Positron Emission Tomography Imaging in Brain Injured Patients

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Director of Neurocritical Care

UCLA Brain Injury Research Center
Outline

• Clinical Context of imaging
• Practical issues
• Major Hypotheses/Questions being addressed
  – Ischemia
  – Metabolic crisis
  – Chronic traumatic encephalopathy
  – Prognosis
ICU Environment
Human PET Center
Limitations to human experimentation

• Timing of studies is dependent on patient stability
• Radiation dosing is limited
• Missing data points require special statistics
Basic Design

• Structural imaging with CT and MRI
• PET image with an available clinical PET ligand
  – Dynamic quantitative image for regional assessment
  – FDG
  – O2
  – F18- MISO
  – FDDNP
  – C-PIB
TBI results in metabolic disturbance

- Cascade of metabolic events after TBI
- Initial depolarization event most important

Katayama et al 1990
Disturbed metabolism after TBI

- Reduced CBF related to decreased demand, impaired microcirculation (low NO), and iatrogenic causes (HV, CPP)
- Decreased rate of CMRO2 related to mitochondrial dysfunction
- Increase glucose utilization
Time course of TBI

• Early hypotension and brain ischemia within the initial 12 hours
• Mass effect that requires surgery
• ICP related to brain edema
• Periodic insults due to seizures
  – Possibly brain ischemia events
• 7-10 days of disturbed brain hemodynamics and altered brain metabolism in the ICU
Classical Ischemia

Increased OEF = 0.79
Reduced CBF = 20
Reduced CMRO2 = 1.2
Classical Ischemia
Oxidative metabolism is reduced to a critical threshold

- Menon et al 2004
- Large regions of the brain have critically low rates of CMRO2
- Regions of not directly adjacent to contusions
Defining Ischemic Burden After Traumatic Brain Injury Using $^{15}$O PET Imaging of Cerebral Physiology

Coles, Menon et al J Cereb Blood Flow Metab 2004
Hyperventilation not inducing ischemia – Diringer et al 2005

19 year old male, 11 hrs post-TBI, GCS 4

$\text{PaCO}_2 = 44$

$\text{PaCO}_2 = 27$

CBF

OEF

CMRO$_2$
Absence of brain ischemia adjacent to a contusion

OEF = 0.25

CBF = 49.6 cc/100gm/min
Asymmetric OEF with right side higher

PET O15 OEF = .50 in red crescent
Goals of treatment

• The goal is to maintain adequate perfusion with cerebral blood flow that is sufficient to supply the increased energy demand
• PET can provide evidence of response in CBF to changes in blood pressure or supplemental fluids or blood
Effect of normal saline bolus on cerebral blood flow in regions with low baseline flow in patients with vasospasm following subarachnoid hemorrhage

*6 patients with SAH vasospasm
*O-15 SBF PET before and after fluid challenge
*1 L Normal Saline fluid challenge

**TABLE 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Baseline</td>
<td>After Vol Expansion</td>
</tr>
<tr>
<td>CVP (cm H₂O)</td>
<td>8.50 ± 5.39</td>
<td>8.83 ± 4.62</td>
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<tr>
<td>PCWP (mm H₂O)</td>
<td>15.33 ± 4.32</td>
<td>17.8 ± 4.35</td>
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<td>MABP (mm Hg)</td>
<td>110.2 ± 16.1</td>
<td>123.7 ± 23.9</td>
</tr>
<tr>
<td>CI (L/[min × m²])</td>
<td>3.37 ± 0.37</td>
<td>3.67 ± 0.61</td>
</tr>
<tr>
<td>Hb (mmol/L)</td>
<td>10.77 ± 2.38</td>
<td>10.95 ± 2.33</td>
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</table>

*Values represent the means ± SD.

