Central Nervous System and Bladder Control

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Disclosures

- Current funding:
  - occasional consulting fees from University of Pittsburgh
- Other financial relationships:
  - occasional consultant for LABORIE
- Conflicts of interest:
  - none

Significance

- Continence implies voluntary control of voiding
- Urgency or urge incontinence is a lack of voluntary control
  - prevalent in old age
  - even with no overt neurological disease
- Voluntary control is exercised from the brain
- Therefore a brain defect could lead to loss of control, manifested as
  - involuntary bladder contractions (detrusor overactivity)
  - involuntary voiding (urge incontinence, UUI).
- The hope:
  - brain imaging will reveal such a brain defect
  - reduction or prevention of the defect will offer an effective mechanism of therapy

State-of-the-art knowledge

- I shall summarize recent knowledge about:
  - mechanism of continence and incontinence in older people
  - mechanism of therapy

- Main body of recent work from Pitt group
  - supported by Ruggieri, Nados, and Khrut
  - other brain imagers
    - have not addressed the same problem
    - or have used animals
    - or have used different measurement routines

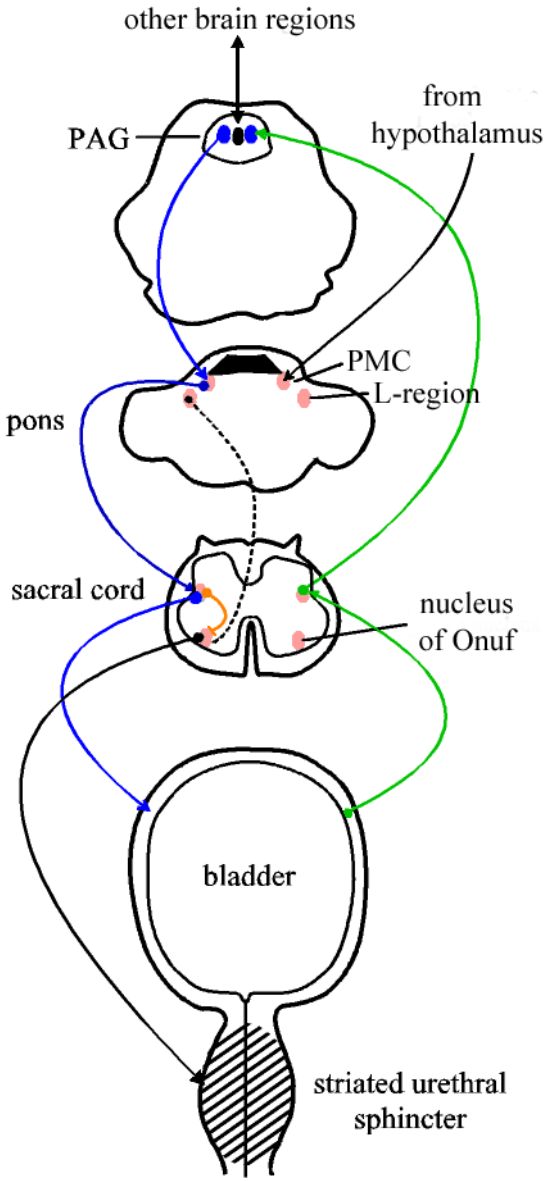
- Subjects are mainly older <u>women</u> with or without urge incontinence
  - Gender issue: why only women?
    - no confounding by BPH
    - large number, high prevalence of urge incontinence

Method used at Pitt

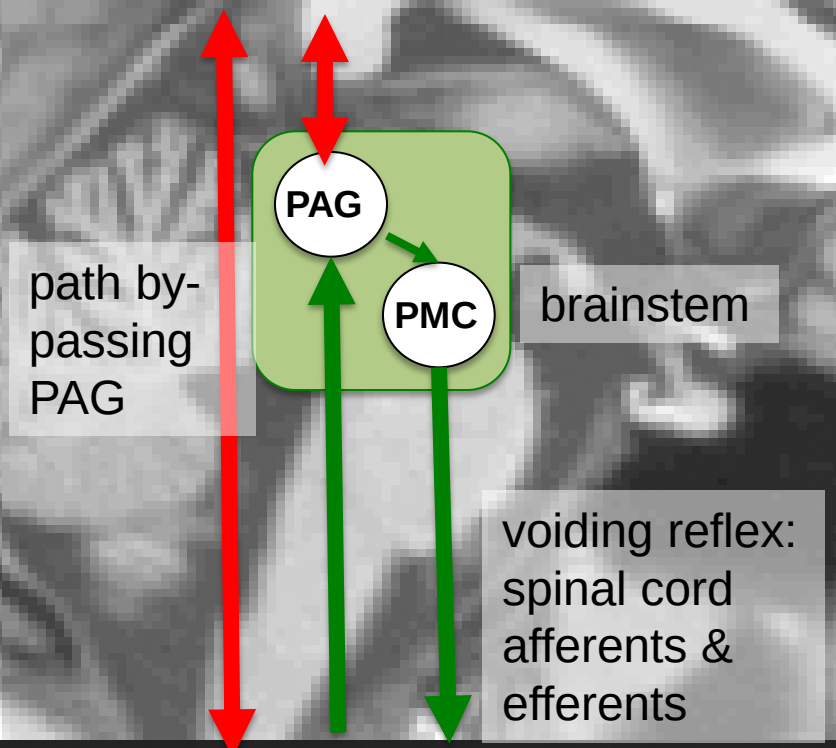
- Brain activation provoked by bladder filling
  - measured by fMRI
- Simulated by repetitive infusion and withdrawal into/out of the bladder, while scanning
- Performed with near-empty bladder
  - weak or no sensation
- and with full bladder
  - strong desire to void or urgency
- Note: results are averages for groups, not single subjects

