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Neurobiology of Anxious Depression: A Review

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Abstract

Anxious depression is a common, distinct clinical subtype of major depressive disorder (MDD). This review summarizes current neurobiological knowledge regarding anxious depression. Peer-reviewed articles published January 1970 through September 2012 were identified via PUBMED, EMBASE, and Cochrane Library, using the following key words: anxious depression electroencephalography (EEG), anxious depression functional magnetic resonance imaging (fMRI), anxious depression genetics, anxious depression neurobiology, and anxious melancholia neurobiology. Despite a general dearth of neurobiological research, the results suggest that anxious depression—when defined either syndromally or dimensionally—has distinct neurobiological findings that separate it from non-anxious depression. Structural neuroimaging, EEG, genetics, and neuropsychiatric studies revealed differences in subjects with anxious depression compared to other groups. Endocrine differences between individuals with anxious depression and those with non-anxious depression have also been noted, as evidenced by abnormal responses elicited by exogenous stimulation of the system. Despite these findings, heterogeneity in the definition of anxious depression complicates the results. Because exploring the neurobiology of this depressive subtype is important for improving diagnosis, prognosis, and treatment, enrichment strategies to decrease heterogeneity within the field should be employed for future research.

Keywords

Anxiety; depression; anxious depression; neurobiology; biomarkers

Introduction

Major depressive disorder (MDD) is a heterogeneous illness with various subtypes[1], including anxious depression. Although several different definitions exist for anxious depression, the two most clinically relevant ones use either dimensional or syndromal criteria (Table 1). Briefly, the dimensional diagnosis of anxious depression is typically based on a diagnosis of MDD (based on either DSM or ICD criteria) plus subthreshold anxiety symptoms (based on cut-off scores from standardized scales).[1–2] Alternatively, the syndromal diagnosis of anxious depression is typically based on a DSM or ICD diagnosis of MDD plus the presence of at least one co-morbid anxiety disorder.[2] In addition, many genetics studies use neither dimensional nor syndromal criteria, and instead use anxious depression scores from various scales, such as the Young Adult Self-Report (YSR).[3–6]

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Anxious depression is common and clinically relevant. Indeed, it has been estimated that 40–50% of MDD patients have at least one co-morbid anxiety disorder,[7–9] and these occur across both inpatient[10] and outpatient[11] patient populations. Clinically, those with dimensionally-defined anxious depression have a unique course of illness characterized by worse outcomes and treatment response. In particular, patients with anxious depression exhibit more severe depressive symptoms, more frequent episodes of major depression, and a higher proportion of significant suicidal ideation and previous suicide attempts than patients with non-anxious depression.[9, 11–12] In addition, they take twice as long to recover from index episodes of MDD and are also more likely to exhibit somatic symptoms (such as gastrointestinal symptoms), depersonalization, and derealization.[13] The large, multi-center Sequenced Treatment Alternatives to Relieve Depression study (STAR*D) found that demographically, individuals with anxious depression are more likely to be older, unemployed, and less educated.[9] Furthermore, some studies have shown that those with anxious depression have poorer response to antidepressants, including significantly lower response and remission rates, more frequent and intense side effects, and more serious adverse events, despite medication changes or augmentation techniques.[14–19]

Because high trait anxiety/neuroticism is a vulnerability factor for MDD,[20] and because subjects with MDD have enhanced fear conditioning,[21] researchers have speculated that a common mechanism may underlie the development of anxious depression. Several proposed psychological models may help to explain anxious depression. First, the tripartite model uses three dimensions as a framework for classifying symptoms of anxiety and depression: negative affectivity, positive affectivity, and physiological hyperarousal.[22] Depression is marked by the absence of positive affectivity (i.e., anhedonia), whereas physiological hyperarousal is relatively specific to anxiety. What unifies the two diagnostic states is the high level of negative affectivity seen in co-morbid disease states.

The second model—the approach-withdrawal model—attempts to correlate the clinical deficits of emotion and motivation seen in anxiety and depression. This model hypothesizes two separate systems for emotion and motivation.[23] The approach system controls behavioral motivation towards reward and implicates left frontal lobe regions, hypothesized to be hypoactive in depression. The withdrawal system controls behavioral inhibition and implicates right frontal lobe regions, hypothesized to be hyperactive in anxiety. This frontal asymmetry may become more apparent in subjects suffering from both depression and anxiety and can be examined through neuropsychiatric tests and neuroimaging techniques.

Third, the valence-arousal model expands on the approach-withdrawal model by suggesting hemispheric differences for arousal in anxiety and depression.[24–25] In particular, depression correlates with decreased activity in the right parieto-temporal brain region associated with arousal properties, and anxiety correlates with increased activity. Taken together, these three theories may help explain the neurobiological differences between subjects with anxiety, depression, and anxious depression.

Although evidence exists that—when defined either dimensionally or syndromally—anxious depression is a clinically distinct diagnosis, little is known about its neurobiology. This review explores the current literature surrounding the neurobiological basis of an anxious depression subtype and incorporates explanations from psychological models when available.

