitivity analysis, it was observed that the study from Tavanti and colleagues (2012) drove the heterogeneity levels (τ<0.000; Q=1.623; df=2 and p<0.444), although the lack of GMV differences persisted (Hedges g=-1.375, SE=0.210; z=-1.787; p=0.08, CI=-0.786—0.036). See **Figure 2.**

3.4.2. Regional Differences in Grey Matter Volume

3.4.2.1. MDD Versus HC analysis: There were two clusters showing significant GMV reductions in patients with MDD compared to HC in the bilateral cerebellum and in the left inferior frontal gyrus (IFG). When applying a more liberal threshold (p<0.01, uncorrected), the volume reductions extended to the right IFG including bilateral insula, left superior frontal gyrus (SFG) including anterior cingulate subregions and right ventromedial prefrontal cortex, bilateral hippocampi and left rolandic operculum including right posterior cingulum (**Figure 3A)**. Patients with MDD did not show regional GMV increases with respect to HC. For

more detailed information about the cluster's statistics, heterogeneity and publication bias see **Table 2** (TFCE p<0.05) and **Supplementary Table 1** (p<0.01, uncorrected).

3.4.2.1.1 MDD Versus HC analysis (excluding t-maps): When excluding the 6 original MDD t-maps (**Figure 4**), the brain region showing the largest GMV reduction was the left insula extending to the rolandic operculum and the IFG. When applying a more liberal threshold (p<0.01, uncorrected), regions were then more similar to those appearing in the analysis including the t-maps (right SFG extending to anterior cingulate and right ventromedial prefrontal cortex). Patients with MDD did not show regional GMV increases with respect to HC (**Supplementary Table 2**).

3.4.2.1.2 MDD Versus HC analysis (excluding remitted patients): When excluding remitted patients (**Supplementary Table 3**), the brain region showing the largest GMV reduction were the left inferior frontal gyrus (BA 48) and the left hippocampus (BA 20). When applying a more liberal threshold (p<0.01 uncorrected), GMV of patients were smaller in bilateral cerebellum, bilateral insula, right gyrus rectus (BA 11), right hippocampus (BA 20), right superior frontal gyrus (BA 8 and 11), right heschl gyrus (BA 48), left ACC (BA 32), right middle frontal gyrus (BA 46) and left angular gyrus (BA 22). Patients with acute MDD did not show regional GMV increases with respect to HC.

3.4.2.2. ANX Versus HC analysis: Patients with ANX had significantly smaller GMV than HC in left STG extending to IFG (**Table 2).** When relaxing the threshold **(Supplementary Table 1),** GMV reductions appeared in left orbitofrontal and dorsolateral prefrontal gyri (BA 10), in the bilateral paracingulate gyrus (BA 24) and in bilateral insula. Patients with ANX did not show regional GMV increases with respect to HC. Results are shown in **Figure 3B.**

3.4.2.3. PTSD Versus HC analysis: Patients with PTSD showed smaller GMV than HC in left lingual gyrus extending to fusiform gyrus and in the bilateral SFG (BA 8) as shown in **Table 2**. When applying a more liberal threshold (see **Supplementary Table 1**), left post central gyrus, right fusiform gyrus, left calcarine fissure, left parahippocampal and left middle cingulate cortex also appeared reduced (**Figure 3C**).

3.4.2.4. MDD vs ANX analysis: The bilateral cerebellum and the superior temporal gyrus (STG) differentiated the MDD and ANX groups, with patients with ANX (compared to HC) displaying smaller temporal volumes and patients with MDD pronounced smaller cerebellar volumes (**Table 3**, **Figure 3D**).

3.4.2.5. PTSD Versus ANX analysis: Participants with ANX showed less GMV in BA 48, including rolandic operculum, right STG and right insula when compared to HC than participants with PTSD. Also, participants with PTSD showed smaller GMV in left fusiform gyrus extending to lingual gyrus and cerebellum (BA 18) (**Table 3**, **Figure 3E**).

3.4.2.6. PTSD Versus MDD analysis: There were no significant differences at any explored threshold between PTSD and MDD, covarying by sex.

3.4.2.7. Conjunction analysis (MDD, ANX and PTSD vs HC): The conjunction analysis did not show significant results at $p<0.05$, TFCE corrected. When applying a more liberal threshold ($p<0.01$, uncorrected), a cluster of reduced GMV in the left middle cingulate cortex (MCC), (**Supplementary Table 4, Figure 3F**) appeared. There were no regions of larger volume in patients compared to HC at any threshold.

3.5. Meta-regressions

Meta-regression analyses of age and sex (**Supplementary Table 5**) indicated that studies with older patients (altogether) had smaller volumes relative to HC in the superior temporal gyrus (BA 38 and 48, including the insula and the rolandic operculum) and in the middle temporal gyrus (BA 20). Those studies with bigger proportion of women found smaller grey matter volume compared with HC in left insula extending to left rolandic operculum, left heschl gyrus, left putamen and also in the right inferior, middle and STG (BA 20, 21 and 22 respectively) and the left middle temporal gyrus (BA 21). Studies including participants with longer MDD duration reported less GMV in the right fusiform gyrus extending to the parahippocampus (BA 37) and the left cerebellum. (**Supplementary Table 5**). The meta-regression with depression severity showed no statistically significance.

Finally, those samples with higher proportion of medicated patients **(Supplementary Table 6)** showed lower GMV in the bilateral angular gyrus (BA 39), right middle occipital gyrus (BA 39), right middle temporal gyrus (BA 20), right hippocampus, right dorsolateral and middle PFC (BA 9) and left ACC (BA 11). When analyzing the effect of medication separately for each disorder, those MDD samples with higher proportion of medication showed lower GMV in bilateral ACC (BA 11), those samples with patients with ANX in bilateral insula and in right rolandic operculum (BA 48), and those patients with PTSD exhibited a positive relationship between GMV and medication intake in left inferior parietal gyri (BA 39, 40 and 7), right angular gyrus (BA 39), right inferior parietal gyri (BA 40) and right middle occipital gyrus (BA 19).

