

Functional Imaging of Cerebral Reorganization in Mild Traumatic Brain Injury with Cognitive Fatigue

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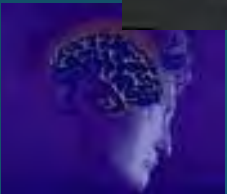
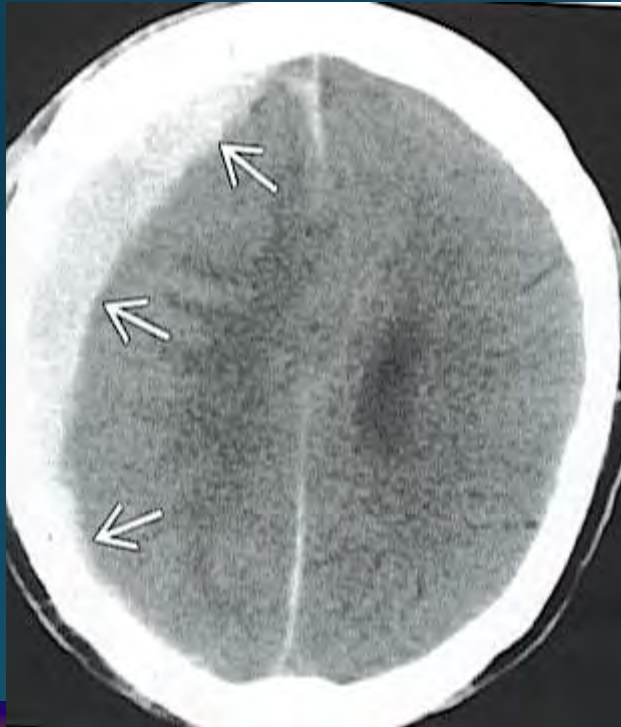
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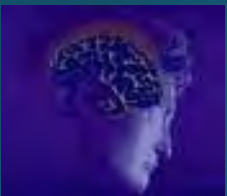
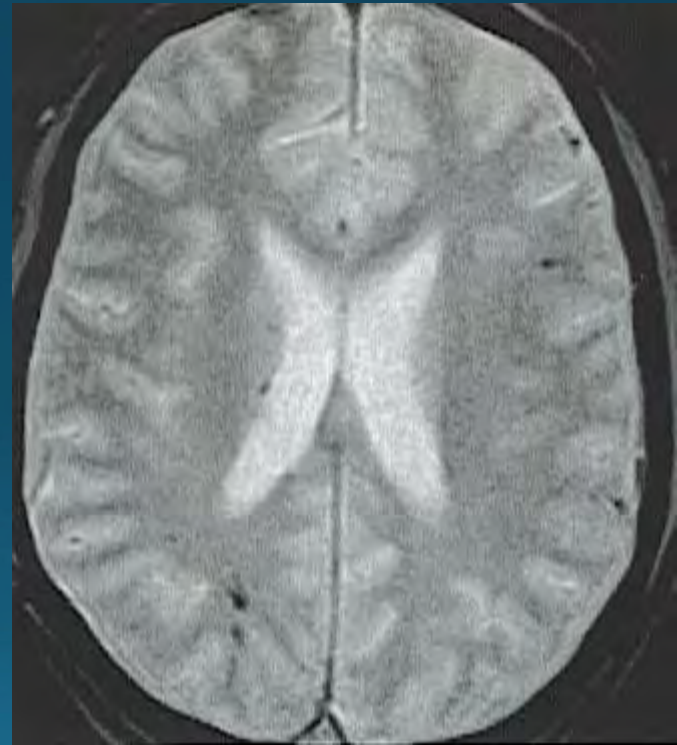
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Traumatic brain injury: Radiology



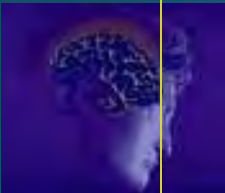
Traumatic brain injury: Radiology

- MRI has lead to earlier diagnosis of subtle but severe injury such as DAI.