Data Sources and Study Selection

Articles published from January 1970 through September 2012 were identified via PUBMED. An initial search for the term *anxious depression* revealed 50,055 articles. Search terms were refined as follows: *anxious depression electroencephalography (EEG)* (541

articles), *anxious depression functional magnetic resonance imaging (fMRI)* (503), *anxious depression genetics* (2389), *anxious depression neurobiology* (335), and *anxious melancholia neurobiology* (113). A similar search was done through EMBASE for the term *anxious depression* (270). A Cochrane Library search for *anxious depression* (3) revealed no relevant titles. Reviewing the titles and abstracts uncovered 24 relevant studies, which were all examined in full. All studies used either dimensional or syndromal definitions of anxious depression, with the exception of several genetics studies that measured anxious depression from a subscale of the YSR. All articles were English-language, peer-reviewed, published studies limited to adult human research only.

Results

Of the 24studies identified as relevant to the neurobiology of anxious depression, six pertained to imaging, three were neuropsychiatric and sensory studies, two were EEG studies, three focused on the endocrine system, and ten were genetics studies. The articles were grouped according to the primary modality applied. Table 2 summarizes these studies and specifies how the various authors defined anxious depression.

Neuroimaging

Several studies used fMRI and structural MRI to investigate the difference between groups of patients with anxious depression versus non-anxious depression.

Functional Neuroimaging: Emotion Induction/Regulation Tasks—Using syndromal criteria of MDD plus co-morbid generalized anxiety disorder (GAD) to define anxious depression, one study compared four groups of unmedicated subjects currently experiencing a depressive episode (anxious depression (N=25), MDD (N=14), anxiety (N=18), and healthy controls (N=32)) during an emotional conflict identification task in which participants had to identify whether happy or fearful faces were labeled correctly while undergoing fMRI.[26] During incongruent stimuli, all patient groups were found to have deficits in both activation and connectivity of the ventral anterior cingulate and amygdala (areas involved in the regulation of emotional conflict), suggesting a shared origin between anxiety and depression. However, unlike the anxiety group and the co-morbid subjects, the MDD group compensated for these deficits by also activating regions of the bilateral anterior lateral prefrontal cortices, improving their ability to adapt to emotional conflict.

Another recent fMRI study compared MDD subjects experiencing a current depressive episode (N=14) to individuals with social anxiety disorder (N=16), healthy controls (N=17), and individuals with syndromally-defined anxious depression (co-morbid MDD and social anxiety disorder (N=17)); all subjects were female and not required to be medication-free. Subjects completed a social evaluative threat task in which they were asked to prepare a speech.[27] Those with anxious depression showed similar activation patterns to the other two patient groups, except for an intermediate level of activation of the middle cingulate cortex and precentral gyrus (less than the MDD group and more than the social anxiety disorder group) and posterior cingulate (conversely, more than the MDD group and less than the social anxiety disorder group). Interestingly, patients with anxious depression and healthy controls showed similar activation patterns in several regions, including greater activation of the insula (during instructions) and middle temporal gyrus (during task recovery), and less activation of the cerebellum (during instructions) and cuneus (during instructions and recovery).

Functional Neuroimaging: Cognitive Tasks—One group[28–29] examined neurobiological differences in two cohorts in later life, given that having MDD plus a DSM-defined anxiety disorder nears 50% in those ≥55 years old.[30] Elderly patients with depression (≥65 years old) were scanned while performing the Preparing to Overcome Prepotency (POP) task, a validated executive control task.[28] Compared to depressed patients with low anxiety, depressed patients with high anxiety had significantly greater and more sustained activation of the dorsal anterior cingulate cortex (dACC), prefrontal cortex supplementary motor area, and posterior cingulate. However, patients were not medication-free at the time of study, and the total sample size was very small (four subjects per group).

Functional Neuroimaging: Resting State—A recent fMRI report of elderly subjects found that those with anxious depression (N=11) had a dissociative pattern in the default mode network (DMN), a functional network of medial brain regions (posterior cingulate, medial prefrontal cortex, and medial temporal cortex) that is typically active during resting states and inhibited during the performance of effortful tasks.[29] This dissociative pattern revealed significantly increased functional connectivity in the posterior regions of the DMN (occipital and parietal association areas) and significantly decreased functional connectivity in the anterior regions of the DMN (rostral ACC, medial prefrontal and orbitofrontal cortex) compared to depressed subjects with low anxiety. Again, because patients were not required to be medication-free, these findings are difficult to interpret. In addition, the definition of anxious depression varied within the sample (Table 2).

Structural Neuroimaging

A structural MRI study compared patients experiencing a current episode (lasting at least six months) of MDD (N=68), anxiety (defined as panic disorder (PD), social anxiety disorder, or GAD; N=66), co-morbid MDD and anxiety (N=88), and healthy controls (N=65). Subjects were not required to be medication-free. All patient groups had lower gray matter (GM) volumes of the rostral ACC (extending into the dACC) than healthy controls, independent of illness severity; this suggests a shared mechanism of impaired emotional processing and regulation between the two disorders.[31] No differences were found between those with anxious depression and other diagnostic subgroups.

In another structural examination of brain regions, 96 subjects with MDD were compared to 49 individuals with dimensionally-defined anxious depression (MDD plus at least one of the following symptoms occurring simultaneously: 1) general rating of anxiety, 2) general rating of phobia, 3) free-floating anxiety, 4) anxious foreboding with autonomic symptoms, and 183 healthy controls. Both patient groups had lower GM volume in the superior parietal lobe than healthy controls. However, those with anxious depression had increased GM volume in the superior temporal gyrus, extending into the posterior middle temporal gyrus and inferior temporal gyrus in the right hemisphere compared to the MDD group; no differences were found in these regions compared to healthy controls.[32] These findings suggest a possible diagnosis-dependent change in GM thickness, or changes in the global patterns of sulcal/gyral structures. Further research is needed to determine whether these changes could be explained by the valence-arousal and/or the approach-withdrawal hypotheses, which imply a hyperactive right hemisphere in patients with anxious depression.[23–25] Although participants were not required to be medication-free, the authors suggest that further research may reveal structural neuroimaging biomarkers to help differentiate the depression subtypes.