3.6. Publication Bias and Heterogeneity Tests

All results reported in meta-analyses and meta-regressions were nonsignificant in the Egger tests ($p>0.05$), suggesting no publication bias. Also, the I^2-statistic percentages ranges between 0 and 40%, which is considered irrelevant regarding heterogeneity (Deeks et al., 2020).

4. Discussion

This is the first meta-analysis providing a quantitative evaluation of GMV alterations across MDD, ANX and PTSD and including information both from reported coordinates and original t-maps. The findings showed disorder-specific GMV reductions in fronto-limbic and cerebellar regions in MDD, fronto-temporal in ANX and fronto-occipital in PTSD. These findings replicate and extend the findings of previous studies and provide a much-needed summary of an often disparate literature that is difficult to integrate.

Contrary to what it was hypothesized based on prior research, there are not statistically significant structural brain correlates overlapping across disorders (Goodkind et al., 2015). Although Goodkind et al. was cited to support the hypothesis of a transdiagnostic marker of psychopathology, they do not include the PTSD category and instead included schizophrenia, bipolar disorder, OCD, or substance abuse patients, partly explaining the lack of replication in the current meta-analysis. In any case, what they do report as common neurobiological substrates are bilateral insulae and dorsal ACC. Insula has shown smaller volumes in many meta-analyses of the current work, including MDD and ANX samples (despite some emerged at uncorrected

level), thus supporting its presence as a transdiagnostic marker for mood and anxiety disorders. On the other hand, the region that has appeared when lowering the statistical threshold (<0.01, uncorrected) in the common meta-analysis (mid-cingulate cortex) is in line with the widely reported role of this corticolimbic structure in mood, anxiety, and trauma-related disorders. In fact, the mid-cingulate region may represent a hub for various brain circuits as it is involved in numerous functions including a cognitive role in decision making, response initiation in the context of free choice, selective/divided/oriented attention, conflict monitoring or encoding reward values (Vogt, 2016). More specifically, MCC has been associated with avoidance (Hayes et al., 1996) and cognitive reappraisal or emotion suppression (Picó-Pérez et al., 2017), which are regulation strategies identified to be disturbed in those patients. Indeed, this cingulate sub-region has been found to play a key role when training emotion regulation in healthy participant's trough neurofeedback (Cohen Kadosh et al., 2016) and to be involved in pain and fear processing (Vogt et al., 2003), so it may be related to the common etiopathogenic factors and shared clinical characteristics of these conditions. In any case, this result should be taken cautiously as did not surpass the FWER correction.

The results of the MDD meta-analyses consolidate the previously described prefrontal alterations but mostly highlight the relevance of the cerebellum in MDD. Probably due to the modest understanding of the cerebellum emotional and cognitive processes, this structure has often been overlooked and less discussed in psychiatric neuroimaging studies. However, a non-negligible part of the cerebellum is linked with affective, cognitive and self-referential functions and participates in functional networks of information processing (Klein et al., 2016); cerebellar GMV reduction have been linked with persistence of cognitive deficits in MDD patients (Depping et al., 2020). This relationship between GMV cerebellar reduction and symptom persistence might also underlie our finding of an association of such reductions and illness duration in MDD. While those structures do not coincide with the few reported to date, the extended use of ROIS in longitudinal studies (of the hippocampus) together with other methodological differences, makes it difficult to draw conclusions now. It is also worth noting that the latest mega- and meta-analytical research in MDD do not analyze volumetric differences in cortical structures, favoring cortical thickness and surface area, which could explain why our main MDD results do not coincide with the ones reported in their latest review (Schmaal et al., 2020). Also,

to truly elucidate the causality of the observed relation between illness duration and brain structure, more whole-brain longitudinal studies are needed. The current meta-analysis of patients with MDD vs HC has also confirmed the GMV reduction of cortical regions like the opercular part of the IFG and, with a wicker statistical significance, of the left insula and the anterior cingulate. Interestingly, prefrontal regions showing smaller volumes in MDD samples, have been linked to MDD prognosis (Belden et al., 2015; Fonseka et al., 2018), providing more evidence of their potential value of reliable MDD biomarker.

Anxiety disorder studies were characterized by a significantly greater GMV reduction in the left STG area when compared with MDD studies. Of the hypothesized altered circuits (Sylvester et al., 2012), GMV decreases in brain structures of the ventral attention network (VAN) show statistical significance. VAN network includes STG amongst other regions and is documented to play an important part in the orientation of the stimulus-driven attention. It has been hypothesized that a similar reorienting mechanism may mediate the shift from internally directed stimuli (i.e., worrisome thoughts) to environmental events, and that VAN may have a main role in this process. Thus, the present meta-analysis confirms the previous findings of reduced temporal and frontal gyrus in patients with anxiety disorders, and points toward a pronounced involvement of the left temporal pole. Also, when directly comparing ANX with PTSD, the former presented smaller volumes of the STG along with insula, rolandic operculum and anterior cingulate, which are areas closely related with the cingulo-opercular network (CON) network, which is the other neuronal circuit described to be altered in ANX (Sylvester et al., 2012).

The meta-analysis comparing patients with PTSD to HC detected reductions of GMV in the left lingual and fusiform gyrus and with superior frontal gyrus (BA8). These structural findings are partially in line with a recent review of MRI studies in PTSD (Kunimatsu et al., 2020; Wang et al., 2020). Such divergence may be explained by the fact that first studies on PTSD were guided by the hypothesis of hippocampal involvement (due to its relationship with stress responses) and hence all research was highly focused on this structure. With most of the literature limited to certain ROIs, it seems easy to devote less attention to brain regions not included in initial operating hypothesis. Neuroimaging biomarker studies of brain structure have as well mainly focused on anterior cingulate and hippocampus, finding inconsistent results (Colvonen et al., 2017). Interestingly,

when comparing PTSD against ANX, PTSD individuals presented with less GMV in fusiform gyrus, extending to lingual gyrus and cerebellum. Thus, these volume differences located in occipital regions might underlie key clinical differences between those disorders. The present meta-analysis of whole-brain studies brings back the focus on occipital and frontal regions and points (with weaker statistical power) to regions highly reported in PTSD neuroimaging research such as the middle cingulate and the parahippocampus.

