PINK-BRAIN PROJECT: Biomarkers of Response to Yoga for Prevention of Cognitive Decline in Older Women

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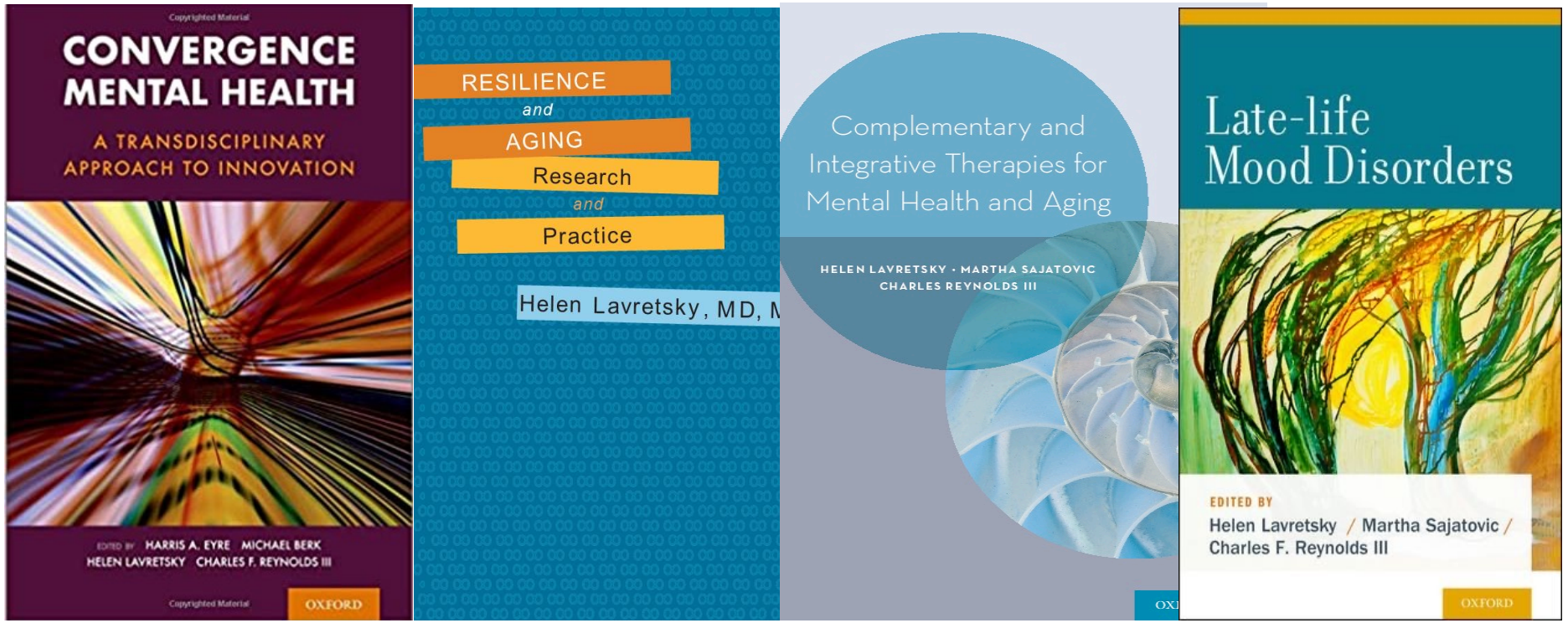


Pink Brain Project

- To date, no studies of yoga have targeted women at high risk for AD (e.g., postmenopausal with SCD and cardiovascular risk factors)
- Aim: Investigate the efficacy and neurobiological mechanisms of response to KK+KY compared to MET on memory performance at 12- and 24-weeks in women at high AD risk.
- Secondary clinical outcomes examined include mood, resilience, and quality of life.
- Biomarkers- inflammatory and neuroimaging

