

The Role of Neuroimaging in Psychiatry and Addiction Medicine

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Bo Adler, On His Sleep Apnea Options :

“First they were going to cut out my tonsils, and if that didn’t work, they would break my jaw and reset it to reposition my tongue, and finally they would cut out the roof of my mouth.”

Sleep Apnea Options (cont)

“I had one question: ‘What if my case is *different?*’

They said, ‘Let’s try the standard course of treatment first, and if that doesn’t work, then we’ll know your case is different.’”

Sleep Apnea Options (cont)

What this proposal really meant:

- His doctors wanted to see him as a *standard* case, because they have treatments for standard cases
- They had no cure for ‘different’

But before he underwent surgery, Bo wanted some evidence that his *was* a standard case.

How often do we treat psychiatric cases as standard because of our limited ability to objectively determine 'different' ?

Why Do Neuroimaging?

“The DSM-IV has 100% reliability and 0% validity. We need to develop biological markers to develop the validity of these disorders... We can use neuroimaging to begin to identify the systems pathology in these disorders, so that treatments can go after the core pathology.”

Thomas Insel, Director of NIMH
APA Meeting 2005

Why Do Neuroimaging?

The Truth

- Virtually all the major psychiatric illnesses (Bipolar Disorder, Major Depressive Disorder, ADHD, Autism, etc.) likely have **multiple etiologies** and **multiple subtypes**.
- **These are not single, simple, or standard disorders!**

Why Do Neuroimaging?

“Recent advances in in-vivo brain monitoring techniques such as fMRI and SPECT make it possible to visualize brain abnormalities in humans and animals... These exciting developments have translational potential to contribute to our understanding of depression and its treatment.”

From “Next Generation Antidepressants: Moving Beyond Monoamines to Discover Novel Treatment Strategies for Mood Disorders”, 2010, edited by Stahl and Beyer

Why Do Neuroimaging?

“Regarding MDD... the current classification criteria encompass a heterogeneous mix of illnesses that share similar final pathways likely reached via multiple pathophysiological processes.”

Berghorst & Pizzagalli, 2010, “Defining Depression Endophenotypes”

Why Do Neuroimaging?

“Depression is a complex heterogeneous disease... the use of wider spectrum methods including biomarkers and non-invasive in-vivo brain monitoring methods can provide an insight into aberrant neurochemical parameters coupled with behavioral phenotypic identification that could improve the translational aspects of depression modeling.”

De Groot, Filip, McCreary, 2010, in
“Developing Novel Animal Models of
Depression”

Why Do Neuroimaging?

- Giving someone the standard diagnosis of “Major Depressive Disorder” is exactly like giving them the diagnosis of “chest pain” - it is a ***symptom***, not a diagnosis.
- What can cause chest pain? Heart attacks, arrhythmias, pneumonia, ulcers, hepatitis, grief, anxiety, GERD, trauma to the chest...

Why Do Neuroimaging?

- Treating Symptoms: If you give everyone the same treatment for chest pain will some people get better? Yes... but for many nothing will happen, and some will get *worse*
- The same is true for depression. It is a **final common pathway symptom with many different causes** (chronic stress, TBI, malnutrition, substance abuse, hypothyroidism, grief/loss, anemia, pancreatic cancer, etc.)

Why Do Neuroimaging?

“Major depressive disorder is so named in recognition that it likely does not represent a single disease, but rather a constellation of symptoms which may arise as a result of varied etiologies. There may be multiple “phenocopies” of MDD - phenotypes with a different genetic and physiologic basis but overlapping phenotypes.”

Perlis, 2010, pg 97, in “Genetic and genomic studies of major depressive disorders”

Why Do Neuroimaging?

“With the advent of imaging technologies, it is now possible to conduct in vivo evaluations of biomarkers in “functional” psychiatric disorders... through this technology, it is possible to evaluate the underlying neurological changes at a systems level and evaluate the therapeutic response to treatment.”

Shamy et al, 2010, “Translational research in mood disorders: using imaging technologies in biomarker research”

Why Do Neuroimaging?

EE Camargo, in the Journal of Nuclear Medicine, 2001:

“Structural and functional images of the brain play an important role as powerful adjuncts in the management of an increasing number of neurologic and psychiatric diseases. Brain SPECT, in particular, with perfusion agents or with neuroreceptor imaging radiopharmaceuticals, is rapidly becoming a clinical tool in many places.”

Why Do Neuroimaging?

EE Camargo (cont):

“The importance of this technique in nuclear medicine today should not be overlooked, particularly in cerebrovascular diseases, dementias, epilepsy, head injury, malignant brain tumors, movement disorders, OCD, Gilles de la Tourette’s syndrome, depression, and drug abuse.”

Why Don't We Look?

- Most psychiatrists have forgotten what little neurobiology we used to know
- Imaging is not part of our training or tradition
- There are residency programs (UCI, UCLA, others) who now teach residents how to order and interpret scans
- Laszlo Mechtler, MD, American Society of Neuroradiology

Myths About Neuroimaging

Myth: Scans Make Diagnoses

- Scans do not confirm DSM-based diagnoses; the DSM is not based on underlying neuroscience, but on historical symptom clusters
- Scans help provide additional information (the BIO of Bio/Psycho/Social evaluation); they add valuable info on function or dysfunction of certain brain regions

Myth: Scans Are Experimental

- SPECT is covered by >50% of insurance companies, including Medicare (Toxin Exposure, TBI, Tumor, Stroke, Epilepsy, Anoxia)
- Over 2500 published studies on neuroimaging in psychiatry and addiction medicine going back 20 years
 - Dementia - 21- studies on 13,261 subjects
 - ADHD - 93 studies on 2010 subjects
 - Brain Injury - 107 studies on 3,335 subjects
 - Treatment effects - 107 studies 4308 subjects

Imaging Research in Psychiatry and Addiction Medicine

- Normal - 76 studies on 4,111 subjects
- Autistic Spectrum Disorders - 63 studies on 2,051 subjects
- Epilepsy 253 studies on 7,382 subjects
- Violence - 41 studies on 1,468 subjects

Myth: Scans Are Dangerous

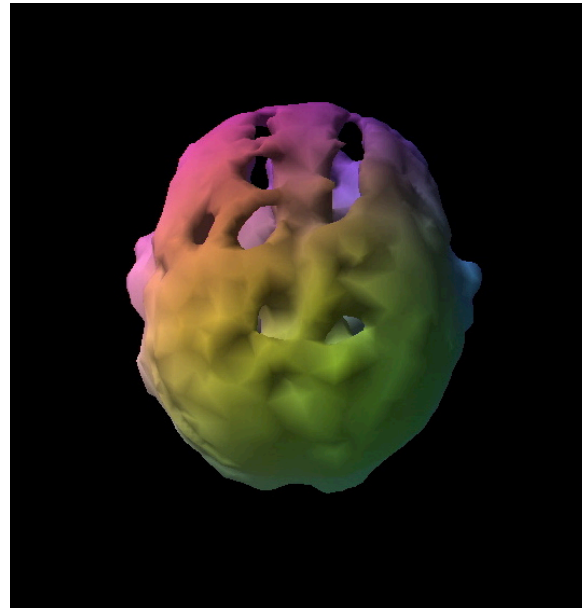
- Radiation of a SPECT study is 2/3 of a routine abdominal CT scan ordered for constipation
- Last year 20 million nuclear procedures done in the US, including 8,000 at Boston Children's Hospital
- No evidence of harm from SPECT or PET study

Myth: Scans Change Moment to Moment

- Less than 3% variability over 3 weeks (Mena)
- Need to do something to change the scan
- Time of menstrual cycle matters if she has PMS
- Age matters - study of 8,000 scans shows brain changes over the lifespan

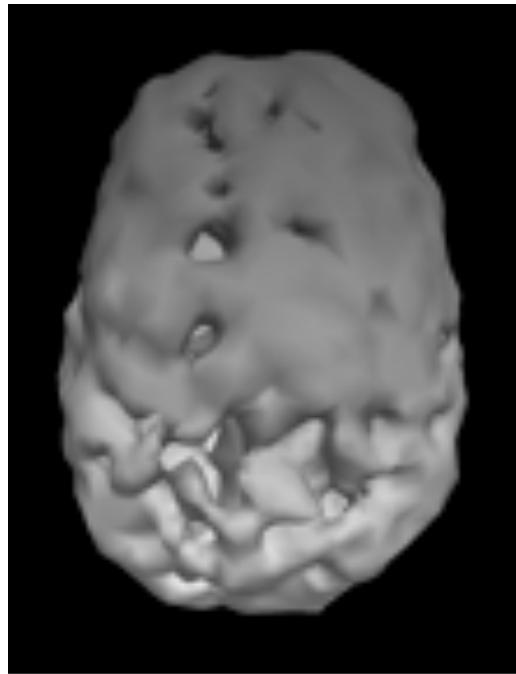
Why Do Neuroimaging?

Evaluate and target treatment to brain areas involved in mood and behavioral problems, such as the PFC and temporal lobes



Why Do Neuroimaging?

