Neuroimaging in Mood Disorders

Outline

- Role of neuroimaging in psychiatry
- Specific roles
- Challenges
- Structural neuroimaging
- Excitotoxicity
- Functional neuroimaging
- Neurological disorders
- Comparison
- Summary

Role of Neuroimaging in Psychiatry

- Demonstrate organic pathology
- Rule out general medical conditions
- Differential diagnosis
- Pathognomonic findings in specific psychiatric conditions

Imaging in CNS

Structural

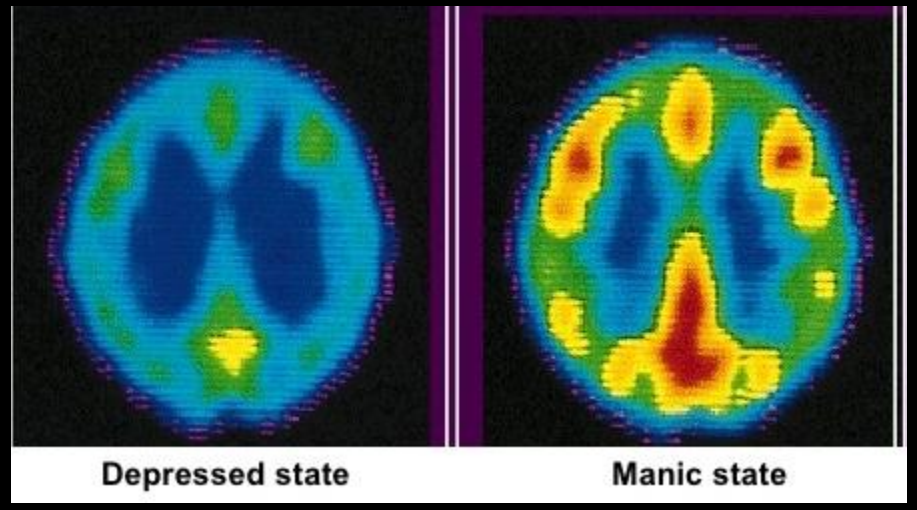
- Detailed, non-invasive visualization of brain morphology
- X-ray CT & MRI

Functional

- Visualization of the spatial distribution of specific biochemical processes
- PET, SPECT, fMRI & MRS

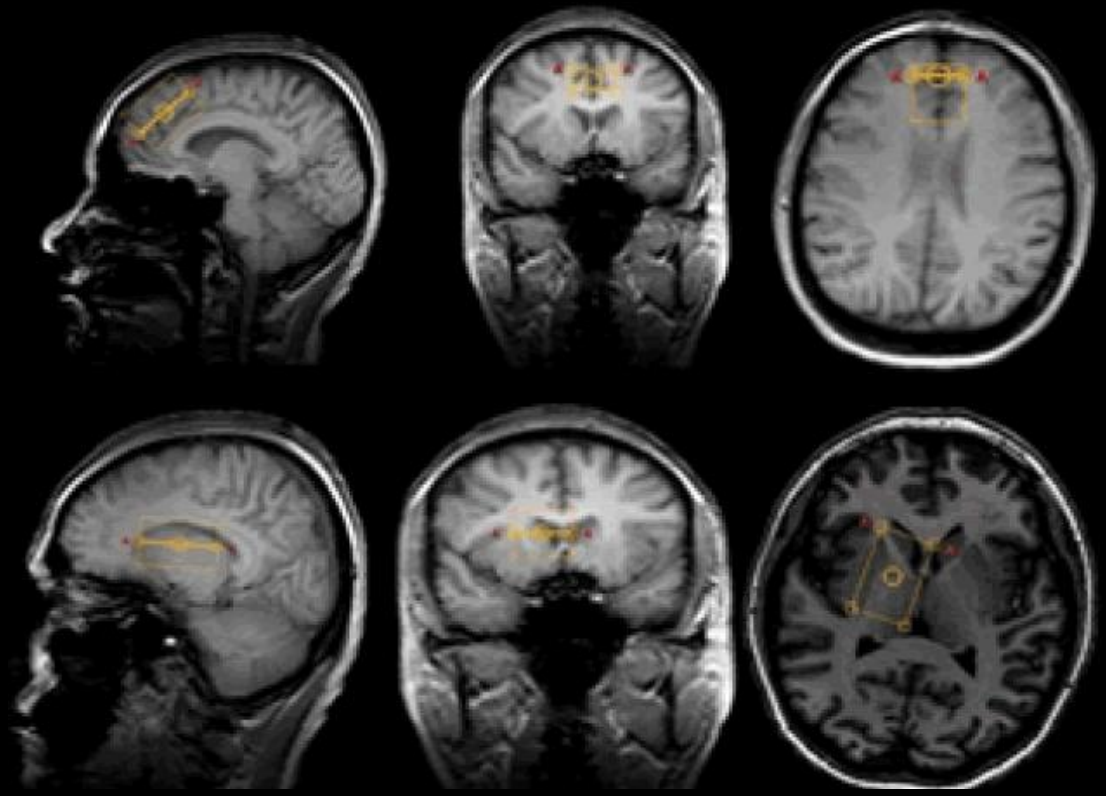
Specific Role

- PET:
  - Information about blood flow and glucose metabolism
  - Binding properties of specific neurotransmitters and other ligands during resting and in relation to specific cognitive and emotional tasks