Voiding reflex: our starting point

- Basic voiding reflex is automatic:
  - bladder fills up,
  - afferents increase
  - PAG activity increases
  - reflex is triggered in the PAG
  - bladder empties automatically
- No voluntary control, therefore incontinence
- Voluntary control exercised by other brain regions via PAG
  - see next slide



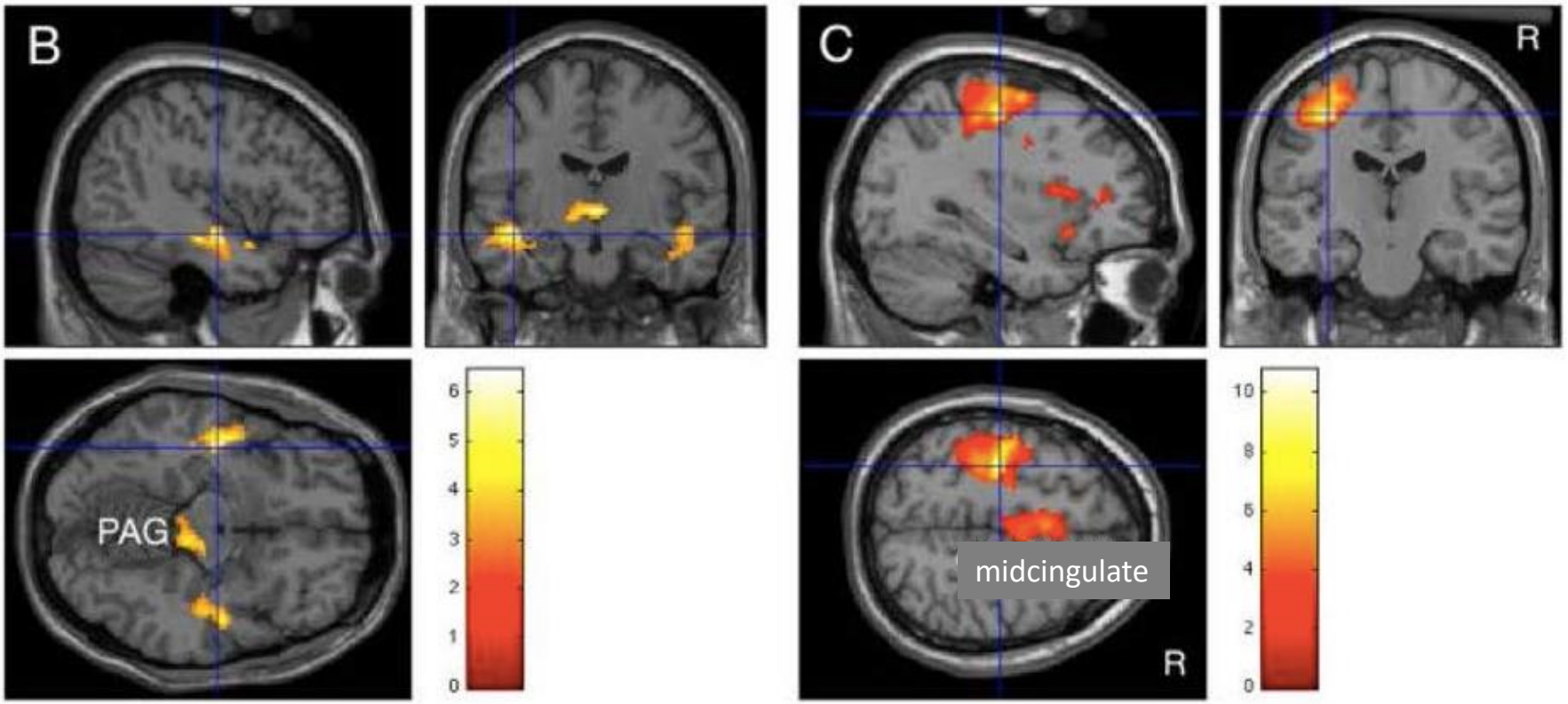
Voluntary control by “higher” brain regions acting on PAG



Results in age-matched continent females ("normals")

near-empty bladder

full bladder



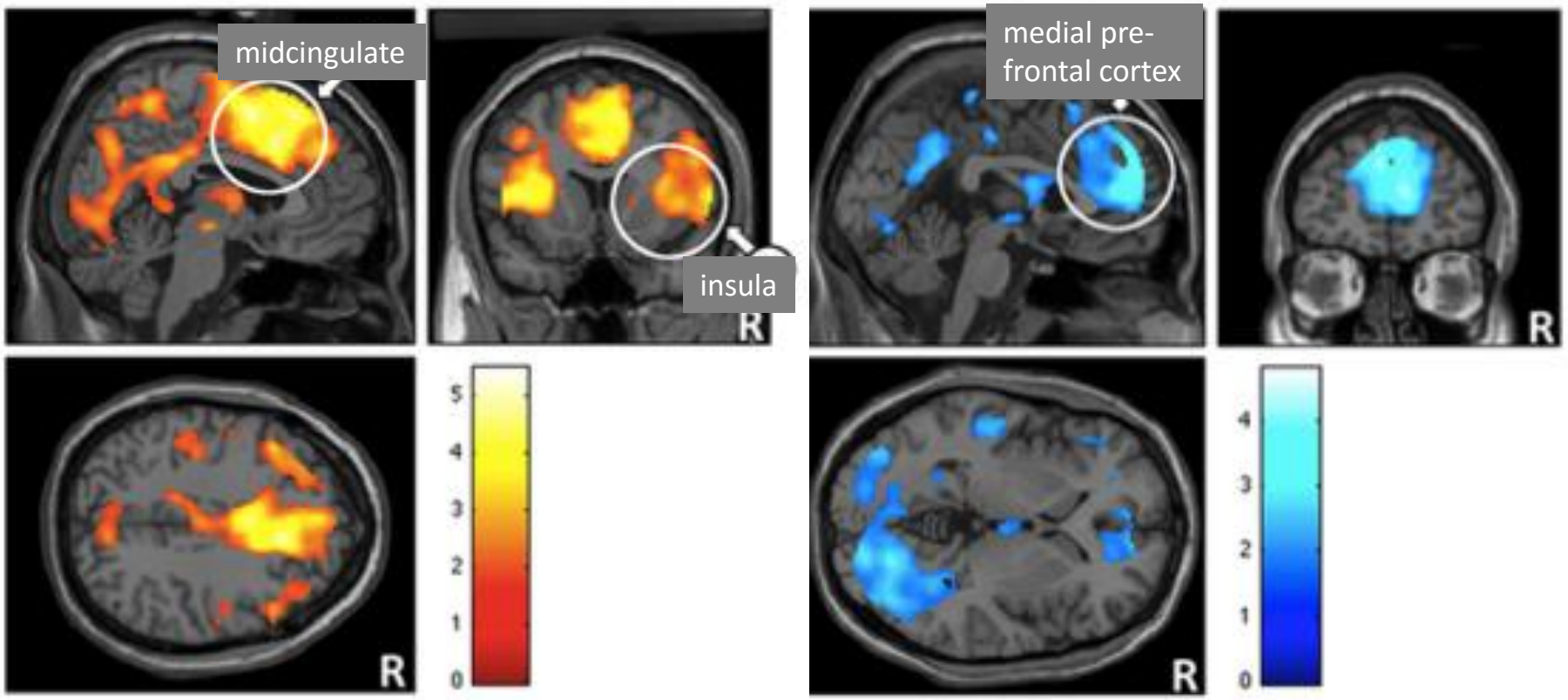
not much sensation, little activation, some in PAG

