Imaging in Cognitive and Clinical Neuroscience

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Massachusetts General Hospital

Harvard Medical School

Disclosures of Potential Conflicts

Source	Consultant	Advisory Board	Stock or Equity >$10,000	Speakers' Bureau	**Research Support**	Honorarium for this talk or meeting	Expenses related to this talk or meeting
NIA-NIMH (RO1) (Aging)					**X**		
NIDA-NIH (RO1) (Drug Dependence)					**X**		
NIH (R21) (Neurodegeneration)					**X**		
NIH (R21) (Neurodegeneration)					**X**		
NIH (R21) (Modeling Deep Brain Stimulation and MRI safety)					**X**		
MGH-MAC Core (Multiple Projects)					**X**		

Center for Morphometric Analysis (CMA)-MGH collaborating PIs

Marek Kubicki, M.D., Ph.D. (BWH/HMS)
Bradford Dickerson, M.D. (MGH/HMS)
Giorgio Bonmassar, Ph.D. (MGH/HMS)
Jill Goldstein, Ph.D. (BWH/HMS)
Larry Seidman, Ph.D.(BIDMC/MMHC/HMS)
Gordon Harris, Ph.D. (MGH/HMS)
Scott Rauch, M.D. (McLean/HMS)
Scott Lukas, Ph.D. (McLean/HMS)
Joseph Biederman, M.D. (MGH/HMS)
Marlene Oscar-Berman, Ph.D.(BUSM)
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Douglas Rosene, Ph.D. (BUSM)
Martha Shenton, Ph.D. (BWH/HMS)
David Kennedy, Ph.D.(UMassMS)
David Caplan, M.D., Ph.D. (MGH/HMS)
Bruce Rosen, M.D., Ph.D. (MGH/HMS)
Helen Grant, M.D., Ph.D.(Children's//HMS)
Hans Breiter, M.D.(NWU)
Anne Blood, Ph.D. (MGH/HMS)

Harvard Medical School affiliated Hospitals

Massachusetts General Hospital (MGH)
Brigham and Women's Hospital (BWH)
McLean Hospital
Beth Israel Deaconess Medical Center (BIDMC)
Mass Mental Health Center (MMHC)
Children's Hospital

Center for Morphometric Analysis (CMA)-MGH Core

Nikos Makris, M.D., Ph.D. (Director)
Verne Caviness, M.D., Ph.D. (Founding Director)
George Papadimitriou, B.Sc. (Computer Science)
Lichen Liang, Ph.D. (MRI Engineering, Modeling)
Takeshi Takahashi, M.D., Ph.D. (Functional Conn.)
Isaac Ng, B.A. (RA)
Anni Zhu, B.A. (RA)
Yeetzou Kao (RA)

Nikos Makris, M.D., Ph.D. (MGH/BWH/McLean/HMS)	**Brain** Connectivity/Aging/Neurodegeneration/Addiction/ADHD/Stroke/ITD
Verne Caviness, M.D., Ph.D. (MGH/HMS)	Brain Development/Laptop Imaging Technology Development/Stroke
Marek Kubicki, M.D., Ph.D. (BWH/HMS)	Schizophrenia/Imaging Technology Development/Aging/Brain Connectivity
Bradford Dickerson, M.D. (MGH/HMS)	Neurodegeneration/Aging/ITD/Brain Connectivity
Giorgio Bonmassar, Ph.D. (MGH/HMS)	Technology Development/MRI Safety/Deep Brain Stimulation
Jill Goldstein, Ph.D. (BWH/HMS)	Stress Response/Sexual Dimorphisms/Aging/MDD/Schizophrenia
Larry Seidman, Ph.D.(BIDMC/MMHC/HMS)	Schizophrenia/MDD/BPD/ADHD/Resting State Brain Connectivity
Gordon Harris, Ph.D. (MGH/HMS)	3D Imaging Visualizations Technology Development/Alcohol Dependence
Scott Rauch, M.D. (McLean/HMS)	OCD/PTSD/Anxiety Disorder/Psychosurgery
Scott Lukas, Ph.D. (McLean/HMS)	Nicotine Dependence/Alcohol Dependence
Joseph Biederman, M.D. (MGH/HMS)	Attention Deficit/Hyperactivity Disorder (ADHD)/Bipolar Disorder (BPD)
Marlene Oscar-Berman, Ph.D.(BUSM)	Alcohol Dependence
Deepak Pandya, M.D. (BUSM)	Brain Connectivity
Douglas Rosene, Ph.D. (BUSM)	Aging in the Rhesus Monkey/Monkey Brain Connectivity
Martha Shenton, Ph.D. (BWH/HMS)	Traumatic Brain Injury/Imaging Technology Development
David Kennedy, Ph.D.(UMassMS)	Neuroinformatics/Imaging Databasing
David Caplan, M.D., Ph.D. (MGH/HMS)	Stroke/Aphasia Research
Bruce Rosen, M.D., Ph.D. (MGH/HMS)	Imaging Technology Development (ITD)/Program in Acupuncture Research
Helen Grant, M.D., Ph.D.(Children's//HMS)	Brain Development
Hans Breiter, M.D.(NWU)	Cocaine Dependence
Anne Blood, Ph.D. (MGH/HMS)	Dystonia Research

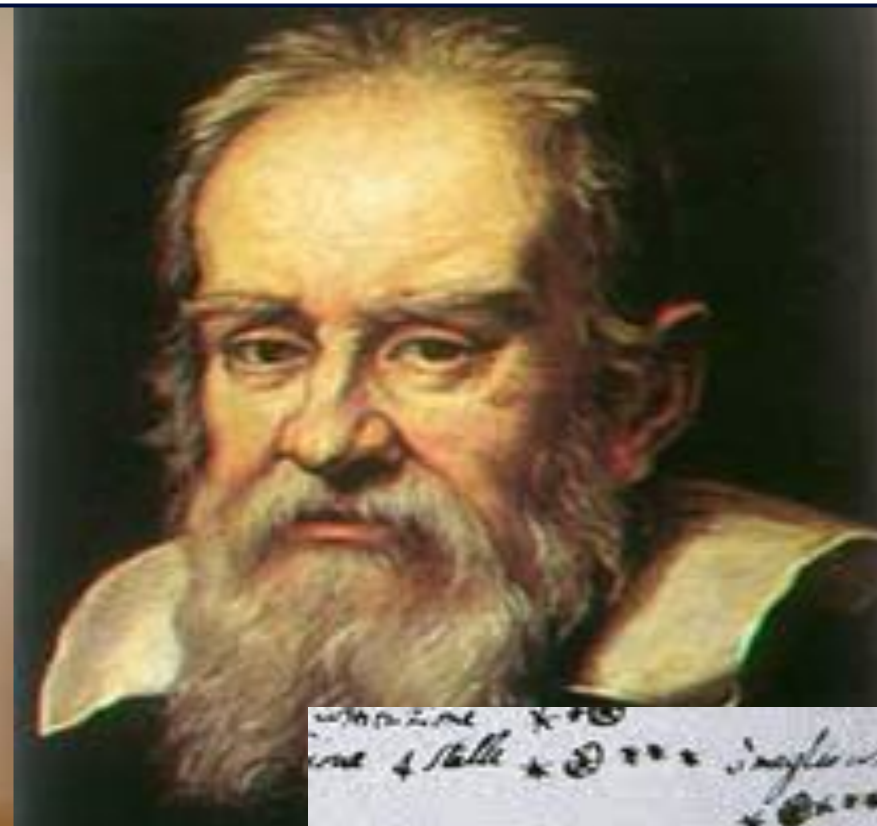
Current Imaging Technology and its Impact in understanding functional anatomy of Neural Systems (i.e., Brain Circuitries)

Imaging of Neural Systems in

- **Cognitive Science, and**
- **Clinical Neuroscience**
  - **ADHD**
  - **Addiction**
  - **Neurodegeneration**

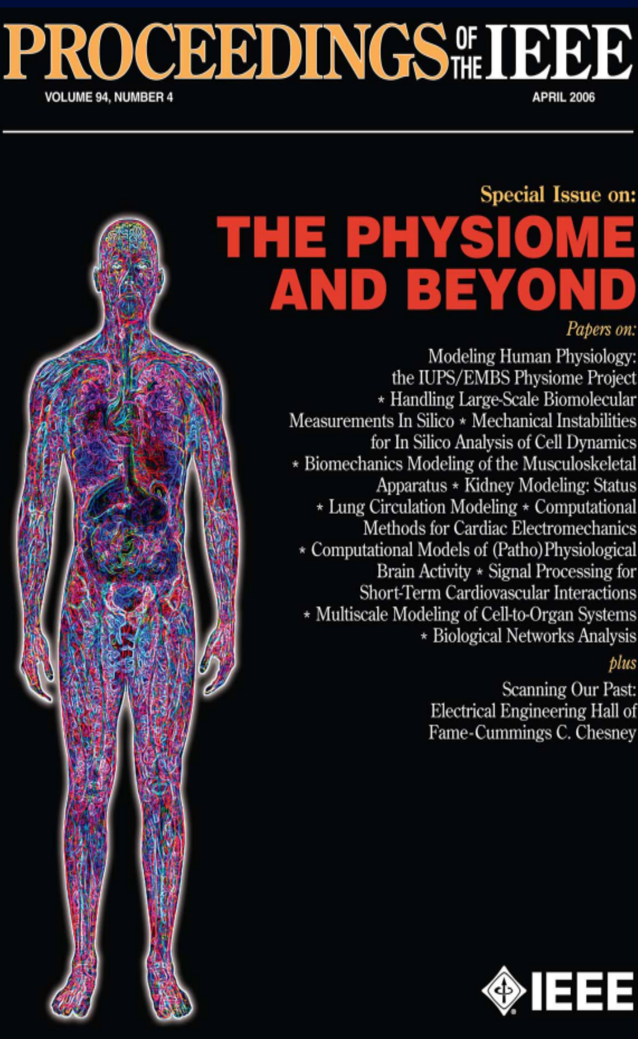
Importance of Technology in Scientific Discovery

(Hypothesis: <u>Great Tools</u> to see <u>lead to Great Discoveries</u>)



Courtesy of Dr. Bruce Rosen

Importance of Technology in Medicine and Neuroscience



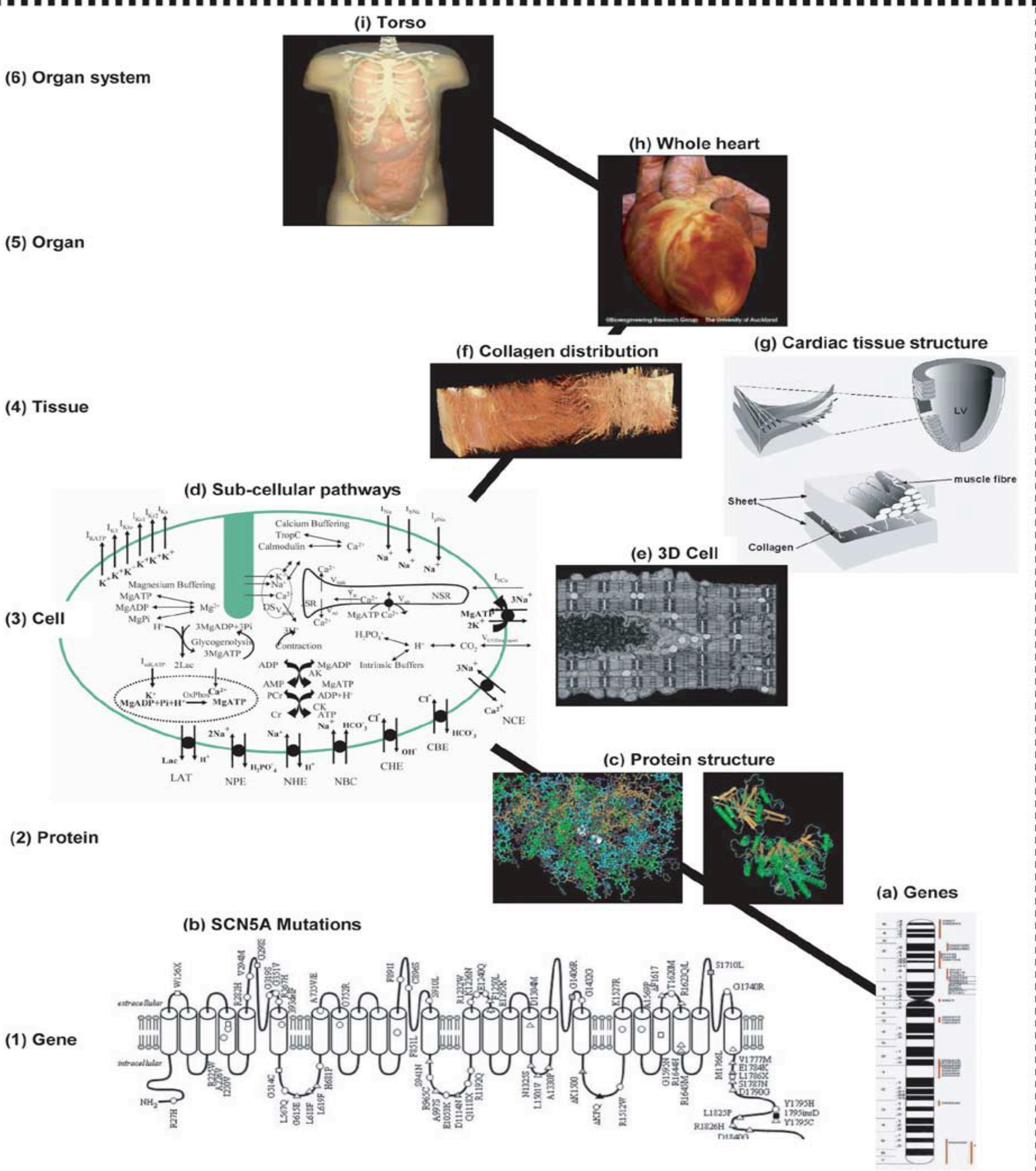
That our understating of the human brain has advanced more in the last two decades than in the rest of human history is a well-known fact.

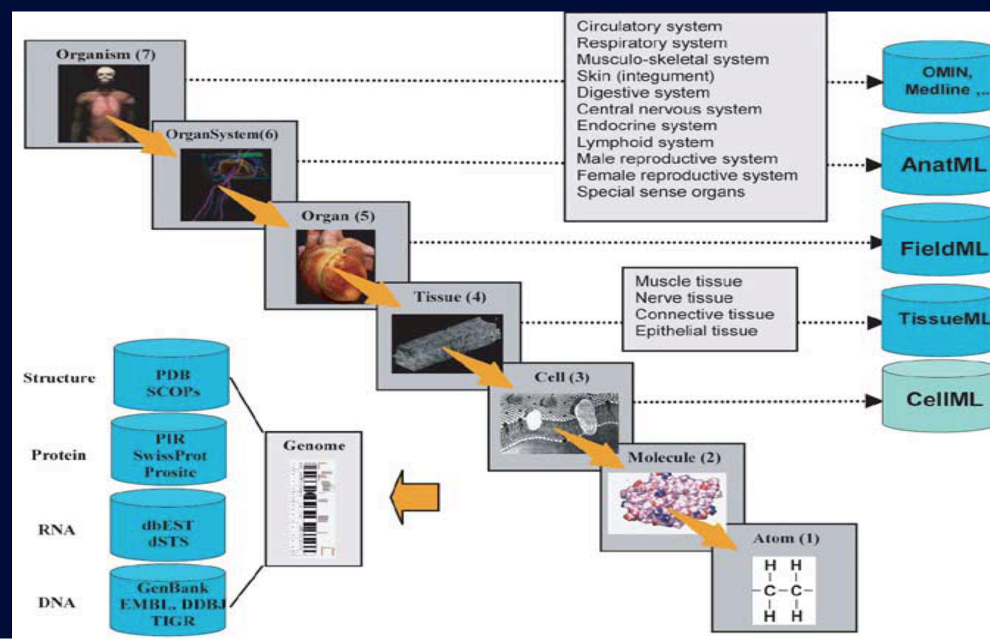
This seems to be a consequence of **key technological discoveries** as has occurred in other fields of science in the course of history.

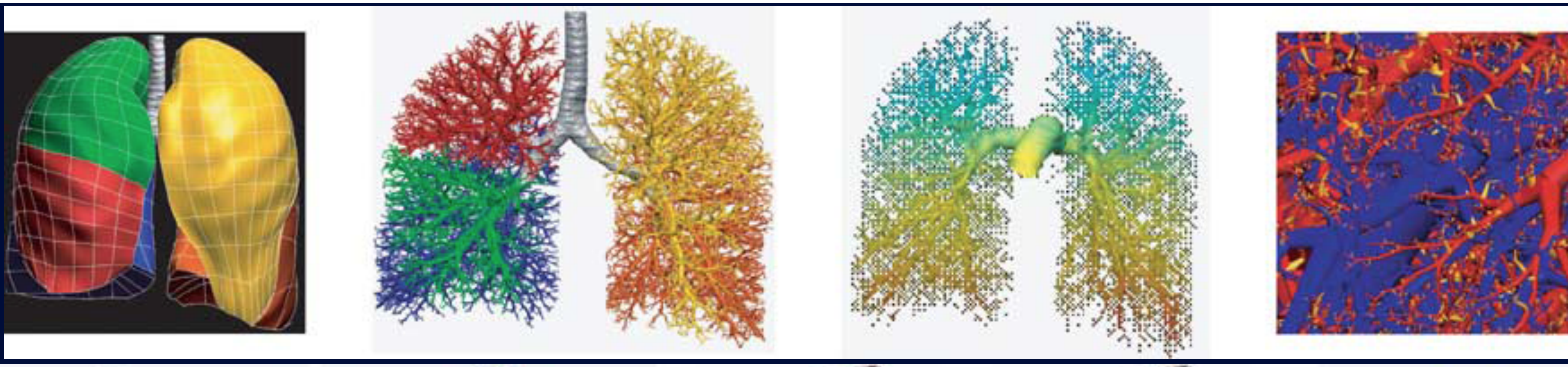
MRI was rated by general practitioners in the USA as the principal contributor to medical practice today over the last decade (i.e., 1991-2000) (Fuchs VR and Sox HC Jr. (2001) Physicians' Views Of The Relative Importance Of Thirty Medical Innovations, Health Affairs: Vol. 20, Number 5).

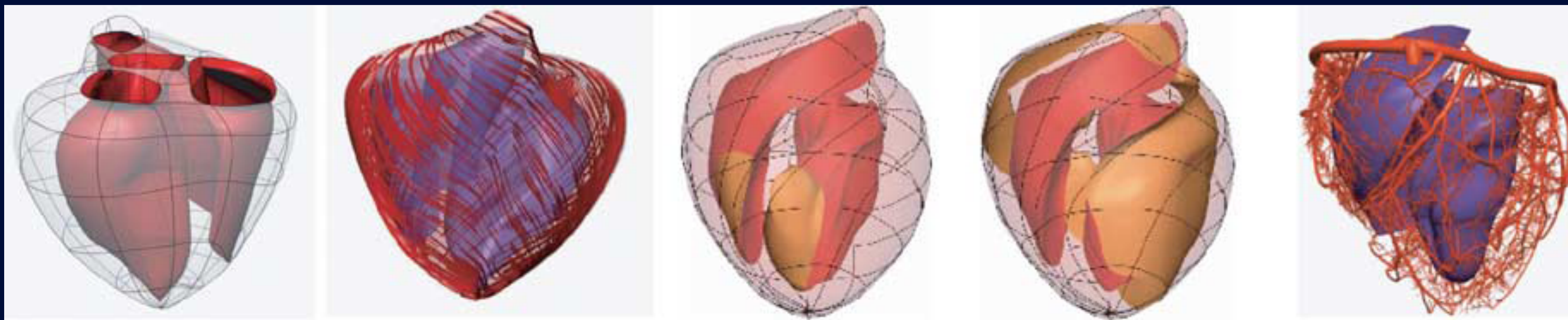
Modeling Human Anatomy and Physiology

(Integration across multiple levels of description is a major goal in medicine)









MRI-PET installations at MGH

Unique Instruments in New England

Nuclear Imaging two ways

Whole Body

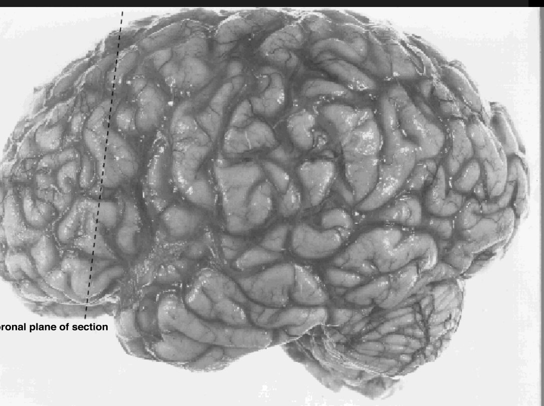
Head-only

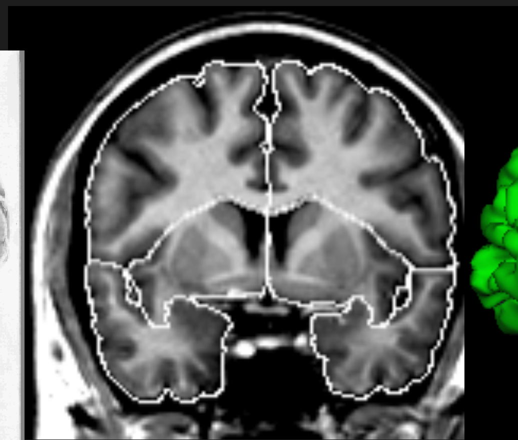
Courtesy of Dr. Bruce Rosen

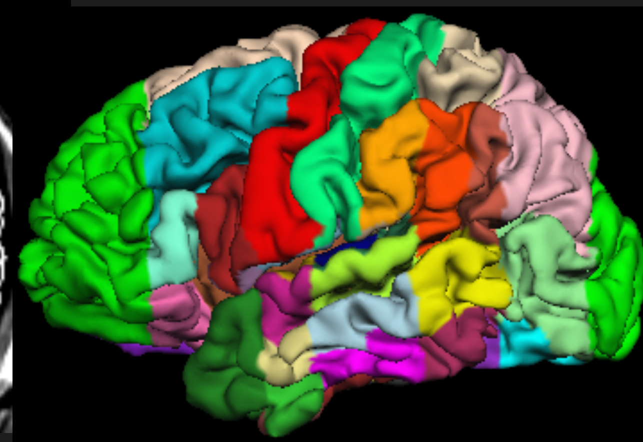
Magnetic resonance imaging (MRI) technology had a critical role in understating of the human brain.

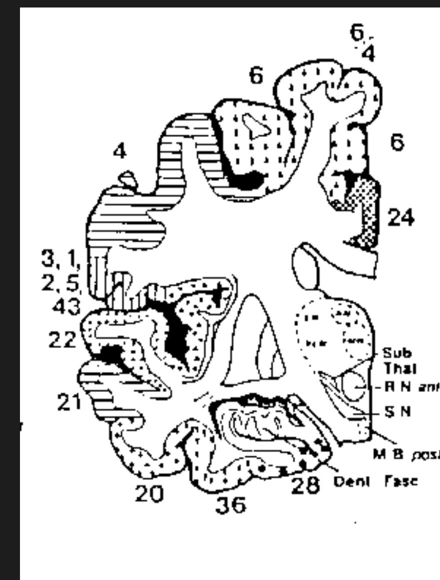
Besides the great cultural and intellectual value of the accrued information and novel conceptualizations in brain science, **these advances had a tremendous impact on the way we are currently facing neurological and psychiatric diseases and the neurosurgical approaches we adopt for diagnosis, surgical planning and treatment.**

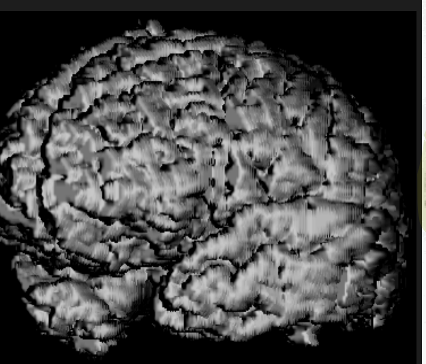
Neuroanatomic Description Hierarchy:

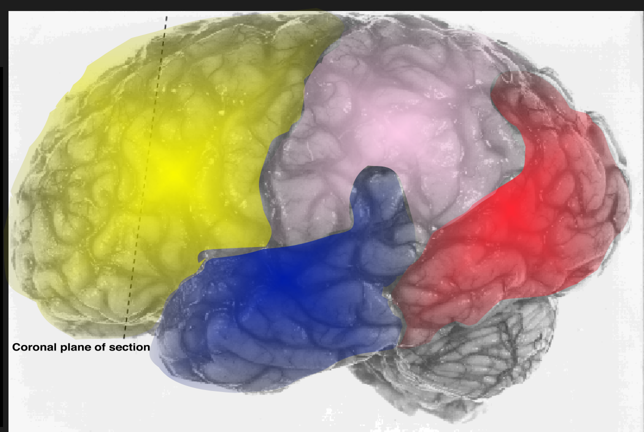


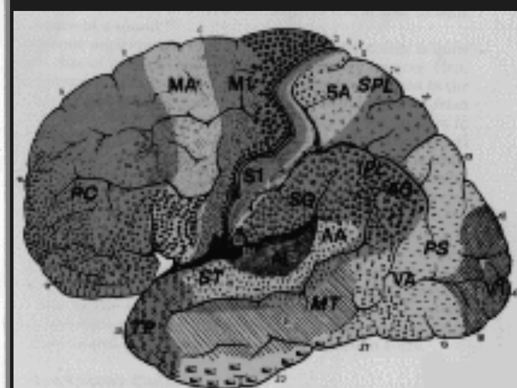












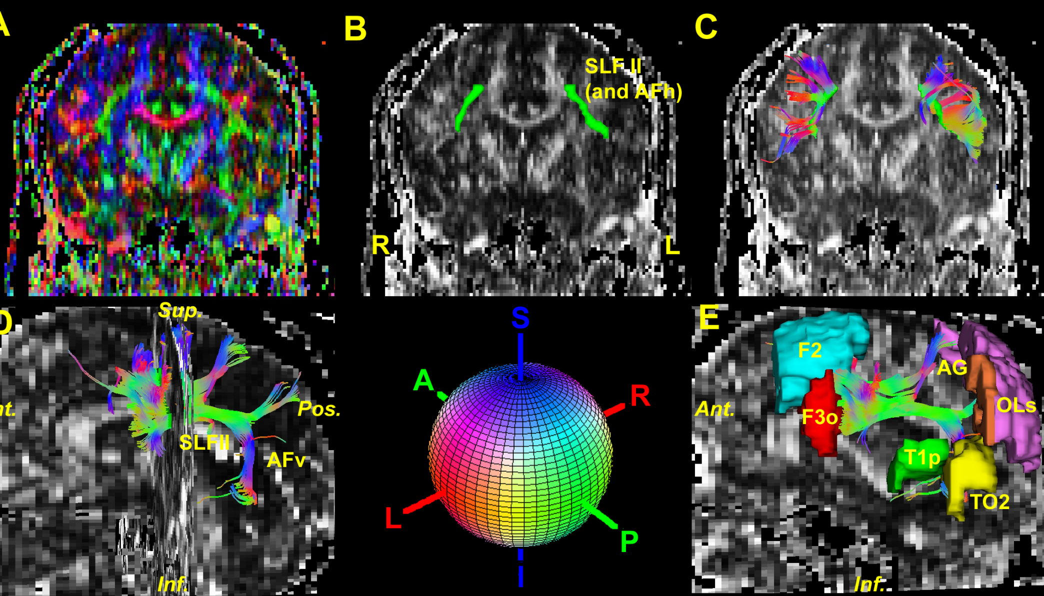
WHOLE BRAIN/STRUCTURE

LOBES

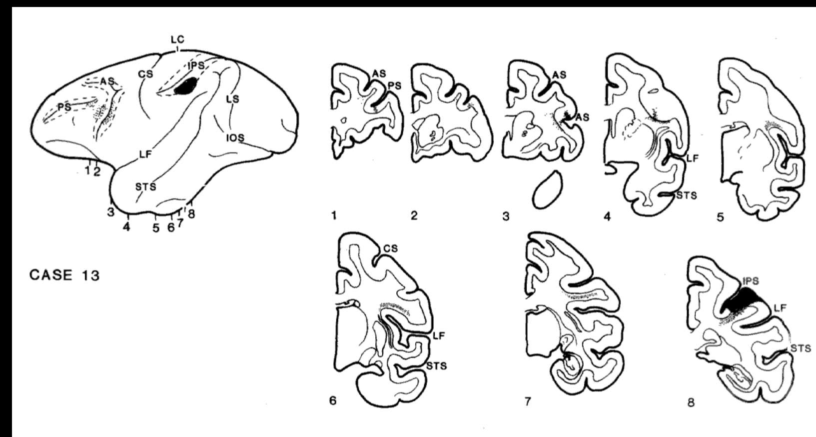
GYRI & SYSTEMS

CYTO- & MYELO-ARCHITECTURE

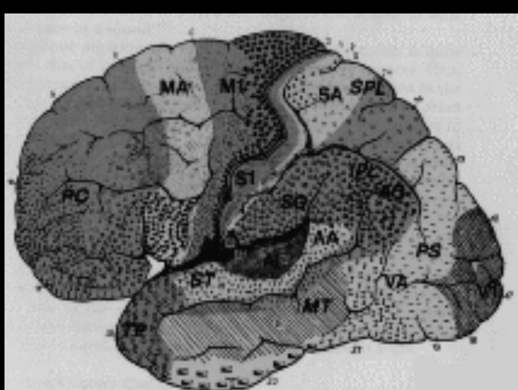
Brain Circuitries (Networks)

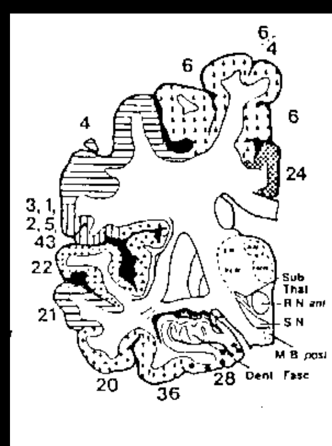


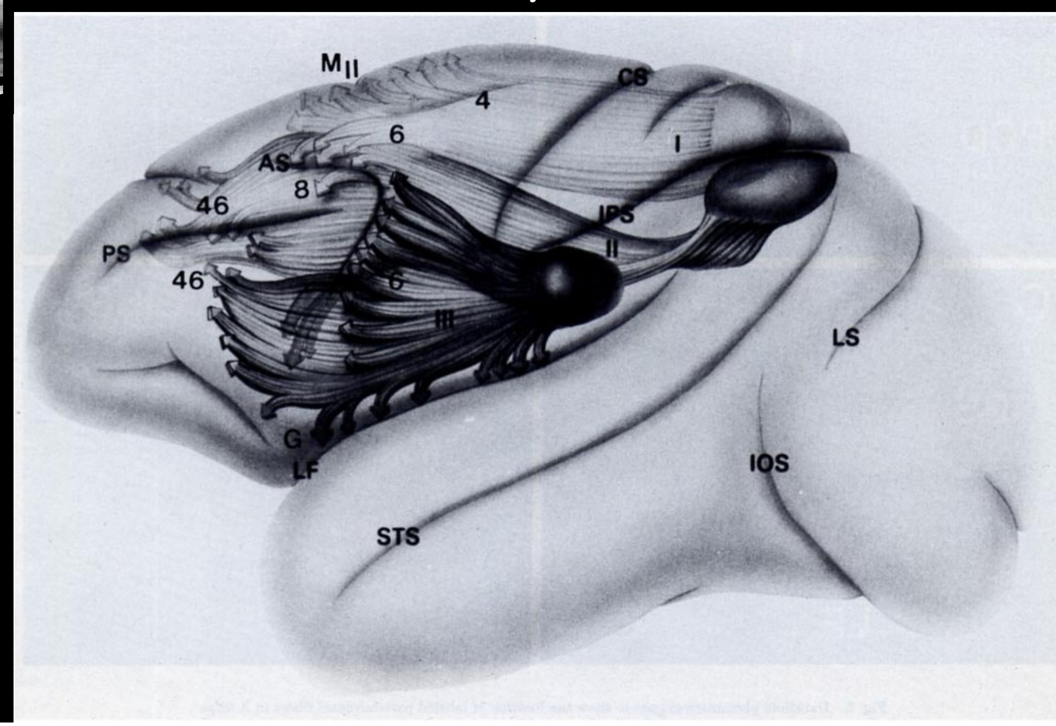
Makris, Pandya,, et al. 2004



Petrides & Pandya, 1984

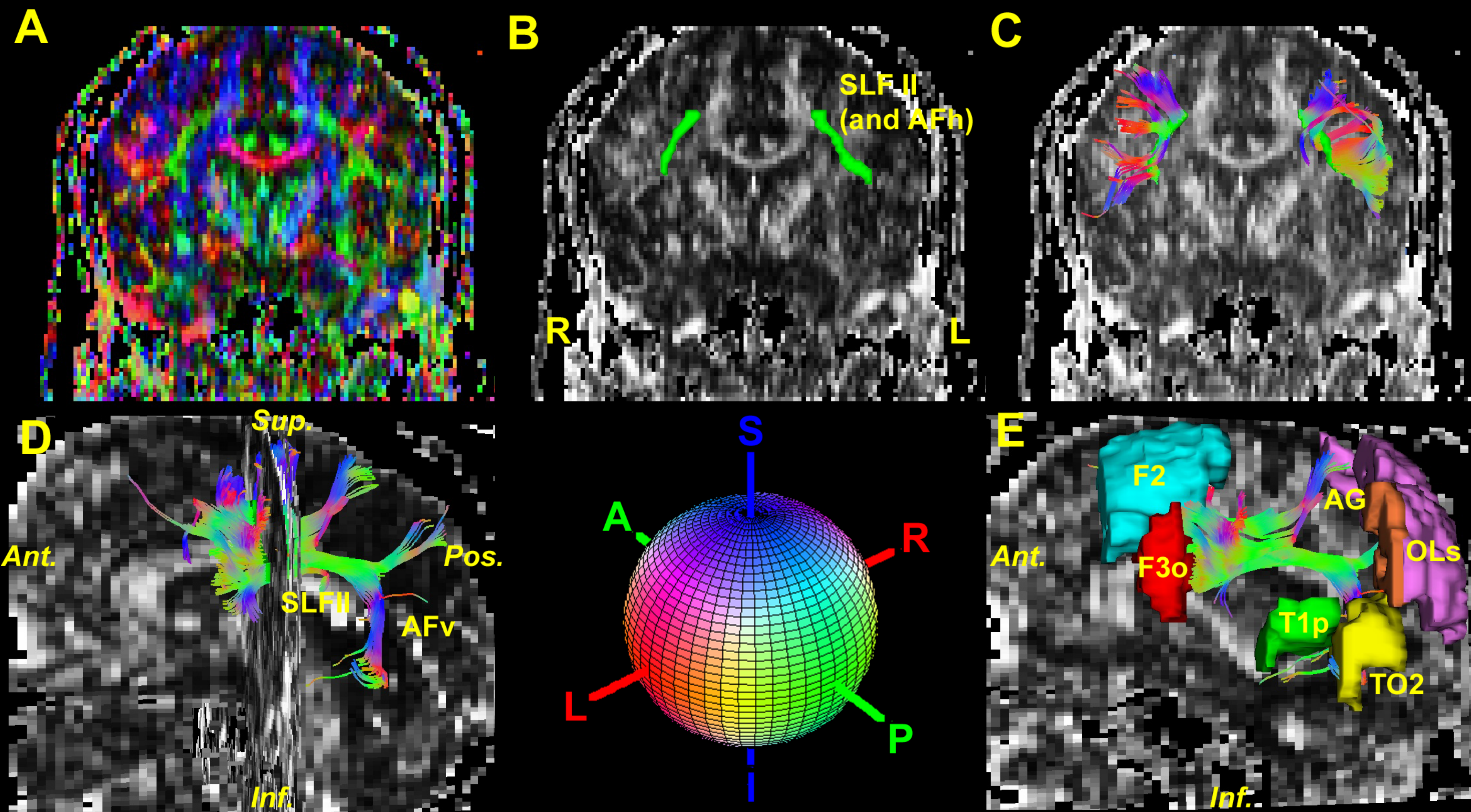






Brain connections are precise and architectonic

Brain Circuitries (Networks)



