Neuroanatomy & Neuroscience: Overview (I) & Mood Disorders (II)

PG2 Core Curriculum
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Neuroanatomy & Neuroscience in the PG2 curriculum

- Behavior, emotion, cognition, thought, perceptions -- the fundamental objects of a psychiatrist’s attention -- depend upon intact brain function
- “Our disorders are brain disorders” (largely)
- Our biological therapeutics target the brain
- Even psychotherapy produces brain changes

Neuroanatomy & Neuroscience in the PG2 curriculum

- Continued evolution in psychiatry will occur during your professional years, in
  - Diagnostics (?) descriptive -> pathophysiologic?)
  - Therapeutics (?) global -> specific brain regions?)
  - Theories & conceptual framework

There is a devil’s advocate position as well ....
CNS Building Blocks

CNS contains
- Neurons - ~100 billion*
- Glia ("glue") - ~1 trillion [much of neuropil]

Gray matter
- Cortical regions & Nuclei

White matter
- Tract, fasciculus, funiculus, lemniscus, peduncle … a rose by any other name …

* Global population ~6.5 billion humans as of July 13, 2005 (www.census.gov)

CNS Component Parts

CNS Macro Components
- White vs Gray matter vs structural changes (periventricular hyper-intensities shown here)
- Gray matter ~ processing units
- White matter ~ connects the network

Neurobiology: Functional aspects
- Synthesis - primarily in cell body
- Enzymes, structural proteins, membrane components, transmitters
- Need transport systems to convey to other parts (microtubules provide cytoskeleton and transport system)
- Any disorders come to mind?*

* Michaelis “Cytoskeletal Integrity as a Drug Target.” Curr Alzheimers Res 2005
Neurobiology: Functional aspects

• **Energetic demands**
  - Brain uses 20% of body’s energy
  - No major storage - must depend on an uninterrupted arterial supply (gluc & O₂)
  - Energy is primarily used to maintain the electrochemical gradients *
  - Functional Neuroimaging methods (PET, SPECT, fMRI) depend on coupling of neuronal activity to energy use to glucose uptake and to blood flow


In general, information flows electrically down the axon, then chemically across synapse. Multiple types of synapse are depicted.

Nolte The Human Brain... 2002

Neurobiology: Dendritic Spines

Dendritic spines on pyramidal cells (arrows).

Correlations:
* enriched environment
* antidepressants and mood stabilizers
* synaptic plasticity

Nolte The Human Brain: an introduction to its functional anatomy 2002: fig 1-15
White Matter Association Tracts

Long association bundles connect cortical areas and support network processing. “Disconnection syndromes” may underlie some cognitive and affective disturbances (Geschwind Brain 1965; Leuchter Brain 1992; Cook Arch Neurol 2002; Kumar & Cook Dev Neurosci 2002).

Nolte The Human Brain: an introduction to its functional anatomy 2002: fig 22-10

Bridging to the Macroscopic

Hemispheric Landmarks

Specific mental functions have been related to activity in specific brain regions.

Theories, diagnostics, and treatments of the future may depend on these relationships.

Haines. Neuroanatomy: an atlas of structures, sections, and systems. 2004

Somatotopic Organization

Penfield & Rasmussen. The Cerebral Cortex of Man. 1950.
Korbinian Brodmann’s Cytoarchitectural Map


Brodman Areas II

Brodman areas (BA) are frequently used in fMRI and other functional neuroimaging reports.


Talaraich Stereotaxic Coordinates

The coordinate system developed by Talairach and Tournaux (1988) provides a common space for comparing or combining data on individuals.

MRI and PET datasets often are transformed or “warped” using this system, though some limitations have been acknowledged.

www.neuro.spc.org/talaraic
www.mrc-cbu.cam.ac.uk/Imaging/Common/brodmann_areas.shtml

Cerebral Circulation (macro level)
Circulation & Watershed Infarcts

The distal branches of the anterior (green), middle (blue) and posterior (red) cerebral arteries overlap to create border zones ("watershed areas") which are susceptible to hypoperfusion-based infarcts.