**TABLE 3**

<table>
<thead>
<tr>
<th>Changes in CBF before and after volume expansion with a 1-L saline bolus*</th>
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<tr>
<td>Mean Value</td>
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<tr>
<td>------------</td>
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<tr>
<td>bihemispheric CBF</td>
</tr>
<tr>
<td>rCBF in areas w/ vasospasm</td>
</tr>
<tr>
<td>rCBF in areas w/o vasospasm</td>
</tr>
<tr>
<td>rCBF in areas w/ high baseline CBF (&gt;25 ml/[100 g × min])</td>
</tr>
<tr>
<td>rCBF in areas w/ low baseline CBF (≤25 ml/[100 g × min])</td>
</tr>
</tbody>
</table>

Jost, Diringer et al 2005
Comparison of induced hypertension, fluid bolus, and blood transfusion to augment cerebral oxygen delivery after subarachnoid hemorrhage

J Neurosurgery, 116, March 2012

Rajat Dhar, M.D., Michael T. Scalfani, M.S.C.I., Allyson R. Zazulia, M.D., Tom O. Videen, Ph.D., Colin P. Derdeyn, M.D., and Michael N. Diringer, M.D.

Departments of Neurology, Neurological Surgery, and Radiology, Washington University School of Medicine, St. Louis, Missouri

Augmenting cerebral oxygen delivery in subarachnoid hemorrhage

Fig. 2. Bar graph showing DO₂ to regions with low delivery at baseline and after intervention.
Reversing ischemia through hyperoxia

- Increase in CMRO2 in tissue at risk by delivery of normobaric hyperoxia (but not for whole brain)
- Reduction in LPR 34.1 to 32.5 (P < 0.035)

Nortje, Menon et al 2008
PET and Microdialysis after SAH
Sarrafzadeh and Unterberg, 2004

(A) and (B) are PET images showing different regions of the brain.

(C) Graphs illustrating changes in glutamate, lactate, and L/P ratio over days after SAH.
PET with SAH cerebral Ischemia using F18-MISO

Saffarzadeh, Unterberg et al 2010
F18- MISO in SAH
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of FMISO-PET</th>
<th>Type of lesion</th>
<th>Neuro-monitoring</th>
<th>Study design</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takasawa et al, 2007 (J Cereb Blood Flow Metab)</td>
<td>7 (rats)</td>
<td>MCA occlusion</td>
<td>—</td>
<td>Experimental</td>
<td>Elevated $^{18}$F-FMISO uptake in the stroke area only in the early phase of MCAo, but neither after early reperfusion nor when tissue necrosis has developed. Validity of $^{18}$F-FMISO as a marker of viable hypoxic tissue/penumbra after stroke.</td>
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<td>Bruehlmeier et al, 2004 (J Nucl Med)</td>
<td>11</td>
<td>Various brain tumors</td>
<td>—</td>
<td>Clinical</td>
<td>Late $^{18}$F-FMISO-PET images provide a spatial description of hypoxia in brain tumors that is independent of BBB disruption and tumor perfusion. The distribution volume is an appropriate measure to quantify $^{18}$F-FMISO uptake. The perfusion-hypoxia patterns described in glioblastoma suggest that hypoxia in these tumors may develop irrespective of the magnitude of perfusion.</td>
</tr>
<tr>
<td>Saita et al, 2004 (Stroke)</td>
<td>38 (rats)</td>
<td>Transient MCA occlusion</td>
<td>—</td>
<td>Experimental</td>
<td>The pattern of $^{18}$F-FMISO-binding rats reproduced the pattern seen in humans, consistent with this tracer being a marker of the ischemic penumbra in both species. This technique may have application in studying the ischemic penumbra in animal models, and correlating this with similar studies in humans.</td>
</tr>
<tr>
<td>Markus et al, 2003(Stroke)</td>
<td>19</td>
<td>Acute MCA territory stroke</td>
<td>—</td>
<td>Clinical</td>
<td>Infarct expansion might occur at the expense of hypoxic tissue from the center to the periphery of the ischemic region in humans, similar to that seen in experimental animal models.</td>
</tr>
<tr>
<td>Read et al, 1998 (Neurology)</td>
<td>15</td>
<td>Acute hemispheric stroke</td>
<td>—</td>
<td>Clinical</td>
<td>FMISO-PET can detect peri-infarct hypoxic tissue after acute ischemic stroke. The distribution of hypoxic tissue may represent the ischemic penumbra. Hypoxic tissues do not persist to the subacute phase of stroke (6 to 11 days).</td>
</tr>
</tbody>
</table>
Non-ischemic Metabolic Crisis
Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study