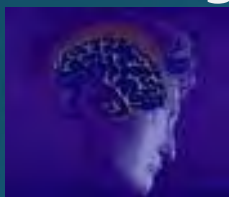
Epidemiology of Mild TBI

- Public Health Problem
 - Accounts for more than 75% of all brain injuries.
 - Frequently underdiagnosed.
- Clinical Definition
 - LOC <30 minutes, PTA <24 hrs, GCS 13-15, short-term confusion, dizziness, & blurred vision²
- Acute and long-term sequelae
 - Headache, dizziness, sensitivity to noise/light, insomnia, chronic pain, depression, & fatigue
 - 83% report fatigue within 1st 7 days P.I. (Gfeller et al., 1994)
 - 75% report persistent fatigue 6 mos. P.I. (McCullagh et al., 2001)
 - 32-73% endure fatigue 5 yrs. P.I. (Masson et al., 1996; Hillier et al., 1997; Olver et al, 1996)
- Objective neurological/neuropsychological findings vs. subjective experience of mental fatigue
 - PASAT as objective measure for producing mental fatigue targeting information processing



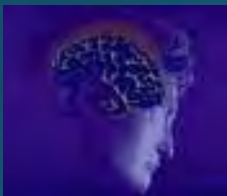
Clinical features of mTBI

- **Common causes** were MVA (70%), sporting injury (<14%) and falls (5-10%).
- **Natural hx** of TBI is toward spontaneous improvement within 3 months of injury.
- **Post traumatic amnesia** is considered one of the more sensitive markers for those who will suffer ongoing symptoms.
- **GCS** has often found to correlate poorly with degree of persisting deficit.



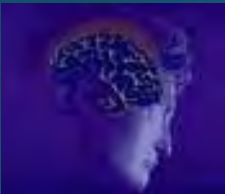
Clinical features of mTBI

- Mechanism of injury:
- Rotational injury is considered more harmful ie more likely to produce shear stress and disruption of neural pathways “woodpecker hypothesis”.
- Hook = knockout punch



Cognitive Fatigue

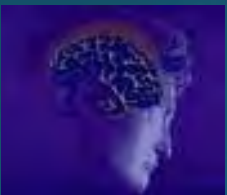
- Common feature of many complaints such as MS; usually subjective.
- Motor fatigue: decline in strength during sustained contractions.
- Cognitive fatigue: decline in cognitive performance over a single testing session in a task requiring sustained attention ^{3,4}
- PASAT used to measure cognitive fatigue in MS



³Krupp, et al. (2000); ⁴Schwid, et al. (2003)

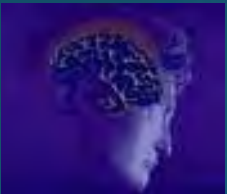
Cognitive Fatigue

- PASAT in MS
 - Percent decline in performance; the ratio of the number of correct responses for the first 20 items to the last 20: MS 5% decline, normals no decline.
 - Some improvement in performance for the first 2-3 trials.



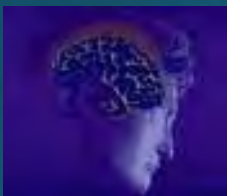
Cognitive Fatigue

- Acute vs. Chronic Fatigue (Piper et al., 1989)
- Acute fatigue of CFS patients experienced whilst engaged in complex tasks requiring memory and timed processing is most analagous to mTBI related fatigue.



Cognitive Fatigue

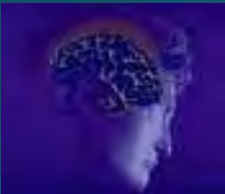
- Mild Traumatic Brain Injury
 - Loss of concentration can lead to difficulty performing activities of daily living.⁵
 - Failure to initiate and/or sustain attentional tasks requiring self motivation⁶
 - “Global mental slowness” most pronounced on tasks requiring complex attention.³



⁵van Zomeren, et al. (1994); ⁶Chaudhuri, et al. (2000)

Hypotheses

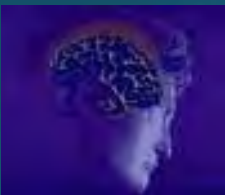
1. During a cognitive task (PASAT), participants with mTBI will demonstrate a relatively greater increase in rCBF compared to healthy controls, demonstrating “cognitive inefficiency.”
2. Cognitive inefficiency demonstrated by SPECT imaging will correlate with a greater decline in performance on PASAT in mTBI compared to normal controls.
3. Cognitive inefficiency demonstrated by SPECT imaging will show greater perceived mental effort in mTBI compared to normal controls.



