McKnight Brain Aging Registry-Cognitive Core: Update and preliminary findings

Ronald A. Cohen, PhD, ABPP, ABCN
Evelyn McKnight Chair of Clinical Translational Research in Cognitive Aging

Professor, Aging and Geriatric Research, Neurology, and Psychiatry

Director, CAM-CTRP

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Cognitive Aging & Memory
Clinical Translational Research Program

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Acknowledgement

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Cognitive Core: Background and Rationale

Background

- Compelling need for studies in advanced aging that adequately screen out early neurodegenerative disease and that expand on the findings presented today.
- Memory and visual functions need to be assessed in a more comprehensive manner
- Metabolic studies (MRS) of factors that influence age-associated cognitive and brain changes
- Support collaborative efforts between the CAM-CTRP and AMRL programs to inform and advance clinical-translation in these areas.

Background

- Compelling need for studies in advanced aging that adequately screen out early neurodegenerative disease and that expand on the findings presented today.
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MBRF Brain Aging Registry

- MBRF funded the four MBI institutes for an inter-institute initiative to develop this registry
- The registry focuses on successful aging in people over the age of 84
- There are currently limited normative data either with respect to cognitive or neuroimaging
- We will expand the cognitive assessment described earlier and focus on different forms of memory and other cognitive functions
- We will collect multimodal imaging across sites

Preliminary Findings:
ACTIVE BRAIN STUDY:

ACTIVE BRAIN COHORT

- Community dwelling older adults
- No evidence of significant cognitive or functional decline
- No evidence of primary amnestic disorder
- Not meeting criteria for MCI (clinical history and screen)
- No history of major medical problems (CVD, Stroke, etc.)
- Not Frail – Mobility WNL

- Current sample consists of 155 participants
- Mean age = 76.6 $\pm$ 12.3 yrs.
- Women = x; Men = x
- MoCA (mean) = 26.5 $\pm$ xx

Assessments

- Medical history
- Neurocognitive battery
- Psychological, behavioral & functional measures
- Neuroimaging
- Laboratory biomarkers (serum)

Neurocognitive Battery

- NIH-Toolbox (Cognitive Module)

- MMSE
- Montreal Cognitive Assessment (MoCA)
- California Verbal Learning Test (CVLT-2)
- WMS- logical memory
- Boston Naming Test
- Semantic and Letter Fluency Tests
- Adaptive Rate Continuous Performance Test (ARCPT)
- Trail Making
- Stroop Test
- Letter-Number Sequencing
- Digit Symbol Coding
- Symbol Search
- Matrix Reasoning Subtest
- Block Design Subtest
- Pegboard Dexterity Test
- Grip Strength Test

NIH Toolbox: Cognitive

- NIH-funded development
- Battery of 9 cognitive tests assessing six cognitive domains
  - Fluid Cognition
    - Attention
    - Executive Function
    - Working Memory
    - Processing Speed
    - Episodic Memory
  - Crystalized Cognition
    - Language
- Norms for 8-85 years of age

Behavioral and functional assessement

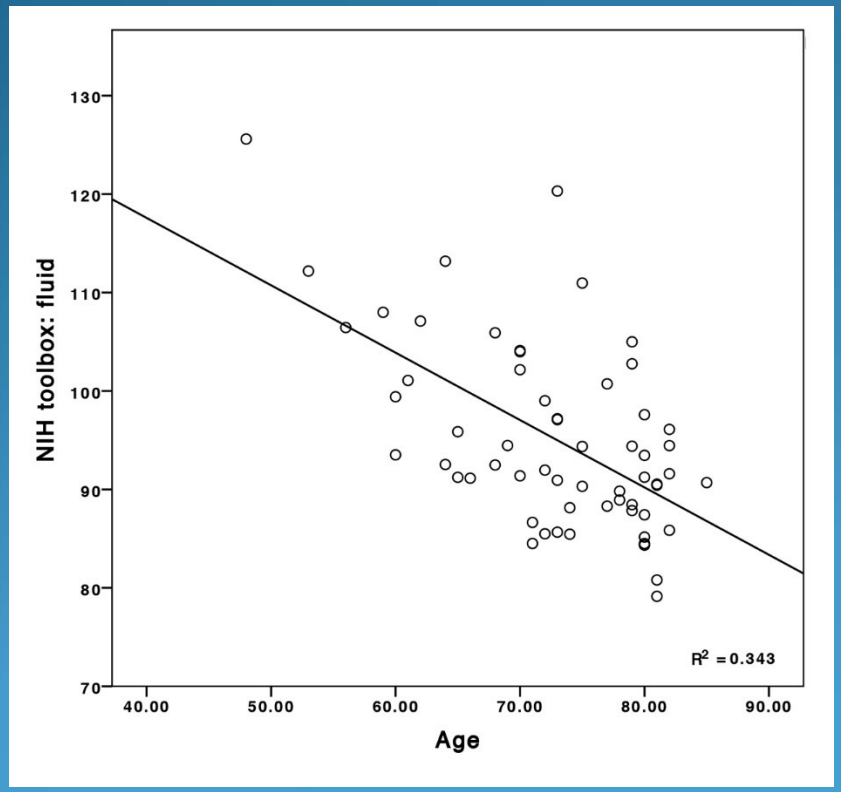
- Daily Activity Questionnaire (CHAMPS)
  Cognitive, Physical, Social Domains
- Beck Depression Scale
- UCLA Loneliness Scale
- Pain Questionnaire