Inclusion/Exclusion criteria

INCLUSION CRITERIA

- Self-reported subjective cognitive decline (SCD) from the prior year's functioning;
- One or more cardiovascular risk factors, including >=7.5th percentile on the ASCVD risk calculator using the Cerebrovascular Risk Factor Prediction Chart and hematologic testing;
- Current pharmacological treatment for blood pressure (>140/90); or hyperlipidemia (LDL>160);
- Sufficient English proficiency to comprehend the intervention instructions and materials

EXCLUSION CRITERIA:

- Prior history of serious psychiatric illness
- Surgery within the past three months or planned surgery within the next year, as well as unstable medical conditions
- Dementia
- Prior experience with Kundalini yoga (KY) and Kirtan Kriya (KK)

Outcome Measures

Cognitive:

- Verbal memory: HVLT; WMS-IV
- Visual-spatial: Rey-O
- Executive function: TMT-B, Stroop Word-Color, Animal Naming.

Mood and Other:

- GDS, AES, CD-RISC

Brain MRI

Moderators: Inflammatory Cytokines and AD biomarkers

Time:

- Baseline, 12 weeks, 24 weeks

Inflammatory mechanisms in depression and cognitive decline

- Inflammation is associated with an increased risk of depression and cognitive in older adults.
- Peripheral whole blood samples were collected at baseline, 12-weeks, and 24-weeks follow-up for RNA sequencing and cytokine/chemokine assays; and in Tai Chi at baseline and 12 weeks.
- Human 38-plex magnetic cytokine/chemokine
- IL-1RA, IL-10, IL-1α, IL-1β, IL-6, IFN-α2, TNF/TNF-α, TNF-β/LT-α, sCD40L, IL-12p40, IFN-γ, IL-12/IL-12p70, IL-4, IL-5, IL-13, IL-9, IL-17A, GRO/CXCL1, IL-8/CXCL8, eotaxin-1/CCL11, MDC/CCL22, fractalkine/CX3CL1, IP-10/CXCL10, MCP-1/CCL2, MCP-3/CCL7, MIP-1α/CCL3, MIP-1β/CCL4, IL-2, IL-7, IL-15, GM-CSF, Flt-3L/CD135, G-CSF, IL-3, EGF, FGF-2, TGF-α, and VEGF.

- RNA sequencing

- Five factors were derived using factor analysis. General linear models were estimated to examine the change in factor scores and the association of these changes on depression or changes in cognition, controlling for age, sex, and body mass index.

Yoga

Kundalini Yoga (KY):

- 60 mins per week, 8 – 10 group.
  - Tuning In; Warm Up; Breath Techniques; Kirtan Kriya; Meditation; Rest.

PLUS

Kirtan Kriya:

- Daily homework, 12 mins.
  - Finger movements, mantras, deep breathing.

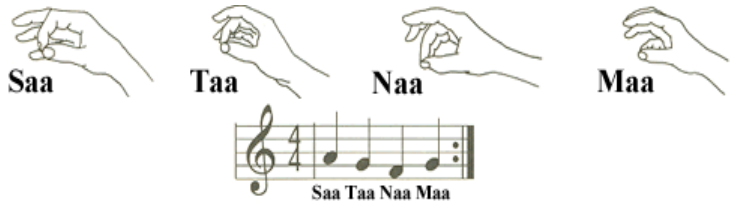
What is Kirtan Kriya?

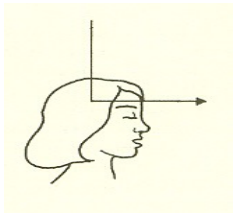
- **Kirtan Kriya** is a 11-minute chanting exercise in the Kundalini yoga tradition that people have been practicing for thousands of years. This meditation involves repetitive finger movements, or mudras, plus verbal chanting and silent chanting of the mantra "Saa Taa Naa Maa."

- **What does Kirtan Kriya mean in English?**
  A kirtan is a song. These ancient primal sounds from Sanskrit mean "birth, life, death, rebirth." Kriya refers to a specific set of movements or chants.

