# HORMONE THERAPY AND REGIONAL CEREBRAL METABOLISM IN WOMEN AT RISK FOR ALZHEIMER'S DISEASE

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# Collaborators

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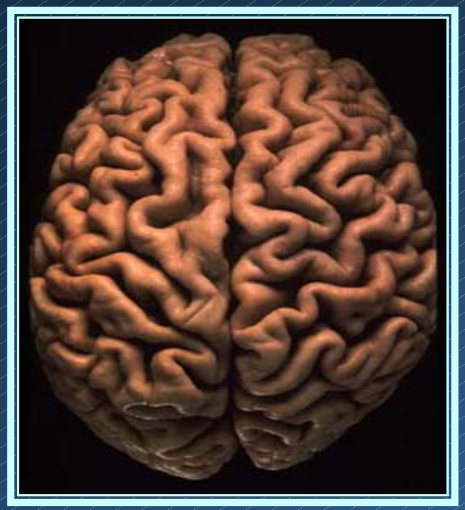
# Background

HT use:

- thought to lower the risk for Alzheimer's disease[1]
- enhanced cerebral and cognitive function in both healthy and demented older women[2,3]
- has been associated with increase in dementia risk in women 65 years and older[4]




1. Kawas et al, 1997
2. Resnick et al, 1998
3. Ohkura et al, 1995
4. Shumaker et al, 2003

# Objective

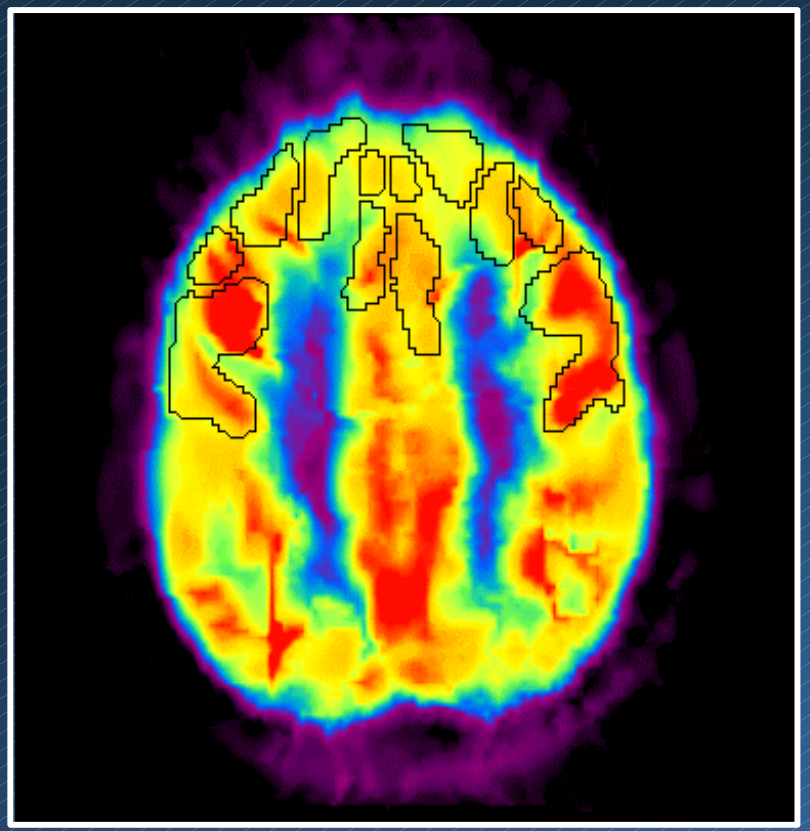
- To evaluate regional cerebral metabolism in women with risk factors for AD.

# Risk Factors for AD

- Hypothyroidism
- Depressive disorder
- APOE-4 carrier status
- Family history of AD

# Overview of Methods

1. Blood laboratory testing, thyroid testing, and brain PET data were acquired.
2. Cognitive impairment and depression were quantified with comprehensive neuropsychiatric assessment tests.
3. Regional normalized brain activity was analyzed by both statistical parametric mapping and conventional region-of-interest (ROI) methods.