There are some limitations that are worth highlighting. First, as voxel-based meta-analyses are mostly based on summarized data (except for those cases in which original maps were available) it is likely to expect some imprecise results. In addition, despite VBM being a relatively consistent methodology, there are many analysis parameters, such as slice thickness, smoothing, statistical threshold, cluster based, standard space, correction and Jacobian modulation, which, although reported, are not possible to be considered in the analysis with current methodologies. Likewise, the covariates included are also heterogeneous as each study controls for age, sex, total intracranial volume or total GMV quite arbitrarily. Likewise, although some clinical characteristics have been considered (i.e., depressive symptomatology, illness duration or medication), factors such as the number of previous episodes or age of onset have not. Also, the fact that we focused mainly on non-comorbid diagnosis reduces the power in the comparisons versus HC, but conversely allowed us to draw strong conclusions about disorder specificity. In this regard, it should be noticed that, although 81% of the total sample explicitly reported no comorbidities, a 19% did not described such sample characteristic. Regarding the method employed, although it controls for false-positive results, false-negative results could not be completely ruled out. Related to this, the meta-analysis comparing all participants with a psychiatric diagnosis versus HC only reached significance with the more relaxed threshold, which leads to take this result with appropriate caveats and require to be replicated in future independent datasets. Finally, as recent clinical and imaging studies on psychiatric population suggest, using data-driven methods instead of only diagnosis guidance would allow studying heterogeneity within clinical populations.

The current meta-analysis points to specific neural correlates for highly comorbid disorders such as MDD, ANX and PTSD: MDD was uniquely characterized by cerebellar and frontal GMV decreases, ANX by temporal lobe GMV decreases, and PTSD by occipital lobe GMV decreases. Also, although the result must

be taken prudently because of lower statistical significance, mid-cingulate cortex appears as the brain structure altered across MDD, ANX and PTSD, which is consistent with the struggle in stress coping experienced by the three disorders.

Funding

PK was supported by a fellowship from the Adrian and Simone Frutiger Foundation. TW was supported by an NIHR PhD studentship and a Sir Henry Wellcome postdoctoral fellowship from the Wellcome Trust. EV was supported by a Río Hortega fellowship, provided by the Carlos III Health Institute (ISCIII), Spain (CM15/000839). NC has received research scholarships from Recercaixa, the Spanish Ministry of Health, the Ministry of Science and Innovation (CIBERSAM) and the Strategic Plan for Health Research and Innovation (PERIS) 2016-2020.

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Table 1. Demographics and clinical characteristics of the study clinical populations

MAJOR DEPRESSIVE DISORDER (n=1866)									HEALTHY CONTRO 73)		
Study/Sample	**n**	**Age Mean (SD)**	**Sex (M, F**	**Illness duratio Years (SD)**	**Age at Onset Years**	**HDRS-17 Mean (SD)**	**Antidepressan (%)**	**Comorbidit (%)**	**n**	**Age Mean (SD**	**Sex (M,F)**
Abe et al., 2010	21	48.1(13.5)	11, 10	6(7.2)	41.13(13.4)	9.2(8.6)	90	0	42	48(13.2)	22/20
Arnone et al., 2012	64	cMDD= 36.3 rMDD= (11)	17/47	cMDD= 14.3 rMDD= 9.4(-	cMDD=22.0 rMDD=25.12(-)*	cMDD= 21.8 rMDD=	NA	0	66	32.1(9.3)	20/46
Bergouignan et al.	20	33.16(9.6)	3/17	8.45(9)	23.80(8.7)	23.11(-)*	NA	NA	21	28.21(5.5)	7/14
Cai et al., 2015	23	30(7.3)	13/10	4.35(2.4)	25.7(6.8)	29.7(6.2)	26	0	23	28.2(3.8)	13/10
Chen et al., 2018	36	30.7(8.5)	20/16	2.68(3.92)	26.8(8.60)	19.83(SD)	50	0	47	29.7(9.2)	22/25
Cheng et al., 2010	68	29.91(7.9)	21/47	10.98(8.2)	28.94(7.8)	22.32(3.7)	Drug-naïve	0	68	30.54(7.3)	21/47
Grieve et al., 2013	102	33.8(13.1)	48/54	11.30(11.8)	22.1(12.2)	21(3.9)	Drug-naïve	PTSD= 0 ANX= NA	34	31.5(12.4)	18/16
Guo et al., 2014	44	27.52(8.6)	22/22	1.59(3.04)	-	25.18(5.2)	NA	0	44	29.39(6.7)	20/24
Jung et al., 2014	50	NR: 40.8(12.7 RE: 43(10.1)	14/36	-	-	NR= 18.8(4.7 RE= 20.9(4.1	100	0	29	43.6(13.4)	8/21

