Evidence for a network of fatigue-related areas in the brain

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Disclaimer
This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure
This certifies that I, Glenn Wylie, have no financial relationship that is relevant to the subject matter of this presentation.
Fatigue is prevalent following brain injury & disease

- Individuals with MS
  - Present in 80-95% of patients
- Individuals with TBI
  - Present in 45-98% of patients
- Individuals with Parkinson’s Disease
  - Considered a warning sign for PD
- Stoke and Polio survivors
- Individuals with Chronic Fatigue Syndrome
- Veterans with Gulf War Illness
What is Fatigue?

• We have all experienced fatigue, but difficult to operationally define
• After over 100 years of inquiry, its definition remains elusive
  • Some have suggested the term be abandoned
    • “The word fatigue has been defined so inconsistently and applied so loosely... that its meaning is now obscure” (Balkin & Wesensten, 2011)
One possible definition

“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 an activity.” (Aronson et al. (1999) Image J Nurs Sch, p. 46)

“fatigue is the decline in performance that occurs in any prolonged or repeated task...” (Fishler, 1999)
“Under fatiguing conditions, performance sometimes declines, sometimes remains unchanged, or sometimes even increases as time on task increases.” (Ackerman, 2011, p. 3)

- Decades of research have replicated this
  - E.g., We and others have shown that cognitive performance can improve as fatigue increases
- The lack of relationship between objective performance & subjective fatigue has been the most consistent finding
Brain activation vs. behavior

- In fatigue-prone populations, there is increasing evidence of compensatory functional re-organization in the brain
  - Hyperconnectivity (Hillary et al, 2011)
  - More cerebral activation in patient vs. control group on the same task
- Fatigue may be a consequence of this increase in brain activity
- Brain activation may be a better dependent measure than behavioral performance
Fatigue induction paradigm

• A task was repeatedly performed to induce fatigue
  • Working memory paradigms
  • Task-switching paradigms
  • Vigilance paradigms
• fMRI was acquired while they performed tasks
• Subjective reports of fatigue were collected before and after each task block
Fatigue-related brain areas

- Anterior Cingulate Cortex (ACC)
- Ventro-medial Prefrontal Cortex (vmPFC)
- Anterior Insula
- Dorsolateral Prefrontal Cortex (DLPFC)
- Striatum
Brain Mechanisms of Cognitive Fatigue

• These areas have been associated with cognitive fatigue in:
  • Healthy individuals
  • Individuals with neurological disease
    • Multiple Sclerosis
    • Parkinson’s Disease
    • Chronic Fatigue Syndrome
    • Gulf War Illness
  • Individuals with neurological insult
    • Traumatic Brain Injury
    • Stroke
• Chadhuri & Behan (2001) model
Research question

- Do these five brain regions form a network?
  - Are they functionally connected?
Functional Connectivity (FC)

Fatigue-related FC

- Functional connectivity (FC)
  - A measure of the extent to which two brain areas are functionally connected

- Fatigue-related FC
  - A measure of how connectivity changes as fatigue increases

- Studied in:
  - Healthy individuals
  - Individuals with MS

Wylie et al. (2020). Scientific Reports vol.10
Fatigue-related FC: Approach

- Used task-related fMRI data, not resting state data
  - Fatigue is unlikely to increase during rest
- Removed variance in data specifically related to the task
  - Leaving fatigue-related variance in data
- Calculate connectivity for each task block, for each seed region
  - vmPFC, DLPFC, Insula, Striatum, ACC
- Used Linear Mixed Effects model to see where connectivity changed as a function of fatigue

Wylie et al. (2020). *Scientific Reports* vol.10
For example: vmPFC seed

<table>
<thead>
<tr>
<th>Location</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Vox</th>
<th>VAS-F Coef</th>
<th>F Stat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior frontal gyrus [SFG]</td>
<td>27.8</td>
<td>70.8</td>
<td>-10</td>
<td>69</td>
<td>-0.058</td>
<td>25.11</td>
</tr>
<tr>
<td>Superior/middle frontal gyrus (DLPFC) [SFG]</td>
<td>-20.4</td>
<td>29.6</td>
<td>46</td>
<td>17</td>
<td>0.042</td>
<td>18.97</td>
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<tr>
<td>Inferior frontal gyrus [IFG]</td>
<td>-34.1</td>
<td>43.3</td>
<td>6</td>
<td>151</td>
<td>-0.056</td>
<td>28.82</td>
</tr>
<tr>
<td>Insula [INS]</td>
<td>45.0</td>
<td>15.8</td>
<td>-2</td>
<td>20</td>
<td>-0.074</td>
<td>26.11</td>
</tr>
<tr>
<td>Caudate nucleus [CN]</td>
<td>17.5</td>
<td>22.7</td>
<td>-10</td>
<td>9</td>
<td>-0.057</td>
<td>25.44</td>
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<tr>
<td>Paracentral lobule [PCL]</td>
<td>0.3</td>
<td>-32.3</td>
<td>74</td>
<td>16</td>
<td>0.033</td>
<td>17.54</td>
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<tr>
<td>Postcentral gyrus [PCG]</td>
<td>20.9</td>
<td>-42.6</td>
<td>58</td>
<td>18</td>
<td>0.027</td>
<td>23.11</td>
</tr>
<tr>
<td>Posterior cingulate cortex [PCC]</td>
<td>0.3</td>
<td>-49.5</td>
<td>30</td>
<td>48</td>
<td>0.053</td>
<td>19.79</td>
</tr>
</tbody>
</table>

Wylie et al. (2020). *Scientific Reports* vol.10
Central regions of fatigue network

Wylie et al. (2020). *Scientific Reports* vol.10
Conclusions

• All five showed fatigue-related connectivity
  • vmPFC, Striatum, Insula, DLPFC, ACC

• Three connections are reciprocal and may be central
  • Striatum <-> Insula
  • Insula <-> vmPFC
  • vmPFC <-> DLPFC

Wylie et al. (2020). *Scientific Reports* vol.10
Conclusions

- Striatum & vmPFC
  - Involved in processing motivation and reward

- Anterior Insula
  - Involved in processing information about internal states
    - E.g., self-reported fatigue

- DLPFC
  - Involved in cognitive control

Together these areas form a fatigue network
- Anterior Insula may register fatigue
- Striatum & vmPFC may monitor whether the reward is worth the effort expended
- DLPFC may maintain the goal to continue
Implications

• Brain activation can be used to measure and study fatigue
  • Allows fatigue to be studied in clinical populations where fatigue is an important problem

• Brain activation in the fatigue network may be a useful target for interventions designed to mitigate fatigue
  • In healthy populations where fatigue is prevalent
  • In clinical populations
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