Neurobiology of Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) is a common illness with diagnostic criteria that have changed substantially over time. Symptoms of GAD overlap with those of major depressive disorder to such an extent that studying one disorder without studying the other may be impossible. Such an overlap, combined with potentially inappropriate diagnostic criteria for GAD, makes diagnosing and researching GAD challenging. Recent research into the genetics and neural circuitry of GAD may suggest solutions for the disorder's diagnostic controversies and point the way to productive future studies of etiology and pathophysiology. *(J Clin Psychiatry 2009;70[suppl 2]:15–19)*

Generalized anxiety disorder (GAD) is a common syndrome, with a lifetime prevalence of approximately 5% in the US population if criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) are used.[1] Diagnosis of the disorder is problematic, and the diagnostic criteria, currently being reviewed for the upcoming DSM-V, may change.[2] Furthermore, the overlap between GAD and other disorders, especially major depressive disorder (MDD), but also other anxiety disorders, complicates diagnosis and poses problems for GAD investigators. New research into the disorder's genetic features and the relationship between cognition and GAD, as well as studies of the neurobiology of GAD using neuroimaging, may inform the diagnosis of GAD and indicate potential topics for future study.

DIAGNOSTIC DIFFICULTIES

Criteria for Diagnosis

The core diagnostic features for GAD, as outlined in the DSM-IV,[3] include excessive anxiety and worry that is difficult to control and pertains to several events or activities. The anxiety must occur more often than not for a period of at least 6 months and be accompanied by 3 or more of the following symptoms: restlessness, easy fatigability, difficulty concentrating, irritability, muscle tension, and sleep disturbances.[3] Currently, controversy surrounds the usefulness of the GAD diagnostic criteria. Two areas of particular concern are duration of symptoms and the requirement that worry be reported as "excessive." Changes in diagnostic criteria could impact not only prevalence and clinical diagnosis but also the types of patients studied in research, including neurobiologic research.

In previous versions of the DSM—DSM-III,[4] for example—GAD diagnosis could be made if symptoms were present for at least 1 month as opposed to the current requirement of 6 or more months. Research[5] has demonstrated that subthreshold cases, that is, cases that meet all GAD diagnostic criteria except for duration of symptoms, have the following similarities with those that meet the threshold criteria: chronicity, functional impairment, comorbidity, age at onset, history of parental GAD, and sociodemographic correlates. Given these similarities, perhaps the duration requirement of 6 months should be revised downward.

The core feature of GAD is worry that is excessive or unreasonable; however, these terms are not defined and are subject to personal interpretation. One study[6] compared subjects who reported worrying a lot but who did not consider their worry excessive with subjects who reported excessive worrying. Results of the study indicated that greater severity, chronicity, and comorbidity of GAD were associated with self-reports of excessive worry, but the groups were comparable in family history, sociodemographic characteristics, functional impairment, and treatment seeking. The researchers concluded that the substantial similarity between patients who report excessive worry and those who do not supports removing the term *excessive* from the diagnostic criterion of worry. This change could potentially increase the lifetime prevalence of GAD by 40%.[6]

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FOR CLINICAL USE

- The current diagnostic criteria for generalized anxiety disorder (GAD) may be inadequate, and clinicians should be especially aware of comorbidity with major depression that may necessitate treatment.
- Cognitive deficits may be a treatment target for improving GAD symptoms.

Overlap of GAD and Depression

The overlap between GAD and MDD is tremendous and bidirectional, meaning that people with GAD often have depression and vice versa.[7] Moffitt and colleagues[7] analyzed a cohort of 1,037 individuals followed from birth to 32 years of age and found that more than 70% of patients with lifetime anxiety also had a history of depression, and almost half of those with lifetime depression also had a history of anxiety. What has not always been clear is the temporal relationship between the 2 disorders, although a prevailing notion has been that anxiety usually precedes depression. Moffitt et al.[7] showed that, among all patients with depression, most of those who developed anxiety did so before or concurrently with depression. Similarly, among all patients with anxiety, most who developed depression had anxiety first (Figure 1). A limitation of this study is the potentially inconsistent diagnosis of GAD in all cases because DSM criteria for GAD changed substantially during the 32 years the study was conducted.

