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**Beyond the Symptom: The Biology of Fatigue**

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

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# Disclaimer and Disclosures

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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.

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# 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

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# 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)

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# 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)

# Or not

*"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

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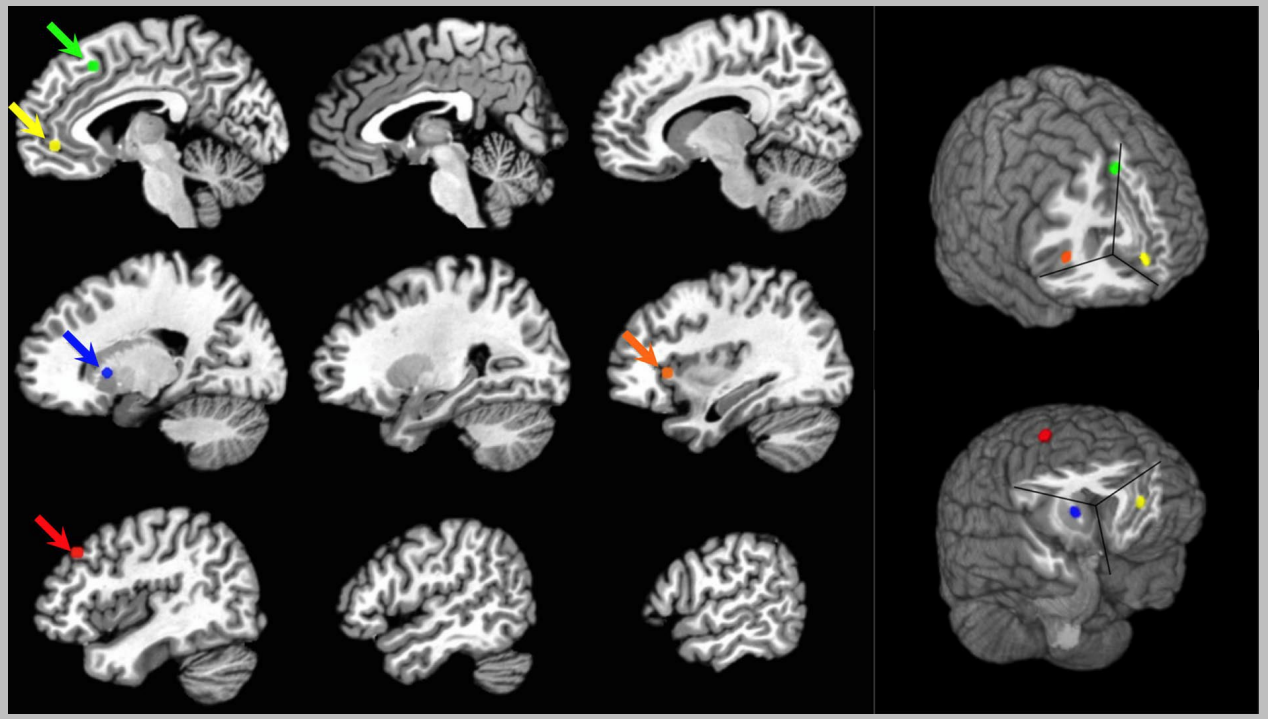
# Brain activation vs. behavior

- 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

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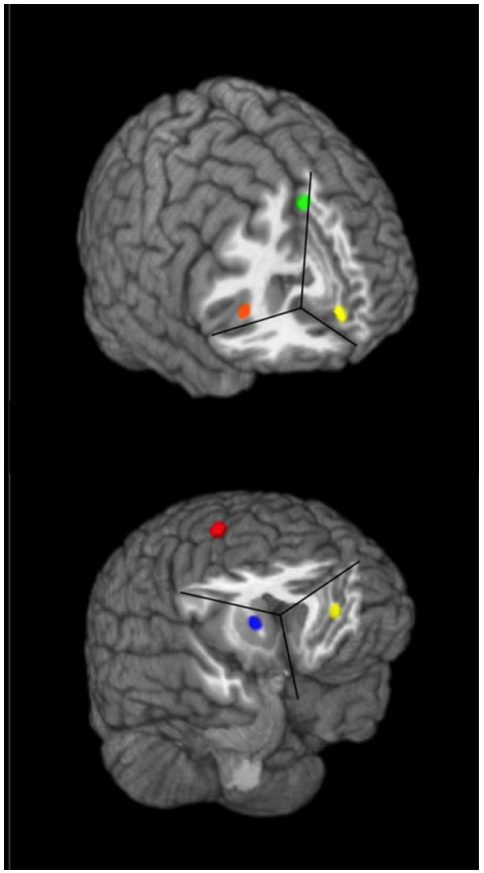
# Brain Mechanisms of Cognitive Fatigue