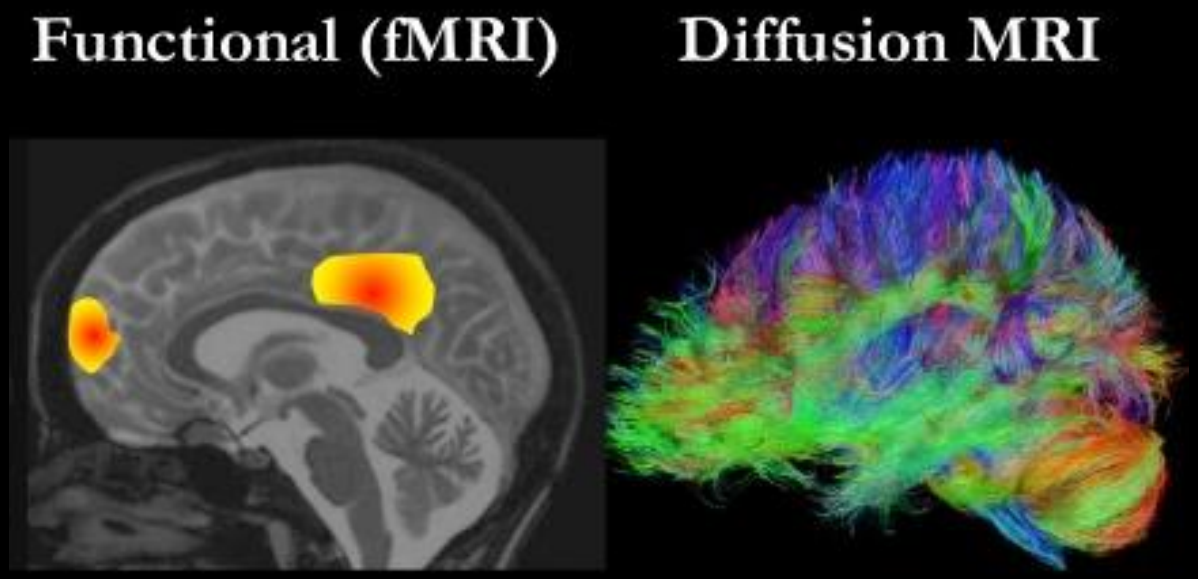
Specific Role

- MR-spectroscopy: determine quantity of specific endogenous and exogenous metabolites in brain



Specific Role

- Functional MRI (fMRI): local changes in blood oxygenation (BOLD) related to neural activity
- Diffusion-based MRI: study microstructural pathologies and track fibers in white matter



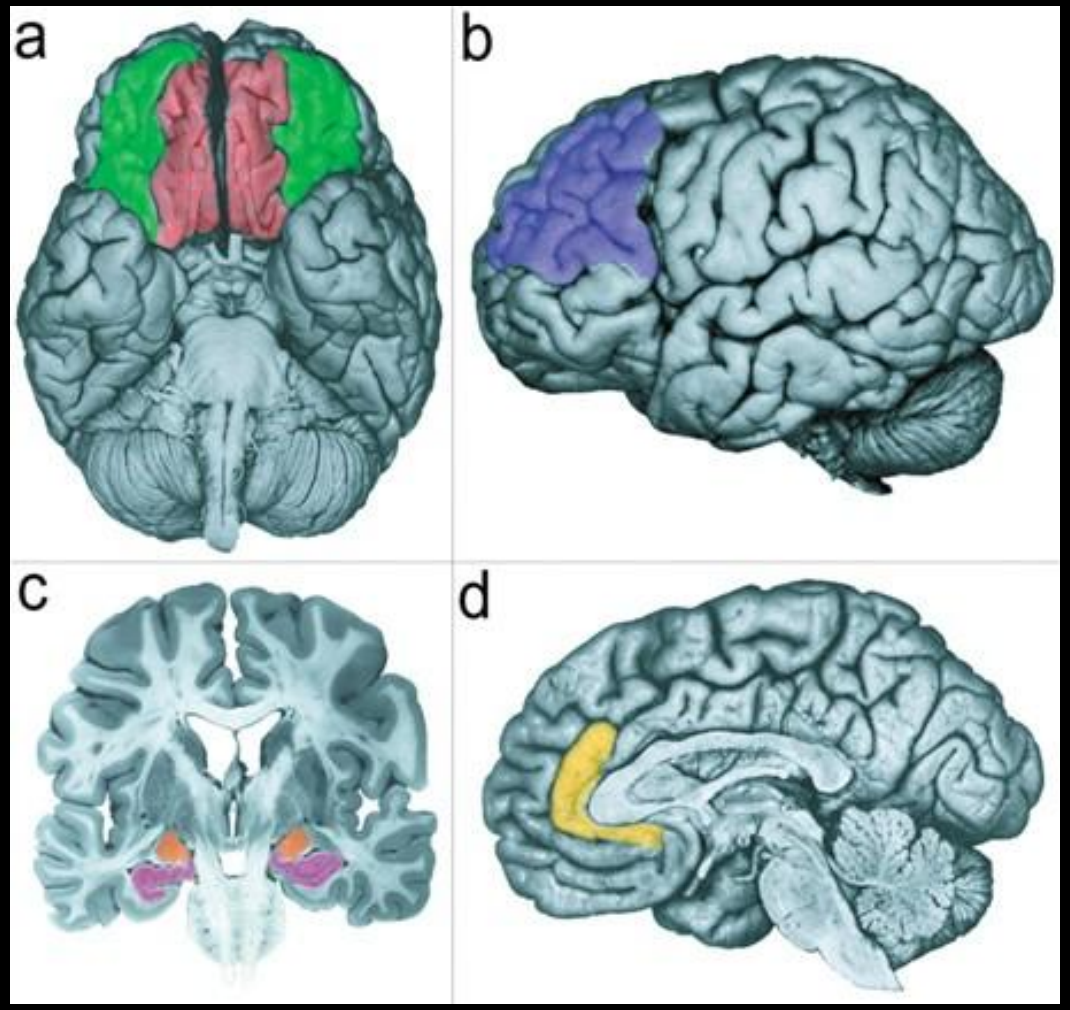
Challenges

- Complexity of the syndromal conformation of symptoms
- Different types of mood disorders
- Changes with age
- Changes with recurrence
- Personality traits
- Genetic background

Challenges

- Comorbid psychiatric and physical conditions
- Time-related changes
- Acute vs. Remission
- Variation in course of cognitive and emotional alterations
- Effect of treatment

Areas of Brain Involved



a) Orbital prefrontal cortex & ventromedial prefrontal cortex
b) Dorsolateral prefrontal cortex
c) Hippocampus & amygdala
d) Anterior cingulate cortex

Structural Neuroimaging

- No difference in total brain volume
- Studies correlating changes to age and onset of illness – neurodegenerative processes important in pathophysiology of BPD
- UPD: increased white matter hyperintensities
- BPD: similar findings in subcortical grey, periventricular & deep white matter
- Findings also seen in ageing and other neuropsychiatric disorders (SCZ/Dementia)

Structural Neuroimaging

A review covering all controlled cross-sectional studies between 1966 and 2002 (Brambilla P et al 2002) :

- UPD: Abnormalities in hippocampus and basal ganglia
- BPD: Abnormalities in cerebellum and amygdala
- Volumetric changes in dorsolateral prefrontal cortex, orbitofrontal cortex