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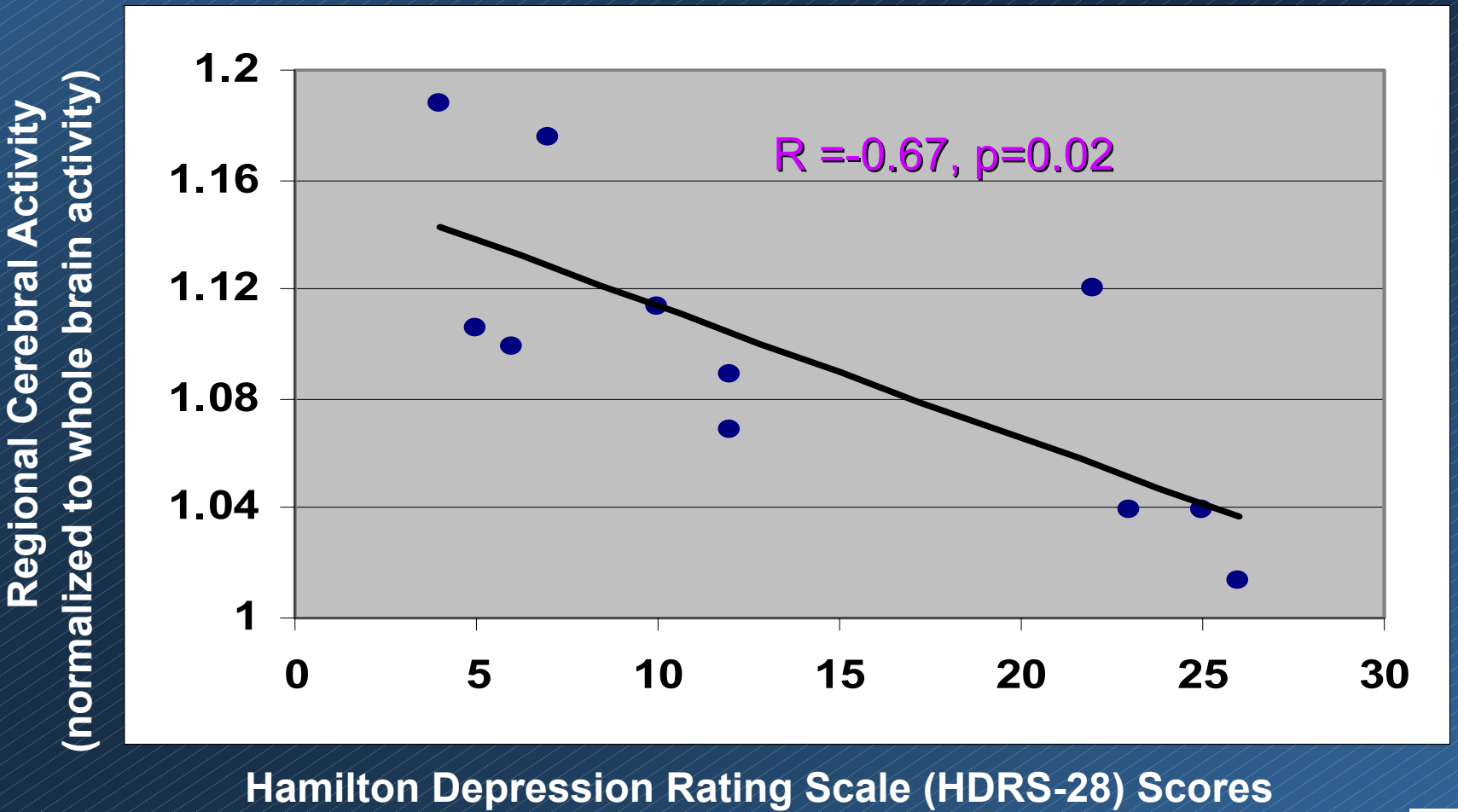
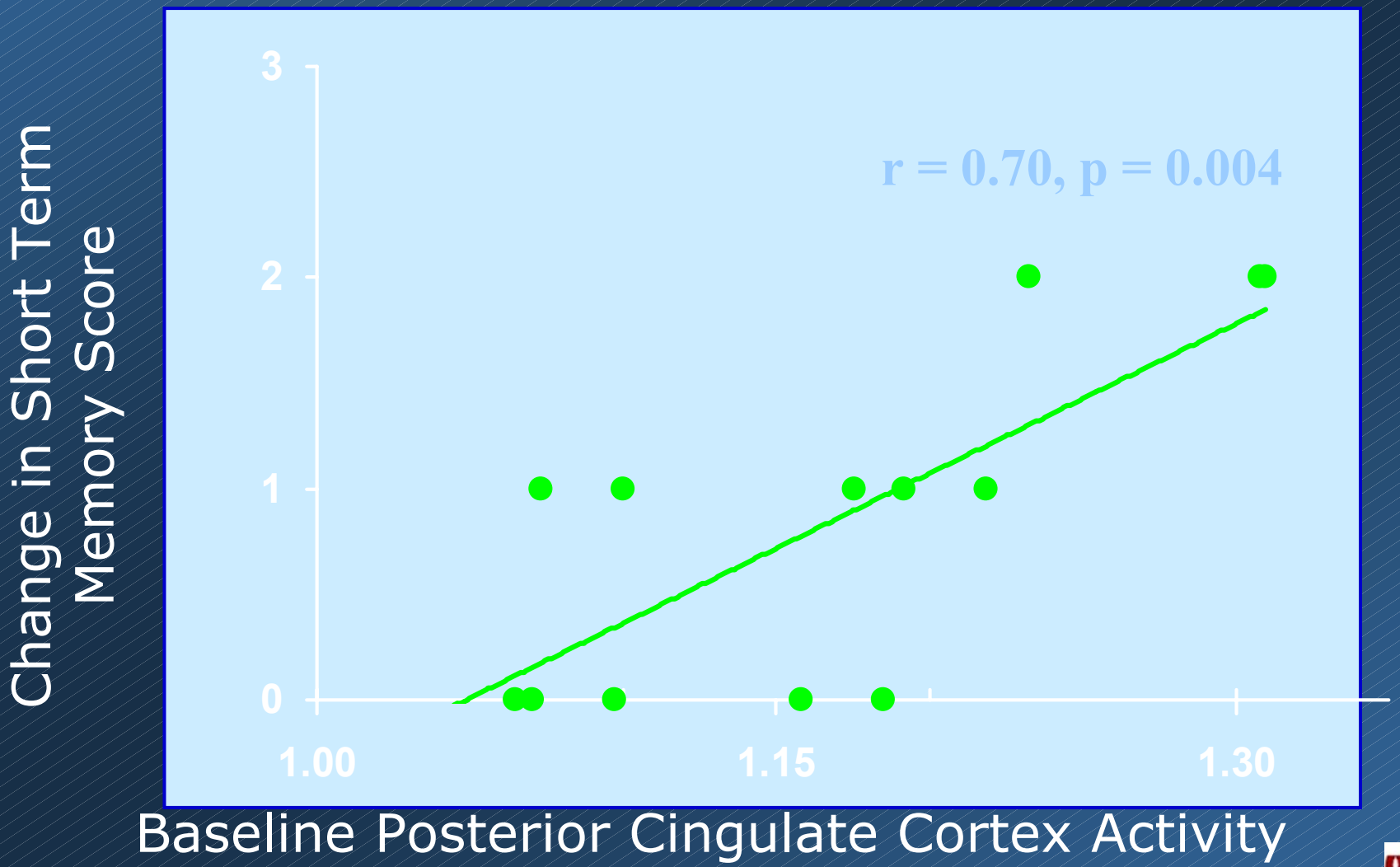
# PET Specifics