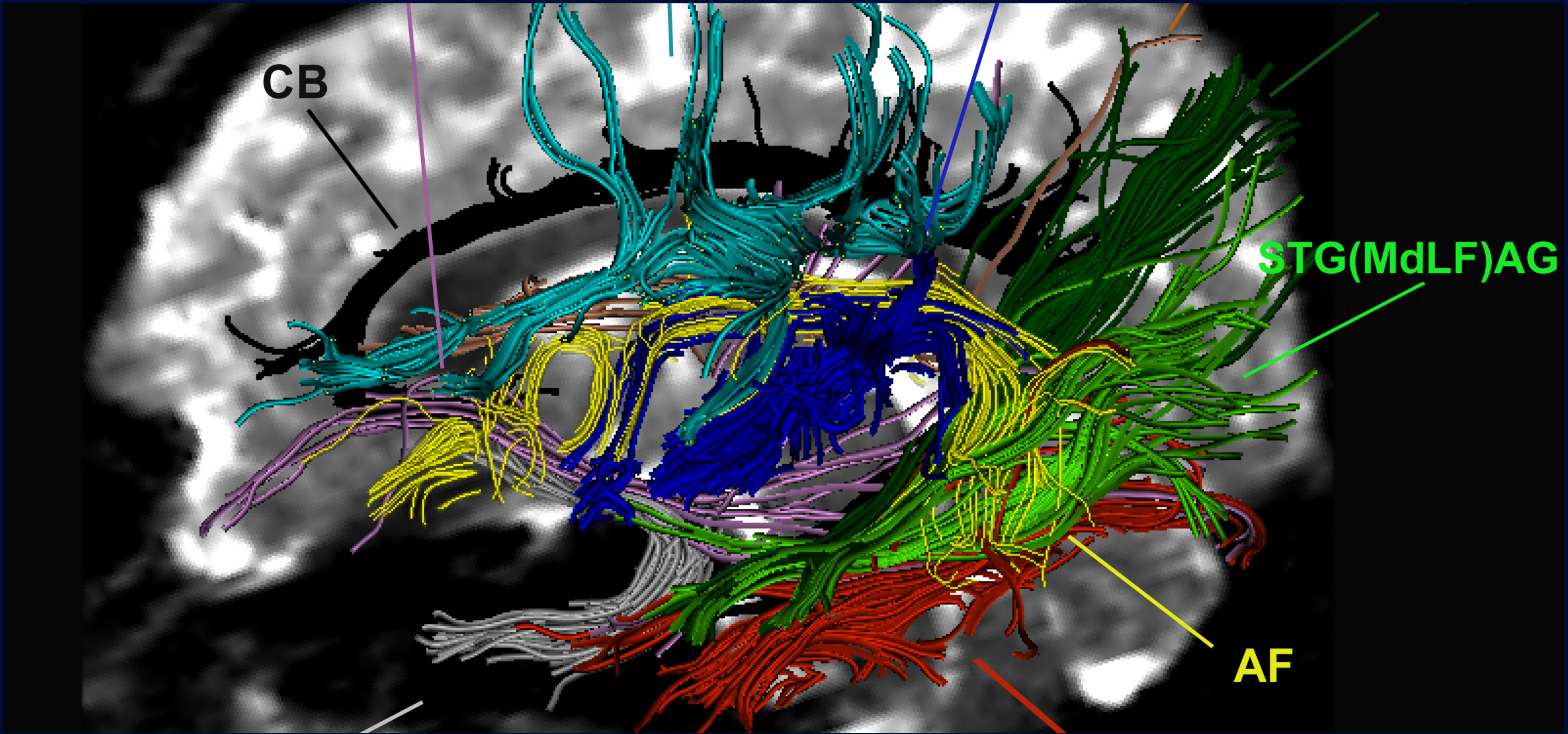
Makris, Pandya,, et al. 2004

”Despite 4000 papers, not a single finding has changed routine clinical care in psychiatry”

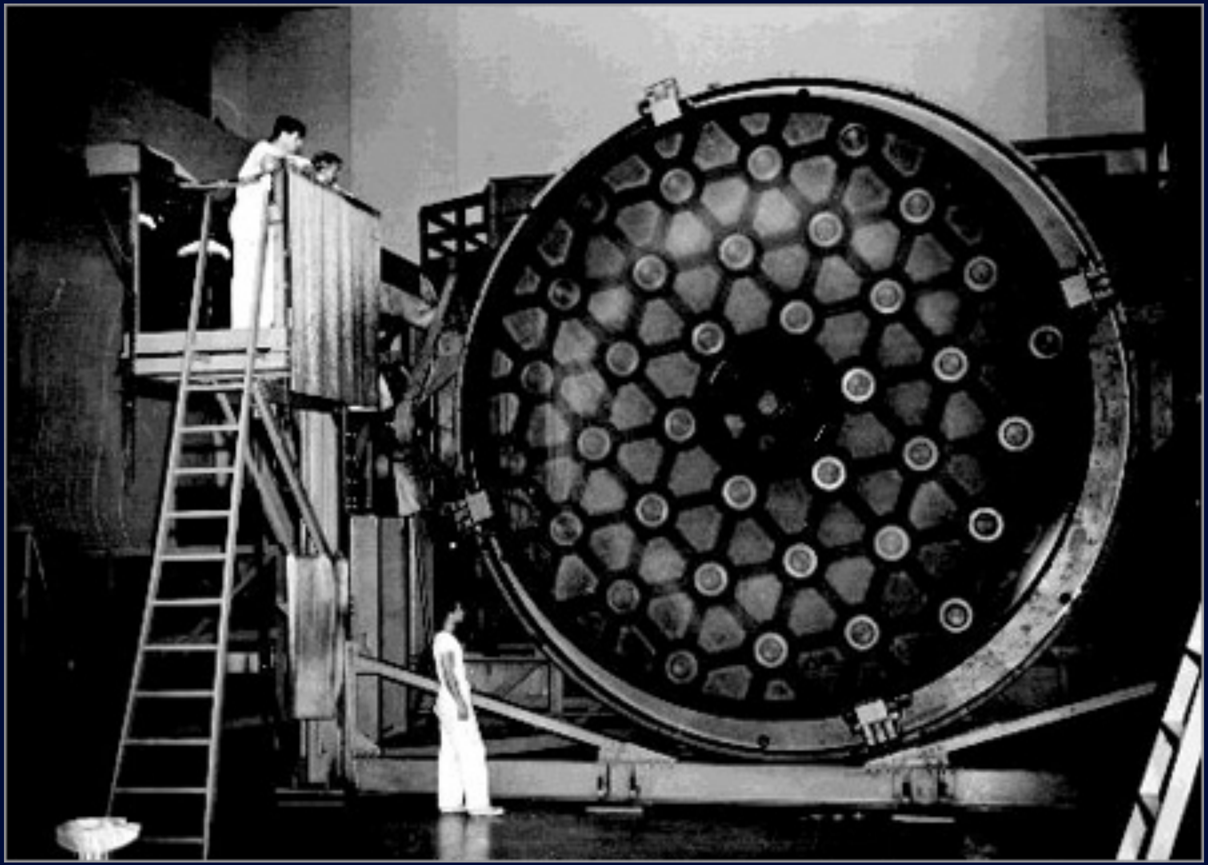
But this will change, and the change will revolve around a new definition of psychiatric diseases as disorders of brain *circuitry* - that this will change our definition of the illnesses, and “our understanding of their causes, treatments, and preventions”

Paraphrasing Tom Insel, Director, National Institute of Mental Health

In Imaging Research, Brain Connectivity is done with Diffusion MRI



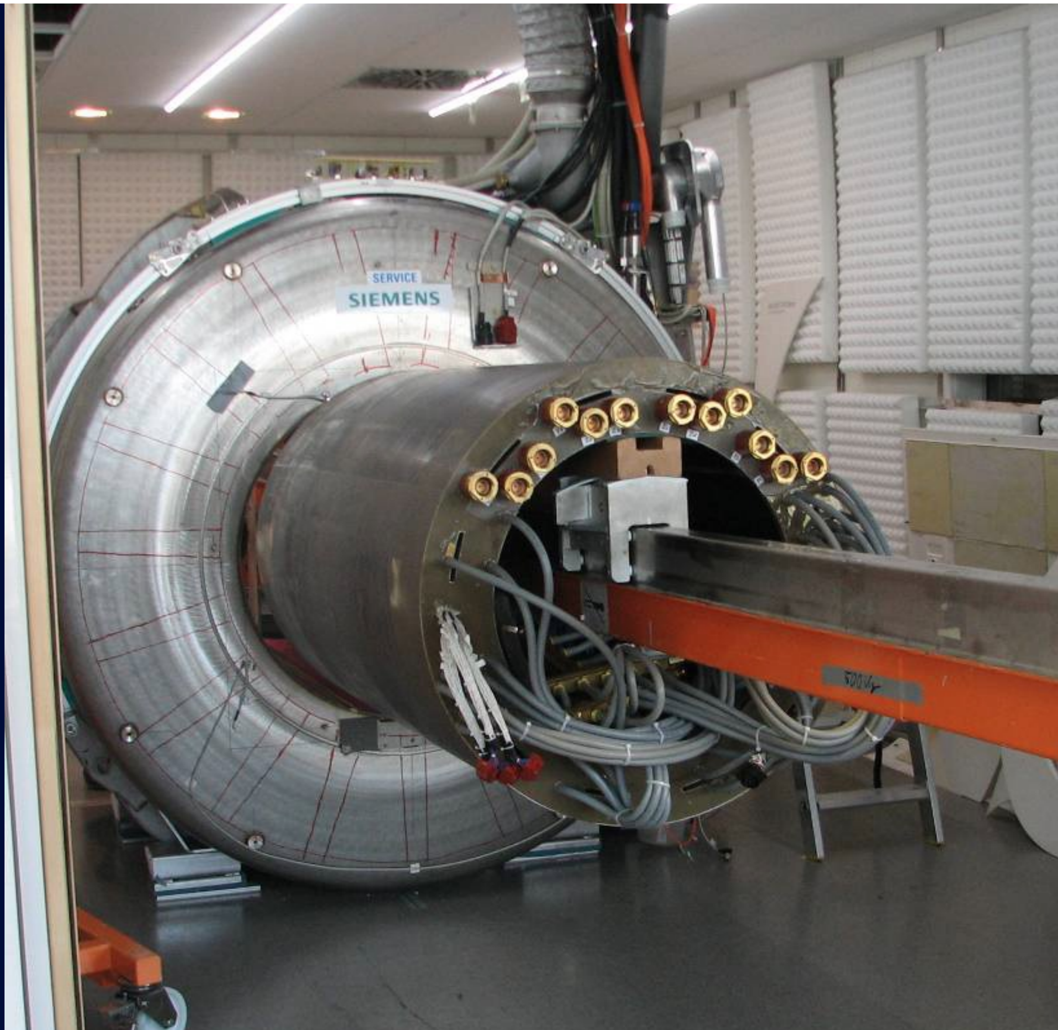
In astronomy, the way to sensitivity and resolution is mirror diameter



Corning 200" mirror for the Hale Telescope at Mt Palomar

Courtesy of Dr. Bruce Rosen

Human Connectome Project



Gmax = 300mT/m
(7x Greater than conventional)

1.5 Ton gradient
24 MWatts peak power

In Diffusion MRI, the way to see micro-structure is gradient strength

Courtesy of Dr. Bruce Rosen

Human Connectome Project – NIH Neuroscience Blueprint

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The NIH Human Connectome Project

WU-Minn Consortium | Harvard/MGH-UCLA Consortium | Neuroscience Blueprint

About

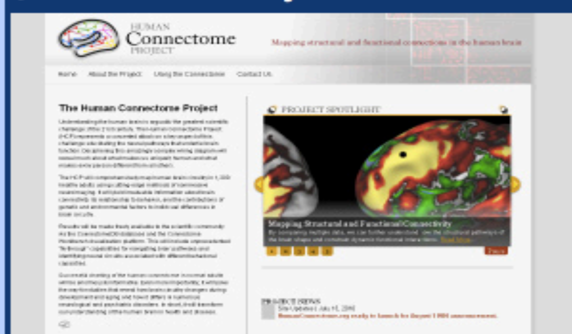
The NIH Human Connectome Project is an ambitious effort to map the neural pathways that underlie human brain function. The overarching purpose of the Project is to acquire and share data about the structural and functional connectivity of the human brain. It will greatly advance the capabilities for imaging and analyzing brain connections, resulting in improved sensitivity, resolution, and utility, thereby accelerating progress in the emerging field of human connectomics.

Altogether, the Human Connectome Project will lead to major advances in our understanding of what makes us uniquely human and will set the stage for future studies of abnormal brain circuits in many neurological and psychiatric disorders.

Consortia

The sixteen institutes and centers of the NIH Blueprint for Neuroscience have funded two major grants that will take complementary approaches to deciphering the brain's amazingly complex wiring diagram.

↗ The WU-Minn Project



↗ The Harvard/MGH-UCLA Project

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HCP In The News

Sporns' 'Networks of the Brain': a roadmap to new
Indiana University
The first of these projects is to develop a "virtual brain," a powerful computational model that can simulate brain function; and the second is called the Human Connectome Project, established to map the human brain's major connections. ...

Data Overload: Scientists Struggle to Streamline
LiveScience.com
The goal of the Human Connectome Project (HCP), for instance, is to map connections among neurons using evidence from brain-imaging studies and link the findings to behavioral tests and DNA samples from more than 1000 healthy adults. ...

Proposal unveiled for revamped Gateway Arch park
Reuters
No specifics were presented for how the money would be raised, but Walter Metcalf, an official of the foundation planning the project, said the cost would be $578.5 million. He said funding was in the "early stage" but would use federal, ...

Apple σημαίνει καινοτομία
SigmaLive
Το προηγούμενο έτος τα εργαστήρια της εταιρείας κατέθεσαν 2.537 αιτήσεις διπλωμάτων ευρεσιτεχνίας, ενώ στα νέα της εγχειρήματα συγκαταλέγεται το Human Connectome Project, μια απόπειρα να χαρτογραφηθούν οι συνδέσεις του ανθρώπινου εγκεφάλου. ...

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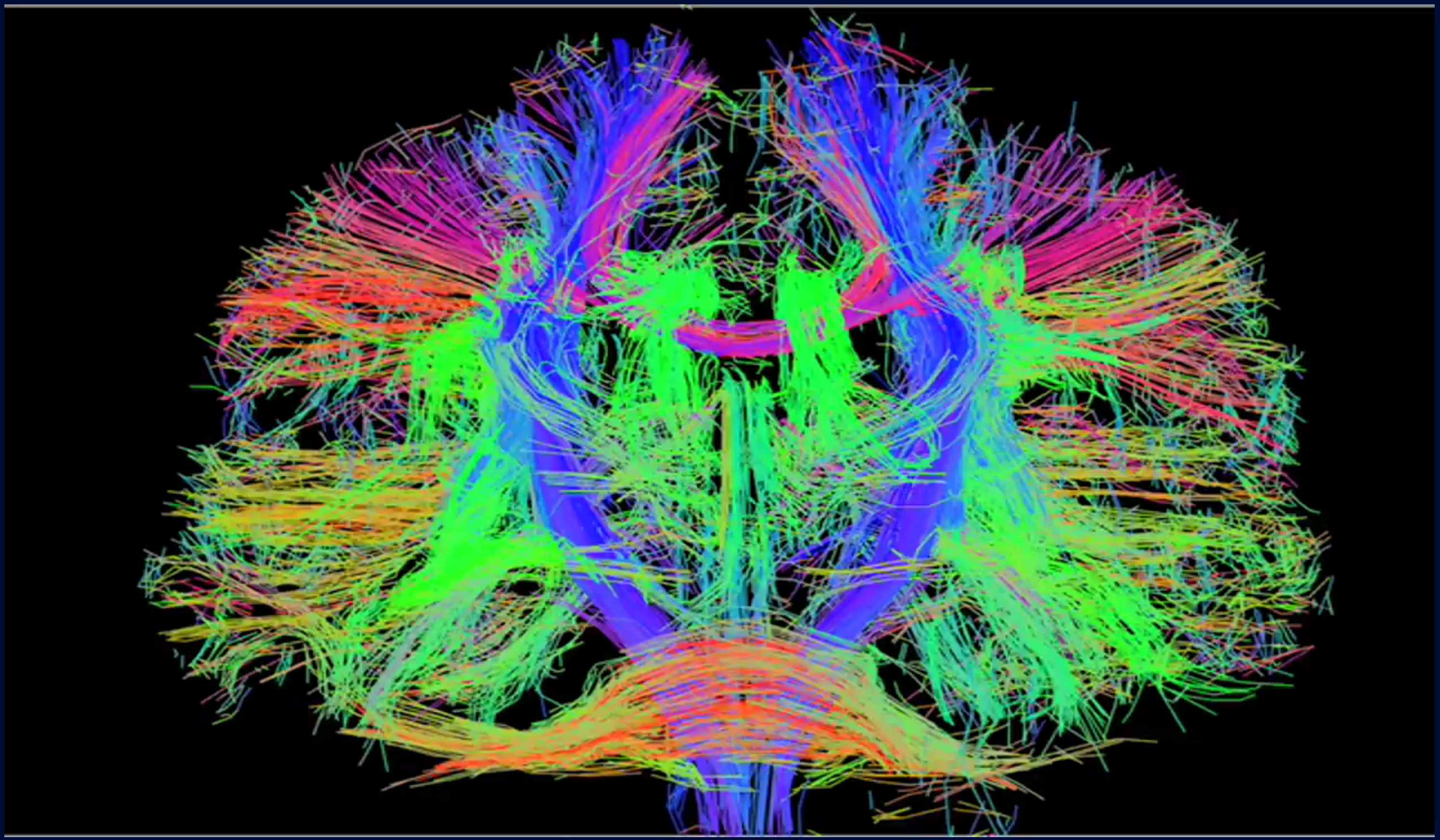
NIH HCP Initiative History

- Human Connectome Project grant published July 15, 2009. (RFA, Press Release)

ourtesy of Dr. Bruce Rosen

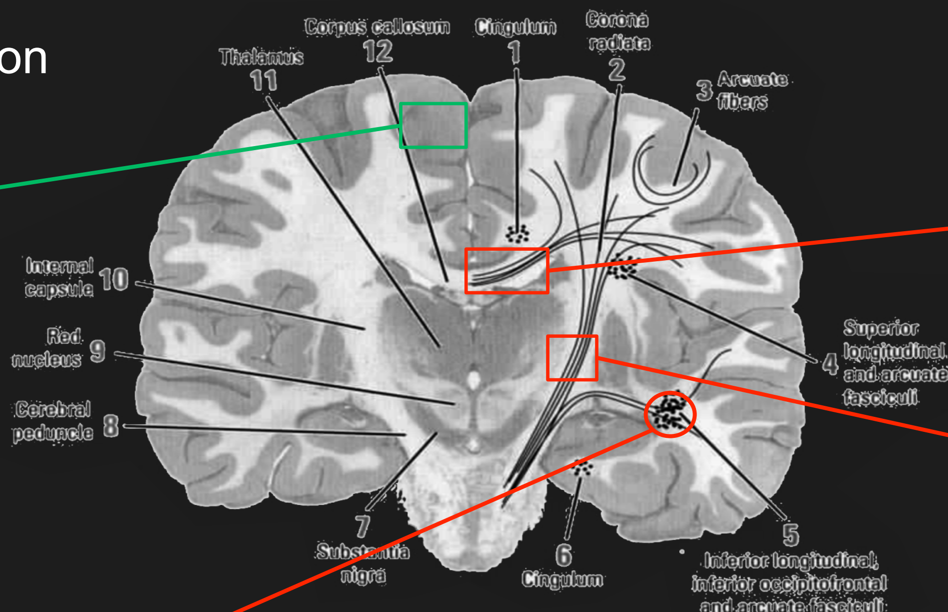
Diffusion Imaging of Microstructure



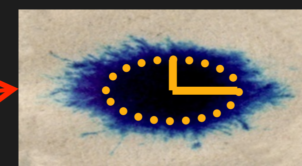
Courtesy of Dr. Bruce Rosen

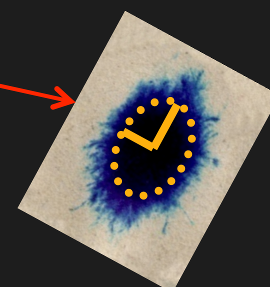
Water Diffusion in the Brain has *Directionality*

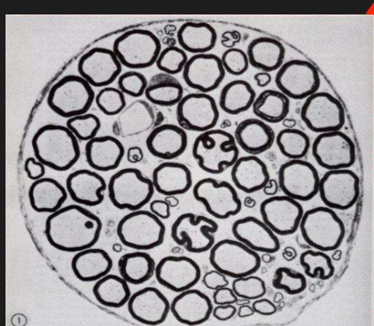
Isotropic diffusion



Anisotropic diffusion





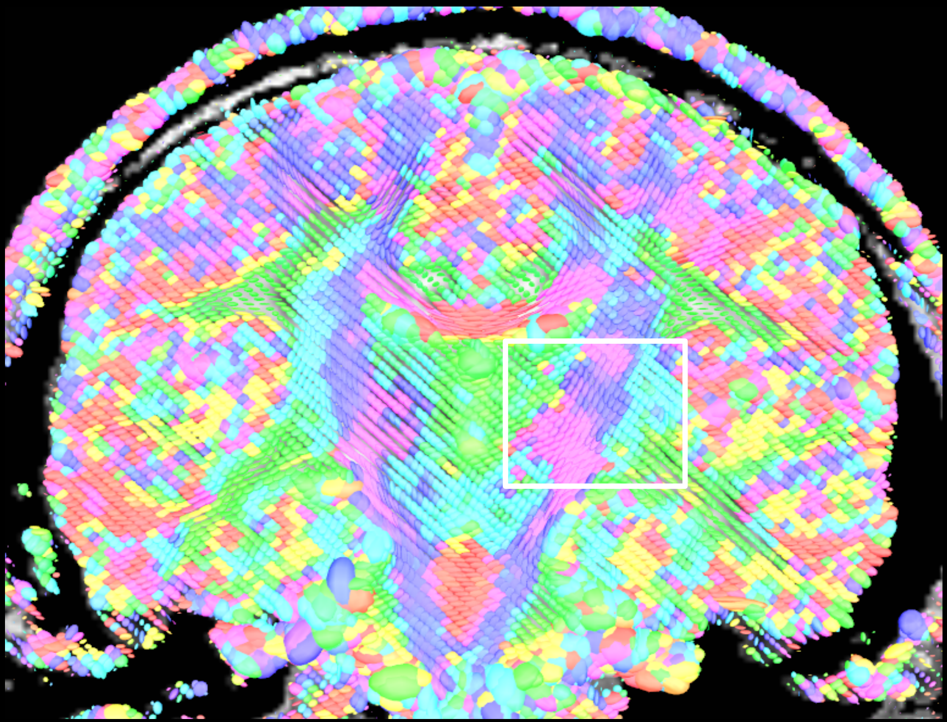


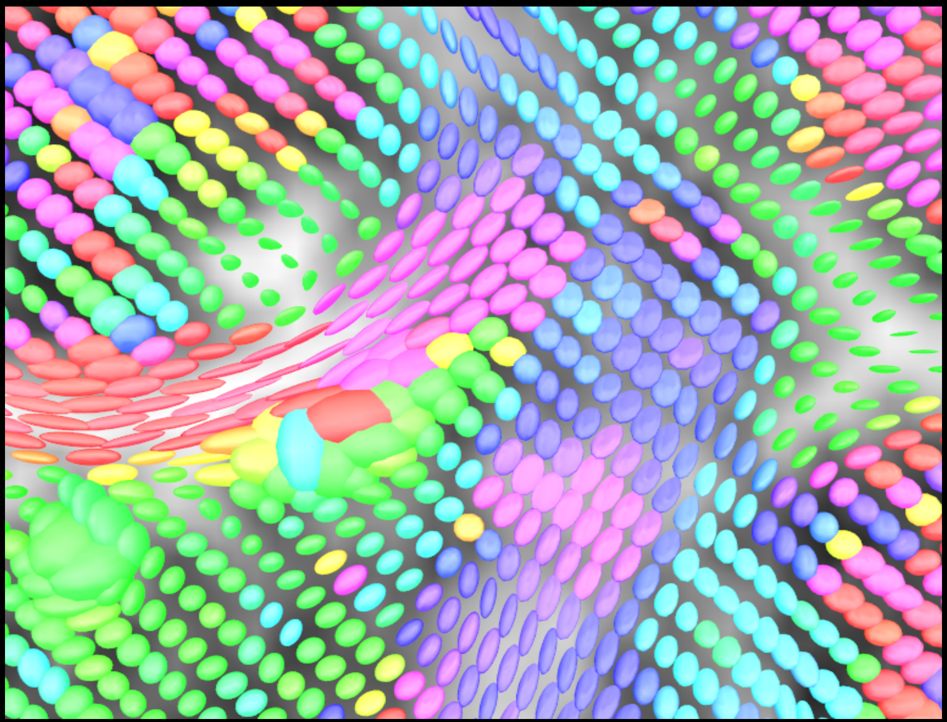
Possible sources of anisotropy:

- Axonal membranes of *densely packed axons hinder diffusion perpendicularly* to the fiber long axis.
- Myelin may also modulate anisotropy.

Psychiatry Neuroimaging Laboratory

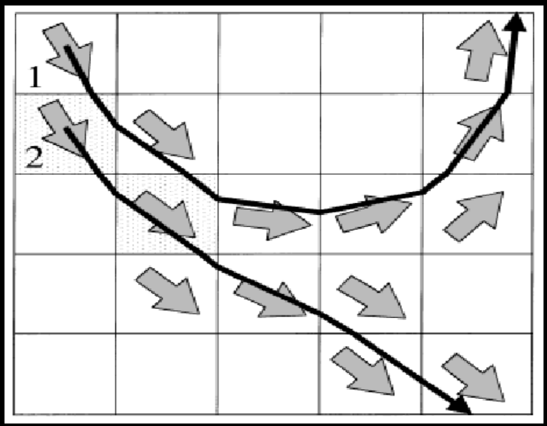
Diffusion Tensor Imaging

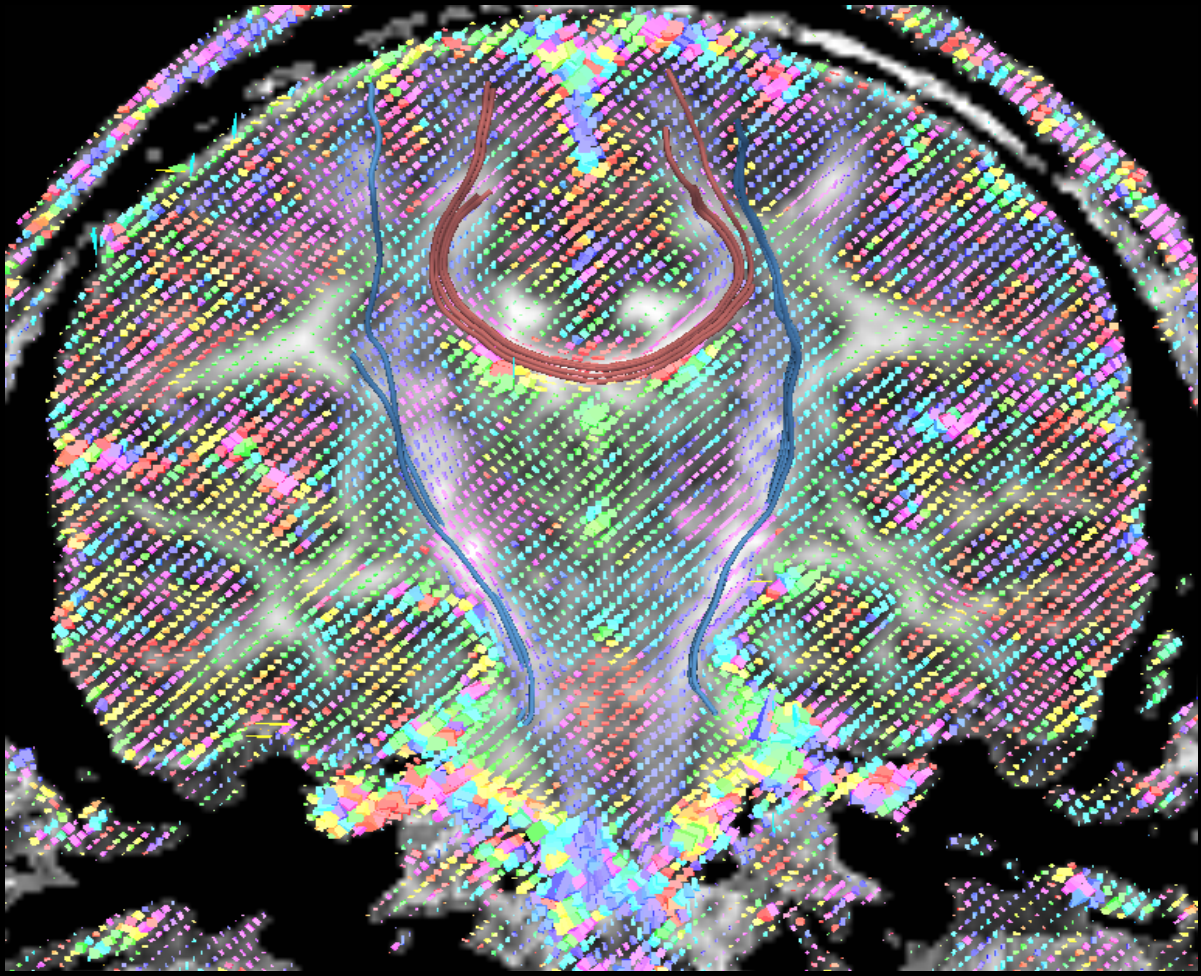




- At each location, the diffusion behavior of water is modeled as an ellipsoid.
- In medical imaging this ellipsoid is called a diffusion tensor.

From Tensors to Tracts

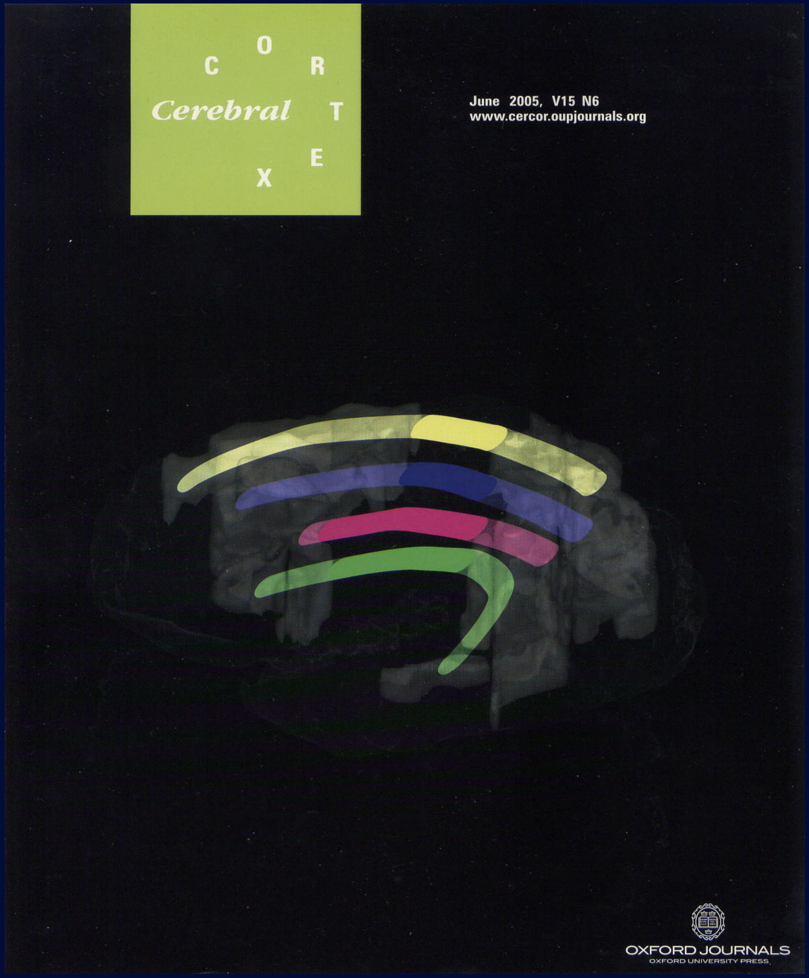




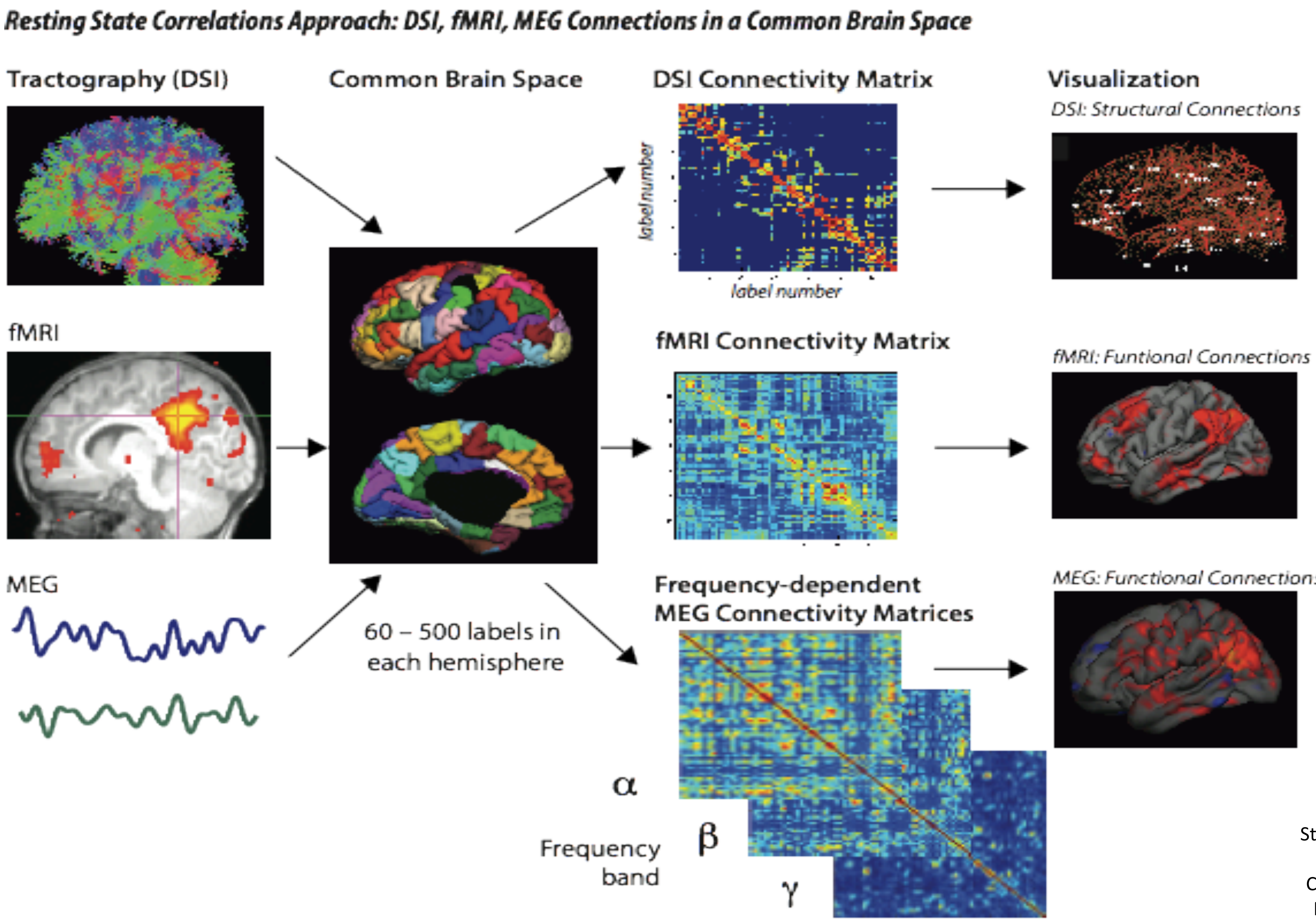
- Associate the major diffusion direction with the tangent to a curve.

