한림대학교

불안장애를 생물학적으로 어떻게 이해할 것인가?

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발표순서

- Introduction: The fear circuit theory and the amygdala
- Imaging studies of anxiety disorders
- Neuroendocrine pathways: the HPA axis and anxiety
- Neurotransmitters and anxiety

Introduction: the nature of fear and anxiety

1. The fear circuit theory and the amygdala
2. Imaging studies: mapping the fear circuit
   - The limbic system: basic neuroanatomy
   - Imaging and the amygdala
   - The limbic forebrain: prefrontal cortex
   - Limbic forebrain: cingulate gyrus
   - BNST (bed nucleus of stria terminalis)
   - Imaging trends for each disorder

Anxiety disorders

- Quite common, with lifetime prevalence estimated as high as 25%
- Often comorbid with each other and with other psychiatric disorders, especially depression.
- Anxiety disorders may come from a similar genetic locus, seems to a common pathological mechanism.

Fear, anxiety and pathological anxiety

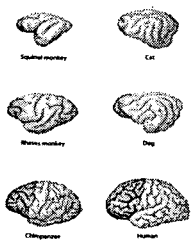
- Anxiety can be distinguished by the presence of subjective uncertainty with respect to the distress inducing stimulus or situation.
- Pathological anxiety is greater than what would be expected for a given situation, thereby causing stress and impairing function.

The nature of fear and anxiety

- Nature's first-line of defense
- An evolutionary key to survival.

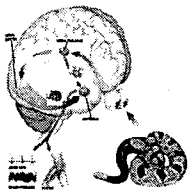
Anxiety: Systems underlying survival mechanism

- 'flight or fight' mechanism: the non-cortical, more primitive animal regions of the brain.
- In Humans, complexity and flexibility from the more evolved cortical regions, which receive and process data from life experience.



Fear circuit

- Cortical and subcortical regions of the brain during anxiety.
- HPA axis and its two main pathways, the CRF-ACTH-cortisol axis
- LC-NE axis
- Other neurochemical systems regulating this axis, involving GABA, serotonin, and other neuropeptides



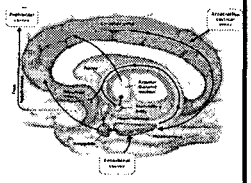
Neural Pathways to Emotion

- **Ventral system** (amygdala, insula, ventral striatum, ventral regions of the anterior cingulate cortex and prefrontal cortex)
  - Involved in appraisal and production of affective state stages.
- **Dorsal system** (hippocampus, dosral regions of the anterior cingulate cortex and prefrontal cortex).
  - Involved in regulation stage.

Phillips et al (2003)

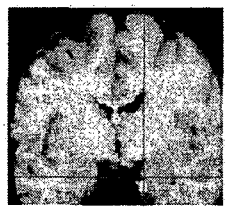
Limbic System:
Emotional control system, first evolving in mammals

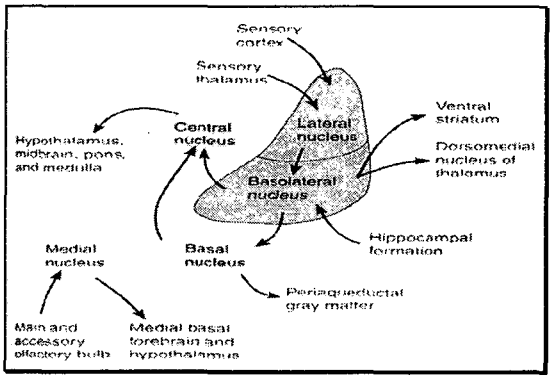
- 3 most important structures:
  - Anterior Cingulate Gyrus: Attention system
  - ? Amygdala: Main emotional center
  - Hippocampus: short-term memories into long-term memory.



Amygdala:
A protection device

- The amygdala participates in an evaluation of the environmental stimuli to ascertain whether there is something that is potentially dangerous.





