Brain Bioenergetics, Cognitive Activity, and Menopausal Vasomotor Symptoms

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Disclosures

- Sharon L. Dormire, PhD, RN
  - Professor and
  - Assistant Dean for Undergraduate Nursing Education
  - College of Nursing
  - No conflicts of interest to report
- Brandon Schmeichel, PhD
  - Professor
  - Psychology
  - No conflicts of interest to report
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Vasomotor Symptom (VMS) Overview

- 80% of women experience VMS.
- 15 million women in the United States experience VMS at any given time.
- 3 million seek hormone therapy for VMS.
- Causal mechanisms of VMS are unknown.

Learning Outcomes 1 and 2

Describe neurobarrier, neurometabolic, and neurovascular coupling as bioenergetic processes of glucose regulation in the central nervous system.

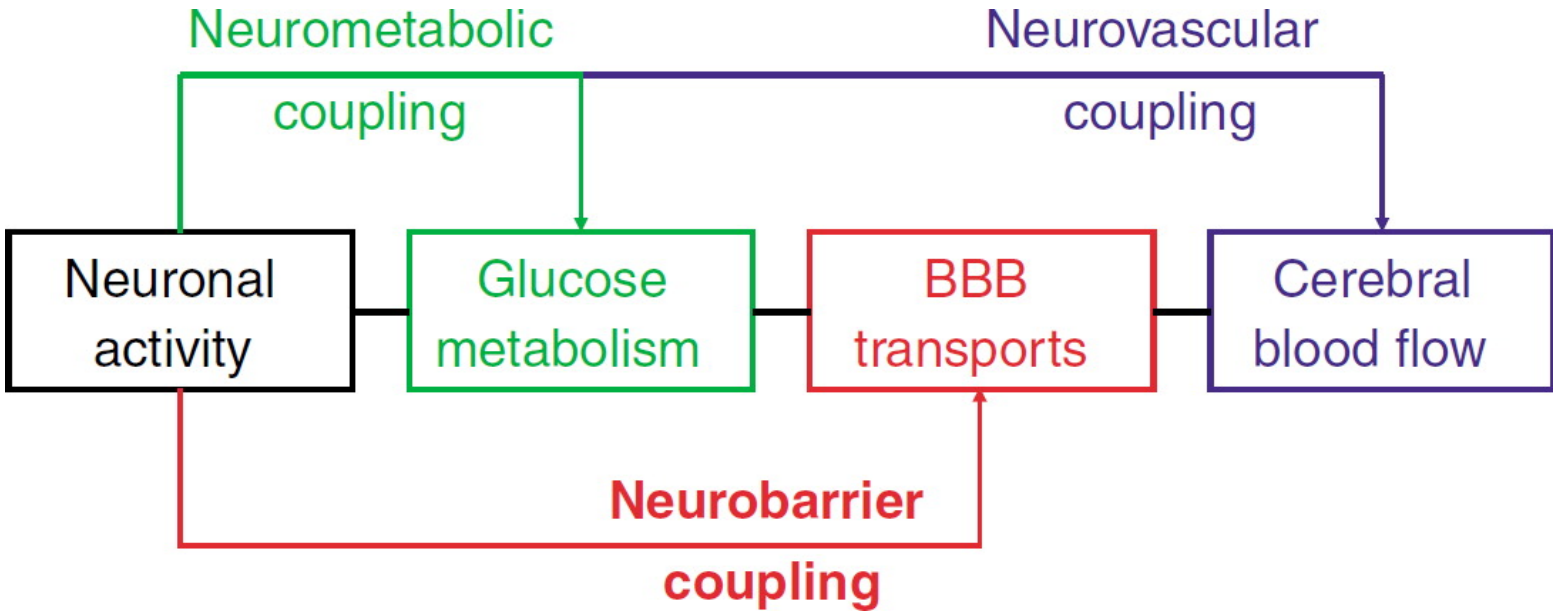
Link neurobarrier coupling, blood glucose, and vasomotor symptoms through the Impaired Glucose Delivery Model of Vasomotor Symptoms.