- Estimate the curve from its tangents.

FromTensors to Tracts



Multimodal Brain Connectivity



Courtesy of
Steven Stufflebeam
Patric Hagmann
Christopher Honey
Matti Hämäläinen

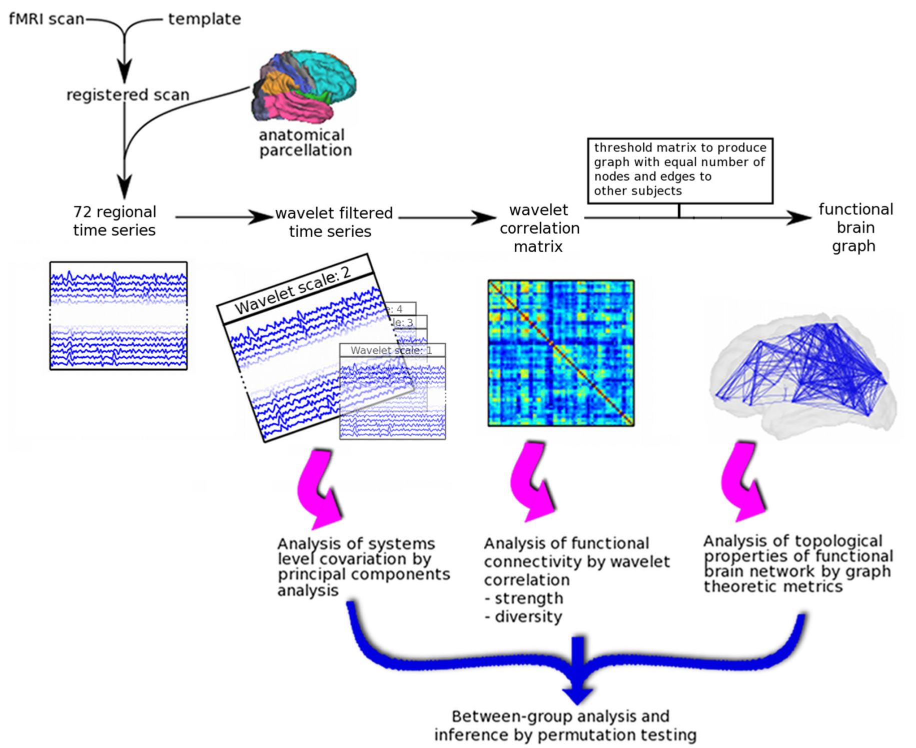


Figure 1. Schematic of fMRI data analysis pipeline. Regional mean fMRI time series were estimated by applying a prior anatomical template image to each individual fMRI dataset after its coregistration with the template in standard space; wavelet analysis was used to bandpass filter the regional time series and to estimate frequency-specific measures of functional connectivity between regions; functional connectivity matrices were thresholded to generate binary undirected graphs or brain functional networks; between-group differences in functional connectivity, principal components, and network topological metrics were assessed by permutation testing.

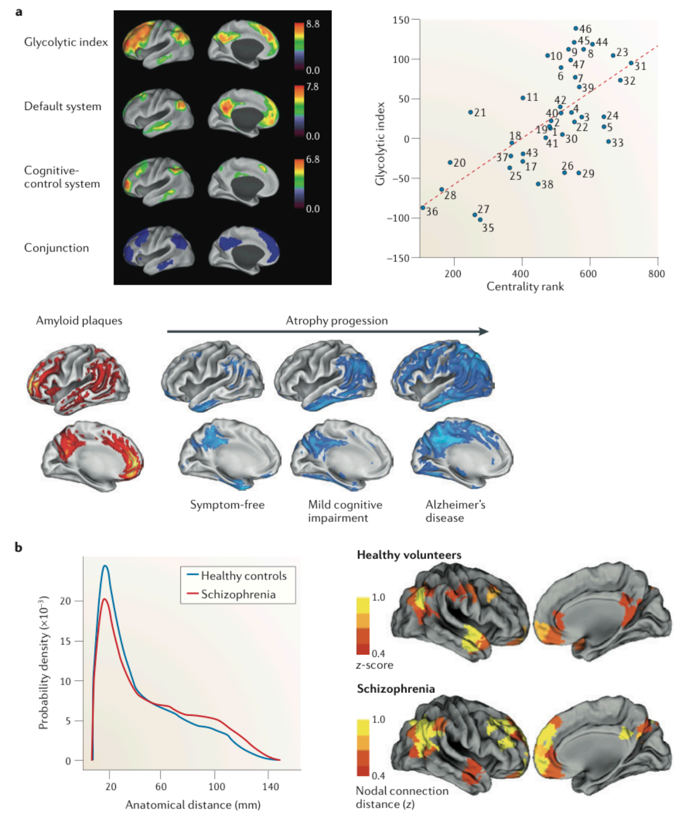
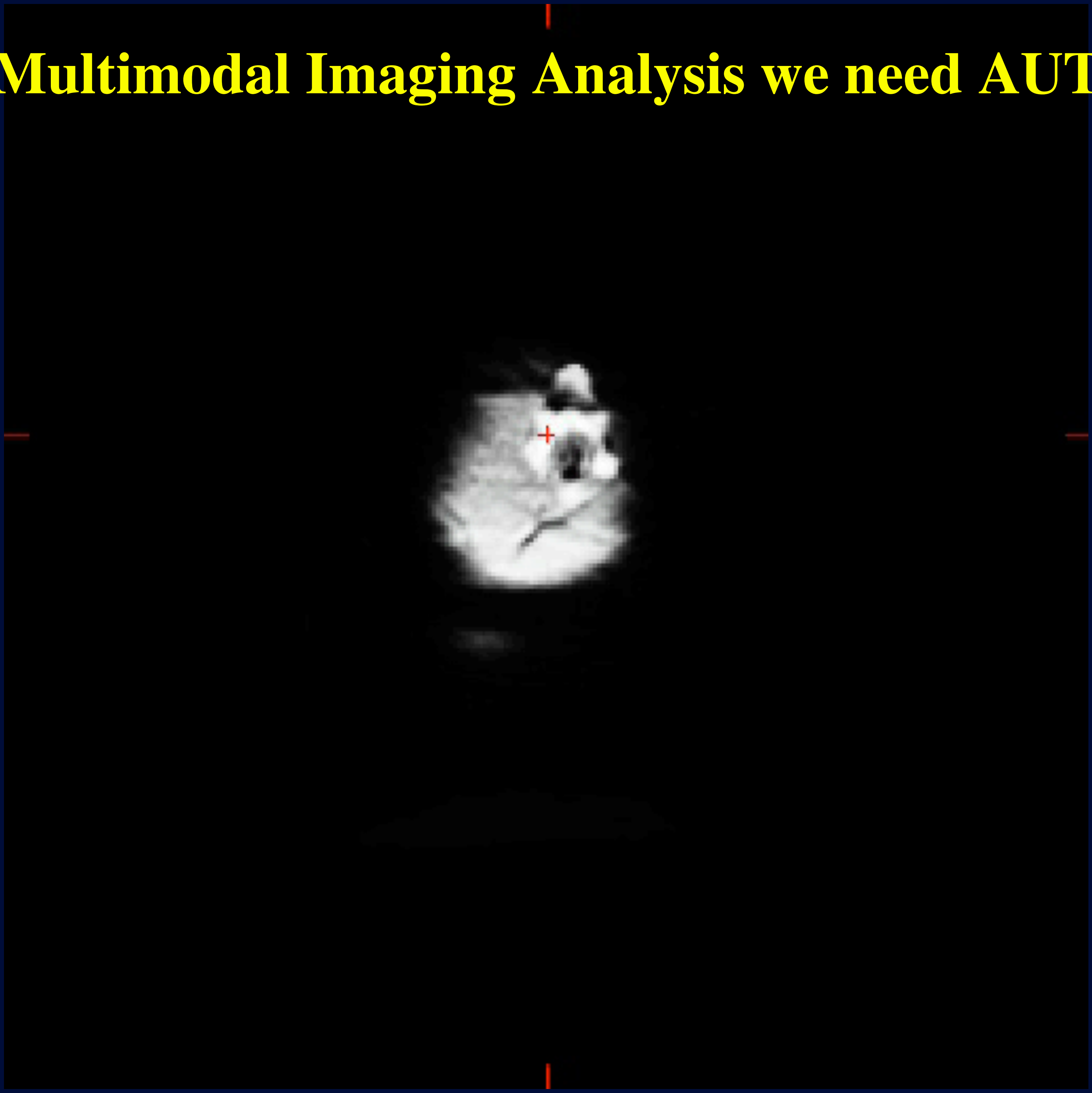
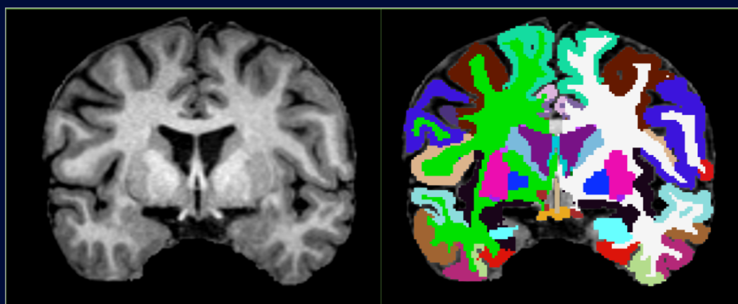


Figure 4 | **Brain disorders affect high-cost components of networks. a** | Brain networks and brain metabolism. The top left panel shows the regional distribution of aerobic glycolysis (as measured using the glycolytic index), the default mode system and the cognitive control system (as mapped by resting-state functional MRI (fMRI)) and the conjunction of these two systems with the glycolytic index, illustrating their overlap[161]. The top right panel shows a scatter plot of the centrality rank (which is estimated from the betweenness centrality of the connectomes of five participants[64]) and the glycolytic index[161] for 41 Brodmann areas of the cerebral cortex. The correlation is highly significant, with $r = 0.66$ ($P < 0.00005$), indicating that areas with high centrality — that is, the structural hubs — have a high glycolytic index[64,161]. Several of these hub nodes are members of the default and cognitive control systems. The bottom panel shows that high-cost hub nodes (including regions comprising the default mode system and the cognitive control system; see top left panel) are typically first affected by amyloid deposition and grey-matter atrophy in Alzheimer's disease, leading to disruption of memory functions that are dependent on large-scale network integrity[162,163]. **b** | fMRI networks in patients with schizophrenia contain proportionally more long-distance connections than fMRI networks in healthy controls (left panel), perhaps owing to excessive developmental pruning of shorter-distance connections. Accordingly, inter-modular connector hubs that have a large number of long-distance connections (indicated by areas with high connection distance in the right panel) are more extensive in functional brain networks of people with schizophrenia than in healthy volunteers[46]. Part **a** is reproduced, with permission, from REF. 161 © (2010) National Academy of Sciences, and from REF. 163 © (2008) New York Academy of Sciences. Part **b** is reproduced, with permission, from REF. 46 © (2012) Oxford Journals.

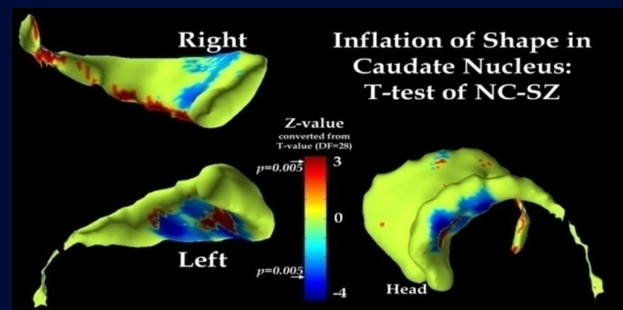
For Multimodal Imaging Analysis we need AUTOMATION



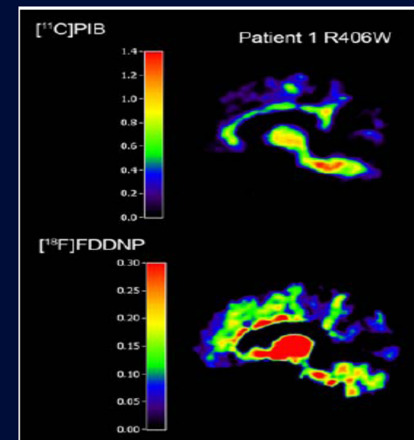
Methodologies



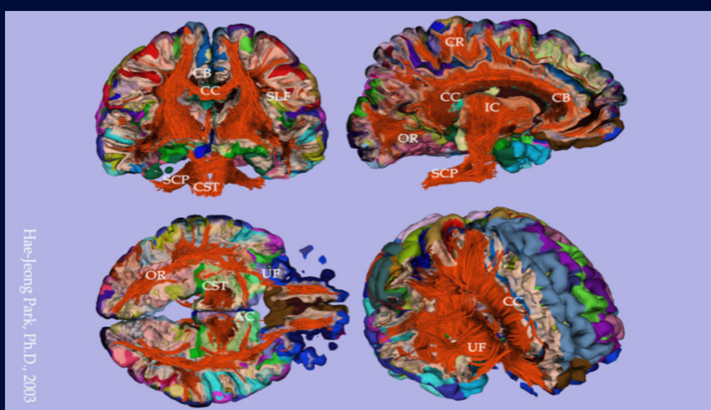
Volume - Morphometry



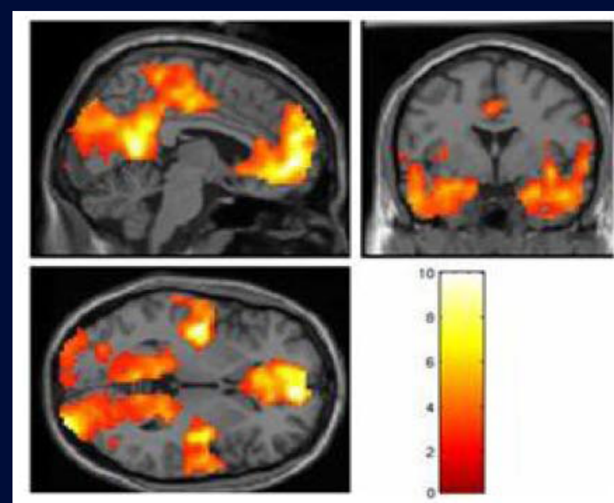
Shape - Morphometry



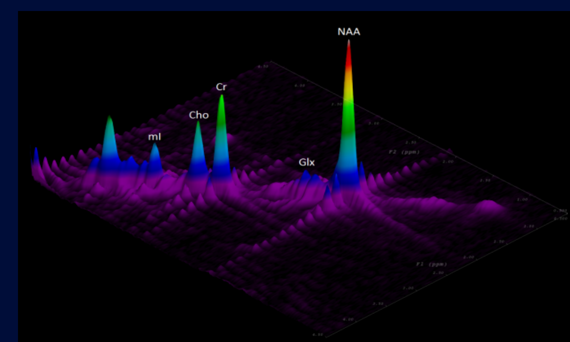
PET



Diffusion Imaging

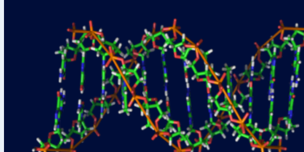


Functional Imaging



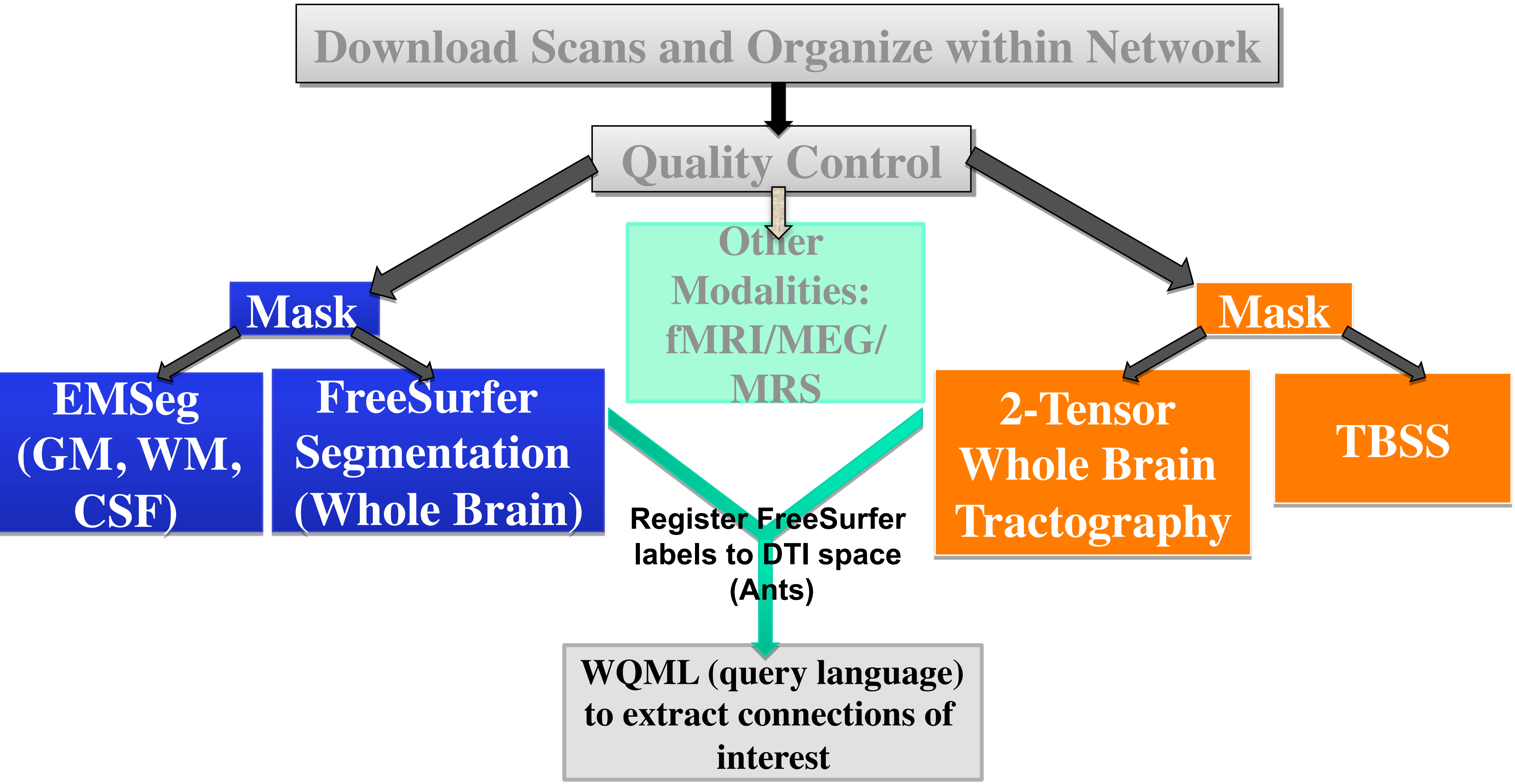
MR Spectroscopy

Data Infrastructure



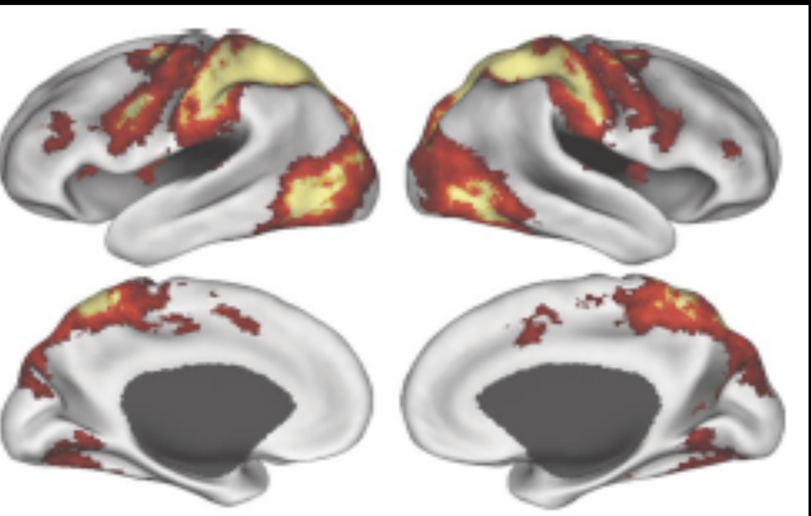
Genetics

PNL Pipeline



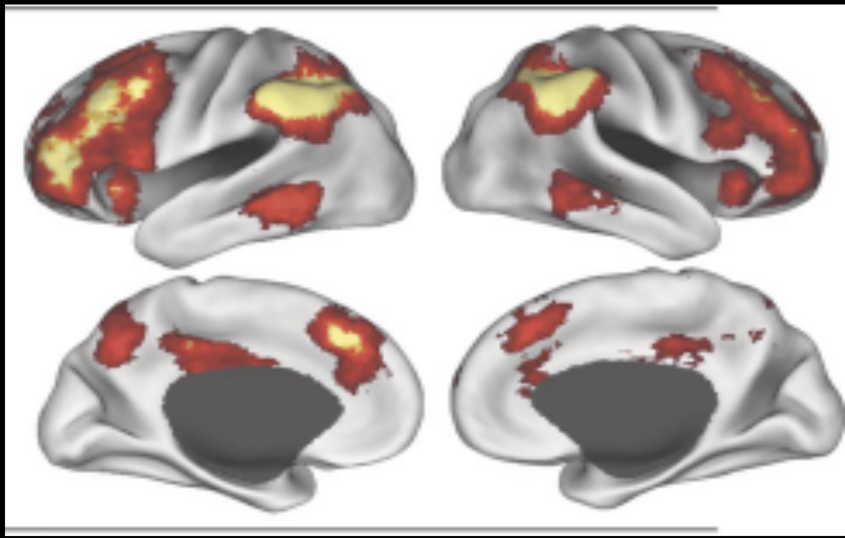
Neural Systems in Cognition and Emotion

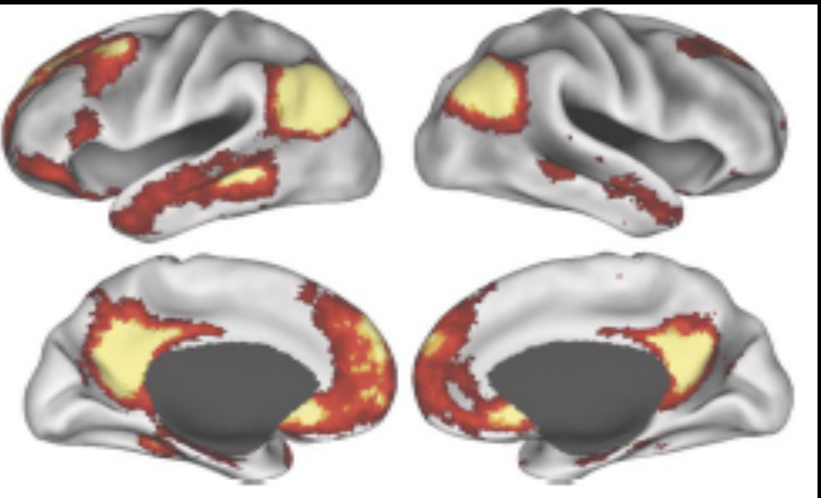
Large-scale cognitive systems
understrood through resting state fMRI



Dorsal visuospatial attention system

Frontoparietal executive control system



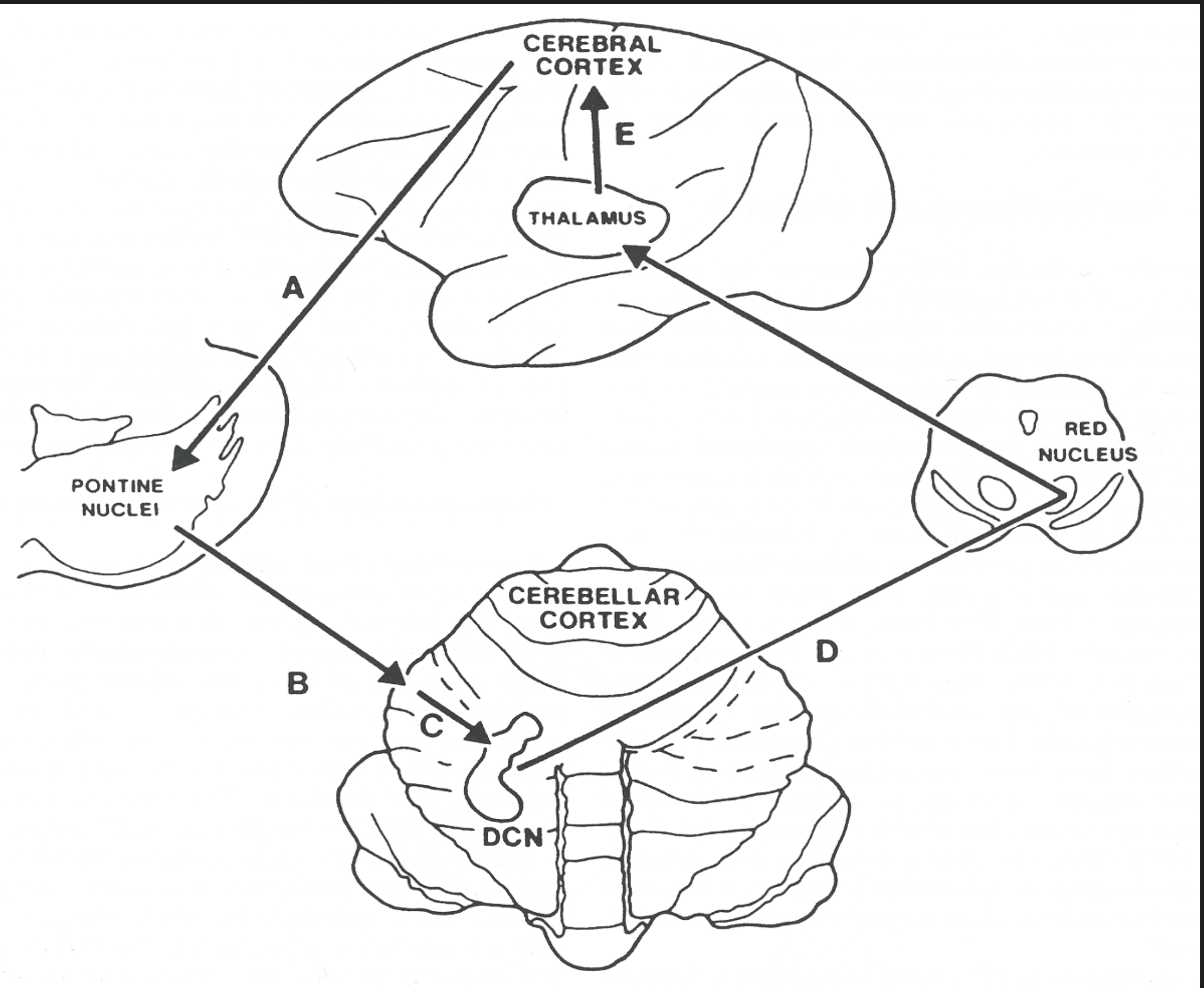


Episodic memory/Default-mode system

Vincent et al., J Neurophys, 2008

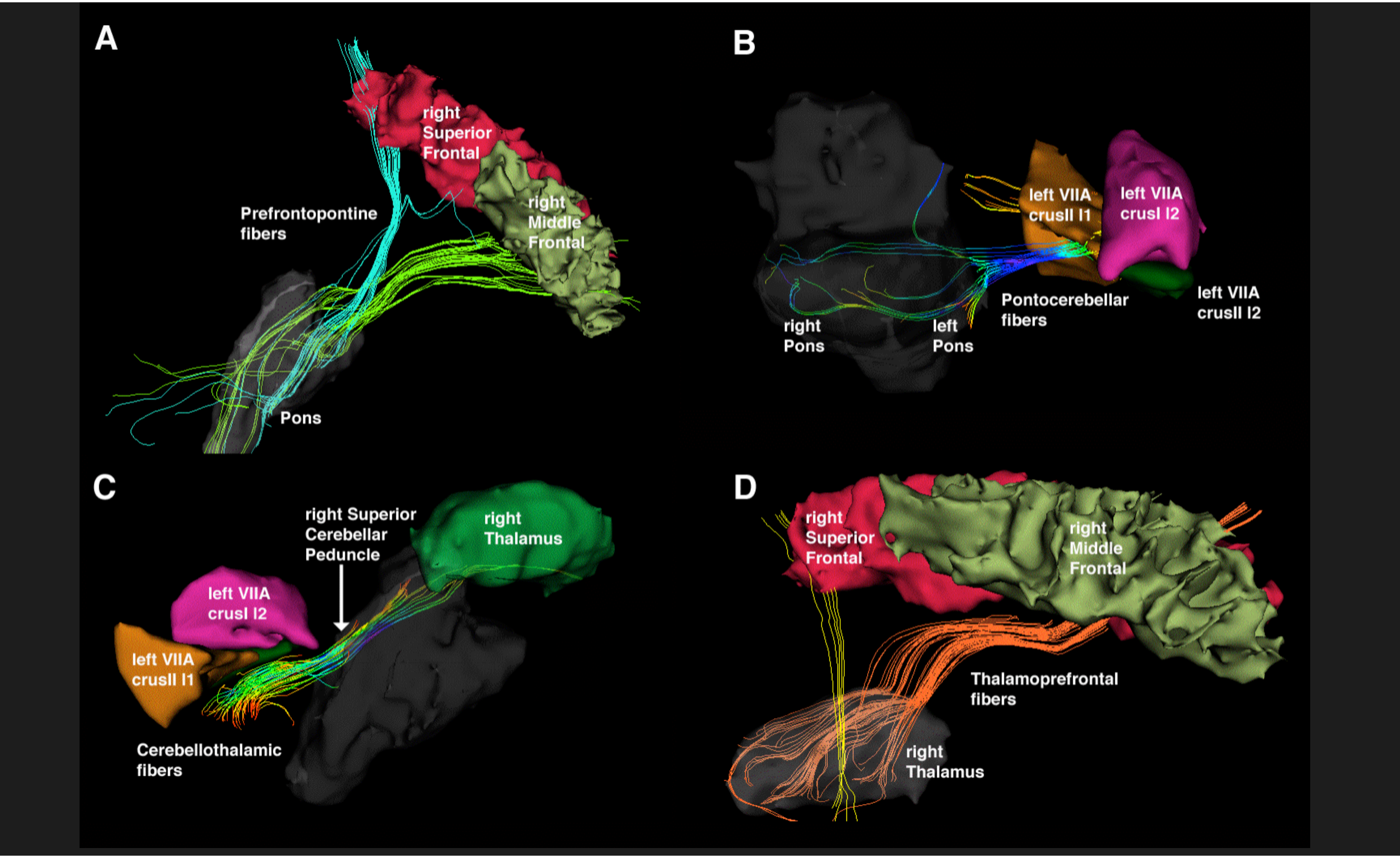
From a structural point of view Neural Systems are:

The *Cortical* and *Subcortical* Anatomical Structures and their connections within the *White Matter* that form the building blocks of a neural systems description of the human brain.

