Neuropsychology of the Frontal Lobes and Other Stories

Robert Bilder
Not much has changed in the last billion years…

- Basic input-output organization
- Sensory apparatus
- Effector apparatus
- More or less complex links between perception and action
- Slightly elaborated in humans…
If I only had a brain… I sort of do!
(but not a thalamus or basal ganglia yet)
The amazing tunicate
Brain Evolution, Elaboration on Basic Input-Output Plan

1 billion years and 100 billion cells later...

Evolution → MacLean 1990

Hill et al., 2010
Frontal Lobe Anatomy

- Medial Frontal Gyrus (BA 6 posterior, 8 anterior)
- Superior FG (6,8,9,10,11; posterior to anterior as your curve around the frontal pole)
- Middle FG (6,8,9,46,10,11)
  - 6: posterior;
  - inferior bank of SFS: p-a 8,9,10,11
  - Superior bank of IFS: p-a 9,46,47
- Inferior FG (44(opercularis) 45(triangularis) 47 (orbitalis)
- Gyrus Rectus (11); orbital gyrus (lateral to GR; 11(12)-47, connects with IFG-orb)
Key to Function: Frontal Lobes are Well Connected!

• Frontal division recapitulates thalamic anatomy
  – One method for defining cortical regions relies on the thalamic projection system
• Frontal “circuits” more important than frontal “regions”
• Frontal “systems” mediate activation states across the entire brain
<table>
<thead>
<tr>
<th>NUCLEUS</th>
<th>MAJOR INPUT</th>
<th>MAJOR OUTPUT</th>
<th>FUNCTIONS</th>
<th>FUNCTIONAL CLASS</th>
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<tbody>
<tr>
<td>Anterior</td>
<td>from mammillary body of the hypothalamus</td>
<td>cingulate gyrus of limbic lobe</td>
<td>mediates visceral, emotional information</td>
<td>specific, limbic</td>
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<td>Ventral Anterior</td>
<td>globus pallidus, substantia nigra and intralaminar and midline thalamic nuclei</td>
<td>premotor and primary motor cortices</td>
<td>motor</td>
<td>specific motor</td>
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<td>Ventro-lateral</td>
<td>Contralateral cerebellar hemisphere through superior cerebellar penduncle, globus pallidus</td>
<td>primary motor cortex</td>
<td>motor: coordinates basal ganglia with cerebellum</td>
<td>specific motor</td>
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<td>Ventral Posterior (lateral and medial)</td>
<td>spinothalamic tracts and medial leminscus (medial=trigeminal nerve)</td>
<td>postcentral gyrus</td>
<td>somatosensory</td>
<td>specific, sensory</td>
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<td>Lateral Geniculate</td>
<td>retinal ganglion cells</td>
<td>Lingual and cuneate gyri of the occipital lobes</td>
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<td>specific, sensory</td>
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<td>Dorso-medial</td>
<td>Prefrontal cortex, substantia nigra, amygdala, hypothalamus</td>
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<td>Pulvinar</td>
<td>primary associational visual cortex</td>
<td>inferior parietal cortex (association cortex)</td>
<td>language formulation, language processing</td>
<td>specific, associational</td>
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<td>Centromedian</td>
<td>globus pallidus, vestibular nucleus, superior colliculus, reticular formation, spinal cord, motor / premotor cortices</td>
<td>basal ganglia and thalamus</td>
<td>modulates excitability of cortex (cognitive) and overall functions of basal ganglia (sensorimotor)</td>
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<td>Reticular</td>
<td>thalamocortical projections</td>
<td>thalamic nuclei and reticular formation</td>
<td>integrates and regulates thalamic neuronal activity</td>
<td>non-specific</td>
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</table>
Corticostriatal Loops
Alexander, Delong, and Strick, 1986
Hierarchic Organization of Cortex and the Perception-Action Cycle

Fuster 2004
The Action-Perception Cycle: Overview
Novelty Yields Shifts in Brain State

Perceive novel input

Stabilize new action plan
When a New Plan Works it is Stabilized and Leads to Action

Stabilize new action plan

Perceive novel input
Neuropsychological Syndrome Analysis a la Luria & Goldberg

- Modular and gradiental organization of neocortical systems
- General roles of 1°, 2°, and 3° divisions
  - 1° - receptotopic/projectotopic organization; Modality specificity; Damage leads to modality specific functional loss (scotoma, anesthesia, acoustic discrimination)
  - 2° - higher order, still modality specific. Categorical stimulus identification; Recognition of specific exemplars fo generic categories; Damage leads to associative "symbolic" agnosias
  - 3° - associative, modality non-specific
Anterior Gradients: Motor-Prefrontal

• **M-1°** - Area 4: somatotopic organization; modality specificity; damage leads to modality specific motor loss (paresis)

• **PM-2°** - Area 6, 8 (partial): higher order, still modality specific. Lesions lead to disorder of sequential, kinetic organization of skilled movements ("melokinetic" or "limb kinetic" apraxias.