Brain Bioenergetics

- Glucose is not stored in the brain: it must have a continual supply for neuron activity.

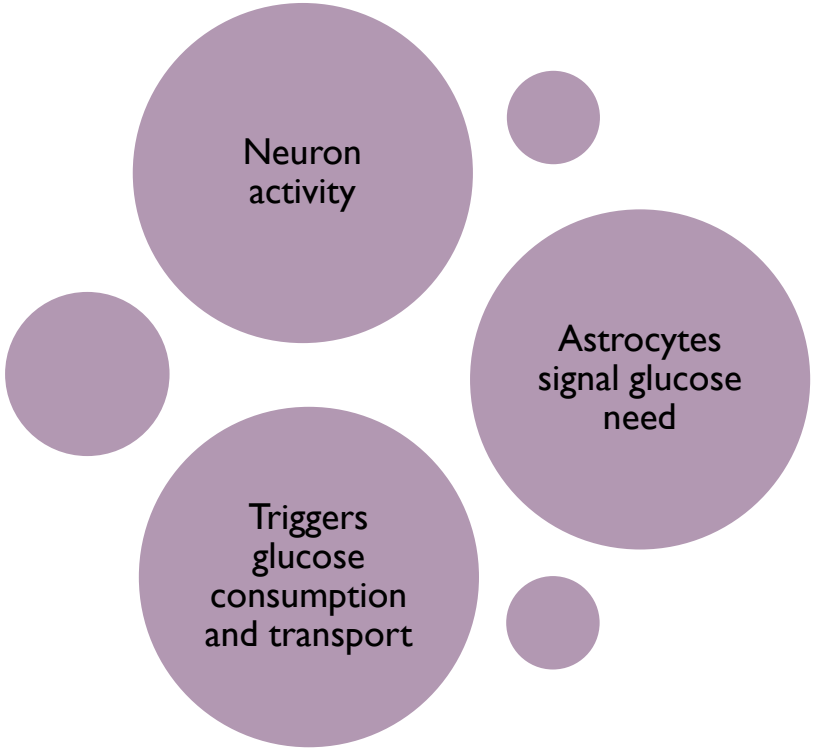
- Capillary endothelial cells limit movement of glucose into the brain given a differential
  - 1 mmol/L of glucose in the brain
  - 5 mmol/L in blood plasma

