Our greatest weariness comes from work not done – Eric Hoffer

Recent Discoveries on Fatigue: Implications for Treatment

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Overview

• What is Fatigue
  – study with caution!
• Cognitive Fatigue
• Neuroimaging and Fatigue

What is Fatigue?

Defining Fatigue

• Concept we all know, but difficult to define
  – Meaning often vague, elusive, difficult to operationalize
• After over 100 years of inquiry, its definition remains elusive
  – Some have suggested the term be abandoned
• “The word fatique has been defined so inconsistently and applied so loosely …that its meaning is now obscure” (Balkin & Wesensten, 2011)
Synonyms of Fatigue

- Tired, worn out, or run down
- Feelings of weakness
- Exhaustion
- Sleepiness
- Lack of energy
- Malaise
- Effort – in relation to a task
- Lack of motivation

Differing prevalence for synonyms of Fatigue

- In community surveys, Fatigue found to be:
  - Twice as common as exhaustion
  - 10 times more common than feeling “generally run down”
  - Up to 10 times more common than weakness

Measuring physical (motor) fatigue

- Schwid et al (1999) in MS examined:
  - Motor fatigue – loss of maximal capacity to generate force during exercise
  - Muscle weakness (strength) – ability to maintain motor output during
    - Sustained muscle contractions
    - Repetitive muscle contractions

Results

- MS group showed both motor fatigue and motor weakness compared to controls
- No significant correlation between Motor fatigue and Weakness (strength) in any muscles tested
- Suggest that motor fatigue and weakness are distinct features of motor dysfunction

What is Fatigue?

“The awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity.” (p46) Aronson et al, (1999) Image J Nrs Sch

“fatigue is the decline in performance that occurs in any prolonged or repeated task…” (Fischler, 1999)

What is Fatigue?

“Under fatiguing conditions, performance sometimes declines, sometimes remains unchanged, or sometimes even increases as time on task increases.”

- Decades of research have replicated this finding.
Time on Task and Cognitive Fatigue

- 239 college students - 3 SAT’s duration
  - 3.5 hrs, 4.5hrs (standard), 5.5 hrs
- Subjective fatigue increased with TOT
- Performance INCREASED with longer test length
- Personality/motivation/interest had greater predictive power on subjective fatigue than TOT
  - Neuroticism, anxiety, worry correlated with subjective fatigue

What is Fatigue?

- “The conditions of experimentation with the purpose of finding a fatigue test are two:
  - That we know what we mean by fatigue;
  - That we have some method [test] … that different degrees of fatigue are present at certain different times.

- That the first of these conditions is necessary is self-evident
- It is obviously absurd to set about finding a test of an undefined entity.”

Muscio (1921), “Is a Fatigue Test Possible.”

What is Fatigue?

- “Before a concept can be measured, it must be defined, and before a definition can be agreed, there must exist an instrument for assessing phenomenology. There is unfortunately no ‘gold standard’ for fatigue, nor is there ever likely to be”

Dittner, Wessely, & Brown, 2004, p.166

Mosso’s Ergograph

- Four components to Fatigue:
  - BEHAVIOR (decrement in performance)
  - FEELING STATE
  - MECHANISM
  - CONTEXT (e.g., stress in one’s life; cultural issues)
- 100 years ago we see the beginning of the separation of the global fatigue concept into measurable components

Mosso’s Findings (1904)

- “Fatigue is so common as to be almost normal” (Wessely et al., 1998, p25)
- Poor correlation between FEELING of fatigue and fatigue BEHAVIOR (Mosso 1904; DeLuca 2005)
- What is NOT fatigue?
  - Depression
  - Sleepiness
  - Cognitive fatigue is not equal to cognitive impairment
Definition of Fatigue in MS

- MS Council for Clinical Practice Guidelines (1998) defines fatigue as:
  - “A subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities”

Questions

- Why should subjective fatigue be the gold standard?
- Why should objective and subjective fatigue correlate?
  - They don’t
- Must behavioral changes be a decrease?
- Lets face it, subjective fatigue correlates with other subjective ratings
  - Depression, pain, subjective sleep, deconditioning, medication effects, hormonal changes, cognitive complaints, stress

Sleepiness and Fatigue

- Sleepiness and fatigue often used interchangeably
- Thus, sleep findings often extended to fatigue
  - e.g., disturbed sleep leads to cognitive dysfunction
- Increasing evidence that sleepiness and fatigue arise from distinct neural mechanisms

Sleepiness and Fatigue

- Excessive sleepiness is defined as:
  "drowsiness or sleep onset that occurs at inappropriate or undesirable times”
- Excessive sleepiness can lead to feelings of fatigue, but are not synonymous
  - Excessive sleepiness usual restored with rest
  - Fatigue is not necessarily restored with rest
- This is important because sleepiness and fatigue may involve different treatments

(Duntley, 2005)
Cognition and Fatigue?