Neuropsychiatric and Sensory Testing

In line with the approach-withdrawal hypothesis of anxious depression, fixed response design fluency tasks ask participants to draw as many novel designs as possible within five

minutes and are intended to test the neuronal circuit underlying withdrawal in the right hemisphere. Nelson and colleagues found that 30 patients with syndromally-defined anxious depression (MDD plus lifetime anxiety disorder (social anxiety disorder, PD, Specific Phobia, post-traumatic stress disorder (PTSD), or obsessive-compulsive disorder (OCD)) had significantly poorer performance on fixed response design fluency tasks (fewer designs and lower total score) than MDD patients (N=34) and healthy controls (N=33) during neuropsychological testing.[33] This hemispheric-specific deficit of the right frontal lobe in individuals with anxious depression aligns with the approach-withdrawal hypothesis that anxiety is associated with right frontal lobe dysfunction, or “frontal asymmetry”. The authors subsequently replicated their results using several different design fluency tasks in a more homogenous group of patients with syndromal anxious depression (MDD plus current PD). Although neither study found significant differences in verbal fluency (left frontal lobe) between the three groups, those with anxious depression performed better on the verbal tasks relative to the design fluency tasks compared to subjects with MDD and healthy controls, further confirming frontal asymmetries.

Assessing another indirect measure of brain hemispheric activation, one study examined differences in dichotic listening task results among 98 subjects with DSM-diagnosed MDD, 57 healthy controls, and 51 subjects with syndromally-defined anxious depression.[34] All patients were medication-free for at least 10 days prior to testing. During auditory presentation of tones and words, those with anxious depression significantly favored the left ear (controlled by the right hemisphere) compared to subjects with MDD. However, this difference was due to poorer right ear accuracy, as opposed to better left ear functioning, implying left hemisphere hypofunction in subjects with anxious depression. Although limited by the fact that both right-and left-handed subjects were studied, the results support a hemispheric asymmetry in anxious depression.

The emotion-modulated startle (EMS) paradigm measures reactivity of emotional stimuli, such as emotionally-valenced pictures. When a startle probe (such as a loud noise through headphones) is presented following emotional stimuli, the startle response (measured by eye-blink) is normally increased when viewing unpleasant pictures, and attenuated during pleasant pictures. Anxiety disorders have been associated with exaggerated emotional reactivity,[35–36] whereas subjects with depression show blunted responses.[37–38] In order to examine the response in individuals with anxious depression, one study compared EMS responses between those with anxiety only (N=33), syndromally-defined anxious depression (N=24), and healthy controls (N=96).[39] Those with anxious depression had blunted EMS, suggesting that co-morbid anxiety with depression is associated with a pattern of emotional response expected in those with depression rather than anxiety. However, in this study, the startle probe was mild. Recent work suggests that depressed patients, regardless of anxiety status, exhibit *elevated* startle reactivity with more potent stimuli, such as threat of shock (Grillon C., et al, in review).

Electroencephalography (EEG)

EEG directly compares hemispheric asymmetries. When compared to 25 patients with MDD and 26 healthy controls on resting EEG, patients with syndromally-defined anxious depression (N=19) showed significantly less alpha activity (greater activation) over the right anterior hemisphere than the left,[40] though both right- and left-handed participants were eligible. Another recent study examined task-related EEG differences among depressed patients with high anxiety (N=14), low anxiety (N=14), and healthy controls (N=21) during verbal (Word Finding) and spatial (Dot Localization) neurocognitive tasks.[41] The self-rated State-Trait Anxiety Inventory-Form Y was used to determine anxiety levels (≥82 for the high anxiety group and <80 for the low anxiety group). Group differences in task performance did not reach statistical significance. However, the high-anxiety group showed

greater activation in the right central and parietal regions during the spatial task compared to the left. Conversely, the low-anxiety group showed greater left frontal and central activation during the verbal task. A major limitation of this study was diagnostic heterogeneity, as subjects could have either MDD or bipolar disorder II. However, these data, along with data from imaging and neuropsychiatric testing, are consistent with the approach-withdrawal theory and the valence-arousal hypothesis positing that anxious depression heightens hemispheric activity (most consistently in the right hemisphere), whereas depression without anxiety heightens left hemispheric activity.