The central nucleus of the amygdala

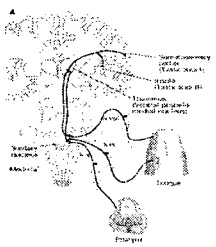
- Projections to:- hypothalamus
  - midbrain
  - pons
  - medulla
- Controls the autonomic and hormonal responses
- Especially important for emotional responses provoked by AVERSIVE stimuli
- Damage to this nucleus → lack of fear response
- Stimulation of this nucleus → agitation + fear

Amygdala and anxiety disorders

- Amygdala has a definite role in all the anxiety disorders
- Left amygdala might be linked more directly to cortical controls in the brain that affect the fear response, and may be shrunken or impaired in anxiety disorders, particularly PTSD.
- Overall hyperactivity in the amygdala (possibly more so in the right) may also be related to pathological states in anxiety, and overactivation of the associated HPA axis and locus ceruleus.

Disgust

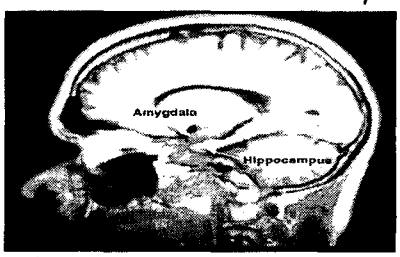
- Phillips et al. (1997) demonstrated that disgust faces failed to activate the amygdala.
- Rather, in response to disgust faces, subjects showed activation in a region implicated in processing gustatory stimuli - the anterior insula.



Insula: generation of affective state

- Activated during anticipation of an aversive stimulus, sadness, experience of guilt (recall of internally generated emotion)
- Conveying the representation of aversive sensory information to amygdala.

Hippocampus facilitate or inhibit defensive behavior and anxiety



A comparator

Hippocampus and anxiety disorders

- Structural MRI studies reported smaller hippocampal volumes in PTSD.
- Functional hippocampal abnormalities in PTSD have been also reported at base line using PET measure of glucose metabolism.

Hippocampus and anxiety disorders

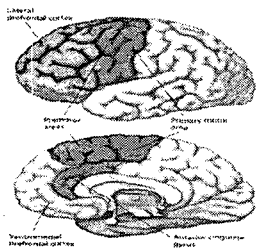
- Functional connectivity between the hippocampus and amygdala crucially involved in decoding the behavioral significance of incoming information.
- Patient with anxiety disorders often display normative affective response but context-inappropriate emotional responding.

Prefrontal Cortex: Executive function

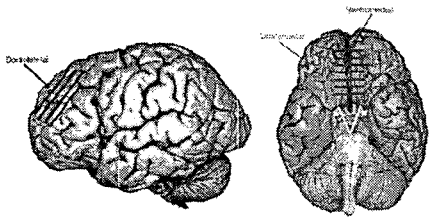
Lateral PFC
Working memory
Conscious strategies

Ventromedial PFC
Consequences of actions
(non-conscious assessment)

Anterior cingulate gyrus
Attention



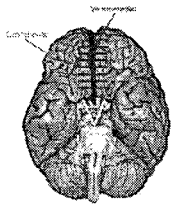
Prefrontal cortex (PFC)



- Representation of goals and the means to achieve them.

Orbitofrontal cortex (OFC)

- Affect-guided planning and anticipation
- Left-sided OFC appears particularly responsive to reward while a lateral right-sided region appears particularly responsive to punishments
  (O'Dohery et al, 2001)

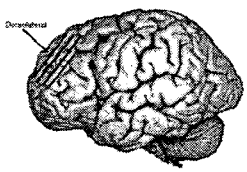


Prefrontal circuitry: Ventral system

- There are extensive reciprocal connections between amygdala and PFC, particularly the medial and orbital zones of prefrontal cortex.
- The orbitofrontal cortex exerts inhibitory control of the amygdala. Hence, the rCBF reductions in the orbitofrontal cortex, together with enhanced rCBF in the amygdaloid complex, may be associated with emotional dysregulation linked with failure to inhibit negative affect.

Dorsolateral prefrontal cortex

- Working memory system devoted to sustaining representation of information stored tin the cortex.



Implication for anxiety disorders

- The prefrontal cortex is a crucial region in the cognitive modulation and interpretation of anxiety-provoking experiences, and in the regulation of amygdalar activation.
- Medial/orbital prefrontal cortex modulated more interpretation/higher-orders of anxiety response and comprehension of social consequences
- Generally decreased blood flow on PET and fMRI to prefrontal regions in anxiety disorders, with increased CBF to limbic regions, especially on symptom provocation.

PTSD and prefrontal cortex

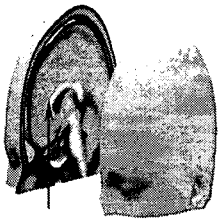
- A recent study by Shin et al. (1998) is consistent with the theory that there is an inverse relationship between prefrontal cortical versus amygdalar activation during stressful tasks in patients with PTSD.
- The prefrontal cortex normally modulates activation of the amygdala; and when there is decreased prefrontal cortical function, amygdalar hyperreactivity might ensue in PTSD.

Generalized anxiety disorder and prefrontal cortex

- *Increased* neuronal viability in GAD patients (via increased *N*-acetylaspartate/creatine ratio) in the right DLPFC (not the left) as compared to normal controls (Mathew et al. 2004).
- Prefrontal hyperactivity in GAD differs from the prefrontal *hypo*activity found in PTSD and panic disorder studies.

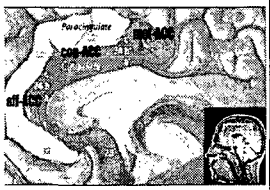
Anterior cingulate cortex (ACC)

- Plays an important role in aspects of attentional processing and acts as a bridge between attention and emotion.
- ACC activation may be present when effortful emotional regulation is required in situations in which behavior is failing to achieve a desired outcome.



ACC and anxiety disorders

- ACC also has an important role in the fear circuit, as lesions of this region result in autonomic hyperactivity in response to stimuli as well as decreased emotional response.



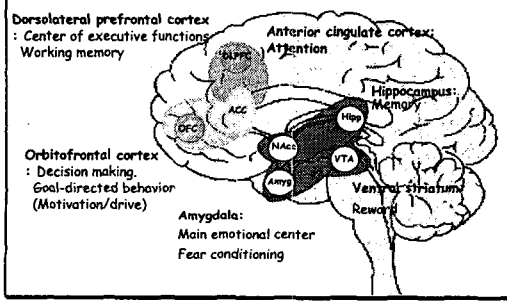
ACC and anxiety disorders

- ACC is considered the *bridge* between the limbic subcortex (especially the amygdala) and the prefrontal cortex.
- Lesions of the anterior cingulate region have also been known to lead to disinhibition of rage and other emotional responses in afflicted individuals, due to severance of the inhibiting regulation of the prefrontal cortex.
- Emotional discomfort in OCD and difficulties in behavior extinction are felt to be linked to this region.

BNST (bed nucleus of stria terminalis)

- The BNST has more recently become understood as a major player in the fear circuit, and the next *important link between (or perhaps parallel to) the* amygdala and the 'downward' neuroendocrine axis that regulates the fear response.
- BNST may regulate longer-term anxiety effects on the individual as opposed to the immediate startle reflex-related mechanisms involving other parts of the fear circuit such as the amygdala.
- The BNST may work via the CRF-cortisol pathway rather than the LC-NE pathway

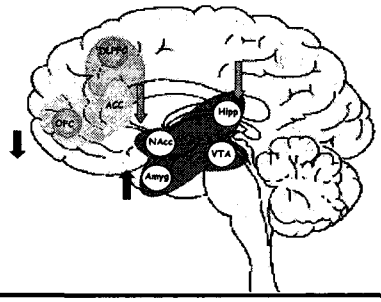
Circuits involved in Anxiety disorders



Circuits involved in PTSD

- PTSD shows possible changes, even atrophy, in the hippocampus and perhaps caudate.
- The hippocampus has been postulated to provide contextual memory for fear in individuals.
- Hippocampal dysfunction may be related to the flashback disturbances in PTSD.
- Most PTSD imaging studies show decreased prefrontal/anterior cingulate CBF, and increased amygdala CBF, which may correlate with difficulty processing and regulating the memory of a discrete traumatic event and its associated emotional phenomena.

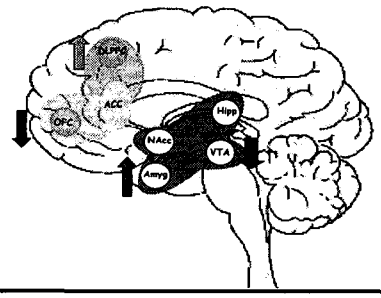
Circuits involved in PTSD



Circuits involved in Social Phobia

- Social phobia overall has shown increased medial temporal lobe activity in response to facial recognition stimuli, and also increased activity in the hippocampus.
- The orbitofrontal cortex exerts inhibitory control of the amygdala. Social phobics may have decreases function in orbitofrontal cortex.
- Increased worry and rumination, reflected in dorsolateral prefrontal activation modulates the orbitofrontal cortex resulting in reduced inhibition of the amygdaloid complex in social phobia.

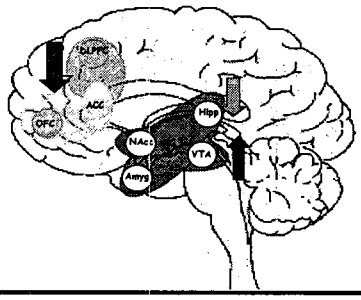
Circuits involved in Social Phobia and specific phobia



Circuits involved in Panic disorder

- Frontal cortex (including orbitofrontal in anticipatory panic) have shown decreased activity compared to temporal/insular lobe regions, indicating possible decreased primary higher-order control in modulating the fear response, possibly explaining the spontaneity of attacks.
- There is increased CBF in the anterior insular and anteromedial cerebellum and midbrain after panic challenges, which are also seen with specific phobias, although the significance of this similarity is unclear.

Circuits involved in Panic disorder



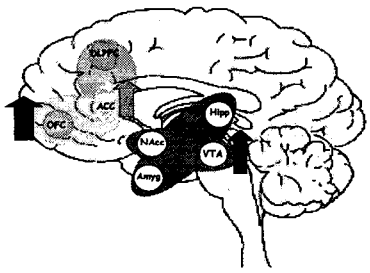
Circuits involved in Panic disorder

- Rauch (1998) noted that baseline abnormalities in hippocampal activity are present in patients with panic disorder, which may theoretically relate to dysfunctional access to appropriate fear memory contexts.
- Anticipatory anxiety in panic disorder may possibly develop through a separate but related mechanism (perhaps even similar to PTSD-type mechanisms of hyperactive fear memory), and needs to be investigated further. In any case, the basic premise of cortical and subcortical interaction and potential dysregulation remains the same.

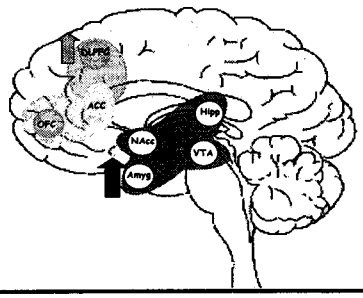
Circuits involved in OCD

- Alterations in the orbitofrontal cortex (a key region in extinction modulation), caudate, anterior cingulate and thalamus and striatum, leading to the theory of a disordered corticostriatal circuit.
- The striatal/anterior cingulate and orbitofrontal areas are felt to have increased CBF (hyperactivity).

Circuits involved in OCD: Corticostriatal pathway



Circuits involved in GAD

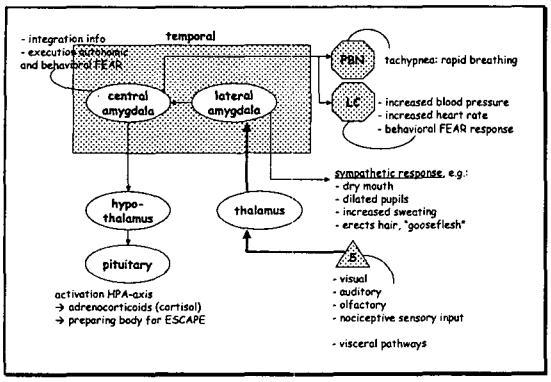


Circuits involved in GAD

- Debellis et al. (2002) demonstrated enlarged amygdala volume in children with GAD as compared to normal controls and children with PTSD.
- GAD showed increased right dorsolateral prefrontal cortex activity as compared to controls (but only those without a history of childhood abuse).
- This study might indicate a variant of cortical dysfunction correlating with the baseline generalized nature of GAD.