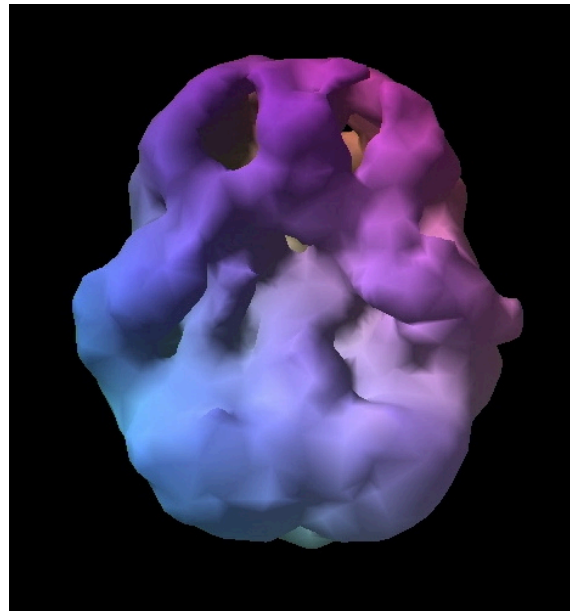
Enhance Motivation and Compliance:
“This is a real wake-up call”



Why Do Neuroimaging?

Decrease Stigma:

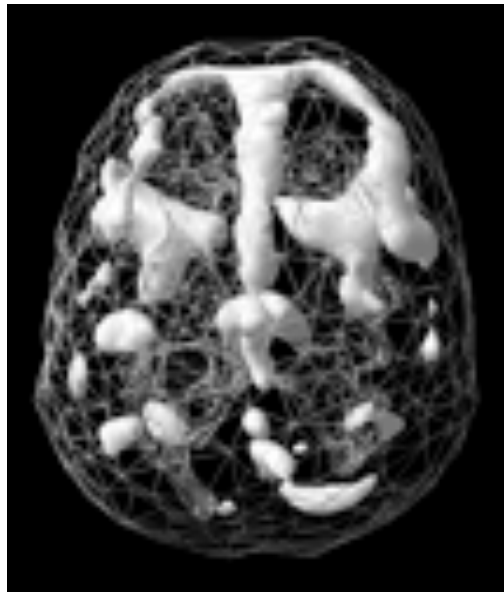
*“I have a **medical illness**”*



Why Do Neuroimaging?

Promotes Compassion, Understanding,
and Patience:

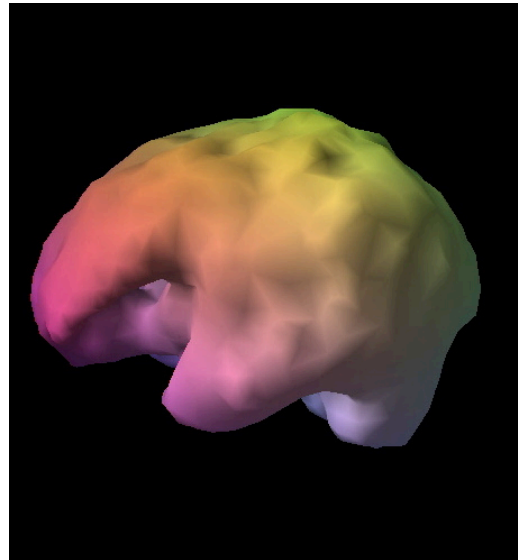
“You have a medical illness”



Why Do Neuroimaging?

Discover unforeseen findings that are contributing to problems - like strokes, seizures, or traumatic brain injury:

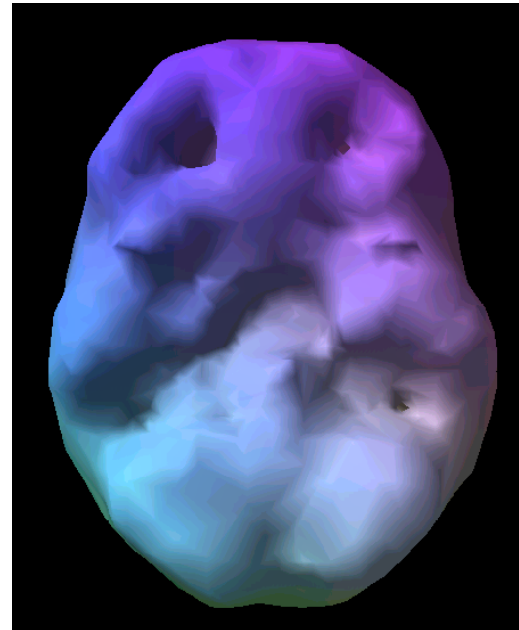
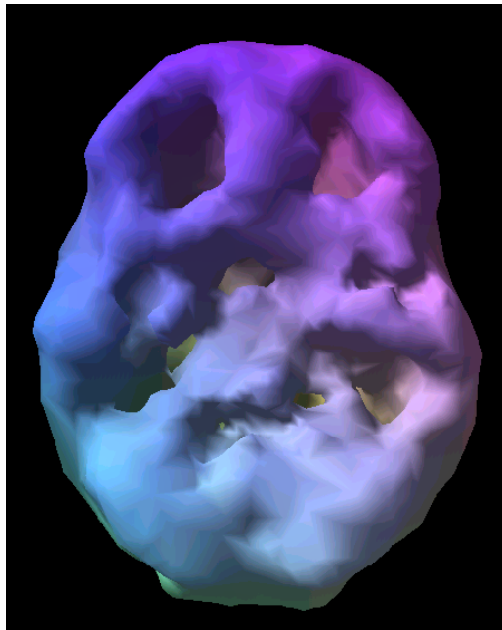
“Wow, I didn’t expect that”



Why Do Neuroimaging?

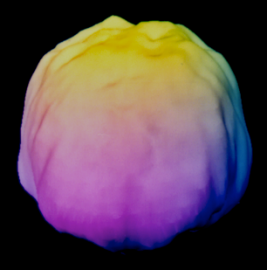
Enhance Our Effectiveness:

“The treatment is really making a difference!”

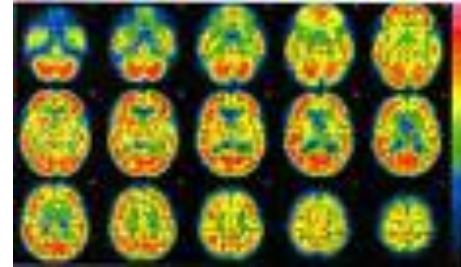


Functional Brain Imaging: SPECT

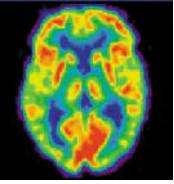
- SPECT
- MEG
- PET
- fMRI
- QEEG



SPECT

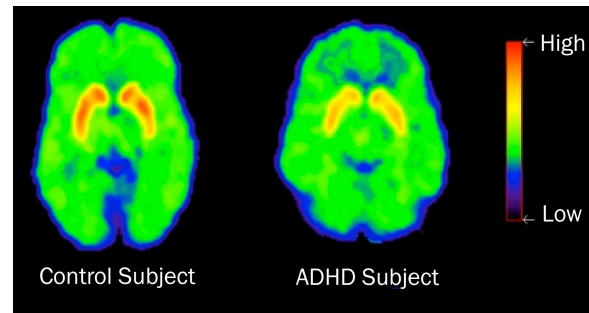


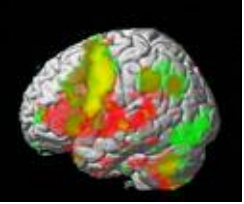
- Single photon emission computed tomography
- Uses a radioisotope, typically Tc99, combined to a pharmaceutical, either HMPAO or ECD, to measure regional cerebral blood flow
- May also measure receptor activity
- Long exposure
- Image happens in injection room
- Up to 6 hours after injection to scan



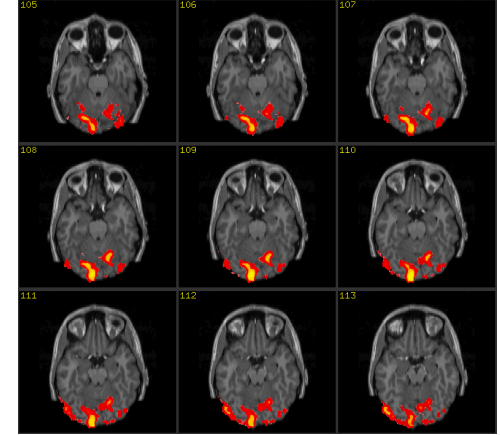
PET

- Positron emission tomography
- A small amount of radioactive glucose is injected into a vein, and a scanner is used to make computerized images that illuminates areas of increased glucose metabolism, rCBF, or receptor activity
- Short exposure