Endocrine System

Corticotrophin-releasing hormone (CRH) is secreted by the hypothalamus and acts on the anterior pituitary gland to stimulate the release of adrenocorticotropic hormone (ACTH), which increases circulating cortisol from the adrenal glands as a response to stress. Meller and colleagues measured ACTH and cortisol levels in 14 dimensionally-defined patients with anxious depression following exogenous CRH challenge. Patients were not required to be medication-free at the time of testing, and depressed patients could meet criteria for either MDD or bipolar disorder. Compared to 11 patients with non-anxious depression and 27 healthy controls, subjects with anxious depression exhibited a significantly attenuated response.[42]

Like cortisol, exogenously administered dexamethasone works through negative feedback to suppress ACTH, thus decreasing cortisol levels. In 17 women with syndromally-defined anxious depression, 50% exhibited impaired suppression of cortisol following dexamethasone challenge, compared to 37% of female subjects with anxiety disorders (PD or GAD; N=9) and 18% of female subjects with MDD (N=12).[43] This study also examined differences in the thyroid hormone system between the groups. Subjects with anxious depression had lower baseline serum levels of thyroid stimulating hormone (TSH), triiodothyronine (T_3), and thyroxine (T_4). When challenged with exogenous thyrotropin-releasing hormone (TRH), 35% of subjects with anxious depression had a blunted TSH response, compared to only 4% of healthy female controls. However, 25% of female subjects with anxiety disorders and 45% of female subjects with MDD also had blunted responses to the challenge, implying that psychopathology impairs TSH response to endogenous TRH administration in all patient groups, not just anxious depression. It is important to note that while subjects needed a lifetime diagnosis of anxiety to be categorized as having anxious depression, they did not need to have a current diagnosis of anxiety.

Both the Trier Social Stress Test (TSST) and clonidine challenge stimulate the hypothalamic-pituitary-adrenal (HPA) axis and are useful for studying this system. Following TSST challenge, subjects with syndromal anxious depression (N=18) were found to have significantly elevated ACTH and cortisol levels compared to 15 subjects with an anxiety disorder (social anxiety disorder or PD), 15 subjects with MDD, and 48 healthy controls.[44] After clonidine challenge, subjects with predominant anxiety symptoms (i.e., those with anxious depression or an anxiety disorder) showed a blunting of growth hormone response to clonidine, an α2- adrenergic agonist; a current diagnosis of anxiety was not required by the investigators.

These results suggest a dysfunction of the HPA axis in subjects with anxious depression. Indeed, a relatively recent review of the literature suggests that chronic stress and hypersecretion of cortisol can initiate a cascade of changes involving the serotonergic system that may be implicated in the pathophysiology of anxiety and depression.[45]

Genetics

A large, longitudinal twin family study collected DNA and survey information in order to uncover specific genetic polymorphisms relevant to anxiety and depression.[46] An overlap was found in the genes conveying susceptibility to anxiety, neuroticism, somatic anxiety, and depression. Indeed, genetic factors accounted for approximately 50% of the variance in anxiety, neuroticism, somatic anxiety, and depression, and genetic influence accounted for most of the covariance between these traits, strongly suggesting that the genetic factors influencing anxiety and depression are largely the same.

Because migraine frequently co-occurs with anxiety and depression, [47] Ligthart and colleagues conducted a twin survey that examined the genetic relationship between migraine and dimensionally-defined anxious depression.[48] Those who scored in the highest quartile for anxious depression had a migraine prevalence of 43%, compared to 20% of those who scored in the lowest quartile. Despite this increased prevalence in those with anxious depression, higher anxious depression scores were associated a *lower* contribution of genetic factors to migraine susceptibility. The authors concluded that frequent migraines may cause depressive and anxious symptoms independent of genetic factors, or that depressed and anxious patients report more somatic symptoms. Of note, a major limitation of this study was that anxious depression was not clinician-assessed, but instead based on self-report. Nevertheless, the authors suggest that “pure” migraine may have a different etiology from migraine associated with anxious depression, which may have treatment implications.

Animal models investigating the genetics of anxiety- and depression-related phenotypes have led to hypotheses aimed at discovering novel therapeutics by targeting the brain’s neuropeptide systems.[49] For instance, neuropeptide Y (NPY), a peptide secreted by neurons and abundantly expressed in the central nervous system (including the amygdala), is believed to play a role in the pathophysiology and treatment response of anxiety and depression.[50–52] Domschke and colleagues examined the effect of single nucleotide polymorphisms (SNPs) of the NPY gene on antidepressant treatment response in 91 subjects with dimensionally-defined anxious depression compared to 165 subjects with non-anxious MDD.[53] The less active -399 C allele of the NPY SNP rs16147 was associated with a slower response to treatment after two weeks in individuals with anxious depression, as well as failure to reach remission after four weeks of treatment. However, after applying false discovery rate correction to the results, the association of rs16147 with slow response within the first two weeks remained strongly suggestive, but lost significance. The authors suggested that lower NPY levels may be implicated in the pathophysiology of anxious depression, given that carrying the -399C allele resulted in an approximately 30% decrease in mRNA expression. Confounding factors included the fact that patients were recruited in a naturalistic setting, were treated with a variety of antidepressants, there was no standardized medication or dosing, and there were no healthy controls for comparison.

Pharmacogenetic studies have implicated the norepinephrine transporter (*NET*) and serotonin transporter (*5-HTT*) as possible candidate genes in major depression. Baffa and colleagues examined the effects of seven polymorphisms of *NET* and two polymorphisms of *5-HTT* (specifically, the serotonin-transporter-linked promoter region (*5-HTTLPR*) and the 5-HTT rs25531 polymorphisms) on antidepressant treatment response in 252 unrelated Caucasian subjects with depression, 91 of whom had dimensionally-defined anxious depression.[54] No overall effect of *NET* or *5-HTT* polymorphisms on overall treatment response were noted in depressed subjects. However, further stratification found that the less active *5-HTTLPR S* allele and the *5-HTTLPR/5-HTT* rs25531 haplotypes had a detrimental effect on treatment response in individuals with anxious depression.

