Understanding Anxiety Disorders

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## Disclosures of Potential Conflicts

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Anxiety is Ubiquitous

- Apprehension
- Uneasiness
- Nervousness
- Worry
- Disquiet
- Concern
- Misgiving
- Having Qualms
- Pent-up
- Troubled
- Wary
- Unnerved
- Unsettled
- Jitteriness
- Sensitivity
- Defensiveness
- Fright
- Dread
- Panic
- Alarm
Why do we have anxiety?

- “Fear and anxiety are crucial and adaptive components of the overall behavioral and autonomic “stress” response to dangerous situations which threaten to perturb homeostasis” Millan, 2003

- There are evolutionary benefits to having anxious people in a society
This evolutionary societal benefit of anxiety

- May explain why anxiety disorders are so prevalent - genetic factors are at times selected for

- May explain why etiology and therapy for anxiety disorders involve social relationships
Anxiety becomes a Disorder When:

- Anxiety is out of proportion to the actual threat or current context
- Anxiety persists over time
- Anxiety causes interference (avoidance) or impairment of functioning
Economics of Anxiety Disorders

- Misdiagnosis and under-treatment of anxiety disorders cost the U.S. more than $42 billion a year

- More than $22.84 billion is associated with the repeated use of healthcare services, as those with anxiety disorders seek relief for symptoms that mimic physical illnesses.

- People with an anxiety disorder are three-to-five times more likely to go to the doctor and six times more likely to be hospitalized for psychiatric disorders than non-sufferers.
DSM-IV Anxiety Disorders

- Generalized Anxiety Disorder (GAD)
- Social Anxiety Disorder (Social Phobia)
- Specific Phobias
- Acute Stress Disorder
- Post Traumatic Stress Disorder
- Panic Disorder (with and without agoraphobia)
- Agoraphobia without history of Panic Disorder
- Separation Anxiety
- Obsessive Compulsive Disorder (OCD)
- Anxiety Due to a General Medical Condition
- Substance Induced Anxiety Disorder
- Anxiety Disorder, NOS
DSM-V Proposed Anxiety Disorders

- Major changes
  - Agoraphobia as separate disorder
  - Panic Disorder as Separate Disorder
- Consider OCD as different class
Outline

- Overview of Anxiety Disorders
- Epidemiology
- Genetic basis
- Pathophysiology
- Neural Circuits
Epidemiology

- Anxiety disorders are the most common psychiatric illnesses affecting both children and adults.
- Lifetime diagnosis of an anxiety disorder occurs in as many as 24.9% of population - an estimated 19 million adult Americans.
- Among the most commonly occurring of seriously impairing chronic conditions.
Midlife Development in the U.S. (Kessler, et al, 2001)

- Surveyed physical and mental disorders and the effects on day-to-day functioning
- Highest reported prevalences in past year in adults:
  - Back problems - 20.3%
  - Arthritis - 19.4%
  - Hypertension - 18.2%
  - Anxiety Disorders - 16.4%
  - Seasonal Allergies - 15.7%
  - Depression - 14.1%
Anxiety Disorders are Getting More Common

- The Effects (Odds Ratios) of Cohort in Predicting Lifetime Anxiety Disorders
- WHO International Consortium of Psychiatric Epidemiology, 2000
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Anxiety Disorders Typically Begin in Childhood
(Median age of onset is 15 years)
Early onset anxiety disorders are associated with:

- 40% increased odds of high school and college failure
- 30% increased odds of teenage childbearing
- 60% increased odds of marital instability
- 150% increased odds of current unemployment
- This constellation of life consequences make up a core part of welfare dependency

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Heritability Estimates

- Based primarily on twin studies
- A - Heritability; C - Shared Environment and E - Non-shared environment
- Examine the correlation of anxiety between MZ twins versus DZ twins
- \( r_{MZ} = A + C; \ r_{DZ} = \frac{1}{2} A + C \)
- \( A = 2 \ (r_{MZ} - r_{DZ}) \)
- \( C = r_{MZ} - A \)
- \( E = 1 - r_{MZ} \)
Heritability Rates (Adults)

- Panic disorder - 44%
- Specific Phobias - 35%
- GAD - 32% (females)
- OCD - very low for actual disorder
- “Obsessional traits” - 44%
  – Eley and Gregory, 2004
Heritability (Child Anxiety)

- More discrepant studies
- Gender and age effects
- Currently, evidence suggests that shared environment (most likely modeling parental behavior) explains a significant amount of variance in childhood anxiety
Shared genetics may help differentiate disorders