Methods

• Participants

- Recruited from a neurology clinic
- mTBI (American Congress of Rehabilitation Medicine Criteria)
- >18 years of age
- Post-injury >1 month
- Complaints of cognitive fatigue (“Inability to maintain attention and concentration during a sustained task”)
- Normal brain MRI imaging
- Exclusions
 - Major Depressive Disorder
 - Co-morbid medical or neurological disorder with fatigue-related symptoms



Demographics

mTBI (n=11)

Age: 42.36 (SD = 9.65)

Education: 15.64 years (3.17)

Gender: 18% male; 82% female

Duration P.I.: 33.2 months (25.74)

Normals (n=15)⁷

Mean Age: 44.4 (SD = 8.35)

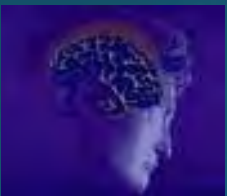
Education: 16.87 years (1.55)

Gender: 20% male; 80% female

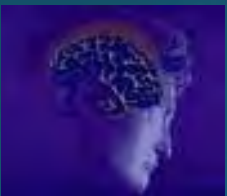
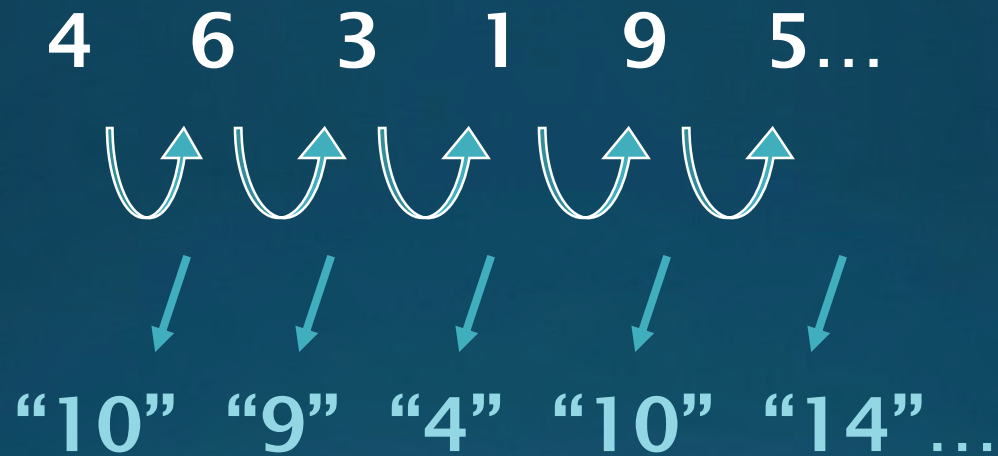
⁷Schmaling, K., Lewis, D., Fiedelak, J., Mahurin, R., & Buchwald, D. (2003). Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome. *Psychosomatic Medicine*, 65, 129-136.