Don’t be fooled!

- Claims of instruments to assess mental vs. physical fatigue (e.g., MFI)
  - I have been forgetful
  - I have been less alert
  - I have difficulty paying attention for long periods of time
  - I have trouble concentrating
  - My thinking has been slowed down

Self Report Instruments

- Typically assesses fatigue without defining it
- The questions included may have little of nothing to do with fatigue at all
- For example: not clear that patients can truly differentiate fatigue from:
  - Motor impairment
  - Cognitive impairment
  - Sleepiness
  - Depression

Chalder Fatigue Scale

- Physical symptoms
  - Do you have a problem with tiredness?
  - Do you need rest more?
  - Do you feel sleepy or drowsy?
  - Do you have problems starting things?
  - Do you start things without difficulty but get weak as you go?
  - Are you lacking in energy?
  - Do you have less strength in your muscles?
  - Do you feel weak?

What Does Self-reported Fatigue Predict?

- Stroke
  - Predicts death at 1 year (Stulemeijer et al, 2005)
  - Reduced long-term survival (Mead et al, 2011).
  - Increased risk of “suicidality” (Tang et al, 2011)
  - Independently associated with pre-stroke
    - Depression
    - White matter changes
    - Diabetes mellitus
    - Pain
    - Sleeping disturbances (Naess et al, 2012)
What Does Self-reported Fatigue Predict?

- Coronary heart disease
  - Independently predict the development of:
    - coronary heart disease
    - risk of future cardiac events
    - survival following myocardial infarction
  - These relationships remain even after controlling for the traditional risk factors
    - elevated cholesterol
    - Hypertension
    - Smoking
    - age, etc.

What Have We Learned About Fatigue in General?

- Systemic Fatigue may differ from factors which exacerbate or perpetuate it
  - Physical illness (e.g., TBI, MS) may cause initial symptoms of fatigue
  - CNS involvement
  - Secondary factors exacerbate the primary symptoms
    - De-conditioning
    - Sleep disturbance
    - Depression
    - etc

What Have We Learned About Fatigue in General?

- Its time to differentiate between
  - Primary mechanism of fatigue
  - Factors which mediate or moderate primary mechanisms

Primary and Secondary Fatigue

- PRIMARY FATIGUE
  - Systemic mechanism(s) responsible for fatigue
    - (i.e., primary neural mechanisms)

- SECONDARY FATIGUE
  - Factors which exacerbate its effects
    - (e.g., Sleep disturbance, de-conditioning, depression, medication, etc)

Cognitive Fatigue
Central or Cognitive fatigue

“the failure to initiate and/or sustain attentional tasks (‘mental fatigue’) and physical activities (‘physical fatigue’) requiring self motivation (as opposed to external stimulation)”

(Chaudhuri & Behan, 2000, p35)

Cognitive performance during high vs low fatigue in MS

• 30 fatigued MS patients
• Cognitive testing during high and low fatigue (within subjects design)
• Results:
  – No differences in objective performance
  – Subjectively rated performance as worse during high fatigue

(Parmenter et al, 2000)

Objective measurement of cognitive fatigue

• Cognitive Fatigue over an extended time
• Cognitive Fatigue DURING sustained mental effort
• Cognitive fatigue AFTER challenging mental exertion
• Cognitive fatigue AFTER challenging physical exertion

1. Cognitive Fatigue over an extended time

• Cognitive testing over several hours
• No difference in performance between MS or TBI and controls
  – Jennekens-Schinkel et al., 1988
  – Johnson et al., 1997
  – Paul et al., 1998
  – Riese et al, 1999
  – Beatty et al., 2003
• In all studies, MS and TBI worse in subjective fatigue


• Examined effects of “induced” fatigue on cognitive performance (PASAT)
• Three fatiguing groups:
  – MS
  – CFS
  – Major Depression
• Also examined subjective fatigue


• PASAT Administered 4 times over 3 hours
• Hypothesized fatigue would “blunt” practice effect
• Examined subjective fatigue just prior to each PASAT session
  – 0 (none) – 4 (severe) likert scale
Mean PASAT Performance Across Sessions