Neuroimaging Assessment

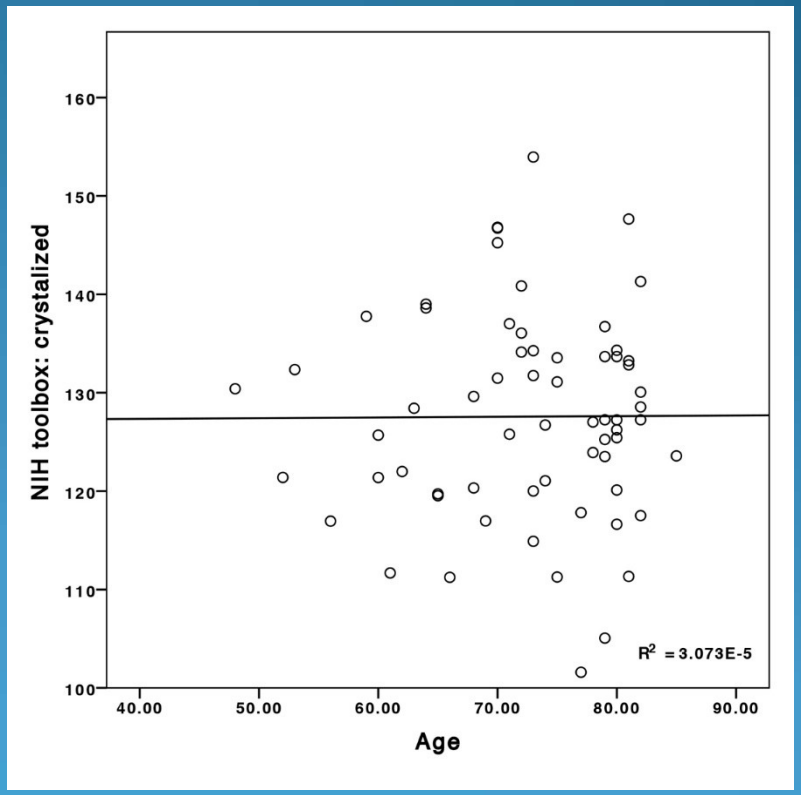
- Scout + parameter setup =~ 3 min
- Sensitivity Reference scan =~2.5 min
- MPRAGE =~ 5 min x 2
- FLAIR =~ 3 min
- ASL =~ 5 min
- Phase contrast =~ 2min +1.5 min locator
- BOLD =~ 2 * 5 min resting state OR 18 min for Task +rest
- DTI = ~ 10 min
- MRS =~ 10 min/~1 ROI (Frontal and Parietal)

NIH Toolbox: Cognitive Aging

Fluid Cognition Score*



Crystalized Cognition



*p<.05

NIH-TB and MoCA

- MoCA = 26.2 ± 2.3 (orientation, language, visual intact)
- Crystalized Cognitive = 123.5 ± 5.3
- Fluid Cognitive = 99.6 ± 10.3

- MoCA – NIH-TB Fluid strongly correlated
- MoCA – NIH-TB Crystalized weakly correlated
- MoCA and MoCA-memory associated with TB-AVLT
- Multiple NIH-TB measuers relate to MoCA and MoCA subdomains (Attention-Executive, Memory)