Kessler and colleagues[8] surveyed 5,001 subjects in a follow-up to the National Comorbidity Survey studies and demonstrated that GAD and major depression are most likely to occur in the same year; the risk of one decreases as time since the other increases. This finding suggests that the disorders are linked in some way, probably biologically, but certainly phenomenologically.[9]

The extensive overlap between depression and anxiety means that studying the neurobiology of GAD to some extent means also studying the neurobiology of depression. Researchers could attempt to exclude people with depression, but that would be difficult and somewhat nonrepresentative of people with GAD because almost three quarters will have depression during their lifetimes. The diagnostic criteria controversies and the substantial overlap of GAD with depression make research on GAD challenging and inconsistent.

GENETICS OF GAD

Of all of the anxiety disorders, GAD has probably been the least well studied from a genetic perspective, possibly due to diagnostic issues making it difficult to find and agree upon study subjects. However, a few relevant studies of the heritability and genetics of GAD exist. When reviewing the literature on *heritability*—a measure of the extent to which a phenotype is influenced by the genotype[10]—it is important to keep in mind the meaning (and context) of the term.

Heritability Studies

A study[11] using diagnostic criteria from the revised edition of the DSM-III[12] examined 3,100 pairs of twins and found approximately 15% to 20% heritability for GAD, which is modest. No effects from gender-specific genes were detected.

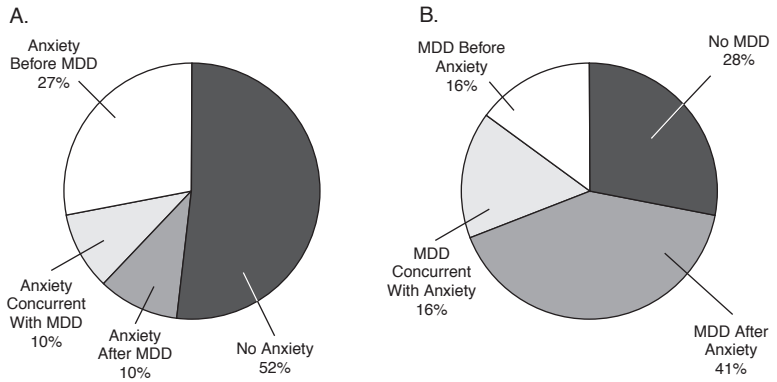
A study[13] of more than 8,000 twins from same-sex and opposite-sex pairs examined the relationship between GAD and the personality trait neuroticism, which predisposes people to depression and anxiety disorders. One way to understand the genetics of a psychiatric disorder for which diagnostic criteria are imperfect is to examine whether personality traits that underlie the disorder might themselves be heritable, giving researchers a better chance of identifying the genetic influences on the disorder. This study[13] confirmed a high genetic correlation between GAD and neuroticism; when gender differences were taken into consideration, GAD and neuroticism were highly correlated at 0.80—a perfect correlation would be 1.0—indicating that whatever genes influence neuroticism also very much influence GAD.

A more recent study[14] of more than 37,000 twins from same-sex pairs examined the genetic interrelation among GAD, MDD, and neuroticism. The genetic correlation between major depression and GAD was very high. A perfect correlation of 1.0 was found in women and a 0.74 correlation was found in men, suggesting that the same genes influence major depression and GAD. Neuroticism was related to both major depression and GAD in men and women, with a genetic correlation of about 0.25. Although neuroticism did not map onto GAD as strongly as it did in the previous study,[13] the conclusion is that, genetically, MDD and GAD are strongly related and have a common connection to the personality trait neuroticism. Finally, a study[15] of approximately 3,900 twin pairs found no shared environmental influences between GAD and neuroticism, but about one third of the genetic influences on GAD were shared with that personality trait.