Brain Bioenergetics (energy transformation): Neurobarrier coupling

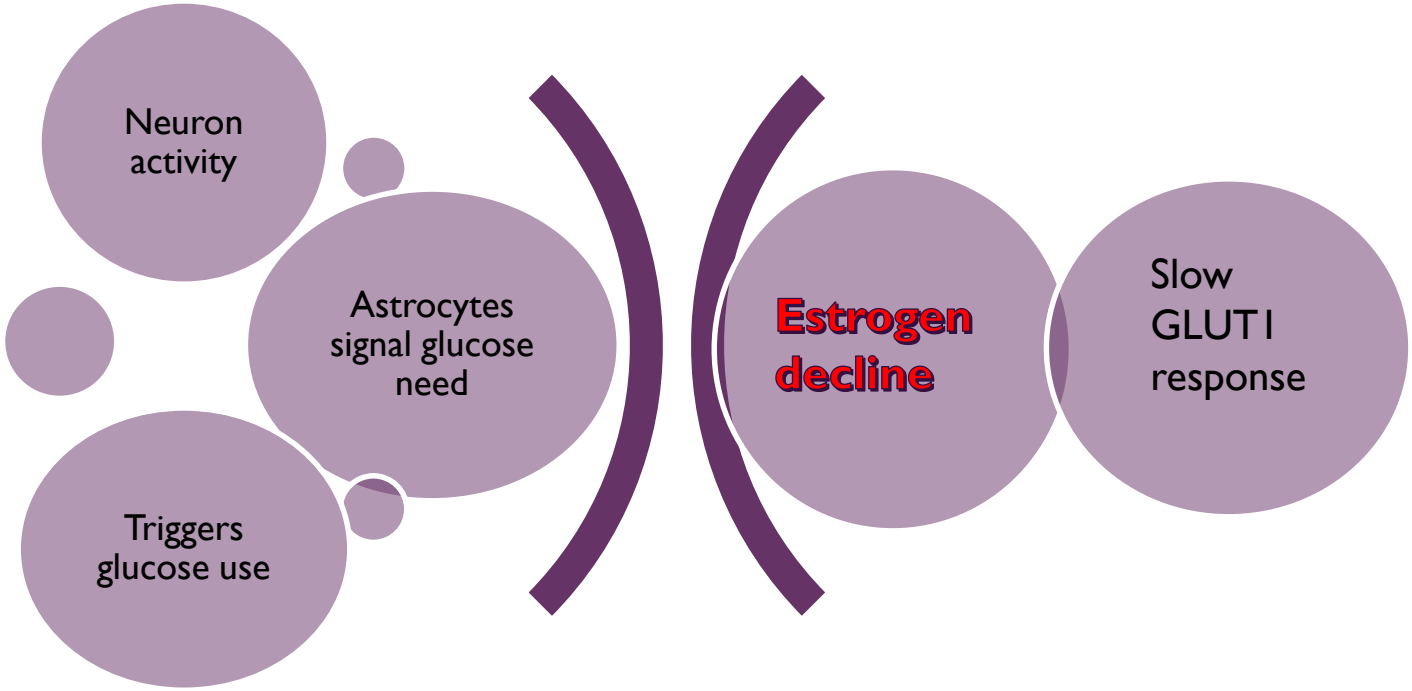


Leybaert, L. (2005). Neurobarrier Coupling in the Brain: A Partner of Neurovascular and Neurometabolic Coupling? *Journal of Cerebral Blood Flow & Metabolism*, *25*(1), 2–16. https://doi.org/10.1038/sj.jcbfm.9600001