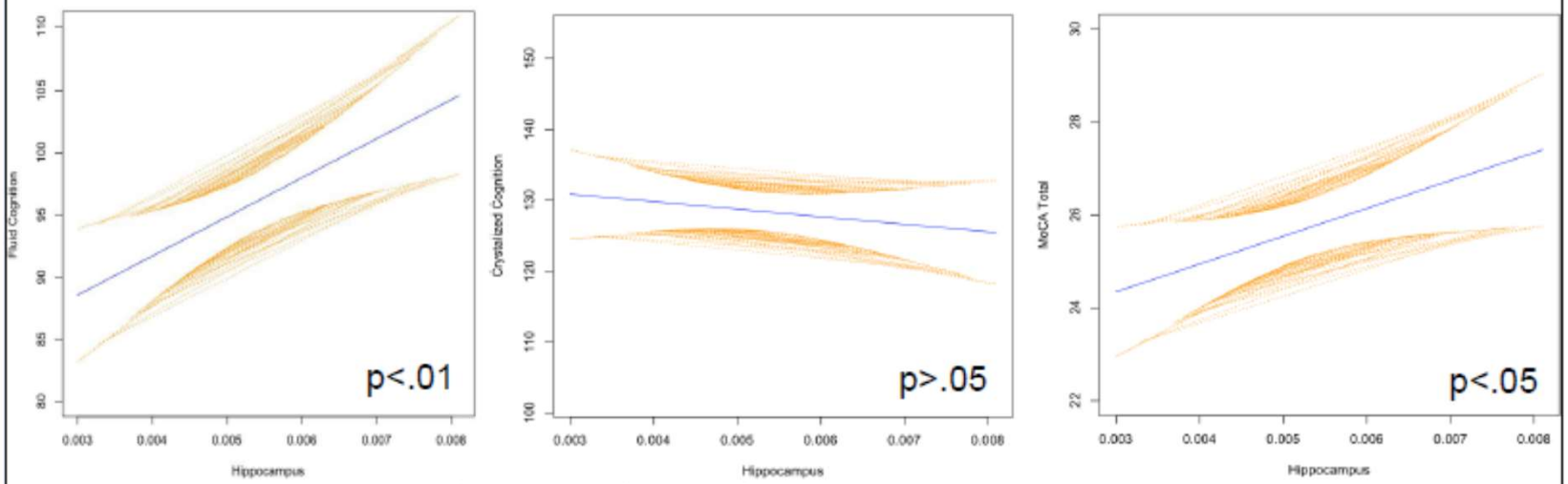
Brain volumes and age

Brain ROI	Correlation (by age)
Hippocampus*	-.48
Parahippocampus*	-.42
Entorhinal Cortex	-.10
ACC *	-.46
MTC *	-.38

* $p < .001$ ACC = anterior cingulate; MTC = medial temporal cortex

Findings: Hippocampus and NIH-TB

Results



Task	Variance Explained	p-value
dimensional change card sort	0.09	0.01
picture sequence memory	0.12	0.004
pattern comparison	0.14	0.002
flanker	0	0.86
list sorting	0.04	0.1
Rey verbal learning	0.16	0.0008
symbol digit search	0.06	0.04

Task	Variance Explained	p-value
MoCA-delayed recall	0.1	0.009
MoCA-attention	0	0.82
MoCA-visuspatial/executive	0.04	0.13

Freesurfer ROIs tested in model

- Hippocampus
- Entorhinal
- Parahippocampal
- Anterior Cingulate Cortex
- Insula
- Medial Temporal Cortex
- Thalamus

Overall cognitive functioning and brain volume

(R = .45)	Beta
Age *	-.32
ACC *	.35
Parahippocampus*	.32

* $p < .01$ ACC = anterior cingulate; MTC = medial temporal cortex

Fluid cognitive function and brain volume

(R = .53)	Beta
Age *	-.50
ACC *	.35
Parahippocampus *	.26

* $p < .05$ ACC = anterior cingulate

Crystalized cognitive function and brain volume

Brain ROI	Beta
-	-

* Neither age or brain volumes retained in the model ($p > .20$)

Verbal learning (AVLT) as a function of brain volume

R = .53	Beta
Entorhinal Cortex *	.32
Age *	-.36

Regions retained in regression model are shown (p <.01)

Visual memory and brain volume (Picture Sequencing)