Kandilarova et al., †	39	46.4(13.9)	13/29	10.8(8.89)	37.3(12.6)	23.45(-)*	77	0	42	42.6(13.7)	13/29
Klauser et al., 201	27	35.02(9.7)	9/18	9.04(6.5)	26.04(9.4)	Not reported	48	ANX= 14.8	33	34.71(9.9)	12/21
Kong et al., 2013	52	Naïve= 34.43 Treated= 2(5.7)	21/31	Naïve= 2.11(Treated= 4.12	-	Naïve= 21.64 Treated= 3.42	Drug-naïve= Treated= 100	0	28	32.07(9.3)	14/14
Koolschijn et al., 2	28	64.04(10.90)	0/28	7.79(1.5)	-	14.18(-)*	60.1	0	38	61.89(11.1	0/38
Kroes et al., 2010	29	33.4(NA)	8/21	-	-	-	76	0	29	32.45(NA	13/16
Lai et al., 2014	38	36.57(5.5)	18/20	5.68(1.5)	-	22.26(2.4)	Drug-naïve	0	27	38.29(11.8	12/15
Lai et al., 2015	53	40.07(9)	25/28	0.42(0.1)	-	22.43(2.3)	Drug-naïve	0	54	40.38(10.5	12/42
Lee et al., 2011	47	46(9.1)	5/42	3.89(6.3)	42.11(-)	20.1(6.9)	62	NA	51	45.7(8.04)	5/46
Leung et al., 2009	17	45.5(8.5)	0/17	7(4.1)	-	-	100	NA	17	45.8(9.8)	0/17
Li et al., 2019	56	35.1(8.9)	20/36	1.1(1.3)	-	-	Drug-naïve	0	56	30.7(8.0)	23/33
Lu et al., 2019	30	23.95(5,3)	17/13	2.61(2.22)	-	-	Drug-free 2 w	0	48	21.5(3.84)	18/30
Ma et al., 2012	35	TRD= 27.39(TSD= 26.71(	21/14	TRD= 2.95(4 TSD= 0.22(0.	-	TRD= 23.89(TSD= 25.58(	TRD=100 TSD=Drug-na	NA	17	24.24(4.4)	10/7
Machino et al., 20	29	39.57(8.3)	16/13	4.38(4.8)	-	13.90(4.3)	97	NA	29	38.66(8.4)	16/13
Mak et al., 2009	17	45.5(8.5)	0/17	-	-	-	100	0	17	45.8(9.8)	0/17
Nakano et al. 2014	36	49(11.4)	14/22	5.56(6.74)	40(19.4)	15.40(10.20)	86	0	54	45.40(16.1	27/27

Peng et al., 2010	22	46.7(8.9)	8/14	0.72(0.5)	45.98(-)	18.50(6.3)	23	0	30	45.9(9)	11/19
Qi et al., 2014	18	31.06(7.4)	7/11	-	-	22.28(3.3)	Drug-free 6 m	0	28	28.61(5.5)	15/13
Rodriguez et al., 2	32	48.68(13)	12/20	10.96(10.5)	37.71(13.7)	21.73(-)*	88	ANX= 9.4	64	46.03(9.8)	26/38
Salvadore et al., 2(	85	dMDD=)(11.1) rMDD=)(12.2)	27/58	dMDD= 18.4 rMDD= 15.1(	-	dMDD= 20.7 rMDD= 0*	dMDD= 86 rMDD= 93	0	107	36.2(10.3)	47/60
Scheuerecker et al	13	37.9(10.1)	10/3	4.36(6)	-		Drug-free 1 y	0	15	35.5(10.9)	10/5
Serra-Blasco et al.	66	FE= 44(6.9) Rem= 48(8.7) TRD= 49(8)	13/53	FE= 0.47(0.4) Rem= 17.86(TRD= 22.62(	FE=43.5(6.6 Rem=29.1(1 TRD=27.4(8	FE= 16(6.5) Rem= 4(5.2) TRD= 21(4.6	FE= 100 Rem= 75 TRD= 86	0	32	46(8.3)	9/23
Shah et al., 1998	40	Rec= 47.70(9 TRD= 48.90(	26/14	Rec=1.58(1.2 TRD=5.48(22	Rec=38.20(TRD=38.90	Rec= 2.6(1.7) TRD= 20.6(5	Rec= 45 TRD= 100	NA	20	49.3(11.8)	13/7
Shen et al., 2016	147	30.5(9.8)	50/97	8.49(7.5)	29.89(3.8)	23.83(4.8)	Drug-naïve	0	130	30.09(7.1)	49/81
Soriano-Mas et al.	70	61.56(9.7)	29/41	10.45(10.1)	51.11(12.6)	28.60(7.6)	71	0	40	59.23(7.1)	17/23
Tae et al., 2015	20	42.5(14)	0/20	9.5(11.3)	31.8(13.1)	21.7(8.7)	Drug-free 3 m	0	21	42.3(10.2)	0/21
Ueda et al., 2016	30	44.3(13)	17/13	-	-	7,7(5.1)	Drug-naïve	NA	48	41.2(11.4)	35/13
Van tol et al., 2010	68	37.16(10.2)	24/44	-	25.62(10.4)	9.61(-)*	26	0	65	40.54(9.7)	24/41
Vasic et al., 2008	15	37.4(8.5)	9/6	3.62(3.1)	-	18.46(-)*	100	0	14	31.4(9.6)	8/6

Wagner et al., 201	30	37.55(11.5)	5/15	5.95(6.8)	31.6(11.6)	20.08(-)*	NA	0	30	35.1(10.4)	5/25
Yang et al., 2017a	35	44.54(11.2)	0/35	2.69(0.8)	41.25(10.1)	28.29(8)	Drug-free 6 m	0	23	39.09(14.4	0/23
Yang et al., 2017†b	84	30.88(7.84)	23/61	0.75(0.66)	-	23.83(5.02)	Drug-naïve	ANX= 15.5	84	30.39(6.71	23/61
Yoshikawa et al., 2	22	48(4.9)	0/22	-	-	-	Drug-free 1 m	0	29	49(5)	0/29
Zhang et al., 2009	15	33.5(10.2)	10/5	10.3(4.8)	-	17.08(-)*	100	NA	15	33.4(10.2)	10/5
Zhang et al., 2012	33	20.52(1.7)	17/16	-	-	-	Drug-naïve	0	32	21.08(1.5)	17/15
Zhao et al., 2017	37	26.7(7.1)	25/12	2(0.5)	-	25(5.2)	Drug-naïve	0	41	27.1(7.2)	26/15
Zou et al., 2010	23	31.1(10.4)	10/13	0.63(0.4)	30.47(-)	24.4(3.9)	Drug-naïve	0	23	36.6(12.9)	10/13

ANXIETY DISORDERS DISORDERS (n=617)								**HEALTHY CONTROLS (n=602)**		
Study/Sample	**n**	**Age (Mean, S**	**Sex (M,**	**Diagnosis**	**Anxiety scores (Mean, SD)**	**Medication (**	**Comorbidities**	**n**	**Age Mean (SI**	**Sex (M, F)**
Asami et al., 2009	24	37.03(10.2)	9/15	PD	-	-	MDD= 12.5 PTSD= 0	24	37.01(9.5)	9/15
Cheng et al., 2015	20	23.3(3.7)	13/7	SAD	SAD=6.2(4.8)[a]	Drug-naïve	0	30	26.2(6.6)	21/9

