The Medial Prefrontal Cortex in Bipolar Disorder

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Bipolar Disorder

- Bipolar disorder (BD) has protean manifestations – mania, depression, psychosis, catatonia, cognitive deficits.
- But single pathology – (treatment response, family history)
  - Dysregulation of emotional/cognitive/motor processing
  - Cellular/synaptic abnormalities
  - Glutamate and GABA systems
- The technology to measure neurotransmitter levels is now available, and may provide a window into the pathology in BD
The Functions of the mPFC

• Cognitive
  – Guidance of decision making (Nauta, 1971; Damasio, 1994)
  – Performance in the face of changing reward contingencies through the maintenance of a “central set” (Mishkin, 1984)

• Social
  – Guidance of social interactions (Myers et al, 1973)

• Visceral
  – ANS modulation (Neafsey, 1989)

• Reward
  – Sensory processing of food and other rewards (Rolls et al, 1999; Schultz et al, 1998); guidance of feeding related behaviors (Bayliss and Gaffan, 1991)
  – Intracranial self-stimulation (Rolls, 1975)
Summary of Connections

• Sensory stimuli (visual, somato-sensory, auditory, visceral, olfactory, gustatory) come into the orbitofrontal cortex and are evaluated for salience.

• Medial PFC elicits appropriate visceral/somatic reactions based on this salience.
The Subgenual PFC

- The cellular correlates of this reduction were studied in postmortem human brains using unbiased stereological counting techniques.
Öngür et al 1998

Graph showing the comparison of glial number across different conditions: Control, fMDD, fBD, oMDD, oBD, and Schizophrenia. The graph includes error bars indicating variability.
Metabolism - regulated by glial-neuronal interactions & coupled to synaptic
TE-averaged $^1$H MRS of Glutamate in Bipolar Disorder

• Subjects:
  – 11 adults with Bipolar I Disorder
    • 8 manic, 3 mixed
  – 17 healthy subjects

• Methods:
  – TE-averaged $^1$H spectroscopy at 4T
  – Single voxel acquisition
    • Anterior cingulate cortex
    • Parieto-occipital cortex

• Analysis
  – LCModel using simulated basis sets
  – Ratio to Cr as internal standard
  – No group difference in Cr
Single-voxel TE-averaged spectra from the anterior cingulate cortex in a control subject (left) and BD patient (right)

Öngür et al 2006
Reduced Glutamate and elevated GABA levels in mania

F(15,1):10.31, p=0.006; no effect of brain region, no brain region x diagnosis interaction

F(14,1):4.78, p=0.046; no effect of brain region, no brain region x diagnosis interaction

Öngür et al 2006
Subtype-Specific Alterations of γ-Aminobutyric Acid and Glutamate in Patients With Major Depression

Gerard Sanacora, MD, PhD; Ralitza Gueorguieva, PhD; C. Neill Epperson, MD; Yu-Te Wu, MPH; Michael Appel, MS; Douglas L. Rothman, PhD; John H. Krystal, MD; Graeme F. Mason, PhD

Arch Gen Psychiatry. 2004;61:705-713
Bipolar Disorder

• Abnormal amino acid levels in the cerebral cortex in mood episodes
• These levels provide a read-out of synaptic/metabolic activity
• No unifying theme has yet emerged about the synaptic abnormality in Bipolar Disorder
• Clinical relevance:
  – Antiglutamatergic agents as antidepressants
    • NMDA receptor antagonists
    • Riluzole
    • B-lactam antibiotics
  – ECT as an antidepressant/antimanic agent