- The uptake period of FDG was carried out while patients rested quietly with eyes open in a dimly lit room.
- Brain PET emission data were collected with 3D acquisition 40 - 70 minutes after i.v. administration of 370 MBq FDG.
- Scans were reconstructed with measured attenuation correction, following a 15-minute transmission scan.
- Regional brain metabolism was assessed for left and right cerebral hemispheres in each of 26 regions, and normalized to whole brain activity levels.

# Severity of Depression Correlated with Inferior Frontal Cortex Activity in Women with Hypothyroidism



# Improvements in a Standardized Measure of Short Term Memory Significantly Correlated with Increased Baseline Posterior Cingulate Cortex Metabolism in Hypothyroid Women

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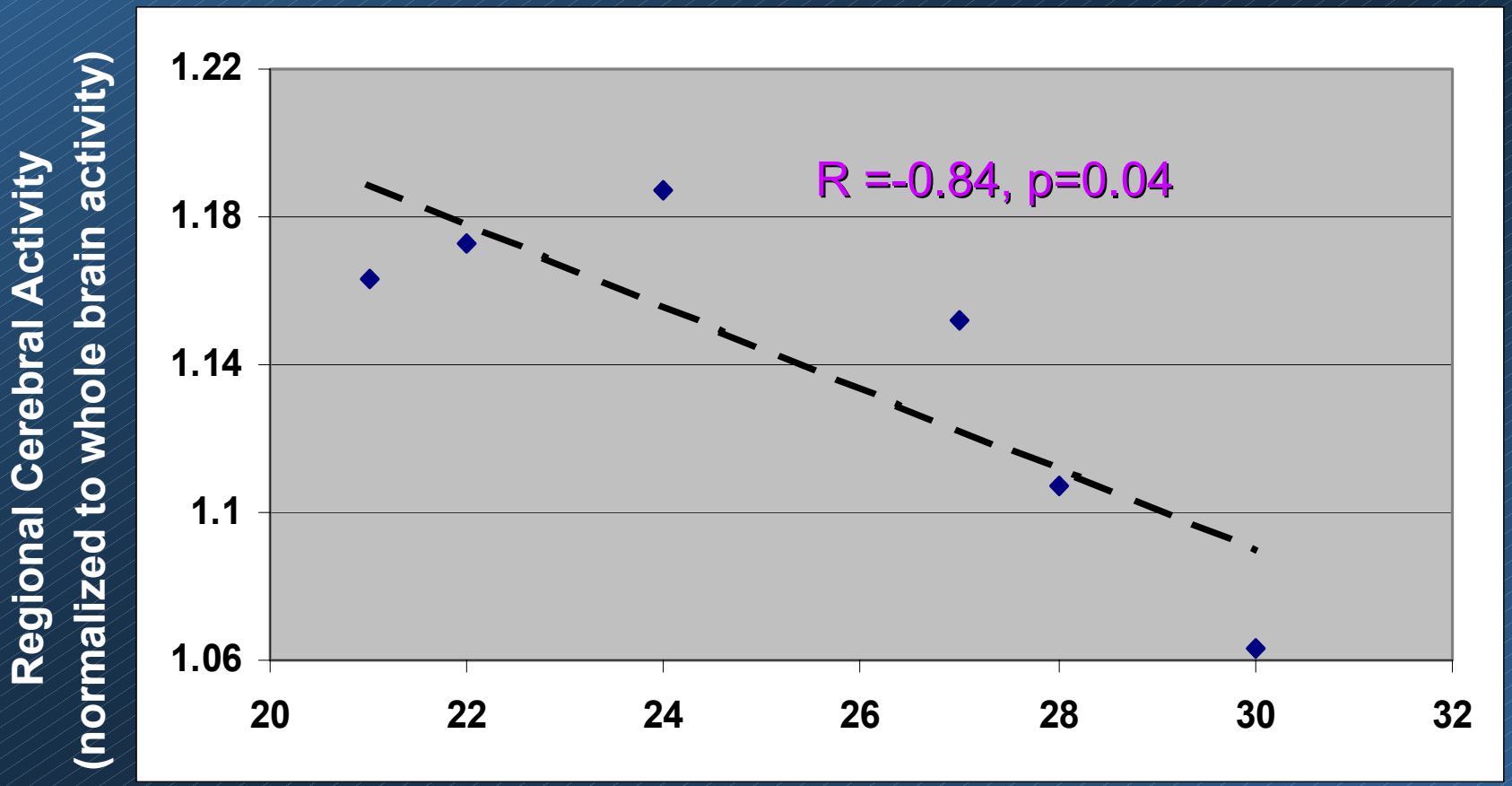
# Depression Severity Correlated with Hypometabolism in the Left Broca's Area in Postmenopausal Women with MDD