strong desire to void, more activation, some in midcingulate

Results for older women with UUI at full bladder, with "urgency"

responders to behavioral treatment

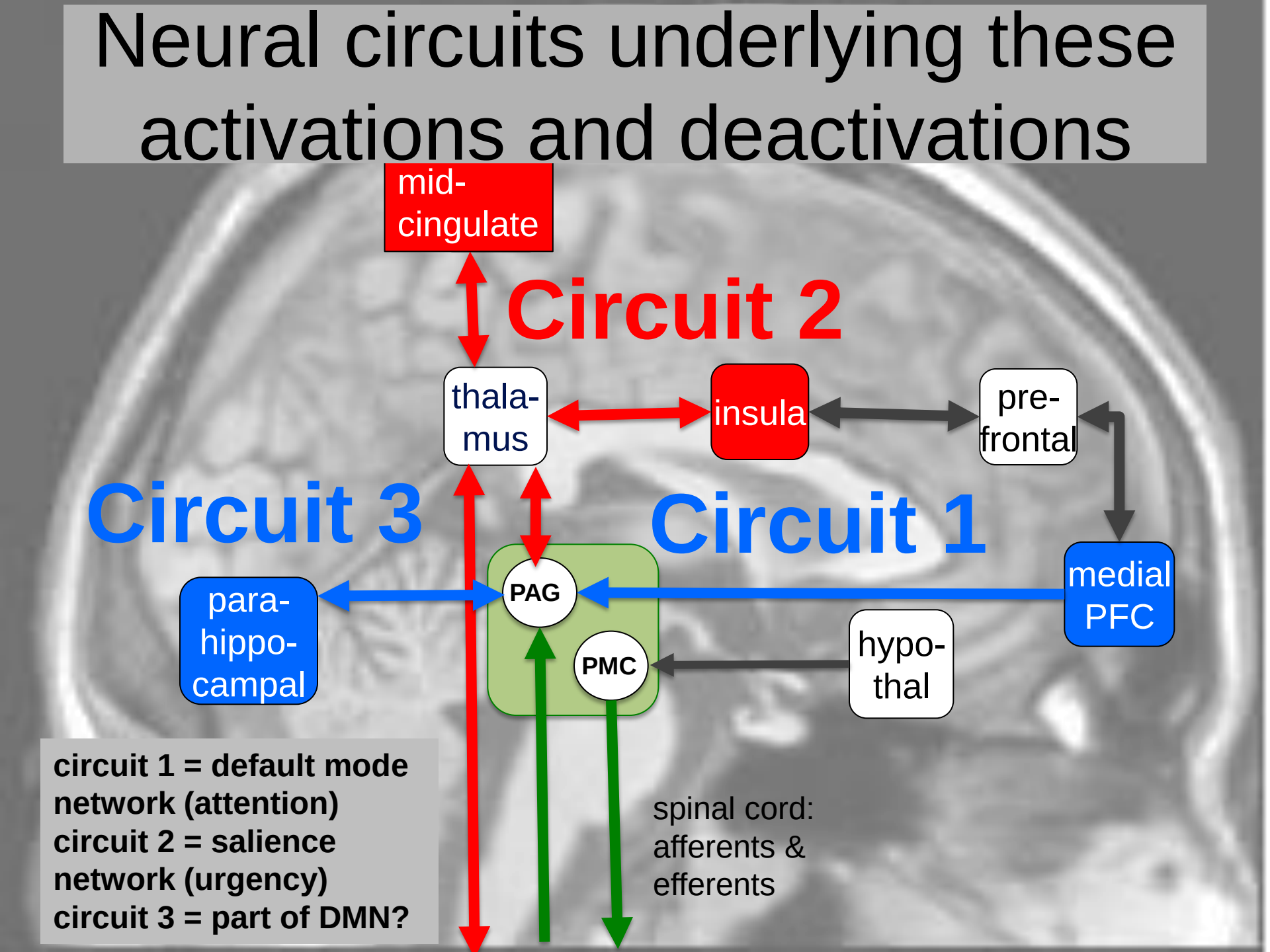
nonresponders



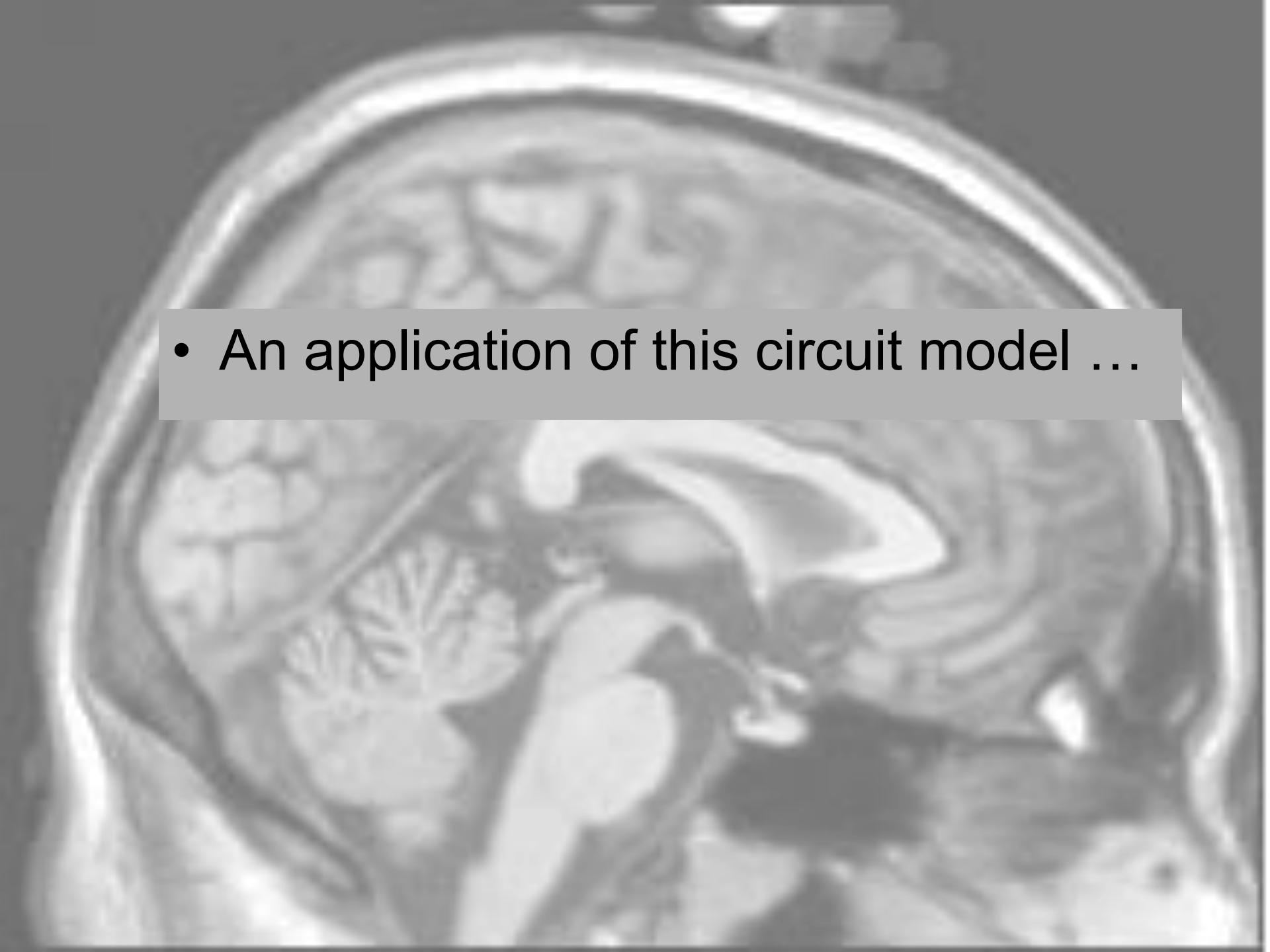
more activation in midcingulate

deactivation in medial frontal brain

Neural circuits underlying these activations and deactivations