- Subjective fatigue higher in the 3 fatigue groups relative to controls
- All 4 groups increased subjective fatigue across 4 sessions
- No significant relationship between objective performance (PASAT) and subjective fatigue

Fatigue over the work day in MS

- Pre-post work day assessment of:
  - 4 NP tests of information processing
  - 25 ft timed walk
  - Subjective fatigue
- 17 MS
- 12 healthy controls

Fatigue over the work day in MS

- Subjective fatigue did not differ at baseline but MS subjects reported significantly more fatigue at the end of the day

Subjective Fatigue Across the Workday
(Beatty et al., 2003)

- No group differences on any NP measure
  - List recall
  - Letter-number sequence
  - SDMT
  - PASAT (3 second trial)
- Subjective fatigue did not correlate with objective NP performance
Fatigue over the work day in MS


- Authors conclude:
  - “…results confirm other reports that patients’ subjective ratings of their fatigue are not valid indicators of their actual performance on cognitive tests”

1. Cognitive Fatigue over an extended time

- Conclusions:
  - Little to no evidence that prolonged activity produces cognitive fatigue which results in decreased objective cognitive performance
  - Subjective fatigue increases over time
  - Subjective and objective measures of fatigue are not correlated

2. Cognitive Fatigue DURING sustained mental effort

- Decreased performance on second half vs first half of a sustained cognitive task
  - Krupp & Elkins (2000)
- Conceptually similar to muscle fatigue studies
- Self reported fatigue generally unrelated to objective performance (except Schwid et al, 2003 in 1 of 2 scales)

Bryant, Chiaravolloti & DeLuca 2004

- 56 MS and 39 HC
- PASAT
- Hypothesized that MS S’s would “fatigue” in second half vs first half of test
- Results:
  - MS significant worse in second half

Krupp & Elkins, 2000

- 35 MS and 12 HC
- Complex concentration task: A-A task
  - Continuous mental arithmetic
- Hypothesized that MS S’s would “fatigue” in second half vs first half of test
- Results:
  - RT slower in MS in second half
  - Accuracy data not reported
2. Cognitive Fatigue DURING sustained mental effort

- Significant evidence for decreased performance during sustained mental effort
- Perhaps this is where we should focus our continued research efforts?

Conclusions on Cognitive Fatigue

- Cognitive fatigue is a complex construct
- Simple subjective questionnaires are not adequate
- Best evidence is for fatigue DURING sustained cognitive performance

Overview

- What is Fatigue
  - study with caution!
- Cognitive Fatigue

- Neuroimaging and Fatigue

Is there a relationship between fatigue and measures of brain functioning?

- Structural MRI
- Electrophysiological (not discussed here)
- Functional neuroimaging

Structural Imaging
Fatigue and Brain Functioning in MS: Structural MRI

- Not related to fatigue
  - brain volume, T2 lesion load, atrophy, BPF, etc
    - Riccitelli et al (2011) (T2 lesion load)
    - Marrie et al (2005)
    - Filippi et al (2002)
    - Van der Werf et al (1998)
    - Codella et al (2002a, 2002b) (DTI or magnetic transfer imaging)

- Yes Relationship with fatigue
  - Grey matter and cortical atrophy
    - Riccitelli et al (2011) (VBM: white and grey atrophy)
    - Calabrese et al (2010)
    - Pellicano et al (2010)
    - Sepulcre et al (2009) (grey and white matter)
    - Calabrese et al (2007)

- DTI
  - Pardini et al (2010)

None of these studies looked at cognitive fatigue!

Basal Ganglia and Central Fatigue
Chaudhuri & Behan, 2000, 2004

- Fatigue involves the non-motor functions of the basal ganglia
- Central fatigue result of
  - “failure in the integration of limbic input and
    non-motor functions within the basal ganglia
    affecting the striatal-thalamic-frontal cortical system”

Subjective Fatigue and Brain Atrophy

- 152 MS divided into hi and low fatigue (FSS ≥ 4)
- F-MS vs NF-MS had atrophy in:
  - Striatum
  - Thalamus
  - superior frontal gyrus
  - inferior parietal gyrus
- Supports BG, fronto-parietal association
- Did not look at cognitive fatigue
Putamen Volume

Middle Frontal Gyrus
Thickness

Figure 1. Lateral views of the pial surface 3D representation with cortical thickness map: representative individuals