KirtanKriyaMeditation.wma

- The physical benefits of the mantra are:
- Saa evokes a sense of expansiveness
- Taa creates a feeling of strength
- Naa stimulates a sense of the universal
- Maa provides the quality of communication.
- In the yogic tradition, kriyas are used to help bring the body, mind, and emotions into balance, thus creating healing.





•Focus of attention

Memory Enhancement Training (MET)

- ‘Gold standard’.
- Developed by UCLA Longevity Center.
- Verbal and visual association strategies and practical strategies for memory.
- Weekly group session of 60 mins and daily homework (memory exercise for about 15 min a day).

Baseline Charcateristics

Characteristic	KK+KY[1] (N=40) Mean (SD) or N(%)	MET[1] (N=39) Mean (SD) or N(%)
Age, years	65.45 (9.11)	67.54 (9.30)
Race: White	27 (68%)	25 (64%)
Education, years	16.15 (1.90)	15.72 (1.99)
Clinical Characteristics		
BDI	7.28 (4.73)	7.49 (5.06)
BMI	26.44 (5.13)	28.01 (6.75)
CD-RISC	76.31 (11.68)	74.74 (13.78)
CVRF	9.72 (4.87)	10.44 (4.37)
MMSE	28.46 (1.71)	28.41 (1.09)
Cognitive Domains		
Delayed recall	0.14 (0.90)	-0.14 (1.07)
Executive functioning	0.08 (0.89)	-0.07 (1.10)

EFFECT SIZES

Measure	12-Week Follow-up Effect Size (95% CI)[1-2]	24-Week Follow-up Effect Size (95% CI)[1-2]
BDI	0.16 (-0.37, 0.68)	0.17 (-0.34, 0.69)
CD-RISC	-0.16 (-0.69, 0.36)	0.05 (-0.47, 0.57)
CVRF	-0.28 (-0.80, 0.25)	
HAM-A	0.28 (-0.24, 0.79)	-0.23 (-0.73, 0.28)
MFQ		
Frequency of Forgetting	-0.49 (-1.03, 0.05)	-0.28 (-0.80, 0.25)
Seriousness of Forgetting	-0.28 (-0.82, 0.25)	-0.73 (-1.26, -0.19)
Cognitive Domains		
Delayed recall		0.69 (0.17, 1.21)
Executive functioning		0.01 (-0.49, 0.52)

At 24-weeks follow-up, YOGA yielded a significant, large effect size improvement in subjective cognitive impairment compared to MET. But displayed a significant, large effect size decline in delayed recall at 24-weeks follow-up but no change in executive functioning.

