SPECT in Neuropsychiatric Diagnosis

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Disclosures

Theodore A. Henderson MD, PhD is President and Chief Medical Officer of The Synaptic Space – a neuroimaging consulting firm

- Co-Founder of Neuro-Luminance Brain Health Centers Inc. – a diagnostic and treatment company
- Past Officer of the Brain Imaging Council of the Society of Nuclear Medicine (Secretary, Treasurer)
- SNMMI Brain Imaging Outreach Working Group
- President of the International Society of Applied Neuroimaging
- Co-Founder of the Neuro-Laser Foundation
- Owner and Principal Dr. Theodore Henderson Inc.

FDA Disclosure

This presentation includes discussion of off-label uses of medications approved by the FDA
Financially Motivated

- Two consulting firms concerning neuroimaging
- Have no ownership interest in SPECT imaging centers
- Refer patients to local independent hospitals for SPECT scans
- 3.4% of total gross income directly from SPECT scans
In Memoriam – Dr. Ismael Mena
Pioneer
Mentor
Gentleman
Teaching Points

- Primates have color vision
- SPECT can accurately differentiate TBI from PTSD
- SPECT scans help to reveal co-morbidities and clinically unrecognized pathology
  - Mysterious illness
  - Clear-cut illness
- SPECT already meet CED criteria
Normal Transverse Brain SPECT Images

Courtesy Dr. M. Devous
 Courtesy Simon DeBruin
Good Lion Imaging
Before Treatment

After Treatment

Segami Software
“SPECT has emerged as a useful tool for the evaluation of a variety of neurological disorders”

- “We must have a systematic way to prepare & obtain data, display the data we obtain and read the images” – Waxman

- Lack of use of SPECT – “inadequate promotion by nuclear physicians” – Tikofsky
“SPECT has emerged as a useful tool for the evaluation of a variety of neurological disorders”

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TTASAAN Report
“3-dimension PET systems record a large fraction of scattered events, such that the scatter correction is on the same order as, or even greater than, that required in SPECT”

- Increased PiB binding is found in most AD patients\textsuperscript{1,2}
- However, not all AD patients show PiB binding.\textsuperscript{3,4}
- Increased PiB binding is found in 61\% of patients with MCI.\textsuperscript{5}
- Unfortunately, increased PiB binding is found in 12\% of 60 year-old normals, 30\% of 70 year-old normals & in 50\% of 80 year-old normals.\textsuperscript{4,6}

Amyloid PET scans face many challenges

- Cost of tracer $1,800 USD or greater
- Cost of scan $3,000 USD or greater
- CMS (Medicare) not reimbursing
- Starting at age 65 may be too late
Precision of Diagnostic Modalities for AD vs. NC

- **Clinical evaluation & neuropsychological testing to autopsy**
  - 76-85% sensitivity; 55-70% specificity; 69% positive predictive value\(^1\)

- **SPECT with single-headed camera**
  - 74-96% sensitivity; 81-84% specificity; 90% positive predictive value\(^2\)

- **SPECT with multi-headed camera**
  - 82-96% sensitivity; 84-90% specificity; 94% positive predictive value\(^3\)

- **FDG PET**
  - 86-96% sensitivity; 70-90% specificity; 90% positive predictive value\(^4\)
  - 90% sensitivity; 98% specificity in one study (Mosconi et al., JNM 49:390, 2008)

- **Amyloid markers**
  - 86-90% sensitivity, 78-91% specificity dep on age\(^5\)

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5. Rowe, Alzheimer’s Association Intern. Conf 2010
Conclusions

• $^{99}$Tc-HMPAO perfusion SPECT is safe and effective modality to distinguish diagnostic patterns of cerebral perfusion in neurodegenerative dementias and progressive cognitive impairment.

• Sensitivity, specificity, and positive predictive value of SPECT is comparable to FDG-PET and superior to amyloid scan in the elderly.
Traumatic Brain Injury (TBI)
SPECT IS WIDELY ACCEPTED FOR TRAUMATIC BRAIN INJURY

- Society of Nuclear Medicine Brain Injury Council-1996
  - Use of SPECT in the management of patients with moderate to severe head trauma is now well recognized.

- Society of Nuclear Medicine-1999 Procedure Guidelines
  - TBI is a common indication for use of SPECT

- European Association of Nuclear Medicine-2002 Procedure Guideline
  - SPECT has prognostic value. All forms of TBI are considered to be common indications for its use.

- Center for Disease Control – 2003 Report to Congress
  - SPECT has diagnostic use in mild traumatic brain injury.