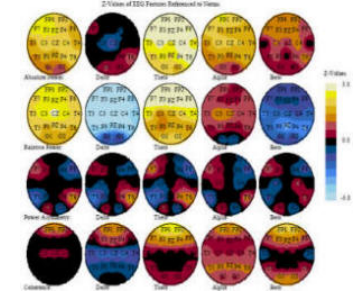
fMRI



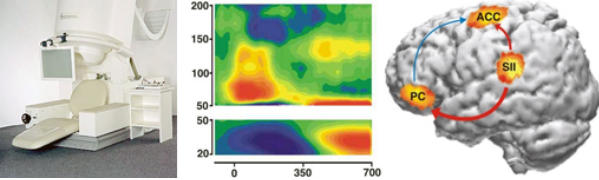
- Functional magnetic resonance imaging
- Compares the differences in blood flow between a resting condition and an active condition (thinking, seeing, touching, hearing) to find regions of the brain that are associated with one task and not another
- Very short exposure
- No radiation
- Can repeat scans as often as desired



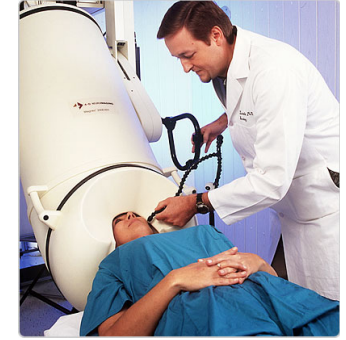
QEEG “Brain Map”



- Quantitative electroencephalography
- A computer analysis of the EEG signal; this is compared against a reference database of normal EEG's, and the analysis identifies variations from the norm
- Often used to inform neurofeedback protocol selection
- Scalp placements may limit information from deep brain structures



MEG



- **Magneto-encephalography**
- Is a technique for mapping brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain
- Applications include localizing regions of pathology before surgical removal, determining the functions of various parts of the brain, and neurofeedback
- For creating functional maps of human cortex during complex cognitive tasks, MEG is most often combined with fMRI

How is SPECT done?

- A SPECT scan's image occurs (as opposed to PET or fMRI) while the pt is sitting upright in an injection room, not while he or she is lying in the camera.
- Within 2 mins of injecting the radiopharmaceutical, it locks in the brain where it stays fixed and measurable for 6 hours. Thus the SPECT image occurs in a more normal state (in the injection room) rather than while lying in an MRI tube listening to what sounds like machine gun fire.

How is SPECT Done?

- This gives SPECT several advantages:
 - We are able to sedate pts after they have been injected, without affecting the images (e.g., hyperactive or autistic patients, or those with claustrophobia)
 - With a 6 hour half life of the SPECT isotope we can easily retake scans if motion artifact is a problem, without further injection of the isotope

How Imaging Helps

- Can see brain changes:
 - Psychostimulant - within 1/2 hour
 - Drunk - immediate
 - SSRI effect - 2 months
 - Sobriety/abstinence - generally within 10 days
 - Resulting from experiential/expressive/somatic therapies (EMDR, acupuncture, SE)

How SPECT Imaging Helps

- If a pt has an overactive brain or brain subsystems, SPECT can help us make recommendations to calm the brain
- If an under-active brain or brain subsystems, can make recommendations to help stimulate it

How SPECT Imaging Helps

- Identify potential underlying seizure activity; more accurately seen by SPECT than standard EEG, especially in the medial temporal lobes
- Specify target areas for treatment, such as overactive basal ganglia, anterior cingulate gyrus (seen on anxiety and OCD spectrum disorders), or an underactive temporal lobe (seen in seizure disorders, brain trauma, etc)

How SPECT Imaging Helps

- Can highlight the specific effect of medication on the brain, and inform how to adjust medication dosages.
- Often pts report that SSRI's are helpful but also cause de-motivation or memory problems. SPECT studies can show when SSRI's are excessively decreasing prefrontal or temporal lobe activity that clinical evaluation only hints at.

How SPECT Imaging Helps

- Can help evaluate those who may be at risk for dementia - the brain often shows changes before people have clinical symptoms of dementia.
- One study reported that there has to be a 30% loss of hippocampal volume before symptoms occur. Using autopsy data in 54 pts, Bonte reported that brain SPECT had a positive predictive value for Alzheimer's Disease of 92%

Neuroimaging Is Never The Complete or Final Answer

- It is part of the answer, which when used with a good clinical history, physical examination, and other assessments gives clinicians and pts more information for diagnosis and to tailor treatments to the specific patient.

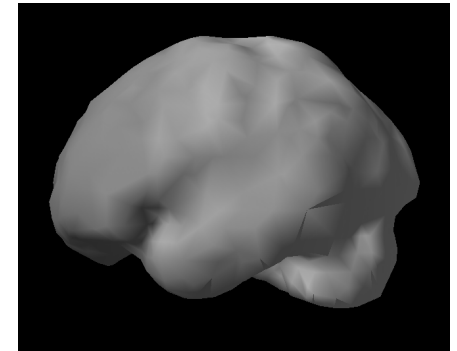
What Functional Brain Scans Cannot Do

- Give a diagnosis in the absence of clinical information
- Give the date of a head injury, infection, or toxin exposure
- Assess or evaluate IQ
- Assess or evaluate the guilt, innocence, motivation, or sanity of a criminal defendant

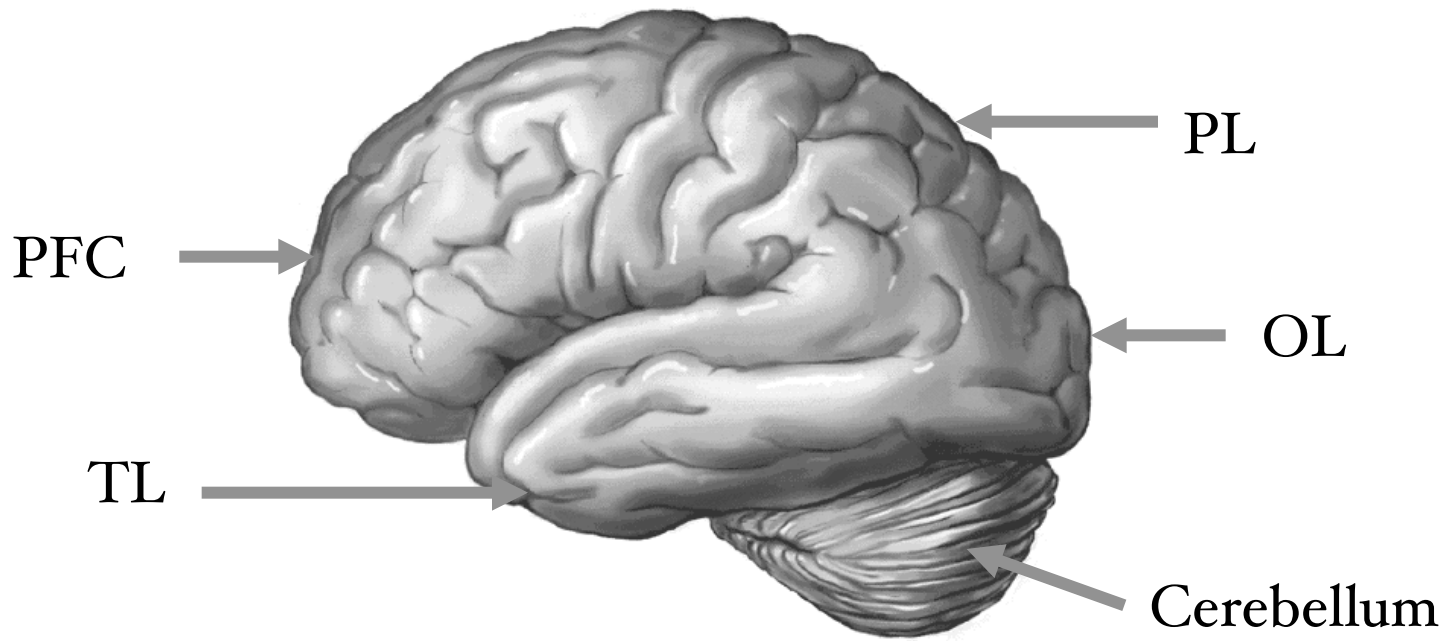
Clinical Rationale for Imaging in Neuropsychiatry:

Three Principles

1. Specific Brain Systems Tend to Be Involved in Specific Brain Functions



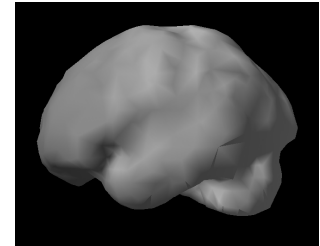
Specific Brain Systems Tend to Be Involved with Certain Brain Functions



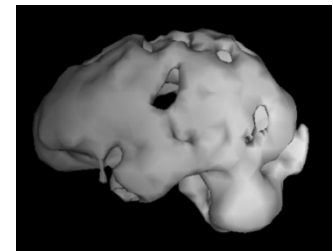
Specific Brain Systems Tend to Be Involved with Certain Brain Functions

- Different brain regions are specialized to perform different sensory, motor, and cognitive functions
- Brain regions become more active metabolically when they perform the activity for which they are specialized
- This increased metabolic activity in “activated” brain regions causes local increases in cerebral blood flow