Neurometabolic Coupling



Neurobarrier coupling



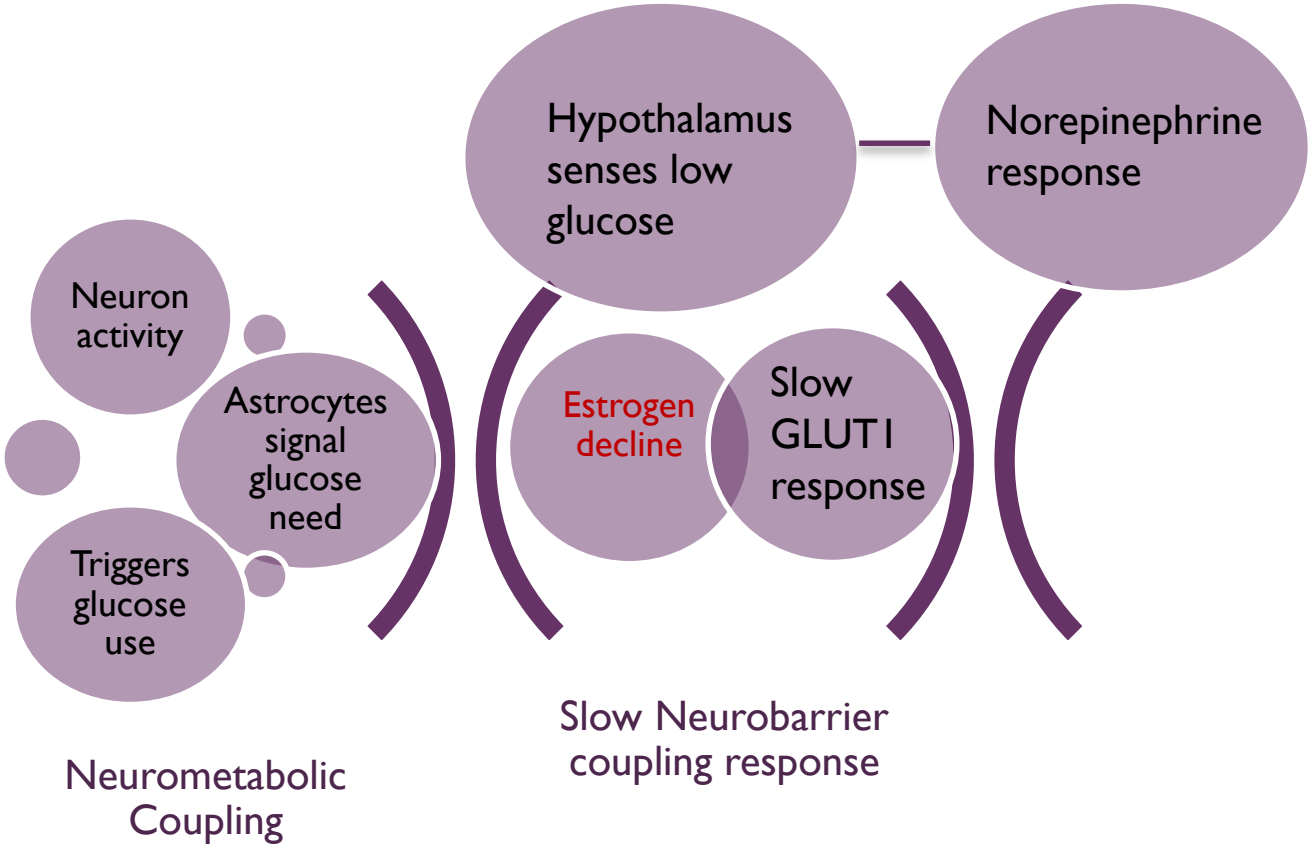
Neurometabolic Coupling

Slow Neurobarrier coupling response

Brain Bioenergetics

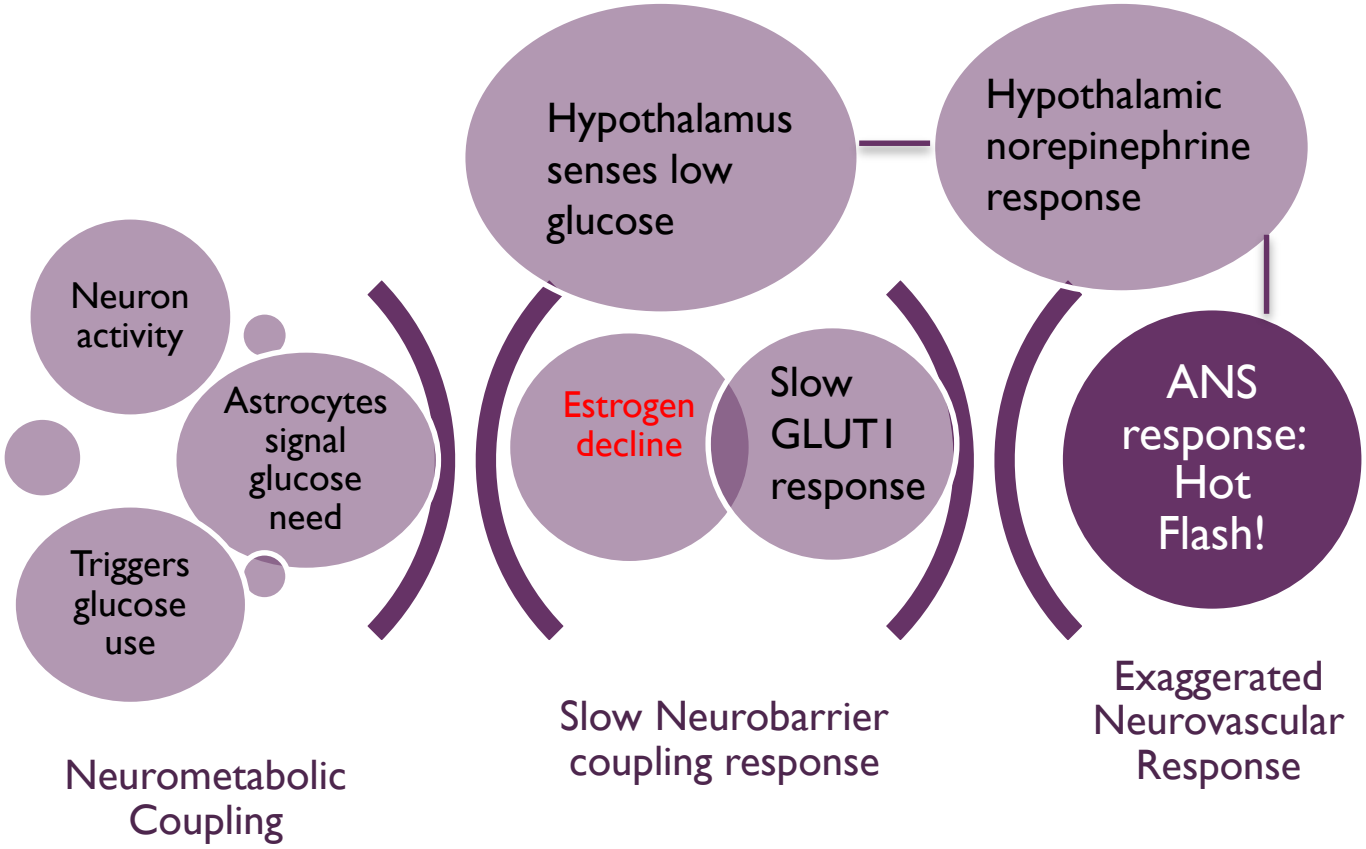
- Glucose movement mediated by facilitated diffusion - glucose transporter 1 (GLUT1).
- Estrogen, estradiol specifically, increases GLUT1 transport by 40% during times of glucose demand.