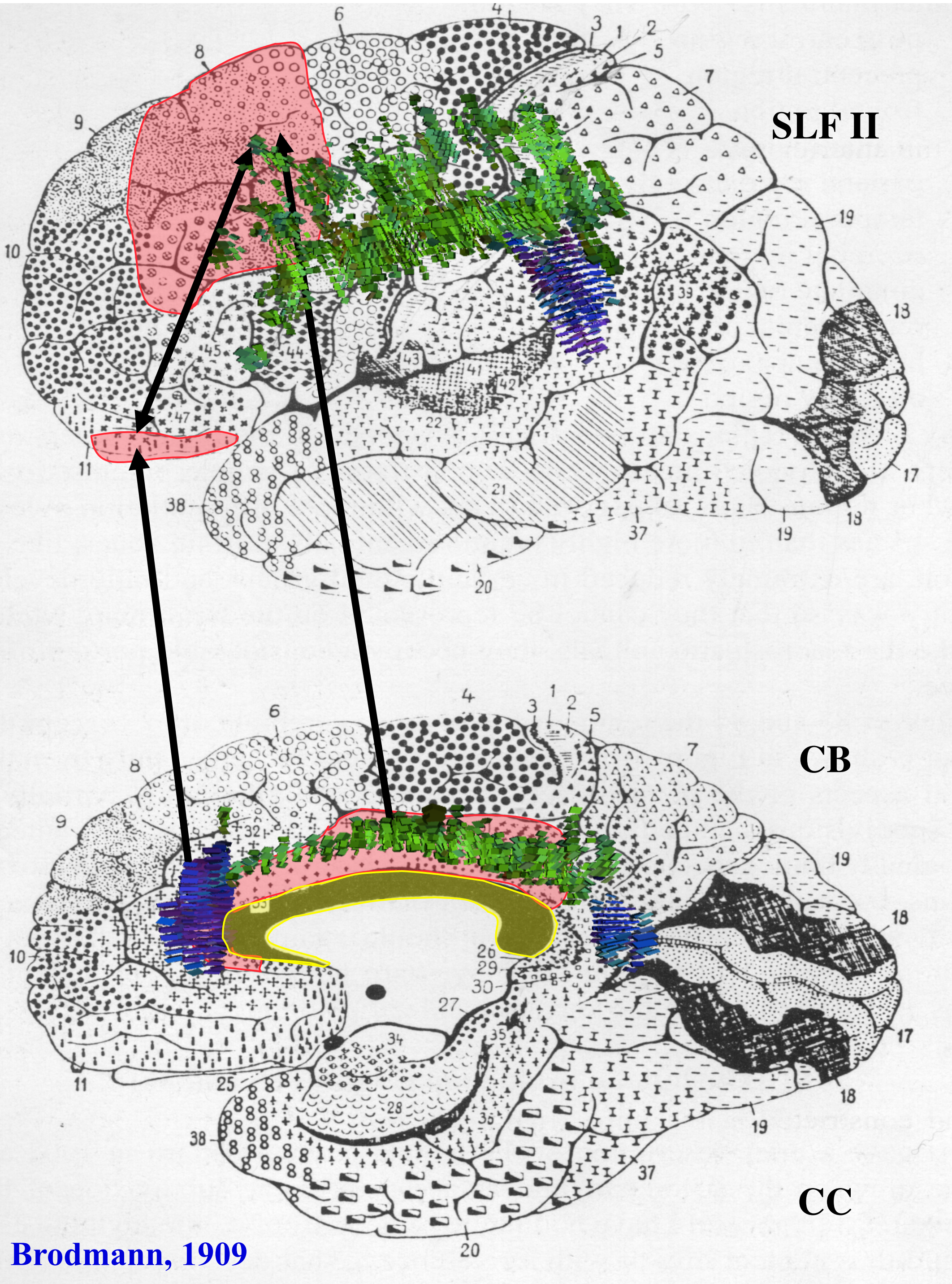


Diagrammatic representation of the cerebrocerebellar circuitry, including corticopontine connections which carry higher-order (*Cognitive*) information as well as sensorimotor inputs to the cerebellar cortex.

From Schmahmann 2000



Prefrontocerebellar circuitry: A) Prefrontoponine ipsilateral projection, B) crossing pontocerebellar projection, C) crossing cerebellothalamic projection, and D) halamoprefrontal ipsilateral projection



Executive Function Cortical System

(Bilateral)

Cortical Areas:

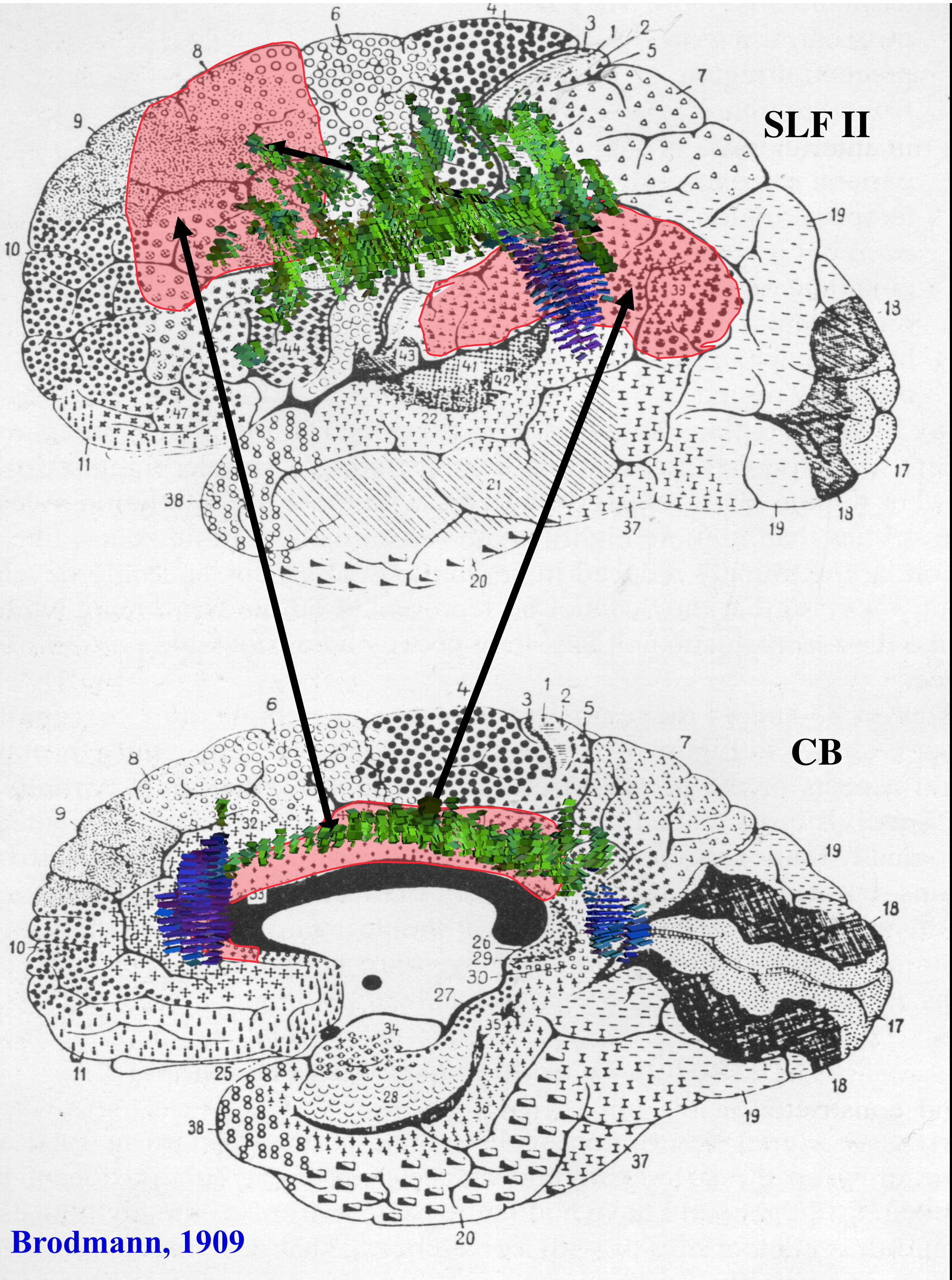
Dorsolateral Prefrontal Cortex
(BA 8, 9, 46)

Cingulate Gyrus
(BA 24, 23)

Orbital Frontal Cortex
(BA 11, 12, 13 14)

Fiber Tracts:

CB, CC and SLF II



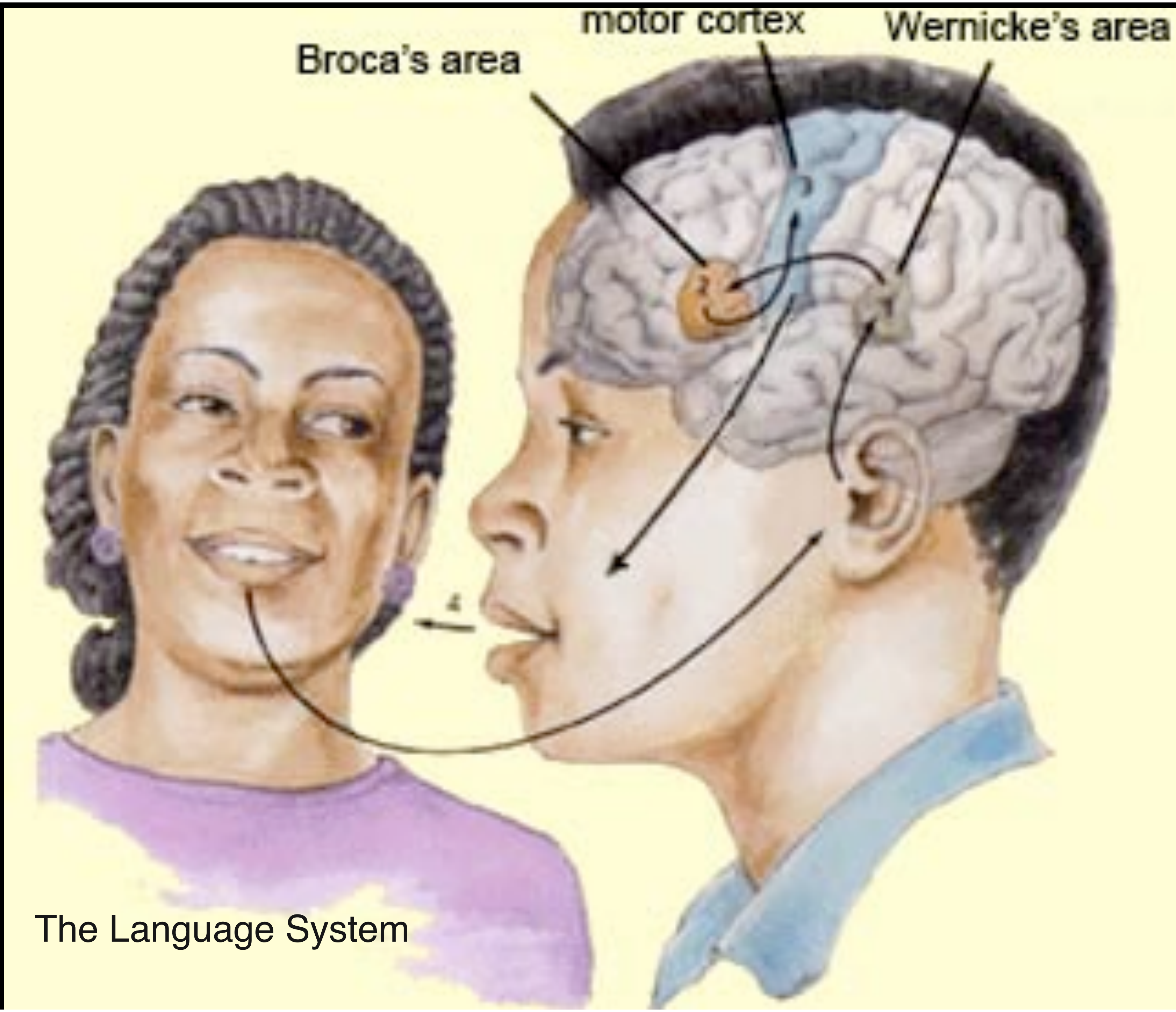
Attention Cortical System

(Lateralized on Right hemisphere)

Cortical Areas:

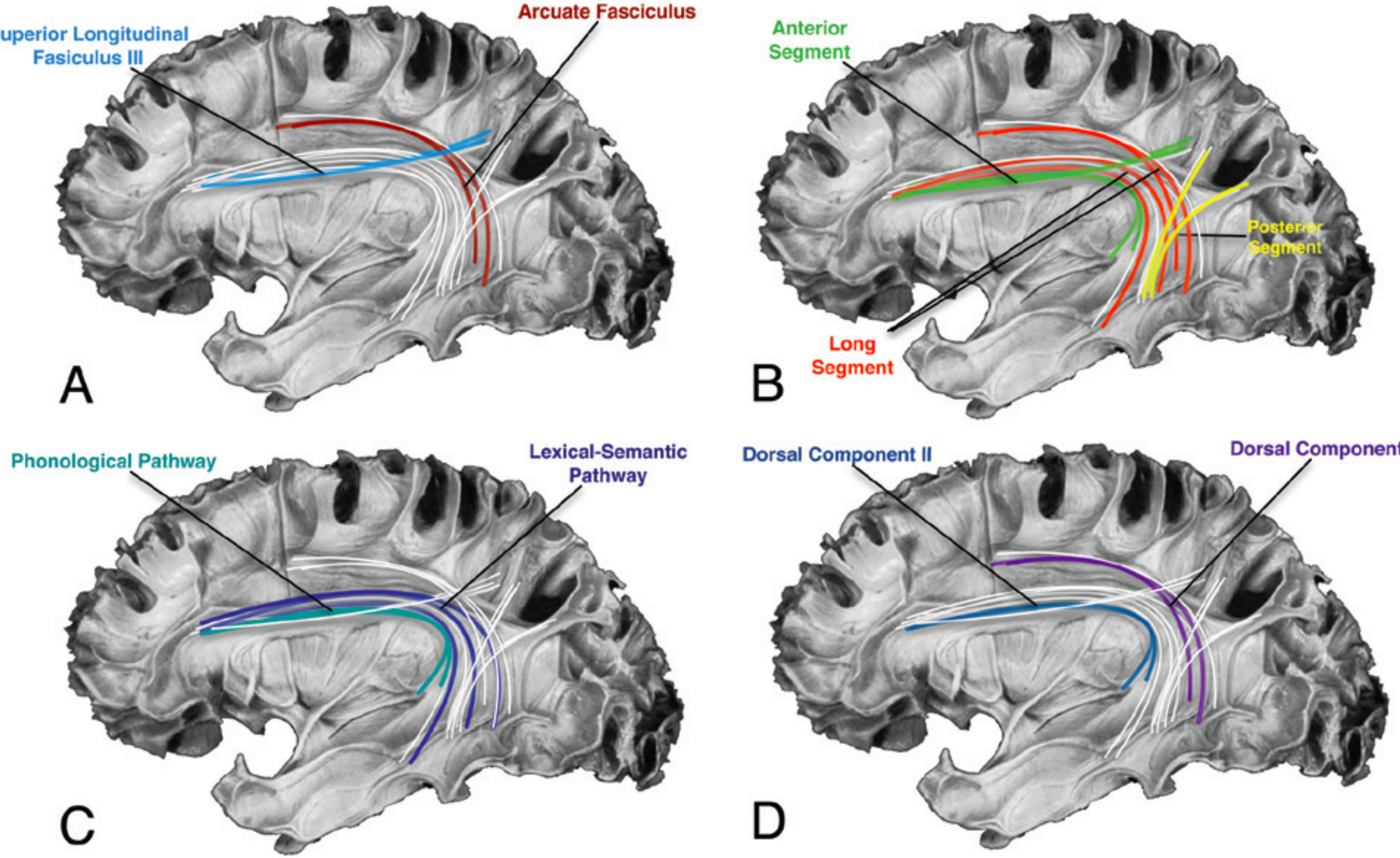
Inferior Parietal Lobule
(BA 39, 40)
Dorsolateral Prefrontal Cortex
(BA 8, 9, 46)
Cingulate Gyrus
(BA 24, 23)

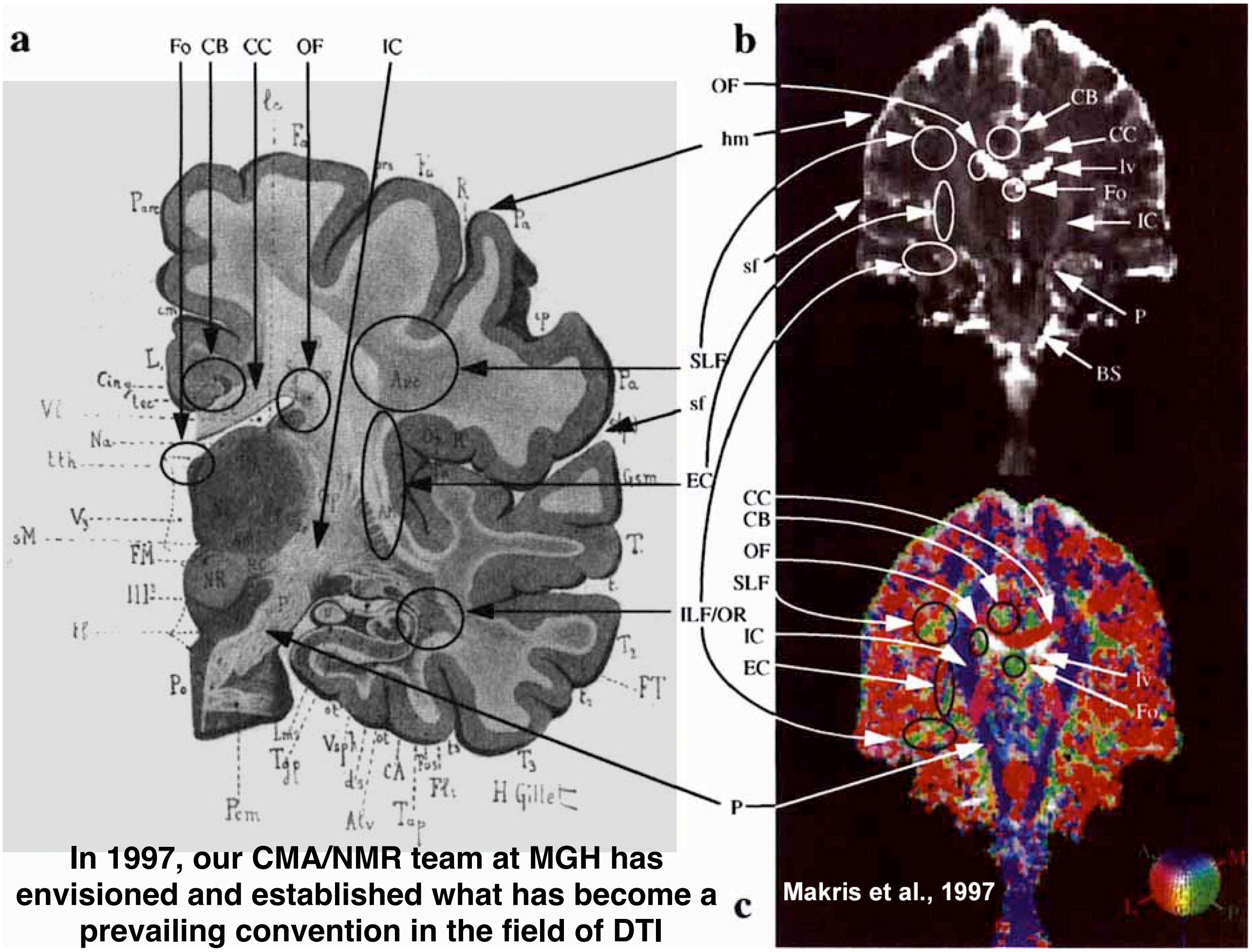
Fiber Tracts:
SLF II and CB



The Language System

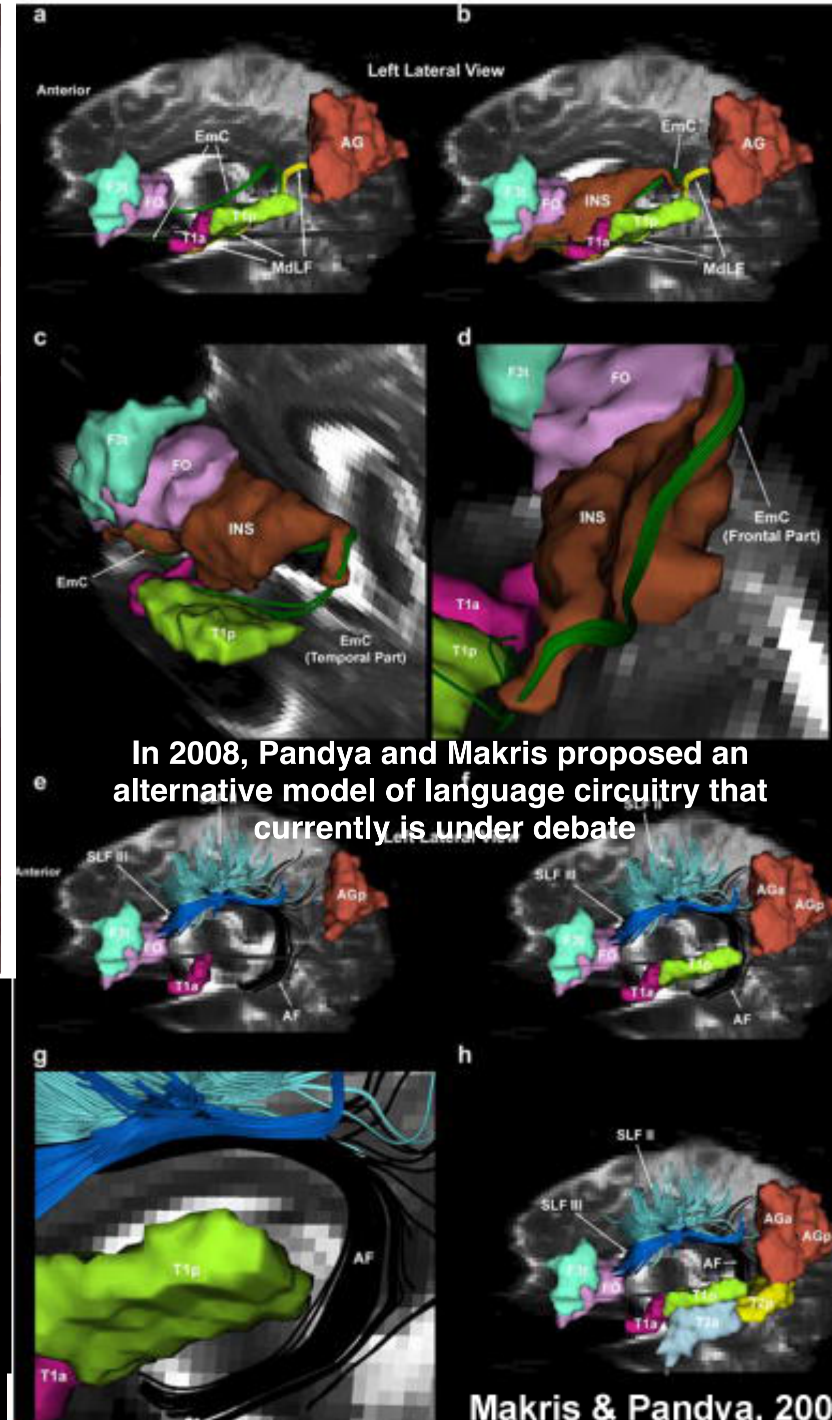
Dorsal Streams





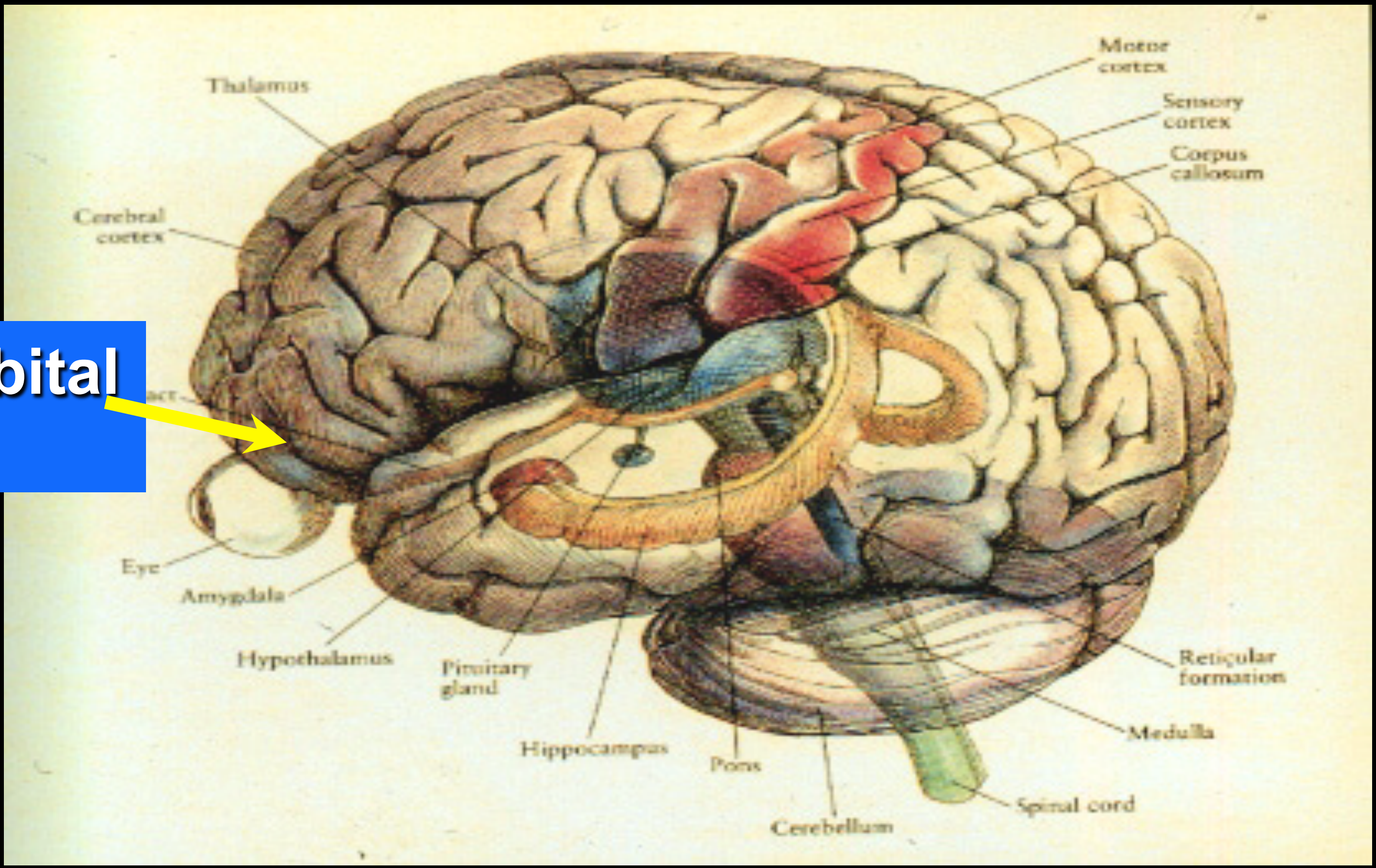
In 1997, our CMA/NMR team at MGH has envisioned and established what has become a prevailing convention in the field of DTI

Between 1999 (Makris PhD thesis) and 2012 (Makris et al., 2008, 2012, 2013), Makris and Pandya have provided evidence for a novel fiber tract in humans, named, by them, the "Middle Longitudinal Fascicle" (MdLF) *(Makris, Pandya, et al., Cer Cor, 2008)*



In 2008, Pandya and Makris proposed an alternative model of language circuitry that currently is under debate

Emotions: Limbic and Paralimbic Systems



Frontoorbital Cortex

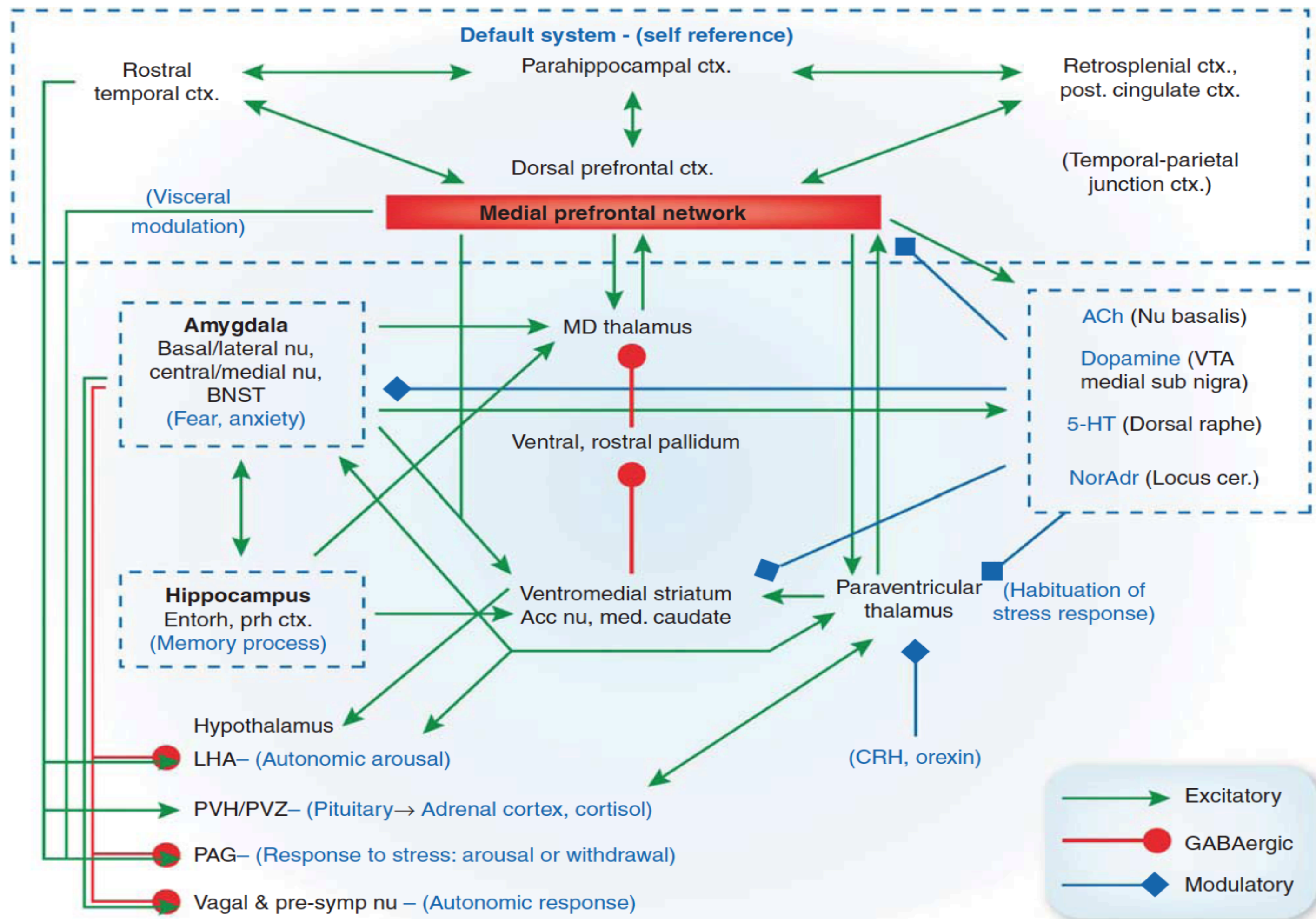
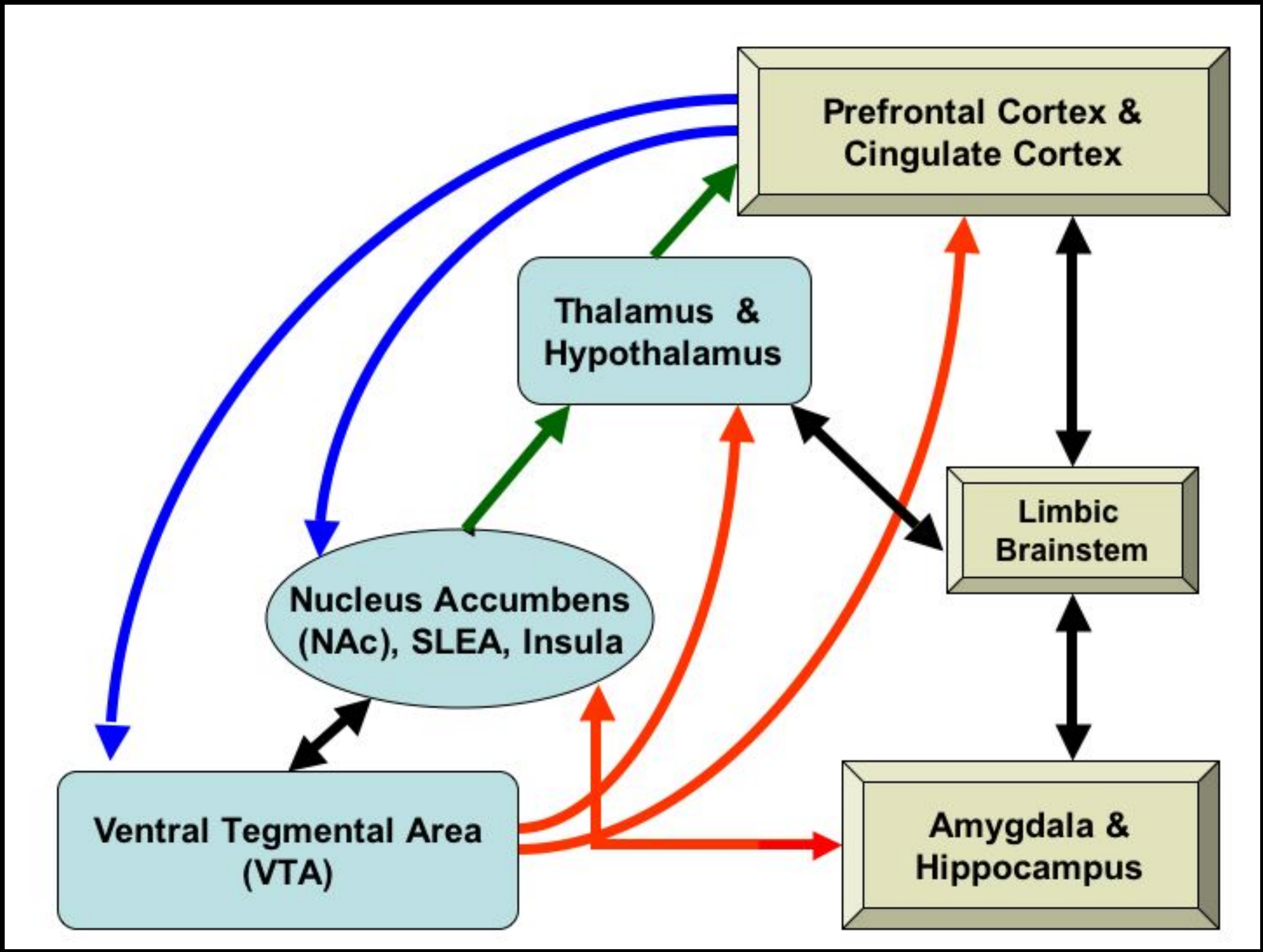


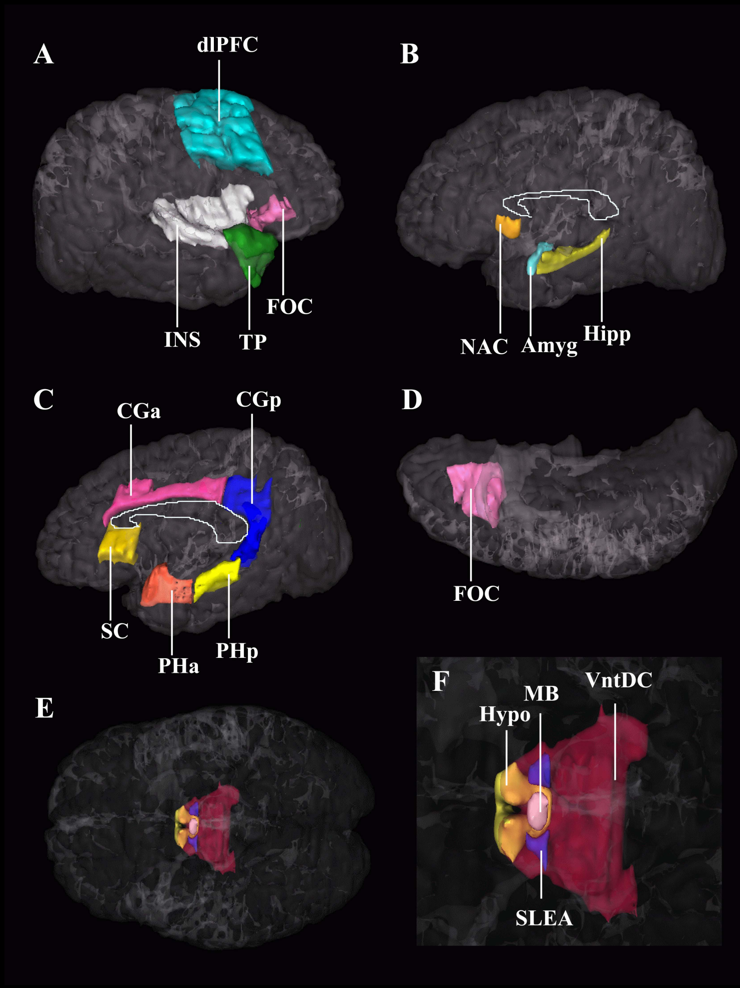
Figure 10. Anatomical circuits involving the medial prefrontal network (medial prefrontal network) and amygdala. Glutamatergic, presumed excitatory projections are shown in green, GABAergic projections are shown in orange, and modulatory projections in blue. In the model proposed here, dysfunction in the amygdala and/or the medial prefrontal network results in dysregulation of transmission throughout an extended brain circuit that stretches from the cortex to the brainstem, yielding the emotional, cognitive, endocrine, autonomic, and neurochemical manifestations of depression. Intra-amygdaloid connections link the basal and lateral amygdaloid nuclei to the central and medial nuclei of the amygdala and the bed nucleus of the stria terminalis (BNST). Parallel and convergent efferent projections from the amygdala and the medial prefrontal network to the hypothalamus, periaqueductal gray (PAG), nucleus basalis, locus ceruleus, dorsal raphe, and medullary vagal nuclei organize neuroendocrine, autonomic, neurotransmitter and behavioral responses to stressors and emotional stimuli (Davis and Shi, 1999, LeDoux, 2003). In addition, the amygdala and medial prefrontal network interact with the same cortico-striatal-pallidal-thalamic loop, through prominent connections both with the accumbens nucleus and medial caudate, and with the mediodorsal and paraventricular thalamic nuclei, which may function to control and limit responses to stress. Finally, the medial prefrontal network is a central node in the cortical 'default system' that appears to support self-referential functions such as mood. Other abbreviations: 5-HT—serotonin; ACh—acetylcholine; Cort.—corticosteroid; CRH—corticotrophin releasing hormone; Ctx—cortex; NorAdr—norepinephrine; PVN—paraventricular nucleus of the hypothalamus; PVZ—periventricular zone of hypothalamus; STGr—rostral superior temporal gyrus—VTA—ventral tegmental area.