MARVIN BERGSNEIDER, M.D., DAVID A. HOVDA, PH.D., EHUD SHALMON, M.D., DANIEL F. KELLY, M.D., PAUL M. VESPA, M.D., NEIL A. MARTIN, M.D., MICHAEL E. PHelps, PH.D., DAVID L. McARTHUR, PH.D., MICHAEL J. CARON, M.D., JESS F. KRAUS, PH.D., AND DONALD P. BECKER, M.D.

N = 28 TBI
Hyperglycolysis in 12/28
Early after TBI day < 5
### Characteristics of six patients demonstrating global hyperglycolysis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Initial GCS Score</th>
<th>CT Findings on Admission</th>
<th>EEG Findings on Day of PET</th>
<th>Post-injury Day of PET</th>
<th>PET GCS Score</th>
<th>Medications at Time of PET</th>
<th>PaCO$_2$ During PET (mm Hg)</th>
<th>g$_e$CMRG (mg/100 g/min)</th>
<th>Global CBF$_{15}$ (corr) on Day of PET (ml/min/100 g)</th>
<th>CMRO$_2$ on Day of PET (ml/min/100 g)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>18, F</td>
<td>4</td>
<td>diffuse edema rt SDH</td>
<td>seizure activity</td>
<td>2</td>
<td>3</td>
<td>vaso, ms, vec, DPH, abx, H2, tyl</td>
<td>31</td>
<td>9.5</td>
<td>77</td>
<td>2.3</td>
</tr>
<tr>
<td>2</td>
<td>23, M</td>
<td>5</td>
<td>contusion, DAI?</td>
<td>slowing</td>
<td>2</td>
<td>7</td>
<td>man, benzo, vec, DPH, abx, H2</td>
<td>23</td>
<td>8.5</td>
<td>51</td>
<td>1.48</td>
</tr>
<tr>
<td>3</td>
<td>27, M</td>
<td>3</td>
<td>multiple punctate hemorrhages</td>
<td>slowing</td>
<td>5</td>
<td>3</td>
<td>man, benzo, ms, DPH, pancuronium, H2, abx, tyl</td>
<td>29</td>
<td>3.1</td>
<td>38</td>
<td>0.93</td>
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<tr>
<td>4</td>
<td>56, M</td>
<td>3</td>
<td>contusions, SAH</td>
<td>slowing</td>
<td>7</td>
<td>11</td>
<td>vaso, ms, DPH, ms, tyl</td>
<td>35</td>
<td>4.9</td>
<td>34</td>
<td>1.36</td>
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<tr>
<td>5</td>
<td>55, M</td>
<td>6</td>
<td>contusions, SAH</td>
<td>slowing</td>
<td>7</td>
<td>3</td>
<td>man, DPH, H2, nifedipine, tyl, abx</td>
<td>27</td>
<td>4.2</td>
<td>36</td>
<td>1.22</td>
</tr>
<tr>
<td>6</td>
<td>17, M</td>
<td>4</td>
<td>rt SDH, multiple contusions</td>
<td>slowing</td>
<td>8</td>
<td>4</td>
<td>DPH, abx, tyl</td>
<td>39</td>
<td>4.7</td>
<td>34</td>
<td>1.53</td>
</tr>
</tbody>
</table>