• **PF-3°** - Areas 9, 10, and 8 (partial), 44-47: associative, modality non-specific. Supramodal (pervasive) perseveration, aspontaneity (inertia of initiation or termination), field-dependent
Consider Broca's aphasia(s):

- kinetic speech disturbance "speech apraxia" (inf. Premotor, Area 6)
- agrammatism (pars opercularis, Area 44) "syntactic agrammatism" - semantic representation of action; defects in use of verbs and action names
- dynamic aphasia (pars triangularis, Area 45) - impairment in initiation of communication; thematic perseveration
Tests of Motor and Premotor Function

- Finger Tapping Test, Purdue Pegboard, Grooved Pegboard, Pin Test
- Bimanual Coordination and Dynamic Praxis (tests for disdiadochokinesia)
- Tests of articulatory agility and buccolingual praxis (e.g., BDAE Oral Agility subtest)
Neuropsychological Testing of Executive Functions

- WM tests
  - Manipulation or “working with memory”: Trails B; digits backwards vs forward; N-back; updating
  - Maintenance: ACT, SWM, various exp. tasks
- Reasoning/problem solving: Matrices; WCST, Categories, etc
- Generation (word; design)
- Tests of response inhibition (Stroop; go-no-go; alternations ala Luria; Stop-Signal) and reversal
- Memory
  - Attention/ initial processing vs retrieval; the role of recall vs. recognition procedures; source memory
Tests of Sensitivity to Reward and Interpersonal Factors

- Iowa gambling task (Bechara et al 1994)
  - Patients with ventromedial PFC lesions make bad decisions
  - Lack of sensitivity to bad consequences that usually steer away from actions with bad outcomes? Lack of “somatic markers”? 
  - “Myopia for the future”? 

- Theory of mind tasks (Frith, others)
The Anatomy of Cognitive Control

• The riddle of the frontal lobes
  – Once thought to be ‘silent’, lesions produce ‘no defect in the intellect’
  – Later seen as the ‘biological basis of intelligence’

• What do they do?
• How do they do it?
The Anatomy of Cognitive Control

• Frontal lobe structure-function relations
• Frontal projections influence activity throughout the rest of the brain
  – Role in generating “expectations” about the future
  – Role in determining the stability and plasticity of cortical activation states
• What can go wrong in frontal function and its connections
Frontal Cortex and Reward-Guided Learning and Decision-Making

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²Centre for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK
³Computation and Neural Systems, California Institute of Technology, 1200 E. California Boulevard, Mail Code 136-93, Pasadena, CA 91125, USA

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DOI 10.1016/j.neuron.2011.05.014
Figure 1. Frontal Brain Regions in the Macaque Involved in Reward-Guided Learning and Decision-Making

vmPFC/mOFC, ventromedial prefrontal cortex and adjacent medial orbitofrontal cortex; lOFC, lateral orbitofrontal cortex; ACCs, anterior cingulate cortex sulcus; ACCg, anterior cingulate cortex gyrus; aPFC, anterior prefrontal cortex.
vmPFC/mOFC

• Activation of this region associated with the “value” of the reward
  – Note: Concept of positive and negative prediction error
• Probably represents both positive and negative values, with decreases in signal representing loss
• Decrease signal also associated with delay before reward is given (consider delay discounting)
Lateral OFC (lOFC)

- More activated by punishment or non-reward?
- “Credit assignment”; i.e., association of value to a specific stimulus based on entire history of experience rather than most recent experience
- Example: monkeys trained with peanuts and raisins – after one is ‘devalued’ (by overfeeding) the lOFC lesioned animals failed to pick the stimuli that would give them the preferred food
Anterior PFC (aPFC)

• “Counterfactual” choices and the aPFC
  – aPFC encodes value of alternative options NOT chosen
  – Could this be the value of alternate choice, for some future action?
  – Activity in aPFC (also some ACC and PCC) predicts switching on future trial

• Represent number of alternate choices?
Anterior Cingulate Cortex (ACC)