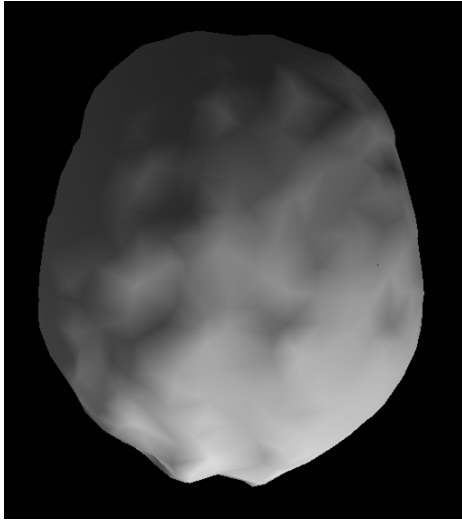
1. Specific Brain Systems Tend to Link to Specific Brain Functions



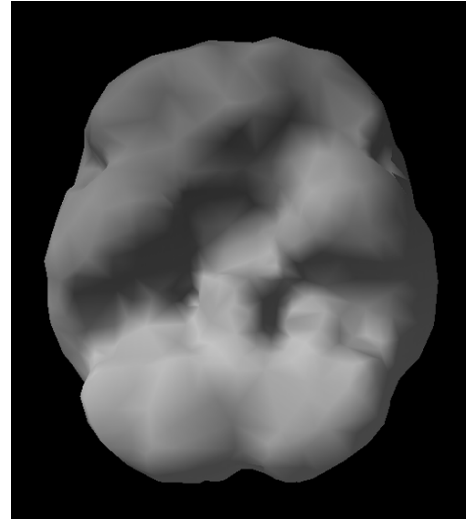
2. Problems in Specific Brain Systems Tend to Cause Specific Symptoms



Pre-Frontal Cortex



Top-Down Surface View
SPECT



Underside Surface
View SPECT

Pre-Frontal Cortex

PFC Functions

PFC Problems

- **PFC Dorsal lateral**

- Attention
- Planning
- Follow through

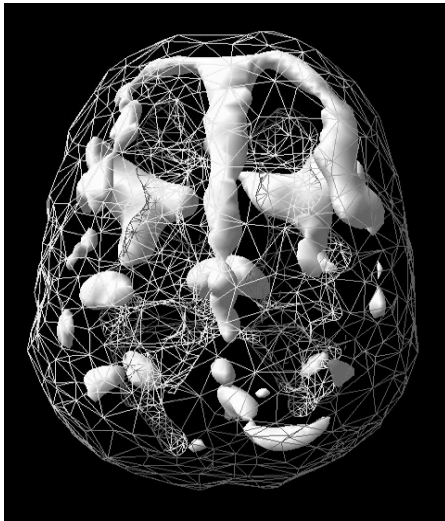
Inattention
Lack of forethought
Procrastination

- **PFC Inferior orbital**

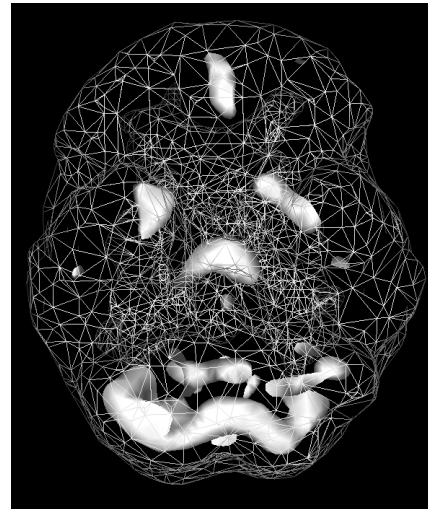
- Impulse control
- Inhibition
- Judgment
- Empathy
- Ethics

Impulsive
Disinhibited
Poor judgment
Lack of empathy
Lack of ethics

Anterior Cingulate Gyrus



Top Down
Active View
SPECT



Underside
Active View
SPECT

Anterior Cingulate Gyrus

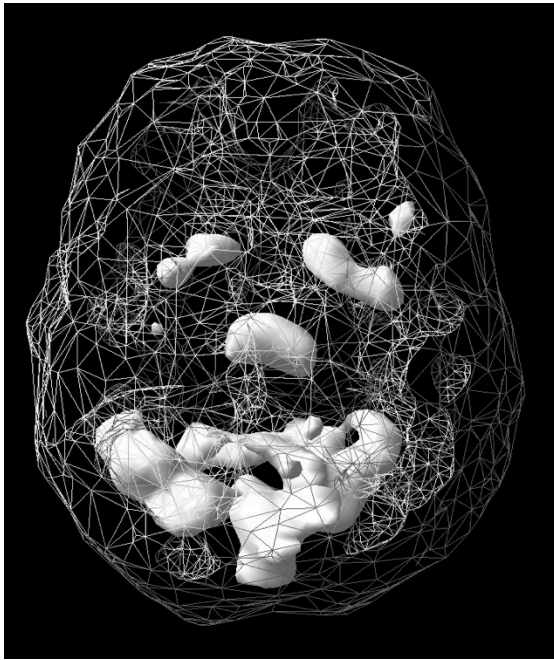
ACG Functions

- Brain's attentional gear shifter
- Cognitive flexibility
- Cooperation
- Go from idea to idea
- Can see options
- Go with the flow
- Error detection

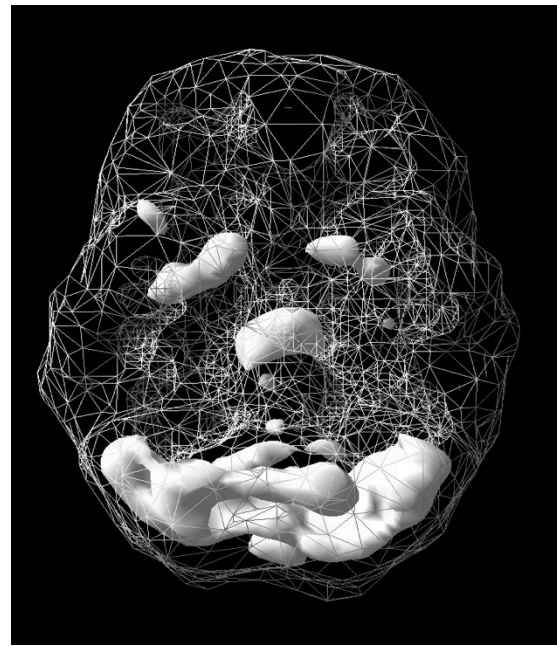
ACG Problems

- Gets stuck - trouble shifting gears
- Cognitive inflexibility
- Holds grudges, oppositional
- Obsessional thinking
- Compulsive behaviors
- Argumentativeness
- Excessive error detection and worry

Basal Ganglia



Top Down Active
View SPECT



Underside Active
View SPECT

Basal Ganglia

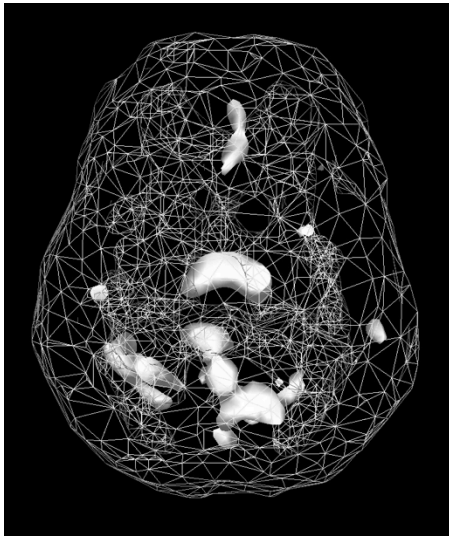
Basal Ganglia Functions

- Set anxiety levels
- Mediates pleasure
- Modulates motivation
- Smooth movement

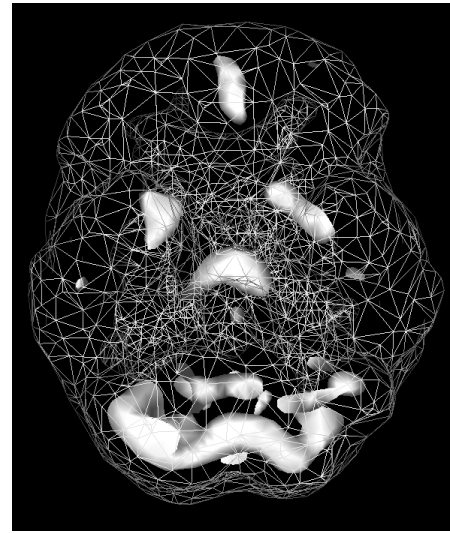
Basal Ganglia Problems

- Anxiety, panic
- Hypervigilance
- Tension
- Predicts worst
- Irritability
- Decreased motivation