Connections at the synapses

Electrical & Chemical Synapses

- Chemical synapses - molecules cross
- Electrical synapses - "gap junctions" connexin proteins form connexons to create aqueous pore, small molecules and currents pass directly.
  - Rare in adult mammalian CNS
  - Horizontal cells of retina
  - Charcot-Marie-Tooth disease - gap junction channelopathy

Small Molecule* Neurotransmitters**

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amines</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td></td>
<td>Monoamines</td>
</tr>
<tr>
<td></td>
<td>Catecholamines (dopamine, norepinephrine)</td>
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<tr>
<td></td>
<td>Serotonin</td>
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<td></td>
<td>Histamine</td>
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<tr>
<td>Amino Acids</td>
<td>Glutamate</td>
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<td></td>
<td>GABA (γ-aminobutyric acid)</td>
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<tr>
<td></td>
<td>Glycine</td>
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<tr>
<td></td>
<td>Aspartate, homocysteine, taurine</td>
</tr>
<tr>
<td>Others</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td></td>
<td>ATP</td>
</tr>
<tr>
<td></td>
<td>Adenosine</td>
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</tbody>
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* namely, < 10 carbons
** Neurons can employ endocytotic vesicle recycling for these
Neuropeptide* Neurotransmitters

- Opioid peptides
  - Enkephalins
  - Endorphins
- Posterior pituitary
  - Oxytocin
  - Arginine vasopressin
- Tachykinins
  - Substance P
  - Neurokinins
- Other
  - Angiotensin II
  - Neuropeptide Y
  - Corticotropin-releasing factor
  - Vasoactive intestinal peptide

* namely, \( \geq 10 \) carbons
** Peptidergic neurons generally do not employ endocytotic recycling

Mood Disorders

www.DepressionLA.com
www.MoodResearch.com

Outline

- Reminder: sources of data
- Specific brain regions show alterations in structure/function in mood disorder patients, but with heterogeneity
- Connected regions form circuits
- Activity levels change with treatment

Structural Neuroimaging Techniques

- Computed Tomography - opacity to x-rays
  - Acute change - hemorrhagic stroke, subdural, foreign body, mass effect from edema
  - Non-acute - cyst, tumor, agenesis, atrophy
  - Low cost, good resolution of bone/blood, rapid
  - Poorer resolution of brain, WM v GM, radiation dose
**Structural Neuroimaging Techniques**

- MRI - depends on chemical differences
  - Where type of tissue is critical - white matter hyperintensities (MS, ischemic), tumor delineation
  - Where individual anatomical differences matter - coregistration for functional measures
  - Higher cost, motion artifact issues

**Types of Functional Studies**

- Cerebral Metabolism
  - PET (positron emission tomography) with $^{18}$Fluorodeoxyglucose (FDG) - positrons -> 2 gamma rays
- Cerebral Perfusion
  - SPECT (single photon emission computed tomography) with $^{99}$Technetium-d,l-hexamethylpropyleneamine oxime (HMPAO) - first-pass perfusion, single gamma-ray
  - $^{15}$O PET - diffuses into brain in proportion to regional flow
  - functional MRI - Oxy/deoxy-Hgb provides signal
- Neurochemistry, with MR Spectroscopy
- Ligand Binding, with PET or SPECT
- Brain Electrical Activity

**Early Observations**

- Autopsy samples - some generalized atrophy and enlarged ventricles, but with little specificity for diagnosis
- For symptoms emerging after focal damage (stroke, tumor, traumatic brain injury (TBI))
  - Left hemisphere, frontal pole - “depressed”
  - Right hemisphere - “manic” (activated, irritable)

Reminder: Hemispheric Specialization

LEFT
- Syntax, comprehension, fluency
- Details of drawings
- Verbal memory
- Selective attention
- Math, logic
- Persecutory delusions
- Classification of things
- Illusions, hallucinations
- Music phonemes

RIGHT
- Pragmatics (“between the lines”) and prosody of language
- Visuospatial constructional
- Visual memory
- Sustained attention
- Nuance, gestalt
- Delusional misidentifications
- Individual variety of things
- Perceptual anomalies (metamorphoses)
- Appreciation of emotion of music

Adapted from Cutting J. The Right Cerebral Hemisphere and Psychiatric Disorders, 1990

3 Prefrontal Regions & Their Syndromes

- Dorsolateral - dysexecutive syndrome
- Orbitofrontal - disinhibition syndrome
- Anterior cingulate - apathy syndrome

Dorsolateral PFC

- Supramodal processing center
- Executive cognitive functions: “CEO” of the brain
- Dysexecutive syndrome:
  - Diminished judgment, planning, insight, temporal organization, sequencing, and abstraction
  - Perseveration
  - Decreased mental flexibility

Mega MS, Cummings JL. J Neuropsychiatry Clin Neurosci 1994

Lateral Orbitofrontal Cortex

- Mediates empathic, civil, and socially appropriate behavior
- Personality change if damaged (irritability, emotional lability, diminished social insight, tactlessness, undue familiarity, stimulus-driven behavior, disinhibition)
- Hyperfunctional in OCD

Mega MS, Cummings JL. J Neuropsychiatry Clin Neurosci 1994
**Anterior Cingulate Cortex**

- Mediates motivation behavior
- Personality change if damaged (apathy, diminished spontaneity, urinary incontinence, few movements, psychic emptiness, poverty of speech, slow response latency, impaired go / no-go performance)

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**Prefrontal-Subcortical-Thalamic Parallel Re-entrant Circuits Subserve Cognition & Behavior**

- Dorsolateral PFC
  - Caudate
  - Globus Pallidus, Substantia Nigra
  - Ventral Anterior & Medial Dorsal Thalamus
- Orbitofrontal
  - Caudate
  - Globus Pallidus, Substantia Nigra
  - Ventral Anterior & Medial Dorsal Thalamus
- Ant Cingulate
  - Nuc Accumbens
  - Globus Pallidus, Substantia Nigra
  - Medial Dorsal Thalamus

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**“Consistent” Findings in Unipolar MDD**

- Late-life: decreased volume (gray matter) and increased hyperintensities (WM)
- Decreased activity
  - Dorsolateral PFC (BA 9)
  - Anterior Cingulate (ACC, 24) and subgenual cingulate (25)
- Increased activity
  - Thalamus (Th)
  - Amygdala (Am)
  - Orbital PFC (11) and medial frontal (10)

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**Gray Matter Deficits in Late-onset MDD**

To determine the pattern of regional GM loss associated with late-onset MDD
17 MDD subjects with onset of illness >60yo and 17 healthy controls, group-matched for gender and age, examined with structural MRI and cortical pattern matching

Significant GM loss was found in right lateral temporal ctx and right parietal ctx, most pronounced in sensorimotor areas; left hemisphere approached significance; frontal regions not significant or trending.

Late-onset MDD may have a different neuroanatomic substrate than early-onset MDD

Ballmaier, Am J Psychiatry 2004
Findings in Bipolar Disorder

• Less consensus than with the unipolar literature
• Amygdala appears to be enlarged
• Subregional gray matter analyses -
  * L - smaller superior and mid frontal
  * R - smaller inferior and mid frontal
  appears to be driven by glial reduction

Altshuler Arch Gen Psychiatry 1998, Biol Psychiatry 2000;
Lopez-Larson Biol Psychiatry 2002; Rajkowska Biol Psychiatry 2001

Metabolism and Mood

Areas of higher (left panel) or lower (right panel) FDG uptake in depressed vs control subjects.

Metabolism in Unipolar MDD vs Bipolar/Depressed vs BAD/Manic vs CON (lower panel)

from Drevets Curr Opin Neurobiol 2001

Putative Circuits for Mood Regulation

Numerous regions participate in mood regulation

from Drevets Curr Opin Neurobiol 2001

Putative Circuits for Mood Regulation

Seminowicz Neuroimage 2004

from Mayberg Am J Psychiatry 2002
The Next Generation Of Shock Therapy

Wall Street Journal 10/18/05

The Human Brain: an introduction to its functional anatomy

2002: fig 22-10

Long association bundles connect cortical areas and support network processing. “Disconnection syndromes” may underlie some cognitive and affective disturbances (Geschwind Brain 1965; Leuchter Brain 1992; Cook Arch Neurol 2002; Kumar & Cook Dev Neurosci 2002).

Nolte The Human Brain 2002: fig 22-10

Tractography (DTI)

Meta-analysis examination of MRI studies of hippocampal volume in mood disorder

12 studies in unipolar depression had examined 351 patients and 279 healthy subjects

Depression was associated with an 8% reduction in hippocampal volume on the left (top) and 10% reduction on the right side (bottom)

Videbech & Ravnikilde Am J Psychiatry 2004

Hippocampal Volume and Depression: A Meta-Analysis of MRI Studies

Tractography (DTI) from Taylor Biol Psychiatry 20024

White Matter Association Tracts

from Taylor Biol Psychiatry 20024
Untreated Depression and Hippocampal Volume Loss

Study of relationship of hippocampal volume to duration of illness and to duration of untreated illness in MDD

Hippocampal volume was measured with MRI in 38 women with recurrent MDD in remission

Duration of untreated illness is better predictor of volume loss than overall illness, suggesting treatment may be neuroprotective

Sheline Am J Psychiatry 2003

Hippocampal Volume and First Major Depressive Episode After Cancer Diagnosis in Breast Cancer Survivors

Study of whether hippocampal volume was associated with developing a first episode of major depression after being diagnosed with breast Ca

Hippocampal volume was measured with MRI in 68 female survivors of breast cancer: 17 with a first MDE after dx, and 51 with no lifetime dx

First major depressive episodes after cancer diagnosis in female cancer survivors do not appear to be associated with hippocampal volume

Inagaki Am J Psychiatry 2004

Regional Brain Activity in MDD Tx

Study of changes in brain metabolism during treatment for MDD with paroxetine or interpersonal therapy (IPT)

24 MDD and 16 controls had FDG-PET before and after 12 wks of treatment

PAR - bilateral PFC decr
IPT - Right PFC only
Both groups - L Ant cing decr

Two interventions yield some similar yet some contrasting patterns of change in brain activity

Brody Arch Gen Psychiatry 2001

Regional Brain Activity in Women Grieving a Romantic Relationship Breakup

Study of grief - sadness - depression using fMRI in women grieving a breakup.

Contrast: recalling their loss vs thinking a neutral through about another person known for a similar length of time

Increases posteriorly (occipital, post temp-par, post brainstem)
Decreases anteriorly (cingulate, thalamus, PFC, striatum, temporal ctx, ant brainstem)

Najib Am J Psychiatry 2004
Physiologic Predictors of Response in MDD

Use of a novel QEEG measure that is correlated with regional perfusion, to study changes in activity during treatment for MDD

51 adults with MDD studied during a 9 wk treatment trial with FLU or VLX vs PBO. QEEG cordance measured at baseline, 48hr, 1wk, 2/4/8 wks of tx.

Prefrontal decreases uniquely characterized the med responders. Physiologic changes emerged as early as 48 hrs into treatment; extent of physiologic change was correlated with extent of final outcome

\[ r=0.51 \ p=0.002 \]


MRS in SSRI Discontinuation

Study neurochemical changes associated with discontinuation of an SSRI medication ("drug holiday")

13 subjects with MDD stabilized on FLU and 13 on PAR underwent PBO substitution for 1 week

Plate A: voxel placement in rostral anterior cingulate
Plate B: spectra while on paroxetine (lower trace) and after 3d on PBO (upper)

Ch:Cr ratio was decreased in subjects reporting discontinuation symptoms, compared with asymptomatic subjects

May reflect altered activity in ACC associated with discontinuation syndrome

Kaufman Biol Psychiatry 2003