- Representation of Action-Reward associations?
- Cost-benefit decision-making (particularly with respect to evaluating costs of actions (i.e., effort)
- Maybe ACC encodes ‘effort’ while vmPFC/mOFC encode delay costs?
Frontal Lobe Functional Divisions: The Dorsal-Ventral Dilemma

• Neurologic tradition: dorsolateral vs orbitofrontal (Benson)

• Neuropsychological tradition: dorsomedial, dorsolateral, orbitofrontal/basal (Luria)

• Processing distinctions:
  – initiation vs suppression (Fuster)
  – what? vs where? (Mishkin/Ungerleider)
  – willed intentions vs stimulus intentions (Frith)
Dorsal-Ventral Frontal Distinctions: Another View

• Dorsal frontal: hierarchically higher order modulation of somatomotor effector systems
  – Via projections to primary motor cortex, pyramidal motor system

• Ventral frontal: hierarchically higher order modulation of visceral-autonomic effector systems
  – Via projections to anterior temporal, amygdala, and lateral hypothalamic systems
Prefrontal Syndromes
Joaquin Fuster

• Dorsolateral (Areas 8, 9, 10, 46)
  – Loss of selective and “intensive” attention (associated w/ low drive and awareness), planning problems, language problems (L)

• Orbital (Areas 11, 13)
  – Distractibility, utilization behavior, pseudosociopathy

• Medial/Cingulate (medial 8-10, 12, 24, 32)
  – Apathy, disorders of coordinated movement (cf. Luria who described “oneiroid” states)
Patricia Goldman-Rakic (dec. 2003)
Definition of highly organized topographically precise columnar organization of fronto-parietal projections

Figure 2. The Photograph of Columnar Inputs to the Principal Sulcal Prefrontal Cortex
Goldman-Rakic – Classic Studies of Oculomotor Delayed Response
• DLPFC and working memory (Nystrom et al ‘00)
Prefrontal Disorders
Joaquin Fuster

• Attention-Perception
  – Low alertness; sensory neglect, distractibility, disorders of visual search/control, difficulty w/ sustained attention, internal interference, defective set maintenance

• Motility
  – Hypokinesia, hyperkinesia (?posterior orbital?)

• Memory
  – Organization, monitoring, temporal integration, ‘source memory’
Prefrontal Disorders
Joaquin Fuster

• Planning
• Intelligence
• Temporal integration
• Language
• Affect and emotion
  – Apathy, depression, euphoria, social and emotional behavior
Heterogeneity of Frontal Lobe Structure

• Sulco-gyral patterns
• Cytoarchitectonic divisions, laminar organization
• Connectional anatomy
• Evolutionary (comparative) anatomy

➢ Dual Trends Theory: Neural systems solution based on comparative anatomy, cytoarchitectonics and connectional anatomy
Dual Trends Theory: History

- Dart (1934 - reptiles), Abbie (1940 - marsupials): suggested dual origins of cortex
- Sanides (1969 - mammals, including primates): architectonic duality
- Pandya and colleagues (1985 - present): primates - modern architectonic and connectional anatomy
Dual Trends Model: Derivation and Differentiation

• Primordial derivation
  – archicortical: “hippocampal” - dorsal-medial
  – paleocortical: “olfactory” - ventral-lateral

• Architectonic differentiation
  – most primitive: allocortex (3 layers)
  – more differentiated: periallocortex, proisocortex (4 or 5 layers)
  – most differentiated: isocortex (6 layers)
  – within isocortex, 1°  2°  3°
Figure 2. (A and B) Diagrammatic representations depicting the evolution of cortical areas from two moieties, archicortical (hippocampus) and paleocortical (olfactory). (C) Block diagram showing the successive steps in the two cortical architectonic trends. OLF, olfactory cortex; PAll and PALL, periallocortex; Pro, proisocortex.
Dual Trends: Overview for the Spatially Gifted

From Pandya, 1999
Figure 15. Diagrammatic representations of the three visual association regions of the inferotemporal cortex (A) and their long association connections to the frontal lobe (B). (C) Long association connections to the frontal lobe of areas subserving peripheral vision (PV) on the medial, dorsal, and ventral surfaces of the cerebral hemisphere.
Fronto-Posterior Anatomic Circuits

- Every post-Rolandic region maintains organized projections with a corresponding frontal subregion (Pandya, Goldman-Rakic)
- Duality in posterior sensory systems (archi vs paleo) is paralleled by duality in frontal effector systems (archi vs paleo)
- Level of differentiation is honored between frontal and post-Rolandic regions
Putting it all together…