Deep Limbic System/ Thalamus



Underside
Active View
SPECT



Underside
Active View
SPECT

Deep Limbic System/ Thalamus

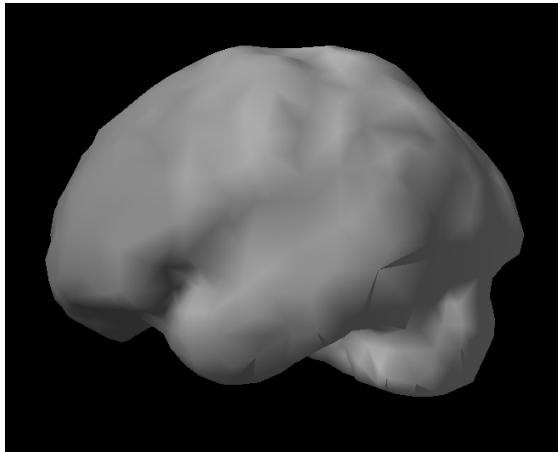
DLS Functions

- Sets emotional tone
- Flight or fight response
- Modulates motivation
- Charged memories
- Appetite/sleep cycles

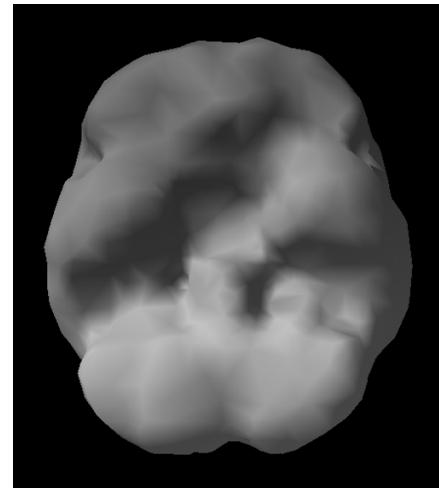
DLS Problems:

- Sadness, negativity
- Guilt, blame
- Anger/irritability
- Low motivation/energy
- Social isolation
- Low self-esteem

Temporal Lobes



Left Side Surface View
SPECT



Underside Surface
View SPECT

Temporal Lobes

TL Functions

Amygdala

- Emotional valence
- Mood stability
- Temper control

Hippocampus

- Memory

Lateral

- Language
- Listening
- Reading
- Read social cues
- Rhythm, music

TL Problems

Emotional reactivity

Moodiness, irritability

Anger, anxiety, fears,
phobias, dark thoughts

Forgetfulness

Trouble finding words

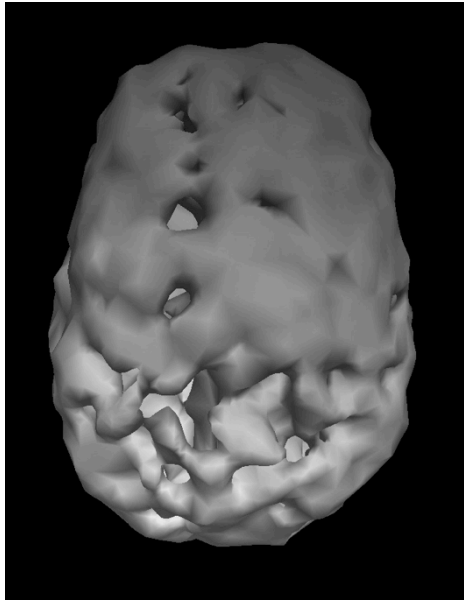
Processing problems

Poor reading

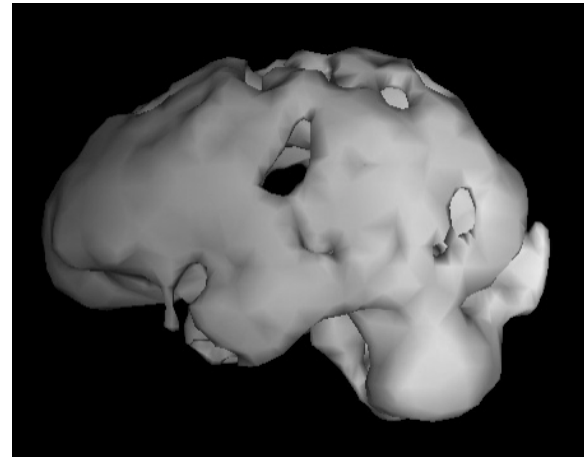
Poor social skills

Rhythm problems

Toxicity/Scalloping



Top-Down Surface
View SPECT



Left Side Surface
View SPET

Toxicity/Scalloping

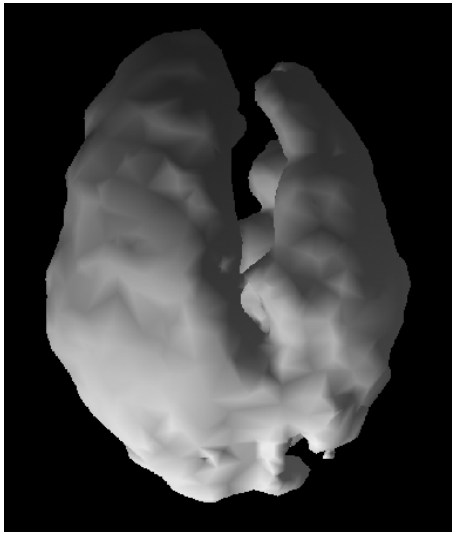
Toxicity/Scalloping Causes

- Drug or alcohol abuse/exposure
- Environmental toxic exposure (paint fumes, solvents, excessive pollution, etc)
- Anoxia
- Encephalitis

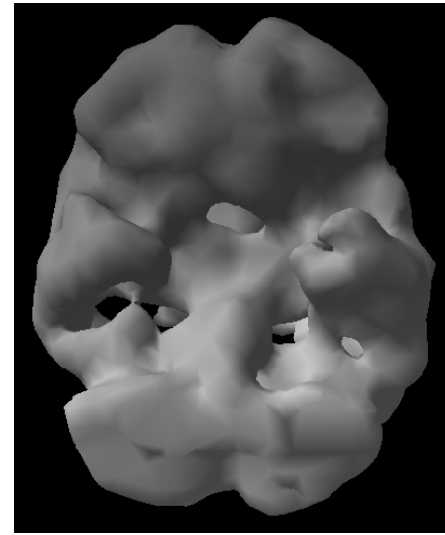
Toxicity/Scalloping Symptoms (depends on system affected)

- Cognitive problems (attention and memory)
- Fatigue
- Irritability
- Prefrontal, temporal, and/or parietal lobe symptoms

Physical Brain Trauma Patterns



Top-Down Surface
View SPECT



Underside Surface
View SPET

Physical Brain Trauma

Trauma Causes

- Blunt force
- Whiplash injuries
- Acceleration/deceleration injuries
- Falls, sports, motor vehicle accidents
- ** Loss of consciousness may not be present

Trauma Symptoms (depends on system affected)

- Cognitive problems (attention and memory)
- Fatigue
- Irritability
- Prefrontal, temporal, and/or parietal lobe symptoms

The DSM-V Workgroup, on the link between diagnostic classification and etiology across the four major anxiety disorders:

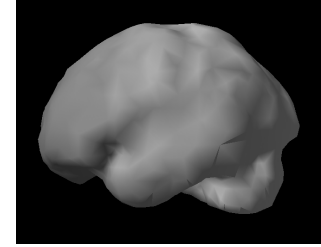
“The DSM anxiety categories do not map neatly onto simple, consistent, and distinct etiological pathways... given this complexity and our current extremely incomplete stage of knowledge, we are unlikely, at this point in time, to define a significantly ‘truer’ anxiety nosology.”

Fyer and Brown, From “Stress-Induced and Fear Circuitry Disorders: Advancing the Research Agenda for DSM, edited by Gavin Andrews, MD et al, 2009

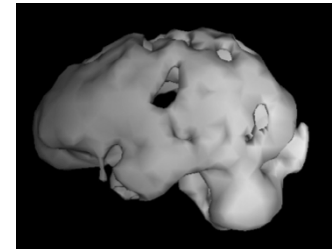
The DSM-V Workgroup, on the link between diagnostic classification and etiology across the four major anxiety disorders:

As a result, they note that “plans to make major modifications in the classification should probably be undertaken with some degree of caution.”

1. Specific Brain
Systems Tend to Link to
Specific Brain Functions



2. Problems in Specific Brain
Systems Tend to Cause
Specific Symptoms



3. Specific Brain Systems
Tend to Respond
Preferentially to Specific
Treatments

Rx?

Different Brain Systems Tend to Respond Preferentially to Different Treatments

- **PFC**

- Psychostimulants
- Non-Stimulant medications
- L-tyrosine
- Stimulating activities
- Neurofeedback
- Goal setting
- Prayer/Contemplative practices

- **Anterior Cingulate Gyrus**

- SSRI' s, SNRI' s
- Atypical antipsychotics in refractory cases
- 5-HTP/STJohn' s Wort
- EMDR, Biofeedback, SE

Different Brain Systems Tend to Respond Preferentially to Different Treatments

- **Temporal Lobes**

- Anticonvulsant

- Neurontin, Topamax, Depakote, Lamictal, Tegretol, etc.