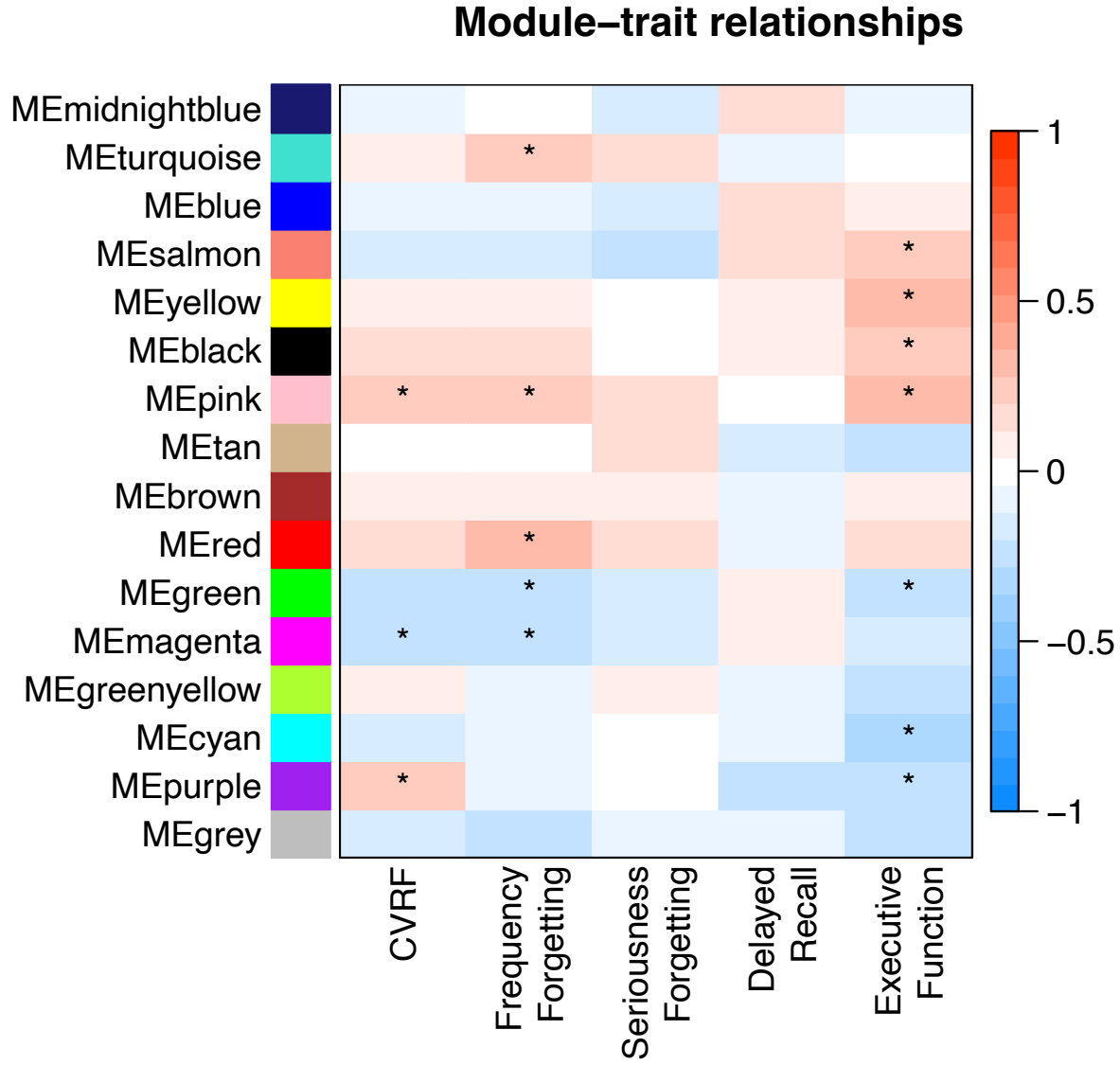
Chemokine/Cytokine Assay

12-Week Follow-Up	YOGA (N=18) Estimate (SD)	Within-Group Statistics	MET (N=27) Estimate (SD)	Within-Group Statistics
Eotaxin-1	-0.07 (0.7)	t(67)=-0.99, p=0.32	-0.11 (0.6)	t(67)=-2.12, p=0.04
FGF2	-0.44 (0.2)	t(67)=-2.5, p=0.01	-0.38 (0.2)	t(67)=-2.4, p=0.02
24-Week Follow-Up	**YOGA (N=26) Estimate (SD)**	**Within-Group Statistics**	**MET (N=32) Estimate (SD)**	**Within-Group Statistics**
Eotaxin-1	0.09 (0.07)	t(67)=1.31, p=0.19	-0.16 (0.6)	t(67)=-2.75, p=0.01