• Connections within and between trends over fronto-posterior networks forms a neural substrate for autoregulatory processes
  – Within trends (short range): hierarchically organized re-representations at different levels
  – Between trends: archicortical and paleocortical contributions at similar levels of processing
  – Fronto-posterior: sensorimotor contributions to integrated perception-action cycle
Cortico-Cortical Connections Within and Between Dual Trends

Archicortical - Dorsal/Medial

Frontal

Paleocortical - Ventral/Lateral
Fronto-Posterior Resonant Architecture Supports Adaptive Tuning of Network Function

• Frontal - plans, “expectations”
• Posterior - stimuli, “reality”
• Resonance: concordance in targets of converging projections
• Compare Grossberg: Adaptive Resonance Theory (ART) networks
Adapative Resonance Theory (ART 1)
Network Function: Resonance Success

- Top down ($F_2 \rightarrow F_1$) = expectation
- Bottom up ($F_1 \rightarrow F_2$) = reality
- $F_1$ nodes that represent intersection of $F_2$ with $F_1$ are preserved (adaptive resonance is achieved)
Summary of Cortico-Cortical Resonance

• Resonant circuits between trends within each modality and effector system, at similar levels of processing
• Organized feed-forward and feed-back connections across levels of processing
• Enables rapid correction of minor mismatch between expectation and inputs
• Automatic ‘error correction’ and refinement of input representations based on expectations (and vice versa)
But what if something truly unexpected happens?

The scientific merit of your application was judged by the review committee not to be within the upper half of the applications that it reviewed. Therefore, the application was not scored.
ART – Resonance Failure

• If difference between F1 and F2 is large (resonance failure)
  • Then mismatch signal (A) cannot be inhibited
  • This causes “reset” of F2
Cortico-cortical and cortico-limbic mechanisms for autoregulation

- Cortico-cortical (minor resonance failures)
  - cortico-cortical interactions between trends, yields adjustments to existing activations
  - enables smooth transitions between subtly different activation states

- Cortico-limbic (major resonance failures)
  - limbic "amplification" produces massive cortical "reset"
  - enables dramatic shifts of activation states
Duality in Fronto-Limbic Projections

- **Cingulate bundle - archicortical**
  - connects archicortical (dorsal/medial) divisions of frontal lobes with presubiculum, adjacent transitional cortex [hippocampocentric]

- **Uncinate bundle - paleocortical**
  - connects paleocortical (ventral/lateral, orbital) divisions of frontal lobes with temporal pole, amygdala, and entorhinal cortex [amygdalocentric]
Dorsal (cingulate) and Ventral (Arcuate/Uncinate) Frontolimbic Bundles
Dual Arousal Systems Provide Autoregulatory Control on “Attention”

- Dual arousal systems (Routtenberg)
  - Reticular activating system (RAS) for phasic arousal
  - Forebrain for tonic activation

- Functional duality (Pribram)
  - Dimension of control: stabile vs labile
  - Bias: redundancy vs novelty
Many thanks!

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http://www.semel.ucla.edu/creativity
http://www.phenomics.ucla.edu

Consortium for Neuropsychiatric Phenomics
investigators (52)
including PI’s: Freimer, Cannon, London,
Jentsch, Parker, Evans
Cognitive Atlas
investigators including: Poldrack, Toga, van
Horn, Sabb
Multilevel Assays of WM investigators
including: Rissman, Loo, Bearden, Gitlin,
Makeig
Relations of Anatomic Duality to Neurotransmitter Systems

• Archicortical: regulation of fronto-striatal system via tonic DA activity (esp. D1)
• Paleocortical: regulation of ventral frontal and “infralimbic” systems via phasic DA (esp. D2), 5HT, and adrenergic
• Hippocampal: regulation of mismatch sensitivity via cholinergic, GABA-ergic, other peptide modulation?