Genes that regulate the CRH system have also been suggested to play a role in the pathophysiology and treatment response of anxiety and depression. Binder and colleagues examined the interaction between the SNP rs10473984 (within the CRH binding protein locus) and anxious depression on treatment response to citalopram in 734 subjects with dimensionally-defined anxious depression.[55] rs10473984 was significantly associated with both remission (p=0.0026) and reduction (p=0.00031) of depressive symptoms, but the T allele was associated with poorer outcomes in African Americans and Hispanics. Interestingly, this association was more pronounced in subjects with anxious depression (p=0.008), suggesting that genetic variants within the CRH system may predict treatment response in anxious depression. Similarly, brain-derived neurotrophic factor (BDNF) has been implicated in the pathophysiology of depression. In 81 subjects with dimensionally-defined anxious depression, the BDNF rs7124442 TT genotype predicted worse treatment response to antidepressants over a six-week period (p=0.003).[56]

In a genome-wide association study examining the relationship between SNPs and treatment outcomes in subjects with MDD and bipolar depression across three different samples, Ising and colleagues found that subjects with syndromally-defined anxious depression (N=283) and a low number of response alleles had the least favorable outcome.[57] The authors suggested that a combination of genetic factors (i.e. specific alleles) and clinical factors (i.e. anxious depression) were important predictors of antidepressant treatment outcomes.

Several negative results from genetics studies also warrant discussion. Middledorp and colleagues[6] conducted an association study between anxious depressive symptoms and specific genes by examining 45 SNPs in genes encoding for several serotonin receptions, as well as for catechol-O-methyltransferase (COMT), tryptophan hydroxylase type 2 (TPH2), BDNF and G-protein regulators, all of which are believed to play a role in the pathophysiology of anxiety and depression. In this large sample of genotyped adults, adolescents, and children (N=2,582), no association was found between the SNPs and anxious depression traits. One key limitation to the study, however, was that subjects did not have to have formal psychiatric diagnoses; instead, anxious depression was measured via self-reported rating scales.

Because life events have also been associated with anxiety and depressive disorders, [58–59] several studies explored the possibility that these associations might be due to gene-environment correlations, but obtained mostly negative findings. Briefly, one group that studied a cohort of monozygotic and dizygotic twins (N=5,782) found that anxiety and depression scores on the YSR both increased after life events and predicted the experience of life events. However, no evidence was found for a gene-environment correlation; in other words, genes that influenced anxious depression did not overlap with genes that increased the risk of exposure to life events.[3] A separate but related study of 1,155 twins and their families similarly found no evidence for an interaction between *5-HTTLPR* and the number of life experiences on anxious depression scores.[5] In contrast, one study by the same research group found that associations between employment/burnout and anxious depression scores were related to overlapping genetic and individual-specific environmental factors (N=4,309 twins and 1,008 siblings). Taken together, the evidence suggests that genetic vulnerability for depression may increase the risk for exposure to high-risk environments, such as unemployment, and that work-related stress may be significant in burnout and in anxious depression.[4] However, these studies were limited by the fact that anxious depression was not clinically diagnosed, but instead based on self-report from the YSR; the authors did note that YSR scores had previously been found correlate strongly with DSM-IV diagnoses of MDD and anxiety disorders.[60]

Conclusions

Despite an overall dearth of neurobiological research, the results presented above suggest that anxious depression—defined either syndromally or dimensionally—is associated with distinct neurobiological findings that separate it from non-anxious depression. Regardless of the heterogeneity involved in the various syndromal and dimensional definitions of depression, the combined presence of anxiety and depression points to a subtype associated with worse outcomes, as indicated by worse psychosocial functioning and treatment response. Uncovering the neurobiology of this subtype is thus particularly important for improving diagnosis, prognosis, and treatment.

Several limitations bear mentioning. Comparing data across studies is difficult because of variations in study design, assessment, and the inconsistent definitions used to diagnose anxious depression. Most notably, no current consensus exists regarding the definition of anxious depression and, indeed, different studies used varying definitions. Some studies used syndromal criteria,[26–27, 31, 33–34, 39–40, 43–44, 57] and others used dimensional criteria.[28–29, 32, 41–42, 53–56] In addition, several studies did not include healthy volunteers,[28–29, 53] and not all studies required that participants have a standard 10–14 day medication-free period.[27–29, 31–33, 39, 42–43, 53] It should also be noted that some studies did not actually provide a diagnosis, per se, of anxious depression, and instead used scales to measure anxious depressive traits and to make correlations.[3–6, 48] Finally, given that anxious depression is a combination of depression *plus* anxiety, subjects would likely be suffering from more severe illness than those with depression only, making it difficult to compare symptom severity between groups.