Linkage and Association Studies

Twin studies help determine how and to what extent disorders may be inherited through similar kinds of

Figure 1. Sequential Order of Onset of MDD and GAD in Patients 11 to 32 Years of Age[a]



[a]Reprinted with permission from Moffitt et al.[7]
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder.

genetic pathways, but they do not indicate which genes might be involved. Linkage and association studies can do that, but this kind of research for GAD does not yet exist. However, several linkage studies of neuroticism exist. Probably the best strategy to gain possible insights into the genetics of GAD with the available research is to turn to studies of the genetics of neuroticism.

A genome-wide linkage analysis[16] of over 10,000 individuals—5,069 sibling pairs—from Australia and the Netherlands found that 3 chromosomal regions exceeded statistical thresholds for what is called suggestive linkage. A specific chromosomal region, 18q117 cM, showed up in both the Australian and the Dutch cohorts, suggesting that this region of chromosome 18 may play a role in neuroticism and hence, by inference, potentially GAD.

No association studies deal specifically with GAD, which may be due to unsettled issues concerning the diagnostic criteria. Researchers may have avoided studying GAD because problems with the phenotype make it difficult to determine the appropriate samples to study. However, studies of anxiety-related traits, also known as anxiety spectrum traits, provide information regarding genes associated with anxiety in general, some of which could be relevant to GAD.[9,17]

One study[18] examined *GAD* genes, but *GAD* here stands for glutamic acid decarboxylase. These genes are part of the synthesis pathway for γ-aminobutyric acid (GABA), a naturally occurring anxiolytic substance through which benzodiazepines have an effect, and are, therefore, relevant to understanding anxiety. Hettema and colleagues[18] studied 2 subtypes of *GAD* genes, *GAD1* and *GAD2*, and determined that variations in *GAD1* account for a small proportion of the individual differences in neuroticism and may increase susceptibility for MDD and anxiety disorders. These preliminary findings are exciting, but replication is needed.

COGNITION IN GAD

Cognitive deficits have not been considered central to the disorder, but people with GAD often report problems with memory and attention. A study[19] compared a sample of GAD patients (n = 19) who were 60 years of age or older with MDD patients (n = 68) and healthy controls (n = 40) from the same age group. Results showed that both GAD and MDD subjects differed from healthy controls when evaluated with multiple measures of cognitive functioning. Subjects with GAD were prone to deficits in short-term and delayed memory. Cognitive abnormalities were also seen in patients with major depression, with no significant difference detected between the 2 groups on any measure of cognitive functioning. More research is needed to understand the relationship between GAD and cognitive function in late-life populations.

One hypothesis about the etiology of GAD has been that children with impaired cognition might feel a lack of control and have problems coping with stressful situations because of a decreased problem-solving ability, which may put them at risk for GAD. Martin et al.[20] evaluated 689 adults who had been followed prospectively since birth and whose cognitive performance was tested at 7 years of age. Results showed that children with higher IQs at age 7 were protected against GAD (Figure 2). A 50% decrease in risk for lifetime GAD was associated with a 15-point advantage (1 standard deviation) in cognitive performance at age 7 years.

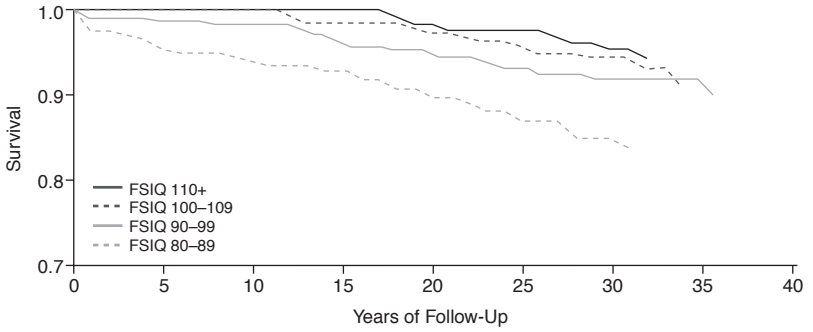
NEUROIMAGING STUDIES OF GAD

If certain cognitive abnormalities are associated with GAD, then examining the structure and/or function of specific regions of the brain may further our knowledge of the disorder. A neuroimaging technique called magnetic resonance spectroscopy (MRS) enables the assessment of relative concentrations of certain metabolites in the brains of living human beings and may be useful in this area of research.