Bilder 1997; Christensen & Bilder 2000; Bilder, Volavka, Lachman & Grace 2004
RDoC
Levels of Analysis
<table>
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<tr>
<th>Units of Analysis</th>
<th>Genes</th>
<th>Molecules</th>
<th>Cells</th>
<th>Circuits</th>
<th>Physiology</th>
<th>Behavior</th>
<th>Self-Report</th>
<th>Paradigms</th>
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<td><strong>Negative Valence Systems</strong></td>
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<td>Active Threat (&quot;fear&quot;)</td>
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Fig. 1. The draft Research Domain Criteria matrix.
RDoC Working Memory Matrix

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<td>*** The Working Memory Workshop created a Matrix with a different format. Please see the Working Memory Workshop Proceedings document to view the Matrix for Working Memory and its subconstructs. ***</td>
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<td>BDNF</td>
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<td>DRD2</td>
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<td>DAT1</td>
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<td>Molecules</td>
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<tr>
<td>Dopamine</td>
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<tr>
<td>D1</td>
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<td>X</td>
<td>X (gain)</td>
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<td>D2</td>
<td>X</td>
<td>X</td>
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<td>Glutamate</td>
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<td>X</td>
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<tr>
<td>NMDA</td>
<td>X</td>
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<td>AMPA ?</td>
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<tr>
<td>GABA</td>
<td>X</td>
<td>?</td>
<td>X</td>
<td>X</td>
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<td>A?</td>
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<td>B?</td>
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<td>Cells</td>
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<tr>
<td>Pyramidal</td>
<td>X</td>
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<td>Distinct Types of Inhibitory Neurons</td>
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<tr>
<td>Calretinin</td>
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<td>Medium Spiny Neurons (Basal Ganglia)</td>
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<td>Key Circuit: PFC-Parietal-Cingulate-</td>
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<td>Behavior and Paradigms</td>
<td>Unit of Analysis</td>
<td>Active Maintenance</td>
<td>Flexible Updating</td>
<td>Limited Capacity</td>
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<td>----------------------------------------------</td>
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<tr>
<td></td>
<td>N-Back</td>
<td>X</td>
<td>X (?)</td>
<td>X</td>
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<tr>
<td></td>
<td>Delayed Match to Sample</td>
<td>X</td>
<td>---</td>
<td>X</td>
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<tr>
<td></td>
<td>Delayed Match to Non-Sample</td>
<td>X</td>
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<td>X</td>
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<tr>
<td></td>
<td>Sequence Encoding and Reproduction</td>
<td>X</td>
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<td>X</td>
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<td>Sternberg Item Recognition (including recent negative variations)</td>
<td>X</td>
<td>X (recent negative task increases demand on updating)</td>
<td>X</td>
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<td></td>
<td>Complex Span Tasks</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>Letter Memory/Running Memory</td>
<td>X</td>
<td>X (?)</td>
<td>X</td>
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<td></td>
<td>Letter Number Sequencing</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>Simple Span Tasks (may be more appropriate for developmental populations, in adults may not capture all key elements of WM)</td>
<td>X</td>
<td>---</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Change Detection Tasks</td>
<td>X</td>
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<td>X</td>
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<td></td>
<td>Keep Track Task</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>
Managing assertions about brain-behavior relations using a neural circuit description framework

Bilder, Howe & Sabb, 2013
Journal of Abnormal Psychology
Schematic illustrating putative links between cognitive (yellow) and circuit (cyan) levels. We hypothesize that 4 components of Working Memory (WM) specified by RDoC are related to 3 circuits.

Abbreviations: SC, Storage Capacity; GM, Goal Maintenance; IC, Interference Control; LTM, Long-term memory [LTM]; LC, Local Cortical;
Models to Validate Circuit Constructs

GM-ROI
CDA, gamma
Posterior Cortical Localized ROI

FA-SLF
alpha-gamma CFC, CNV

LC
FP

Functional Connectivity PFC-FFA, DMN

CH

Functional Connectivity FFA-H, H-PFC

FA-CH
Theta-gamma CFC
Validating Cognitive Markers of Circuit-Level Constructs

LC

SC

FP

GM

CH

IC

LTM

LCD-K

DMS

DPX

SCW

RN

LCD-I

DFR

RISE
Mapping to Functional Status

Do symptoms or diagnosis add useful prediction over basic measures of circuit, cognitive or neuropsychological measures?

To avoid extreme group bias, sampling strategy is agnostic to diagnosis, and comprises two groups:
- Care-seeking
- Not Care-seeking

Diagnoses assigned after enrollment, as one of the dependent variables under study

Multi-Level Assays of Working Memory and Psychopathology: R01 MH101478
Dual Trends Theory, the Anatomy of Attention, and Schizophrenia

• Anatomic Constraints
  – Riddle of the frontal lobes: revisited, again
  – Duality of anatomic systems - evolutionary cytoarchitectonic trends

• Functional Significance
  – Adaptive resonance architecture and autoregulation
  – Attention as an autoregulatory process