Neurovascular response



The targets of neurobarrier coupling are the endothelial cells that make up the blood-brain barrier.

Impaired Glucose Delivery Model of Vasomotor Symptoms



Neurovascular coupling acts to relax smooth muscle cells of arterioles to increase the local cerebral blood flow.

Learning Outcomes 3

Explain the effect cognitive activity on VMS in symptomatic menopausal women.

We propose that the Impaired Glucose Delivery Model of Vasomotor Symptoms is the link between menopause and cognitive change/risk for Alzheimer's Disease.

Study 1: Cognitive activation of vasomotor symptoms

- We first needed to reliably stimulate VMS in order to conduct neuroimaging.

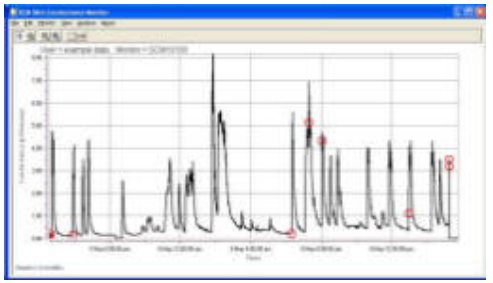
- Objective: Identify cognitive stressors that reliably stimulate HF in symptomatic women

Sample Characteristics

Characteristic	Category	n
Age	44-50	2
	51-56	12
	57-62	5
	>62	4
Ethnicity	Hispanic	2
	Non-Hispanic	21
	Black	6
	White	17
Education	High school diploma	1
	Undergraduate school	15
	Graduate school	6
Marital status	Married	17
	Divorced	4
	Widowed	3
Income	< $20,000	2
	$20,000 - $49,999	11
	$50,000 - $99,999	7
	>$100,000	3