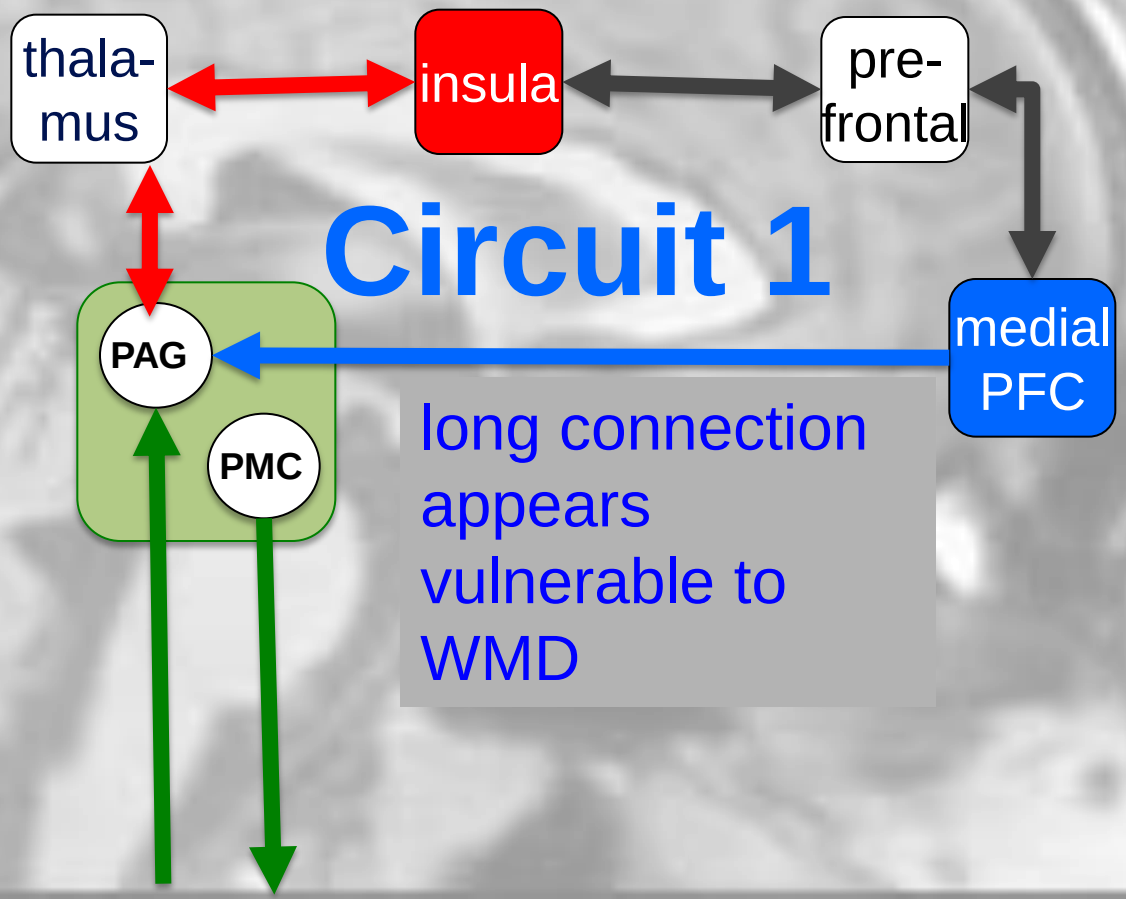


circuit 1 = default mode network (attention)
circuit 2 = salience network (urgency)
circuit 3 = part of DMN?



- An application of this circuit model …

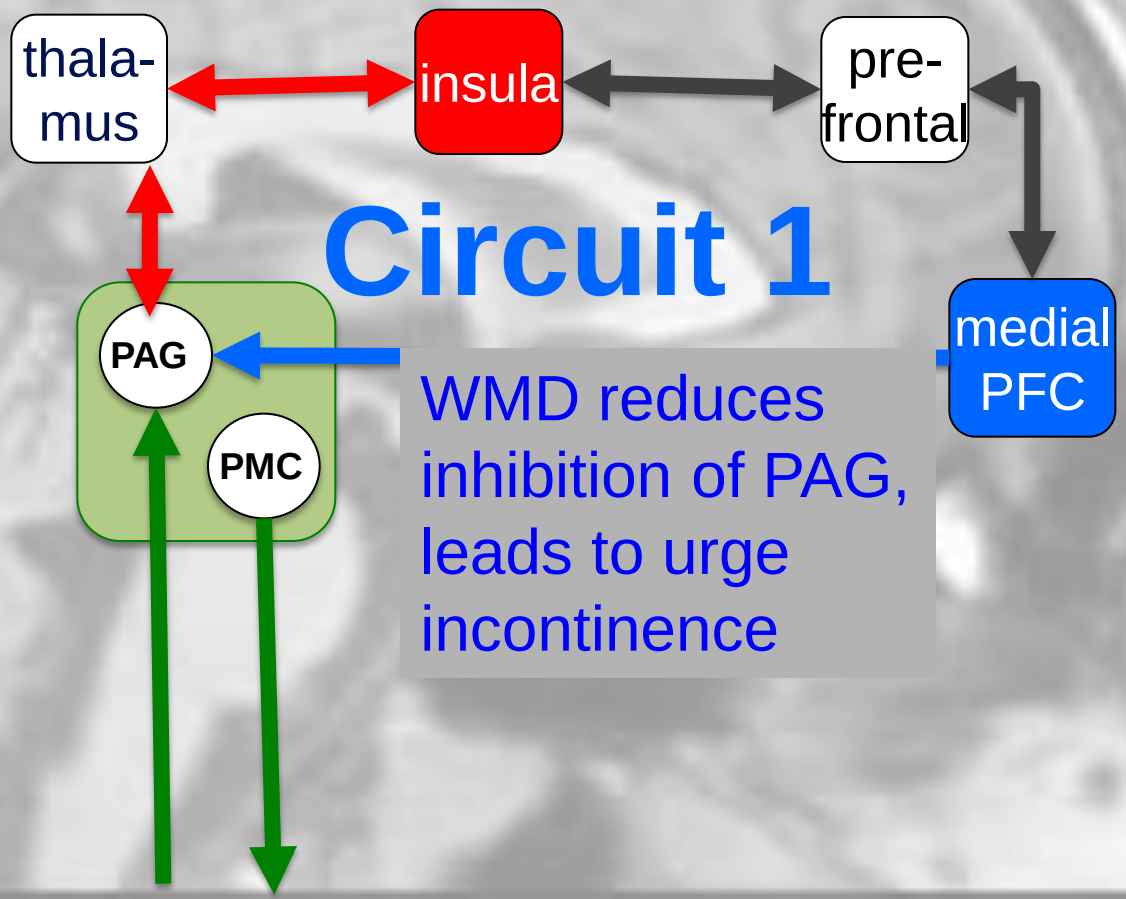
An application: white-matter damage in circuit 1



An application: white-matter damage in circuit 1

- Circuit 1 (voluntary control) relies on long white-matter tract from frontal cortex to midbrain PAG
  - appears vulnerable to white-matter disease (WMD)
  - if damaged, reduces inhibitory input to PAG, leading to loss of voluntary control
  - may suggest site of WMD that should be targeted by preventive measures (diet, exercise, e-stim)
    - see next slide