- American College of Radiology-2003 Practice Guideline
  - Symptomatic TBI, especially in the absence of CT and/or MRI findings is considered to be a clinical indication for use of SPECT.
Abu-Judeh et al., JALASBIMN, 2(6), 2000

- Study of 228 patients with mild to moderate TBI from charts
- All had CT or MRI which were read as normal
- Read blinded to clinical condition interspersed with 132 controls who were scanned for other reasons and 30 severe TBI cases
- Each case was read twice in the course of study
- In patients with no LOC – 68% abnormal SPECT, 32% normal
  - 46% had frontal lobe hypoperfusion
  - 55% had basal ganglia/thalamic hypoperfusion
  - 18% had temporal lobe hypoperfusion
Shin et al., Brain Injury 20:661, 2006

- 13 patients with moderate TBI vs. 21 carefully screened controls
- GCS 6.92 ± 3.88
- MRI and SPECT (ECD) at 2 weeks
- MRI negative in 50% of cases; 100% of controls
- SPECT positive in 100% of cases; none of controls
- Hypoperfusion found in anterior cingulate, frontal lobes, temporal lobes, and parahippocampal gyrus
- Statistical parametric analysis relative to control group
## SPECT’s Ability to Track Treatment Results

<table>
<thead>
<tr>
<th>No. of Months Post-trauma</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>12</th>
</tr>
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<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>78%</td>
<td>91%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>61%</td>
<td>61%</td>
<td>53%</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Negative Predictive Value</strong></td>
<td>92% (3)</td>
<td>89%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Positive Predictive Value</strong></td>
<td>44%</td>
<td>64%</td>
<td>52%</td>
<td>83%</td>
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</table>


Functional neuroimaging with default mode network regions distinguishes PTSD from TBI in a military veteran population

Cyrus A. Raji¹ · Kristen Willeumier² · Derek Taylor² · Robert Tarzwell³ · Andrew Newberg⁴ · Theodore A. Henderson⁵ · Daniel G. Amen²

• bilateral angular gyrus
• anterior and posterior cingulate gyri
• precuneus
• inferior orbital frontal cortex
• superior parietal lobe
• hippocampus
• parahippocampal gyrus
### Diagnostic utility of quantitative brain SPECT using default mode network

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD from TBI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>92</td>
<td>85</td>
<td>94 (88–99)</td>
</tr>
<tr>
<td>PTSD/TBI from TBI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>85</td>
<td>81</td>
<td>83 (76–90)</td>
</tr>
<tr>
<td>PTSD/TBI from PTSD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87</td>
<td>83</td>
<td>92 (86–99)</td>
</tr>
</tbody>
</table>
Brain Scans May Lead to Better Diagnoses

Over a million soldiers have served in the wars in Iraq and Afghanistan. Of the men and women who have returned from combat, more than 100,000 have been diagnosed with post-traumatic stress disorder (PTSD). Over 500,000 more have been told they have a traumatic brain injury (TBI). In many cases, symptoms are the same: insomnia, anxiety, irritability, poor concentration, and limited impulse control.

The treatments for these two conditions are very different. The problem is, there hasn’t been a consistently accurate diagnostic test to distinguish between PTSD and TBI. That changed earlier this year when two studies, one of which involved 20,746 patients, found that a type of medical imaging called single photon emission computed tomography (SPECT) showed clear differences in the brains of people with TBI or PTSD. Largely through analyzing how well blood flows (or doesn’t) through various parts of the brain, SPECT scans show with 80 to 100 percent accuracy whether someone has TBI, PTSD or both.

Understanding which is which is huge. Physical damage from TBIs, for example, can depress brain activity. If a doctor mistakes it for PTSD and prescribes sedatives that are often helpful for that condition, those drugs can further dampen cerebral function and worsen symptoms.

“If you go for help and the help is ineffective, it’s not a neutral experience,” says Daniel Amen, founder of Amen Clinics and lead author of the larger study, which was published in July. “It wastes time and money, it’s demoralizing, and it can hurt people.” —CHRISTIAN MILLER
Neuroimaging in Autism Spectrum Disorders
Incidence and factors regarding Autism

Incidence: now 1 in 68 (8 year olds) (ASD in 1980 1 in 10,000)

330M x 18% (<19 years)(1:68) = 1 Million kids/young adults

Why no overt concern?
(at its highest incidence - Polio 1 in 2000)

- No known cause
- Not “terminal” illness, and there is no “cure,”
- Therefore millions of autistic individuals (and their atypical behavior, and their co-morbidities) will “be with” our children and grandchildren for the rest of the Century
- Estimated management costs?
$1.2 Trillion per 100,000 over next 50 years
Brain function information can be used to document:

**Co-morbidity** = other neurological conditions that frequently occur with autism and which add their own element of brain dysfunction to the autism dysfunction:

- Seizure – 50+% (non-propagating)
- Anxiety
  - post traumatic stress disorder (PTSD)
  - “Bullying”
- Obsessive behavior (repetitive behavior)
- Cognitive inflexibility/ADHD
- Mood disorder – “depression” or “bipolar”
“Reframing” the Paradigm about treating the symptoms of Autism ©

Both these children present with symptoms of Autism - delays in speech development, limited social reciprocity, no eye contact, obsessive, odd play, repetitive motor movements, anger outbursts, poor attention, uneven fine and gross motor skills development, and echolalic speech.

However, their treatments must be significantly different based on the results of their brain scans.

Pt 1: underactive brain areas

Pt 2: overactive brain areas
ADHD – Also not a single entity
Behavioral Phenotype

- Fidgeting
- Unable to stay seated
- Moving excessively (restlessness)
- Difficulty paying attention
- “On the go”
- Talks excessively
- Blurting out answers
- Loses things/disorganized
- Interrupting/Intruding
## Overlapping Diagnostic Criteria

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ADHD</th>
<th>GAD</th>
<th>Mania</th>
<th>Depression</th>
<th>CD/ODD</th>
<th>TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restlessness</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Poor Concentration</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Increased motor activity</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Distractibility</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Irritability</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Prefrontal Cortex functioning

The prefrontal cortex increases from green and yellow at Baseline to brown and red during Test, indicating increased activity while concentrating.
• The patient is a 13-year-old female diagnosed by psychiatrist with Bipolar Disorder
• Primary insomnia, distractibility, elevated mood, irritability, anxiety, talkativeness, impulsivity
• Failed trials of lithium and valproate.
• Psychiatrist wanted to prescribed quetiapine (Seroquel)

See frontal lobes go from white, pink, red, and brown at Baseline to yellow and green during Test below, indicating decreased activity while concentrating.
Lee et al., Human Brain Mapping 24:157, 2005

- 40 drug-naïve children with ADHD (9.7 ± 2.1 years)
- 17 children in comparison group with negative SPECT scans
- SPECT scans at start and at 5 weeks of treatment
- Dual head camera with parallel coll. (LEHR) analyzed with SPM99
- Methylphenidate 0.7 mg/kg divided BID
- Untreated ADHD patients showed hypoperfusion relative to controls
  - Medial frontal lobes
  - Orbital frontal lobes
  - Cerebellum
- Untreated ADHD patients showed increased perfusion of occipito-parietal cortex
Comprehensive review of current neuroimaging literature on ADHD

Reviewed fronto-striatal literature

Emphasized cerebellum
- ADHD patients made more errors and showed decreased cerebellar activity with unexpected stimulus timing
- Often posterior cerebellar vermis involved overlapping with autism

Emphasized parietal cortex
- Correlated with decreased working memory, inhibition, spatial working memory, alertness, and performance monitoring
Emphasized temporal lobe

- Perfusion in temporal lobe lower in subjects with worse impairment from ADHD (Gustafsson, Acta Paediatr 2000)
- Reduced temporal lobe activity during odd-ball task in ADHD subjects
- Reduced temporal lobe activity during response switching task
- Reduced posterior temporal lobe activity during auditory continuous performance task
Lorberboym et al., J Child Neurol 19:91, 2004

- 19 children with research criteria diagnosis of ADHD (12.0 ± 2.4)
  - 8 with pure ADHD
  - 11 with ADHD comorbid for ODD, Conduct d/o, Mood d/o, or learning d/o
- SPECT scans during TOVA
- Compared to 9 normal controls (age matched)
- Pure ADHD group had frontal lobe hypoperfusion
- Comorbid group had frontal and temporal lobe hypoperfusion
Images from a healthy adult subject (top) and in an adult patient with ADHD (bottom), both obtained 1 hour after injection of 99m-technetium HMPAO after SPECT acquisition and post-processing (1) without cognitive stress and (2) again 24 hours later during cognitive stress. Note the relative fullness of the infraorbital prefrontal cortices and lack of change in the healthy subject. At baseline, images from the ADHD patient’s scan demonstrate only mild reduced blood flow in these regions as well as in the right inferior temporal lobule at baseline; reduced flow becomes markedly worse, however, upon cognitive stress, with new bilateral frontal and temporal defects developing.
Specifically examined orbitofrontal cortex hypoperfusion