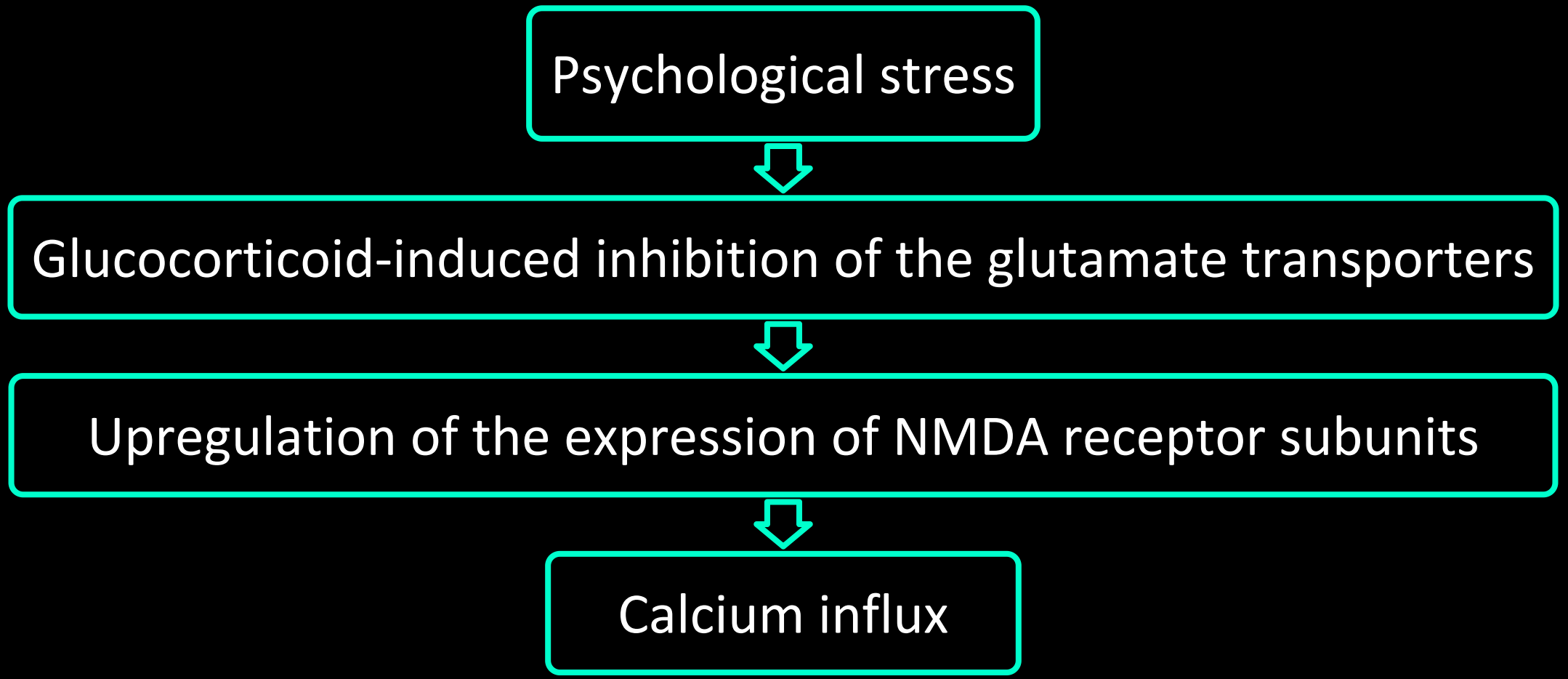
Structural Neuroimaging

- UPD: decreased prefrontal cortical volume; decreased caudate & putamen volume (inconsistent)
- Chronic treatment resistant depression: decreased density of temporal lobe grey matter in anterior hippocampus
- Association b/w clinical severity of depression and decrease in prefrontal lobe volumes
- Association b/w global gray matter volume and duration of illness in female patients with recurrent depression

Structural Neuroimaging

- BPD: inconsistent findings; increased amygdala; increased basal ganglia (inconsistent); decrease in size and changes in morphology of anterior cingulate architecture
- Similar observations in cerebellum, corpus callosum, pituitary & brainstem
- UPD/BPD: Enlargement of lateral and/or the third ventricles (~schizophrenia)

