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.”
“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 assessment and treatment methods 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
Without Imaging

- Diagnoses still made similar to how Lincoln was diagnosed with depression in 1840
- DSM is hurting us, because it is not based on underlying physiology
Psychiatrists only medical specialists who rarely looks at organ they treat

- Cardiologists look
- Neurologists look
- Orthopedists look
- All other specialties look
- Psychiatrists… guess
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.”

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 (Vit B deficiency, TBI, malnutrition, substance abuse, hypothyroidism, grief/loss, anemia, pancreatic cancer, etc.)
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.”

Why Don’t We Look?

• 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
• Conversation with Laszlo Mechtler, MD, American Society of Neuroradiology
SPECT

- Single photon emission computed tomography
- Radioisotope, Tc99, + HMPAO or ECD
- Measures rCBF and activity
- Gives three pieces of information: good activity, too little, or too much
Healthy Brain SPECT Scans

Surface View                      Active View
Healthy vs 2 Strokes

Healthy

Stroke
Healthy vs Alzheimer’s Disease
Healthy vs Traumatic Brain Injury

Healthy vs TBI
Healthy vs Drug Abuse

Healthy

Drug Affected
Healthy vs OCD

Healthy

OCD
Healthy vs Seizure Activity

Healthy

Seizure Activity
Two Patients with Depression

Rx needs to be tailored to individual brains
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.”
Current Paradigm

Symptoms = Diagnosis = Treatment

- Depressed = Depression = Antidepressant
- Attent/Impulse = ADHD = Stimulant
- Panic attacks = Panic Dis = Anti-anxiety
- Explodes intermittently = I. E. D. = ????
There Is A Better Way

Comprehensive Clinical Assessment

(through history + focused psychometric testing

+ Detailed Lab Work

+ Functional Imaging

= Revolution

→ More targeted treatment and significantly improved patient outcomes
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 in Family Members:

“Oh, 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?

Clarify Co-Occurring Illnesses
Why Do Neuroimaging?

Enhance Our Effectiveness:

“The treatment is really making a difference!”
How Does SPECT Change Clinical Practice?

- 109 consecutive patients
- SPECT changed diagnosis &/or treatment 79%
- 22% unexpected brain injury
- 22% unexpected toxicity
- 60% new targets for medication or other Tx’s

Better Outcomes

- 500 consecutive patients
- On average our patients have 4.2 diagnoses, 3.3 prior providers and 6 medications failures
- 75% significantly improved across all measures
- QOLI significantly increased in 85%
- Cleveland Clinic QOLI in <50%
Early Lesson

- Mild traumatic brain injuries are a major cause of psychiatric illness
Mild Traumatic Brain Injury

Mild?
Undiagnosed Brain Injuries Are a Major Cause of:

- Homelessness
- Drug/alcohol abuse
- Depression
- Panic attacks
- ADHD symptoms
- Suicide
Early Lesson

- Infectious diseases are a common cause of psychiatric symptoms
More Lessons

- Judges and defense attorneys sought our help to understand criminal behavior
- > 500 convicted felons, including 90 murderers
- Our work taught us that people who do bad things often have troubled brains
- Many of these brains could be rehabilitated
Radical Idea?

- What if we evaluated and treated troubled brains

- Rather than simply warehousing them in toxic, stressful environments? (Bruce Alexander)

- We could save tremendous $$ by making people more functional

- So when they got out of prison they could work, support their families and pay taxes.
“A society should be judged not by how it treats its outstanding citizens, but by how it treats its criminals.”

Instead of just Crime and Punishment

→ Crime, Evaluation and Treatment
Could functional neuroimaging have prevented this tragedy and others like it?
In 1994 NFL Formed Concussion Committee

- In 2009 Goodell said to Congress: “We (NFL) don’t yet know if playing football causes long term brain damage. *We are still studying the issue.*”

- NFL never sponsored a functional brain imaging study for players … instead studied rats

- NFL acted like many employers: delay… deny… and blame the employee when they’re hurt
Problem with NFL’s Position

- If you don’t admit you have a problem, you cannot do anything to solve it!

- Many brain damaged NFL players were left without help or hope

- 2009-2011 Amen Clinics with the LA Chapter of NFLPA performed first large functional imaging study on players

- Brain SPECT imaging helped to change everything
Impact of Playing American Professional Football on Long-Term Brain Function

Daniel G. Amen, M.D.
Andrew Newberg, M.D.
Robert Thatcher, Ph.D.
Yi Jin, M.D.
Joseph Wu, M.D.
David Keator, M.C.S.
Kristen Willeumier, Ph.D.

The authors recruited 100 active and former National Football League players, representing 27 teams and all positions. Players underwent a clinical history, brain SPECT imaging, aEEG.
Healthy

16 Year Guard
2011 … NFL Radically Changed Its Position On TBI

None of this was possible without the clinical application of neuroimaging.

### Concussion Facts
Concussion is a **brain injury** that alters the way your brain functions.
Concussion can occur from a blow to the head/body:
- following helmet to helmet contact, and / or
- contact with the ground, object or another player
Most concussions occur without being knocked unconscious
Severity of injury depends on many factors and is not known until symptoms resolve and brain function is back to normal!
All concussions are not created equally. Each player is different, each injury is different and all injuries should be evaluated by your team medical staff

### Concussion Symptoms
Different symptoms can occur and may not show up for several hours. Common symptoms include:
- Confusion
- Headache
- Amnesia / Difficulty remembering
- Balance problems
- Irritability
- Dizziness
- Difficulty concentrating
- Nausea
- Feeling sluggish, foggy or groggy
- Sensitivity to noise
- Sensitivity to light
- Double / fuzzy vision
- Slowed reaction time
- Feeling more emotional
- Sleep disturbances
- Loss of consciousness
Symptoms may worsen with physical or mental exertion (e.g. lifting, computer use, reading)

### Why Should I Report My Symptoms?
- Practicing or playing while still experiencing symptoms can prolong the time to recover and return to play.
- Unlike other injuries, there may be significant consequences of “playing through” a concussion. Repetitive brain injury, when not treated promptly and properly may cause permanent damage to your brain.

