Panic Disorder and GAD

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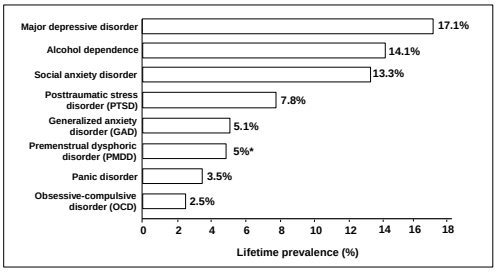
Panic Attack—Definition

•A discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes:

(a) palpitations, pounding heart, or accelerated heart rate
(b) sweating
(c) trembling or shaking
(d) sensations of shortness of breath or smothering
(e) feeling of choking
(f) chest pain or discomfort
(g) nausea or abdominal distress
(h) feeling dizzy, unsteady, lightheaded, or faint
(i) derealization (feelings of unreality) or depersonalization (being detached from oneself)
(j) fear of losing control or going crazy
(k) fear of dying
(l) paresthesias (numbness or tingling sensations)
(m) chills or hot flushes

DSM-IV-TR 2000.

Lifetime Prevalence of Common Psychiatric Disorders



*In menstruating women.

Kessler 1994; Kessler 1995; *DSM-IV-TR*™ 2000.

Panic Disorder—*DSM-IV-TR*™

•Key features of panic disorder with or without agoraphobia

– Recurrent and unexpected panic attacks
  and
– At least 1 of the attacks has been followed by 1 month (or more) of 1 (or more) of the following:
  (a) persistent concern about having additional attacks
  (b) worry about the implications of the attack or its consequences (eg, losing control, having a heart attack, going crazy)
  (c) a significant change in behavior related to the attacks
– Panic attacks are not due to effects of a substance or general medical condition
– Panic attacks are not better accounted for by another psychiatric disorder

General Characteristics

- Generally begin in childhood
- Interaction of heritable factors and adverse life events
- Main components:
  -acute fear: freezing, autonomic signs, glucocorticoid response
  -contextual fear: phobic avoidance
  -worry and apprehension

Agoraphobia—*DSM-IV-TR*™

– Anxiety about being in places or situations
  - From which escape might be difficult (or embarrassing) or
  - In which help may not be available in the event of having a panic attack or panic-like symptoms, for example
    - Being outside the home alone
    - Being in a crowd or standing in a line
    - Being on a bridge
    - Traveling in a bus, train, or automobile
– The situations are avoided (eg, travel is restricted) or else are endured with marked distress or with anxiety about having a panic attack or panic-like symptoms, or require the presence of a companion
– The anxiety or phobic avoidance is not better accounted for by another mental disorder

DSM-IV-TR 2000.

Limitations of DSM

- The categorical nosology implies that if you have less than the full criteria for "disorder" you have nothing.
- Diagnostic criteria for some of the anxiety disorders lack a solid empirical base
- Subthreshold disorders might be as clinically significant as those meeting full DSM criteria

Separation Sensitivity

(loss sensitivity)

- Did you stay in a relationship even when it was not in your best interest, rather than risk being alone?
- What about pets? Are you the type of person who gets very attached to your pets and gets very upset if the pet dies or is lost?

The Panic-Agoraphobia Spectrum: 8 Key Components

- Separation sensitivity
- Panic-like symptoms
- Stress sensitivity
- Medication and substance sensitivity
- Anxious expectation
- Agoraphobia
- Illness phobia and hypochondriasis
- Reassurance orientation

Panic-Like Symptoms

(atypical symptoms)

Have you ever felt…..

- …..disoriented, as if you have lost your bearings?
- …..that you were about to lose control of your behavior?
- …..nervous, uncomfortable, or as though you were about to suffocate, because of hot, stale or humid air, or because of perfume, or other smells, even if they weren't that strong?

Separation Sensitivity

(separation anxiety)

In the past month, did you experience a lot of distress….

- ……because of thoughts that you might lose someone close to you or some harm might come to them (for example, did you worry a lot if your family members or close friends argued, or they did risky things or had an illness)?
- Did you have trouble going to sleep without someone nearby or trouble sleeping away from home?

Substance and Medication Sensitivity

Did you ever experience panic-like symptoms when you used…..

- …..coffee, tea, or other caffeinated beverages?
- …..cold medicine, nasal sprays, thyroid, sleep, or antidepressant medications?