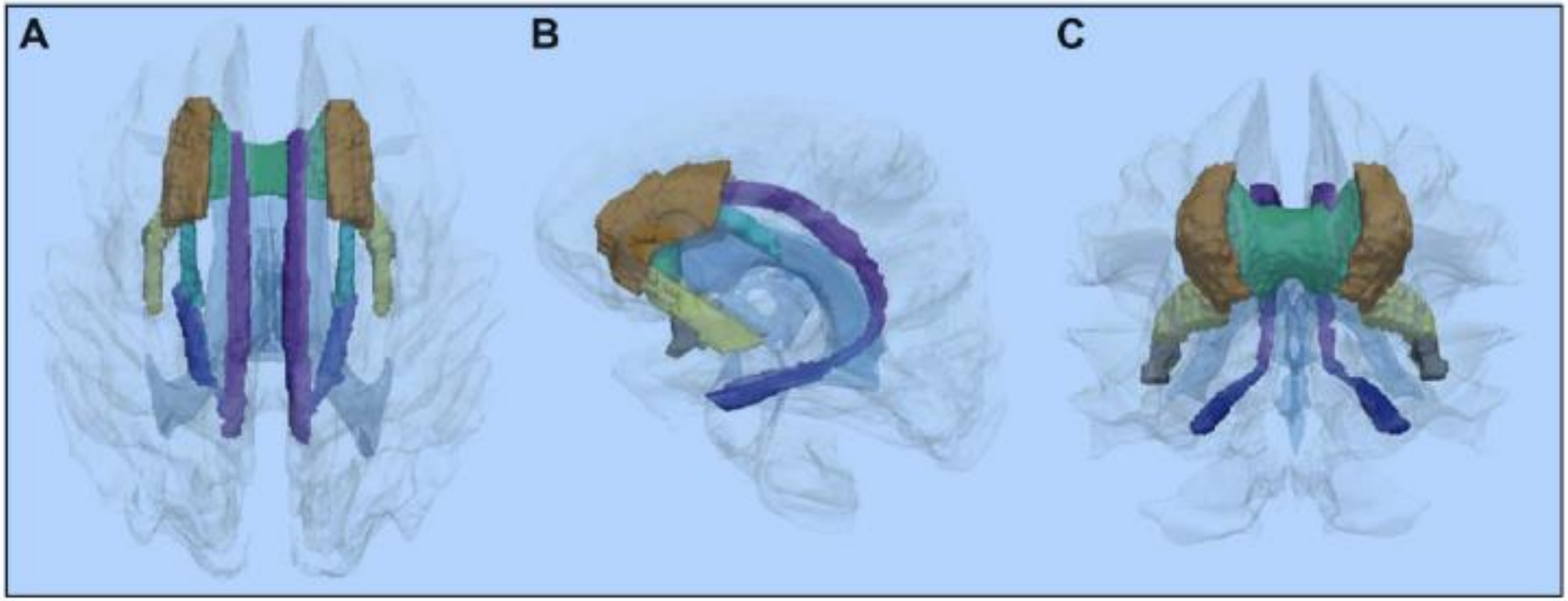
White-matter damage in circuit 1



Evidence for white-matter damage in circuit 1

- Kuchel group, in elderly men and women:
  - urge incontinence associated with WMD, especially in cingulum tract (circuit 1)
  - Pitt results are concordant :
    - WM disease in similar tract (anterior thalamic radiation) is correlated with brain responses to bladder filling characteristic of urge incontinence
- Supports idea that WM damage in circuit 1 may contribute causally to urge incontinence
  - point of view championed by Sakakibara

WM tracts: cingulum (Kuchel et al)



- Cingulum is purple tract from front of brain to midbrain = circuit 1
- Implications for treatment ?

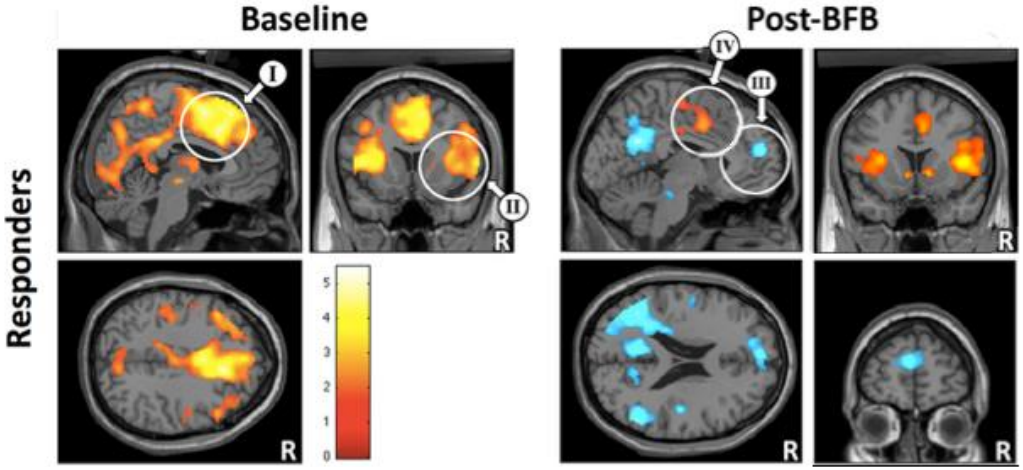
A second application of the bladder control model: Toward better treatment

- Biofeedback-assisted pelvic floor muscle training (BFB) for urge incontinence (UUI) can be used
  - as a test of BFB's therapeutic mechanism
  - hopefully, to improve BFB
- With a protocol like Burgio's we attain approximately 50% reduction of UUI frequency in 50% of older women with UUI
  - enables division into responders ($\geq$50% improvement in UUI frequency) and nonresponders (<50% improvement)