Despite these limitations, important patterns have emerged from this research. For instance, although only a few studies examined differences between the right and left hemispheres of individuals with anxious depression versus those with non-anxious depression or healthy controls, data from structural neuroimaging, EEG, and neuropsychiatric testing suggests that structural and functional asymmetries may be present in those with anxious depression. In particular, individuals with anxious depression appear to have increased activity in the right hemisphere compared to the left, in line with the approach-withdrawal and valence-arousal hypotheses.[24–25, 32–34] In addition, individuals with anxious depression may have a dysfunctional HPA axis, as evidenced by abnormal responses elicited by exogenous stimulation of the system.[42–44] Although one study [61] found that neither syndromally- nor dimensionally-defined anxious depression were sufficiently robust predictors of outcome in helping clinicians choose between SSRIs and tricyclic antidepressants, several genetics studies found molecular differences that might help predict treatment outcome for subjects with anxious depression defined in this manner; in notable contrast, those genetics studies that used neither syndromally-defined nor dimensionally-defined anxious depression often found no such distinguishing features.[53–57]

No neurobiological studies appear to have been conducted in patients with subclinical symptoms of mixed anxiety and depression, defined as mixed anxiety depression (based on ICD-10 criteria)[62] or mixed anxiety depressive disorder (based on DSM-IV criteria).[63] Interestingly, due to its inability to separate from MDD or GAD in DSM-5 field trials, mixed anxiety depressive disorder will no longer be a diagnosis in the forthcoming DSM-5. However, the heterogeneity of MDD and its frequent co-morbidities lowers its reliability as a diagnosis. To address this issue, the DSM-5 has added an anxious depression specifier to the diagnosis of MDD, moving towards a more dimensional approach.[64]

Given the data reviewed above, we propose that using a standard dimensional definition of anxious depression may lead to improved neurobiological and clinical differentiation. In

particular, the dimensional definition of anxious depression as DSM- or ICD-diagnosed MDD plus a score of ≥7 on the anxiety/somatization factor score of the Hamilton Depression Rating Scale (HAM-D) [9, 11, 15] has been shown to separate anxious depression as a clinically distinct depressive subtype and may be useful in future neurobiological studies. Decreasing heterogeneity within research is a key enrichment strategy that will lead to better identification of neurobiologically salient subgroups, provide important insights into the neurobiology of anxious depression, and eventually lead to the development of novel targets for its treatment. As the paucity of current studies underscores, there is an urgent need for further neurobiological explorations of anxious depression.

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Table 1

Dimensional and Syndromal Definitions of Anxious Depression

Term Used	Definition
Dimensionally-defined Anxious Depression	ICD or DSM Axis 1 diagnosis of MDD, plus high levels of anxiety symptoms defined by a cut-off score on a standardized scale. Example: MDD plus a score of ≥7 on the anxiety/somatization factor score of the HAM-D
Syndromally-defined Anxious Depression	ICD or DSM Axis 1 diagnosis of MDD, plus ICD or DSM Axis 1 diagnosis of an anxiety disorder. Example: MDD plus GAD

* ICD= International Classification of Diseases; DSM= Diagnostic and Statistical Manual of Mental Disorders; MDD = major depressive disorder; HAM-D=Hamilton Depression Rating Scale; GAD=generalized anxiety disorder

Table 2

Anxious Depression Neurobiology Studies: Definition, Findings, and Limitations

Neuroimaging Studies			
Authors	**Definition Used**	**Findings**	**Limitations**
Andreescu et al.[28]	Dimensional: DSM-IV SCID diagnosis of MDD. High vs. low anxiety determined by categorical BSI anxiety measure; N=4.	During an executive control task, subjects with AD had a greater and more sustained activation of the dACC, prefrontal cortex supplementary motor area, and posterior cingulate. Modality: fMRI.	All patients ≥65 years old; not medication-free; no control group; small sample (8 total)
Andreescu et al.[29]	Dimensional: DSM-IV SCID diagnosis of MDD. High anxiety determined by total HARS score ≥15 (in 15 of 19 subjects) OR total BSI anxiety score ≥1 in (4 of 19 subjects); N=11.	Subjects with AD had a dissociative pattern in the DMN, in particular, increased connectivity in the posterior regions (occipital and parietal association areas) and decreased connectivity in the anterior regions (rostral ACC, medial prefrontal and orbitofrontal cortex). Modality: fMRI.	All patients ≥65 years old; not medication-free; used two different ways to define anxious depression; no control group
Etkin and Schatzberg[26]	Syndromal: DSM-IV diagnoses of co-morbid MDD and GAD; N=25.	During an emotional conflict task, all patient groups (14 with MDD, 18 with anxiety, and 25 with AD) had deficits in both activation and connectivity of the ventral anterior cingulate and amygdala. Unlike anxious and co-morbid subjects, the MDD group compensated for these deficits by also activating regions of the bilateral anterior and lateral prefrontal cortices. Modality: fMRI.	GAD was the only co-morbid anxiety diagnosis allowed for AD group
Waugh et al.[27]	Syndromal: DSM-IV SCID diagnoses of co-morbid MDD and social anxiety disorder; N=17.	During a social evaluative threat task, subjects with AD showed similar activation patterns to the other two patient groups (MDD, N=14; social anxiety disorder, N=16), except for an intermediate level of activation of the middle cingulate cortex and precentral gyrus (less than MDD and more than social anxiety disorder) and posterior cingulate cortices (more than MDD and less than social anxiety disorder). Compared to healthy controls (N=17), AD also showed similarities in activation patterns in several regions: greater activation of the insula (during instructions) and, middle temporal gyrus (during task recovery), and less activation of the cerebellum (during instructions) and cuneus (during instructions and recovery). Modality: fMRI.	Female only; not medication-free; social anxiety disorder was the only co-morbid anxiety diagnosis allowed for AD group
Van Tol et al.[31]	Syndromal: DSM-IV SCID diagnoses of MDD plus anxiety disorder (GAD, PD, or social anxiety disorder); N=88.	All patient groups (MDD, N=68; Anxiety, N=66; and AD, N=88) had lower gray matter volumes of the rostral ACC, extending into the dACC, independent of illness severity, compared to healthy controls (N=65). Modality: structural MRI.	Not medication-free
Inkster et al.[32]	Dimensional: DSM or ICD criteria for MDD, plus ≥1 of the following anxiety symptoms concomitantly with depression: 1) general rating of anxiety; 2) general rating of phobia; 3) free-floating anxiety; 4) anxious foreboding with autonomic symptoms. N=49.	Subjects with AD had significantly increased gray matter volume in the right superior temporal gyrus, extending into the posterior middle temporal gyrus and inferior temporal gyrus when compared to the MDD (N=96) group; no differences were found in these regions when compared to the healthy control group (N=183). Modality: structural MRI.	Not medication-free; unlike depression, the duration of anxiety was not controlled for