Hayano et al., 200	27	38.2(9.9)	10/17	PD	-	-	MDD= 11.1 PTSD= 0	30	35.3(10.5)	9/21
Hilbert et al., 2015	59	23.95(5)	14/45	SP	-	-	0	37	22.76(3.9)	11/26
Irle et al., 2014	67	31(10)	32/35	SAD	43(10)[b]	9	MDD= 23.9 PTSD= 0	64	32(10)	33/31
Lai et al., 2012	30	47.03(10.6)	11/19	PD	-	Drug-naïve	0	21	41.14(11.8)	10/11
Lai et al., 2015	53	43.28(10.1)	25/28	PD	23.35(1.9)[a]	Drug-naïve	0	54	40.38(10.5)	25/29
Liao et al., 2011	18	22.67(3.8)	12/6	SAD	6.39(5)[a] / 41.11(8.7)[b]	Drug-free	0	18	21.89(3.7)	13/5
Ma et al., 2019	21	34.92(9.48)	12/9	GAD	17.09(5.3)[a]	Drug-free (>6)	0			
Massana et al., 20	18	36.8(11.3)	7/11	PD	-	-	0	18	36.7(8.8)	8/10
Meng et al., 2012	20	21.8(3.7)	14/6	SAD	5.85(5)[a]	Drug-naïve	0	19	21.58(3.7)	13/6

Moon et al., 2014	22	37(10.7)	13/9	GAD	17.9[a]	-	0	22	33.4(9.7)	13/9
Na et al., 2013	22	PD= 43.08(9. PDA= 36.7(1	13/9	PD=12 PDA=10	PD=47.09(7.8)[b] PDA=40.60(5.3)[b]	-	0	22	40.18(12.4)	11/11
Schienle et al., 201	16	22.9(4.1)	0/16	GAD	-	Drug-free	0	15	23.7(3.7)	0/15
Talati et al., 2013	49	PD= 31.8(10) SAD= 34.1(6.	12/37	PD=16 SAD=33	PD=35.5(10)[b] SAD=42(NA)[b]	PD=56 SAD=27	NA	37	31.4(7.8)	3/34
Tükel et al., 2015	27	27.7(6.7)	12/15	SAD	6.83(5.4)[a]	Drug-naïve=(Drug-free=37	0	27	27.7(6.7)	12/15
Uchida et al., 2008	19	37.05(9.8)	3/16	PD	-	78.9	MDD= 15.8 PTSS= 0	20	36.46(9.9)	4/16
Van Tol et al., 201	68	35.96(9.5)	18/50	PD=20 SAD=25 Comorbid ANX	14.12(9.6)[c]	31	0	65	40.54(9.7)	24/41
Yoo et al., 2005	18	33.3(7.1)	9/9	PD	8.7[a]	-	0	18	32(5.8)	11/7
Zhao et al., 2017	24	24.5(4)	15/9	SAD	-	Drug-naïve	0	41	27.1(7.2)	26/15

POST-TRAUMATIC STRESS DISORDER (n=203)							**HEALTHY CONTROLS (n=329)**		
Study/Sample	**n**	**Age (Mean, SD)**	**Sex (M, F)**	**Anxiety scores (Mean, SD)**	**Medication (%)**	**Comorbidities (%)**	**n**	**Age (Mean, SD)**	**Sex (M, F)**
Bossini et al., 2017	19	40(9)	10/9	75.8(21.8)[d]	Drug-naïve	0	19	41(6)	15/4
Chen et al., 2006	12	34.56(4.9)	4/8	-	-	0= MDD NA= ANX	12	33.25(5.3)	4/8
Cheng et al., 2015	30	26.3(8.1)	21/9	10.9(2.3)[a]	Drug-naïve	0	30	26.2(6.6)	21/9
Corbo et al., 2005	14	33.36(12.1)	6/8	-	-	0	14	33.29(12.3)	6/8
Hakamata et al., 2007	14	45.6(6.2)	0/14	-	-	MDD= 0 ANX= NA	100	47.1(5.7)	0/100
Kroes et al., 2010	24	35.9(NA)	9/15	30.39(14.4)	41.7	MDD= NA ANX= 0	29	32.45(NA)	13/16
Nardo et al., 2010	21	41.7(9.4)	15/6	-	2.39	0	22	40.8(8.9)	16/6

Herringa et al., 2012	13	28.9(4.2)	11/2	-	Drug-naïve	0	15	30.1(6.3)	14/1
Tan et al., 2013	12	37.6(3.7)	12/0	53.8(7.3)[b]	Drug-free (>1 month)	0	14	40.8(5.2)	14/0
Tavanti et al., 2012	25	38.16(10.9)	8/17	25.8(6.6)[a]	Drug-naïve	0	25	38.08(11.01)	8/17
Yamasue et al., 2003	9	44.6(16)	5/4	-	-	0	16	44.4(14)	10/6
Zhang et al., 2011	10	40.8(6.8)	10/0	-	-	MDD= 0 ANX= NA	10	34.3(5.4)	10/0

Footnote: SD=Standard Deviation, M=Male, F=Female, MDD= Major depressive disorder, HDRS= Hamilton depressive rating scale, cMDD=Current MDD, rMDD= remitted MDD, NR= Non-responder, RE=Responder, TRD= treatment-resistant depression, TSD= treatment-responsive depression, dMDD= depressed MDD, FE= first episode, Rem= remitted, Rec= recovered, PD=Panic disorder; PTSD= posttraumatic stress disorder, PDA=Panic Disorder with agoraphobia; SAD=Social anxiety disorder; SP=Specific phobia; GAD= generalized anxiety disorder, . NA=Not available.