- Memory Enhancer Meds

- Aricept, Reminyl, Namenda

- Supplemental GABA

- Relationship counseling, anger management

- DBT, EMDR

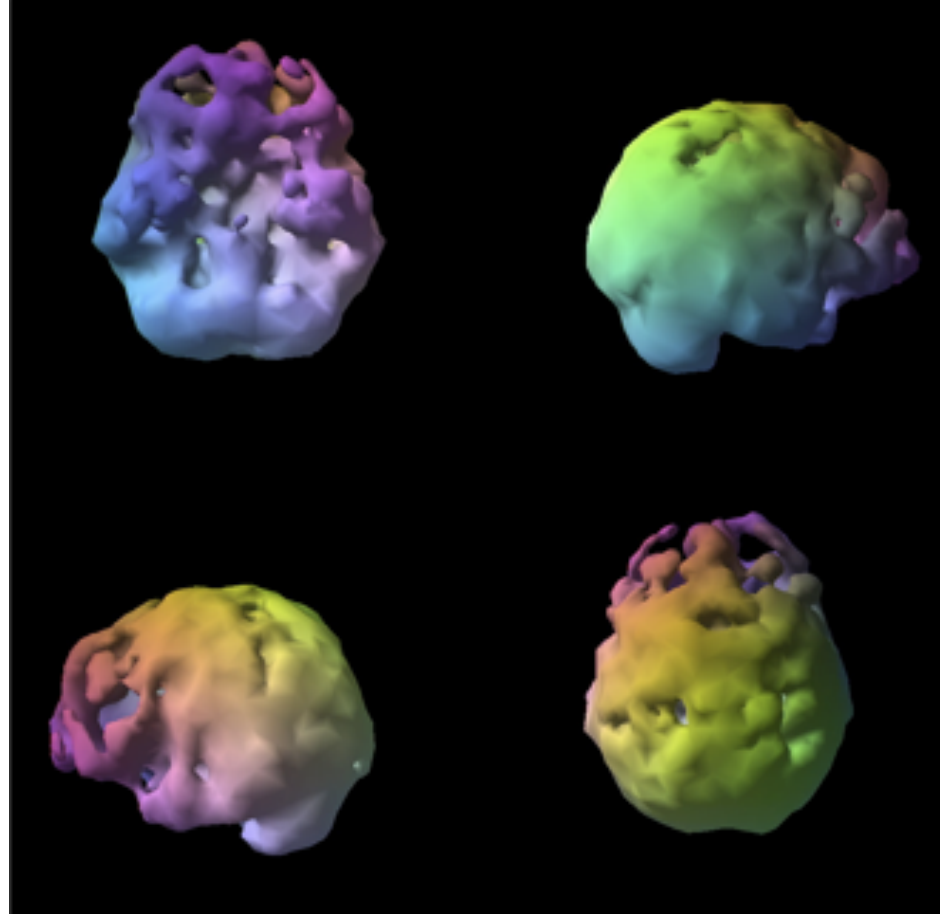
Different Brain Systems Tend to Respond Preferentially to Different Treatments

- **Deep Limbic System/Thalamus**
 - Antidepressants: Wellbutrin, Norpramin, Effexor, Cymbalta, MAOI's, SSRI's (if ACG present)
 - Anticonvulsants
 - Lithium for focal increased activity or cyclic mood changes
 - DL Phenylalanine, SAME, L-tyrosine
 - CBT, EMDR

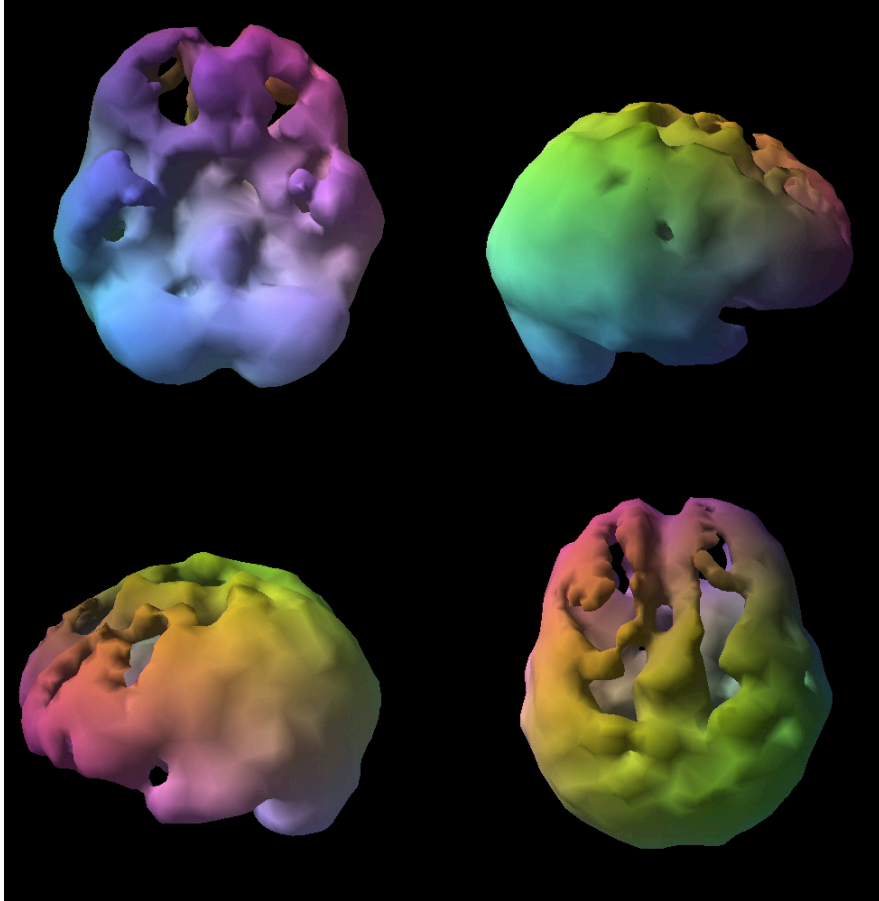
Different Brain Systems Tend to Respond Preferentially to Different Treatments

- **Physical Brain Trauma**
 - Eliminate risk for future injuries
 - Maximize brain nutrition
 - Hyperbaric Oxygen Therapy
 - Neurofeedback
 - Brain Healthy Strategies
 - Physical and mental exercise
 - Omega 3 FA' s
 - Alpha lipoic Acid, 100-300 mg 2X/day
 - Phosphatidal Serine 100 mg 3x/day

