Fatigue: a hypothalamic basis?

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Disclosure
This certifies that I, Patrick M. Fuller, have no financial relationship that is relevant to the subject matter of this presentation.
Challenges to understanding the neurobiological basis of fatigue

- We lack a consensus operational definition of ‘fatigue’
  - Is fatigue the same as sickness behavior, or a bad contingency matrix, or hypersomnia, etc.?
- We lack a model (mouse or otherwise) of fatigue
  - How can this be approached?
- I am not an expert in fatigue (to put it nicely)
- So why am I talking about the hypothalamus in the context of fatigue?
  - While only the size of an almond in the human brain, the hypothalamus exerts potent control over virtually all physiological and neurobehavioral ‘systems’, including the sleep-wake cycle.
  - That fatigue might impact the function of hypothalamic sleep-wake circuits, or that dysfunction of these circuits might produce/underlie fatigue, is a compelling hypothesis.
  - Here I discuss an example of how discrete/delimited viral-induced inflammation in the hypothalamus can produce dramatic and chronic alterations in the level of arousal.
Encephalitis lethargica and sleep-wake circuitry

von Economo, 1920
Posterior Hypothalamus
Fig. 54.—Case XI. General Appearance. Constant State of Lethargy. Tilney and Howe, 1920
Experimental recapitulation of “hypersomnolence” following posterior hypothalamic lesions

Ranson, Arch Neurol Psychiatr 41:1, 1939
Supramammillary Vglut2 neurons

Pedersen et al., Nature Comm, 2017
hM4Di inhibition of SUM\textsuperscript{vglut2} neurons

Pedersen et al., *Nature Comm*, 2017
Parting thoughts

• The clinical example [Encephalitis lethargica] provided illustrates how neuroinflammation of a delimited node of cells/brain region can produce dramatic alterations in the level of arousal, i.e., reductions in arousal can be localizable and may not reflect a ”brain-wide” phenomenon.

• To the extent that a reduced level of arousal may contribute to, be a manifestation of, or be the basis of, fatigue, then further investigation of the underlying role of arousal circuitry, such as the glutamatergic SuM, in fatigue would merit further exploration.
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