Advances in Neuroscience Applications to Clinical Practice

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Part I

- Update on Network Theory
- Update on Neuroimaging

Selected References

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Overview

- The new neuroscience of the 21st century
  - How neuroimaging has altered our understanding of the human brain
  - Advances in single unit recordings
  - Combined to lead to understanding of processing networks

  - With increased understanding of synaptic processes in learning LTP, genes, proteins, and disease
  - And neuroplastic capabilities from infancy through adulthood

The problem

- Where have all the Loci gone?
  - Why lesions matter less than recovery mechanisms
  - The new links between cognitive neuroscience, systems neuroscience and imaging neuroscience applied to rehabilitation

Old lesions studies used in localization replaced by imaging

- New imaging techniques and single unit response research provide new data
- New Data on how brain regions work simultaneously - networks
- New Data on how these networks develop and become wired - neuroplasticity

Led to advances in Network Theory

- Network theory is an expansion of connectionistic theory that:
  - Was proposed after early neuroimaging results (PET and MEG scanning) revealed that distributed cortical regions fire in parallel and simultaneously during standard cognitive tasks like language processing
  - Based on Hebbian stance that – neurons that fire together wire together

Dorsal and Ventral Language processing networks

- The cortical organization of speech processing
  - *Gregory Hickok and David Poeppel*
  - ***NATURE REVIEWS NEUROSCIENCE*** VOLUME 8 | MAY 2007 | 393

Hierarchical organization of human behavior (Koechlin and Jubault, 2006)

But… the questions remains

- What about cortical thickness – does that change with age and experience?
- How do the cortical areas communicate with each other
  - How do the major subcortical networks develop the links
  - What is the role of genes vs. experience
- How can that be visualized with fMRI

Brain Morphometry

Mapping of Cortical Thinning with Longitudinal MRI Data

Gogtay et al., PNAS, 2004

Longitudinal Mapping of Cortical Thickness and Brain Growth in Normal Children

(Sowell et al.,J. Neurosci., 2004)

The role of fiber tract connections

Diffusion Tensors and Development

Diffusion Tensor Imaging

- Measures diffusion (motion) of protons in water molecules.
- Direction of proton motion within a voxel can be described by a "tensor".
- Proton diffusion tends to be relatively isotropic in gray matter.
- The linear structure of fiber tracts constrains proton diffusion and produces **anisotropy**.

Fiber Tract Development Observable with DTI

(from Hermoye et al., 2006)

Learning to Juggle Produces Transient Change in Cortical and Tract Morphology

(Draganski et al., Nature, 2004; Scholz et al., 2009)

- Normal volunteers with no juggling skills were scanned at baseline.
- Subjects were taught a simple juggling task to criterion and re-scanned.
- After 3 months (Draganski et al.) or 4 week (Scholz et al.) without practice, jugglers were scanned a third time.
- Focal increases in gray matter were observed in middle temporal and left intraparietal sulcus areas, FA was increased in underlying white matter, and these were apparently diminished after 3 months.

Summary

- Although the changes may be visually subtle, when examined closely, the brain exhibits a complex pattern of age-associated and damage-associated tissue alterations well into adulthood.
- We are just beginning to understand the biology and the role that these dynamic changes play in evolving/recovering mental functions
- We are also just beginning to understand how neuroplastic changes occur after injury.

PSHA part 2

Part II

Etiological Issues

Part II

- 10:45 - 12:14 Etiological issues
- * Autism spectrum disorders
- * Apraxia and Aphasia
- * Cognitive disorders
- * Update on Neuroplasticity

Selected References

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- Zilles, K and Amunts, K (2010) Centenary of Brodmann's map – conception and fate. *Nature Reviews Neuroscience* **11**(2) 139-145

Overlap of Autism and SLI Across the Genome

-early research

Autism
13q21
CLSA 1999,2001
7q
IMGSAC 1998, 2001
CLSA 1999, 2001
Alarcon et al. 2002 (Onset of Word QTL)
2q Bauxbaum et al 2001 Shao et al 2002, IMGSAC 2002

New genetics research, Smalley, 2007

Abrahams and Geschwind (2008) Advances in autism genetics: on the threshold of a new neurobiology

Figure 1 | **Loci implicated in ASD etiology.** Entries in the ID column of the table map link entries to the ideograms of individual chromosomes.
Red and yellow bars correspond tode novo losses and gains, respectively, that are observed in cases but not in controls.
Green bars correspond to genes that are observed to modulate autism spectrum disorder
(ASD) risk (either through a rare syndrome or genetic association): light green and dark green bars represent promising or probable candidate genes, respectively

ASD Related Syndromes (Abrahams and Geschwind, 2008)

- Fragile X
- Angelman Syndrome
- Joubert Syndrome
- Rett Syndrome
- Timothy Syndrome
- Tuberous Sclerosis
- Cortical Dysplasia Focal Epilepsy
- Potocki-Lupski
- Smith Lemli Opitz

Brain Development

- Sensory and Motor skills
- Language
- Memory
- Executive Function

Auditory Processing Disorders

- Genetics
- Linked to early exposure to:
  - Noise
  - Environmental Toxins (PCB's PDBE's)
  - Chronic Otitis Media

New research on causes

- Origins of human impairment and illness
  - Merzenich, 2003 – animal research
  - A1 processing is "specialized" as the infant is exposed to specific sound stimuli – auditory cortex maps
  - Perinatally generated maps can be distorted and persist into adulthood
  - Variations occur depending on
    - Input modulation rate
    - Input intensity
    - Complexity of stimuli
    - Continuous noise

The critical period is the cortical 'setup' epoch – Merzenich, 2006

- **Early exposure drives and shapes the initial form of the cortex's processing machinery.**
- **That machinery is "specialized" to process environmental inputs.**
- **In babies, the primary sound processing specialization is for the child's native language.**
- **Cortical specialization crucially enables the development of selective attentional control.**

The critical period is the cortical 'setup' epoch – Merzenich, 2006

- **Cortical specialization generates important functional changes that enable subsequent skill learning.**

- **At the end of the critical period, cortical maturation is paralleled by (causes) the maturation of modulatory control systems that results in the subsequent dominance of attentionally-controlled plasticity.**

- **From the end of the critical period forward to the end of life, cortical plasticity is powerfully gated by these modulatory control systems.**

Variations occur by…

- input modulation rate
- input intensity
- Complexity of stimuli
- pulsed noise, variable rate
- continuous noise

Four ways to degrade sensory cortex (aural language and somatosensory cortex) development

- structured noise **Zhang et al (2004) PNAS**
- continuous, unmodulated noise **Chang et al (2003) Nature Neurosci; Chang et al (2005) PNAS**
- perinatal anoxia **Strata et al (2005) PNAS**
- non-coplanar PCBs (PBDEs?) **Kenet et al (2006) submitted, Nature Medicine**

A1 does not mature in infants raised in continuous noise

- In continuous noise reared rats, the critical period remains open indefinitely

Aphasia and Apraxia

- Very complex processes
- Related to language as well as praxis
  - Tool use
  - Sequential processing of motor acts
  - Speech/language is just one
- OT, PT, Speech – we should be working very closely with each other

Basics: anatomy and physiology
So, what does Broca's area do?

- Damage to this region alone does not cause Broca's aphasia
- In particular, it is clear from lesion studies that no one brain region can account for Broca's form of language disturbance.

So what do these regions actually do?

- Action recognition and imitation (mirror neuron role) – to be discussed later
- Production of actions (Bonda, et al., 1995; Parsons, et al., 1995)
- Hierarchical organization of behavior (Koechlin and Jubault, 2006) – see next slide
- Movement preparation and imagination (Thoenissen, Zilles, & Toni, 2002)
- Local visual searching (Fink et al., 2006)
- Visual spatial cognition (Sluming et al., 2007)

Hierarchical organization of human behavior (Koechlin and Jubault, 2006)

Helen Neville, 2010

- Findings on the overlay of language to the motor sequences of tool use
- Video

More recent data

N. T. Sahin et al., Science 326, 445-449 (2009)

Intracranial electrophysiology (ICE)

(Sahin, et al., 2009)

- Recorded local field potentials from populations of neurons using electrodes implanted in language-related brain regions while people read words verbatim or grammatically inflected them (present/past or singular/plural)
- Neighboring probes within Broca's area revealed distinct neuronal activity for lexical (~200 milliseconds), grammatical (~320 milliseconds), and phonological (~450 milliseconds) processing, identically for nouns and verbs, in a region activated in the same patients and task in functional magnetic resonance imaging

Cognitive Disorders

- So what is….
  - Dyslexia?
  - Agnosia?
  - Acalculia?

Possible functions mediated by the two pathways connecting visual processing centers (Kandel, 2000)

So what about reading?

Stroke causes disconnection syndromes

- See especially Mesulam, 2000

Stroke recovery processes

- Murphy T & Corbett D (2009)*Nature Reviews Neuroscience***10**, **861-872**

Summary
Murphy, T. and Corbett, D. 2009

- The timing of rehabilitation
  - designed to optimally engage neuroplasticity processes during critical period of early post-stroke recovery phase,
  - With sustained upregulation of growth-promoting genes predominating (solid red line in part **d**).
- Most growth-inhibitory genes (solid green line) tend to be upregulated gradually,
  - several weeks after stroke,
  - towards the end of the critical period of stroke recovery.
- A few growth-promoting and growth-inhibiting genes are transiently upregulated (dashed lines) in the early and mid post-stroke recovery period.

Summary (cont)
Murphy, T. and Corbett, D. 2009

- Post Stroke critical period observed in animal studies might be quite different from that of human stroke, where spontaneous recovery can extend for the first 90 days after injury.
- Most evidence suggests that in humans earlier rehabilitation is better,
- …but we direct readers to other work - Dromerick, A. W. *et al*. **Very early constraint-induced movement during stroke rehabilitation (VECTORS): a single-center RCT**. ***Neurology*** **73**, 195–201 (**2009**). .

Functional & physical changes associated with normal aging are broadly reversible

UCSF.

AFTER CHRONIC NOISE EXPOSURE, the cortex functionally resembles that of an infant rat that has had little or no auditory experience!

And the ‘critical period’ re-opens

On this basis…

- **We have extended studies to include a documentation of learning-driven changes in the frontal cortex.**
- **We have turned our focus to processes/mechanisms that support memory association, sequencing, syntax & ‘prediction’**
- **We’ve discovered (we think) an effective strategy for recovering stronger ‘background suppression’ (the suppression of ‘non-targets’, or ‘distractors’).**
- **We’re extending (more than doubling) our functional & physical indices of ‘impairment’.**
- **We’re building tools (and others) into next-generation training programs.**

DEMO – rehabilitation programs