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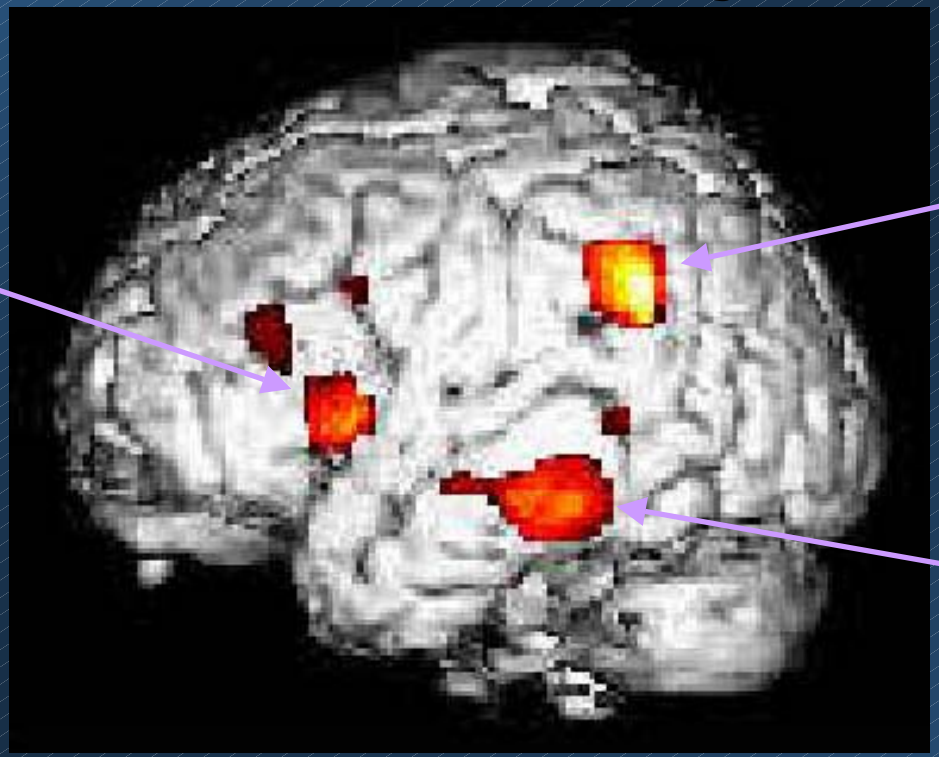
# APOE-4 Allele is Associated with Decreased Metabolism of Cerebral Language Areas in Undemented Subjects

motor speech (Broca's) area



receptive language area

reading and silent word generation area

**(Color-scale voxels are decreased in *3/4* relative to *3/3* group (p<0.01). (All labeled regions have peak regional significance of p<0.001)**

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# Lessons Across Paradigms

- Hypoestrogenism and hypothyroidism associated with lower metabolism in regions known to be important to language function (*Broca's area*).
- Presence of a single APOE-4 allele in well-matched groups of healthy subjects is associated with decreased activity in cerebral cortical regions specialized for subserving language.

# Lessons Across Paradigms (Cont.)

- For patients with cognitive impairment, low *posterior cingulate metabolism* occurring in the clinical context of either incipient Alzheimer's disease or hypothyroidism serves as a common predictor of poor prognosis for memory function.

# Objective II

- To compare changes in cerebral glucose metabolism between women HT users and non-users at familial/genetic risk for AD

# Subjects

| Study 1 | Total N | APOE4 (+) | APOE4 (-) |
|---|---|---|---|
| Estrogen Users | 4 | 2 | 2 |
| Estrogen Non-Users | 8 | 4 | 4 |
| Men | 10 | 4 | 6 |

| Study 2 | | | |
|---|---|---|---|
| Estrogen Users | 11 | 6 | 5 |
| Estrogen Non-Users | 8 | 4 | 4 |