[a]HAMA

[b]STAI

[c]BAI

[d]Clinician Administered PTSD Scale (CAPS)

†Studies that provided original t-maps

*Studies originally reporting Montgomery-Åsberg Depressing Rating Scale scores converted to HDRS equivalents (Heo et al., 2007)

Table 2. Results of the brain volumes showing differences between MDD and HC (A), ANX and HC (B) and PTSD and HC (C) with TFCE[b] correction ($p<0.05$)

A) MDD < HEALTHY CONTROLS	Num. voxels	MNI coordinates (x,y,z)	SDM-Z	Voxel p	I^2	Effect size[a]	Egger test p
L cerebellum, hemispheric lobule VIII	2067	-26,-60,-54	-5.149	<0.001	0.000	-0.222	0.919
R cerebellum, hemispheric lobule VIII		14,-60,-48	-4.452	0.001			
L cerebellum, hemispheric lobule VIIB		-36,-62,-46	-4.427	0.002			
L cerebellum, hemispheric lobule IX		-10,-60,-44	-3.900	0.003			
Cerebellum, vermic lobule IX		2,-60,-42	-3.894	0.003			
Cerebellum, vermic lobule VIII		-2,-64,-42	-3.886	0.003			
R cerebellum, crus II		36,-70,-44	-3.835	0.019			
R cerebellum, crus I		28,-82,-34	-3.622	0.024			
L inferior frontal gyrus, opercular part, BA 48	162	-48,14,8	-5.593	0.004	0.680	-0.251	0.545

B) ANX < HEALTHY CONTROLS							
L temporal pole, superior temporal gyrus	105	-36,16,-20	-5.713	0.01	7.263	-0.450	0.391
L inferior frontal gyrus, orbital part		-36,22,-16	-4.922	0.017			
C) PTSD < HEALTHY CONTROLS							
TFCE corrected *(p<0.05)*[b]							
L lingual gryus, BA 18	731	-14,-64,-4	-5.247	<0.001	4.220	-0.686	0.713
L fusiform gyrus, BA 18		-24,-70,-14	-4.196	<0.001			
L fusiform gyrus, BA 37		-30,-58,-16	-3.733	<0.002			
L superior frontal gyrus, medial, BA 8	94	0,30,52	-4.452	0.012	1.067	-0.564	0.598
R superior frontal gryus, medial, BA 8		5,28,50	-4.163	0.012			

Footnote: MDD= major depressive disorder, HC= healthy controls, ANX= anxiety disorders, PTSD= posttraumatic stress disorders, MNI=Montreal Neurological Institute, SDM= Signed Differential Mapping, p= p-value; I^2= Percentage of variance attributable to study heterogeneity; L= left, R= right, BA= Brodmann area, unc= uncorrected p value.

[a]Extracted from Hedges' *g* value

[b]Threshold-free cluster enhancement TFCE correction at p<0.05

*Areas already reported in the TFCE corrected analysis are not shown

Table 3. Results of the brain volumes showing common (A) and different (B, C, D) grey-matter differences in MDD, ANX and PTSD. Threshold-free cluster enhancement TFCE correction at p<0.05.

MDD, ANX and PTSD	Num. voxels	MNI coordinates (x,y,z)	SD M-Z	Voxel p	I^2	Effect Size[a]	Egger test p
A) Reductions in MDD, ANX and PTSD vs HC	*No suprathreshold clusters*						
B) MDD < ANX*							
L cerebellum, hemispheric lobule VIII	1823	-24,-62,-50	2.390	<0.001	0.000	0.219	0.614
Cerebellum, vermic lobule, IV/V		0,-50,-6	2.267	0.002			
R cerebellum, hemispheric lobule VIII		18,-62,-50	2.194	<0.001			
Cerebellum, vermic lobule XI		0,-60,-40	2.156	<0.001			
MDD > ANX*							
L temporal pole, superior temporal gyrus, BA 38	1145	-42,18,-20	-4.872	<0.001	0.008	-0.432	0.322
L heschl gyrus, BA 48		-54,-10,10	-2.978	0.003			

L temporal pole, superior temporal gyrus, BA 38		-50,12,-14	-2.942	<0.001			
L superior temporal gyrus, BA 22		-58,-12,-4	-2.852	0.005			
L rolandic operculum, BA 48		-46,-6,10	-2.228	0.005			
L superior temporal gyrus, BA 48		-58,-6,0	-2.103	0.011			
R superior temporal gyrus, BA 38	430	58,0,-4	-3.465	0.003	1.416	-0.312	0.474
C) PTSD vs MDD**	*No suprathreshold clusters*						
D) PTSD > ANX***							
Right heschl gyrus, BA 48	1112	52,-6,4	3.138	<0.001	1.846	0.535	0.569
R rolandic operculum, BA 48		54,-2,8	3.096	<0.001			
R insula, BA 48		48, -6,6	2.923	<0.001			
L superior temporal gyrus, BA 48	213	-52,-4,-2	2.302	0.026	0.022	0.384	0.669
L anterior cingulate / paracingulate gyri, BA 10	70	-2,52,-2	2.541	0.013	1.255	0.397	0.658
PTSD < ANX***							

L fusiform gyrus, BA 18	602	-26,-70, -14	-2.784	0.002	0.009	-0.492	0.594
L lingual gyrus, BA 18		-14,-62,-6	-2.419	0.012			
L cerebellum, hemispheric lobule VI, BA 18		-16,-64,-16	-1.614	0.037			

Footnote: MDD= major depressive disorder, ANX= anxiety disorders, PTSD= posttraumatic stress disorder, MNI=Montreal Neurological Institute, SDM= Signed Differential Mapping; p=p-value; I^2= Percentage of variance attributable to study heterogeneity, L= left, R= righ