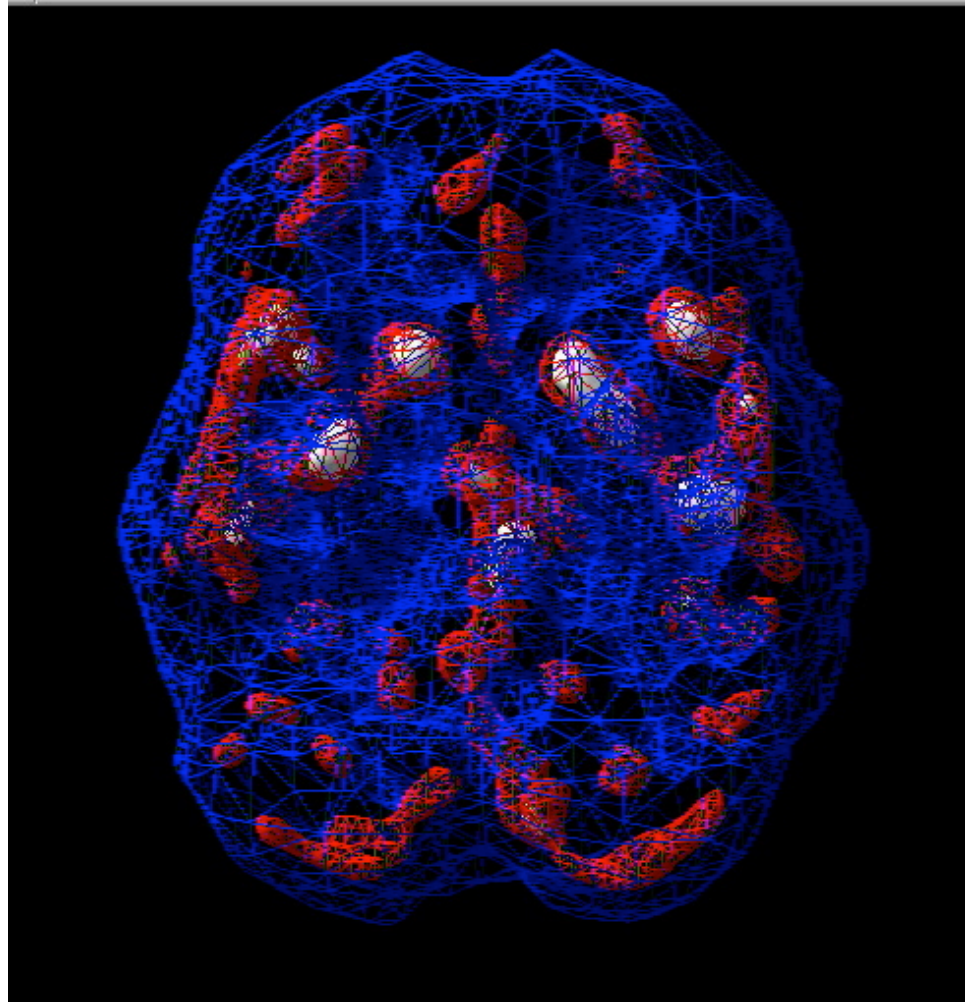
Case Examples

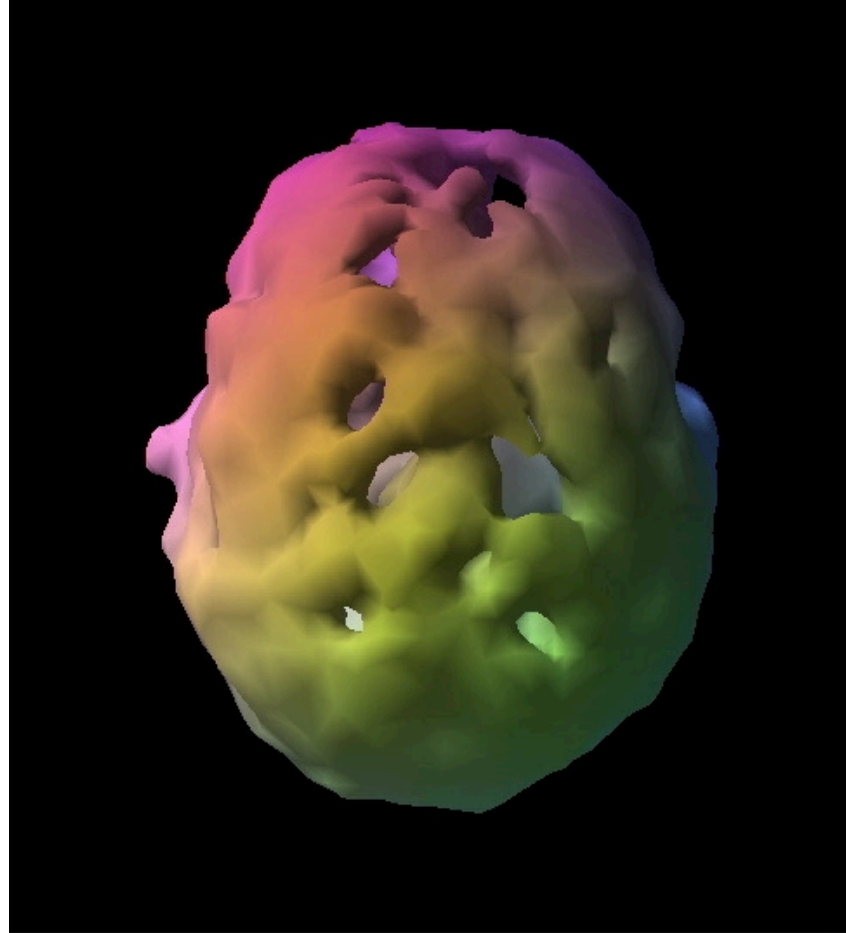


46 y/o attorney, hx polysubstance abuse. “No head injuries”. With further questioning, “Fell onto forehead when intoxicated”; dropped onto head at birth; “My partner threw me down a set of marble stairs” and was subsequently symptomatic. “I have serious cognitive problems” Short attn span, impulsivity, low motivation, disorganization, distractibility, mood instability, irritability, memory problems, periods of anxiety or irritability with little provocation.

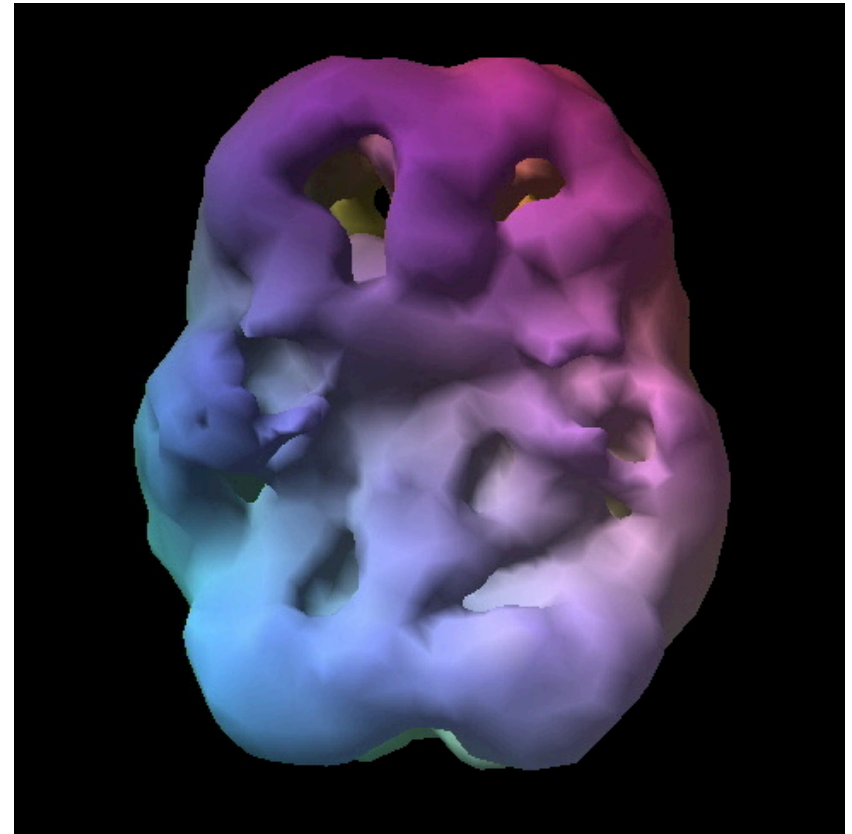
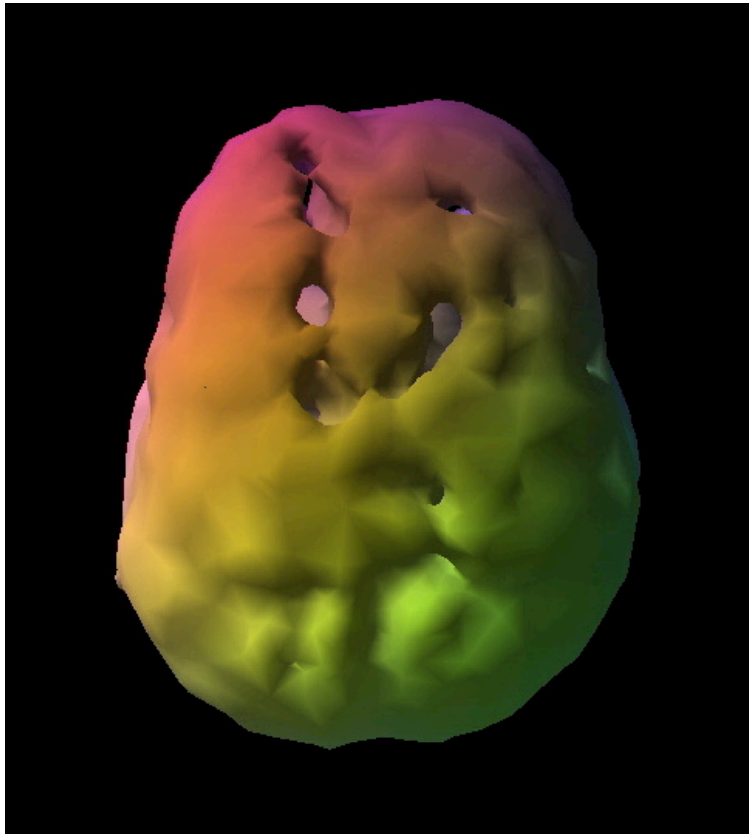


63 y/o female; history of head on, roll-over MVA 12 years prior;
“goose egg” on forehead with subsequent severe tinnitus.
Symptoms: Oxycontin abuse, inattention, memory problems,
emotional reactivity, poor judgment and impulse control, difficulty
foregoing immediate gratification.