Compared to DSM-IV ADHD diagnostic criteria

Conventional tomogram interpretation
- Sensitivity 4%, Specificity 97%, PPV 44%

3-D rendering interpretation of baseline scan
- Sensitivity 54%, Specificity 76%, PPV 60%

3 D rendering interpretation of concentration scan
- Sensitivity 69%, Specificity 84%, PPV 79%

- Adults ADHD patients without comorbidity
  N = 340
- Adult ADHD patients with comorbidity
  N = 7,549
- Healthy adult controls  N = 116
- Largest study ever undertaken by 1 order of magnitude (2 orders of magnitude if comorbid patients included)
Comparing single diagnosis ADHD vs. Controls

SPECT scan at baseline (rest)

Region of Interest (ROI) analysis

- 100% sensitivity
- 100% specificity
- 100% accuracy

- Left calcarine
- Left Heschl
- Bilateral precuneus
- Left supramarginal gyrus
- Left posterior mid-temporal
- Left temporal pole
Comparing single diagnosis ADHD vs. Controls

SPECT scan at baseline (rest)

Visual Read
- 87% sensitivity
- 81% specificity
- 92% accuracy

- genu of anterior cingulate
- Left putamen
- Right occipital cortex
- Right parietal cortex
- Medial anterior prefrontal cortex
- Left prefrontal cortex
- Left posterior temporal
- Left medial temporal
Comparing single diagnosis ADHD vs. Controls

SPECT scan on-task (concentration)

Region of Interest

- 100% sensitivity
- 100% specificity
- 100% accuracy

- Left anterior cingulate
- Left superior orbital frontal cortex
- Left caudate
- Left putamen
- Right Heschl’s gyrus
- Left posterior temporal
- Right temporal pole
Comparing comorbid ADHD vs. Controls

SPECT scan on-task (concentration)

Region of Interest
- 100% sensitivity
- 100% specificity
- 100% accuracy

Visual Read
- 99% sensitivity
- 99% specificity
- 99% accuracy
Seeing beyond the group data…

Neurobiological phenotypes presenting with the behavioral phenotype of ADHD
Case Example

- 7 yr old female
- Diagnosed with ADHD, but became wildly out of control on stimulant medication.
- Aggressive on Strattera
- Still having lots of problems in school, unable to sit still, irritable around homework, and impulsive
Mitigates against ADHD-like processes

See prefrontal cortex remain red, pink and white at Baseline and during Test below.
Improved dramatically on oxcarbazepine (Trileptal) which is a non-toxic metabolite of carbamazepine (Tegretol).

- Grades improved over 6 weeks
- Stable for 37 months
Case Example

- 10 yr old female
- Evaluated by qEEG and diagnosed with severe visual and auditory attention problems.
- Recommended qEEG Neurofeedback. $10,000 later, no change or benefit.
- Evaluated by “Behavioral Optometrist” and diagnosed with eye tracking problems
- Recommended vision therapy
- $7,000 later, no difference.
- Treated with stimulant – became agitated and anxious
On interview, she is bright, articulate, cooperative and inquisitive

Math comprehension at 35% tile

Reading comprehension at 10% tile

Writing at 15% tile

Connor’s Continuous Performance Test – negative

Paragraph with incomplete sentences, fragmented ideas and poor penmanship
Started on Aricept (donepezil) 5 mg qD

1 month later –
- Reading speed has increased
- Math skills increased
- Writing paragraphs with full sentences and nice penmanship

3 months later –
- Gained 2 years in math skills
- Gained 1.5 years in reading comprehension
- Writing stories for fun
21 year old female who had always done well in school, achieving A’s and B’s.

Over the past year, she had developed difficulty sustaining attention, distractibility, low energy, severe anxiety, and feeling “sad” and “down”.

Treated with fluoxetine, venlafaxine, and topiramate with little or no benefit.

Her family history included two parents with ADHD and a father with OCD.
Based on the results of the SPECT scans, the patient was re-assessed by a physician with expertise in chronic fatigue syndrome. The patient was started on a regimen of valacyclovir and amantadine, in addition to her venlafaxine.

Within weeks, she experienced resolution of her symptoms of poor concentration, distractibility, and low energy.
43 year old male photojournalist

Over the past three years, he had found it increasingly difficult to manage his schedule, make deadlines, and successfully manage his busy travel schedule.

He was in danger of losing his job due to scheduling errors.

However, he had always done well in school and had not struggled with attention throughout his academic career.