Excitotoxicity



Excitotoxicity

Depolarizes

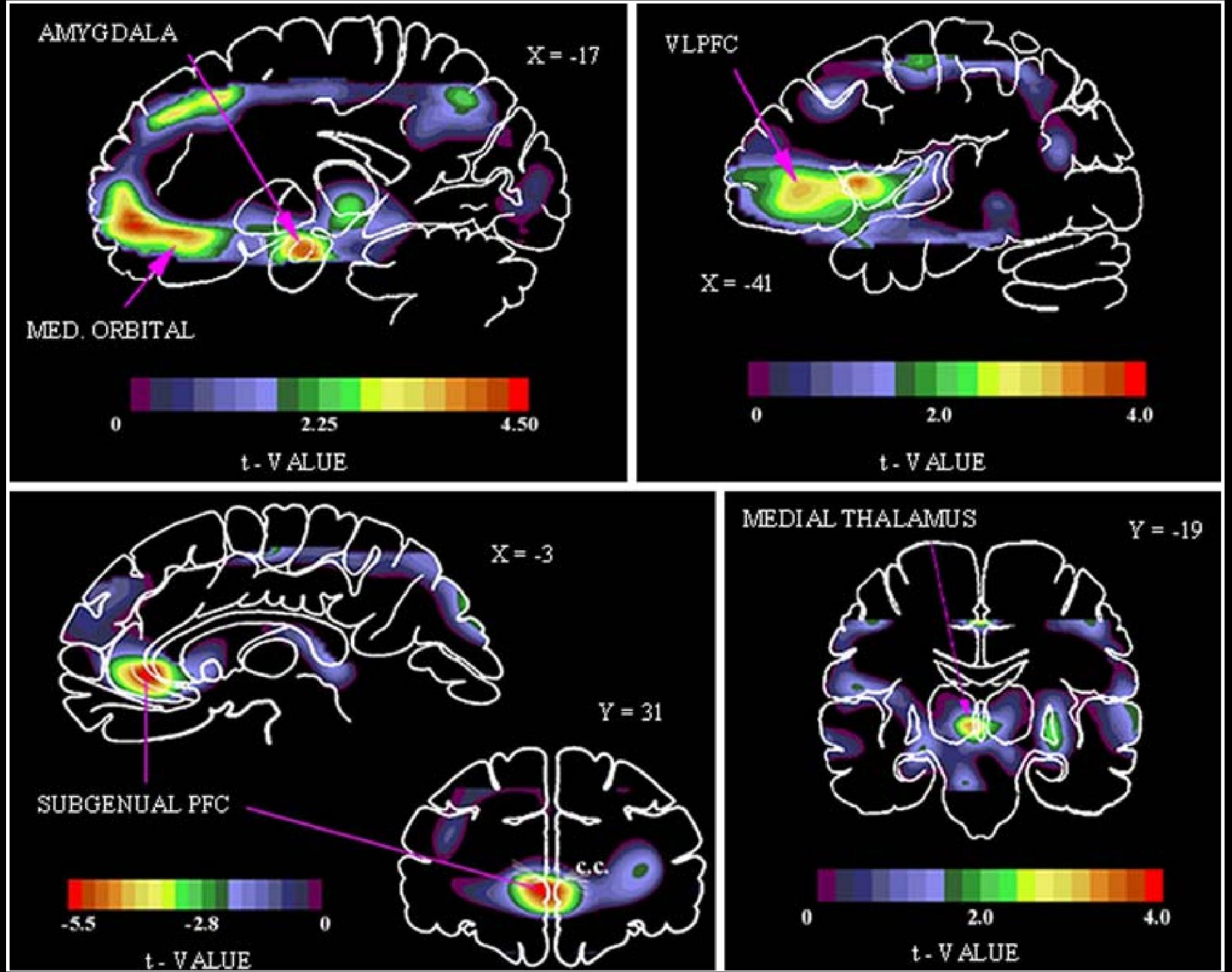
Rise in the intracellular mitochondrial

- Free Radicals
- Proapoptotic protease

Functional Neuroimaging

Drevets et al (1992)

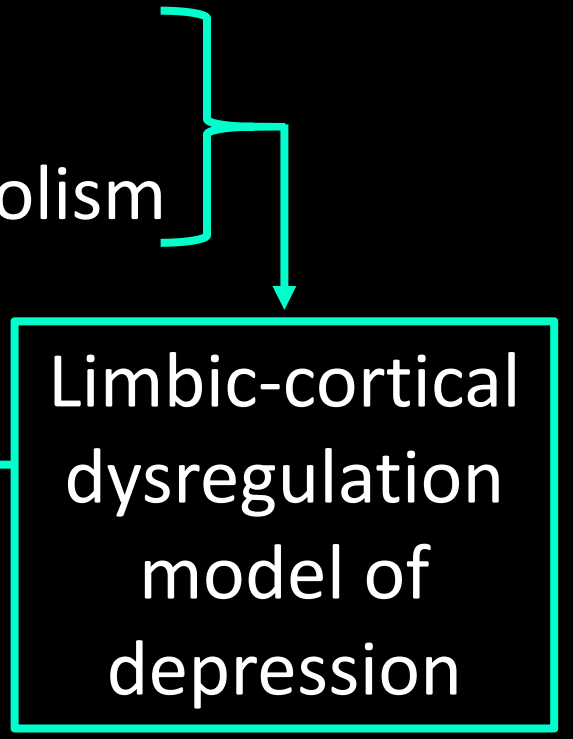
- PET – increased resting state blood flow in medial prefrontal cortex, lateral orbital & ventrolateral prefrontal cortex, amygdala & medial thalamus
- Decreased glucose metabolism within subgenual portion of anterior cingulate cortex


AMYGDALA
X = -17
MED. ORBITAL
0
2.25
4.50
t - VALUE
VLPFC
X = -41
0
2.0
4.0
t - VALUE
X = -3
Y = 31
SUBGENUAL PFC
c.c.
-5.5
-2.8
0
t - VALUE
MEDIAL THALAMUS
Y = -19
0
2.0
4.0
t - VALUE

Functional Neuroimaging

- BPD/UPD – Decreased anterior paralimbic and cortical activity (Cerebral Blood Flow study)
- UPD: Reversal on treatment
- BPD-D: Increased subcortical paralimbic metabolism

- Dorsal neocortical hypofunction
- Ventral paralimbic overactivity



MR Spectroscopy

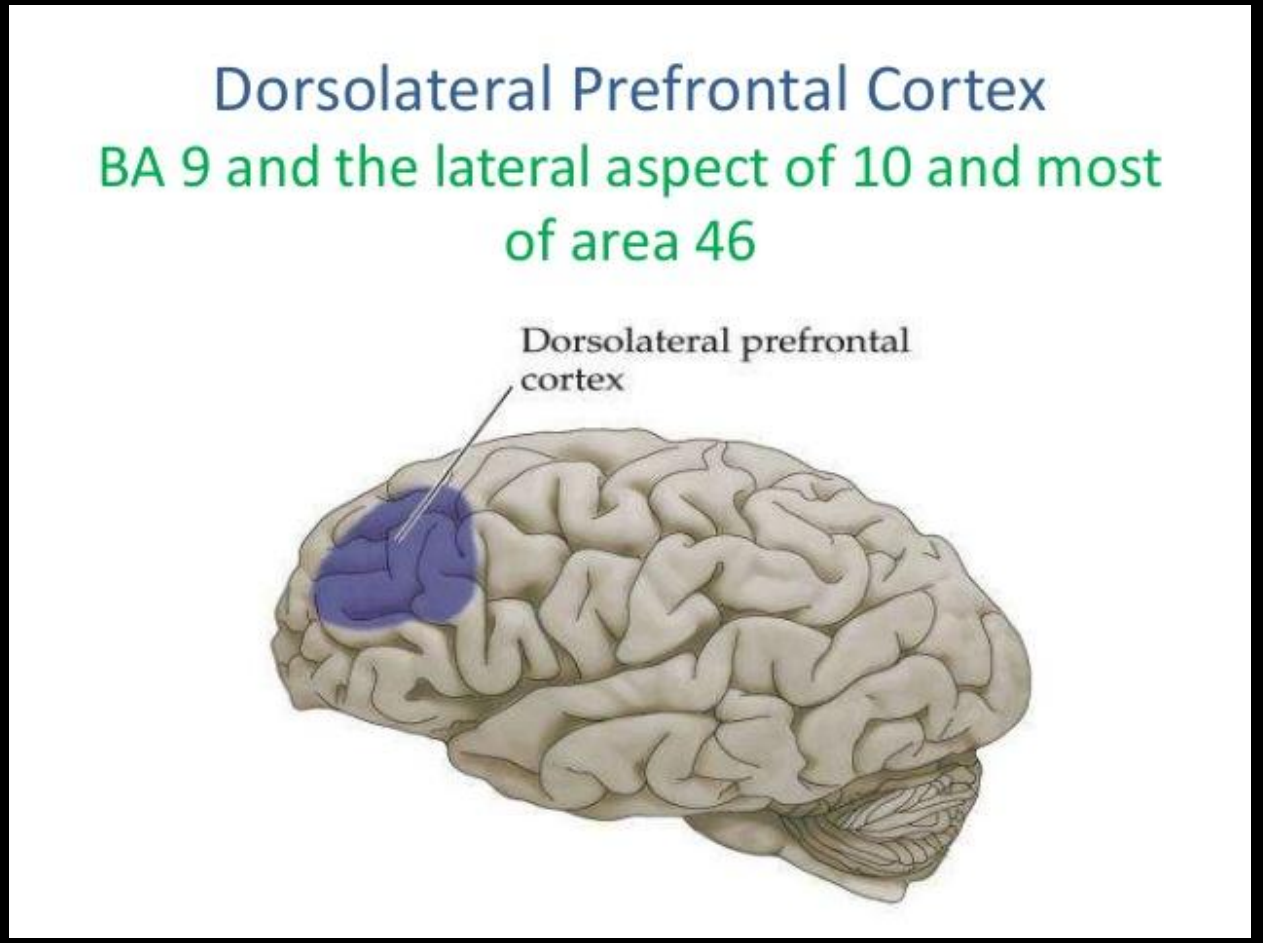
- Depression – increase in choline in basal ganglia and anterior cingulate (Mood-state related)
- Decreased dorsolateral prefrontal N-acetylaspartate (NAA) and creatine (Cr) levels – decrease in neuronal density
- BPD: Decreased levels of NAA in hippocampus, basal ganglia & orbito-frontal grey matter
- Early onset affective disorders: increase in myo-inositol levels