Price and Drevets
Trends Cogn Sci, 2010

Brain Reward Circuitry:

Consists of cortical and subcortical structures involved in controlling emotion and regulating sensitivity to reinforcements.





Makris et al., Biological Psychiatry, 2008

Neural Systems in Clinical Conditions

Attention-Deficit/Hyperactivity Disorder

(ADHD)

Neural Systems approach addresses at least three questions

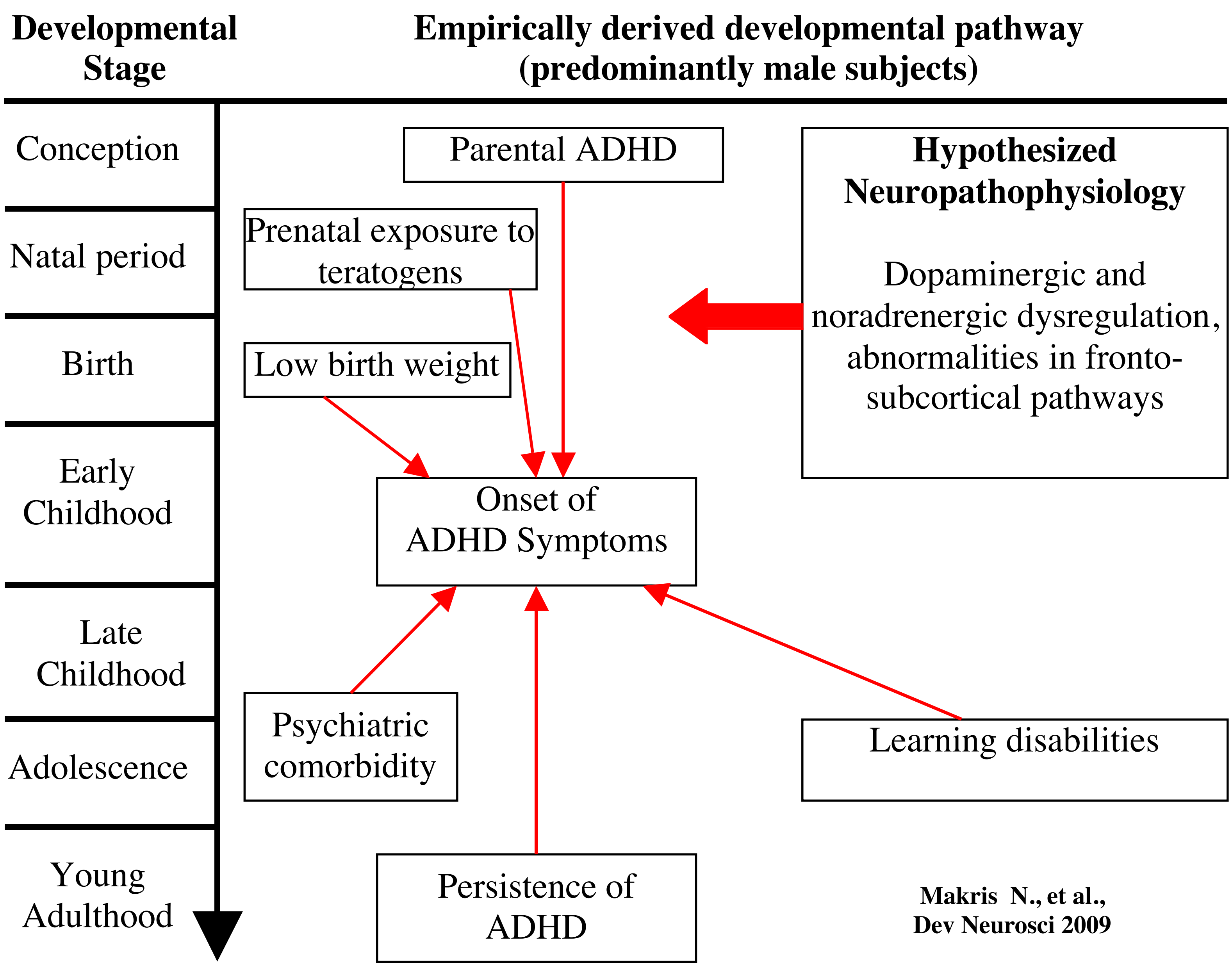
1) Are the structures shown to be altered in ADHD indeed component parts of well-understood neural systems?

2) Do these structural neural systems correlate with specific behaviors?

3) Are these neural systems associated with specific genotypes?

Makris N., et al.,
Dev Neurosci 2009

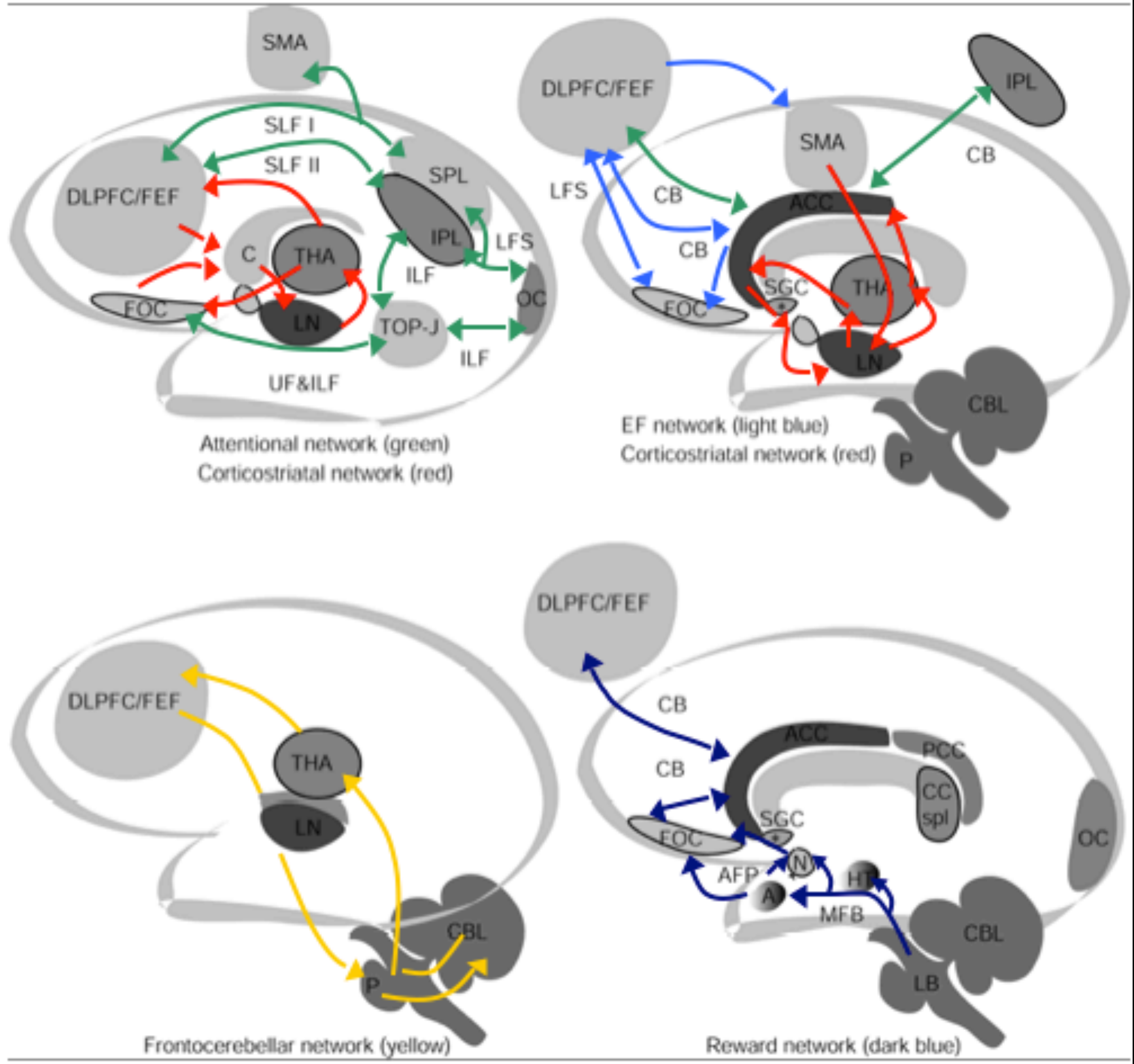
Figure 1: Conceptual model of the pathophysiology and etiology of ADHD



Neural Systems approach in ADHD (cont.d)

1) Are the structures shown to be altered in ADHD indeed component parts of well-understood neural systems?

Figure 2: Functional neuroanatomy of circuits involved in the pathophysiology of ADHD



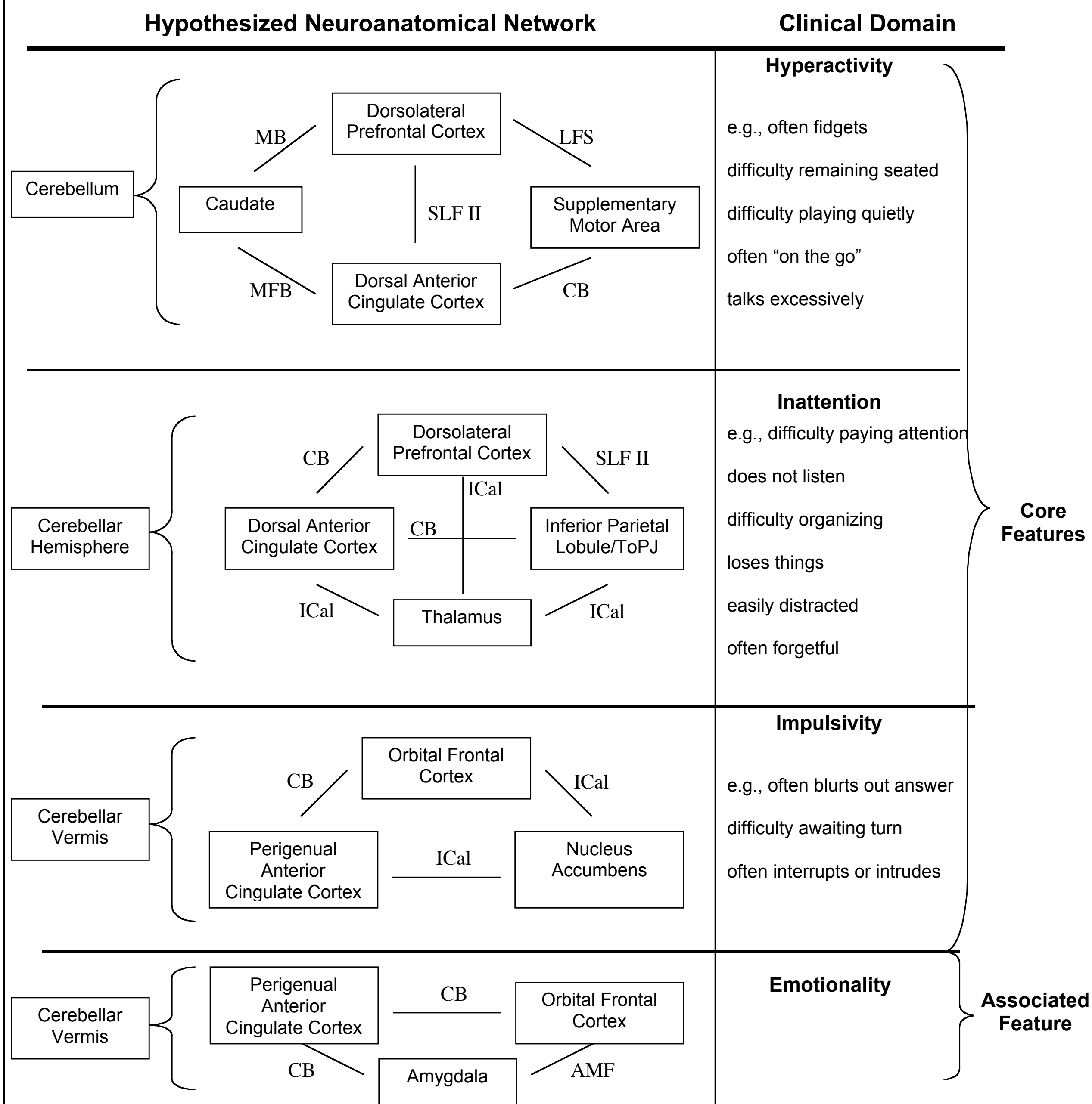
A=amygdala; ACC=anterior cingulate cortex; AFP=amygdalofugal pathway; C=caudate nucleus; CB=cingulum bundle; CBL=cerebellum; CCspl=splenium of corpus callosum (incl. isthmus); DLPFC=dorsolateral prefrontal cortex; FEF=frontal eye field; FOC=fronto-orbital cortex; HT=hypothalamus; ILF=inferior longitudinal fascicle; IPL= inferior parietal lobule; LB=limbic brainstem; LFS=local fiber system; LN=lenticular nucleus; MFB=medial forebrain bundle; N=nucleus accumbens; OC=occipital cortex; P=pons; PCC=posterior cingulate cortex; SGC=subgenual cingulate cortex; SLF=superior longitudinal fascicle; SMA=supplementary motor area; SPL=superior parietal lobule; THA=thalamus; TOP-J=tempro-occipito-parietal junction; UF=uncinate fascicle

Makris N., et al.,
Dev Neurosci 2009

Neural Systems approach in ADHD (cont.d)

2) Do these structural neural systems correlate with specific behaviors?

Figure 3. Conceptual Model of the Neuroanatomical Substrates of ADHD



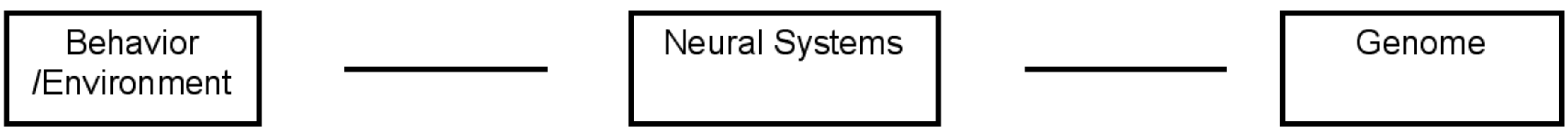
AMF=amygdalo-fugal pathway; MFB=medial forebrain bundle; LFS=local fiber systems; SLF II= superior longitudinal fascicle; CB=cingulum bundle; ICal=internal capsule anterior limb; ToPJ=temporo-occipito parietal junction

Makris N., et al., Dev Neurosci 2009

Neural Systems approach in ADHD (cont.d)

3) Are these neural systems associated with specific genotypes?

Figure 4: Neural systems biology acts as an interface between behavior and the genome

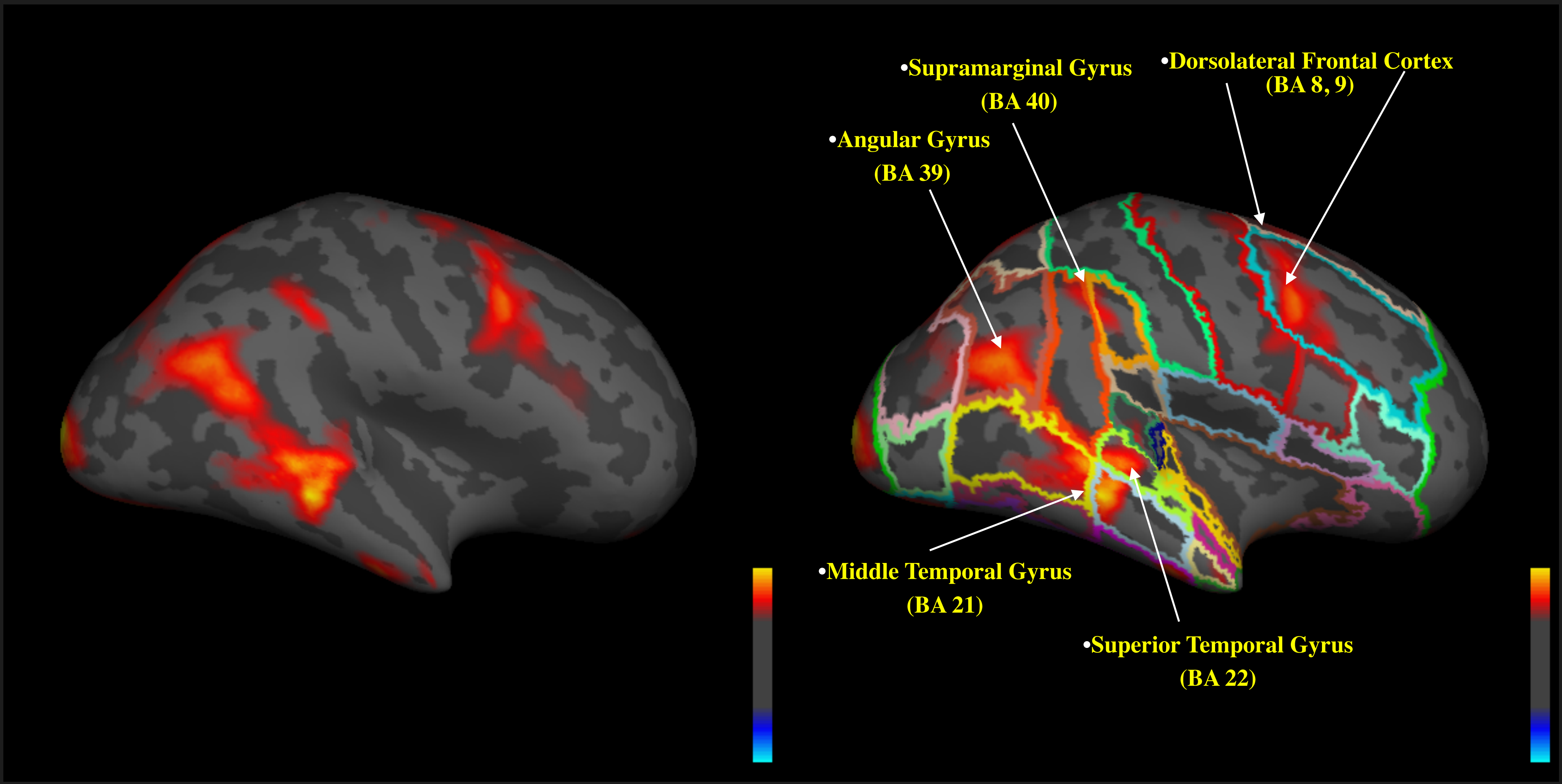


Makris N., et al.,
Dev Neurosci 2009

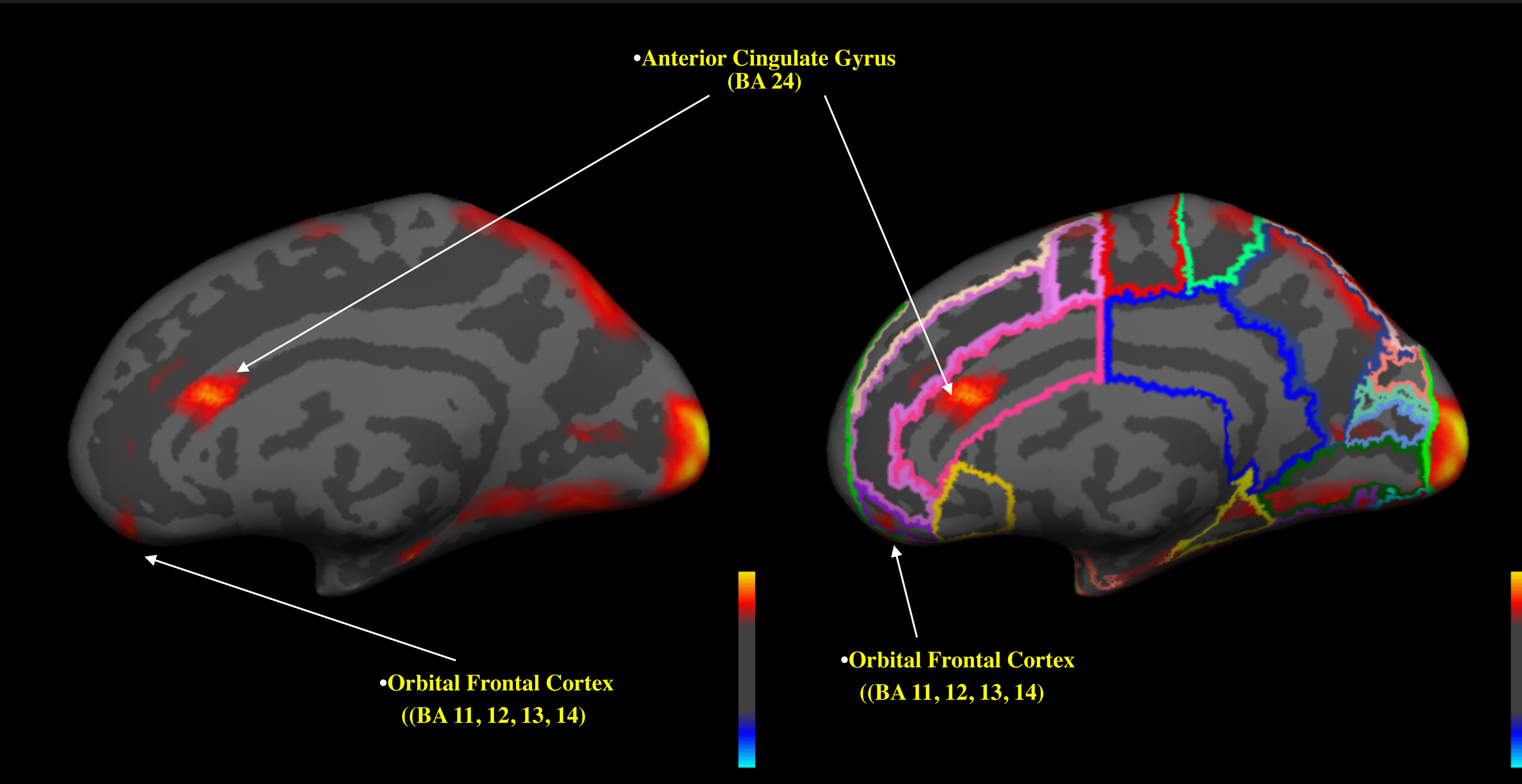
Biological Psychiatry

Volume 60, Number 10
November 15, 2006

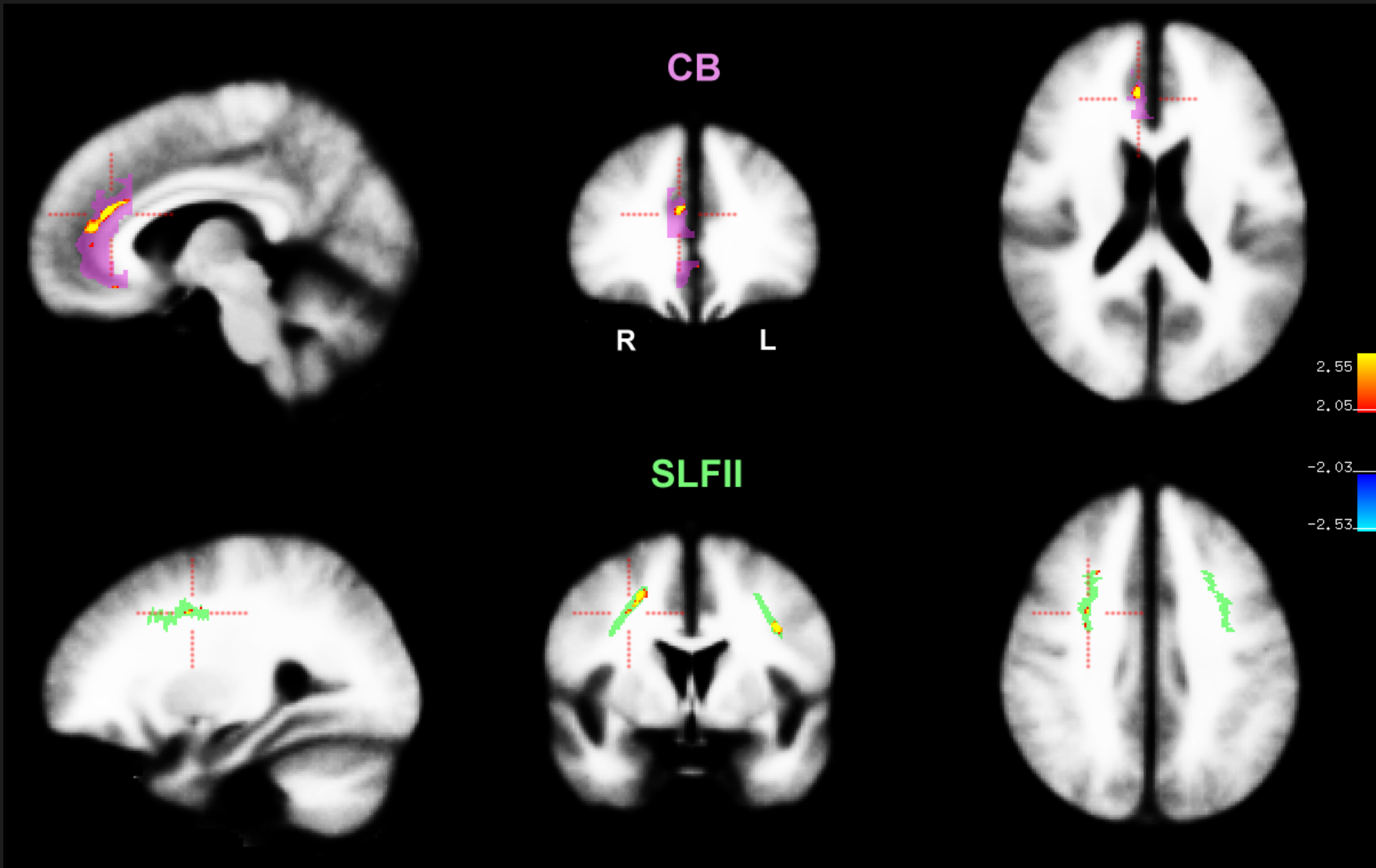
ISSN 0006-3223
www.sobp.org/journal
Official Journal of the Society of Biological Psychiatry



•Supramarginal Gyrus
(BA 40)
•Dorsolateral Frontal Cortex
(BA 8, 9)
•Angular Gyrus
(BA 39)
•Middle Temporal Gyrus
(BA 21)
•Superior Temporal Gyrus
(BA 22)

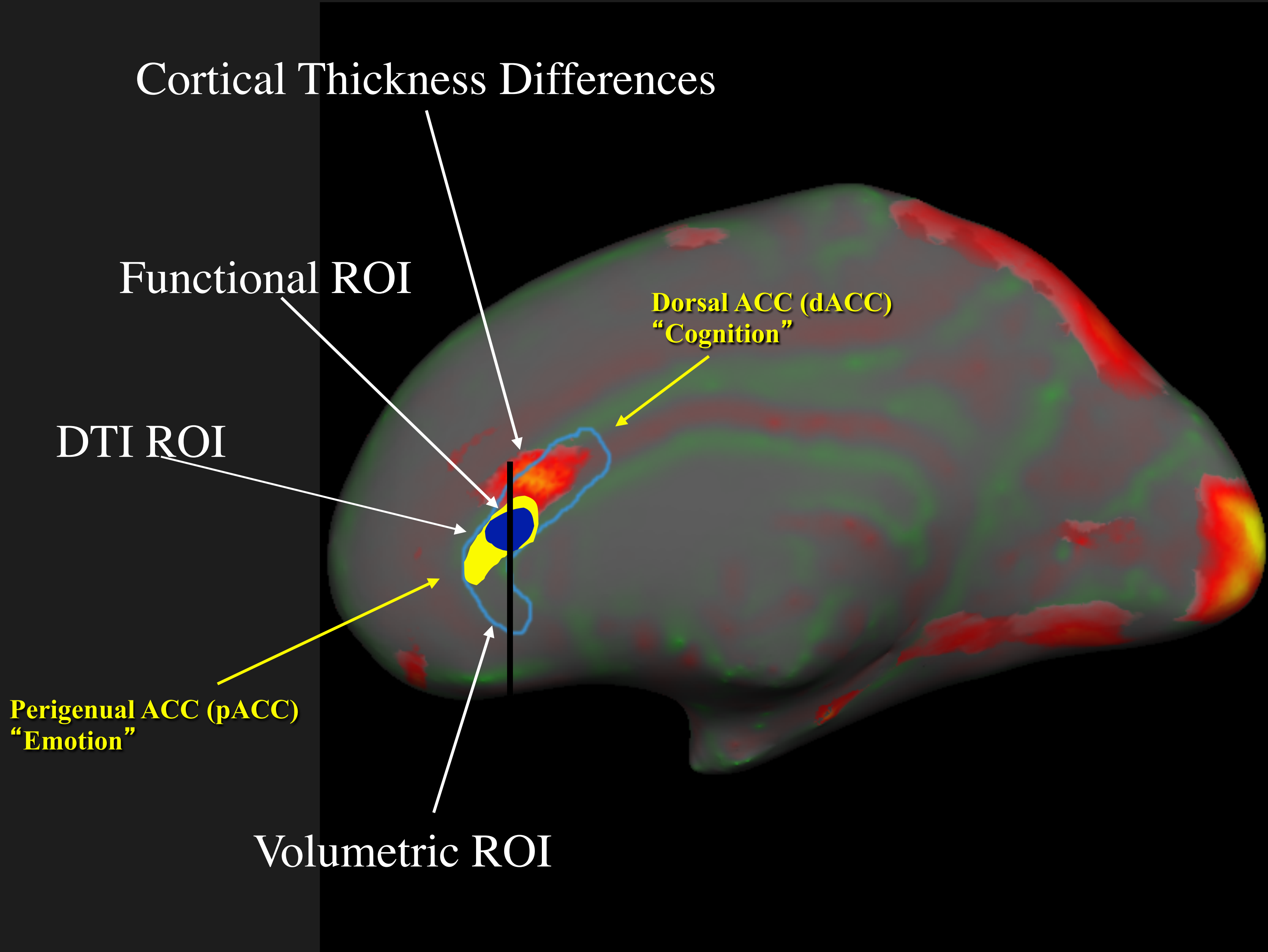


•Anterior Cingulate Gyrus
(BA 24)
•Orbital Frontal Cortex
((BA 11, 12, 13, 14)
•Orbital Frontal Cortex
((BA 11, 12, 13, 14)