- Generalized anxiety shares genetic variance with depression
  - Environmental stressors differentiate
    - Trauma or neglect lead to anxiety
    - Loss leads to depression

- Panic disorder, phobias, social anxiety, and PTSD have shared genetic variance
  - “Stress induced and Fear Circuitry Disorders”
Linkage and Association Studies in Humans

- Essentially negative thus far, even with most heritable disorder, Panic Disorder
- No association of panic disorder with mutations in adrenergic receptor loci on chromosomes 4, 5, or 10
- No linkage of panic disorder with GABAa receptor genes
- Recent reports from a genomic survey of panic disorder using 600 markers have not yielded evidence of linkage
Need to study endophenotypes

- Aspects of cognitive or brain functioning that may be better markers of underlying genetic risks
- Ideally, should be developmental precursors of the disorders, be heritable, and share genetic influences with the disorder
Behavioral inhibition

• In response to unfamiliar objects and people:
• Behavioral - cessation of play, latency to interact
• Physiologic - accelerated heart rate, increased cortisol, pupillary dilatation
• If this persists in late childhood, likely that anxiety disorders will develop in adolescence
Anxiety Sensitivity

- Highly sensitive interoception
- Beliefs that anxiety sensations are indicative of harmful physiological, social or psychological consequences
- A “fear of fear”
- Predicts anxiety disorders, but not depression
  – McNally, 2002; Reiss, 1986
Heritability of “Anxiety Sensitivity”

- Estimated at 50% in adults and adolescents; slightly lower in children
  - Stein, et al., 1999
  - Eley et al., 2008

- In child sample, this genetic risk overlapped with that for panic symptoms
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Sensitive periods of development

- Overview of how genetic risks interacting with early life stress may impact the formation of neural circuits during a developmentally sensitive period and thus influence the risk of future development of anxiety.
Sensitive period

- Whenever experience has a particularly strong and lasting effect over a limited time. Effects of experience are not readily amenable to change after the sensitive period
  - Ito, 2004; Knudsen, 2004
- Classic example is filial imprinting
  - Lorenz, 1937
- Periods are actual properties of neural circuits
  - Hensch, 1998; Horn, 2004; Knudsen, 2004
Early life is a sensitive period for development of anxiety

- Rat pups who get high licking and grooming from mothers in 1st 3 weeks of life have decreased anxiety compared to pups with low levels
  - Meaney, 2001; Champagne, et al., 2003
- Rat pups with lengthy separations from mother during 1st 3 weeks develop increased anxiety
  - Boccia and Pedersen, 2001
- In primates, developmental period may be third trimester pregnancy through peri-adolescence
  - Andersen, 2003
Neuroendocrine components

- Parity of mother is inversely correlated with cortisol level in newborn monkeys.
- Presumably mothers’ past experience with pregnancy and child rearing may contribute to individual differences in infant cortisol levels.
- Evidence that long-lasting dysregulation of the CRH system may in part underlie harmful consequences of early developmental stressors.
Stress on Mothers

- Monkey paradigm:
- CSF levels of CRH are basally and chronically elevated in adult bonnet macaques whose mothers were exposed for 3 months to unpredictable variable foraging demands, versus mothers with predictable high or low foraging situation (Coplan, 1996; 2000)
Stress on Mothers

- Humans:

- Children of Mothers who reported high levels of stress 3 weeks after their child was born were more likely to develop asthma than children of lower stress mothers (controlling for genetic risk factors) (Mrazek, 1996)
Role of serotonin

- Innervates regions that play a role in anxiety
  - Amygdala, hippocampus, anterior and posterior cingulate, prefrontal cortex
- Can modulate a number of developmental events
  - Cell division, neuronal migration, cell differentiation, synaptogenesis
    - Azmitia, 2001; Gaspar et al, 2003)
Serotonin is a complex system

- 30 viable serotonin receptors located throughout body and brain
- Expression is temporally and spatially dynamic
- Depending on receptor type, location and developmental timing, stimulation of the receptor can be excitatory or inhibitory
- Serotonin further regulated at synthesis, reuptake and degradation. Disruption at any of these relates to anxiety
  - Gaspar, et al., 2003
Increased or decreased serotonin in early development leads to increased anxiety and aggression in mice

- 3 weeks RX with fluoxetine after birth
  - Ansorge, et al., 2004
- Gene knockout combined with 5-HT1A receptor replacement - only decreases anxiety if done in 1st 3 weeks of life
Early life - Neural Circuit Development

- Rat Hippocampus in 1st 3 weeks
  - Rise and fall of dendritic growth and spine formation
  - Dramatic increase in spontaneous synchronous firing of neurons
In humans