# Exclusion Criteria

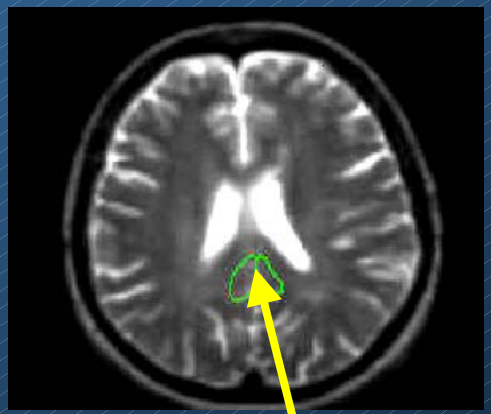
- Subjects with any other neurological, medical, or psychiatric condition (e.g., depression) that could affect memory or cognitive processing were excluded.
- Subjects who had participated in our previous study of APOE and PET[1]

1. Small et al, 1997

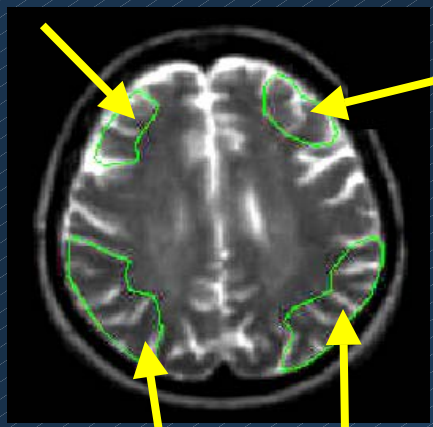
# Assessment of Estrogen Exposure

- **Endogenous** exposure: ages at menarche and menopause, parity, and menopause type
- **Exogenous** exposure: ET/HT type and duration
- Subject's length of reproductive life calculated by subtracting the age at menarche from the age at menopause.

# Regions of Interest

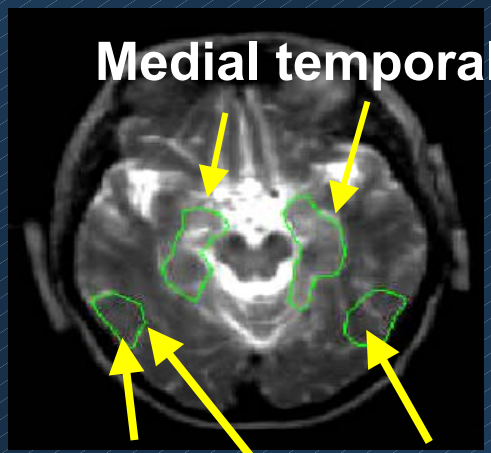


Posterior cingulate



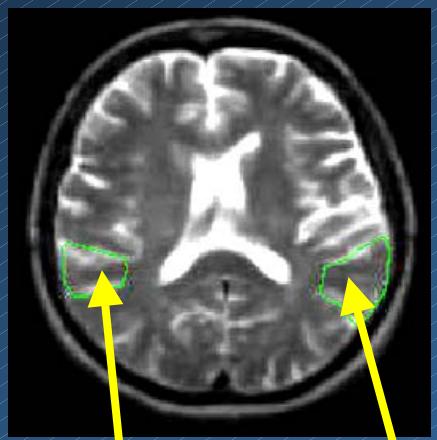
DLPFC

parietal



Medial temporal

Lateral temporal



Lateral temporal

# ROI Analysis

- Computed a repeated measures analysis of covariance
  - subject group and APOE-4 status as inter-subject classification variables
  - region of interest as intra-subject classification variable
  - Age a covariate in all analyses
  - All tests were two-tailed with a significance level of $<0.05$.

# SPM Analysis

- Nine regions were specified *a priori*, based on previous published results: posterior cingulate, left and right inferior parietal, left and right medial temporal, left and right lateral temporal, left and right dorsolateral prefrontal cortex.
- Analyses involving pre-specified regions were considered significant at $p \leq 0.005$. Voxels outside of those regions were regarded as significant only if $p < 0.05$ after Bonferroni-type correction for multiple comparisons based on entire set of over 125,000 cubic voxels (8 mm3 each).

# Results for Both Studies

#1:

- Estrogen users mean age = 65.5, SD=9.5
- Non-users mean age =71.8, SD=9.2
- Men mean age = 66.91, SD=7.1

#2:

- Estrogen users mean age = 60.36, SD=7.30
- Non-users mean age = 71.11, SD=8.77

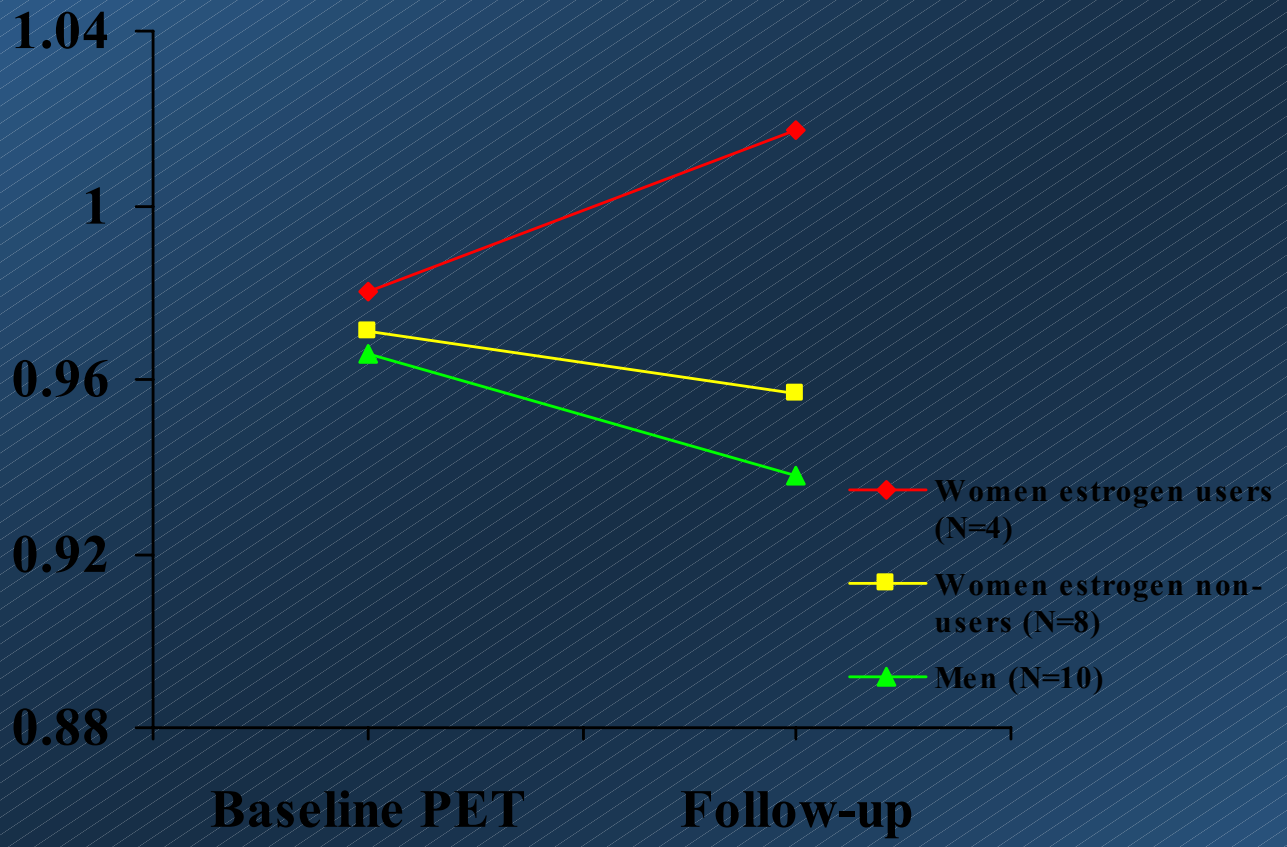
MMSE and memory (Buschke-Fuld), Delayed Paragraph recall and Benton Visual Errors) performance scores for all subjects were **within the normal range** for cognitively intact persons of the same age and educational level

# Results (cont.)

In both studies, no differences were found between women estrogen users and non-users in:

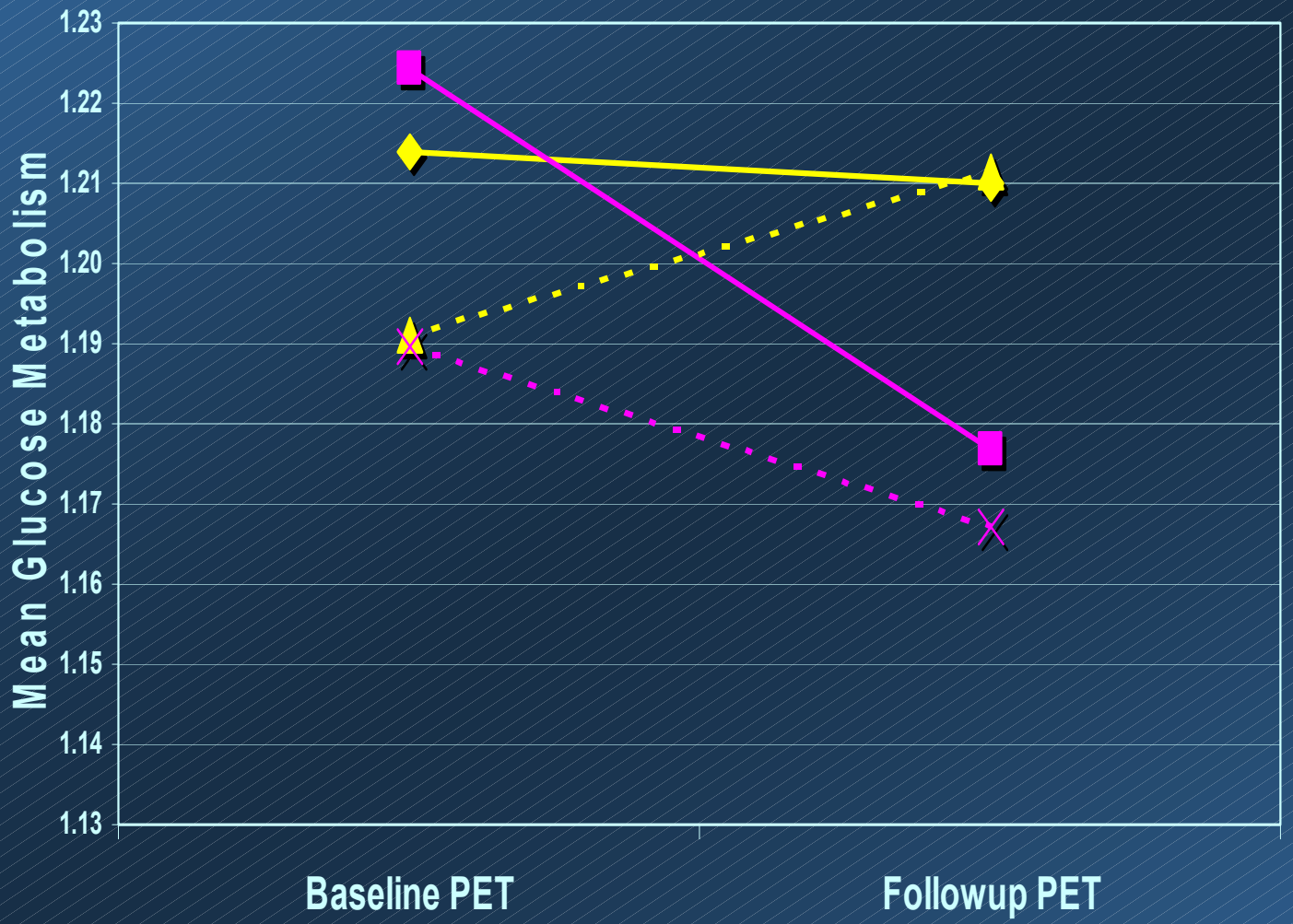
- Parity
- Length of reproductive life
- Body mass index
- Level of educational attainment