Procedures

- Paced Auditory Serial Addition Test (PASAT)
 - Sensitive measure of information processing speed and divided attention
 - Series of 50 single digit numbers verbally presented across four trials of increasing speed (2.4s, 2.0s, 1.6s, 1.2s)
 - Add each digit to the preceding digit, state aloud
 - PASAT targets cognitive functions affected by mTBI ie sustained attention and processing speed with a high level of intensity & difficulty => cognitive fatigue



Paced Auditory Serial Addition Test (PASAT)



Procedures

- Brain SPECT Acquisition

- Tracer injected 1st trial, 11th digit of PASAT

- 24 seconds into the 1st trial

- Cerebral radiotracer uptake would be completed during the remaining 2 minutes, 6 seconds of 1st trial

- SPECT scan started 45 minutes after injection of radio-image

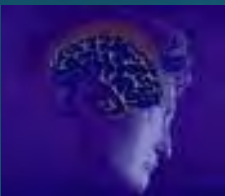
- Phillips ADAC Dual Genesys (Phillips Medical Systems)

- Dual-head gamma camera w/low energy high resolution fan beam collimators

- NEUROSTAT (Dept. of Internal Medicine, University of Michigan, Ann Arbor, MI)

- Pair-wise subtraction analyses conducted between resting & PASAT scans using global average counts per pixel for normalization

- Z-score maps of >4.0 statistical threshold = significant increased perfusion



Results

• mTBI & Healthy Controls

- Right insula
- Right medial frontal cortex



• Healthy Controls

- Left dorsolateral prefrontal cortex
- Right superior temporal gyrus
- Left posterior thalamus/fornix
- Right cerebellum



• mTBI

- Left medial frontal gyrus



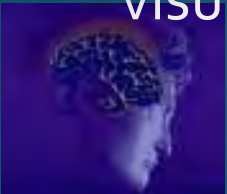
Corresponding Cognitive Function

Actively attending to and processing digits presented auditorily

Actively processing string of digits while retaining each immediate one in short-term memory

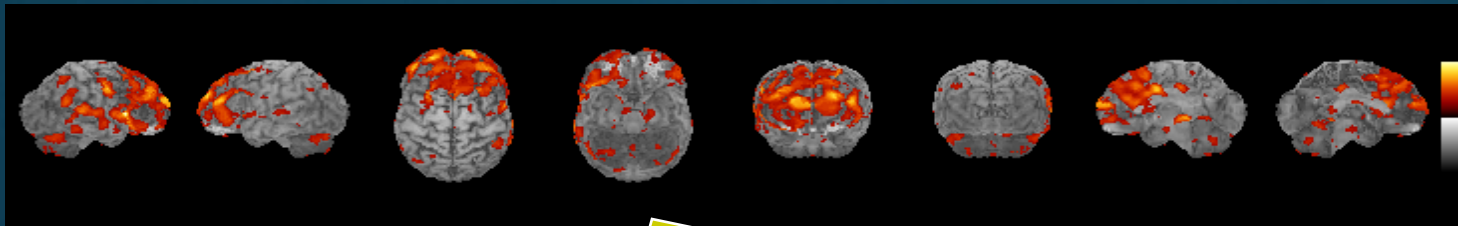
Results

- Short-term memory: short term storage of information .
- Working memory: differently described by various theorists: a theoretical framework that refers to structures and processes used for temporarily storing and manipulating information, and can also be referred to as working attention.
- There are short-term memory components to working memory models.
- Baddeley and Hitch model of w.m.: two short-term storage mechanisms: the phonological loop and the visuospatial sketchpad.

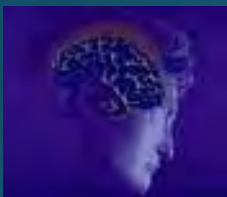
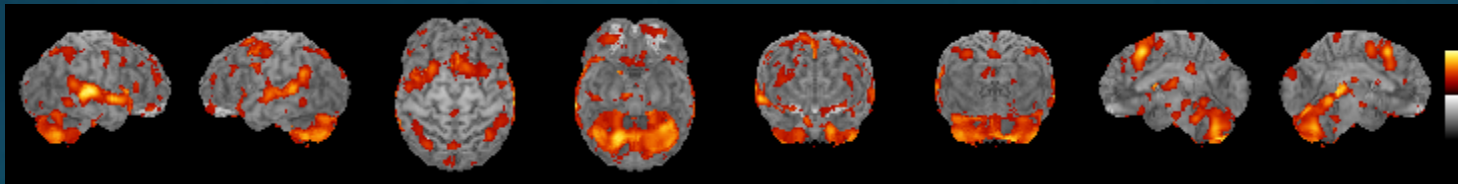