### Characteristics of five patients demonstrating presumed regional hyperglycolysis

| Case No. | Age (yrs), Sex | Initial GCS Score | CT Findings on Admission | EEG Findings on Day of PET | Post-injury Day of PET | PET GCS Score | Medications at Time of PET | PaCO$_2$ During PET (mm Hg) | g$_e$CMRG (mg/100 g/min) | Local CMRG of Focus (mg/100 g/min) | Volume (ml) | g$_e$CMRG (mg/100 g/min) |
|----------|----------------|-------------------|--------------------------|---------------------------|------------------------|--------------|----------------------------|----------------------------|-----------------------------|--------------------------------|--------------------------|----------------|--------------------------|
| 7        | 80, M          | 5                 | bilat SDH, ICH, contusions | focal status epileptic    | 3                      | 7            | clonidine, enalapril, DPH, abx, H2 | 33                         | 9.4                         | 5.2                            | ND                         | ND                   |
| 8        | 73, M          | 3                 | bilat SDH, contusions    | ND                        | 4                      | 5            | DPH, digoxin, nitroglycerin drip | 37                         | 9.3                         | 14.0                           | 4.6                        |                     |
| 9        | 31, F          | 4                 | lt SDH                   | seizure activity          | 5                      | 5            | man, vec, ms, tyl, abx, DPH, H2, somatostatin | 30                         | 7.3                         | 5.0                            | 4.3                        |                     |
| 10       | 37, M          | 6                 | contusions               | ND                        | 6                      | 7            | DPH, haldol, vec, ms, benzo, Mg, abx | ND                         | 7.2                         | 0.9                            | 3.8                        |                     |
| 11       | 37, M          | 7                 | rt SDH                   | slowing                   | 14                     | 8            | man, DPH, benzo, abx            | ND                         | 7.8                         | 0.6                            | 3.5                        |                     |
Regional Hyperglycolysis
Seizures associated with hyperglycolysis
PET in TBI showing regional metabolic crisis and low CBF

Microdialysis:
- Glucose 2.0
- Lactate 0.8
- Glutamate 1.6
- Glycerol 44
- L/P 56

CMRglc 2.9-3.2

CBF 37

CBF 21-24

CBF 37
Elevated LPR without ischemia

LPR = 100 during PET

Vespa et al J Cereb Blood Flow Metab 2005
Post TBI seizures lead to additional disturbance of metabolism without ischemia.
Post-traumatic seizures elicit increased glycolysis
Use of PET to determine optimal glucose delivery

Vespa et al Crit Care Medicine (in press for 2012)
Increase in hyperglycolysis under conditions of tight glycemic control

• Regional variation of baseline glucose metabolism
• Increased glucose metabolism when serum glucose is restricted
• Similar changes in white and grey matter
• Least change in pericontusional tissue
• MD glucose decreased and glycerol higher under tight glycemic control

Vespa et al Crit Care Med 2012
Progressive Disease and Prognosis

- TBI and other acute neurocritical care illnesses are disease processes, not just acute injuries
- PET can be used to study the prognosis of the chronic disease and to investigate possible disease mechanisms
  - Programmed cell death
  - Tau and Amyloid deposition
Early nonischemic oxidative metabolic dysfunction leads to chronic brain atrophy in traumatic brain injury

Yueqiao Xu\textsuperscript{a}, David L McArthur\textsuperscript{b}, Jeffry R Alger\textsuperscript{a}, Maria Etchepare\textsuperscript{c}, David A Hovda\textsuperscript{a}, Thomas C Glenn\textsuperscript{a}, Sungcheng Huang\textsuperscript{a}, Ivo Dinov\textsuperscript{a} and Paul M Vespa\textsuperscript{a,2}
Chronic Atrophy at 6 months
Primary acute injury is hemorrhagic, not ischemic
Metabolic Rates acutely after TBI