MR Spectroscopy

- Measurement of cerebral psychotropic drugs (lithium & SSRI)
- Poor correlation between serum and cerebral levels of lithium – relapse/toxicity
- Li-MRS: non-invasive means to measure brain lithium (research purposes)
- F-MRS: SSRI and its metabolites

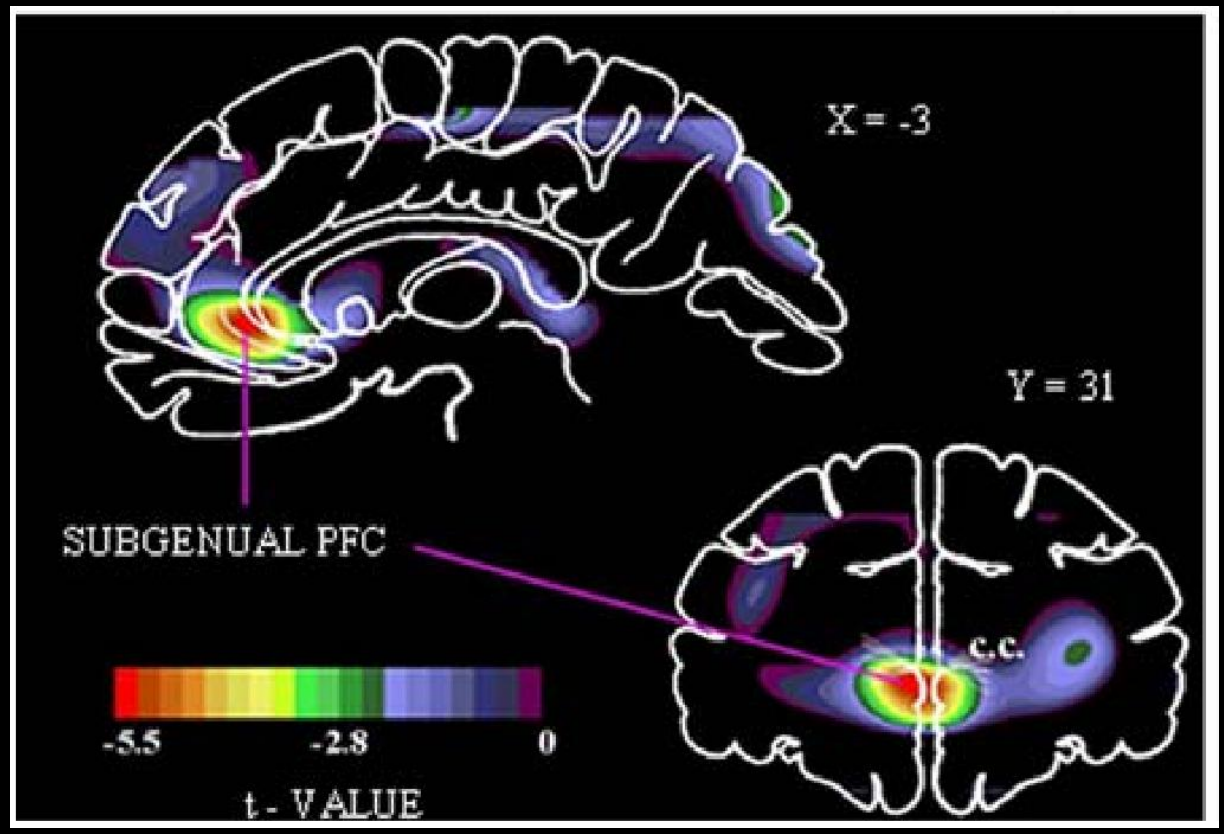
Functional MRI

- Depression: decreased activity in dorsal prefrontal cortex (BA9)
- Responses noted in healthy subjects during memory driven sadness & happiness
- BA9 - important destination for limbic projections; plays role in modulating mood states



Functional MRI

- BPD-D: decreased metabolism & perfusion in subgenual prefrontal cortex
- BPD-M: increased metabolism & perfusion in anterior cingulate