# Study #1 ROI Analysis




A group difference in metabolism in the lateral temporal cortical region (F=4.93, df=2,14, P=0.024).

# Study # 2 ROI Analysis




Estrogen Users (LPC)

Non-Estrogen Users (LPC)

Estrogen Users (RPC)

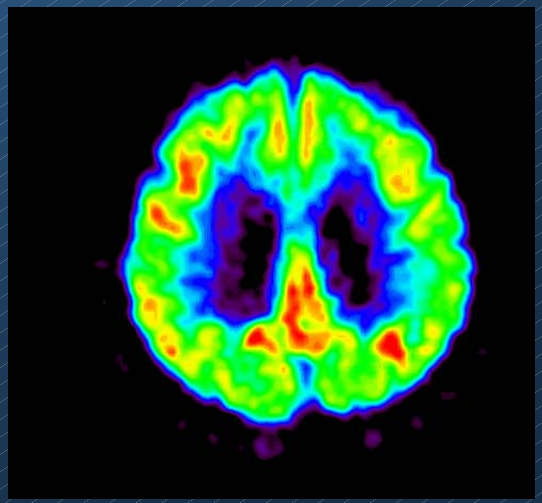
Non-Estrogen Users (RPC)

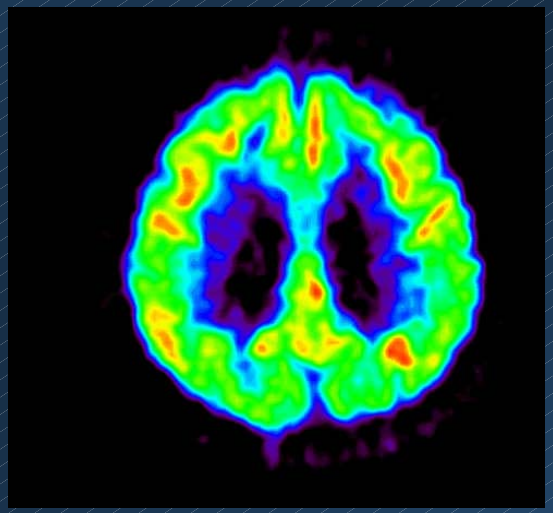
Left Posterior Cingulate = LPC

Right Posterior Cingulate = RPC

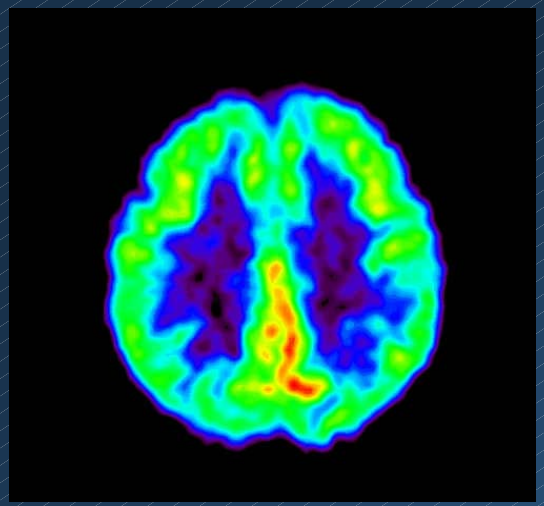
# Posterior Cingulate and Estrogen Use

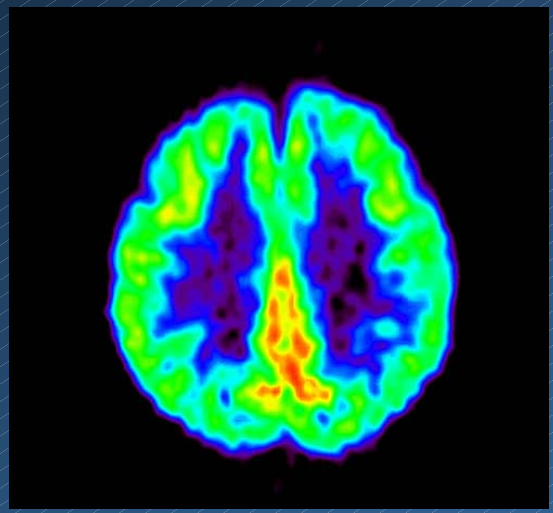
PC Decline in Estrogen Non-User