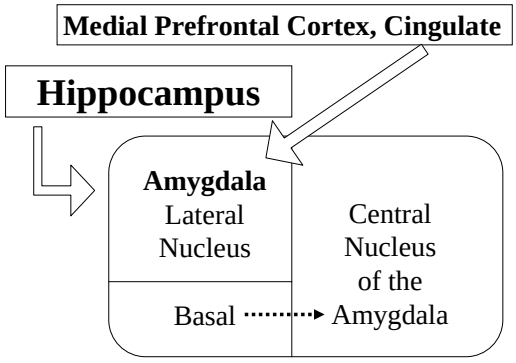
Have you ever been afraid of or did you ever avoid….

- …..taking prescribed medications because you thought they might harm you or that you were overly sensitive to side effects or "allergic"?
- Do you read the package insert more carefully than most other people because of feeling nervous or uncomfortable about taking medication?

Agoraphobia (atypical)

In the past month, did you avoid, feel nervous or uncomfortable….

- …..wearing high-necked shirts, ties, or tight fitting clothes because they made you feel trapped?
- …..being physically intimate because you felt trapped?
- …..going to places where you were not sure there was a bathroom available?

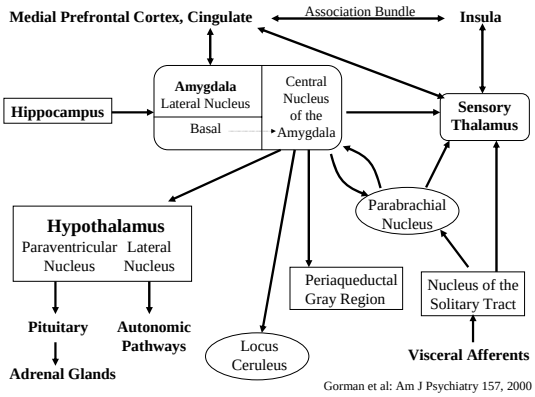


Gorman et al: Am J Psychiatry 157, 2000

Panic Disorder—Epidemiology

- Age at onset: typically 15-34 years
- Women are at least twice as likely to be affected
- Prevalence of panic disorder among patients in cardiology clinics: as high as 60%
- 10% to 30% prevalence among patients in vestibular, respiratory, or neurology clinics
- Very rare in elderly

DSM-IV-TR™ 2000; Sadock and Sadock 2003.



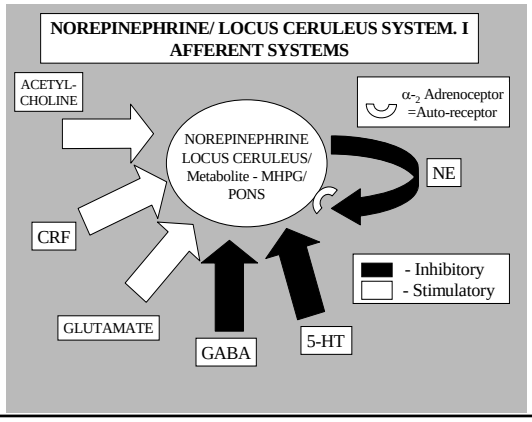
Gorman et al: Am J Psychiatry 157, 2000

Fear Circuitry: a Context for Pathophysiology of Anxiety

- Research on fear in animals has identified specific circuits involved in fear conditioning
  - Amygdala: acquisition, storage, expression, and extinction of fear memory
  - Hippocampus: contextual control of fear
  - Medial PFC: regulation of fear by changes in environmental circumstances
- Stress-induced alterations in fear circuits may contribute to the development and/or maintenance of pathologic fear

Limitations of Conditioned Fear as Model of Panic Disorder

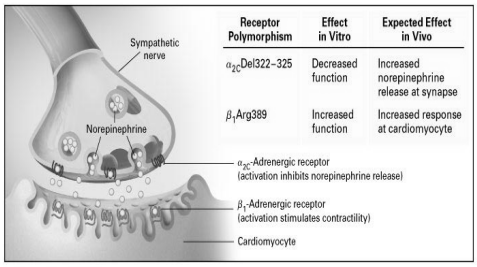
- It is unclear what is being "conditioned" in panic disorder, as attacks typically occur "out of the blue."
- Fear might not be equivalent to panic and/or anxiety
- Not clear that the panic disorder is associated with elevations in cortisol and HPA axis overactivity
- Anti-panic treatments do not blunt ability to mount appropriate fear responses