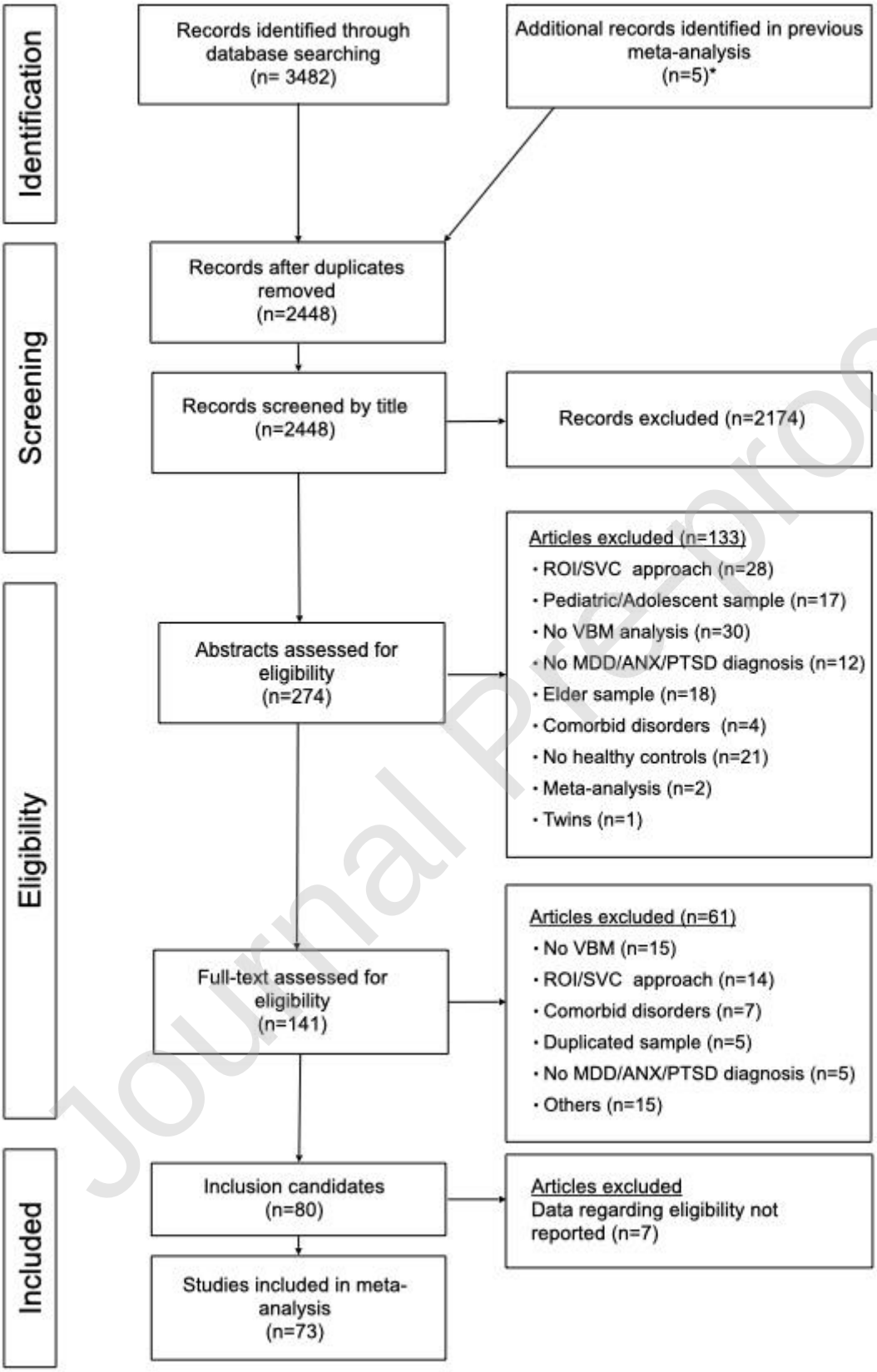
[b]Extracted from Hedges' *g* value

[*]Comparison including age as covariate

**Comparison including sex as covariate

***Comparison including age and sex as covariates

Figure 1. Flowchart of the systematic literature search



Footnote: ROI=region of interests, SVC= small volume correction, VBM= voxel-based morphometry, MDD= major depressive disorder, ANX= anxiety disorders, PTSD= posttraumatic stress disorder

*** (**34, 47, 48**)**

Figure 2. Forest plots of the the mean (Hedge's g) along with its corresponding z and P values, the standard error (SE) and the confidence interval (CI) of global gray matter volume differences between patients with major depressive disorder (MDD), anxiety disorders (ANX) and post-traumatic stress disorder (PTSD) versus healthy controls (HC).