**Table 2** Cerebral PET metabolism in acute period

<table>
<thead>
<tr>
<th>Brain lobe</th>
<th>CBF (n = 64) (ml per (100 g/min))</th>
<th>OEF (n = 64) (%)</th>
<th>CMRO₂ (n = 62) (ml per (100 g/min))</th>
<th>CMRglc (n = 56) (ml per (100 g/min))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal</td>
<td>37.3 ± 11.9</td>
<td>38.0 ± 15.3</td>
<td>2.24 ± 0.87</td>
<td>3.23 ± 0.96</td>
</tr>
<tr>
<td>Frontal</td>
<td>36.3 ± 11.4</td>
<td>37.7 ± 15.7</td>
<td>2.13 ± 0.87</td>
<td>3.25 ± 1.06</td>
</tr>
<tr>
<td>Parietal</td>
<td>38.4 ± 11.4</td>
<td>37.7 ± 14.5</td>
<td>2.17 ± 0.86</td>
<td>3.23 ± 1.05</td>
</tr>
<tr>
<td>Occipital</td>
<td>43.4 ± 12.7</td>
<td>36.3 ± 14.0</td>
<td>2.41 ± 0.92</td>
<td>3.08 ± 0.96</td>
</tr>
</tbody>
</table>

CBF, cerebral blood flow; CMRglc, cerebral metabolic rate of glucose; CMRO₂, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; PET, positron emission tomography.

Mean (±s.d.) values by region of oxidative metabolism (CMRO₂), CBF, glucose metabolism (CMRglc), and OEF.

**Table 3** Acute and chronic brain lobar volumes

<table>
<thead>
<tr>
<th>Brain lobe</th>
<th>Acute MRI (mm²)</th>
<th>Chronic MRI (mm²)</th>
<th>Contusion (mm²) (number of involved lobes)</th>
<th>Atrophy (%)</th>
<th>Mixed effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal</td>
<td>182,574 ± 26,572</td>
<td>164,905 ± 20,531</td>
<td>21,051 ± 19,259(26)</td>
<td>10.1 ± 7.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Frontal</td>
<td>262,400 ± 44,777</td>
<td>243,962 ± 39,384</td>
<td>33,072 ± 31,247(30)</td>
<td>8.4 ± 8.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Parietal</td>
<td>183,799 ± 31,289</td>
<td>170,592 ± 29,196</td>
<td>42,088 ± 42,597(7)</td>
<td>8.1 ± 6.6</td>
<td>0.016</td>
</tr>
<tr>
<td>Occipital</td>
<td>111,470 ± 17,293</td>
<td>106,790 ± 17,153</td>
<td>21,526 (1)</td>
<td>4.6 ± 4.0</td>
<td>NA</td>
</tr>
</tbody>
</table>
Chronic atrophy

Figure 4 Example of chronic brain atrophy: Three-dimensional rendering of skull-stripped SPGR MRI T1 image in an example patient. The top row shows the acute MRI and the bottom row shows the chronic MRI at 6 months after trauma. The widespread atrophy, sulcal enlargement, and ventricular enlargement must be noted.

Table 5 Whole brain volume comparisons

<table>
<thead>
<tr>
<th></th>
<th>Whole brain volume</th>
<th>Gray matter</th>
<th>White matter</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>1,274,834 (68,840)</td>
<td>663,305 (53,430)</td>
<td>611,529 (53,577)</td>
<td>192,253 (33,165)</td>
</tr>
<tr>
<td>TBI acute</td>
<td>1,327,595 (146,433)</td>
<td>688,142 (140,570)</td>
<td>673,800 (142,547)</td>
<td>202,205 (45,819)</td>
</tr>
<tr>
<td>TBI chronic</td>
<td>1,191,338 (102,441)</td>
<td>582,457 (121,718)</td>
<td>600,306 (129,354)</td>
<td>329,005 (78,139)</td>
</tr>
</tbody>
</table>
Long term atrophy

Acute

Chronic at 6 months
Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy

P.M. Vespa, MD, FCCM
D.L. McArthur, PhD
Y. Xu, MD
M. Eliseo, BS
M. Etchepare, BSN, RN
I. Dinov, PhD
J. Alger, PhD
T.P. Glenn, PhD
D. Hovda, PhD

ABSTRACT

Objective: To determine if posttraumatic nonconvulsive electrographic seizures result in long-term brain atrophy.