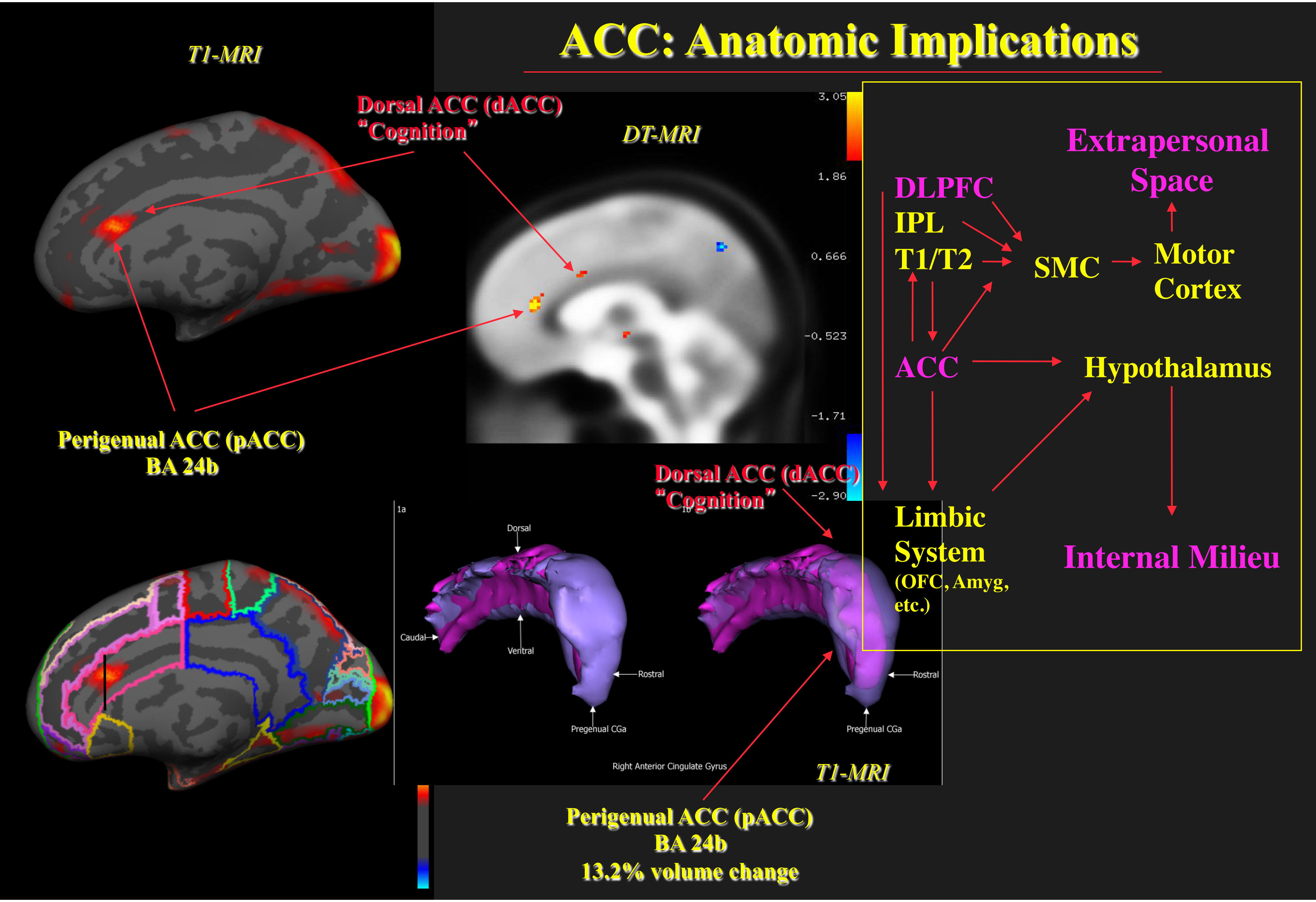


Fractional anisotropy decrease in ROIs for the cingulum bundle and the superior longitudinal fascicle II (SLF II) in adults with ADHD

Makris, Seidman et al, 2007



Cortical Thickness Differences
Functional ROI
Dorsal ACC (dACC)
"Cognition"
DTI ROI
Perigenual ACC (pACC)
"Emotion"
Volumetric ROI


ACC: Anatomic Implications
T1-MRI
Dorsal ACC (dACC) "Cognition"
DT-MRI
3.05
1.86
0.666
-0.523
-1.71
-2.90
Perigenual ACC (pACC) BA 24b
1a
Dorsal
Caudal
Ventral
Rostral
Pregenual CGa
Dorsal ACC (dACC) "Cognition"
Rostral
Pregenual CGa
Right Anterior Cingulate Gyrus
T1-MRI
Perigenual ACC (pACC) BA 24b 13.2% volume change
Extrapersonal Space
DLPFC
IPL
T1/T2
SMC
Motor Cortex
ACC
Hypothalamus
Limbic System (OFC, Amyg, etc.)
Internal Milieu

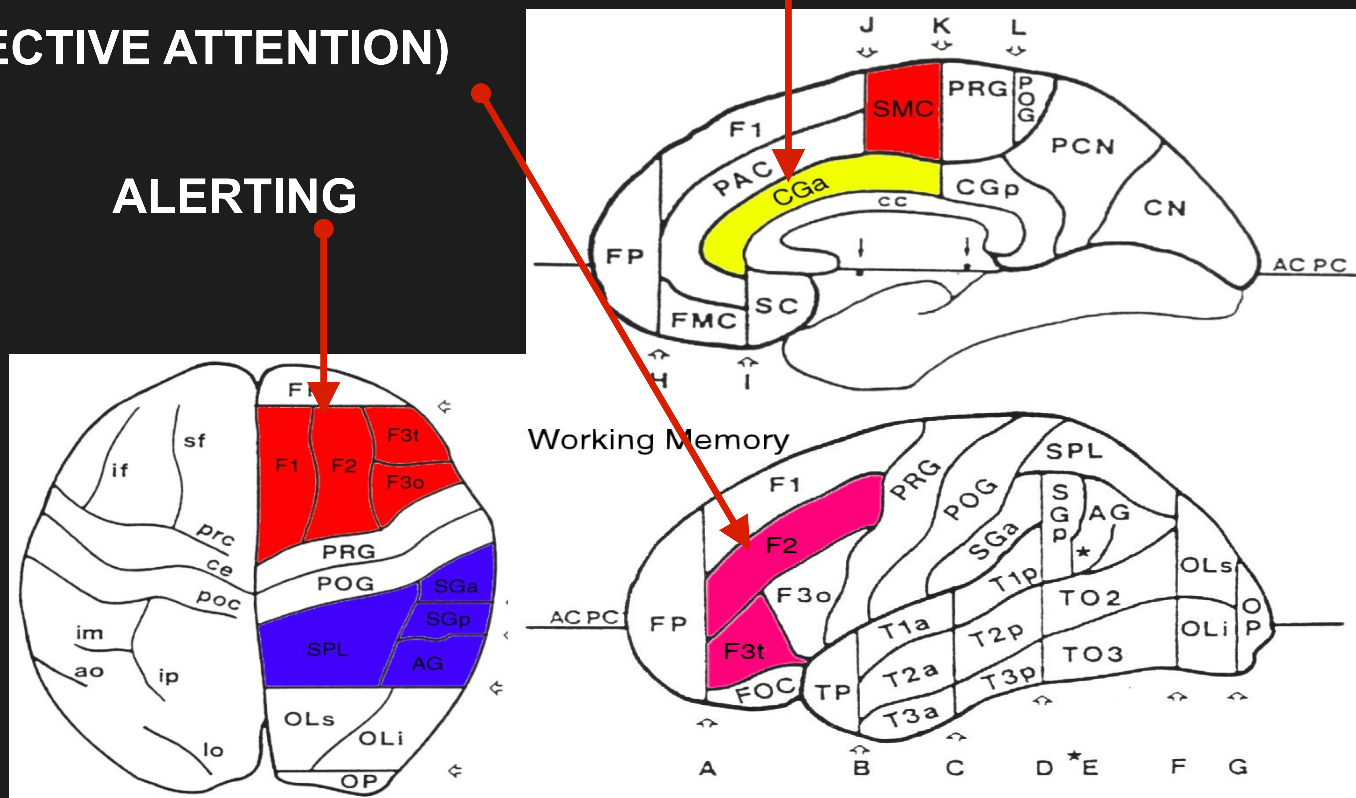
ADHD: Neurobiological Basis – Neural Systems

Attention Networks

EXECUTIVE CONTROL

ORIENTING (SELECTIVE ATTENTION)

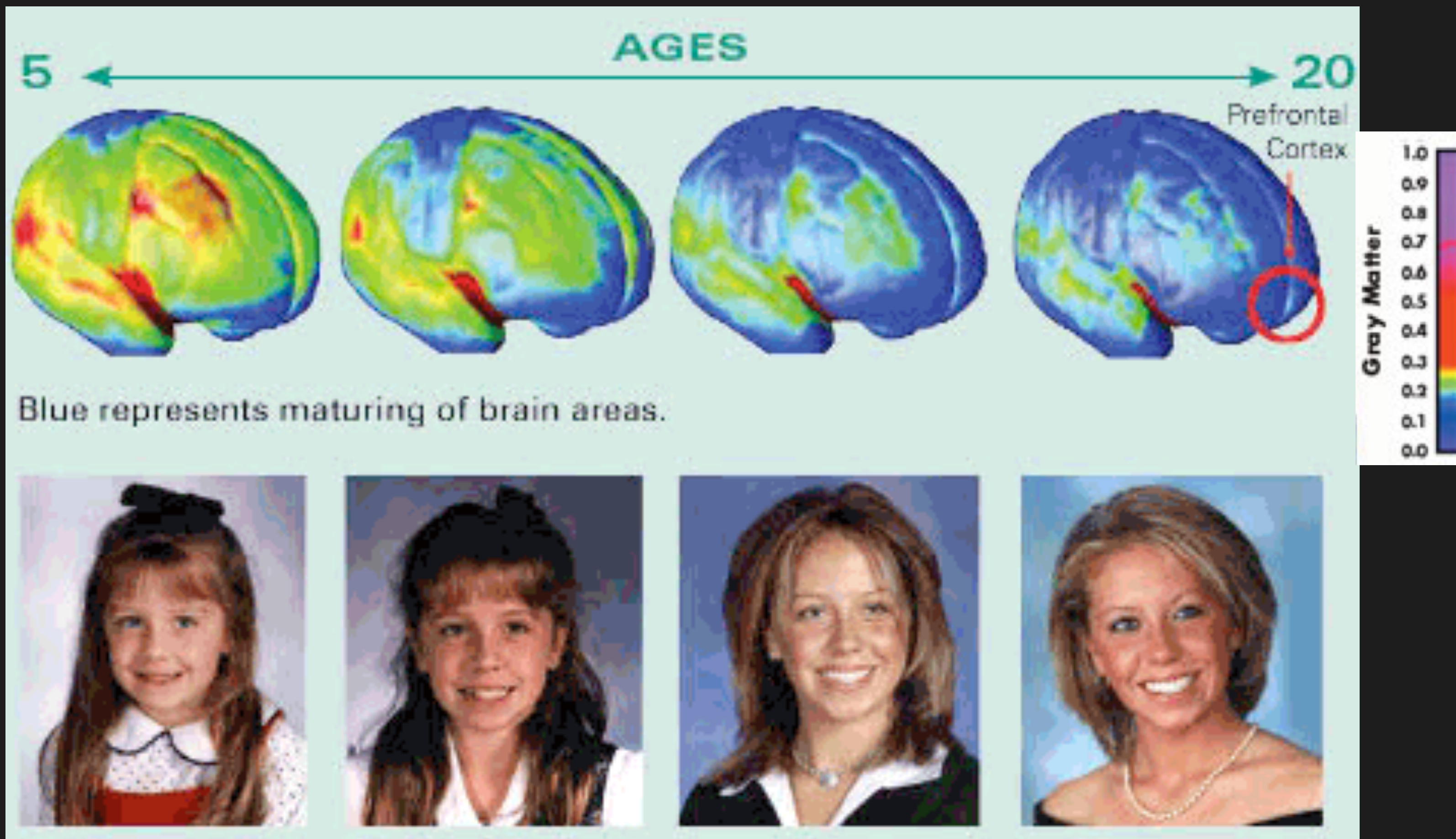
ALERTING



Posner MI, Raichle ME. *Images of Mind*. New York, Scientific American Books; 1996.

Drug Abuse and Brain Reward System

The Developing Brain



The above composite MRI brain images show top views of the sequence of gray matter maturation over the surface of the brain.

Courtesy of Dr. Scott Lukas

The Developing Brain

Prefrontal Cortex

- Planning behavior
- Use of strategies
- Cognitive flexibility (can you change your mind)
- Fluid methods of solving problems

--The *Executive Office* of the brain is still being built during the teenage years--

Courtesy of Dr. Scott Lukas

The Developing Brain

- The brain matures from the back to the front, so the frontal cortex is the last area to be completed.
- Insight, judgment, decision-making, risk taking, impulse control, are all impaired in adolescents.
- During this most vulnerable period is when teens are more likely to experiment with drugs and other damaging activities.

Courtesy of Dr. Scott Lukas

Tobacco
Marijuana
Alcohol
Cocaine

In all these conditions there are observed brain alterations using neuroimaging.

Tobacco: Role in Drug of Abuse

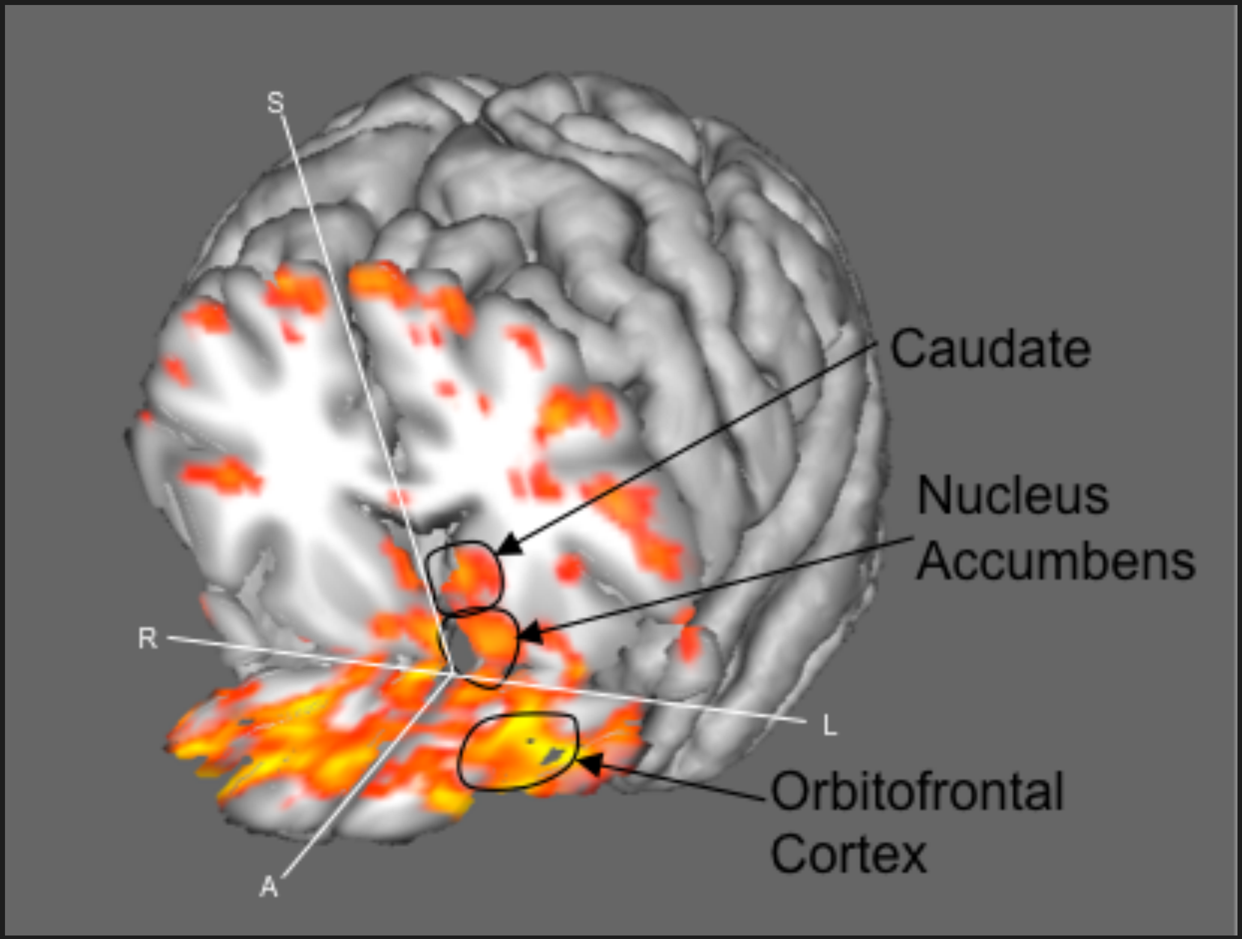
Reduced brain metabolism in smokers

- Lower test scores
- Poor athletic ability
- Lower cognitive function
- Poor decision making

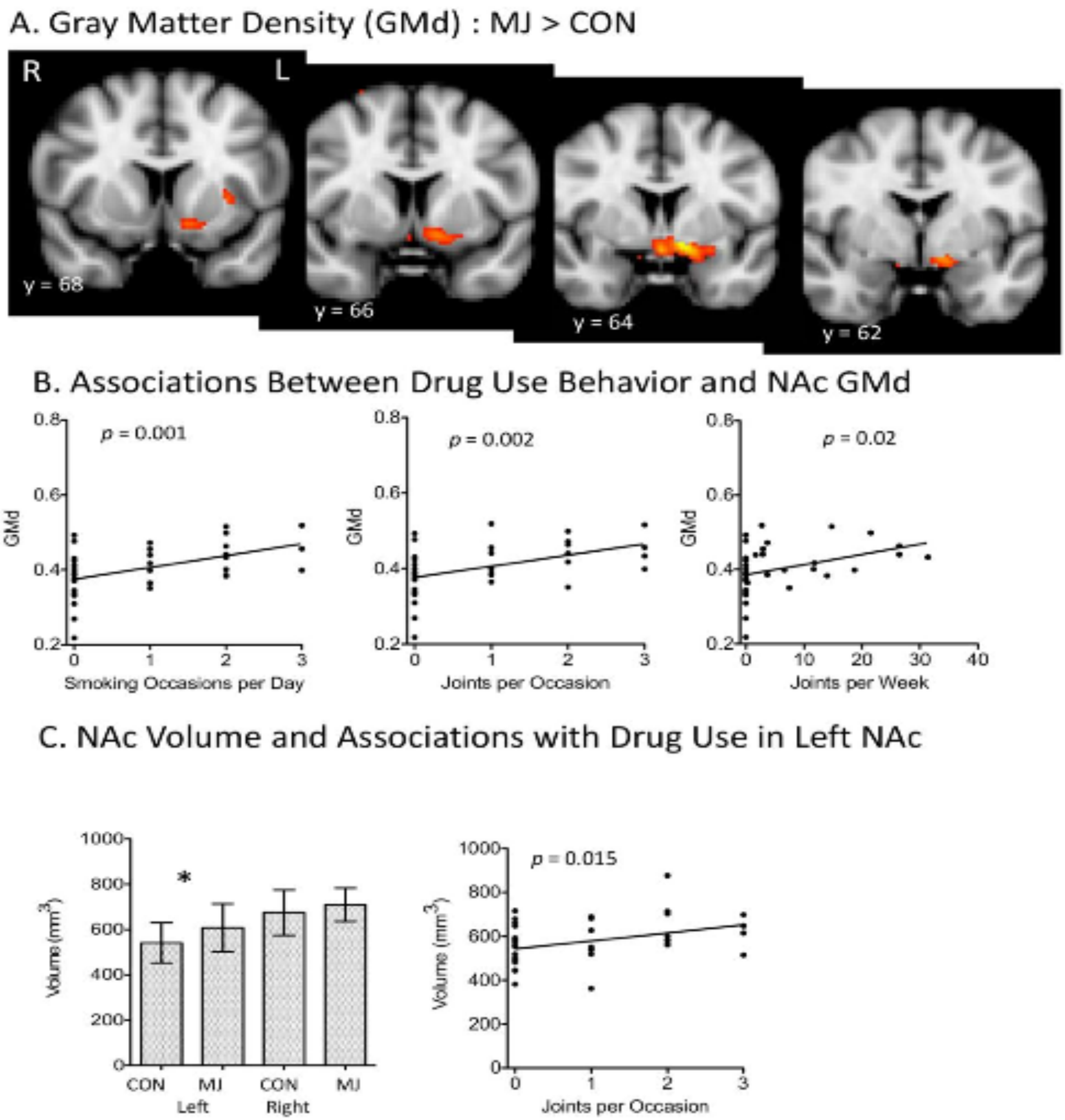
Courtesy of Dr. Scott Lukas

Smoked Marihuana and fMRI

GLM analyses reveals extensive orbitofrontal and ventromedial prefrontal cortical regions with significant group differences (marihuana > placebo smoking ($p<0.05$ corrected, shown in red-yellow). The single-group analysis shows that marihuana activated these regions and bilateral caudate and nucleus accumbens, while placebo smoking did not.



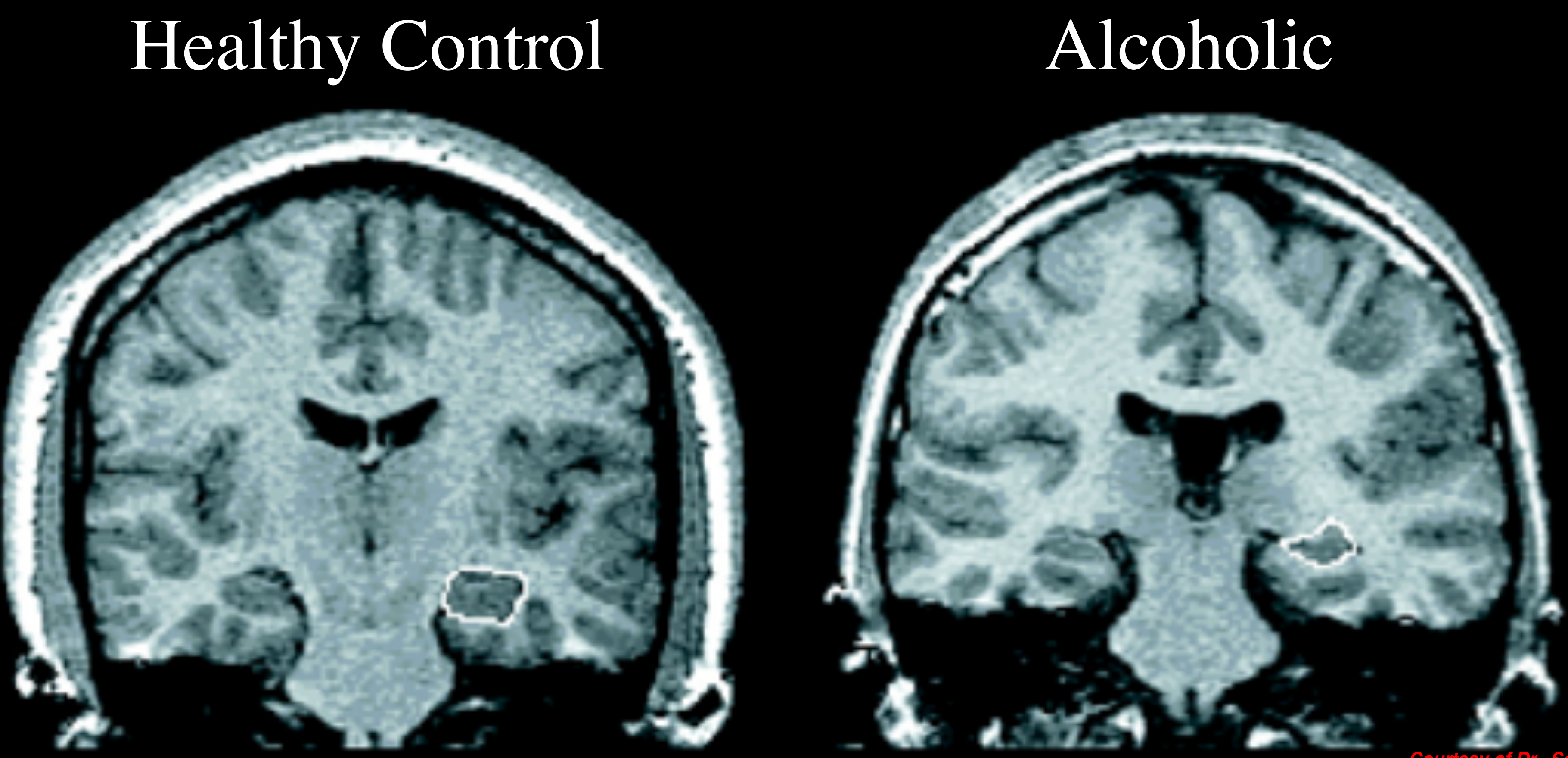
Courtesy of Dr. Scott Lukas



Gilman, et al.
(Journal of Neuroscience, 2014)

Health Consequences in Alcohol dependence

Alcohol Dementia--Adolescents



Courtesy of Dr. Scott Lukas

Health Consequences

Brain Activity--Adolescents

15-year-old male non-drinker	15-year-old male heavy drinker

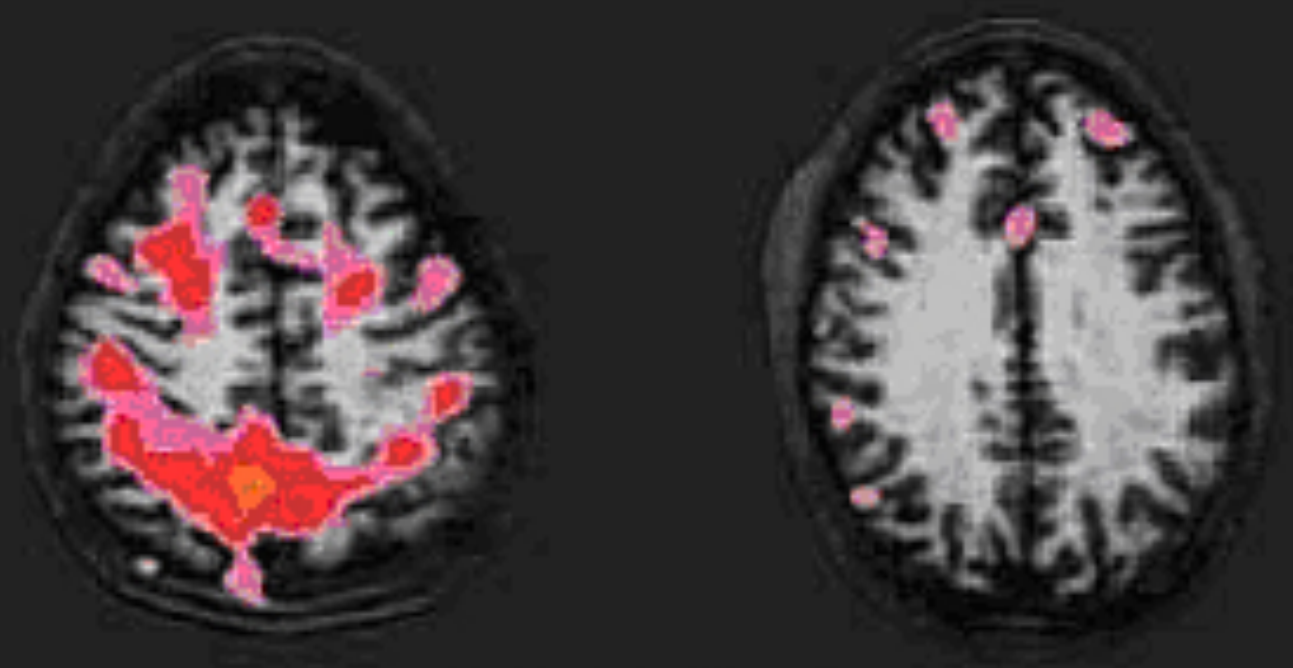
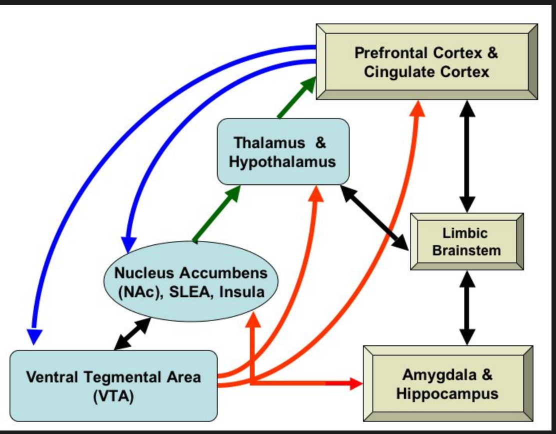


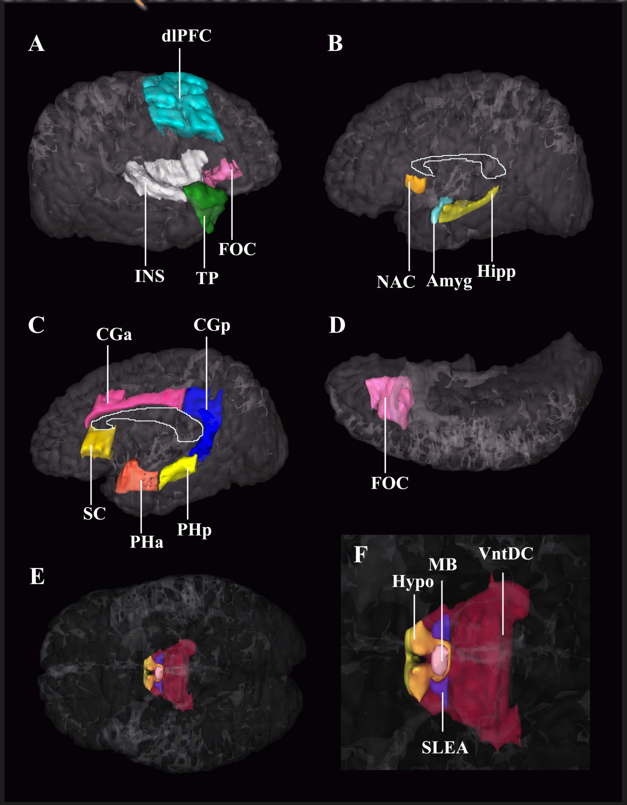
Image by Dr. Susan Tapet, UCA

Brain Reward Circuitry:

The Extended Reward and Oversight System (EROS) consists of cortical and subcortical structures involved in controlling emotion and regulating sensitivity to reinforcements.

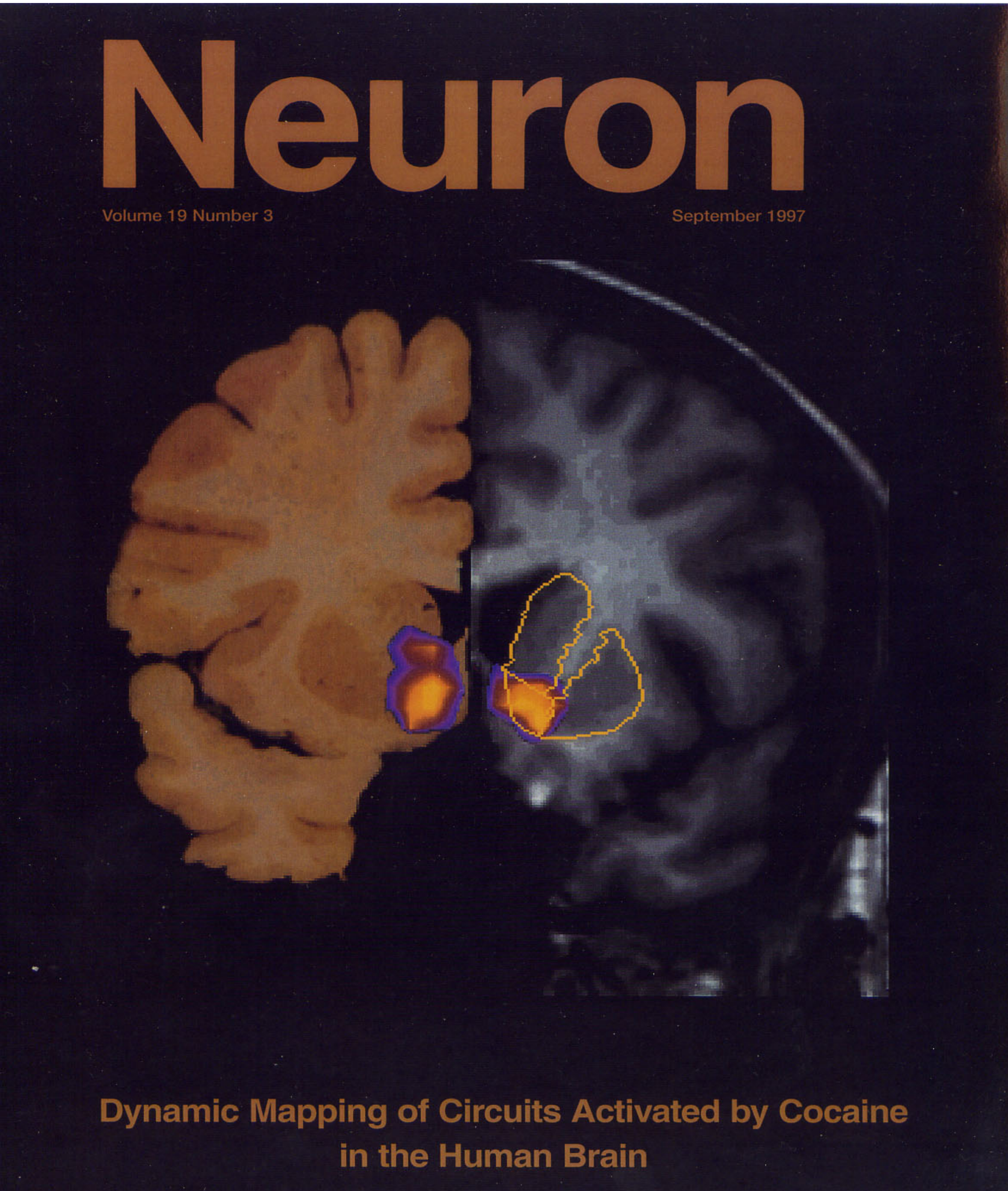
As a whole, EROS is smaller in alcoholics than in nonalcoholic controls. Four separate structures (shaded and with asterisks*) are especially involved.