- Functional polymorphism in HTR1A promoter is associated with
  - increased anxiety traits (Strobel 2003)
  - Increased incidence of Panic with agoraphobia (Rothe, et al., 2004)

- Polymorphism in SERT (s/s) is associated with 5-fold increase in the sensitivity of the amygdala to fearful or threatening stimuli
  - Hariri & Weinberger, 2003
In humans

- Individuals with at least one copy of the short allele in SERT had increased amygdala activation and increased coupling of amygdala and prefrontal activity
  - Heinz 2005

- This change in fear responsiveness may underlie increased risk for anxiety disorders
  - McNaughton and Corr, 2004
In humans

- Normal functioning (l/l) allele of SERT polymorphism appears to be protective against many of the consequences of early life stress in humans
  - Caspi, 2003; Jorm, 2000

- And primates
  - Barr, 2003, 2004; Suomi, 2003
Pathophysiology of anxiety disorders

- Current working model is that there is a combined gene (alterations in serotonin system) and environment (early maternal deprivation) interaction to yield an amygdala that is over-responsive to threats in the environment, and long lasting dysregulation of the CRH/HPA system.
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Neuroanatomic circuits

- Fear and anxiety are normally adaptive responses to threat or stress.
- Emotion-behavioral sets arise in response to exteroceptive visual, auditory, olfactory, or somatosensory stimuli or to interoceptive input through viscera, endocrine or autonomic nervous system.
- Anxiety is also produced by cognitive processes that mediate anticipation, interpretation, or recollection of perceived stressors and threats.
Emotion processing is key

- Need appropriate emotion processing to have anxiety be adaptive, and not become persistent, excessive, inappropriate to reinforcement contingencies, or otherwise maladaptive
- Evaluation (appraisal, relationship with previous conditioning and reinforcements, and context)
- Emotional expression (behavioral, endocrine, and autonomic responses)
- Emotional experience (subjective feeling)
Amygdala is Key in “Fear Learning”: the Association of conditioned stimulus or operant behavior with emotionally salient unconditioned stimulus
Basolateral Amygdala

- Thalamus
- Hippocampus
- Direct Sensory Input
- Cortex
- Orbital Frontal cortex
- Hippocampus
- Dorsal and Ventral Striatum
- Central N. Amygdala And/or Lateral BNST

Choice Behavior Memory of emotional events
Memory consolidation Of emotional events
Instrumental Approach Or Avoidance Behavior
Autonomic; somatic signs of fear. Attention to stimuli
Process of Extinction

- Inability to suppress unwanted fear memories or worry is a problem in anxiety disorders.
- What processes are involved with extinction - i.e., reduction in conditioned fear when CS is presented many times?
- Fear is not erased, but new learning competes with it.
- Fear can be recovered spontaneously, after another stressor, or in a new context.
- Extinction is mediated by GABA release.
Neuro-transmitters

- CRH, Serotonin (5-hydroxytryptamine) and GABA have been implicated in mediating stress-related behavioral effects

- Norepinephrine - modulation of anxiety states

- CNS peptides - e.g., cholecystokinin (CCK), Neuropeptide Y, and Substance P
Treatment

- Education
- Breath re-training
- Cognitive Behavior Therapy
- Exposure and Response Prevention (Extinction)
- Relaxation Therapies
- Marital or family therapy when indicated
- Pharmacology
Pharmacologic: Types of Medications

- Anticonvulsants
- Azapirones
- Benzodiazepines (usually very short term only)
- Beta-blockers
- Monoamine Oxidase Inhibitors (MAOIs)
- Serotonin reuptake inhibitors (SSRI’s)
- Tricyclic antidepressants (TCA’s)
- Other Antidepressants
However, drug treatment is only half the story

- Meta-analysis of DBPC trials and open trials of SSRIs from 1991 - 2002
- 40 - 60% of patients with OCD do not respond to SSRI’s
- Best treatments require combined behavioral and pharmacologic approaches

(Kaplan and Hollander, 2003)
PTSD prevention

- Traumatic events are hypothesized to be followed by a critical period of increased brain plasticity, during which long-lasting neuronal changes may occur in those who develop traumatic stress disorders (Shalev 2000).
- Physiologic arousal during the traumatic event and in the post-immediate phase may trigger the neurobiological processes that lead to PTSD.
- Propranolol has been shown to reduce memory for emotional events through a central adrenergic blockade (Cahill et al 1994)
- Two groups have shown that propranolol given for 7 days following acute trauma reduces PTSD (Putnam, 2002; Vaiva, 2003)