His family physician gave him a trial of Adderall for the presumptive diagnosis of ADHD, but he became irritable.
ADHD Symptoms from TBI

- fell 20-30 feet off a cliff on location
SPECT Brain Imaging Already Meets CED Criteria
(Coverage and Evidence Development)
NOPR – National Oncology PET Registry

- Model for PET or SPECT neuroimaging as reimbursable by CMS (Centers for Medicare and Medicaid Services)
- Applied as model for Coverage and Evidence Development (CED) program for PET amyloid imaging
- Criteria
  - Provide real world data on actual patients
  - Provide timely data
  - Utilize large population cohorts
  - Utilizes modern technology
  - Shows a benefit
- **Provide real world data on actual patients**
  - Tens of thousands of real patients with outcome data from dozens of clinics across US/Canada/Japan/Korea/Etc

- **Provide timely data**
  - Both retrospective and prospective data
  - Clinical outcome data with demonstrated scan changes

- **Utilize large population cohorts**
  - Raji et al, 2015 – 196 Veterans – TBI vs. PTSD
  - Amen et al 2015 – 20,000 subjects – TBI vs. PTSD
  - Raji et al, in prep – 8,000 subjects – ADHD
  - Large control cohorts (hundreds)

- **Utilizes modern technology**
  - New analysis software; GE software now FDA approved

- **Shows a benefit**
  - Multiple studies on changes in management and outcome
Thornton JF, Schneider H, McLean MK, van Lierop MJ, Tarzwell R.

Amen DG, Jourdain M, Taylor DV, Pigott HE, Willeumier K.
- Multi-site six month outcome study of complex psychiatric patients evaluated with addition of brain SPECT imaging.

- Specific ways brain SPECT imaging enhances clinical psychiatric practice.
SPECT Biomarkers Predicting Treatment Response

- Cho 2007 (N=34) – ADHD children non-responders to stimulants had higher rCBF in AC and right BG. 88% classified correctly
- Amen 2008 (N=157) – Absence of deactivation of PFC in ADHD associated with negative response to stimulants
- Navarro 2004 (N=47) – Late onset severe depression, left fronto-cerebelar perfusion ratio PPV = 94% for treatment response
- Brockmann 2009 (N=93) – Increased PFC rCBF predicts poor response to SSRI
- Langguh 2007 (N=24) – Increased AC rCBF predicts positive response to rTMS
- Richieri 2011 (N=18) – Decreased AC rCBF predicts poor response to rTMS
- Hanada 2013 (N=45) – decreased rCBF in PFC and AC predicts poor response to SSRI
SPECT Biomarkers Predicting Treatment Response

- Hoehn-Saric 2001 (N=16) – OCD treatment responders to SSRIs have higher pre-treatment PFC rCBF
- Noel 2002 (N=20) – Alcoholics with low PRC rCBF more likely to relapse
- Warwick 2006 (N=31) Low insula rCBF predicts positive response to citalopram or moclobemide in social anxiety disorder
- Jacobs 1996 (N=136) – abnormal 1 mth SPECT predicts persistent symptoms in mild TBI with 100% sens/85% spec; normal SPECT predicts symptom-free at one year with 100% accuracy
- Guedj 2007 (N=17) – fibromyalgia patients with decreased bilat. Medial PFC rCBF predictive of poor response to ketamine with 100% PPV; 91% NPV
SPECT Biomarkers Predicting Treatment Response

- Bonte 2004 (N=20) – Posterior cingulate rCBF differentiates Alzheimer’s vs FTD
- Bonte 2006 (N=49) – Autopsy-confirmed Alzheimer’s disease based on posterior cingulate perfusion. Sens = 87%; spec 89%.
- Jobst 1997 (N=391) – SPECT can predict Alzheimer’s disease with 89% sens; 80% spec
- Tanaka 2004 (n=70) – Alz. Dz increased temporal rCBF predicts positive donepezil response
- Kanetaka 2008 (N=91) – Alz Dz increased PFC r CBF predicts positive donepezil response
- Henderson 2013 – Meta-analysis – SPECT 82-96% sens/84-90% spec. with 94% PPV
- Henderson 2013 – Meta-analysis – SPECT for AD vs. FTD – 88-90% accuracy with posterior cingulate being key structure
Demonstrates Treatment Response
**Criteria**

- Provide real world data on actual patients
- Provide timely data
- Utilize large population cohorts
- Utilizes modern technology
- Shows a benefit
  - Improves treatment outcomes
  - Predicts treatment response
  - Reveals unrecognized co-morbidities
  - Demonstrates treatment response
Every great advance in science has issued from a new audacity – of the imagination.

John Dewey