- 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



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# Research question

- Do these five brain regions form a network?
  - Are they functionally connected?

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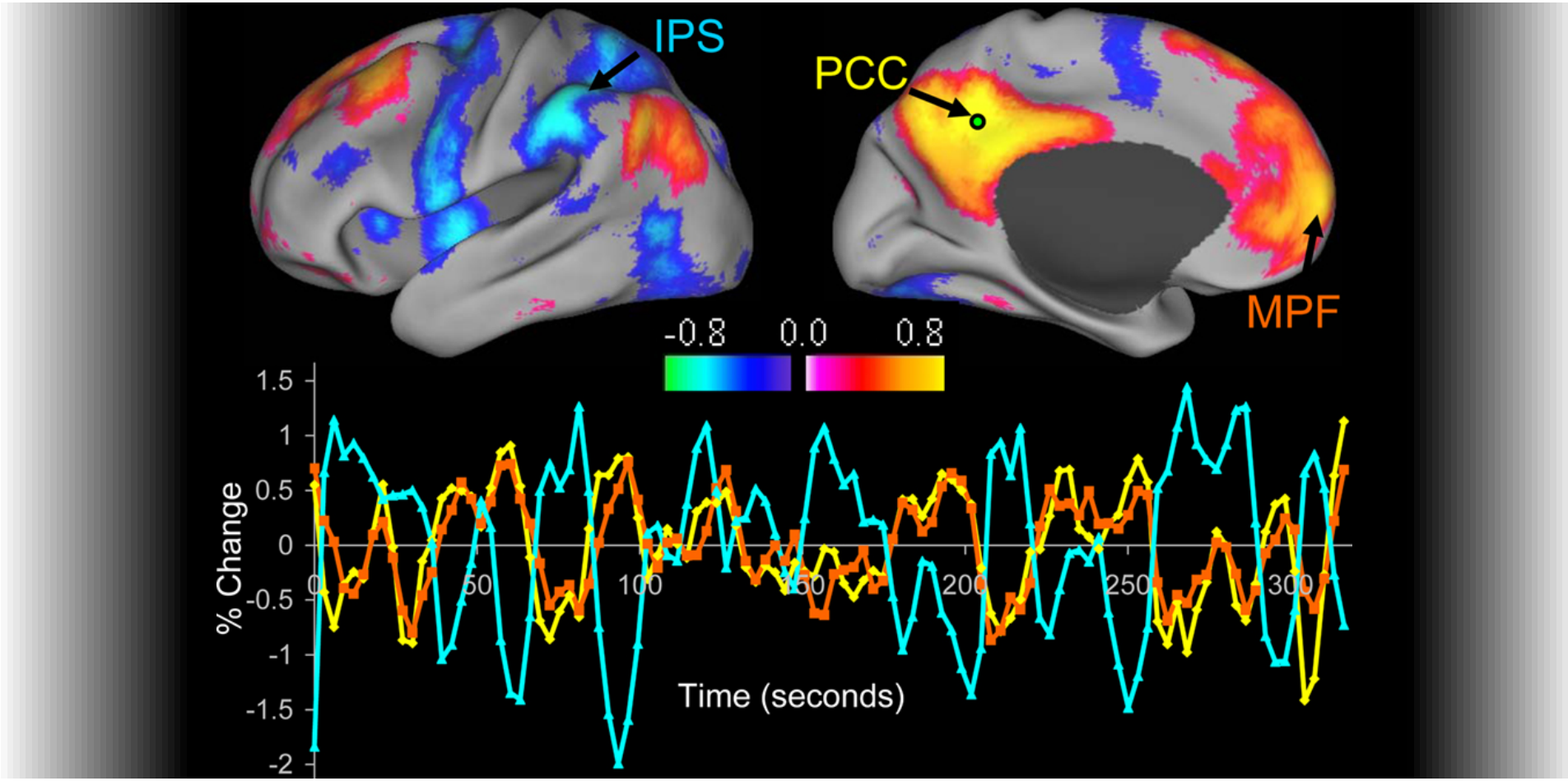
# Functional Connectivity (FC)