Neuropsychiatric & Sensory Studies

Authors	Definition Used	Findings	Limitations
Nelson et al.[33]	Syndromal: Study 1: DSM-IV SCID diagnoses of co-morbid MDD and lifetime or current anxiety disorder (PD, Specific Phobia, PTSD, OCD, or social anxiety disorder); N=30. Study 2: Co-morbid MDD and current PD; N=43.	Study 1: Those with AD performed worse on design fluency tasks compared to MDD patients (N=34) and healthy controls (N=33). No differences in verbal fluency were found. Study 2: Results replicated from Study 1 with a more homogenous AD group and higher N. Note, MDD N=35 and healthy control N=50.	Current co-morbidity for AD not necessary (only lifetime); not required to be medication-free.
Bruder et al.[34]	Syndromal: DSM-IV criteria during semi-structured interview of co-morbid MDD and anxiety disorder (social anxiety disorder, PD, GAD, or OCD); N=51.	Compared to those with MDD (N=98) during auditory presentation of tones and words, those with AD favored the left ear (controlled by the right hemisphere). However, this difference was due to poorer right ear accuracy as opposed to better left ear functioning. Neither group differed significantly from healthy controls (N=57) in perceptual asymmetry.	Allowed for right and left handed subjects
Taylor-Clift et al[39]	Syndromal: DSM-IV SCID diagnosis of current co-morbid MDD and any anxiety disorder; N=24.	Compared to those with anxiety (N=31) and healthy controls (N=96), those with AD displayed blunted emotion-modulated startle.	No depression-only group; some subjects later went on to develop bipolar disorder; not medication-free

Electroencephalographic Studies

Authors	Definition Used	Findings	Limitations
Bruder et al. [40]	Syndromal: DSM-III criteria for co-morbid MDD and an anxiety disorder (social anxiety disorder, PD, GAD, or OCD); N=19.	Compared patients with MDD (N=25) and healthy controls (N=26) on resting EEG, patients with AD (N=19) showed less alpha activity (greater activation) over the right anterior hemisphere than the left.	Allowed for right- and left-handed subjects
Manna et al.[41]	Dimensional: DSM-IV criteria during structured interview for depression (MDD, dysthymia, or bipolar disorder II with depression), plus high anxiety based on self-rated anxiety on the State-Trait Anxiety Inventory-Form Y, with trait scores ≥82 for the high anxiety group; N=14.	Subjects with AD showed greater activation in the right central and parietal regions during the spatial task compared to the left. Conversely, the low-anxiety group (N=14) showed greater left frontal and central activation during the verbal task. The healthy controls (N=21) had a similar pattern to the low-anxiety group. Group differences in cognitive task performance did not reach statistical significance.	Allowed for heterogeneous depression population, including bipolar II subjects

HPA Axis Studies

Authors	Definition Used	Findings	Limitations
Meller et al.[42]	Dimensional: DSM-III criteria for depression (MDD or bipolar disorder) plus a score of ≥16 on six items from the SADS-L: 1) worry, brooding, painful pre-occupation, and inability to get rid of unpleasant thought; 2) panic attacks; 3) somatic anxiety; 4) psychic anxiety; 5) phobia; 6) obsessions or compulsions. N=14.	Compared to 11 depressed subjects without anxiety and 27 healthy controls, subjects with AD exhibited an attenuated ACTH response to exogenous CRH.	Allowed for heterogeneous depression population, including bipolar II subjects; not required to be medication-free
Rao et al.[43]	Syndromal: DSM-III criteria during semi-structured interview for MDD plus anxiety disorder (PD or GAD) meeting criteria either concomitantly or separately during life-time; N=17.	Part 1: In females with AD, 50% exhibited impaired suppression of cortisol following dexamethasone challenge, compared to 37% of female subjects with anxiety disorders (PD or GAD; N=9) and 18% of female subjects with MDD (N=12). Part 2: Subjects with AD had lower baseline serum levels of TSH, T_3, and T_4. When challenged with exogenous TRH, 35% of those with AD had a blunted TSH response, compared to 4% of healthy female controls with a similarly slowed response. However, 25% of female subjects with anxiety disorders and 45% of female subjects with MDD also had blunted responses to the challenge.	Current co-morbidity for AD not necessary (only lifetime); not required to be medication-free; females only in the AD and anxiety group, and in the significant MDD group