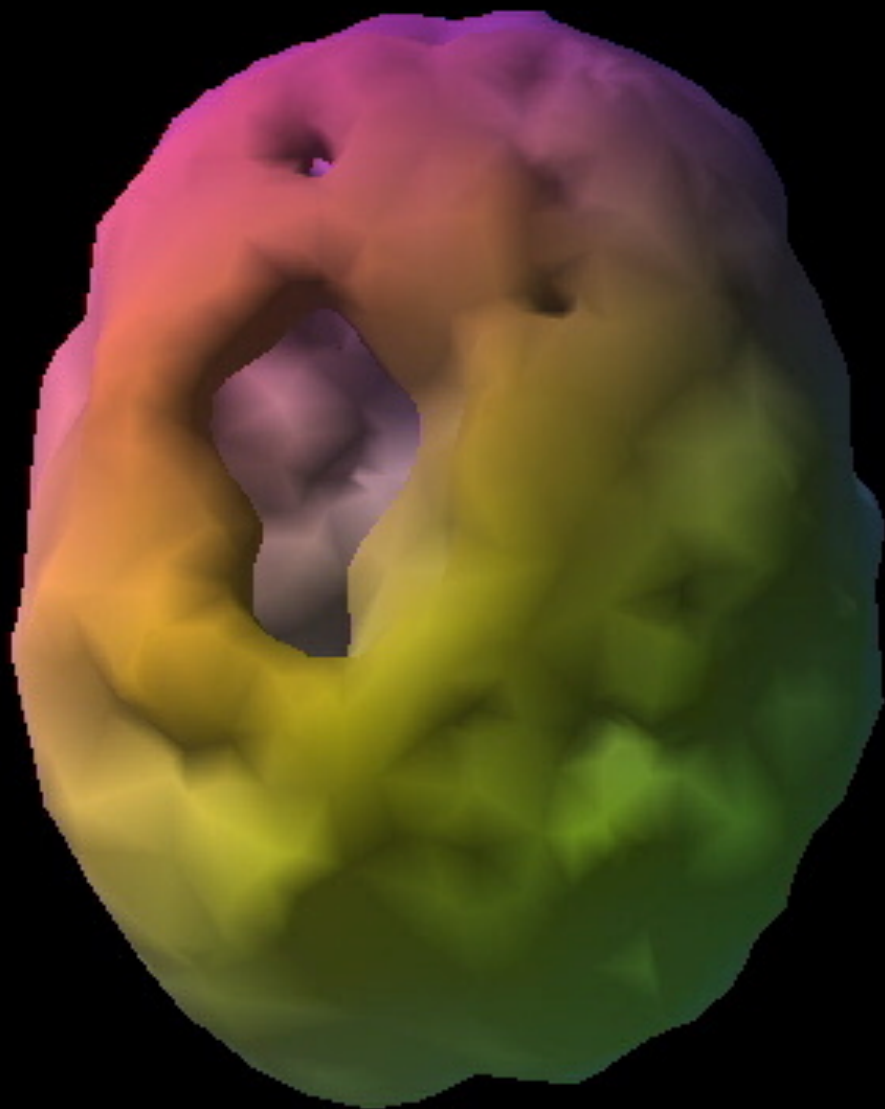


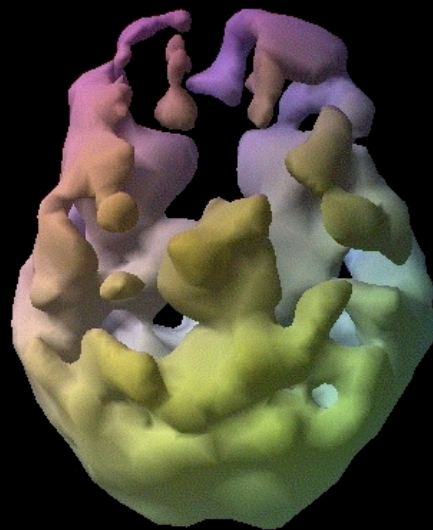
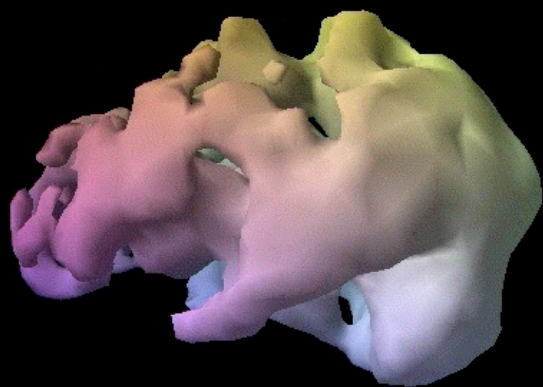
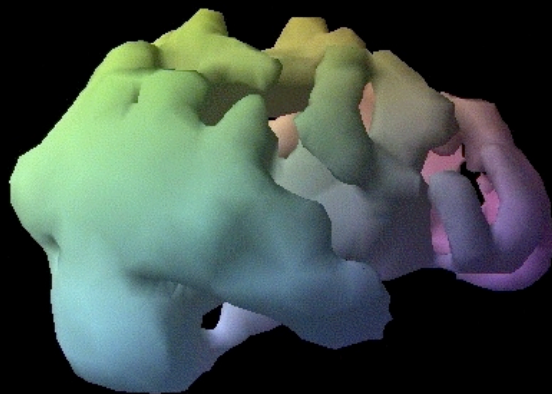
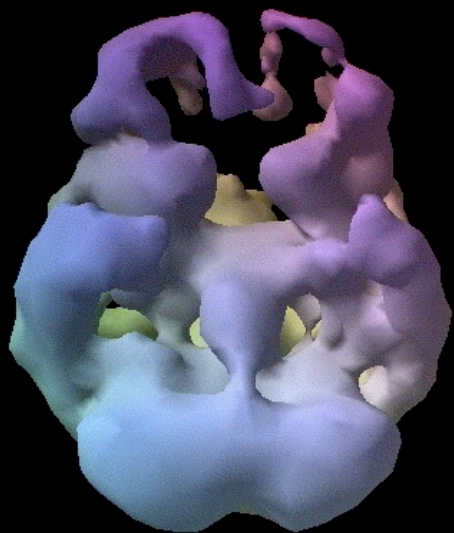


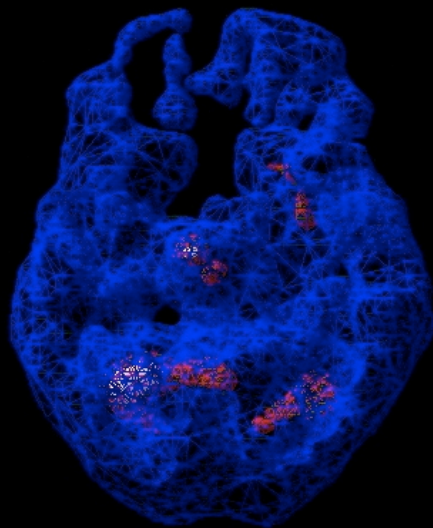
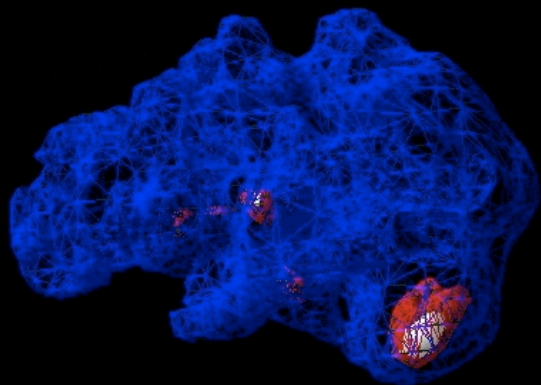
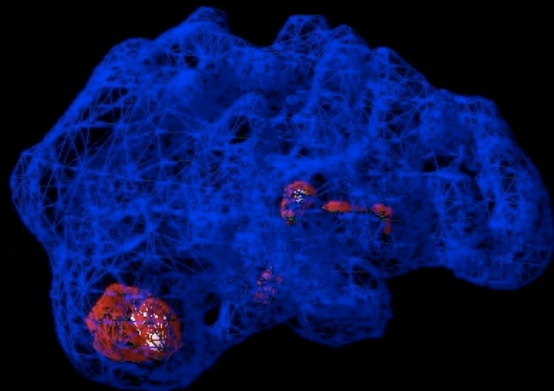
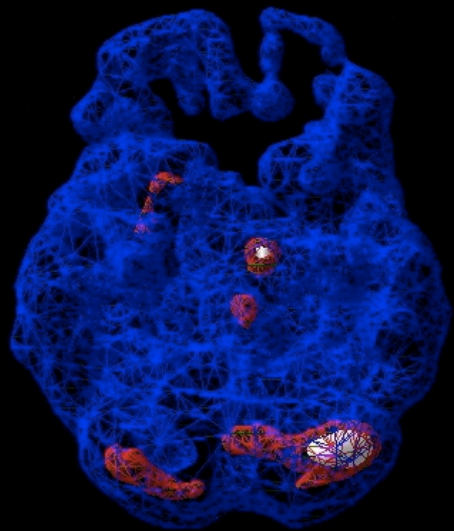
40 y/o cauc male; history of father beating him “for years”; also had concussions from football, hit in face, fell forward unconscious while intoxicated (alcohol, cocaine, MJ), breaking all front teeth



49 y/o cauc male; was pulled unconscious from pool in 1997 --> 14 day coma, 3 mos rehab. Also hit with rock on head with LOC. History of subsequent alcohol, nicotine, and cocaine abuse; symptoms of depression, dark/negative thoughts, obsessionality, seizure activity, mild dementia, PTSD, anxiety, and oppositional behavior







The Role of Neuroimaging in Psychiatry and Addiction Medicine

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