### What Should I Do If I Think I’ve Had a Concussion?
**Report it.** Never ignore symptoms even if they appear mild. Look out for your teammates. Tell your Athletic Trainer or Team Physician if you think you or a teammate may have had a concussion.
**Get Checked Out.** Your team medical staff has your health and well being as its first priority. They will manage your concussions according to NFL / NFLPA Guidelines which include being fully asymptomatic, both at rest and after exertion, having a normal neurologic examination, normal neuropsychological testing, and clearance to play by both the team medical staff and the independent neurologic consultant.
**Take Care of Your Brain.** According to the CDC*, “traumatic brain injury can cause a wide range of short- or long term changes affecting thinking, sensation, language, or emotions”. These changes may lead to problems with memory and communication, personality changes, as well as depression and the early onset of dementia. Concussions and conditions resulting from repeated brain injury can change your life and your family’s life forever.

*for more information about traumatic brain injury and concussion, go to http://www.cdc.gov/concussion

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Brain Rehab Program

- Damage so severe, we performed a “real-world” rehabilitation study

- Brain healthy strategies *(healthy nutrition, sleep, exercise, sobriety, weight loss if needed)*

- Brain boosting supplements *(5.6 grams fish oil, B6, B12, folic acid, gingko, vinpocetine, huperzine A, NAC, carnitine, and alpha lipoic acid)*
Significant Rehabilitation Possible

- 65 players
- 80% statistically significant improvement
- Especially in:
  - Memory 69%
  - Attention 53%
  - Mood 40%
  - Motivation 40%

Reversing Brain Damage in Former NFL Players: Implications for Traumatic Brain Injury and Substance Abuse Rehabilitation

Daniel G. Amen, M.D.; Joseph C. Wu, M.D.; Derek Taylor & Kristen Willenmier, Ph.D.
Guard for 16 Years

Before

After 18 mos
Tight End for 12 Years

Before

After 18 mos
Reversing Brain Damage Is An Exciting New Frontier, But the Implications Are Wider
Andrew
Ray and Nancy
Nancy
Ray and Nancy

• Aggressive treatment program:
  • Aricept, Namenda
  • HBOT
  • Neurofeedback
  • Brain-directed nutraceuticals
  • High dose Omega-3 FA’s
  • Anti-inflammatory diet

• Ray lost 30# via same nutritional plan
Before

After 10 Weeks
SPECT Treatment Prediction Biomarkers

- **Cho 2007 (n34)** -- ADHD children non-responders to stimulants had higher rCBF in AC and right BG. 88% classified correctly.

- **Amen 2008 (n157)** – ADHD deactivation PFC pole + with concentration stimulant, activation associated with – stimulant response.

- **Navarro 2004 (n47)** – Late onset severe depression, left frontal-cerebellar perfusion ratio positive predictive value of treatment 94%.

- **Brockmann 2009 (n93)** – Depression hyperfrontality + SSRI response, low – SSRI.

- **Langguth 2007 (n24)** – Depression rTMS responders ↑ AC rCBF.

- **Richieri 2011 (n18)** – Depression rTMS non-responders with lower PFC rCBF.

- **Hanada 2013 (n45)** – Depression, older, non-responders lower middle frontal cortex and insular rCBF.
**SPECT Treatment Prediction Biomarkers**

- **Hoehn-Saric 2001 (n16)** – *OCD* treatment responders to *SSRIs* higher pre-treatment PFC rCBF
- **Noel 2002 (n20)** – Alcoholics ↓ PFC rCBF predicts relapse
- **Warwick 2006 (n31)** – Social Anxiety Disorder treatment response lower insular cortex citalopram (also AC) and moclobemide
- **Tanaka 2004 (n70)** – *Alzheimer’s* ↑ temporal-parietal predicts positive response to donezepil
- **Kanetaka 2008 (n91)** – *Alzheimer’s* ↑ PFC perfusion predicts positive response to donezepil
- **Jobst 1997 (n391)** – Predict *Alzheimer’s* 89% sensitivity, 80% specific, 83% accurate, with *CT* 80% sensitive, 93% specific, and 89% accurate
SPECT Treatment Prediction Biomarkers

- **Bonte 2006 (n49)** – Autopsy confirmed Alzheimer’s, sensitivity 87%, specificity 89%, ppv 93%, npv 83%, accuracy 88%
- **Bonte 2004 (n20)** – 95% separates Alzheimer’s & FTLD PC sign
- **Guedj 2007 (n17)** – Fibromyalgia ↓ bilateral medial PFC rCBF predicts negative response to ketamine (100%ppv, 91% npv)
- **Eturgul 2009 (n22)** – Schizophrenia, treatment responders showed higher frontal basal ganglia perfusion with treatment
- **Rodriquez 1997 (n39)** – Schizophrenia ↑ thalamus, left basal ganglia, right prefrontal predicts positive response to clozapine
- **Kao 1994 (n18)** – Childhood viral encephalitis – early healthy SPECT predicts positive outcome at 1 year
- **Jacobs 1996 (n136)** – mTBI predicts outcome at 1 year, sensitivity 100%, specificity 85%, 83/89% positive/negative predictive value
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