R = .45	**Beta**
Age **	-.35
Insula *	.24

* $p < .05$; ** $p < .01$

Executive functioning (Sorting) and brain volume

R = .60	Beta
Age*	-.48
Parahippocampus*	.41
ACC	.39
Insula *	.30
Thalamus *	.41

Executive functioning (Sorting) and brain volume

R = .60	Beta
Age*	-.48
Parahippocampus*	.41
ACC	.39
Insula *	.30
Thalamus *	.41

Attention-Executive function (Flanker Task) and brain volume

R = .36	Beta
Age*	-.36
Parahippocampus*	.34

Focus and Processing Speed (Coding) and brain volume

R = .60	Beta
Age*	-.46
Hippocampus*	.36
Thalamus *	.49

Visual Processing Speed (Pattern Comp.) and brain volume

R = .60	Beta
Age*	-.30
ACC *	.50
Fusiform *	.35
Parahippocampus *	.32
Entorhinal Cortex *	.30

Frontal metabolites (MRS) and brain volume

	Beta
Hippocampus	
NAA	.50
Parahippocampus	
NAA	.62
Myo-inositol	-.43
Entorhinal (NS)	-

Summary

- Age associated with reduced volume of the hippocampus, PC, and most other ROIs, but not EC volume
- EC volume but not PC volume significantly associated with verbal memory performance on AVLT.
- PC volume associated with performance on symbol coding, flanker task, and pattern comparison.
- Frontal NAA concentrations (MRS) associated with PC and hippocampal volume, but not EC volume.
- Different relationships exist for EC, PC and other paralimbic-associated regions relative to memory and other cognitive functions (NIH-TB) in the context of aging.

Cognitively Engaging Activity is Associated with Preserved Cortical and Subcortical Volumes

Talia R. Seider, Robert Fieo, Adam J. Woods, and Ronald A. Cohen

Figure 1. Sample CHAMPS test item

Table 1. Cognitive activities assessed by CHAMPS

Reading
Using a computer
Doing arts/crafts
Playing a musical instrument
Attending a concert/movie/lecture/sport event

Results

- More time spent in cognitive activity was associated with larger volumes of all brain regions studied (see Table 2).
- These effects remained even after accounting for the positive association between cognitive activity and education.
- No other activity variable was associated with brain volumes, however more heavy physical activity was associated with younger age and male gender.

Table 2. Regression coefficients for brain volume associations with cognitive activity

	β	p
Frontal lobe	.276	.019
Parietal lobe	.305	.009
Occipital lobe	.256	.030
Temporal lobe	.275	.020
Total cortex	.289	.014
Thalamus	.310	.010
Caudate	.233	.049
Hippocampus	.286	.017
Amygdala	.336	.004

Cognitively Engaging Activity is Associated with Preserved Cortical and Subcortical Volumes

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Results

- Greater time spent in social activities was associated with more words recalled on the CVLT-II short delay free recall ($F(1,63) = 5.1$, $p = .027$, $R^2 = .075$) and long delay free recall ($F(1,63) = 10.5$, $p = .002$, $R^2 = .129$) (Figure 1).
- Social activity was measured on an ordinal scale with 6 options reflecting ranges from 0 – 9+ hours per activity per week (Figure 2).
- Follow-up linear regressions showed no association between social activity and other cognitive domains.
- The relationship between social interaction and memory was not explained by age, BDI, or general cognitive functioning.

Figure 1. Positive association between social activity and memory

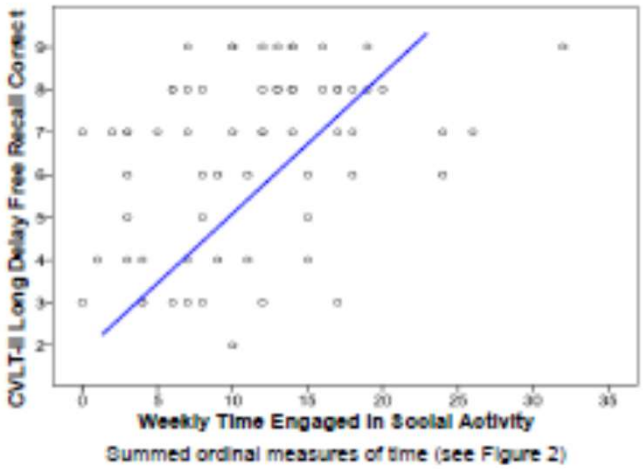

Figure 2. Sample CHAMPS test item

Summary of findings

- Time spent on a daily basis engaged in cognitive tasks associated with cortical and subcortical volumes
- This relationship was not found for social or physical activities
- NIH-TB Fluid measures and CHAMPS cognitive activities were also significantly associated
- Social activity associated with verbal memory performance
- Physical function associated with caudate volume

