Etiology and Neurobiology of Social Anxiety Disorder

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Social anxiety disorder (SAD) is influenced by multiple genetic and environmental factors. Imaging genomics combines genotyping with neuroradiological techniques, such as functional MRI (fMRI) and positron emission tomography (PET), to investigate samples relevant to psychiatric pathophysiology. Neuroanatomical areas implicated in SAD include the amygdala, prefrontal cortex, hippocampus, and striatum. Recent investigations have suggested that allelic polymorphisms may play a role in the disorder; 2 candidate genes, the serotonin transporter (SLC6A4) and catechol-O-methyl transferase (COMT), are described. The biology of extinction learning is relevant to therapeutic approaches that aim to augment existing psychotherapies. In the future, novel uses of imaging genomics integrated with rational, biologically informed treatments will offer a more refined understanding of this complex and disabling disorder.

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ocial anxiety disorder (SAD) is characterized by fear and/or avoidance of most social situations. The phenotype is influenced by genetic and environmental risk factors, as well as by temperament and socialization. Thus, development and pathogenesis of SAD appear to depend on multiple factors.

Traits such as behavioral inhibition, neuroticism, and shyness can be inherited via complex genetic mechanisms. For example, in a twin study, the fear of being negatively evaluated was moderately heritable. Environmental risk interacts with these genetic factors. For instance, parental style marked by overprotection and rejection may influence genetic predisposition to increase risk of SAD.

There is a well-known link between inhibited temperament in infancy and the occurrence of SAD in adolescence. Schwartz et al. found that 61% of adolescents who had been inhibited as toddlers had current SAD, compared with 27% of subjects who had been uninhibited—a greater than 2-fold increase. Additionally, this study found that 44% of girls and 22% of boys who were inhibited at 2 years of age had social anxiety by age 13. A recent 21-year, longitudinal study of 1265 children in New Zealand found that those with anxious/withdrawn behavior at age 8 had significantly higher rates of social phobia at ages 16 to 21. Thus, SAD is increasingly conceptualized as a chronic neurodevelopmental illness that begins early in life and may be persistent into adolescence, young adulthood, and later.

NEUROIMAGING OF SOCIAL ANXIETY DISORDER

Background

Imaging genomics combines 2 powerful tools, while studying interindividual differences as well as diagnostic group differences. One objective is to identify subgroups or subtypes of patients who may have genetic characteristics in common. Another is to identify intermediate phenotypes (e.g., task-dependent brain activation) that may explain a greater degree of variance than genotype alone. The combination of genotyping with functional magnetic resonance imaging (fMRI), positron emission tomography (PET) scanning, and other techniques may identify neuroanatomical substrates for previously identified neurochemical abnormalities (e.g., alterations in serotonergic or dopaminergic regulation via pharmacologic challenge studies).

Neuroimaging tools may be divided into 3 broad categories: structural—location and lesions (MRI); functional—flow and metabolism (e.g., fMRI); and molecular—chemical (e.g., magnetic resonance spectroscopy [MRS] and PET—single photon emission computed tomography [SPECT]). The MRI produces detailed images of brain structures in the form of cross-sectional slices. While fMRI is focused on regional blood flow and reflects neuronal activation in discrete regions, proton MRS is an in vivo measurement of brain neurochemistry. More recently, PET and SPECT have been used to examine dopaminergic receptors.

Neural processing of fearful events appears to involve a complex interaction of the amygdala, hippocampus, and prefrontal cortical circuits. Defensive responses are integrated in regions such as the striatum, hypothalamus, and brain stem. In addition to the amygdala and prefrontal...
cortex, the putamen and thalamus may play a role in the circuitry of social phobia.\textsuperscript{11} Supporting data for neuroanatomical and neurochemical studies in humans come from preclinical investigations, such as rodent fear and auditory conditioning.\textsuperscript{7} The circuitry for extinction learning appears to be similar to that for acquisition of fear, and has served as a model for human anxiety disorders. Extinction is the progressive weakening of the conditioned response, e.g., freezing in the rat, by repeated presentations of a tone (conditioned stimulus) without the unconditioned stimulus (shock). Extinction is active learning, which inhibits rather than erases the original association.\textsuperscript{12} Extinguished fear-conditioned responses reappear with the passage of time (spontaneous recovery), a shift of context (renewal), and unsignalled presentations of the unconditioned stimulus (reinstatement).\textsuperscript{12}

Preclinical studies of these phenomena have important implications therapeutically. Tonic inhibitory projections from the infralimbic region of the prefrontal cortex to central, lateral, and basal nuclei in the amygdala result in extinction of fear memories. These inhibitory projections may lead to decreased fear response during auditory fear conditioning. The hippocampus plays an important role in this process by giving context to the pattern of extinction through modulating responses in the lateral amygdala or infralimbic region of the medial prefrontal cortex (Figure 1).