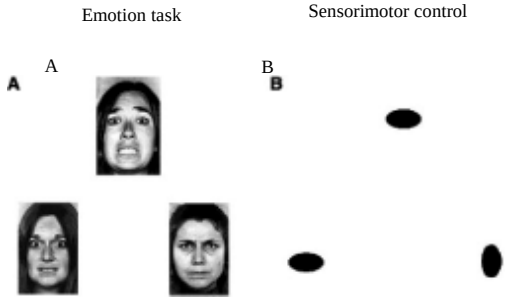
5-HT Transporter Genetic Variation and Amygdalar Activity

- Regulation of 5-HT synapses depends in part of 5-HT reuptake, which is mediated by the serotonin transporter (5-HTT).
- Anxiety traits have been linked to alterations in 5-HTT genes
- the short allele of the 5-HTT promoter polymorphism is associated with reduced 5-HTT expression and function and increased fear and anxiety-related behaviors
- fMRI has been used as an "endophenotypic assay" to evaluate whether brain activity response of amygdala to fearful faces was associated with variation in the 5-HTT S/L polymorphism

Adrenergic receptor polymorphisms

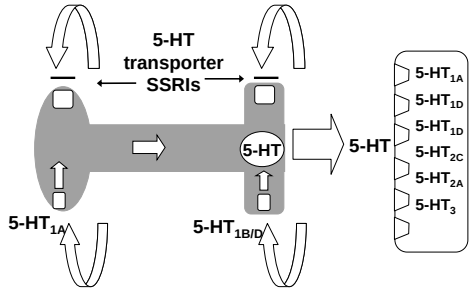


Small et al, 2002, NEJM

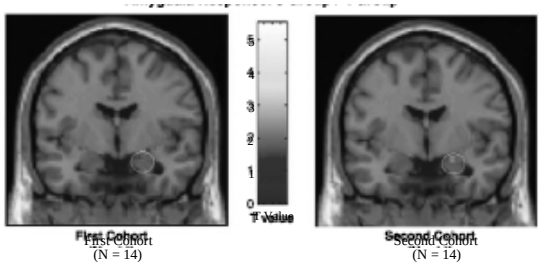


(Hariri *et al.*, 2002, *Science)*

Serotonin Receptors

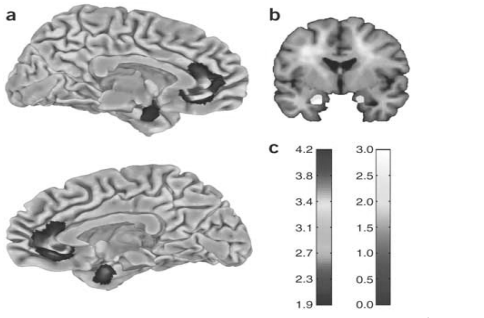


BOLD fMRI
Amygdala Response: s Group > I Group



(Hariri *et al.*, 2002, *Science)*

Gray matter volume reductions of s allele carriers compared to l/l genotype (n=114)



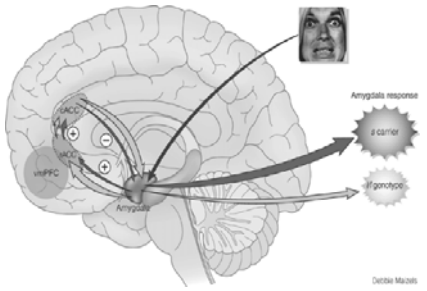
Pezawas et al 2005

5-HT1A PET Study in Panic Disorder

- 16 panic disorder patients
- 7 of these had current major depression
- 15 matched healthy controls
- Used selective 5-HT1A R radioligand FC-WAY

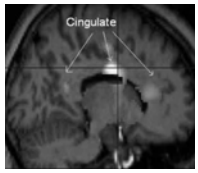
Neumeister et al, J Neuroscience, 2004

Differences in processing of emotional stimuli between s allele carriers vs l allele carriers

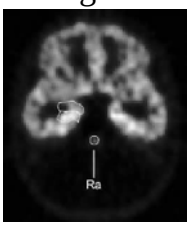


Hamann, 2005

PD has marked reductions in 5-HT1A R binding



Statistically-analyzed PET scan data superimposed on structural MRI scan (front of brain is at right) shows areas in the anterior and posterior cingulate where panic disorder patients had nearly one third fewer serotonin 5-HT1A receptors compared to healthy control subjects. The lighter the color, the greater the difference between patients and controls.

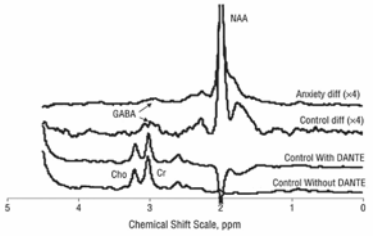


PET scan shows distribution of serotonin 5-HT1A receptors (front of brain is at top), which were reduced by about a third in the raphe (Ra) in panic disorder patients.