- Amygdala*
- Cingulate Cortex*
- Dorsolateral Prefrontal Cortex
- Orbitofrontal Cortex
- Hippocampus
- Hypothalamus
- Insula*
- Mammillary Bodies
- Nucleus Accumbens (dopamine)*
- Parahippocampal Gyrus
- Subcallosal Cortex
- Sublenticular Extended

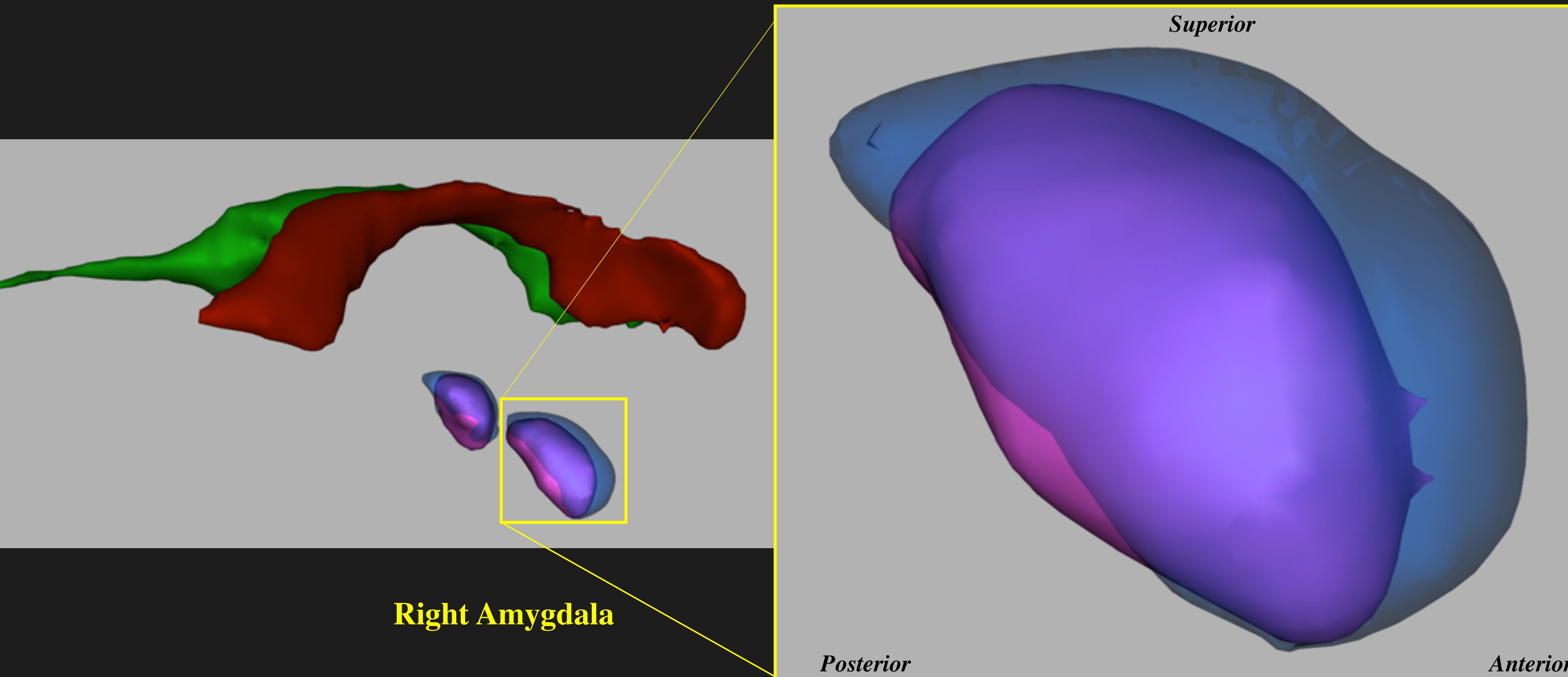
Makris et al., Biological Psychiatry, 2008



Breiter, Hyman, et al., Neuron, 1997

In cocaine abuse there are also observed alterations in the brain network for reward

Amygdala in Cocaine Addiction



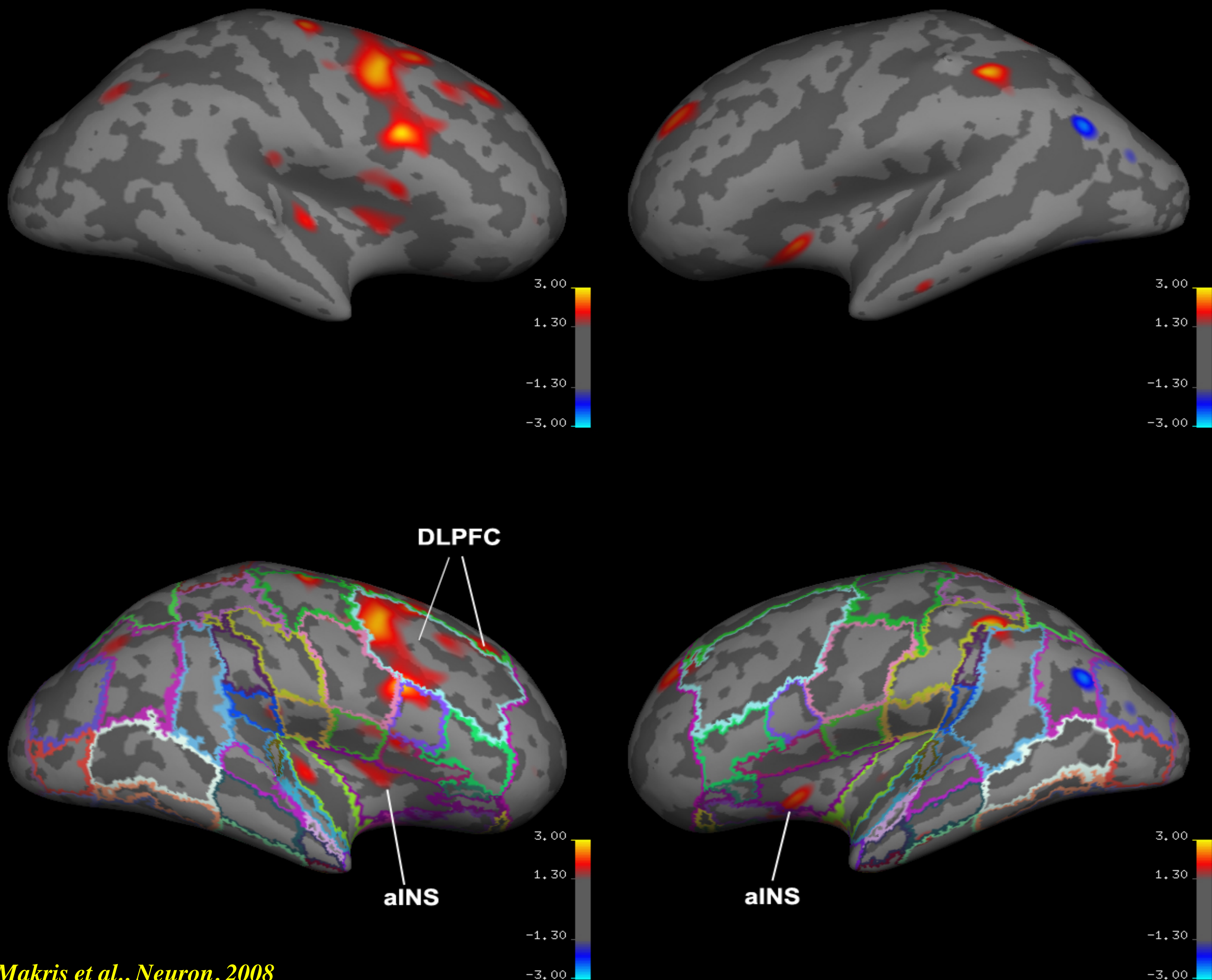
Right Lateral Ventricle = red
Left Lateral Ventricle = green

Patients
Normal Controls
Common

23% Volume Reduction

Makris et al., Neuron, 2004

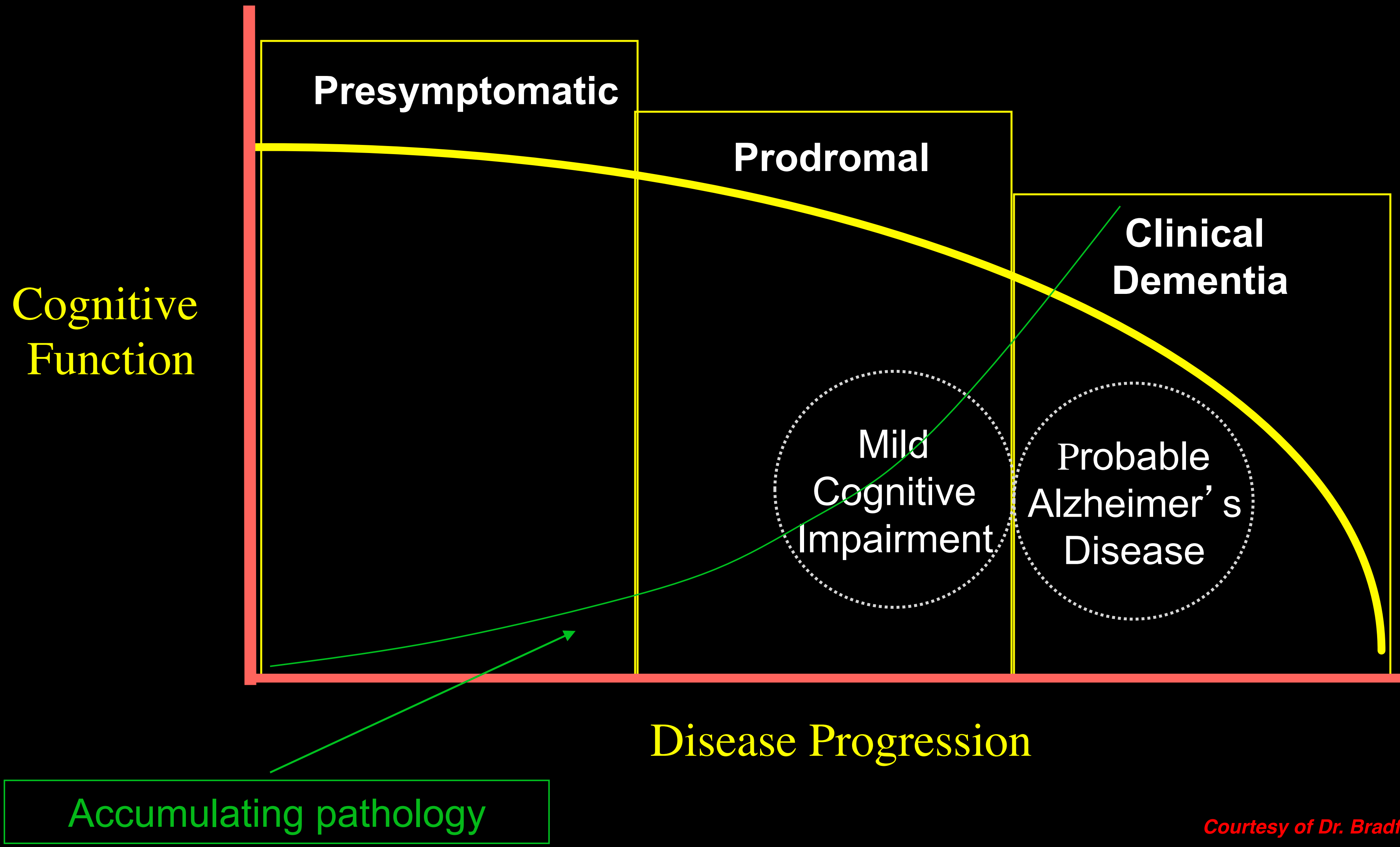
Cortical Thinning in Reward System in Cocaine Addiction



Makris et al., Neuron, 2008

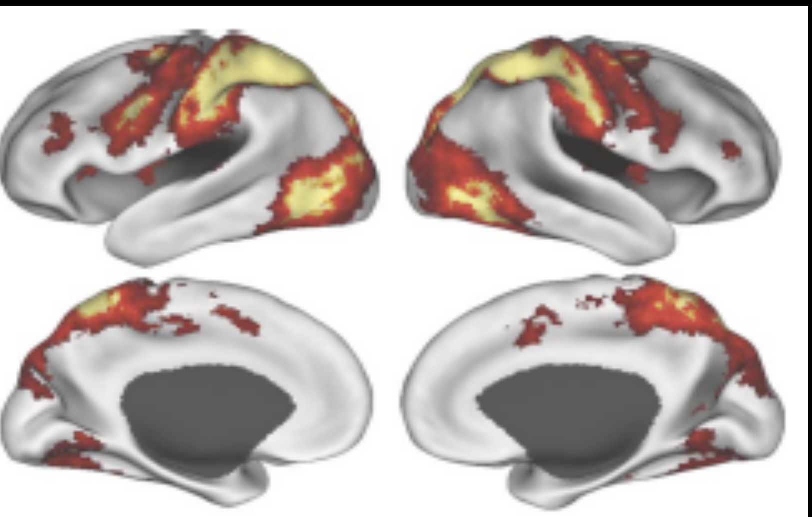
Neurodegeneration

Progression of Alzheimer's Disease:
similar model for many other diseases



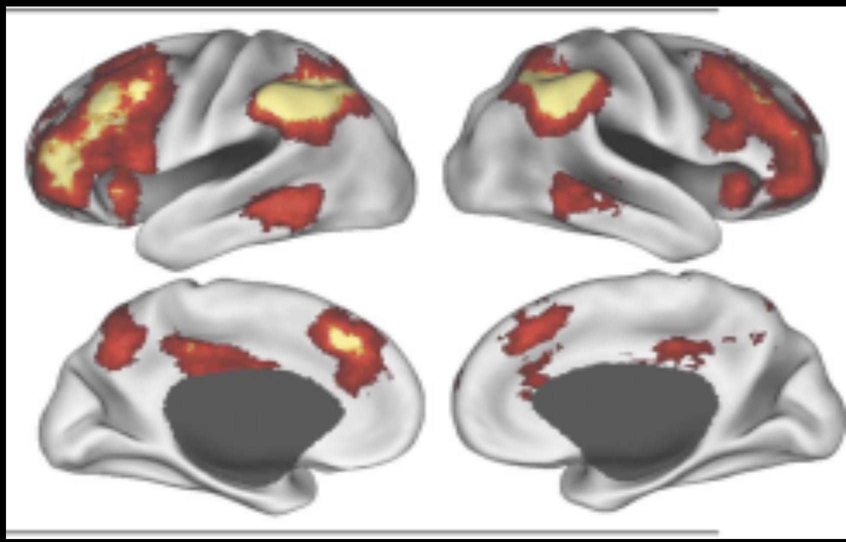
Courtesy of Dr. Bradford Dickerson

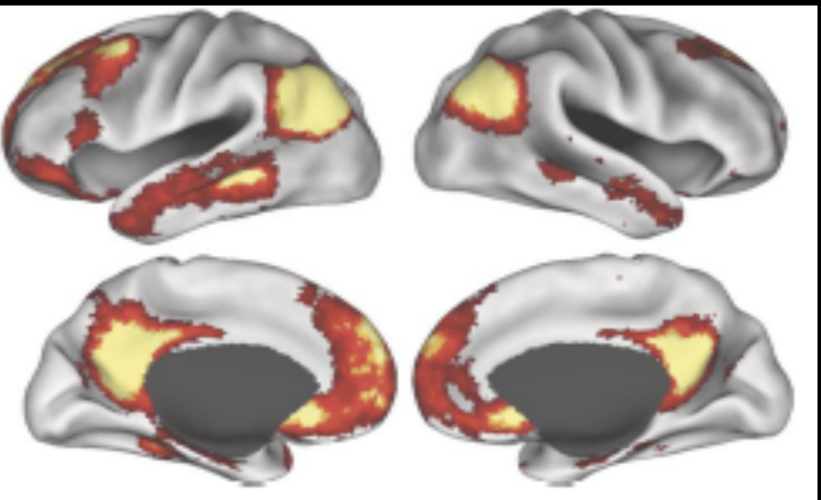
Large-scale cognitive systems
understrood through resting state fMRI



Dorsal visuospatial attention system

Frontoparietal executive control system

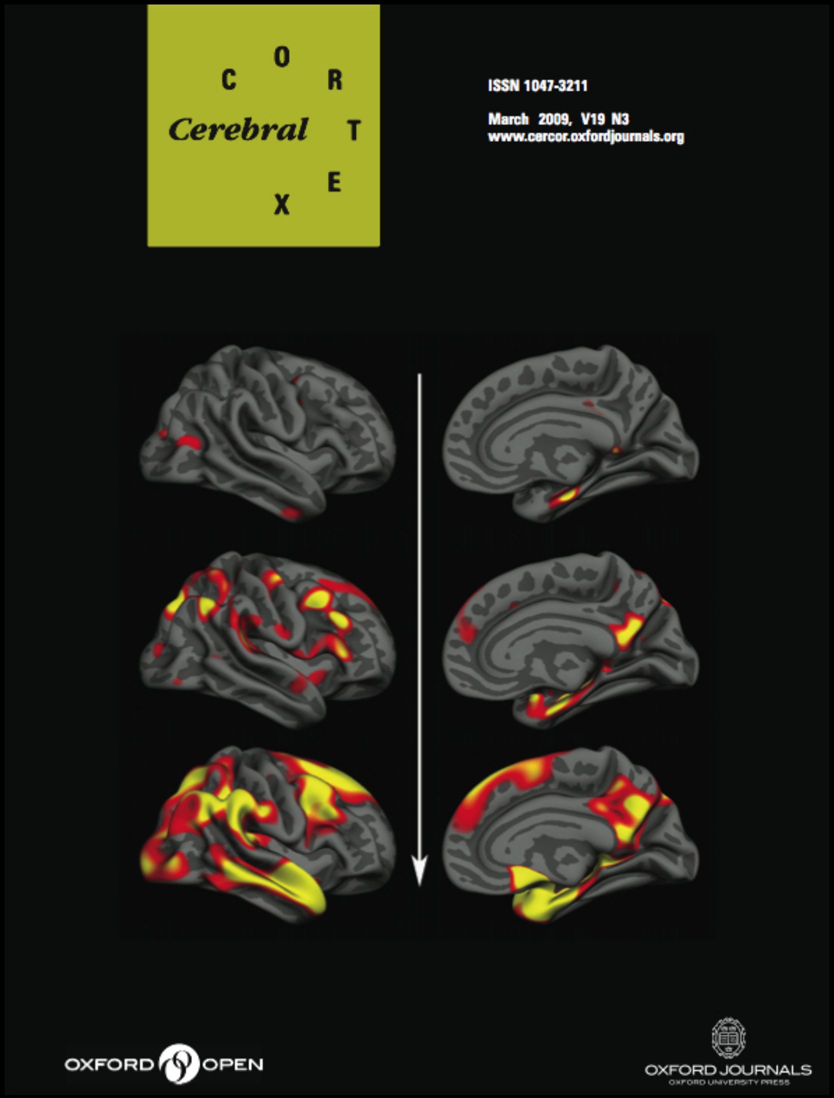




Episodic memory/Default-mode system

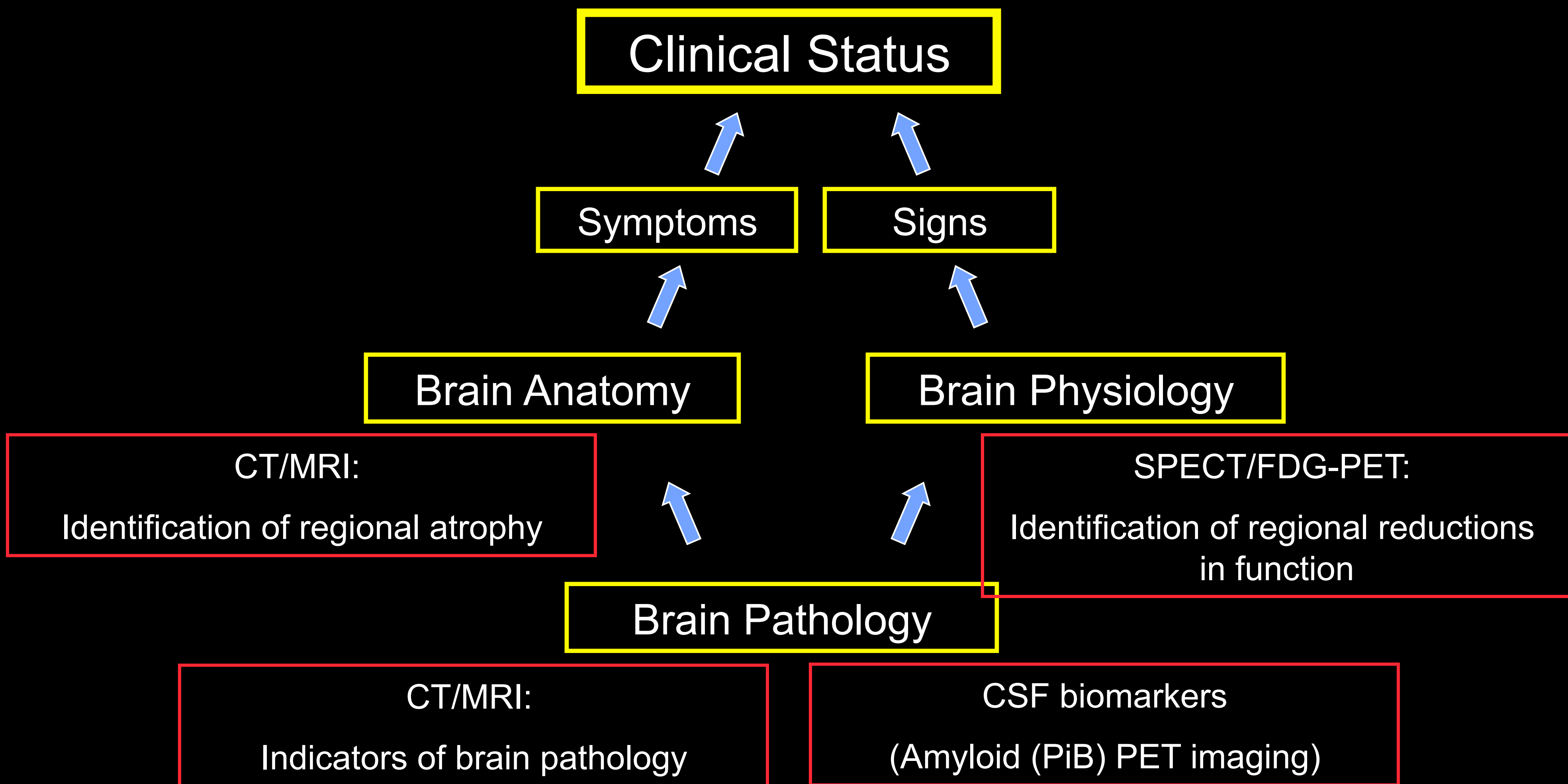
Vincent et al., J Neurophys, 2008

AD cortical signature:
Cortical atrophy compared to normals



Dickerson et al, Cerebral Cortex 2009

Roles of biomarkers in dementia: Clinical practice, 2014

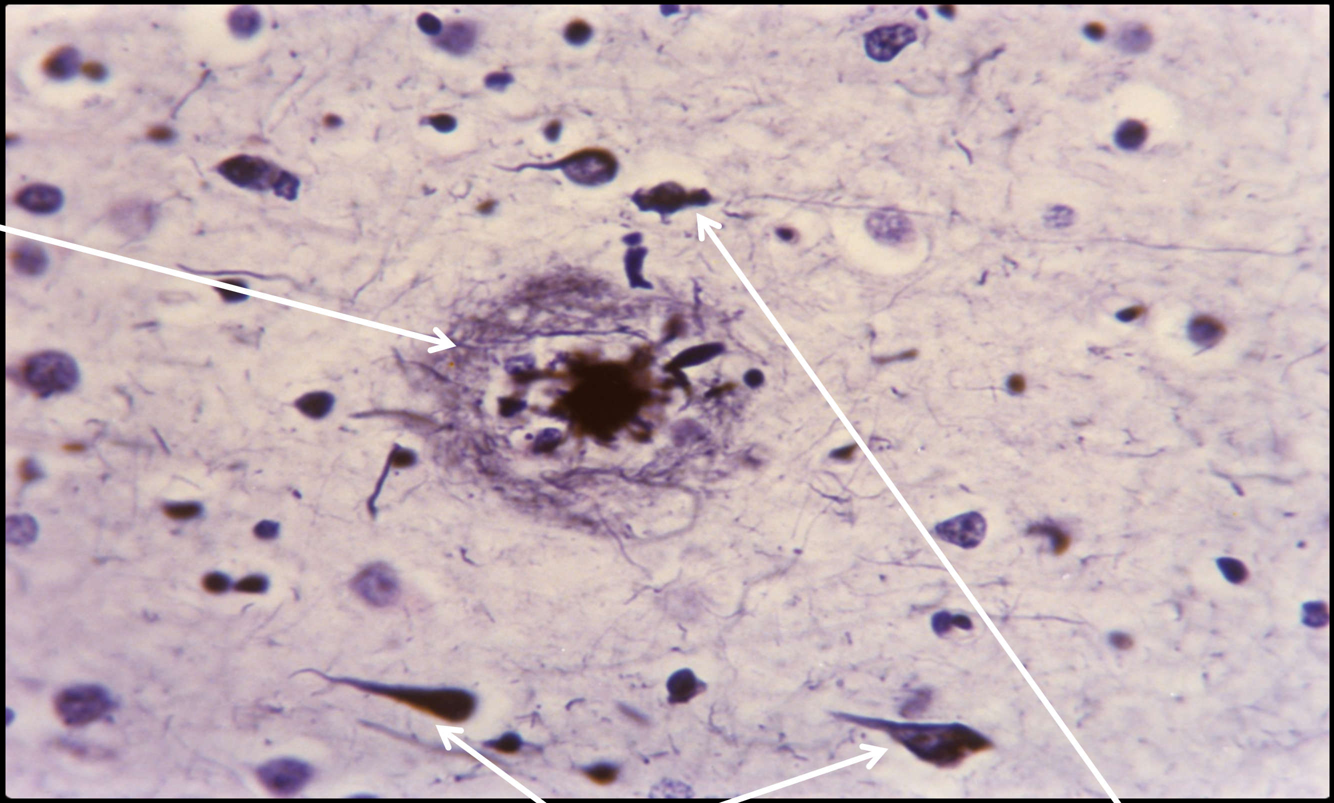


Courtesy of Dr. Bradford Dickerson

Plaque and Tangles

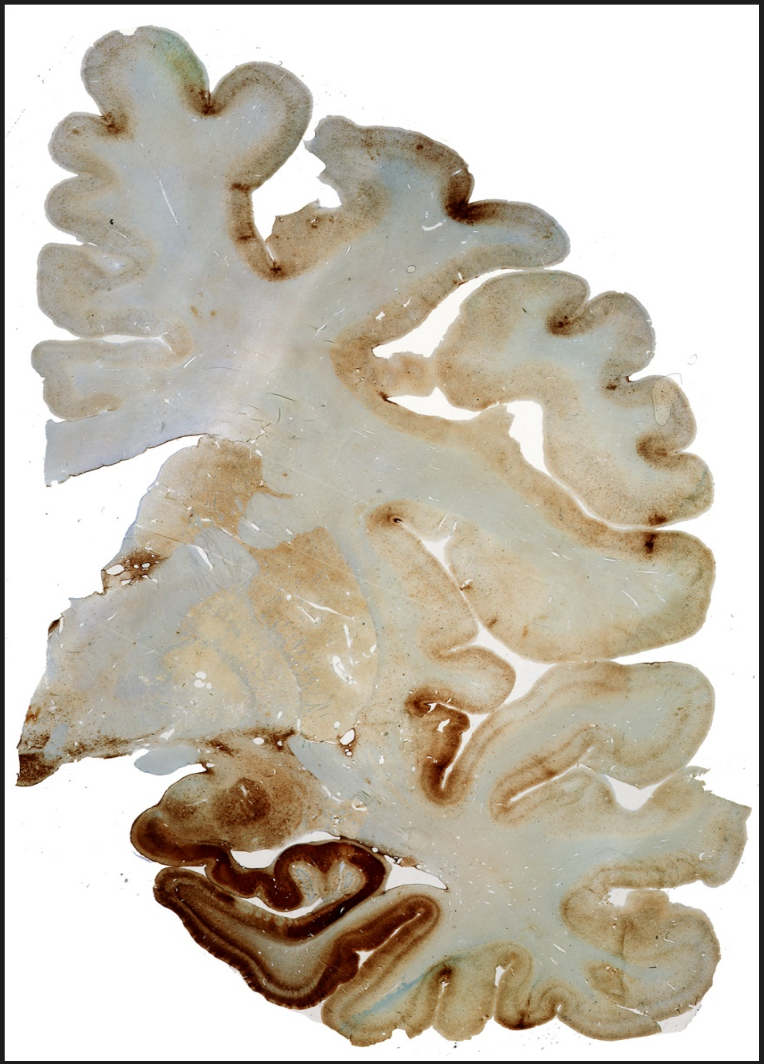
(Bielschowsky silver stain, association cortex of the temporal lobe)

Neuritic plaque



Neurofibrillary tangles, in neurons and as tomb-stones, where neurons used to be

Only Post-Mortem Tau Pathology



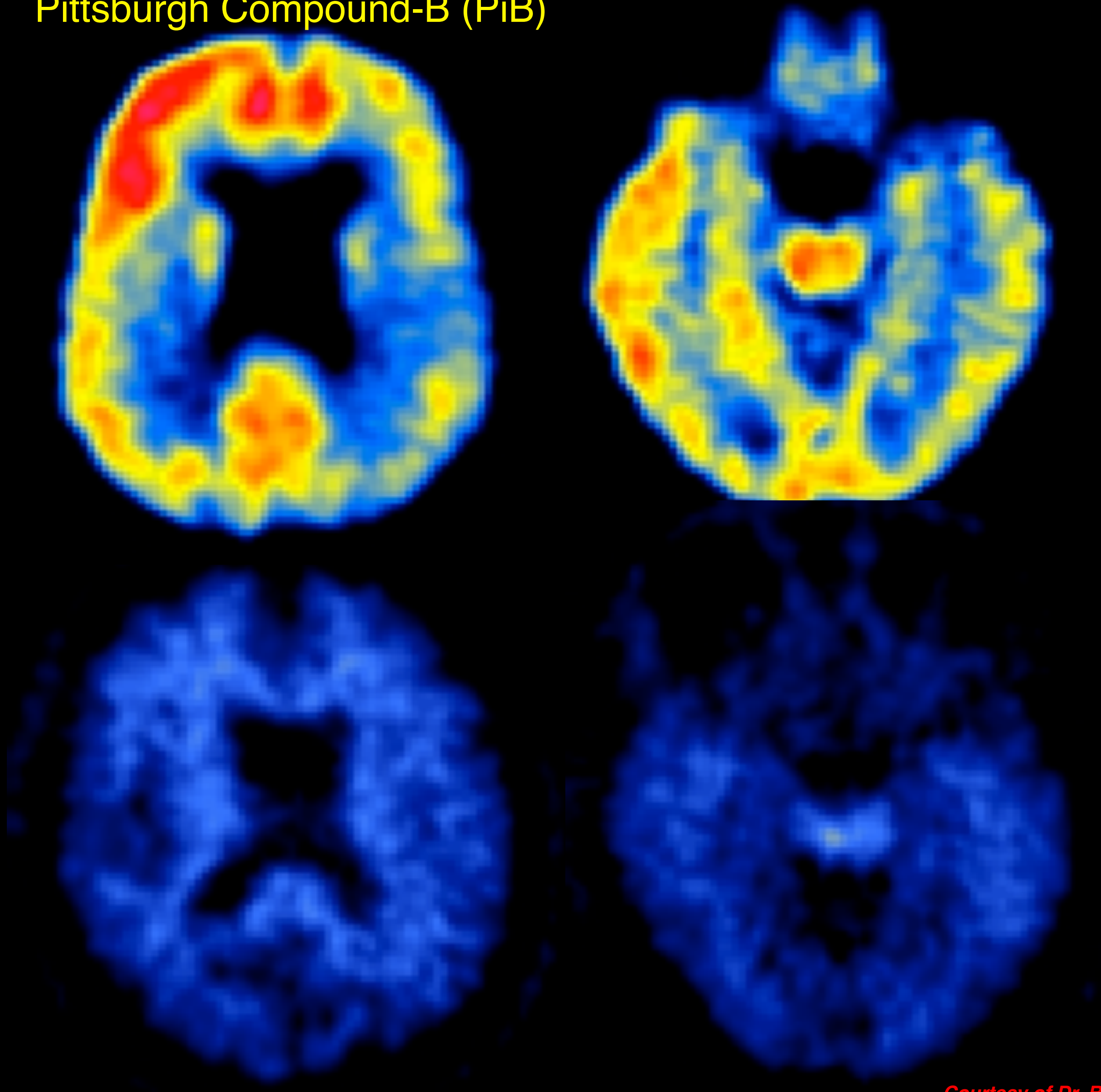
(McKee et al., 2009)

Amyloid imaging with PET

Pittsburgh Compound-B (PiB)

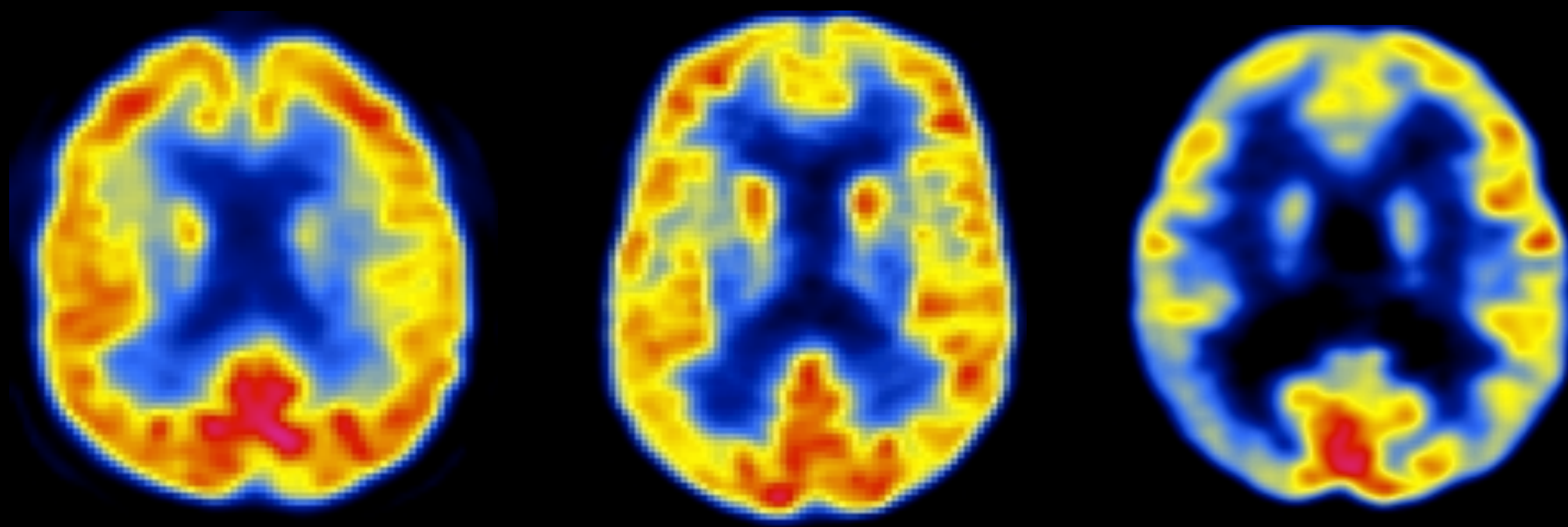
Alzheimer's disease

Normal aging



Courtesy of Dr. Bradford Dickerson

Aging, MCI, AD: FDG-PET



Cognitively intact older adult | **Mild Cognitive Impairment** | **Alzheimer's Disease**

Courtesy of Dr. Bradford Dickerson

Pre-Clinical PET Tracer Used in Animals

Journal of Alzheimer's Disease 31 (2012) 1–12
DOI 10.3233/JAD-2012-120712
IOS Press

A Highly Selective and Specific PET Tracer for Imaging of Tau Pathologies

Wei Zhang, Janna Arteaga, Daniel K. Cashion, Gang Chen, Umesh Gangadharmath, Luis F. Gomez, Dhanalakshmi Kasi, Chung Lam, Qianwa Liang, Changhui Liu, Vani P. Mocharla, Fanrong Mu, Anjana Sinha, A. Katrin Szardenings, Eric Wang, Joseph C. Walsh, Chunfang Xia, Chul Yu, Tieming Zhao and Hartmuth C. Kolb*
Siemens Molecular Imaging, Inc., Culver City, CA, USA

Next Step PET in Humans

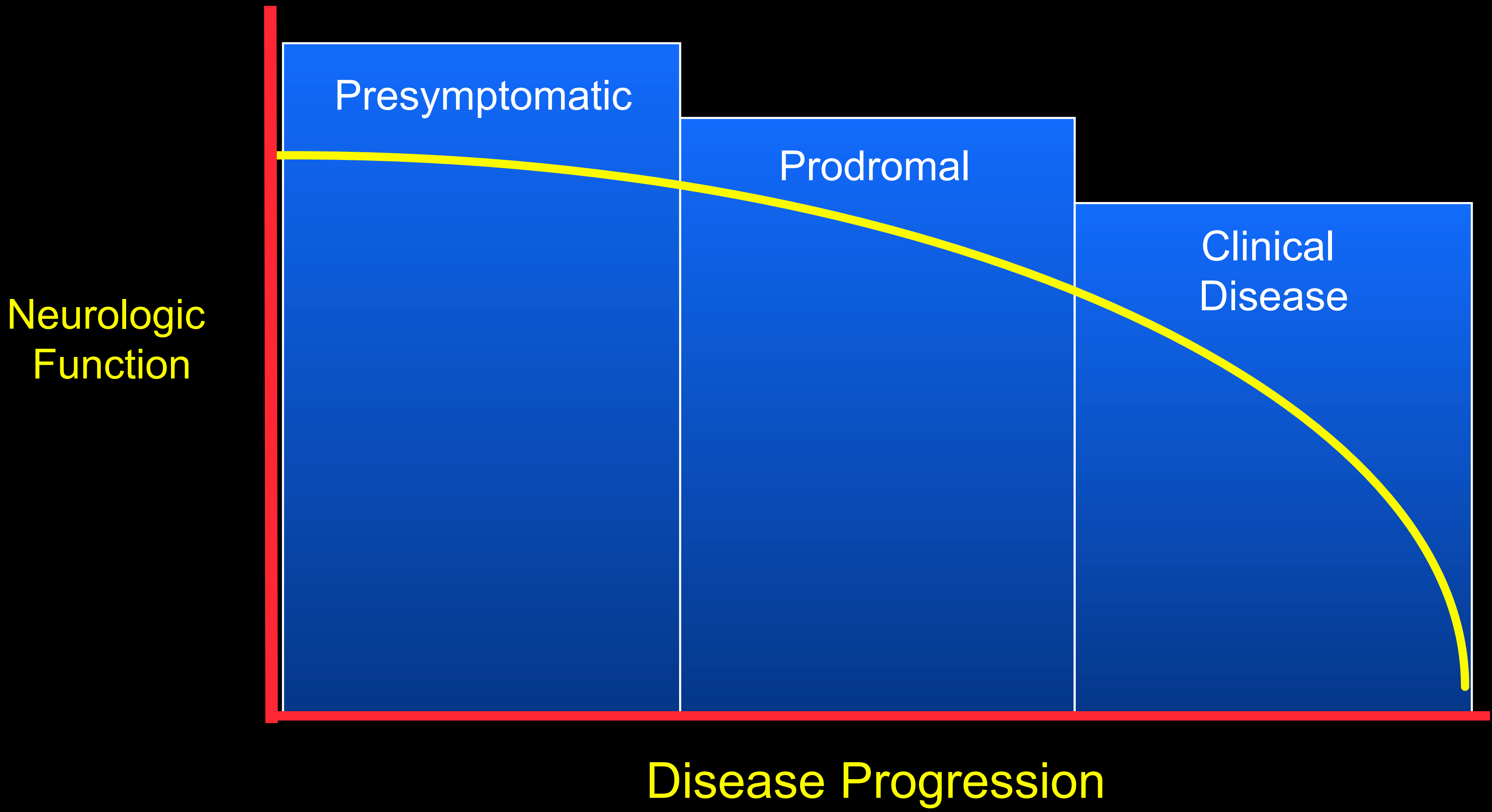
- Rule out Alzheimer's Disease (AD) in suspected CTE.
- Rule in Tauopathy in CTE – the Holy Grail. Positive *in vivo* tau imaging (paired helical filament Tau) using new PET Tau ligand from Siemens.
- Predictions: Amyloid-Beta retention in AD, but not CTE or controls (PiB), and Tau retention in AD and CTE but not controls (Tau; see table, below).

