Functional Neuroimaging Findings in Panic Disorder

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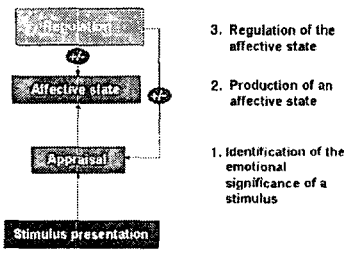
The main processes important for emotion perception



Phillips et al., 2003

Three processes for emotion perception

- Allowing the generation of contextually appropriate, complex affective states, emotional experiences (feelings), and behaviors

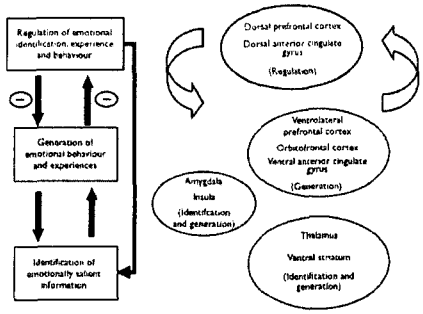
Ventral system

- Regions
  - Amygdala, insula, ventral striatum, and ventral regions of the ACC, prefrontal cortex
- Function
  - The identification of the emotional significance of environmental stimuli (Rapid appraisal of emotional material)
  - The production of affective states
  - Automatic regulation and mediation of autonomic responses to emotive stimuli and contexts

Dorsal system

- Regions
  - Hippocampus, dorsal regions of the ACC, prefrontal cortex
- Function
  - The performance of executive functions, including selective attention, planning, and effortful rather than automatic regulation of affective states

Reciprocal functional relationship



Phillips et al., 2003

Symptomatology of panic disorder

- Panic attack
- Anticipatory anxiety
- Trivial physical symptoms

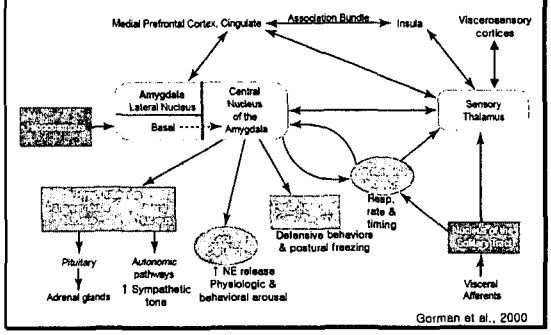
Conditioned fear

- A tone or flash of light (C)
- A mild electric shock simultaneously (UC)
- Rat learns to respond to the conditioned stimulus without UC stimulus

Neurocognitive deficit in cortical processing pathway

- The misinterpretation of sensory information (bodily cues)
- Leading to an inappropriate activation of the "fear network"

Neuroanatomical Pathways of Viscerosensory Information



Gorman et al., 2000

Contextual learning in panic disorder

- When simply placed in the cage in which the conditioning experiment took place, even without presentation of the tone
- Require intact hippocampal neurons

	Fearful Response	
Lesion	to tone	Placed back in the cage
Amygdala	–	+
Hippocam	+	–

Phillips et al., 1992; Kim & Fanselow, 1992

Functional neuroimaging paradigms in studies for panic disorder

- Neutral state paradigms
  - Resting state or while performing a non-specific continuous task
- Symptom provocation paradigms
- Treatment studies
- Cognitive activation paradigm

Rauch et al., 2003

During auditory discrimination in unmedicated patients: FDG-PET

- Abnormally low L/R hippocampal region asymmetry (rightward shift of normal asymmetry)
- Metabolic rate
  - ↓ Left inferior parietal lobule & in ACC
  - ↑ Medial orbital frontal cortex

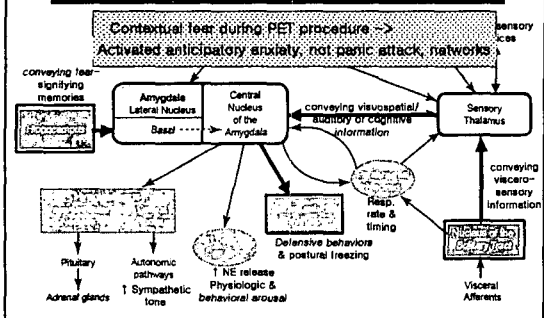
Nordahl et al., 1990

Activation of amygdala-based fear network in resting state: FDG-PET

- Significantly higher levels of glucose uptake in pretreatment panic disorder
  - Bilateral amygdala, hippocampus, thalamus, midbrain, caudal pons, medulla, and cerebellum
  - Not include the locus ceruleus or the parabrachial nucleus assumed to be associated with panic attack symptoms

Sakai et al., 2005

Hyperactivity in both afferent pathways to the amygdala & part of the startle circuit



Lactate or yohimbine-induced panic : SPECT study

- Xenon inhalation method[1]
  - Global cortical decreases in CBF in patient with lactate induced panic experience, compare with control or patients with no experience
- SPECT & yohimbine[2]
  - ↑ anxiety & ↓ rCBF in bilateral frontal cortex in patient with panic disorder

[1]Stewart et al., 1988; [2]Woods et al., 1988

Lactate-induced panic: PET study

- Significant increases in blood flow
  - Bilaterally in the temporal poles (muscular artifact?)
  - Insular cortex, claustrum, lateral putamen
  - Bilaterally in the superior colliculus
  - Left anterior cerebellar vermis

Reiman et al., 1989

Spontaneous panic attack: case report

- Decreased rCBF
  - Right orbitofrontal (BA 11)
  - Prelimbic (BA 25), anterior cingulate (BA 32)
  - Anterior temporal cortices (BA 15)

Reiman et al., 1989

CCK4 induced anxiety attack in healthy volunteer

- Benkelfat et al (1995)
  - Anticipatory anxiety condition (saline injection)
  : ↑ Left orbitofrontal cortex & cerebellum
  - CCK-4 condition
  : ↑ ACC, cerebellum, bilateral claustrum-insular-amygdala
- Javenmard et al(1999)
  - 1 min or 2 min after CCK-4
  - Anticipatory anxiety condition: ↑ ACC & ↓ visual cortical area
  - Early phase: ↑ Hypothalamic region
  - Late phase: ↑ claustrum-insular region
  - Both phase: ↓ medial frontal region

During auditory CPT in the untreated & treated

- No change of abnormally low L/R hippocampal and posterior inferior prefrontal rCMRglc ratios in both untreated and treated patients with panic disorder
- Posterior orbital frontal rCMRglc decreases in the imipramine-treated panic disorder patients compared with the unmedicated panic disorder patients

Nordahl et al., 1998

After CBT or antidepressant: 18FDG study

- Similar change with prominent right-left difference
  - ↓ right hemisphere in superior, inferior (AD/CBT), middle, medial (AD) frontal gyrus, superior (AD/CBT), middle (AD), inferior (CBT) temporal gyrus
  - ↑ mainly left hemisphere in medial, middle (AD), inferior (CBT), superior (AD), middle (AD/CBT), insula (CBT)
  - No change in the limbic region
- Normalize L/R asymmetry?
- Small sample size (AD=5, CBT=5), too simplified results

Prasko et al., 2004

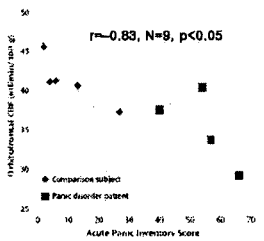
Activation by threat-related words in panic disorder

- More right>left asymmetry of activation in the mid-parahippocampal region
- More activated in left posterior cingulate and left middle frontal cortices

➢ Panic disorder patients engage in more extensive memory processing of threat-related stimuli

Meddock et al., 2003

Baseline perfusion of the orbitofrontal cortex predicted panic attacks



- $[^{15}O]H_2O$ PET
- Anxiogenic doxapram
- Orbitofrontal cortex
  : Important in the regulation of responding to fear
  : A potential area of aberrant functioning in panic disorder
- Small sample size

Kent et al., 2005

Disorder-Specific Neuroanatomical Correlates of Attentional Bias: fMRI study

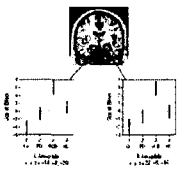
- A cognitive and emotional Stroop task
  - Congruent and incongruent color words, OCD-related and panic-related negative words, and neutral words
- Medication-free patients with OCD (n=16), panic disorder (PD) (n=15), hypochondriasis (n=13), 19 controls
- To investigate functional neural correlates and disease specificity of attentional bias across different anxiety disorders

Van den Heuvel et al., 2005

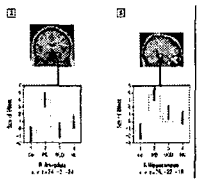
- During color stroop, additional activation in posterior brain regions in all anxiety patient groups
- ↑ Activation of *fronto-striatal region*
  - In OCD, OCD-related, but not PD-related, words
  - In PD, both OCD- and panic-related words
- Patients with hypochondriasis showed a similar activation pattern to patients with PD.

Van den Heuvel et al., 2005

- OCD
  - During OCD related word task
  - Unimpaired performance
  - ↑ Activation of both amygdala



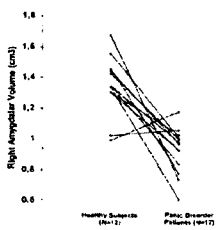
- *Panic disorder*
  - During panic related word task
  - Impaired performance
  - ↑ Activation of the right amygdala & hippocampus



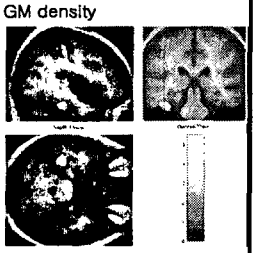
Van den Heuvel et al., 2005

Structural MRI studies in panic disorder

Both amygdalar atrophy



Lower left parahippocampal GM density



Massana et al., 2003a; 2003b

MRS studies in panic disorder

- Greater rise in brain lactate in response to hyperventilation[1]
- Greater brain lactate level during lactate infusion[2]

➢ Global or widespread abnormality in cerebral vascular function in panic disorder

Dager et al., 1995; 1999

5-HT_{1A} receptor PET study

- A role of 5-HT_{1A} receptors in the development of chronic anxiety[1]
- PET study with highly selective 5-HT_{1A} R radioligands in unmedicated panic disorder[2]
  - Lower volume of distribution in anterior cingulate, posterior cingulate, raphe
  - Reduction of 5-HT_{1A} R expression
  - ➢ Associated genetic risk factor?

[1]Overstreet et al., 2003; [2]Neumeister et al., 2004

Neurobiological model in panic disorder

- Dysregulated ascending noradrenergic &/or serotonergic systems
- Aberrant responsivity to CO_2 at the level of brain stem (false suffocation alarm)
- Global cerebral abnormalities in lactate metabolism
- Abnormalities in the interactions between hippocampus and amygdala
- Recurrent panic attacks

➢ Learning theory & fear conditioning model

But in first spontaneous attack...

- Aberrant event by homeostatic deficits or *fundamental monoamingergic dysregulation*
- Hippocampal deficit–> failures in limiting *normal response to minor anxiety*
- Recruit anxiety circuitry without awareness (implicitly) by *fundamental amygdala hyper-*responsivity to subtle environmental cue

Summary of previous results (1)

- Smaller volume in both amygdala or left parahippocampal gyrus
- Abnormalities in hippocampal &/or amygdalar activity at rest
- Activation of insular and motor striatal regions & reduced activity in cortical regions including prefrontal cortex

➢ Support for theories regarding hippocampal or amygdala dysfunction

Rauch et al., 2003

Summary of previous results (2)

- Exaggerated hemodynamic response to hypocapnea
- Abnormalities in the GABAergic/BDZ system
- Reduced 5-HT_{1A} receptor expression

➢ Fundamental abnormalities in monoaminergic neurotransmitter system, originating in the brain stem, may underlie the abnormalities of metabolism, hemodynamics, chemistry.

Rauch et al., 2003