Using proton MRS, Mathew et al.[21] evaluated 15 medication-free individuals with GAD and 15 age- and sex-matched healthy controls. The researchers examined concentrations of the metabolite *N*-acetylaspartate (NAA) in the right and left dorsolateral prefrontal cortex—areas involved in cognitive functions such as decision-making, a cognitive process that may be impaired in patients with GAD. The GAD subjects had higher ratios of NAA to creatine in the right dorsolateral prefrontal cortex

compared with controls. The association between asymmetry in the NAA/creatine ratio and GAD suggests a prefrontal cortex marker of neuronal viability, but one would expect a lower ratio when dealing with a problem with neuronal viability. The patients with GAD who had been abused as children had NAA/creatine ratios that did not significantly differ from the mean ratio of controls. Replication of these findings is needed.

Figure 2. Time to GAD Onset by FSIQ Group[a]



[a]Reprinted with permission from Martin et al.[20]
Abbreviations: FSIQ = full scale intelligence quotient, GAD = generalized anxiety disorder.

A neuroimaging study[22] employed an emotional faces task while examining activity in subjects' prefrontal cortexes using functional magnetic resonance imaging (fMRI). During the task, 18 adolescents with GAD and 15 control subjects with similar age and IQ and similar proportions of genders looked at pairs of pictures of faces displaying anger or neutral emotion. Compared with the healthy subjects, individuals with GAD had increased activation in the right ventrolateral prefrontal cortex when viewing angry faces. However, subjects with the highest activity were the ones with the least severe anxiety symptoms. A possible explanation is that the right ventrolateral prefrontal cortex may be working to somehow compensate for anxiety symptoms. People who are better able to engage this part of the brain may be protected against anxiety symptoms.

Another study[23] used fMRI to evaluate adolescents (15 patients and 20 controls) who were asked how afraid they felt while viewing fearful faces versus happy faces. Subjects with GAD had increased activation in the ventral prefrontal cortex and in the anterior cingulate cortex, a region of the brain involved in self-reflection. Researchers concluded that people with GAD might have an abnormality in the anterior cingulate cortex. Additionally, GAD subjects were found to have increased activity in the amygdala—a component of the brain's fear circuitry—when viewing fearful faces, suggesting that people with GAD have elevated activity in the brain's fear circuitry network compared with controls. These results, while exciting, were garnered from a small sample and require replication.

SUMMARY

Controversy surrounds the diagnostic criteria of GAD on points such as symptom duration and self-reports of excessive worry. Changes in diagnostic criteria over time are problematic in terms of ensuring that similar groups of individuals were studied. Uncertainties concerning the diagnostic independence of GAD and MDD further complicate the study of the neurobiology of GAD. The field needs to come to a consensus regarding the diagnostic conundrums in GAD. However, because multiple pathways to GAD and multiple GAD-like disorders with varying etiology may exist, a single diagnostic definition may not be sufficient for providing a consistent phenotype suitable for replicable neurobiologic studies.

Available research has suggested that GAD is modestly heritable and shares substantial genetic variation with major depression and the personality trait neuroticism. Genetic association studies are starting to identify promising leads in the search for genes that may increase susceptibility to anxiety disorders. Neuroimaging studies in GAD suggest increased activity in the brain's fear circuitry, as well as increased activity in the prefrontal cortex, which appears to have a compensatory role in reducing GAD symptoms. Preliminary findings from studies of cognitive ability in GAD suggest a relationship between cognitive deficits and the prefrontal cortex being unable to activate properly when needed to reduce symptoms, which may explain why cognitive capacity is associated with GAD risk. Cognitive impairment in GAD is a new topic in the literature and provides new avenues for further investigation. New treatment for GAD may include a cognitive rehabilitation approach.

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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