• Example: Schizophrenia as a disorder of autoregulation and impairment of cognitive control
Extra stuff
Genomic Effects on Neurocognitive Function: The COMT Story

- catechol-\textit{O}-methyltransferase (COMT), catabolizes DA, NE, other catechol compounds
- Functional polymorphism, Val158Met in exon III of the (COMT) gene (codominant)
  - Met allele associated with low activity COMT (DA)
  - Val allele associated with high activity COMT (DA)
- Several reports show association of Met allele with better WCST performance (Egan, Malhotra)
- One report links Met allele with more prefrontal activation using fMRI (efficiency) (Egan)
Role of COMT in Regulating Tonic vs Phasic DA Activity

Adapted from Cooper, Bloom and Roth 1996; Grace, 1997; Bilder et al, 2004
Tonic/Phasic DA Transmission - nucleus accumbens:

**Tonic:**

1. slow, irregular firing
2. DA
3. COMT
4. D_{1}

**Phasic:**

5. burst firing
6. DA
7. DAT
8. D_{2}

DA Transmission - PFC:

1. burst firing
2. DA
3. COMT
4. D_{1}
Role of COMT Polymorphism in Regulation of Tonic-Phasic DA in PFC and NAc

*Met* allele (decrease COMT activity)

*Val* allele (increase COMT activity)
Hypothetical effects of Met Val substitution
(Bilder, Volavka, Lachman & Grace, 2004)

<table>
<thead>
<tr>
<th>COMT activity</th>
<th>Met</th>
<th>Val activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA transmission</td>
<td>tonic, phasic; [DA]/PFC</td>
<td>tonic, phasic subcortically</td>
</tr>
<tr>
<td>PFC dynamics</td>
<td>D1, maintenance</td>
<td>D2, updating, ‘resetting’</td>
</tr>
<tr>
<td>Dual trends</td>
<td>archicortical ‘activation’, stability</td>
<td>paleocortical ‘arousal’, plasticity</td>
</tr>
</tbody>
</table>
Effect of COMT Genotype on “Conflict” Index

Conflict Index = (Imitation – Conflict)/(Imitation + Conflict)

Note: low activity, increased tonic DA;
Higher “conflict index” ~ greater gap between ability to imitate and ability to switch; excessive cognitive rigidity
Variance Shared by COMT Genotype and Cognitive Phenotypes

- WCST-Egan
- WCST-Bilder
- Attn-Bilder
- Conflict Index

Pct Var Shared w/ Genotype

Cognitive Phenotype
Frontal Lobe

• Sources of evidence on FL functions
  – Lesion/head injury studies
  – Unit recordings in monkeys (mostly delayed match to sample; WM studies
  – Activation studies in Humans
Pathways

- Dorsal pathway: parietal-DLPFC connections
- Ventral pathway: OFC as primary projection site of the limbic system (W. Nauta)
Lesion studies

- Head injuries (TBI) common source
- Syndromes and deficits; likely anatomical correlates: orbital pathway
  - Arousal changes: Adynamia or agitation:
  - Likely due to orbital frontal damage, usually extensive.
  - ACA territory lesions and adynamia
  - Low motivation; decreased initiative: Probable loss of reward/motivation due to decreased striatal input
  - Reduced insight. Concept of “theory of mind” recent data on role of anterior medial frontal gyrus in TOM, may underlie deficits in insight.
  - Control of attention and selection in anterior cingulate damage.
  - Reduced impulse control; deficits in response inhibition in OF lesions
Syndromes and deficits; likely anatomical correlates: Dorsal pathway

- Eye motor control deficits: Frontal Eye fields direct EM based on spatial information from PL
- Working memory impairment: Lesions in DLPFC; also single unit studies in monkey PFC; delayed component; manipulation component; response selection component
- Reasoning, problem solving deficits; poor “fluid” reasoning
  - Integration of information
- Perseveration: 46/44 direct stimulation produces perseveration deficits
  - Appears separate from WM
- Memory retrieval deficits
  - Probable anterior, BA 10 contribution to active search/retrieval from LTM; probable RH contribution
  - HERA model (Heispheric encoding/retrieval asymmetry; found in verbal memory tasks: LH active during learning of new (verbal) memories; RH active during retrieval
Neuropsychological Testing of Executive Functions

- WM tests (Trails B; digits backwards vs forward; N-back, etc)
- Reasoning/problem solving: Matrices; WCST, Categories, etc
- Generation (word; design)
- Tests of response inhibition (Stroop; go-no-go; alternations ala Luria)
- Memory
  - Attention/ initial processing vs retrieval; the role of recall vs. recognition procedures.
Frontal Lobe