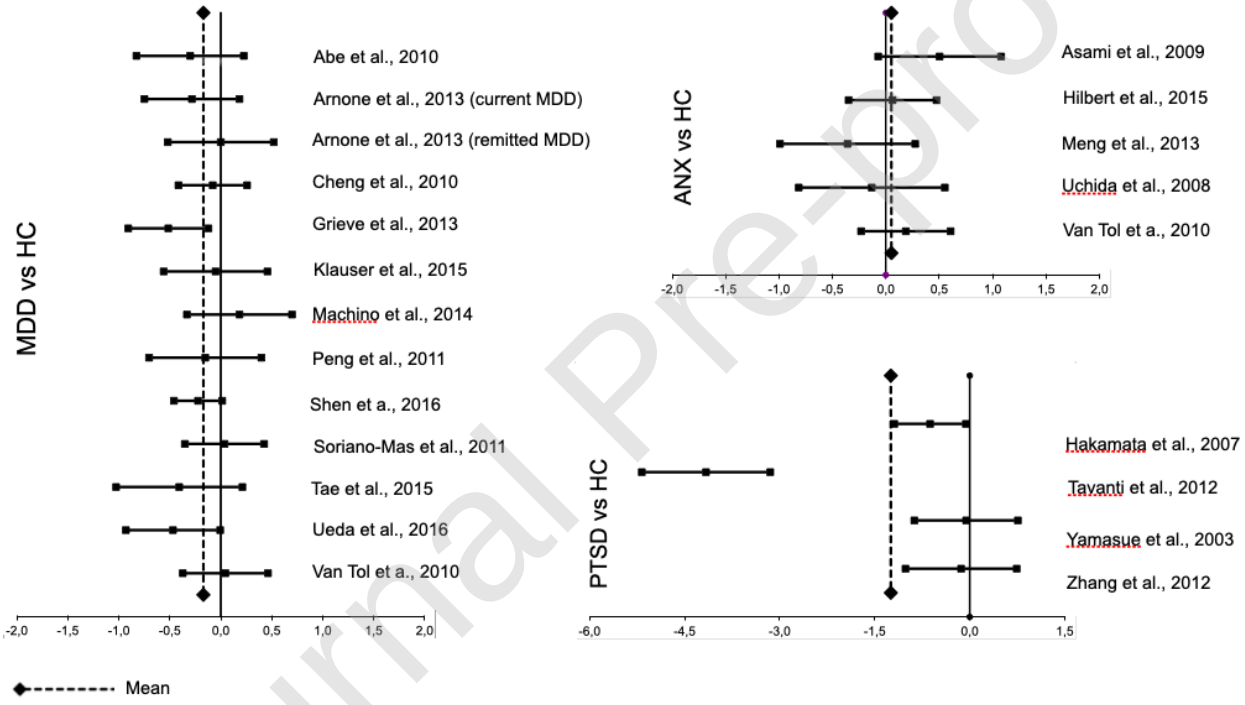
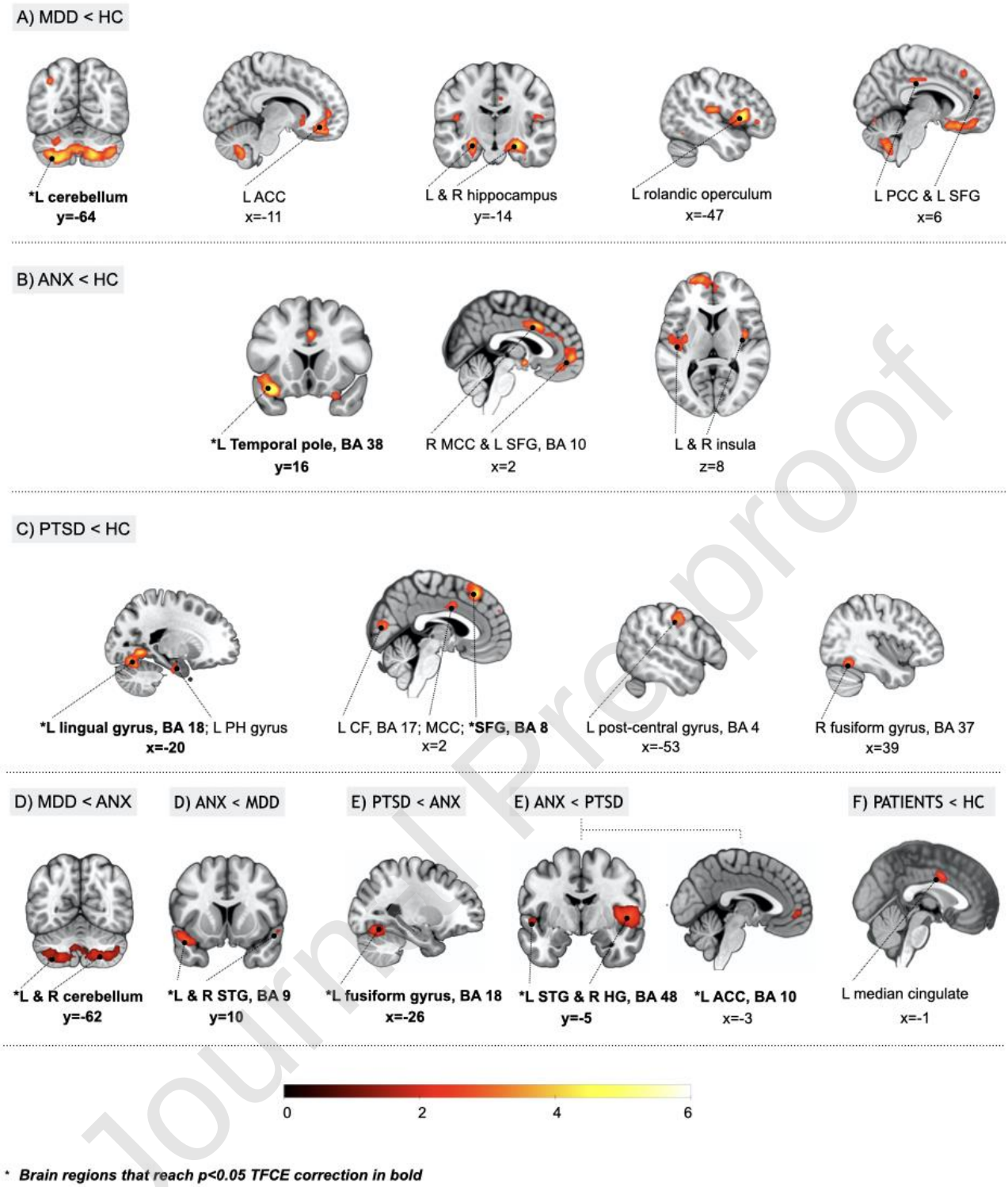


Figure 3. (A) Results of meta-analysis between patients with MDD and HC. (B) Results of meta-analysis between patients with ANX and HC. (C) Results of meta-analysis between patients with PTSD and HC. (D) Results of meta-analysis between all patients and healthy controls (HC). (E) Results of meta-analysis between patients with MDD and patients with ANX. (F) Results of meta-analysis between patients with ANX and patients with PTSD.



* ***Brain regions that reach p<0.05 TFCE correction in bold***

**** Brain regions that reach p<0.05 TFCE correction in bold***

Foonote: MDD= major depressive disorder, HC= healthy controls, ANX= anxiety disorders; PTSD= posttraumatic stress disorder, L= left, R= right, STG= superior temporal gyrus, BA= Brodmann area, IFG=

inferior frontal gyrus, ACC= anterior cingulate cortex; MCC= middle cingulate cortex; SFG, superior frontal gyrus, PH= parahippocampal, CF= calcarine fissure, HG= heschl gyrus. Color bar indicates SDM z scores.

Figure 4. Major depressive disorder versus healthy controls without t-maps
Footnote: L=left, R=right, BA= Brodman area