Fox et al. (2005). Proc. Natl. Acad. Sci. U.S.A. 102, 9673–9678.

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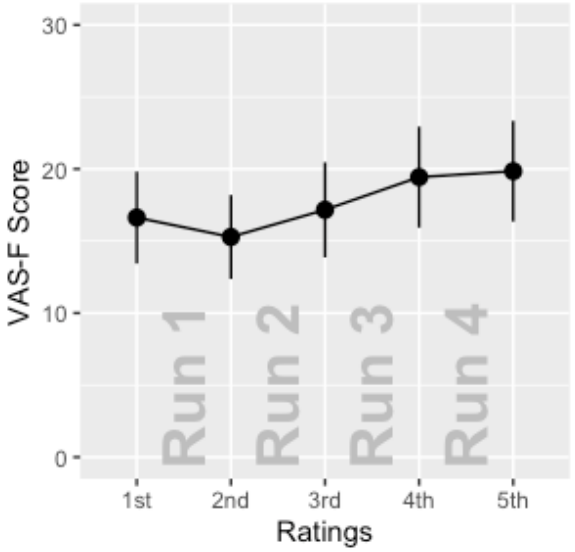
# Fatigue-related FC

- 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

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# 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

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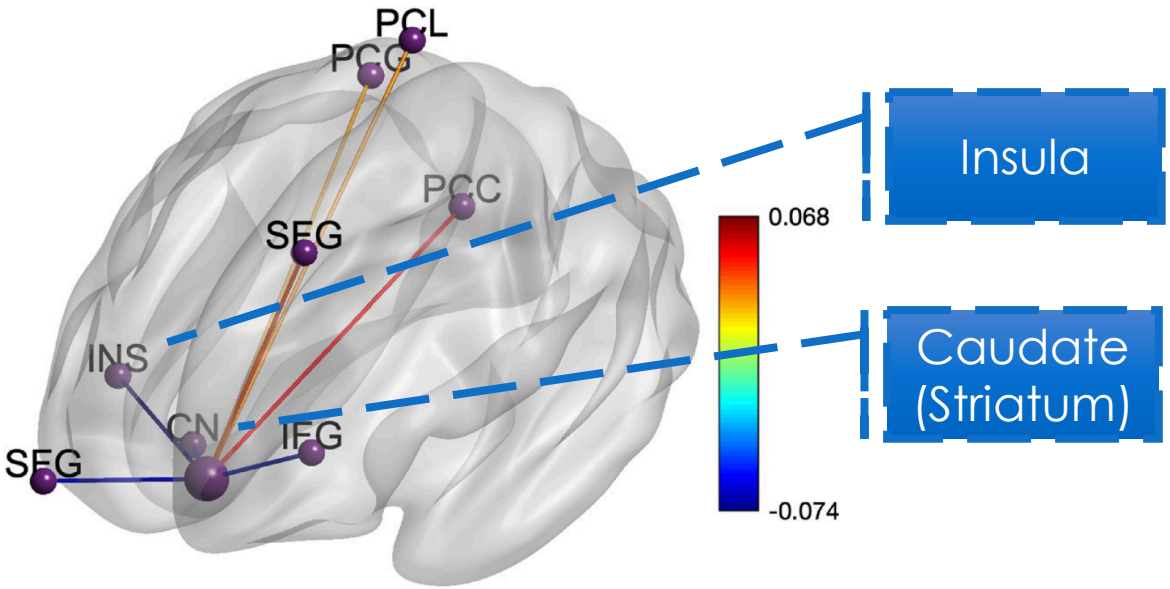
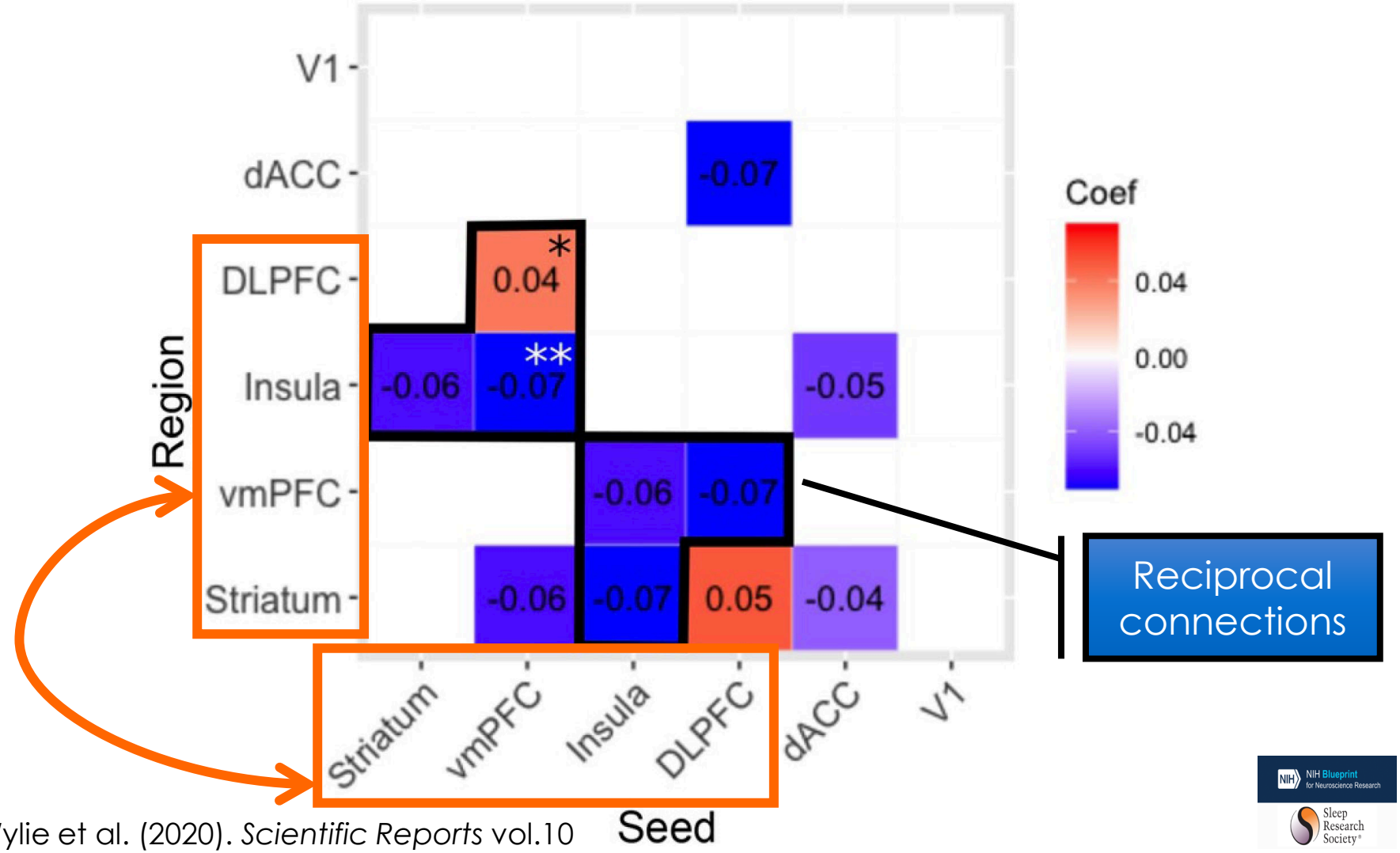
# For example: vmPFC seed

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




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

# Central regions of fatigue network

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# 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

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# 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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National Multiple Sclerosis Society

NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

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