Neuroendocrine pathways: the HPA axis and anxiety

1. The HPA axis and CRF
2. CRF in the fear circuit
3. HPA axis regulation and variation in the anxiety disorders
4. The HPA axis and trauma: genes and the environment
5. The LC-NE axis



HPA axis and CRF

- Affect the contextualization of fear memory via associations of stress and trauma with physical symptomatology.
- Adjust the body's neurochemical regulation in response to stress; blood pressure, heart rate, immune system regulation, stress hormone levels, etc.

CRF in the fear circuit

- Corticosteroids regulate the production and release of neuroactive steroids that have primary brain effects via GABA and serotonin (HT) receptors.
- Steroids also regulate the release of catecholamines which activate the fight or flight sympathetic response leading to physiological symptoms of anxiety.

CRF in the fear circuit

- CRF may also have a direct feedback effect with NE in the locus ceruleus, leading to a strong primary sympathetic response,
- CRF functions as a neurotransmitter in other regions of the brain.
- CRF modulates anxiety response (including startle reflex, social inhibition and 'freezing' behavior in rats) in subjects via these receptors.
- CRF blockade results in decreased anxiety, especially via R1 blockade.
- CRF administration intracerebrally causes increased anxiety in rats

HPA axis regulation and variation in the anxiety disorders

- OCD patients have elevated baseline levels of cortisol in blood and CSF, whereas panic disorder patients have not had any clearcut baseline elevations.
- Patients with PTSD have decreased baseline levels of cortisol in most studies, possibly indicating increased ACTH feedback and downregulation of hypothalamic CRF receptors over time.

The LC-NE axis

- The LC-NE system is responsible for producing the most immediately unpleasant symptoms of anxiety such as the fight or flight response.
- The release of NE from the locus ceruleus leads to the activation of the autonomic nervous system via the adrenal gland, which releases epinephrine.
- Direct cardiovascular effects such as increased heart rate and blood pressure result accordingly.
- Sympathetic dysfunction has been well-studied in patients with panic disorder, who upon receiving yohimbine, an alpha-2 blocker, developed a heightened autonomic response.

Neurotransmitters and anxiety

1. GABA
2. Serotonin
3. Norepinephrine
4. Glutamate
5. Dopamine

GABA

- The GABA system was the first to be used as a treatment modality, given its known general inhibitory effects on the CNS as well as its rapid mediation of anxiolytic effects.
- GABA receptors are found throughout the brain, including the regions implicated in anxiety disorders like the amygdala.
- GABA knockout mice have been shown to exhibit fear-related behaviors such as behavioral inhibition and fear hyperresponsiveness, particularly when the GABA-A type receptor is involved.

Serotonin

- Serotonin receptors are primarily found in the dorsal raphe nuclei of the brainstem, but are also found throughout other parts of the brain and body.
- Serotonin knockout mice, particularly with the 1A receptor deletion, have also exhibited increased fear behaviors.

Norepinephrine

- Norepinephrine is also a crucial neurotransmitter in anxiety; in addition to its role in the sympathetic noradrenergic axis described earlier, norepinephrine also appears to serve other primary anxiety-related neurotransmitter functions in the brain.
- Possible abnormalities in levels of catecholamines and their metabolites in patients with GAD.

Glutamate

- Glutamate has also been postulated to modulate anxiety, given its excitatory role in the CNS.
- The interaction between glutamatergic receptors and GABA receptors serves as the main on-off switch in the brain, and a dysregulation in the balance between the two may affect anxiety levels.

Dopamine

- Dopamine has been considered to play a role in social phobia and may relate to the social-specific nature of this anxiety disorder.
- Reductions in D2 receptor binding have been noted in primates that exhibit subordinate and introverted/fearful behaviors.
- Imaging studies have borne out lower D2 receptor binding in the striatum in patients with social phobia.