Implications of this work

- There is genetically driven variation in the response of brain regions underlying emotional behavior
- The increased anxiety and fear associated with the s allele may reflect the hyperresponsiveness of their amygdala to relevant environmental stimuli
- Similar work in panic disorder remains to be performed

GABA Reductions in Panic Disorder



Representative -aminobutyric acid (GABA) spectra from a control subject and a patient with panic disorder (not paired). Top 2 traces, Subtraction spectra (control and patient) highlighting the GABA peaks. Bottom 2 traces, Control spectra with and without application of the DANTE (Delays-Alternating with Nutations-for Tailored Excitation) pulse. Cho indicates choline; Cr, creatine; NAA, N-acetylaspartate; and diff, difference.

Goddard et al. 2001, Arch Gen Psych

But GABA is also lowered in Major Depression

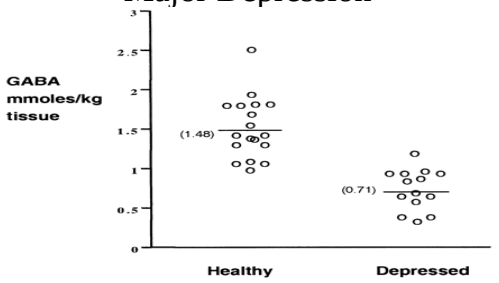


Figure 2. Occipital cortex GABA concentration in the brains of depressed and healthy control subjects as measured by ^{1}H-MRS.
Sanacora et al. 1999

Challenge for Research in Panic Disorder

FIND WHAT IS SPECIFIC TO PANIC DISORDER VS. DEPRESSION OR GAD!

Functional Interactions between 5-HT system and GABA system

- May be relationship between decreased 5-HT_{1A} and decreased benzodiazepine receptor function
- In one study of 5-HT_{1A} knockout mice, a downregulation of BNZ GABA $alpha_1$ and $alpha_2$ receptor subunits was reported
- Pathological pathway originating from 5-HT_{1A} receptor deficit leading towards dysfunctions within GABAergic systems, resulting in increased levels of anxiety.

Can We Use These Recent Biological Findings to Guide Treatment in Panic Disorder?

Chronic SSRIs increase cortical GABA

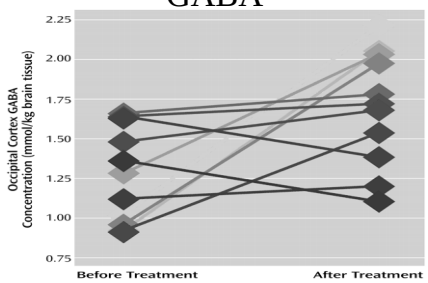


Figure 1. Change in Occipital Cortex GABA Concentrations After SSRI Treatment of Major Depression in 11 Patients[a]
[a]Each patient was treated for at least 5 weeks. Eight patients received fluoxetine, and three received citalopram.
Sanacora et al. 2002, Am J Psych

Treatment options for Panic Disorder

- Psychotherapy alone
- SSRI alone
- SSRI plus psychotherapy
- SSRI plus Benzo
- SSRI plus Benzo plus psychotherapy
- Other

Cognitive Behavioral Therapy (CBT)

- Robust and effective treatment for panic, with good durability of effect
- Exposure treatment overcomes avoidant behavior, allowing deconditioning; however may not eliminate spontaneous panic attacks
- Teaches patients skills such as abdominal breathing and relaxation responses
- One popular method emphasizes that physical sensations are not harmful (e.g. chest pain does not mean heart attack)

Rapid Stabilization with combination treatment

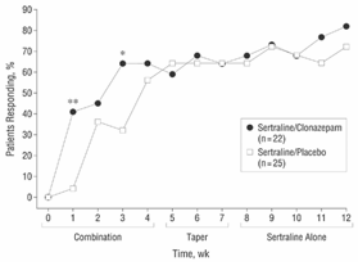


Figure 2. Percentage of treatment responders (intent-to-treat population). Double asterisk indicates a statistical difference between groups, $P = .003$ (Fisher exact test). Single asterisk indicates a statistical difference between groups, $P = .05$ (Fisher exact test).