Surprising result of BFB treatment

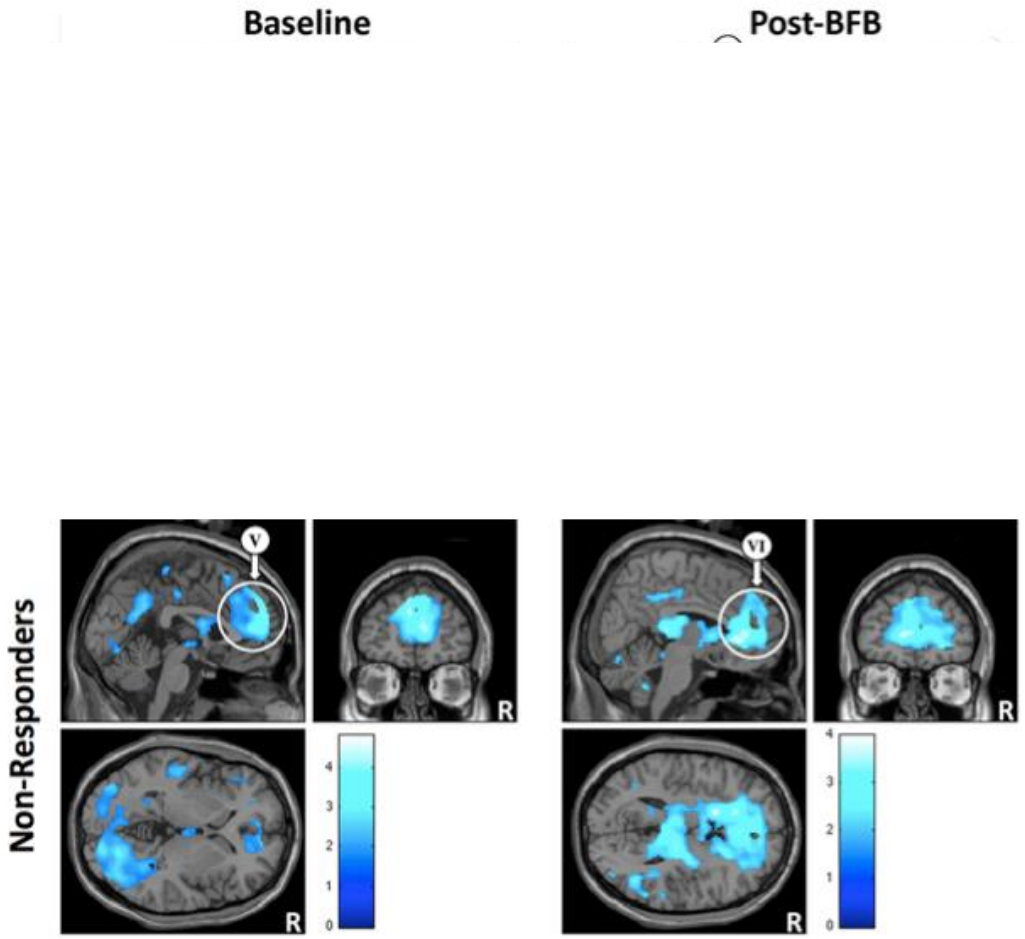
- As mentioned, responders and nonresponders to BFB show completely different brain responses to bladder filling
  - Two phenotypes of urge incontinence?
- Responders use circuit 2 – salience network
- Nonresponders use circuit 1 – default mode network
  - but there is more …

Brain activation and deactivation before and after BFB treatment



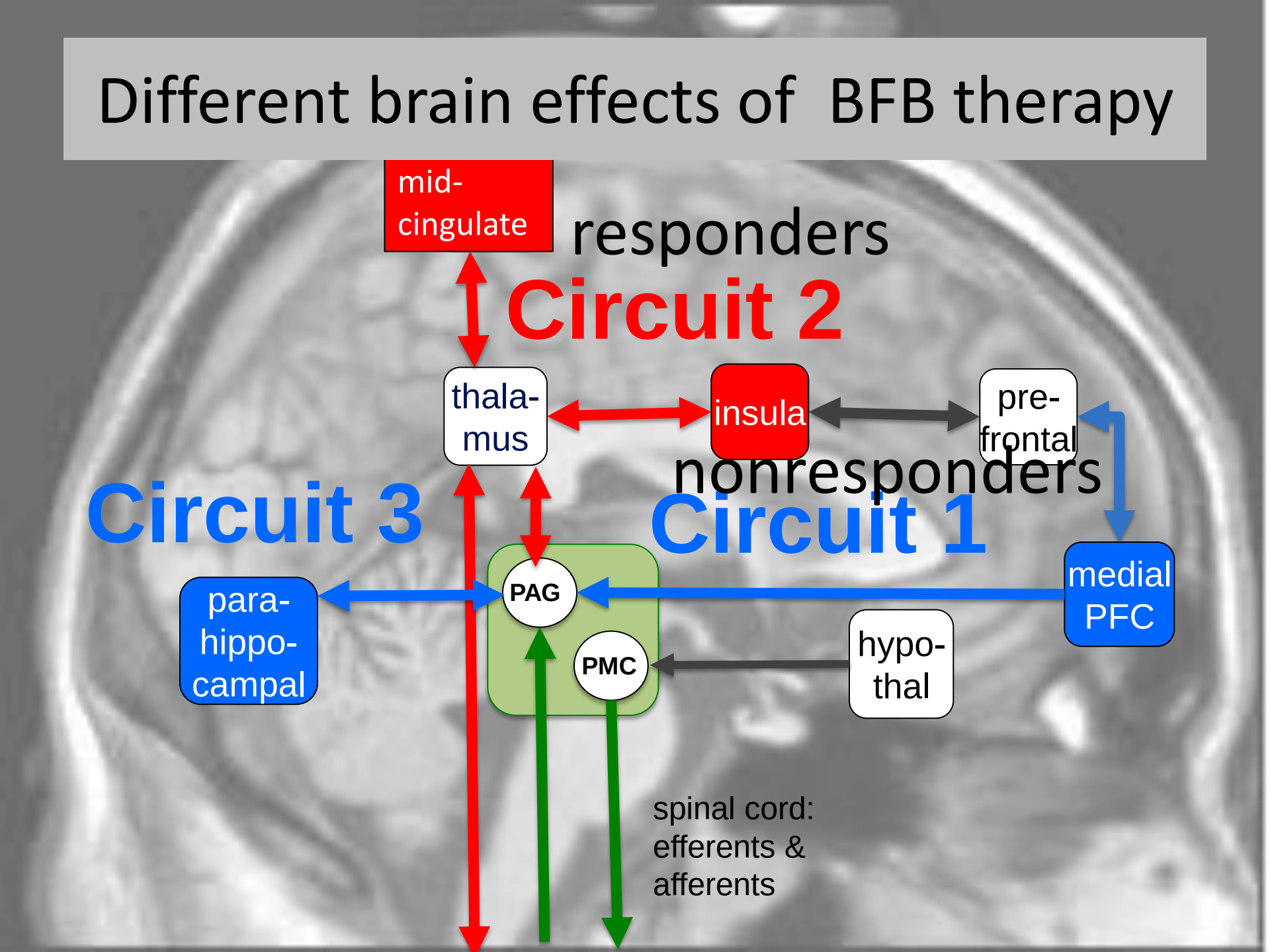
- Post-BFB, responders tend to change the pattern of activation and deactivation:
- Is this the mechanism of therapy?