Active (PASAT) SPECT

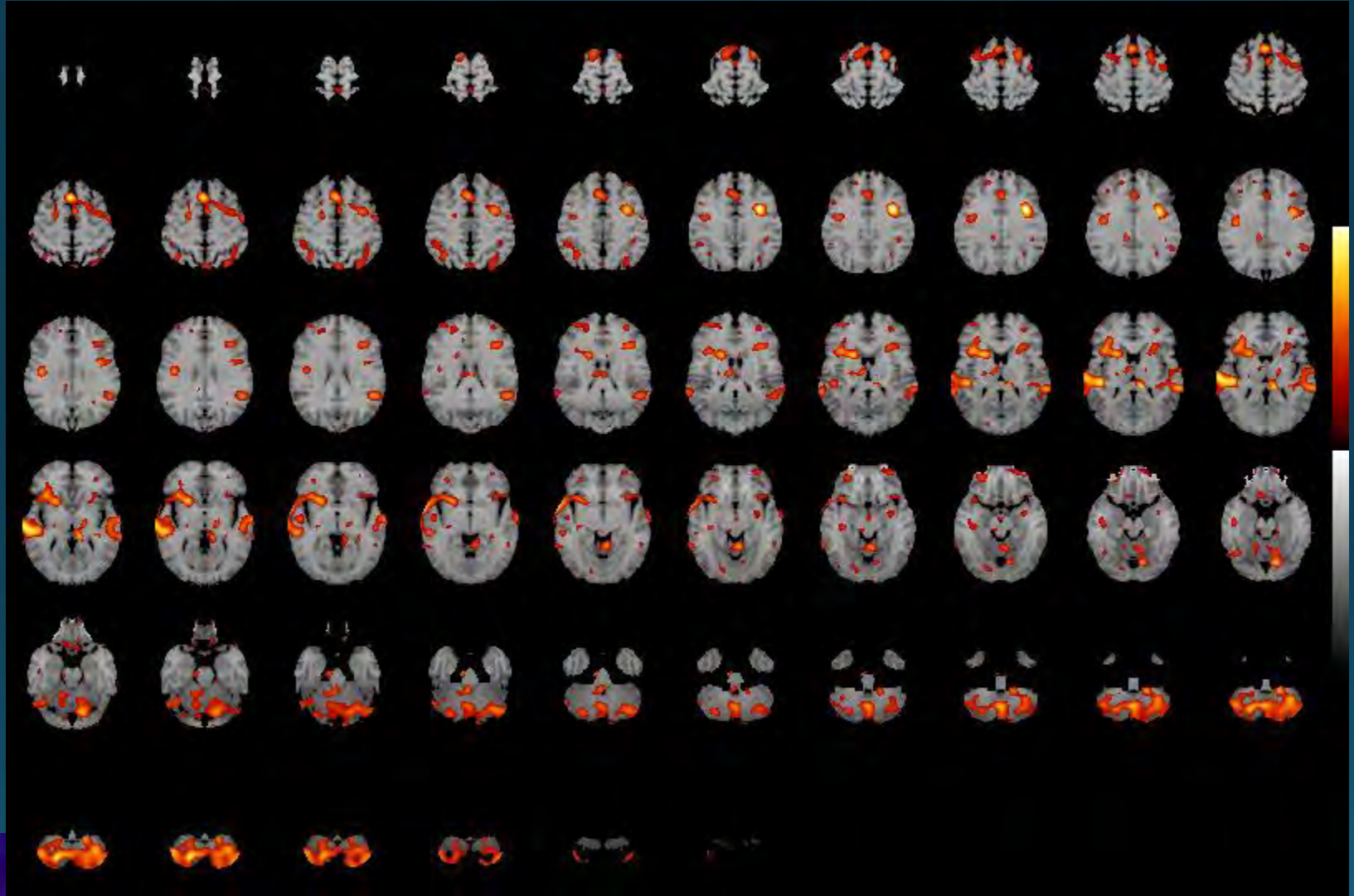
mTBI