5-Day Observation Period

- Bahr® Skin Conductance Monitor



- FreeStyle Pro® Glucose Monitor

Day 5: Cognitive experiment

- Participants completed 4 computer- based cognitive tasks in a standard psychology laboratory
  - Stroop task (Hard and Easy)
  - N-Back task (1- and 3-Back)
  - 3 minute music interlude for rest between testing periods
- Bahr and FreeStyle Monitors were removed after cognitive testing was complete

Findings

Cognitive Activity	VMS
Stroop Easy	3
Stroop Hard	4
1-Back	4
3-Back	11

N = 24

Results

- **93%** experienced VMS during the cognitive activation.
- Average time to VMS was **28.65 minutes.**
- Mean blood glucose during VMS was **87.1 mg/dL**

Significance of Findings

- This is the first study to demonstrate cognitive activity can stimulate VMS
  - (Heat applied to the truck is the accepted experimental stimulus for VMS.)

- Empirical evidence for the theoretical model: lack of estrogen for rapid production of GLUT 1 results in a glucose deficit stimulating VMS.

Learning Outcome 4

List areas of metabolic change in the brain during VMS compared to baseline in symptomatic women.

Background

- **Women** are disproportionately affected by Alzheimer's Disease (AD). In fact, two-thirds of patients with AD are women,
- **Menopause** is a sex-linked risk factor for AD.
- **Brain imaging** studies have demonstrated hypo-metabolism in the brains of women with hot flashes (HF) and those with AD.
- **Estrogen** related changes in brain glucose transport and metabolism may result in an increased risk for AD.

Study 2:
fMRI Imaging during VMS Pilot

- Participants completing the cognitive stimulation of VMS study were invited to participate in the imaging study.

- Before the MRI, participants fasted for 4 hours; blood glucose was checked via finger stick before and after the MRI.

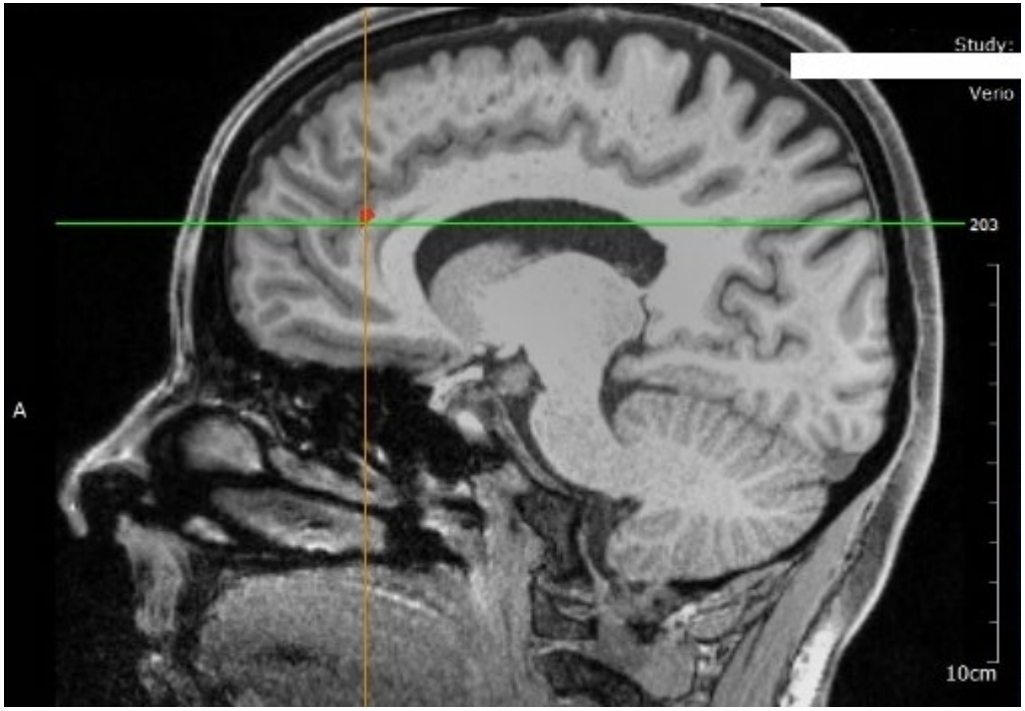
fMRI Procedures

- Functional magnetic resonance imaging (fMRI) performed followed by echo-planar blood oxygen level dependent (EPI-BOLD) sequences.
  - Four scans were performed while Stroop and N-back cognitive tests were administered.
  - Indicated beginning and end of VMS with emergency bulb.
- Completed Utian Quality of life scale, The Women's Health Questionnaire, and Menopause Health Questionnaire. (These findings will not be presented here.)