Frontal neural correlates of working memory performance in older adults

- Working memory is an executive memory process that allows transitional information to be held and manipulated temporarily in memory stores before being forgotten or encoded into long-term memory.
- The current study aimed to determine the neural correlates of working memory decline in the frontal lobes by comparing cortical thickness and cortical surface area from two demographically matched groups with high versus low N-Back working memory performance (N=56).
- High-resolution structural T1-weighted images (1mm isotropic voxels) were obtained on a 3T Philips MRI scanner.

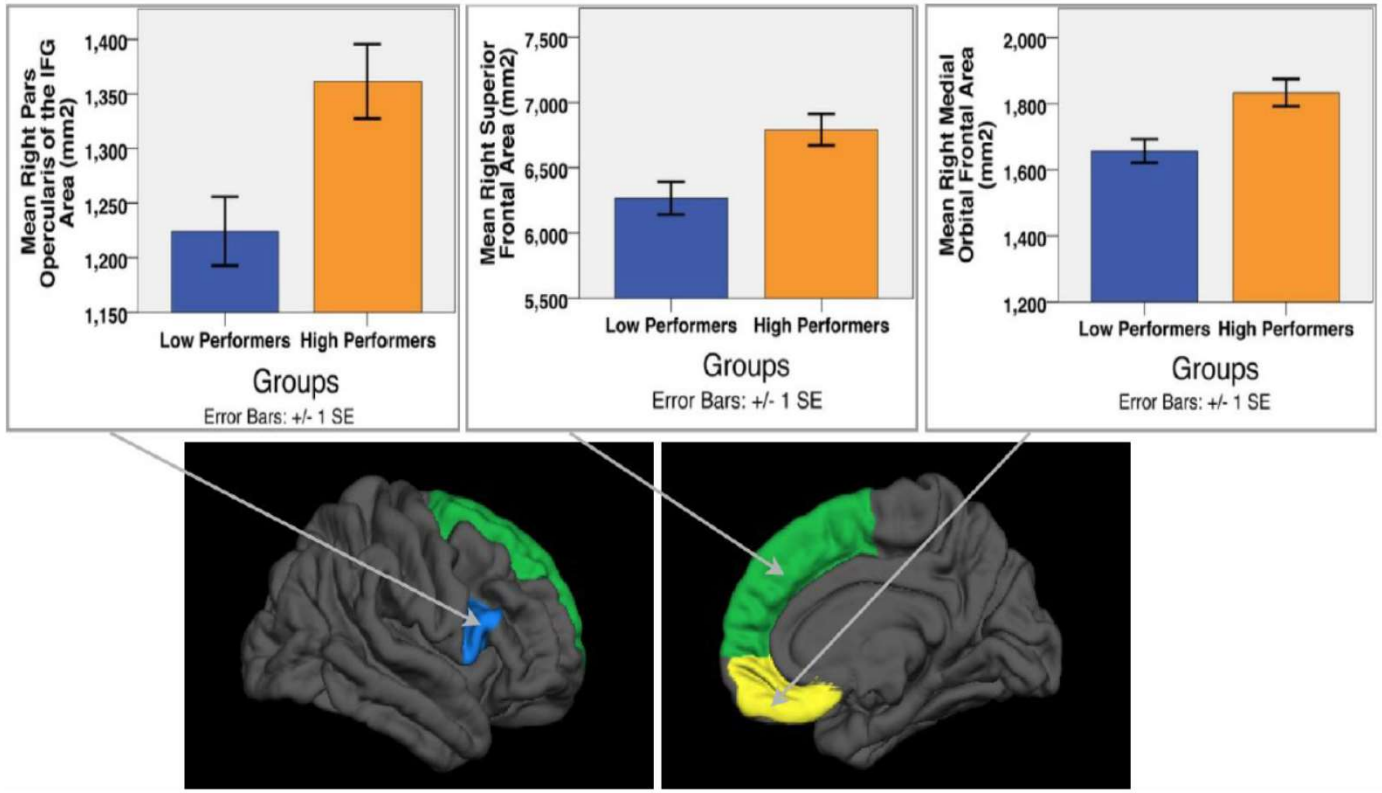

Figure 3. Bar graphs depicting three significantly different cortical surface areas when comparing low versus high working memory groups. Graphs point to the significant gyri highlighted on a FreeSurfer brain model (IFG=inferior frontal gyrus).