Goddard et al. 2001, Arch Gen Psych

Drugs Used in the Treatment of Panic Disorder

- SSRIs (Prozac, Zoloft, Paxil)
- Benzodiazepines (Xanax, Klonopin, Ativan)
- Tricyclic antidepressants, MAOIs
- Newer antidepressants (Venlafaxine, Mirtazapine)
- Anticonvulsants (Gabapentin, Depakote, Lamictal)

Why Combination Treatments Might Work Best

Brain Region	Effects of Stimulation	Human Analogue	Treatment
Amygdala	Freezing Cortisol Autonomic	Panic Attack	Medication
Hippocampus	Contextual Memory	Phobias	Exposure Techniques
Prefrontal Cortex	Suppress Amygdala Extinction	Reason Anticipatory Anxiety	Cognitive Therapy

Who is the Ideal Candidate for SSRI/Benzo co-administration?

- Clinical severity requires rapid anxiolysis
- Past or current mood disorder in self or first degree relative
- No substance dependence history
- Past jitteriness with SSRI

Generalized Anxiety Disorder

DSM-IV-TR Diagnostic Criteria for Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

B. The person finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). **Note:** Only one item is required in children.

(1) restlessness or feeling keyed up or on edge
(2) being easily fatigued
(3) difficulty concentrating or mind going blank
(4) irritability
(5) muscle tension
(6) sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)

D. The focus of the anxiety and worry is not confined to features of another Axis I disorder.

E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism)

Comorbidity in GAD

- 90% of those with lifetime GAD reported at least one other lifetime DSM disorder
- Most common comorbid conditions, besides depression, are panic disorder, social and specific phobia, and PTSD
- Comorbidity is a powerful predictor of help-seeking among people with GAD, leading to an especially high rate in clinical samples
- Although frequently comorbid, "pure" GAD can result in significant impairments, akin to other disorders

Key Diagnostic Question

"Do you worry excessively about minor matters?"

has been suggested to be a necessary, if not sufficient, feature for diagnosis of GAD

Genetic aspects of GAD

- Family studies: 19.5% of first degree relatives of GAD probands developed disorder, versus 3.5% of controls (Noyes et al. 1987)
- Twin studies: relatively low concordance rates for monozygotic (21%) and dizygotic (13%) twins
- Most studies suggest that MDD and GAD share similar genotype, but the expression of these disorders depend on environmental influences unique to each patient

Course of GAD

- Chronic condition, with episodes commonly persisting for a decade or longer
- HARP study: prospective, naturalistic study
  - only 15% with baseline GAD had a full remission for 2 months or longer in the first year after baseline
  -25% had remission 2 years after baseline
  -38% had full remission after 5 years

Cognitive Theories of GAD

- Avoidance function of worry in GAD: worry allows individuals to process emotional topics at an abstract, conceptual level and consequently, avoid aversive images, autonomic arousal, and intense negative emotions
- "worrying about most of the things I worry about is a way to distract myself from worrying about even more emotional things that I do not want to think about" (this statement discriminates GAD worriers from control worriers)

Cognitive distortions in GAD

- Selective attentional biases when presented with threat-related information
- Explicit memory bias for threat words
- Perception of uncontrollability and negative appraisal of worrying

Other systems mediating anxiety

- Tachykinins: substance P, neurokinin-A, B
- Corticotropin-releasing factor, HPA Axis
- Neuropeptide-Y: endogenous anxiolytic?
- Opiate system: powerful suppressors of NE system
- Glutamate: NMDA antagonists prevent fear conditioning and might have direct anxiolytic activity
- Neuroactive steroids

Psychotherapies for GAD

- Psychotherapy
  - Cognitive Behavioral Therapy (CBT)
  - Interpersonal Therapy (IPT)
  - Psychodynamic Psychotherapy/Psychoanalysis
  - Group therapy
  - Family/Couples therapy

Future Directions in Anxiety Therapeutics

- Subtype-selective benzodiazepines
- Voltage-gated Ca Channel inhibitors (e.g. pregabalin)
- Glutamate antagonists (e.g. riluzole, memantine)
- Substance P (NK-1 receptor) antagonists
- CRF antagonists
- Agents that augment extinction in psychotherapy (e.g. D-cycloserine)

Medications for GAD

- Benzodiazepines
- Buspirone (Buspar)
- Venlafaxine XR (Effexor XR)
- SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram)
- Other antidepressants (nefazodone, mirtazapine, tricyclics, MAOs)

Specific Tips for Worry

- Ask yourself if worrying is productive or unproductive
- Are you willing to accept uncertainty? Think of all the things you do that involve uncertainty
- Write out your worries for 30 min/day
- Put time on your side. Go back in time and look at things you used to worry about and see if they bother you know. Worriers tend to live in a future that never occurs. Enjoy the moment.