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Dorsal pathway

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- Memory
  - Attention/ initial processing vs retrieval; the role of recall vs. recognition procedures.
- DLPFC and working memory (Nystrom et al. '00)
Auditory N-back
Ventral lateral PFC in emotion regulation
Response Inhibition

Stroop

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<tr>
<th>XXXX</th>
<th>ROT</th>
<th>BLAU</th>
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<tr>
<td>ro gr bl ge</td>
<td>ro gr bl ge</td>
<td>ro gr bl ge</td>
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baseline | congruent | incongruent

red color

Imitation-inhibition
Figure 1. A basal-ganglia model and the Stop-signal paradigm

Figure 2. Activated networks for Going and Stopping and key peristimulus time courses for the hemodynamic response

Figure 3. ROI analyses for experiment 1

Retrieval Effort and Success
(Buckner et al)
Figure 5. Diagrammatic representation of the distribution of different architectonic areas within the two trends in the visual system. Note the locations of the root (R), core (C), and belt (B) lines in each trend.
Figure 7. Diagram showing the root, core, and belt lines culminating, respectively, in second sensory areas, primary areas, and association areas. ProSt, prostriate area.
Figure 10. Diagrams showing the common patterns of laminar origins and terminations of intrinsic connections of the auditory (A) and visual (B) association areas.
Houston Guidelines for Training in Clinical Neuropsychology

1. Generic Psychology Core
   A. Statistics and methodology
   B. Learning, cognition and perception
   C. Social psychology and personality
   D. Biological basis of behavior
   E. Life span development
   F. History
   G. Cultural and individual differences and diversity
Houston Guidelines for Training in Clinical Neuropsychology

2. Generic Clinical Core

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>A.</td>
<td>Psychopathology</td>
</tr>
<tr>
<td>B.</td>
<td>Psychometric theory</td>
</tr>
<tr>
<td>C.</td>
<td>Interview and assessment techniques</td>
</tr>
<tr>
<td>D.</td>
<td>Intervention techniques</td>
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<td>E.</td>
<td>Professional ethics</td>
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Houston Guidelines for Training in Clinical Neuropsychology

3. Foundations for the study of brain-behavior relationships

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<tbody>
<tr>
<td>A.</td>
<td>Functional neuroanatomy</td>
</tr>
<tr>
<td>B.</td>
<td>Neurological and related disorders</td>
</tr>
<tr>
<td>C.</td>
<td>Non-neurologic conditions affecting CNS functioning</td>
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<tr>
<td>D.</td>
<td>Neuroimaging and other neurodiagnostic techniques</td>
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<tr>
<td>E.</td>
<td>Neurochemistry of behavior (e.g., psychopharmacology)</td>
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<tr>
<td>F.</td>
<td>Neuropsychology of behavior</td>
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</table>
# Houston Guidelines for Training in Clinical Neuropsychology

## 4. Foundations for the practice of clinical neuropsychology

<table>
<thead>
<tr>
<th>A.</th>
<th>Specialized neuropsychological assessment techniques</th>
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<tbody>
<tr>
<td>B.</td>
<td>Specialized neuropsychological intervention techniques</td>
</tr>
<tr>
<td>C.</td>
<td>Research design and analysis in neuropsychology</td>
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<tr>
<td>D.</td>
<td>Professional issues and ethics in neuropsychology</td>
</tr>
<tr>
<td>E.</td>
<td>Practical implications of neuropsychological conditions</td>
</tr>
</tbody>
</table>
Houston Guidelines for Training in Clinical Neuropsychology

VII. Skills.

1. Assessment
   - Information gathering
   - History taking
   - Selection of tests and measures
   - Administration of tests and measures
   - Interpretation and diagnosis
   - Treatment planning
   - Report writing
   - Provision of feedback
   - Recognition of multicultural issues
# Houston Guidelines for Training in Clinical Neuropsychology

## 2. Treatment and Interventions

- Identification of intervention targets
- Specification of intervention needs
- Formulation of an intervention plan
- Implementation of the plan
- Monitoring and adjustment to the plan as needed
- Assessment of the outcome
- Recognition of multicultural issues
# Houston Guidelines for Training in Clinical Neuropsychology

## 3. Consultation (patients, families, medical colleagues, agencies, etc.)

- Effective basic communication
- Determination and clarification of referral issues
- Education of referral sources
- Communication of evaluation results and recommendations
- Education of patients and families
Houston Guidelines for Training in Clinical Neuropsychology