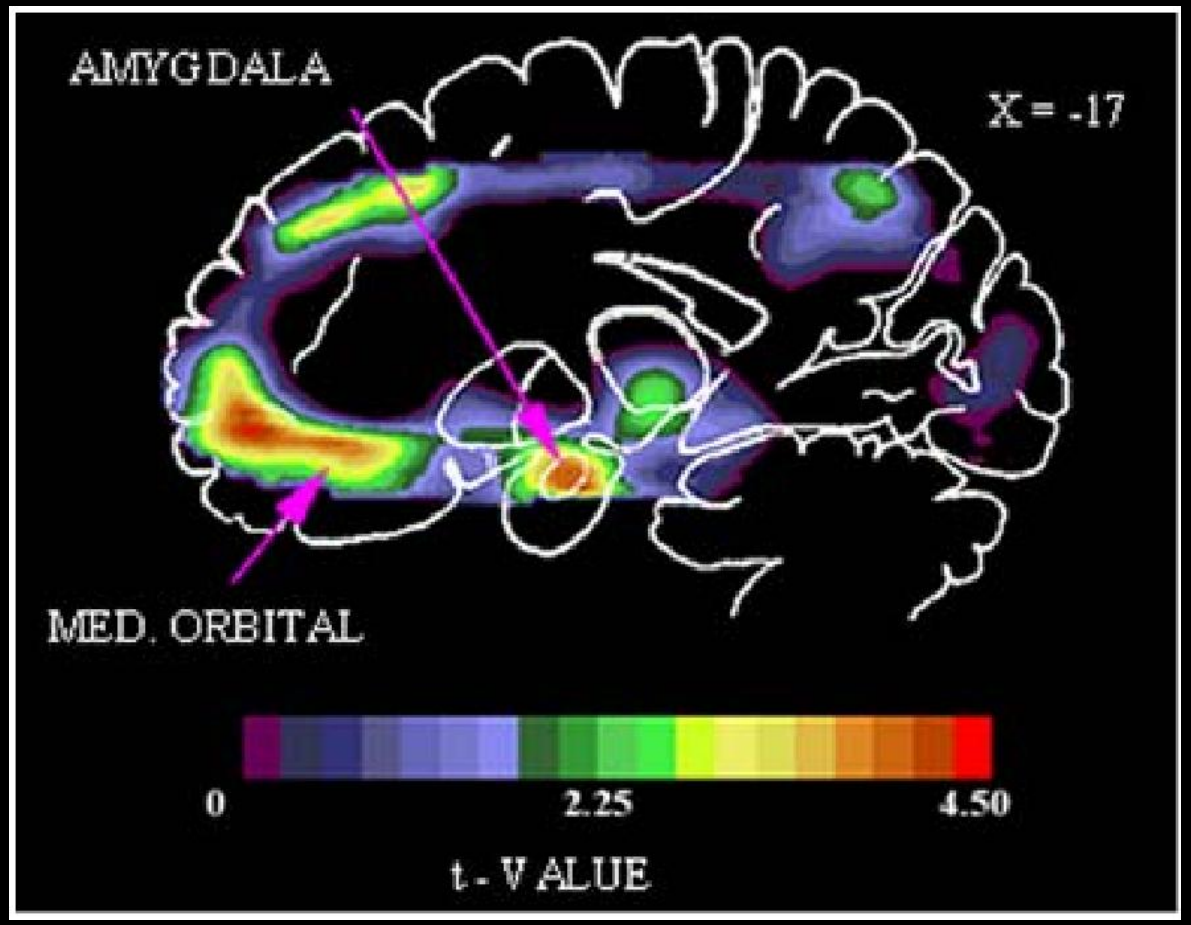
Functional MRI

- Anterior cingulate - Reciprocal connections to orbital frontal cortex, amygdala and insula
- Pathogenesis of clinical depression
  - Functional activation
  - Resting-state treatment studies
  - Neuropsychological
  - Lesion studies

  } Subgenual cingulate (BA25)
- Not definitive – processes cognitive aspects

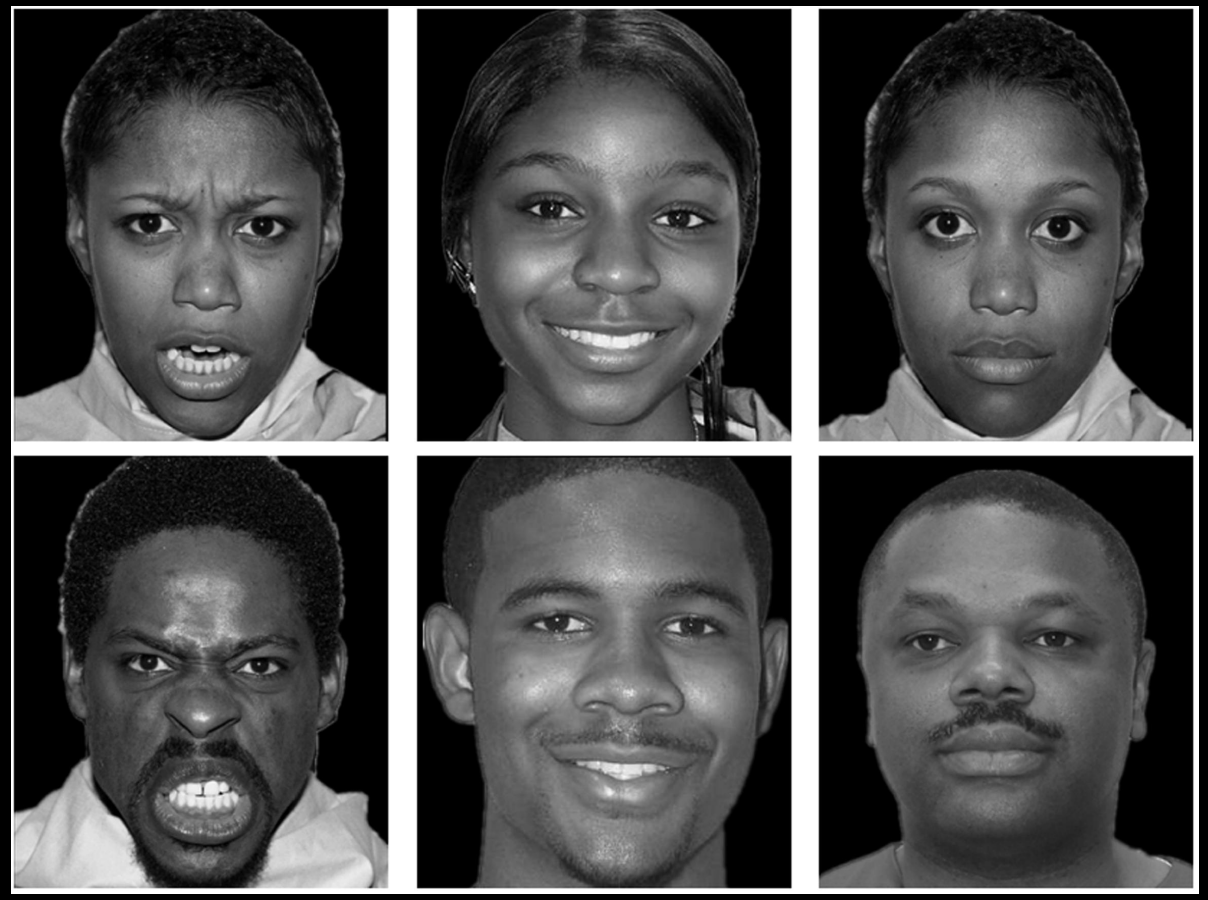
Functional MRI

- Amygdala - activated in response to environmental threat and experience of fear
- May determine the dangerousness of affective stimuli
- Sad and happy affect – activation of amygdala in fMRI in UPD/BPD/healthy controls



Functional MRI

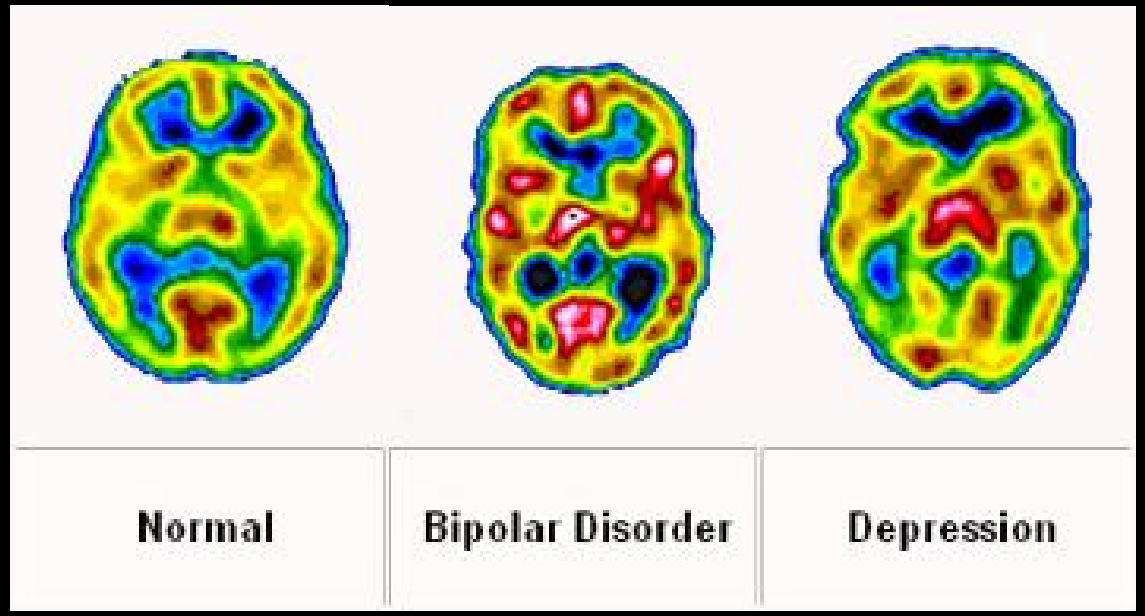
- Facial affect discrimination task: decreased dorsolateral prefrontal cortical activation when presented with fearful faces
- Non-emotional tasks – inappropriate activation of emotional brain areas – more vulnerable to mood disorders



Functional MRI

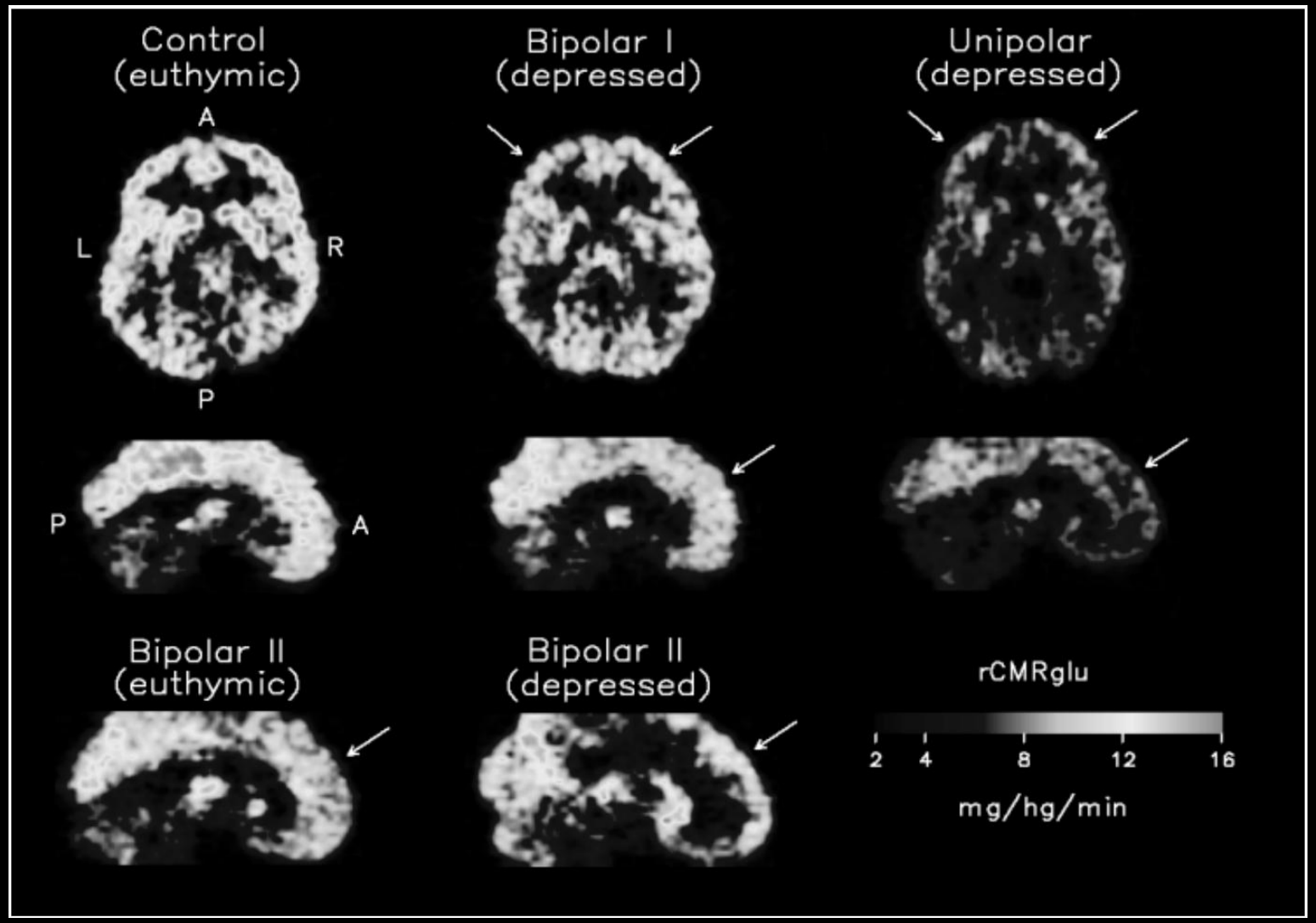
Blumberg *et al:*

- Depression: increased area of activation in right VPC
- Mania: decreased area of activation in right VPC



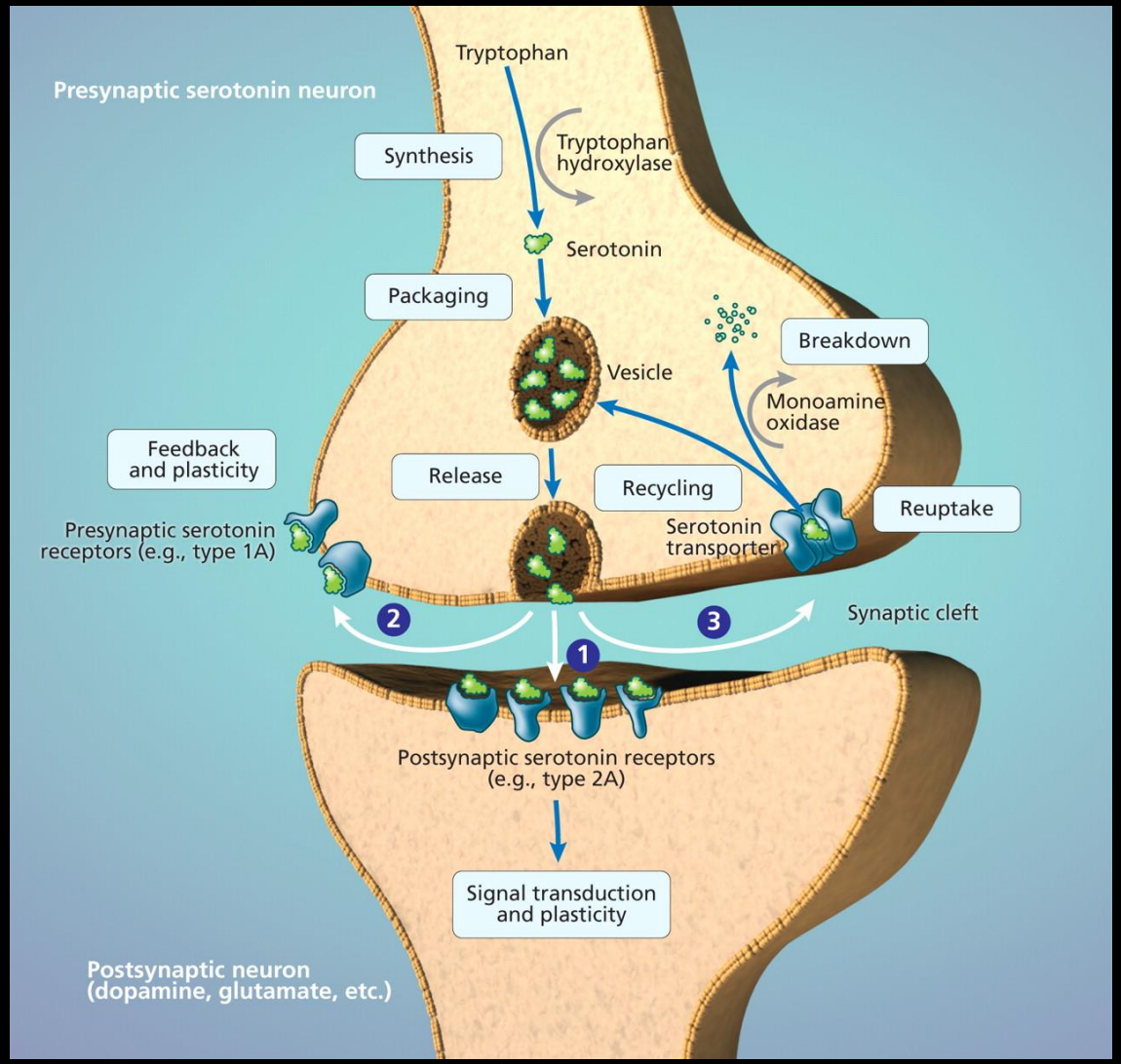
Functional MRI

- Depression → Hypomania
- Reversal of hypofrontality



Receptor Binding

- Depression - dysfunction of presynaptic serotonin transporter (SERT)
- PET – determine availability of SERT by selective PET radioligands
- Binding corresponds to intrasynaptic serotonin/serotonergic nerve terminals



Receptor Binding

- Drug naïve UPD & BPD-D v/s controls: increased availability of thalamic SERT
- Mood disorders: thalamus + altered serotonergic functioning
- BPD & UPD:
  - 5-HT 1A: decreased binding in limbic, frontal and temporal cortical regions
  - 5-HT 2A: similar findings/no difference
- Psychotic symptoms: Increased density of dopamine D_2 receptors in caudate

Sub-cortical & Medial Temporal Activation

- Functional abnormalities in striatum & other sub-cortical structures
- BPD-D: Decreased caudate metabolism
- BPD-M: Increased blood flow in basal ganglia (R>L)
- Rapid cyclers:
  - Decreased prefrontal cortex & paralimbic cortical metabolism
  - Increased metabolism in ventral striatum, thalamus and amygdala
- Untreated pts. – higher activation throughout motor cortex, basal ganglia and thalamus

Depression in Neurological Disease

- CT & MRI in stroke: Left sided lesions of frontal cortex & basal ganglia - depressive symptoms
- Head trauma, SOLs, neurosurgical: dorsolateral PFC > ventrolateral PFC
- Traumatic frontal lobe injury - high co-relation b/w affective disturbances & right hemisphere pathology
- Secondary mania - right basal frontotemporal/subcortical damage

Comparisons

Unipolar depression vs. Bipolar disorder:

- Size of basal ganglia and amygdala:
  - BPD: increased
  - UPD: decreased

Depression vs. Autism:

- Serotonin
- Left hemisphere, PFC, amygdala, hippocampus

Comparisons

Bipolar disorder vs. Schizophrenia

- Mood disorder – Basal ganglia (NA & Hypothalamus) affected
- SCZ - Limbic system, and structural asymmetry affected

PTSD vs. Bipolar disorder

- Hyperactive amygdala
- Hippocampus with volume reduction
- Cingulate gyrus & orbitofrontal cortex volume reduction

Summary

- Neuroimaging in mood and other psychiatric disorders is an exciting area of research with a bright future.
- Neuroimaging in combination with other neurobiological and psychological approaches
- May be limited in diagnosis
- Development of more efficient and individually tailor-made treatment options.

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Thank You