RED: Cortical areas thicker than 2.0mm
GREEN: Cortical areas thinner that 2.0mm

Localization of acute infarcts (%)

Multivariate model of clinical and radiological predictors of PSF

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<tr>
<th>Predictor</th>
<th>p value</th>
<th>Odds Ratio</th>
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<td>Infarcts in B. Ganglia</td>
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<td>Depression</td>
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<tr>
<td>Number of infarcts</td>
<td>NS</td>
<td>1.1</td>
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Independent predictors of PSF

### Functional Imaging

#### Fatigue and brain functioning in MS:
**Functional neuroimaging**

- **Positive Relationship**
    - During coordinated hand and foot movements
  - Tartalglia et al (2004), (MRS)
  - Filippi et al (2002), (fMRI)
    - During coordinated finger movements
  - Roelcke et al (1997), (PET)

None of these studies looked at cognitive fatigue!

#### Cognitive Fatigue using fMRI

- **Purpose** - objectively assess cognitive fatigue in MS using fMRI
- **Hypothesis** - persons with MS would show altered cerebral activation across trials of behavioral task compared to controls
- This was interpreted as cognitive fatigue.

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**Multivariate model of clinical and radiological predictors of PSF**

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<tr>
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<td>Sex (female)</td>
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<tr>
<td>Depression</td>
<td>0.001</td>
<td>1.2</td>
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<tr>
<td>Infarcts in Putamen</td>
<td>NS</td>
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**Independent predictors of PSF**

Cognitive Fatigue using fMRI

- 15 HC and 15 MS
- Induced cognitive fatigue during scanning
  - 4 trials of mSDMT during fMRI scanning
- Hypothesized interaction effect in BOLD response across trials
  - Increased activation in MS
  - Decreased activation in HC

DeLuca et al, 2008, J Neurol Sci

Hypothesized Fatigue Effect

DeLuca et al, 2008, J Neurol Sci

Response time: within- and across- run fatigue

DeLuca et al, 2008, J Neurol Sci

Cerebral Activity in Orbital Frontal Gyrus

DeLuca et al, 2008, J Neurol Sci

Cerebral Activity in Parietal Cortex

DeLuca et al, 2008, J Neurol Sci

Cerebral Activity in Caudate

DeLuca et al, 2008, J Neurol Sci
Method (Kohl et al., 2009)

- 11 moderate-severe TBI and 11 HC
- Induce fatigue in the scanner
  - 3 trials of processing speed task (SDMT)
- Hypothesized interaction effect BOLD response across trials
  - Increased activation in MS
  - Decreased activation in HC

Behavioral Results

Accuracy was 95% in HC and 96% in TBI

Left Basal Ganglia (Caudate/Putamen)

Left Middle Frontal Gyrus

Left Anterior Cingulate

Kohl et al., (2009), Brain Injury
Cognitive Fatigue using fMRI

- Altered fMRI activation on mSDMT in MS and TBI interpreted as cognitive fatigue
- Found only in brain areas hypothesized to subserve cognitive fatigue (Chaudhuri & Behan, 2000)
- Suggests fatigue can be measured objectively using fMRI

Towards an operational definition of fatigue

- Two ways to relate subjective reports of fatigue to brain activation:
  - **State**: "Online" measure of fatigue (during task performance)
  - **Trait**: "Offline" measure of fatigue (e.g., over last 2 weeks)
“State” or “On-line” Fatigue

- Use fMRI to examine relationship between self-reported fatigue and brain activity during performance of the mSDMT
  - In MS and TBI
- Cognitive task 8 times in the MRI
- Rate fatigue before and after each task

VAS-F

On a scale of 0-100, how mentally fatigued do you feel, right now, at this moment?

Also given for anger, tension, happiness, sadness and pain

Prediction

- Prediction: Individuals (MS and TBI) with higher ratings of fatigue will show increased brain activity in ROIs (areas thought to subserve fatigue) compared to individuals with lower ratings of fatigue
- ROIs:
  - Caudate
  - Parietal (Precuneus)
  - Prefrontal

Cognitive Fatigue: MS vs HC

Genova et al (2014), PLOS one

Fatigue-related Activity in the Brain

State vs Trait Fatigue

Unpublished data
High vs. Low Fatigue

- High vs Low STATE Fatigue
  - Post hoc groupings

- Compared BOLD activation (associated with induced cognitive Fatigue) in
  - High Fatigue vs. Low Fatigue Group

fMRI, Cognitive Fatigue and self-reported Fatigue

- mSDMT was used to induce fatigue in
  - Administered 8 times during fMRI acquisition