Methods: Prospective continuous EEG (cEEG) monitoring was done in 140 patients with moderate to severe traumatic brain injury (TBI) and in-depth study of 16 selected patients was done using serial volumetric MRI acutely and at 6 months after TBI. Fluorodeoxyglucose PET was done in the acute stage in 14/16 patients. These data were retrospectively analyzed after collection of data for 7 years.

Results: cEEG detected seizures in 32/140 (23%) of the entire cohort. In the selected imaging subgroup, 6 patients with seizures were compared with a cohort of 10 age- and GCS-matched patients with TBI without seizures. In this subgroup, the seizures were repetitive and constituted status epilepticus in 4/6 patients. Patients with seizures had greater hippocampal atrophy as compared to those without seizures (21 ± 9 vs 12 ± 6%, p = 0.017). Hippocampi ipsilateral to the electrographic seizure focus demonstrated a greater degree of volumetric atrophy as compared with nonseizure hippocampi (28 ± 5 vs 13 ± 9%, p = 0.007). A single patient had an ictal PET scan which demonstrated increased hippocampal glucose uptake.

Conclusion: Acute posttraumatic nonconvulsive seizures occur frequently after TBI and, in a selected subgroup, appear to be associated with disproportionate long-term hippocampal atrophy. These data suggest anatomic damage is potentially elicited by nonconvulsive seizures in the acute postinjury setting. Neurology® 2010;75:1-1
Brain Atrophy after NCSE in TBI
Hippocampal atrophy after post-traumatic seizures

Acute FLAIR MRI
Subdural Hemorrhage

Acute ADC MRI
Hippocampus = 1001 u²/s

Chronic MRI
Hippocampal Atrophy

Status Epilepticus on post injury day 5
Increased hippocampal atrophy in patients with post-traumatic seizures

Vespa et al Neurology 2010
Impaired long term cognition and cortical atrophy after metabolic crisis

Atrophy and Neuropsychological Performances 12 months Post-Injury

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>SDMT Oral</td>
<td>.62*</td>
<td>.60*</td>
<td>.66*</td>
<td>.39</td>
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<td>.21</td>
<td>.47</td>
<td>-.06</td>
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<tr>
<td>SDMT Written</td>
<td>.39</td>
<td>.56</td>
<td>.60*</td>
<td>.18</td>
<td>.40</td>
<td>.20</td>
<td>.31</td>
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<td>ROCFT Imm.</td>
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<td>.20</td>
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<td>SRT-6 Total</td>
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<td>.10</td>
<td>.18</td>
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<td>.08</td>
<td>-.08</td>
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<td>SRT-6 Delay</td>
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<td>-.04</td>
<td>-.09</td>
<td>-.17</td>
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<td>TMT-B</td>
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</tbody>
</table>

SDMT Oral= Symbol Digit Modalities Test, oral trial (attention); SDMT Written= Symbol Digit Modalities Test, written trial; ROCFT= Rey One-Word Picture Test Immediate Recall; ROCFT Delay= Rey One-Word Picture Test Delay Recall; SRT-6= Standard Reaction Time-6; TMT-B= Trail Making Test-B; COWAT= Controlled Oral Word Association Task; GPT Dom. = Grooved Pegboard Test, dominant hand;
FDG in Mild TBI – relation to memory disorder
Z scores showing differences in FDG in various regions
Chronic tau deposition in long term CTE in NFL players - Small et al 2013
FIGURE 3. FDDNP binding levels versus number of concussions in retired players. Examination of plots showing FDDNP DVR binding values according to number of concussions in retired players suggests an association between a greater number of concussions and higher binding in regions that were found to show significantly higher FDDNP binding in players compared with controls. FDDNP binding is expressed in terms of the DVR derived by the Logan graphic method, with the cerebellum as the reference region.
Mild traumatic brain injury from primary blast vs. blunt forces: Post-concussion consequences and functional neuroimaging

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N = 12 military blast injury
N = 12 blunt TBI
Resting state FDG PET
- semi quantitative
Comparison of ROI vs Normals
Summary of imaging in acute brain injury