**Neuroimaging Findings in Social Anxiety Disorder**

Adults with SAD, as compared with controls, exhibit decreased activity in secondary visual, right parietal, retrosplenial, right temporal, and insular cortex in response to a stressful task such as simulated public speaking. In addition, there is increased amygdala activity in response to anxiety-provoking tasks.\textsuperscript{10,13}

Reduced regional cerebral blood flow has been noted in medial prefrontal cortex (Brodman areas 10/32 and 24/25) during anticipatory anxiety in normal subjects.\textsuperscript{14} Increased heart rate and anticipatory anxiety have been associated with elevated regional cerebral blood flow in the right dorsolateral prefrontal cortex, left inferior temporal cortex, and left amygdaloid-hippocampal region on PET scans in patients with social phobia; in these same patients, task repetition was associated with decreased regional cerebral blood flow in right dorsolateral prefrontal cortex.\textsuperscript{15} A recent study found exaggerated dorsal anterior cingulate cortex (ACC) activity in response to “disgust” (vs. “neutral”) faces in SAD.\textsuperscript{16}

In general, increased amygdalar activation toward neutral faces has been observed during fMRI.\textsuperscript{7} Stein et al.\textsuperscript{17} found greater reactivity in left allocortical (amygdala, uncus, and parahippocampal gyrus) areas in response to “harsh” (angry, contemptuous, fearful) faces as compared with “happy” faces, in patients with social phobia as compared with controls. The left amygdala was activated with novel tasks compared with that of task repetition (process-
tion of personality. They found that, when shown a fearful face, healthy controls, as expected, demonstrated amygdalar activation bilaterally. There was no correlation of response to this stimulus with extraversion. However, amygdalar activation for happy faces correlated positively with degree of extraversion. This finding suggests that personality is a factor when healthy controls are used as a comparison group, i.e., extraversion correlated strongly with the propensity of the amygdala to respond to a given stimulus.

Schwartz and Rauch studied a group of adults in their twenties who had been identified as inhibited or uninhibited at the age of 2. Subjects underwent fMRI and were exposed to either novel faces or familiar faces of people they knew. Both the right and left amygdala in the inhibited group showed increased blood-oxygen-level-dependent (BOLD) signal change in response to a novel stimulus, as compared with the uninhibited group. As expected, there was no difference in response to familiar faces. Though phenotypically most of these adults did not have SAD, they were characterized as inhibited at age 2, indicating a possible association between childhood social inhibition and subsequent amygdala response to novel stimuli in adulthood.

BOLD signal change on fMRI is believed to correlate better with synaptic inputs to a region than with spiking outputs. A recent case study suggests that impaired fear recognition arising from the amygdala may arise not from basic visuoperceptual inability to process information but rather from a failure of the amygdala to direct the visual system. While the sensory discrimination of emotional stimuli such as faces remain preserved, the discrimination of emotional valence is severely impaired in patients with bilateral amygdala lesions. Thus, amygdalar activation may not reflect hyperactivity in the amygdala itself, but rather overactivity in other parts of the brain which synapse with it. It is important to note that BOLD signal activation may reflect activity in either excitatory (e.g., glutamatergic) or inhibitory (GABAergic) neurons. The BOLD signal does not identify specific neurochemistry.

Serotonin Transporter Gene

Mood and anxiety can be modulated by serotonergic neurotransmission, and interest in the serotonin transporter gene in particular stems from the widespread use of selective serotonin reuptake inhibitors (SSRIs) for treatment of many psychiatric disorders. The serotonin transporter gene is comprised of short (S) and long (L) alleles in a variable repeat sequence of the (5-HTT) promoter polymorphism (5-HTTLPR) on human chromosome 17q11. The S allele confers reduced transcription, 50% lower transporter levels, and decreased serotonin uptake. The presence of one or 2 copies of the S variant of the serotonin transporter gene influences predisposition to anxiety, avoidant behaviors, and negative affect in many, but not all, studies of adults. Hariri et al. examined healthy volunteers who had no psychopathology or axis I disorders in themselves or first-degree relatives. Patients were exposed to angry or fearful faces. Right amygdalar BOLD response on fMRI was then measured, and patients were characterized as having the LL genotype or as being S carriers. (The groups homozygous and heterozygous for the S allele were combined in this study.) Amygdalar response to angry or fearful faces was increased in carriers of the S allele, suggesting a genetically driven variation in amygdalar response to fearful stimuli. There was no influence of gender.

In a study of 17 adults who had social phobia, the presence of an S allele was associated with enhanced amygdalar excitability (determined by PET blood flow) in response to a public speaking stressor task. Interestingly, the anxiety levels of the group with the L allele were significantly lower than that of the group with the S allele. Thus, the group with the S allele had exaggerated regional blood flow; was more anxious at baseline; and became more anxious in response to provocative stimuli.

Genomics have recently been combined with event-related potential (ERP) testing to examine a unique cohort of third and fourth grade children in Italy. ERPs are scalp potentials that occur immediately following a stimulus. There may be heritability of particular late (P-300 and N-400) waveforms. Children were selected from a group who had previously been evaluated with psychometric tests for degree of shyness and behavioral inhibition. Forty-nine of these children underwent ERP testing as well as genotype analyses. Children who rated highest in shyness or had 1 or 2 copies of the S allele had significantly altered N-400 values on ERP testing. Responses differed to specific facial probes, e.g., joyful, neutral, hostile, or angry. Shyness predicted smaller N-400 amplitudes in response to anger and to a neutral face. The SS genotype was associated with higher shyness levels. Type of expression and genotype did not influence N-400 amplitudes, but a significant interaction between genotype and type of expression was found.

**GENETIC BASIS OF SOCIAL ANXIETY DISORDER**

Recent investigations have suggested that allelic polymorphisms may play a significant role in the development of psychiatric morbidity. Candidate genes for susceptibility to mood and anxiety disorders include the serotonin transporter (5-HTT) gene (SLC6A4) and gene for catechol-O-methyl-transferase (COMT). Other candidates include the genes for the dopamine transporter (DAT) and dopamine receptors D1 (DRD2), D3 (DRD3), and D4 (DRD4); β-1-adrenergic receptor (ADRB1); monoamine oxidase A (MAOA); tryptophan hydroxylase (TPH1); and dopa decarboxylase (aromatic L-amino acid decarboxylase) (DDC). The serotonin transporter and COMT genes are discussed below.
Reports in adult healthy volunteers have also examined several brain regions concurrently and their relationship to genotype. Amygdala-prefrontal cortical coupling may depend on genetic variation of the serotonin transporter. Heinz et al. examined healthy male carriers of the S allele. They showed bilateral amygdalar activation on fMRI in response to aversive, but not pleasant, pictures. S carriers also showed greater coupling between the amygdala and ventromedial prefrontal cortex.

Not all studies, however, confirm the associations between the S allele and anxiety traits. A study of childhood shyness/behavioral inhibition found an association with the LL genotype. A longitudinal study from infancy to adolescence found that the L allele, rather than the S allele, was associated with higher anxiety at ages 13 through 16. One explanation of these discrepant findings is the variability in phenotypic measurements used across studies; a recent meta-analysis has found that associations with personality traits may depend on the specific choice of instrument.

**Catechol-O-methyltransferase (COMT)**

The COMT enzyme degrades the catecholamines dopamine, epinephrine, and norepinephrine. A functional polymorphism in the gene substitution of methylene (met) for valine (val) results in a COMT enzyme with decreased activity. The decreased activity met allele is approximately one third to one fourth the activity of the val allele. Thus, low activity of COMT results in reduced degradation of dopamine, and increased dopaminergic activity.

The high-activity val allele has been theorized to impair prefrontal cognition by increasing activity of COMT, thereby increasing prefrontal dopamine catabolism. A recent study of 1234 Caucasian nurses demonstrated that “feeling panicky in crowds” was weakly associated with the val allele, while COMT val heterozygosity was associated with increased risk of phobic anxiety. However, in a study of perseveration, the COMT gene accounted for only about 3 percent of the variance.

Another study of healthy adults, without psychopathology, examined the effect of genotype on the processing of emotional stimuli (aversive, neutral, or happy) in the amygdala and prefrontal cortex. The group homozygous for the met allele had a significant decrease in BOLD signal change in response to aversive stimuli, in ventral lateral prefrontal cortical regions. A similar pattern emerged in the amygdala as well as left hippocampus and right thalamus. Genotype accounted for up to 38% of individual response to aversive stimuli, one of the largest genetic contributions to brain activation patterns to date in this nascent field.

**FUTURE STUDY AND THERAPEUTIC IMPLICATIONS**

Future directions in imaging genomics of SAD include extending phenotypic variability of samples with the use of additional behavioral instruments. Studies might include patients with nongeneralized as compared with generalized social anxiety, for example, looking at different personality constructs. Analyses of extraversion and careful histories of behavioral inhibition may be useful. Longitudinal neuroimaging would be of interest in high-risk or remitted populations in order to identify trait markets of illness. Circuity analysis should continue to evaluate amygdala-prefrontal cortex coupling as well as circuitry involving striatal regions.

Performing multiple genotypic or neuroimaging investigations in the same individual holds promise in elucidating the link between neuroanatomy, neuronal function, and neurochemistry. For example, concurrent spectroscopy and fMRI in a social phobic group found that, as compared with healthy controls, patients with social phobia had increased glutamate as measured by the glutamate/creatinine ratio in rostral anterior cingulate cortex. The social phobic group also had increased BOLD response in the same region in response to a fearful faces paradigm. Multimodality neuroimaging studies such as that by Phan and colleagues may enable the researcher to delineate whether the BOLD signal indicates an inhibitory or excitatory neurochemical response.

Several compounds have been explored in preclinical studies for therapeutic use in phobic disorders. Enhanced extinction learning in psychotherapy is possible. Candidate compounds include N-cycloserine and yohimbine.

Norepinephrine is released in the amygdala after aversive stimuli and is crucial to acquisition and consolidation of emotional memory. Experiments with yohimbine, an α₂-receptor antagonist, and propranolol, a β-receptor antagonist, suggest that norepinephrine positively modulates the formation of fear extinction memories in mice. One clinical implication is that propranolol treatment may be counterproductive when used concurrently with behavioral therapy, although this notion is controversial and awaits empirical testing.

Preclinical studies have also shown that extinction learning is enhanced if the time between extinction trials is short. However, pharmacologic treatment with compounds such as yohimbine may overcome this factor to allow for significant extinction even when training is spaced. This possibility suggests that behavioral techniques such as exposure therapy might work better if given frequently over a short period, and that the addition of yohimbine might reduce the number of sessions needed.

As glutamate is the primary excitatory neurotransmitter in humans, its varied and numerous receptors offer potential therapeutic targets. Research on glutamatergic amygdala systems holds promise for treatment approaches in patients with anxiety. N-methyl-D-aspartate (NMDA) receptors, a subset of glutamate receptors that have been a focus of therapeutic intervention, contain a neuromodulatory site for glycine, another excitatory neurotransmitter. Like many forms of learning, fear acquisition and extinc-
tion depend on NMDA activity.12,38 Acute treatment with d-cycloserine, a partial agonist at the NMDA receptor, enhances extinction learning in rodent fear-potentiated startle models,38 and in conditioned freezing.39 Clinically, acrophobia within a virtual reality environment has been shown to improve with administration of d-cycloserine (DCS).40 The use of DCS to enhance the therapeutic efficacy of a group psychotherapy for SAD is now being investigated at several institutions.

Neuroimaging findings that social phobia is associated with dysfunction of the dopaminergic striatal system also suggest that selective MAO blockers such as selegiline, or dopamine reuptake inhibitors, such as aminoprine, may prove useful.3 More selective dopamine agonists are needed to test this notion in patients with SAD.

The ultimate goal of biological investigations of SAD is to provide an informed understanding of brain function in the quest for more potent and selective treatments. The integration of neuroimaging and genetics approaches, with particular attention to treatments that can facilitate extinction learning, are exciting new developments that offer unprecedented opportunities for research and future clinical applications.

Drug names: propranolol (Innopran, Inderal, and others), selegiline (Eldepryl and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, amineptine, propranolol, selegiline, and yohimbine are not approved by the U.S. Food and Drug Administration for the treatment of social phobia.

REFERENCES


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