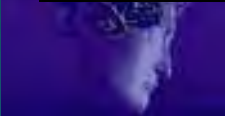
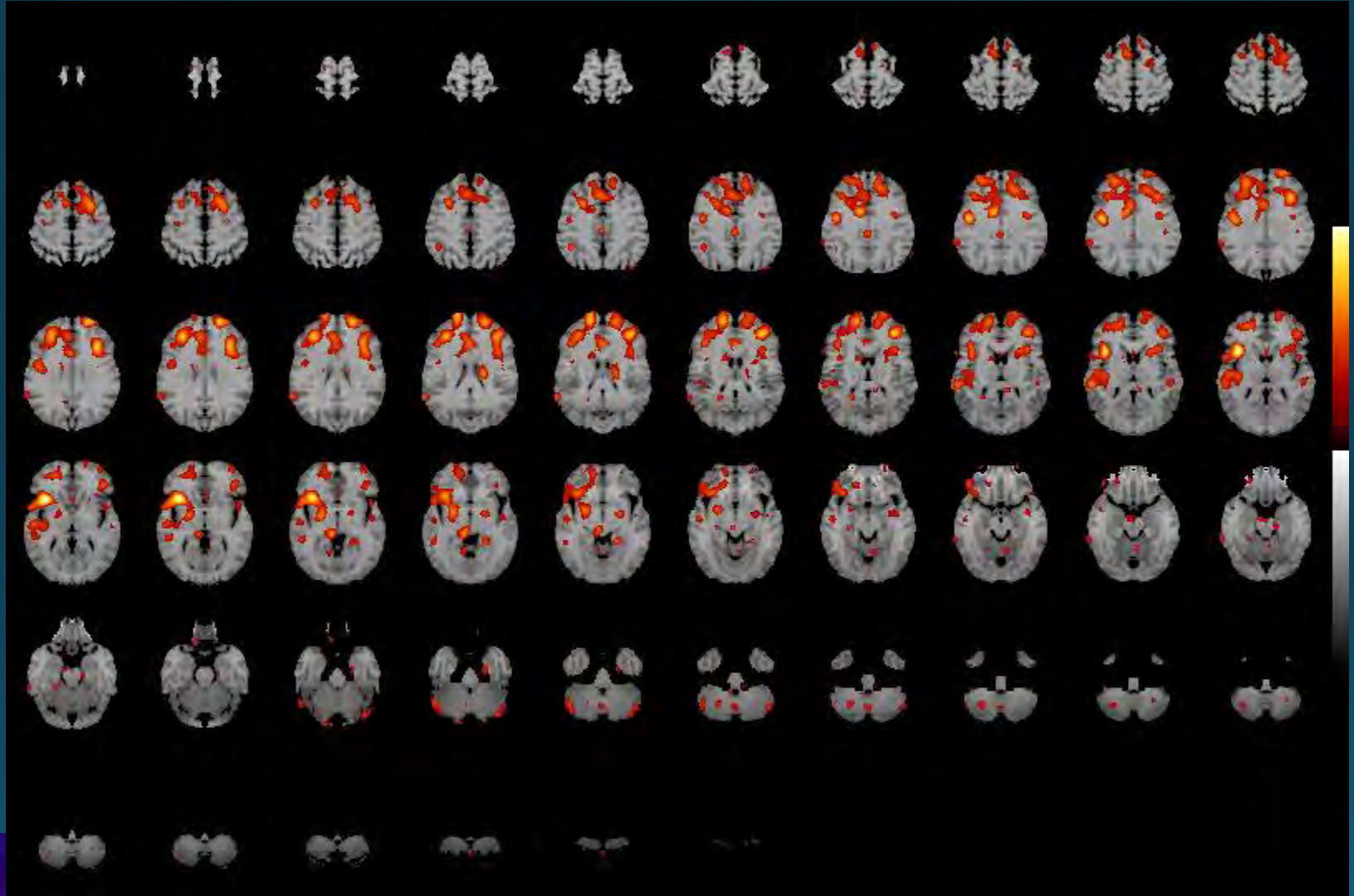
Healthy controls