	AD	CTE	Control
PiB	+	-	-
Tau	+	+	-

Imaging technology is not just making pretty pictures or even simply increasing our scientific understanding of Alzheimer's and related diseases; it is in fact enabling new revolutions in testing treatments that may lead to real benefits for patients, possibly even forms of prevention.

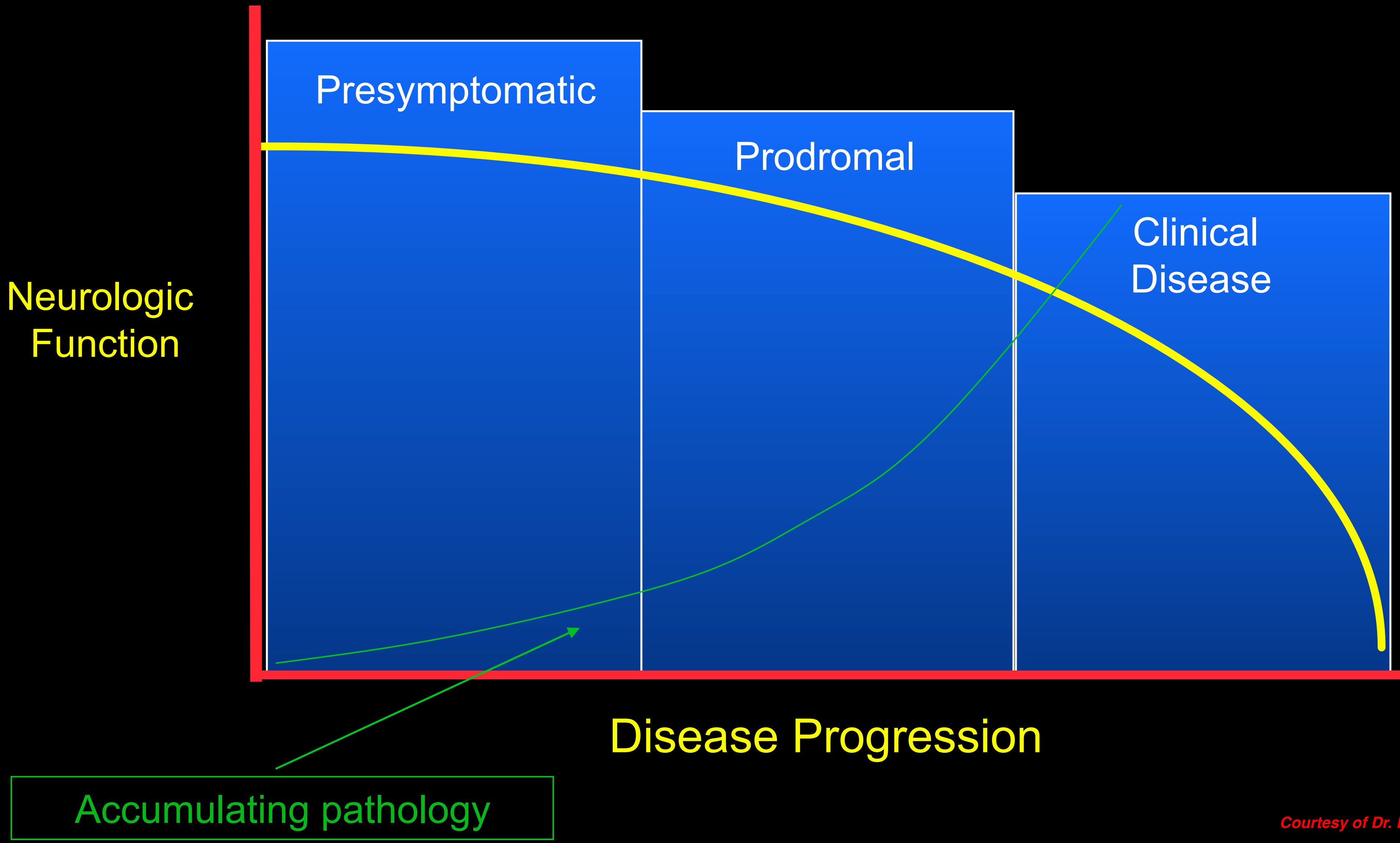
e.g., anti-amyloid treatment with monoclonal antibodies in mildly symptomatic patients (MCI) or even asymptomatic individuals with brain amyloid.

Progression of neurodegenerative diseases



Courtesy of Dr. Bradford Dickerson

Progression of neurodegenerative diseases



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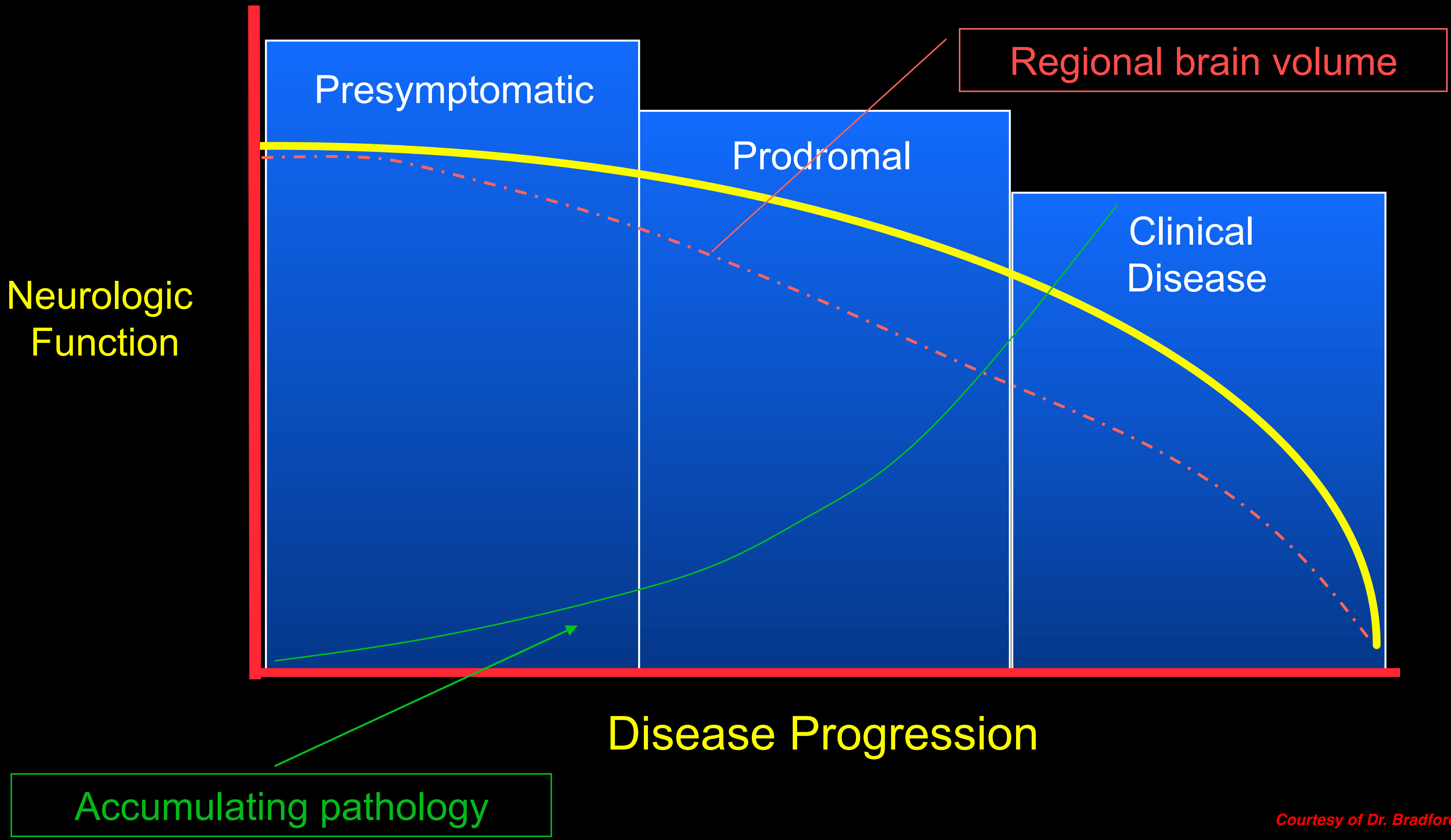

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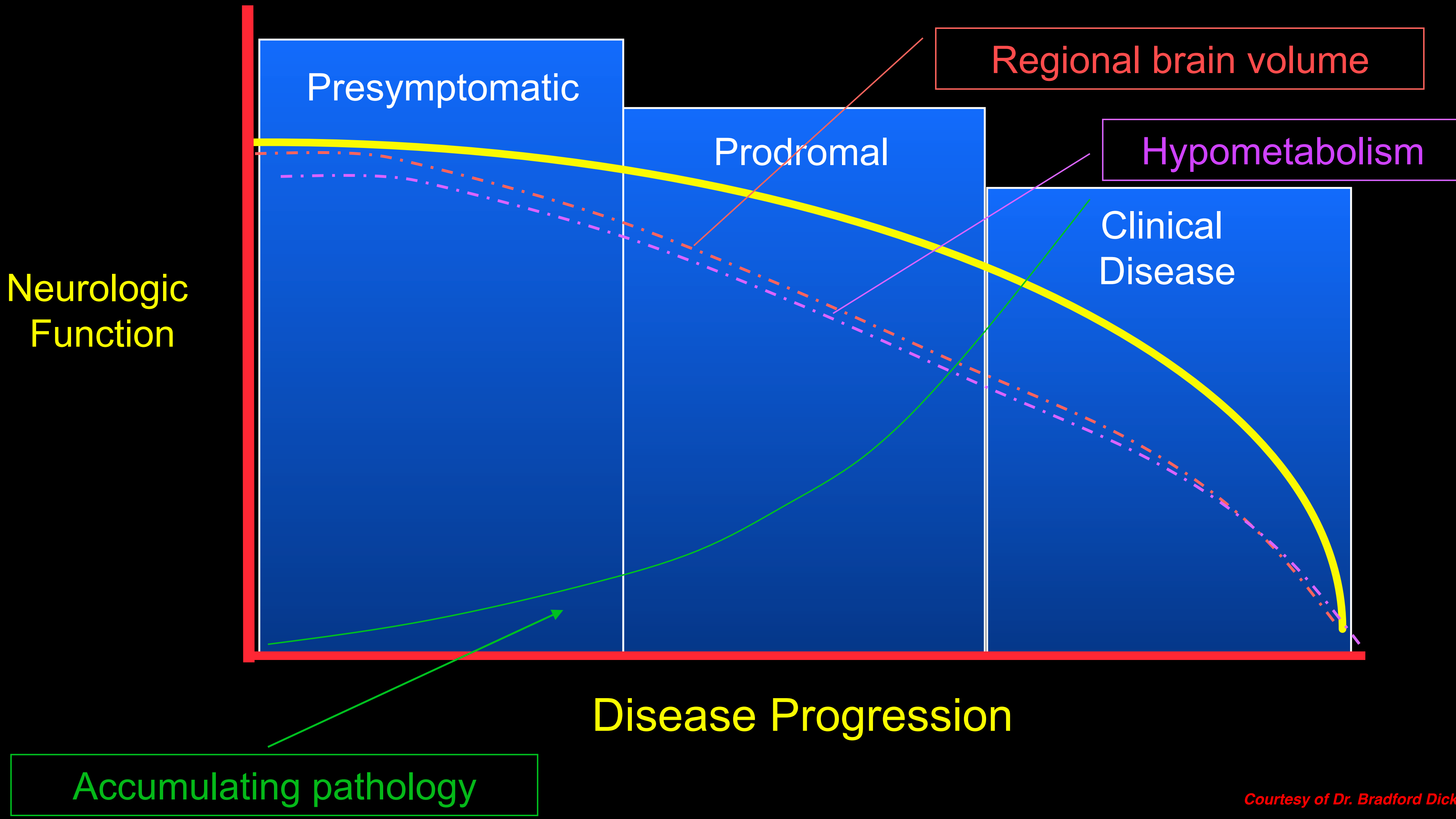

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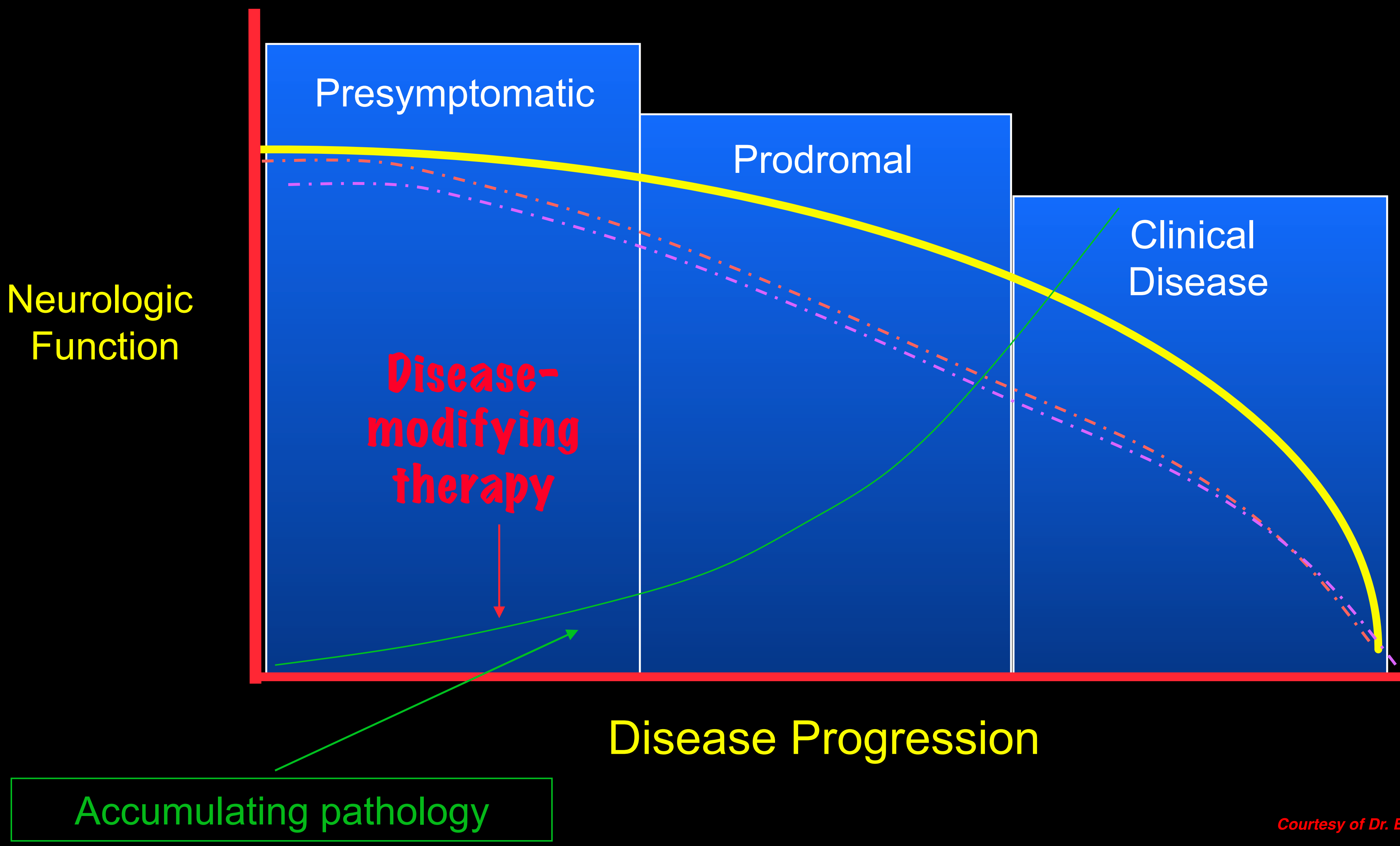
Progression of neurodegenerative diseases



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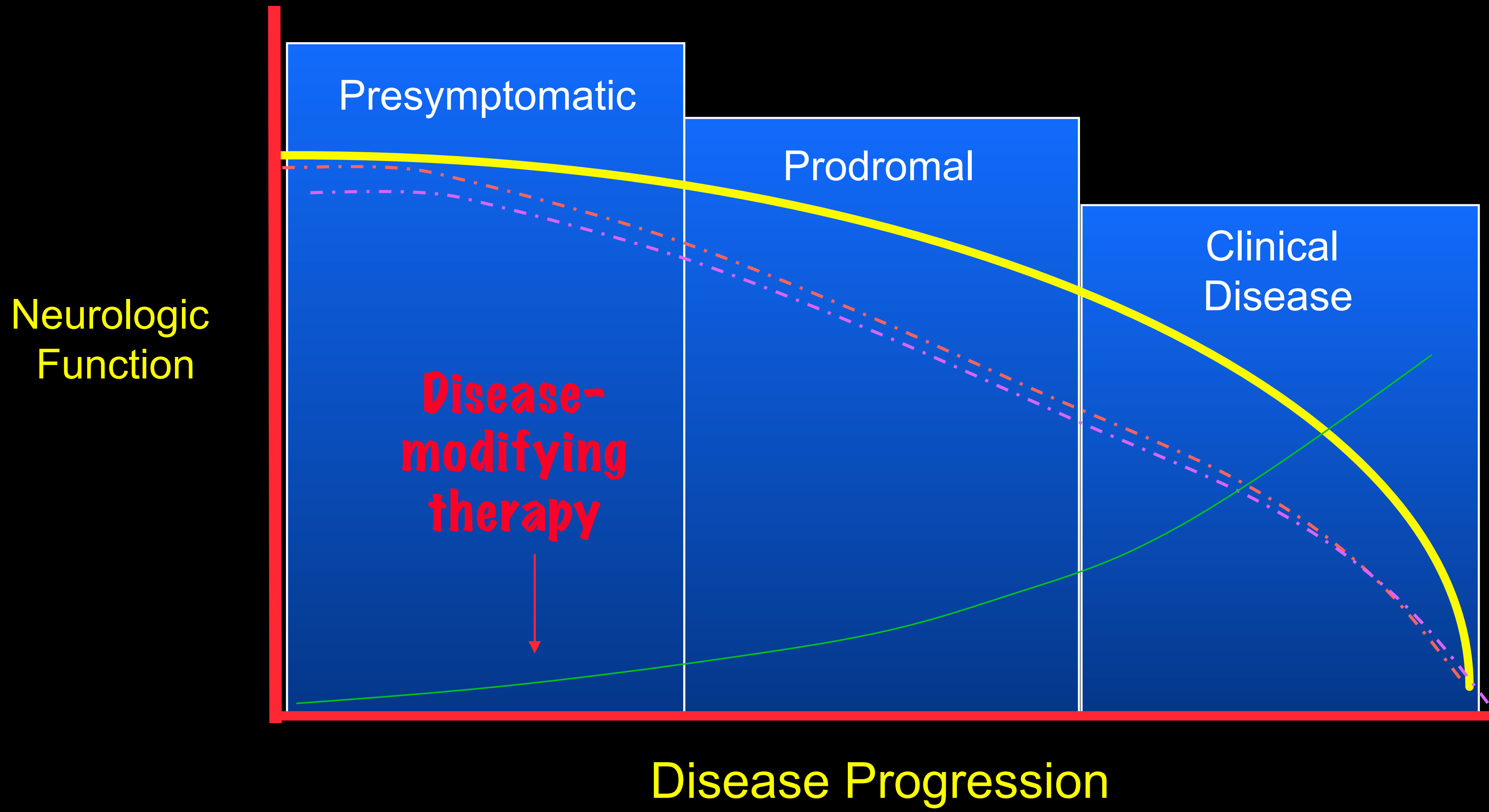
Progression of neurodegenerative diseases



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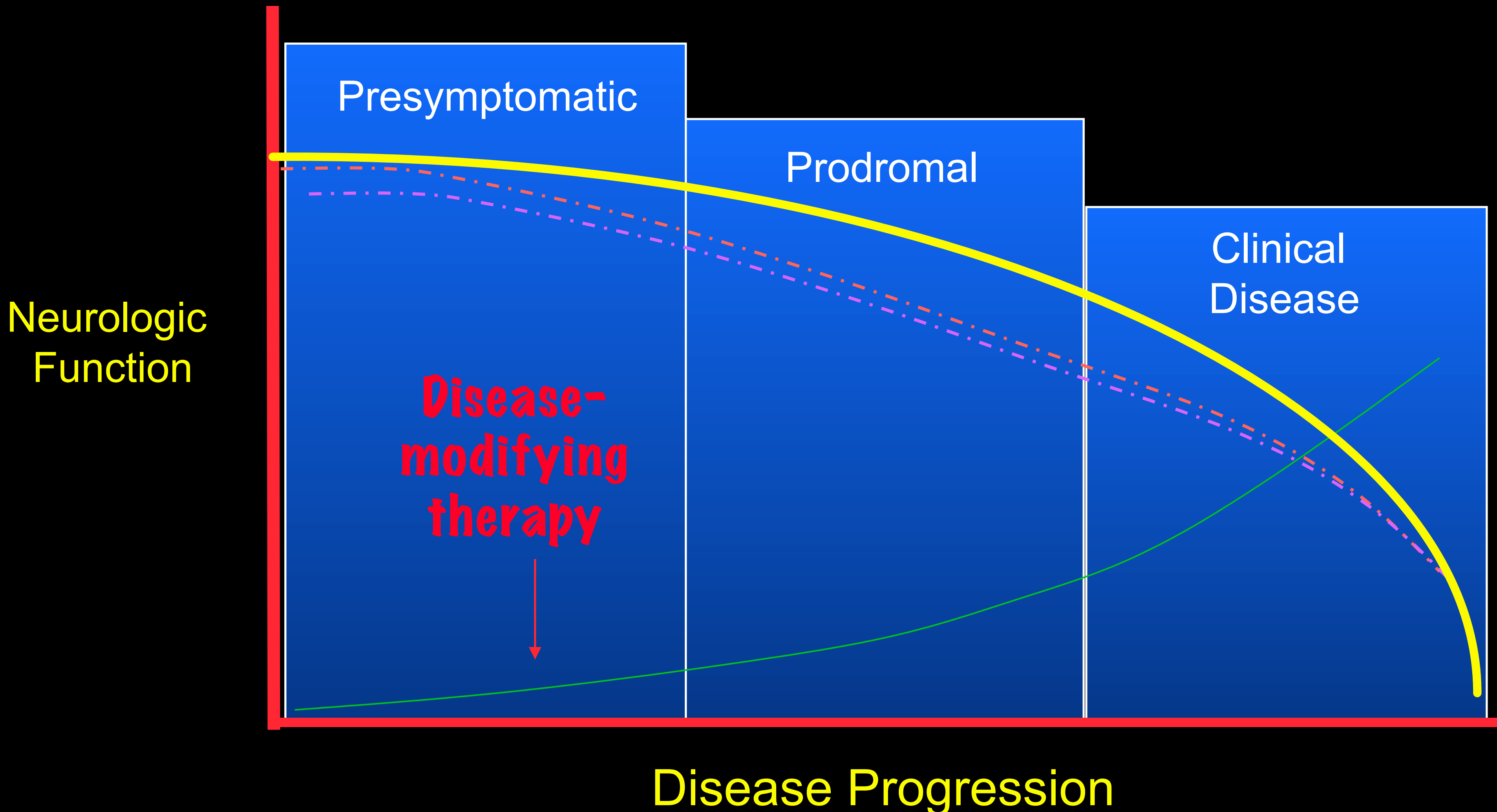

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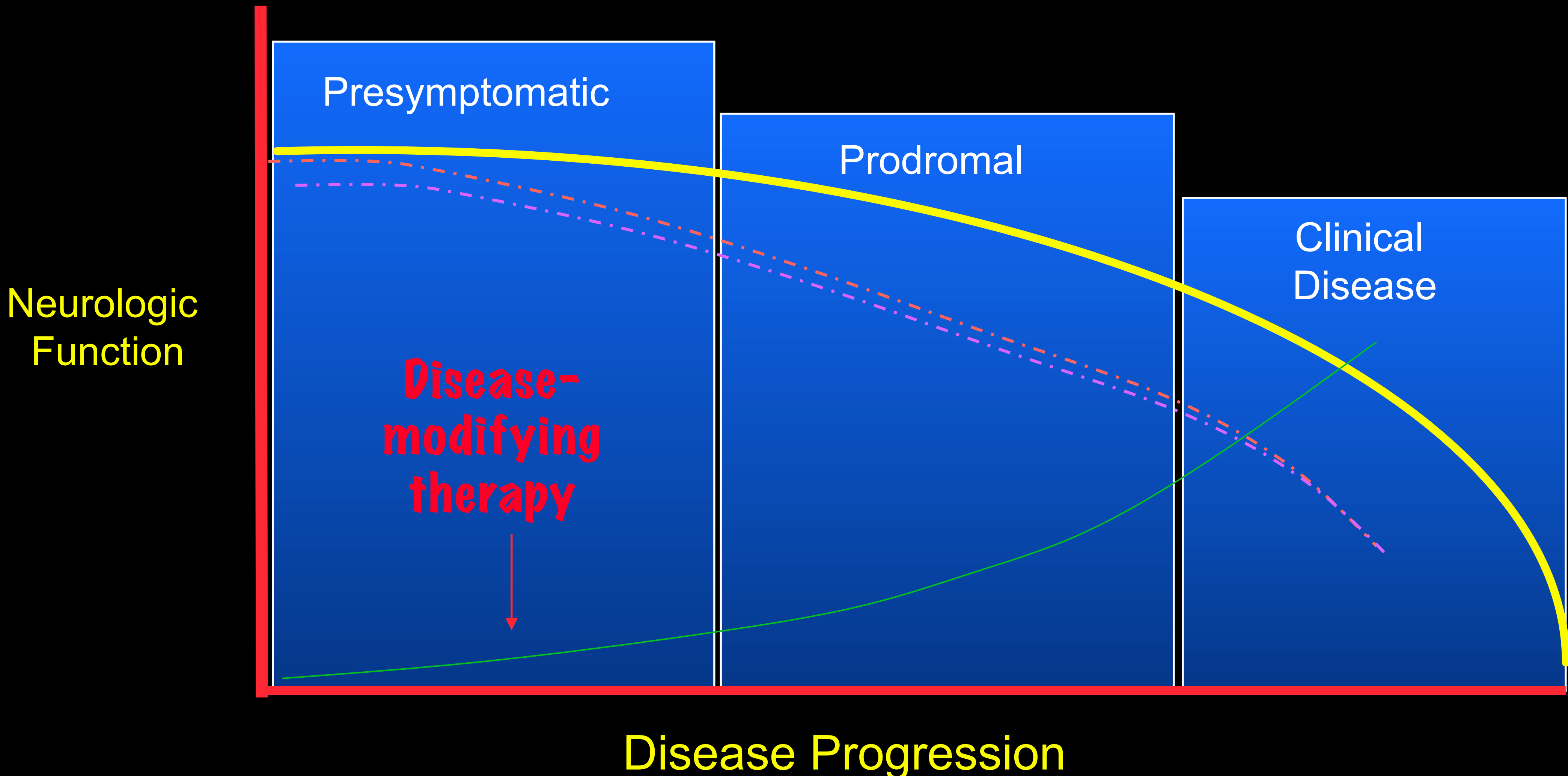
Progression of neurodegenerative diseases



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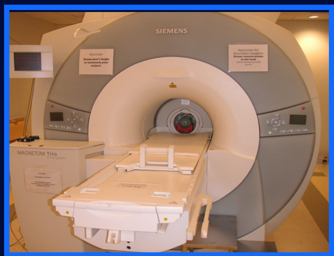
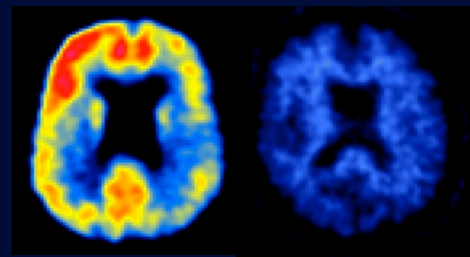
Imaging Research for Novel Diagnostics/therapeutics and Better Care





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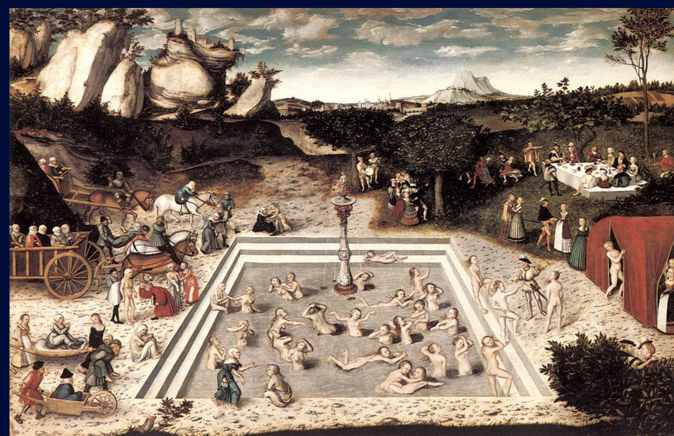
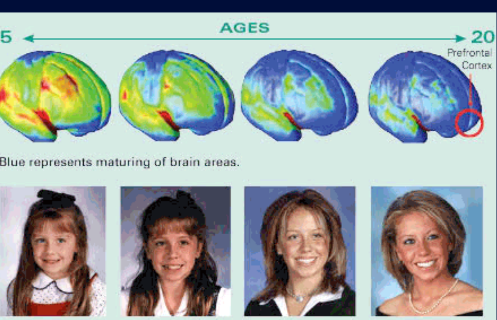


Figure 4: Neural systems biology acts as an interface between behavior and the genome

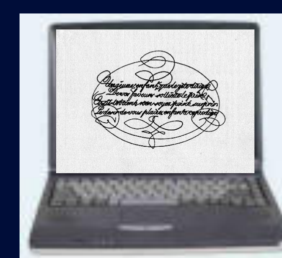
Behavior /Environment —— Neural Systems —— Genome

Automation and Databasing



Translational (from bench to bedside)

Translational (from experimental animal to human)



THANK YOU!