HPA Axis Studies

Authors	Definition Used	Findings	Limitations
Cameron[44]	Syndromal: DSM-IV SCID diagnoses of MDD plus an anxiety disorder (social anxiety disorder or PD); anxiety meeting criteria either currently or within the past year; N=18.	Following TSST challenge, subjects with AD were the only group found to have elevated ACTH and cortisol levels compared to 15 subjects with an anxiety disorder (social anxiety disorder or PD), 15 subjects with MDD, and 48 healthy controls. After clonidine challenge, subjects with predominant anxiety symptoms showed a blunting of GH response to clonidine.	Current co-morbidity for AD not necessary (only lifetime); limited anxiety disorders to social anxiety disorder and PD

Genetics

Authors	Definition Used	Findings	Limitations
Ligthart et al.[48]	Factor score based on measures of anxiety, depression, and neuroticism; high AD score was given to those in the 4th quartile of 1,491 complete twin pairs.	Genetic correlation found between migraine and AD. However, migraine was more heritable when *not* accompanied by AD.	Limited power; no formal psychiatric diagnoses were assessed, as the diagnosis was based on self-report only
Domschke et al.[53]	Dimensional: DSM-IV SCID diagnosis of MDD plus HAM-D anxiety/somatization factor score ≥7; N=91.	The less active -399 C allele of the NPY SNP rs16147 was associated with a slower response to treatment after two weeks in subjects with AD, as well as failure to reach remission after four weeks of treatment.	Recruited in a naturalistic setting and treated with a variety of antidepressants, with no standardized medications, dosing, or controls; after applying FDR, findings after 2 weeks became insignificant
Baffa et al.[54]	Dimensional: DSM-IV diagnosis of MDD plus HAM-D anxiety/somatization factor score ≥7; N=91.	Significantly detrimental effects were found for the less active *5-HTTLPR S* allele and the *5-HTTLPR/5-HTT* rs25531 haplotypes on treatment response in those with AD.	Recruited in a naturalistic setting and treated with a variety of antidepressants, with no standardized medications, dosing, or controls
Binder et al.[55]	Dimensional: DSM-IV diagnosis of MDD plus HAM-D anxiety/somatization factor score ≥7; N=734.	The T allele of the SNP rs10473984 within the *CRHBP* locus was associated with poorer outcomes in African Americans and Hispanics. This association was more pronounced in subjects with AD.	Lack of a formal replication study
Domschke et al.[56]	Dimensional: DSM-IV SCID diagnosis of MDD plus HAM-D anxiety/somatization factor score ≥7; N=81.	In those with AD, the BDNF rs7124442 TT genotype predicted worse treatment response to antidepressants over a six-week period.	Recruited in a naturalistic setting and treated with a variety of antidepressants, with no standardized medications, dosing, or controls; no subjects were drug naïve.
Ising et al.[57]	Syndromal: DSM-IV diagnosis of MDD or bipolar disorder plus comorbid anxiety disorder; N=283	Those with AD who had a low number of response alleles showed the least favorable antidepressant treatment outcomes.	Allowed for unipolar and bipolar depression; effect size for single SNPs to predict drug response was lower than expected.
Middeldorp et al.[6]	AD scores were obtained from the YSR or CBCL (parental report for children).	No SNPs in the serotonergic system or in core regulators of neurogenesis showed a consistent effect on anxious depression scores.	No formal psychiatric diagnoses were assessed. AD was based on a score without a cut-off delineating those with or without AD
Middeldorp et al.[3]	AD scores were obtained from the YSR in 5,782 twins.	AD scores increased after life events and predicted the experience of life events. However, no evidence was found for a gene-environment correlation.	No formal psychiatric diagnoses were assessed
Middeldorp et al.[5]	AD scores were obtained from the YSR in a sample of 1,155 twins and their families.	No evidence was found for an interaction between *5-HTTLPR* and the number of life events on AD scores.	No formal psychiatric diagnoses were assessed
Middeldorp et al.[4]	AD scores were obtained from the YSR in a sample of 4,309 twins and 1,008 siblings.	Associations between employment/burnout and AD scores were related to overlapping genetic and individual-specific environmental factors.	No formal psychiatric diagnoses were assessed

*DSM= Diagnostic and Statistical Manual of Mental Disorders; SCID= Structured Clinical Interview for DSM; MDD = major depressive disorder; BSI= Brief Symptom Inventory; AD= Anxious Depression; dACC= dorsal anterior cingulate cortex; fMRI= functional magnetic resonance imaging; HARS= Hamilton Anxiety Rating Scale; DMN= default mode network; GAD= generalized anxiety disorder; PD= panic disorder; ICD=

International Classification of Diseases; PTSD= post-traumatic stress disorder; OCD= obsessive compulsive disorder; SADS-L= Schedule for Affective Disorders and Schizophrenia Lifetime version; TSST= Trier Social Stress Test; ACTH= adrenocorticotropic hormone; GH: growth hormone; NPY SNP= Neuropeptide Y single nucleotide polymorphism; ACC= anterior cingulate cortex; TRH= Thyrotropin releasing hormone; TSH= thyroid stimulating hormone; T_3= triiodothyronine; T_4= thyroxine; HAM-D= Hamilton Rating Scale for Depression; FDR= false discovery rate; YSR=Young Adult Self-Report; CBCL=Child Behavior Check List; *5-HTTLPR*=serotonin transporter length polymorphism; SNP=single-nucleotide polymorphism; CRHBP=corticotropin releasing hormone binding protein; BDNF=brain derived neurotrophic factor