- Subjective reports collected before and after each block
  - Cognitive fatigue
  - Happiness
  - Sadness
  - Anger
  - Pain
  - Tension

Wylie, Genova et al, unpublished data

High vs. Low Fatigue- TBI

<table>
<thead>
<tr>
<th></th>
<th>Low Fatigue (11)</th>
<th>High Fatigue (14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.67(10.6)</td>
<td>46.15(11.7)</td>
<td>.09</td>
</tr>
<tr>
<td>Education</td>
<td>14.77(2.3)</td>
<td>16.67(2.3)</td>
<td>.14</td>
</tr>
<tr>
<td>FSS</td>
<td>28 (16.49)</td>
<td>29.67(8.3)</td>
<td>.41</td>
</tr>
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</table>

Groups did not differ on FSS – “trait” fatigue

TBI VAS-F Scores

SDMT in TBI

- "High Fatiguers" greater activity in caudate than "Low-fatiguers" (orange)
- "Low-fatiguers" greater activity than "High-Fatiguers" in cerebellum (blue)

High vs Low Fatigue

- What if we compared when fatigue was Low vs High?
- Using n-back
  - Low fatigue: first half of the experiment
  - High fatigue: second half of the experiment
Cognitive Fatigue in TBI
fMRI Results: Caudate

- Comparison: Fatigue-related activation (AMR) during the second 2-back block minus the first 2-back block
- \( p < 0.05 \) (corrected)

Wylie et al., unpublished

Cognitive Fatigue in TBI
fMRI Results: PCC

- Comparison: Fatigue-related activation (AMR) during the second 2-back block minus the first 2-back block
- \( p < 0.05 \) (corrected)

Wylie et al., unpublished

General Findings: State Fatigue

- No correlation between cognitive performance and self-reported fatigue
- Consistent with our hypotheses, increased activation in subjects with higher fatigue
  - Caudate
  - Frontal regions
  - Cuneus
- Support for Chaudhuri and Behan Model of Central fatigue

New Treatments?

Neuroscience approach to new treatments

Neural Mechanism

- Due to non-motor function of the basal ganglia (Chaudhuri and Behan, 2000)
- The Basal Ganglia
  - Not only a motor region
  - Involved in
    - Decision-making
    - Learning
    - Language
- Widespread projections to the prefrontal cortex

Motivational Loop in Animals & Healthy Adults

- Animal studies
  - VMPFC & striatal neurons fire to reward delivery (Schultz, 1992; Schultz et al., 2011; Padoa-Schioppa & Cai, 2011)
- Human studies
  - Greater VMPFC & striatal activation to reward presentation (Dobryakova & Tricomi, 2013; Delgado et al., 2000; Jessup & O’Doherty, 2011; Balleine et al., 2011)
Background Summary & Hypothesis

• Summary
  – VMPFC & striatum involved in motivation
  – VMPFC & striatum functionally impaired in populations with fatigue

• Hypothesis
  – Motivation will affect the activity of the fronto-striatal network in MS individuals reporting cognitive fatigue
  – Motivation will decrease fatigue

The Task: Card Guessing task

• 2 Conditions: Reward and no reward
  – Reward condition: subjects told they win money (but probability is chance)
  – No Reward: control condition

Less Fatigue after Reward Condition

Average VAS change

-1.5 -1 -0.5 0 0.5 1 1.5

Win Money

Less Fatigue after Reward Condition

Reward in Fronto-Striatal Network

• Main effect of valence (win vs loss)
  – VMPFC
  – Ventral Striatum

Parameter Estimates

-0.4 -0.3 -0.2 -0.1 0 0.1 0.2 0.3 0.4

Win

Less

Summary and Future Directions

• Less fatigue after reward condition:
  – win money decreases cognitive fatigue

• Future
  – There are different types of rewards with different values (vary types of reward)
  – Further studies needed
    • Can Increase reward decrease fatigue in TBI and MS?

Overall Conclusions

• Fatigue is a multidimensional construct which is difficult to define
• Self report does not correlate with objective measures of fatigue
• Cognitive fatigue is not straightforward
  – Sustained cognitive effort
• Basal ganglia plays a critical role in fatigue
• Functional imaging offers a new technique to show:
  – self-reported fatigue may correlate with brain activity
  – The need to correlate self report with objective performance may no longer be necessary
  – Studies Primary fatigue?
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