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Default mode deactivation and cognitive function in older adults

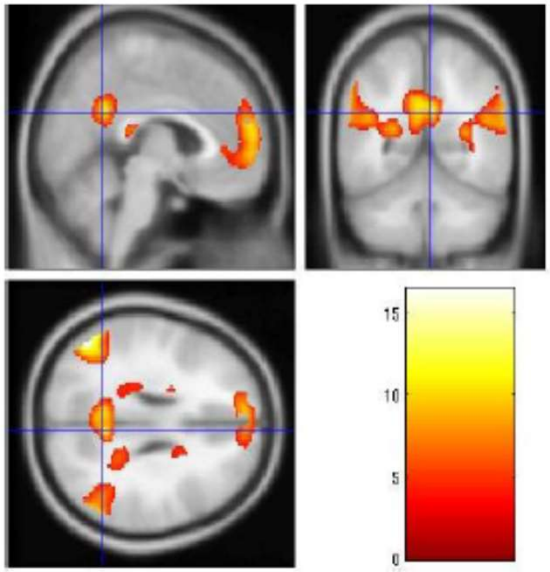
The Default Mode Network (DMN) of the brain has been described as a set of regions that are more active at rest than during task. Studies of the DMN in older adults suggest alterations in both activation and connectivity. Older adults typically demonstrate decreased ability to inhibit the DMN during task, as well as decreased connectivity between anterior and posterior nodes. Generally, though, the more the DMN is inhibited (i.e. greater "swing" between the activation patterns while on- and off-task), the better the performance on cognitive tasks. We hypothesized, therefore, that greater DMN activation at rest (i.e. greater "swing") would be positively associated with intelligence measures.

Sample

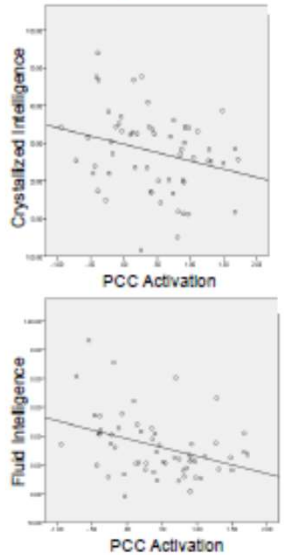
Participants

- **Sample**: N = 69 older adults
- **Age**: M = 72.9 (SD = 9.6 years)
- **Education**: M =16.1 (SD = 2.75)
- **Sex**: 44.9% Male

Results



Areas of activation Rest > Task, whole brain $p < .0001$



Region-Variable	R-Value	p value	R^2
PCC-Crystallized	-0.27	< .05	0.08
PCC-Fluid	-0.37	<.05	0.14

- Activation of the PCC was significantly negatively correlated with both fluid and crystallized intelligence. No other measures were significantly related to DMN activation.

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Results

- Compared to High performers, low performers exhibited significantly decreased cortical surface area in three frontal lobe regions lateralized to the right hemisphere: medial orbital frontal gyrus, inferior frontal gyrus, and superior frontal gyrus (FDR $p<.05$).
- No significant differences in cortical thickness between groups, a proxy for neurodegenerative tissue loss.
- Results suggest that decreases in cortical surface area (a proxy for brain structural integrity) in right frontal regions may underlie age-related decline of working memory function.

Discussion

- Older Adults demonstrated robust Default Mode Network activation during fixation periods of a visual memory task.
- The amount of activation in the PCC was negatively correlated with NIH toolbox measures of crystallized and fluid intelligence.
- Other regions of the Default Mode Network were not significantly correlated with offline measures of intelligence.
- Contrary to our hypothesis, older adults with better performance on measures of intelligence demonstrate decreased "swing" of the DMN during a visual memory task.
- This pattern suggests that they may not fully disengage from the task during periods of fixation. Rather, participants with higher intelligence scores may have been actively rehearsing the stimuli they would be asked to recall later.

Where do we go from here?" Answering the need for studies of successful cognitive aging

Thank you