Healthy Controls (N = 15)

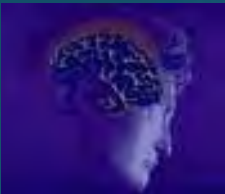


Mild Traumatic Brain Injury (N = 11)



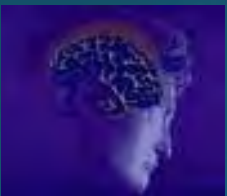
Discussion

- mTBI lack of activation in the cerebellum suggests dysfunction of verbal working memory and/or inability to efficiently process & verbally respond to verbally presented information, needed to complete PASAT
- Normals' activation of regions responsible for inhibition of automatic responses, spatial mapping, & verbal working memory = multitude of cognitive functions & brain regions needed to successfully complete the PASAT



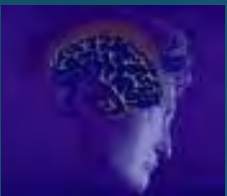
Discussion

- Dissimilarity of activated regions and fewer recruited regions, as well as the lack of cerebellar activation by mTBI patients suggests inefficient and disconnected neural processing which may, in turn, lead to feelings of cognitive fatigue



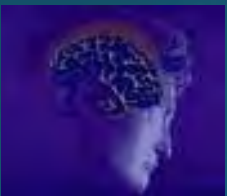
Discussion

- MRS and MR volumetry demonstrated a decrease in brain volume and NAA concentration in chronic sufferers of post mTBI symptoms.
- fMRI study of working memory challenge in normals vs mTBI sufferers:
 - minimal increase in activation with increased load
 - mTBI patients significantly increased activation during more demanding memory tasks.



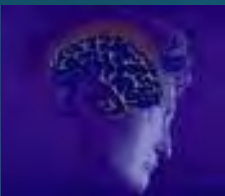
Discussion

- Previous study of CFS subjects using PASAT and SPECT:
 - Focal uptake in normals and diffuse uptake in CFS sufferers.
 - No evidence of decrease in task performance, despite subjective feelings of memory difficulty.



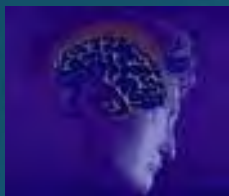
Study Limitations

- No measure of headache or pain in place
- Normal SPECTs completed on different scanner, different study
- Temporal limitation of SPECT vs. (i.e., fMRI) – PASAT within-trial repetitious-in-nature



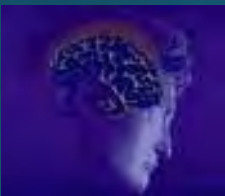
Conclusions

- In healthy controls focal activation with PASAT occurred in frontal, temporal and cerebellar regions, whereas mild TBI subjects primarily had diffuse activation in frontal regions.
- Normal activation describes network of regions responsible for information processing, inhibition of automatic responses, spatial mapping and verbal working memory which is needed to efficiently complete PASAT.
- mTBI lack of activation of cerebellum suggests dysfunction of this network of working memory, or the inability to efficiently process and verbally respond to the paced information in the test.



Future Directions

- Include “non cognitive fatigue” mTBI patients to assess presence of cerebellar lack of activation
- 3-arm study:
 - “Recovered” mTBI (non-fatigued)
 - Acute mTBI (fatigued)
 - Healthy controls (non-fatigued)
 - * Study the potential regeneration of cerebellar rCBF



Future Directions

- Imaging of recovering TBI:
 - Sequential scans of chronic mTBI patients undergoing motor rehabilitation (HANDLE) demonstrated increased cerebellar, anterior cingulate gyrus and medial frontal cortex activation with time.
 - This suggests improvements in motor coordination can be documented on imaging.