No PC Decline in Estrogen User





Baseline

Follow-up

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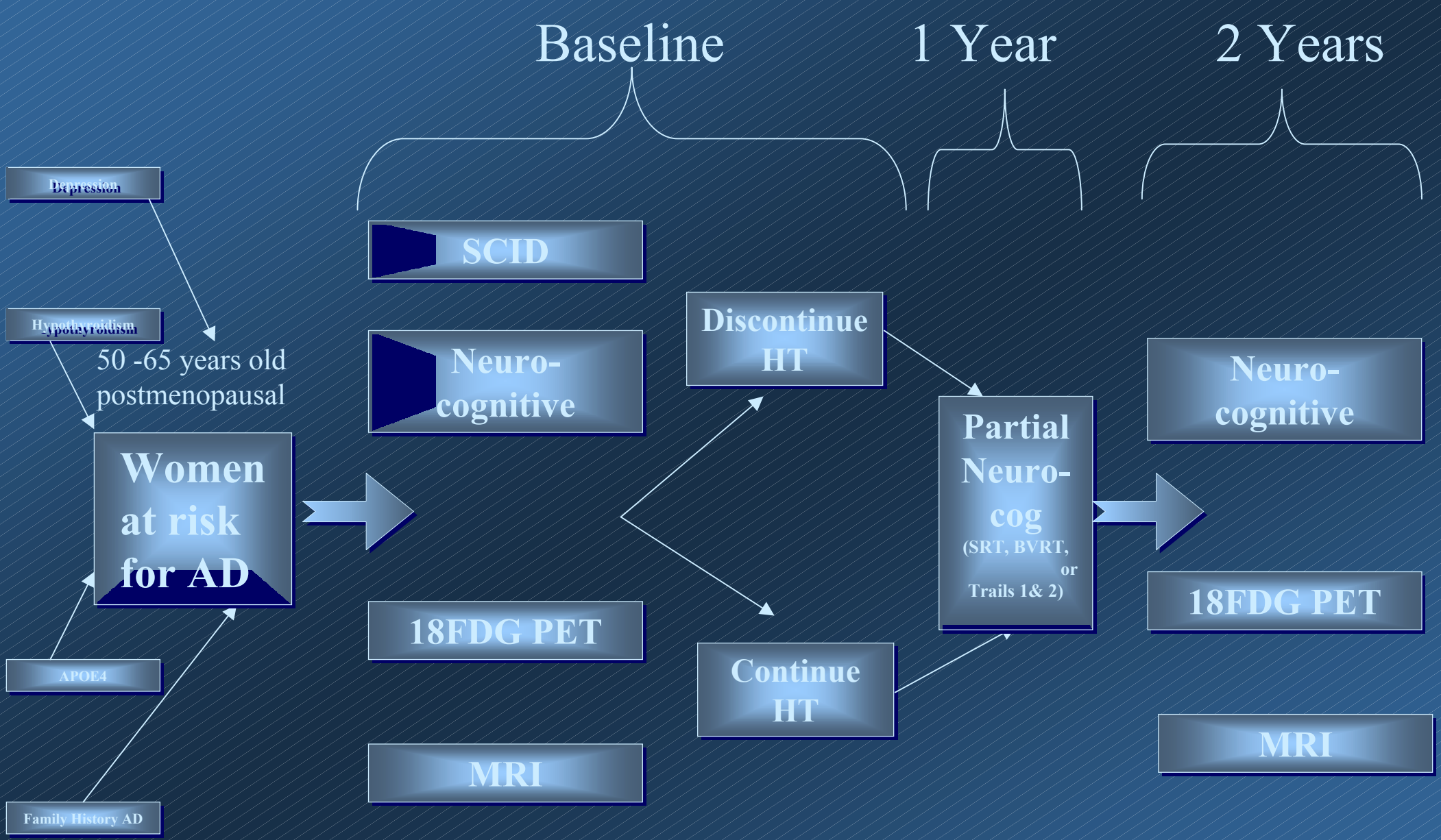


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# Conclusions:

- Decreased posterior cingulate metabolism is associated with higher risk of developing progressive cognitive impairment -- whether in the context of hypothyroidism, in asymptomatic subjects at genetic risk for AD, or hypoestrogenism.
- HT use may be protective of posterior cingulate metabolism in hypoestrogenic (postmenopausal) women at risk for AD