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<tr>
<th>4. Research</th>
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<tr>
<td>o Selection of appropriate research topics</td>
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<td>o Review of relevant literature</td>
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<tr>
<td>o Design of research</td>
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<td>o Execution of research</td>
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<td>o Monitoring of progress</td>
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<td>o Evaluation of outcome</td>
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<td>o Communication of results</td>
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5. Teaching and Supervision

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<td>o</td>
<td>Methods of effective teaching</td>
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<td>o</td>
<td>Plan and design of courses and curriculums</td>
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<tr>
<td>o</td>
<td>Use of effective educational technologies</td>
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<tr>
<td>o</td>
<td>Use of effective supervision methodologies</td>
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</table>
6: SMA: homunculus
Foot (posterior) to
Mouth (anterior)

2 cm anterior:
speech
SMA
Frontal eye fields

MFG

DLPFC
Generation and Fluency

Word generation compared to rhyming- Buckner’s group: DLPFC activity is greater during word generation
Response Inhibition

Stroop

Imitation-inhibition
Ventral lateral PFC in emotion regulation
Working memory

Auditory N-back
Prefrontal Disorders
Joaquin Fuster

• Attention-Perception
  – Low alertness; sensory neglect, distractibility, disorders of visual search/control, difficulty w/ sustained attention, internal interference, defective set maintenance

• Motility
  – Hypokinesia, hyperkinesia (?posterior orbital?)

• Memory
  – Organization, monitoring, temporal integration, ‘source memory’
Prefrontal Disorders
Joaquin Fuster

• Planning
• Intelligence
• Temporal integration
• Language
• Affect and emotion
  – Apathy, depression, euphoria, social and emotional behavior
Figure 11. Diagrams showing the progressive architectonic steps from the medial proisocortex (A) and orbital proisocortex (B) of the frontal lobe.
Figure 12. Depictions of camera lucida diagrams showing the differential laminar organization within the dorsal (archicortical) and ventral (paleocortical) architectonic trends of the frontal lobe.
Hierarchic Organization of Cortex and the Perception-Action Cycle

Fuster 2004
**Dual Origins of Cortex**

<table>
<thead>
<tr>
<th>ARCHICORT EX</th>
<th>PALEOCORT EX</th>
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<tbody>
<tr>
<td>OUTPUT oriented</td>
<td>INPUT Oriented</td>
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<tr>
<td>Internal plans for action</td>
<td>Externally guided action</td>
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<tr>
<td>Willed Intention</td>
<td>Stimulus intention</td>
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<tr>
<td>Proactive</td>
<td>Reactive</td>
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<td>Stability</td>
<td>Flexibility</td>
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<td>Novelty</td>
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<td>Predictable</td>
<td>Unpredictable</td>
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<tr>
<td>UTILITY</td>
<td>NOVELTY</td>
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</table>

Bilder 1997; Christensen & Bilder 2000; Bilder et al 2004

Pandya 1999
The Action-Perception Cycle: Overview
Novelty Yields Shifts in Brain State

Stabilize new action plan

Perceive novel input
When a New Plan Works it is Stabilized and Leads to Action

Stabilize new action plan

Perceive novel input
Cycle of Attention: Tonic (activation) - Phasic (arousal)

• When reality matches expectations, fronto-posterior resonance success ("match") - maintain tonic action program

• When reality does not match expectations, resonance failure, stop tonic activation, engage phasic arousal, plasticity

• When new state reduces resonance failure, stabilize with tonic activation
The Hippocampal System as “Mismatch” Detector


- Hippocampal role in memory: “index” representations (Wickelgren, Eichenbaum)

- Hypothesis: map of cortical representations in hippocampus is map of resonance states; i.e., novelty-familiarity key
The Cycle of Attention: When Reality Matches Expectations

Frontal “expectation”  →  Post-Rolandic “reality”

Resonance success  →  Resonance failure

Hippocampal “mismatch” detector

200Hz

Tonic inhibition
The Cycle of Attention: When Reality Violates Expectations

Resonance success

Resonance failure

Input

, 200Hz

Hippocampal “mismatch”

Tonic inhibition

RAS

RAS
When expectations resonate with reality…
When expectations deviate from reality…
Until a new resonant state is achieved…
Self-Monitoring: Experience Sampling and Logging

• Mood monitor, c/o Margie Morris
• Affectiva tools, measuring skin conductance and facial expression for marketing, personal development?

• Reading-Homework: