Studying structure-function relationships in the human brain

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• Historical background
• Experimental design
  – From “faculties” to component processes to information represented in neural tissue…
• Cognitive neuroscience methods
  – Methodological advantages & disadvantages
  – Inferential strengths and weaknesses
• The case for converging methods
• An overview of lesion methods
• The challenges of converging methods
Cognition & the brain

• The brain or the heart as the seat of the mind?
  – Observations of the effects of head injury by physicians and philosophers, including Hippocrates and Galen, argued for the brain
    • Galen, and many after him, focused on the ventricles and CSF as critical
    • Descartes helped to shift the focus towards the brain matter, although still in its interaction with CSF
    • The development of sensory-motor physiology, first at the spinal level, and then moving up to the brain through the 18th and 19th centuries, began in earnest the study of the brain’s role in perception and action.
The brain as a whole, or as a set of parts?

- Cerebral localization, c. 19th century
  - An extension of sensory-motor physiology
    - Experimentally: Hitzig, Ferrier
  - Applied to cognition
    - Conceptually: Franz Josef Gall (phrenology)
    - Clinically: Broca, Wernicke
- Holism, localism, connectionism
Holism

• Cortex as “equipotential”
• Flourens a prominent proponent (mid 19th century), a critic of Gall’s phrenology (a form of localization)
• A position more comfortable to many given the religious view of the soul as unitary
Localism

- Franz-Josef Gall:
  - 27 basic human faculties ranging from memory to vanity to love for one’s offspring
  - Localized to specific parts of the brain
    - (In turn identifiable through examination of the skull)
  - Sources of evidence: clinical cases, individual differences, animal models

- Bouillaud, Broca:
  - “the second and third frontal convolutions … as the seat of the faculty of language”.
  - Evidence: clinical case with pathological correlation
  - (Early views regarding lateralized functions)
Connectionism

• Localism in more detail:
  – Technological advance: Stimulation experiments in animal models (Hitzig, Ferrier)
    • E.g. establishing somatotopic organization of sensory & motor cortex
  – There were explicitly linked to clinical-pathological correlations in humans

• Wernicke:
  – Detailed study of aphasia syndromes
    • Component processes of language
Language supported by specialized and interconnected centres in the brain

Speech production

‘sound images’

Non-fluent aphasia
Fluent aphasia
Global aphasia
Conduction aphasia
Connectionism back to holism

• Hughlings Jackson & others:
  – Connections and hierarchical organization too complex to be understood ‘piecemeal’

• Another technological advance:
  – Microscopy demonstrating cytoarchitectonic structure that strongly supported localism
The development of a neuroscience of human cognition

- From case studies to experimental neuropsychology
  - Systematic studies of groups of patients
  - Statistical methods, more rigorous measurement of behavior
  - Addressed questions of
    - Localization (of abilities, of ‘task performance’)
    - Functional organization of behavior

- Cognitive psychology meets clinical neuropsychology in early 1980’s: cognitive neuroscience
  - Bringing theories/models of cognition to the brain, and clinical observations and explanatory frameworks to psychology
    - Component processes of ‘abilities’, understood at the level of information processing, implemented in neural tissue
The goal of cognitive neuroscience

- “To understand the mechanisms that underlie cognition
  - i.e. To identify the causal chain of neural events that produce cognition”

Methods of Cognitive Neuroscience

• Studying effects of ‘loss-of-function’
  – Lesion studies
  – Pharmacological manipulations
  – Transcranial magnetic stimulation (TMS)

• Observing brain activity and its relationship to (experimentally manipulated) behaviour
  – Functional imaging (fMRI, PET)
  – EEG methods (event-related potentials, intra-operative recordings, MEG)

• Developing detailed models of cognitive processes (and their relationships to the brain)
  – Computational modelling
General inferential pitfalls

- Defining component processes
- Operationalizing those processes
- Individual variability in structure-function relationships
- The assumption of one-to-one structure-function relationships
- *Ceteris paribus* assumptions
cognitive neuroscience ≠ functional neuroimaging
Method-specific inferential issues

- Functional imaging provides information on *correlation* - i.e. between regional brain activity and the occurrence of a particular process
  - Causal?
  - Optional?
  - Epiphenomenon?

- Lesion methods provide information about causality
  - That the integrity of some brain region is *necessary* for a particular process
These methods are complementary

- Functional imaging
  Study of the normal brain
  Relatively good spatial resolution
  The opportunity to study network properties

- Lesion studies
  Abnormal brain
  (potential issues of reorganization)
  Relatively coarse spatial resolution
  ‘Natural’ tendency to localism
  Although newer methods in group studies partially address all of these issues
Lesion study designs

- Single case
  - Can be powerful (think H.M.)
  - ‘Existence proof’
  - But prone to idiosyncratic effects, may be hard to generalize with much confidence, not so useful for processes where behavioural effects are more subtle

- Group studies
  - Region-of-interest designs
  - Behavior-of-interest designs
  - Voxel-based lesion-symptom mapping
Lesion methods: structure

• Anatomical imaging: MRI (DWI, DTI), CT
• Spatial normalization:
  – Template methods, manual methods, automatic methods
• A priori region of interest groups
• (Post hoc) overlaps based on behaviour
• Statistical maps of lesion-behaviour relationships
Lesion methods: Function

• Tasks must measure the process of interest
• ‘non-specific’ effects of brain injury make careful choice of control tasks vital
• Small samples make careful choice of control groups vital as well
Lesion methods: general

• Acute vs chronic damage
• Cause of damage
  – Stroke
  – Tumour resection
  – Epilepsy surgery
  – Trauma
• Co-morbidity, treatment effects
• Access to patients
  – McGill Cognitive Neuroscience Research Registry
An example of ROI design

Tsuchida et al., in prep
Voxel-based lesion symptom mapping

Tsuchida et al., in prep
Tsuchida et al., in prep
An example of disconfirming evidence: Conflict monitoring and ACC

Fellows & Farah (2005) *Brain*
An example of converging evidence: Error monitoring and ACC

Modirrousta & Fellows (2008) *JNeurosci*
The importance of converging evidence

- All methods have unique strengths and weaknesses
- The overall goal of cognitive neuroscience requires clear theories of brain function, supported by converging evidence from complementary methods
- This requires:
  - ‘Cross-training’
  - Collaboration
  - Thoughtful review of the literature
‘Dysfunctional imaging’: Lesion methods in the 21st century

17 April 2010
A one day meeting on the latest advances in lesion-symptom mapping and related topics, right here at the MNI.