Bioenergetics Imaging Procedures

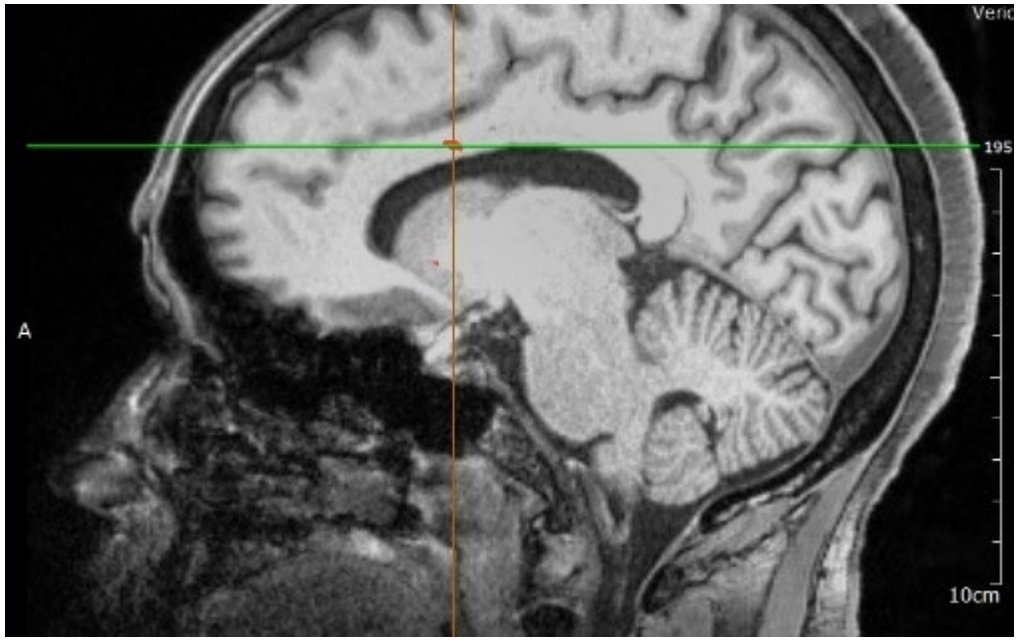
- A total of 9 symptomatic women were scanned:
  - 3 were excluded due to the absence of HF during the imaging.
  - Data from 2 subjects was excluded due to the short duration of HF (< 20 seconds) precluding data analysis.

Anterior cingulate cortex activation



Anterior cingulate cortex is used in complex cognitive functions, such as empathy, impulse control, emotion, and decision-making.

Corpus callosal activation



The corpus callosum is responsible for transmitting neural messages between both the right and left hemispheres.

Note regarding the insula

- The insula was activated in studies using heat to induce VMS.
- It was not activated during VMS stimulated by cognitive activity.

Conclusion

- Cognitive activity effectively and reliably stimulated VMS in the laboratory setting.
- Areas of metabolic activation were identified using fMRI during VMS inducted by cognitively activity.
- Changes in brain glucose metabolism similar to those seen in AD are noted during fMRI imaging of VMS stimulated by cognitive activity.

Conclusion

- Additional research is needed to explore the relationship between VMS-related brain glucose metabolism and postmenopausal cognitive change:
  - Larger representative sample using this research model.
  - Longitudinal examination of changes both in VMS and cognition.
  - Comparison of methods of VMS stimulation.

Thank you!

Questions?

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