Brain activation and deactivation before and after BFB treatment



- Post-BFB, nonresponders continue to show marked deactivation:
- And cannot employ this therapeutic mechanism?

Different brain effects of BFB therapy



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Knowledge gaps:

- Some of results shown are trends, of borderline significance
- Need for better protocol than our current infusion/withdrawal maneuver
- Need to study to other patient groups:
  - men, younger women, neurological disease (e.g. Parkinson's disease)

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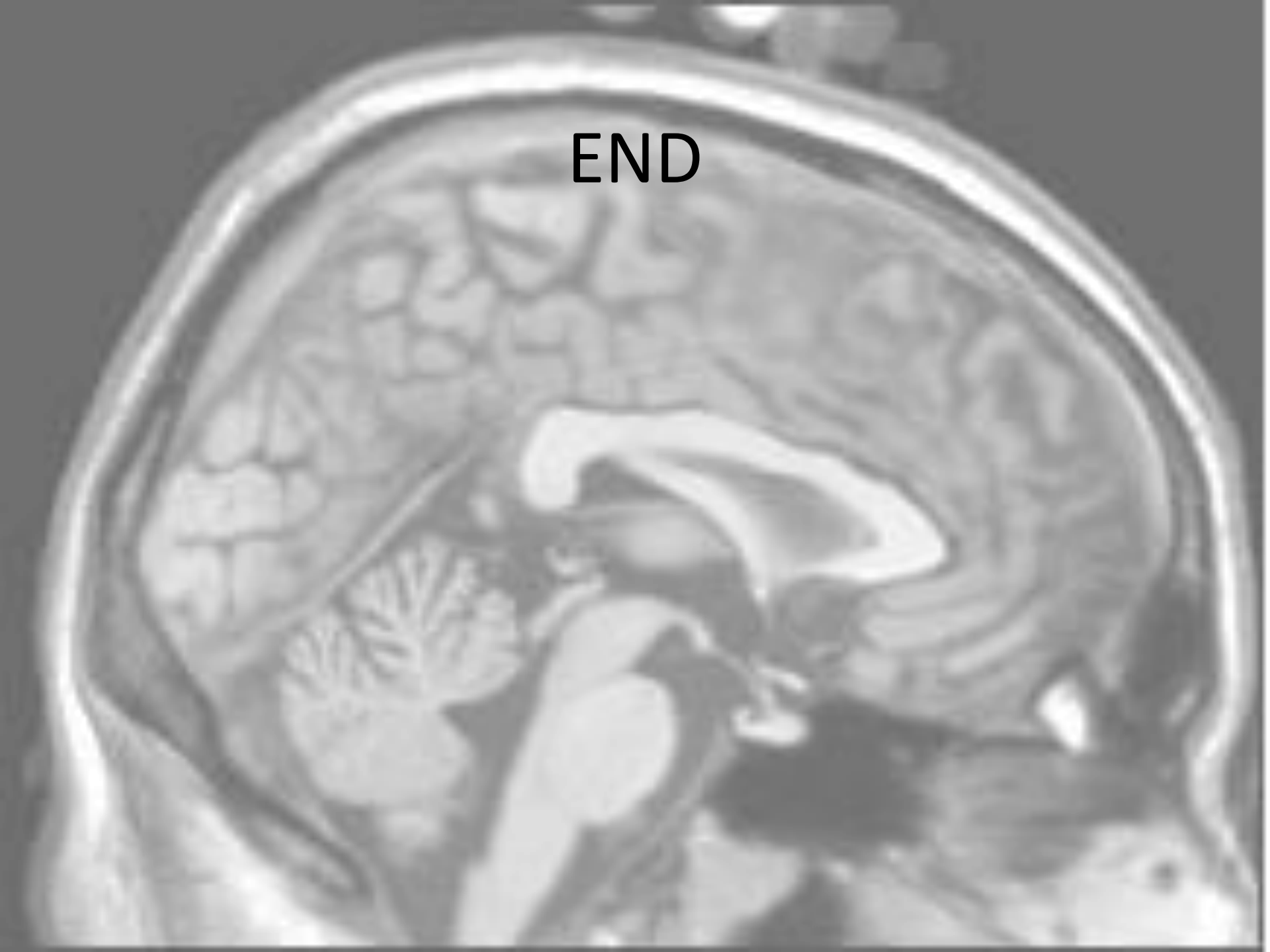
Research opportunities:

- Use new analysis methods, more sensitive and specific:
  - resting-state or seed-based connectivity
  - diffusion tensor imaging
- Study other therapies (may have surprising results, like BFB – different phenotypes?)
  - antimuscarinics (Ruggieri), beta-agonists, botox
  - e-stim (Blok)

Central Nervous System and Bladder Control: Summary

- Much learned about brain/bladder control
  - summarized in simple “circuit” model
- Impairment of critical white-matter pathways reduces inhibition and thus contributes to UUI
  - cingulum may be critical
- Brain imaging can suggest mechanism of behavioral therapy
  - surprisingly, suggests phenotypes with different susceptibility to treatment
  - is this true of other therapies?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