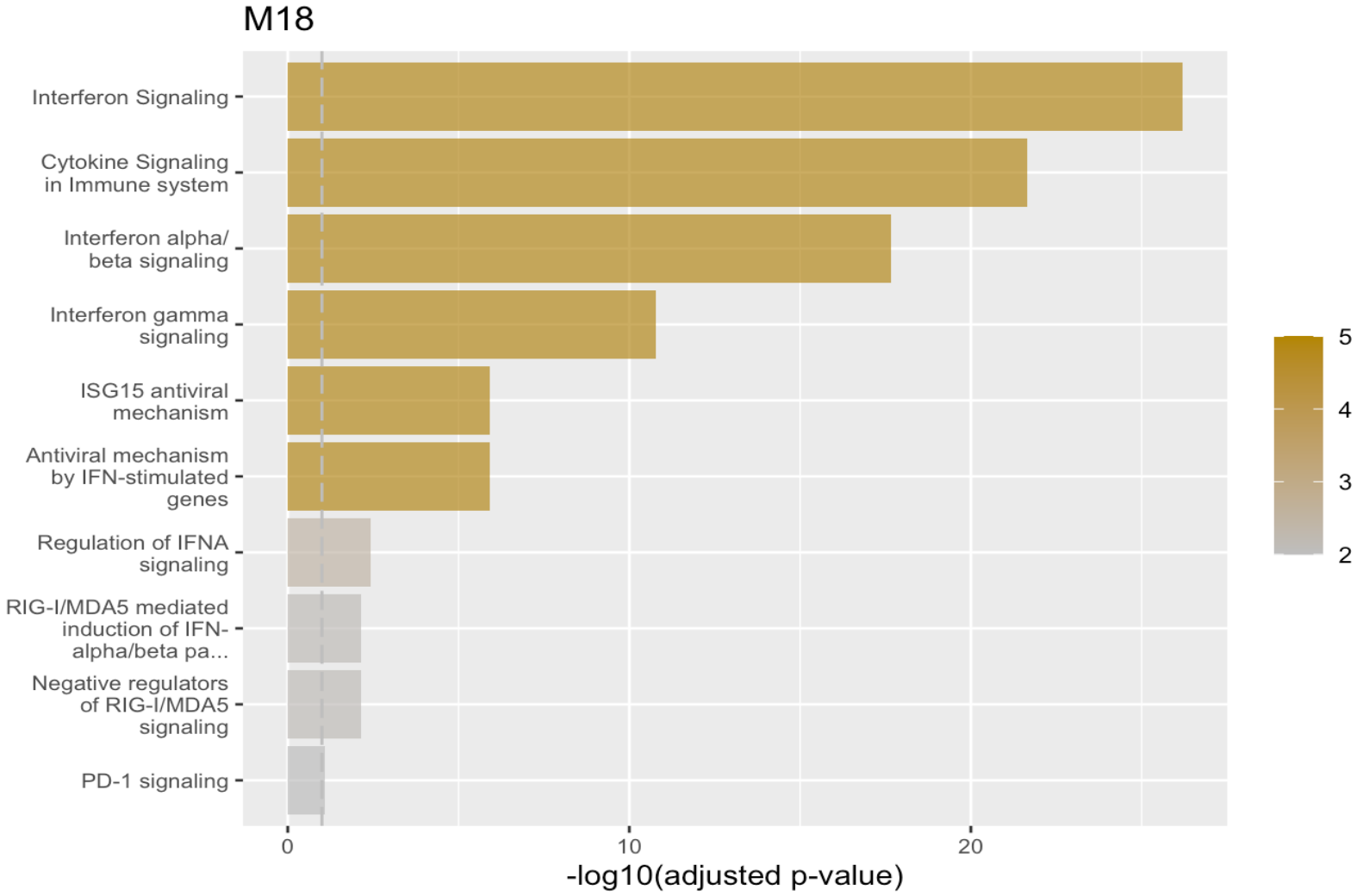
MET but NOT YOGA participants displayed higher Eotaxin-1 levels at 12- and 24-weeks follow-up. *Eotaxin-1 levels have previously been shown to increase in linear fashion with age and cognitive decline. In mouse models, higher eotaxin-1 levels correlate with impaired learning and reduced neurogenesis. Crosses the BBB to exert its effects on the brain.*

Both MET and YOGA participants showed higher FGF levels at 12- and 24-weeks follow-up. *FGF2 is neuroprotective. Decreased in the DLPFC & hippocampus in post-mortem MDD samples. Upregulated in response to anti-depressant administration.*

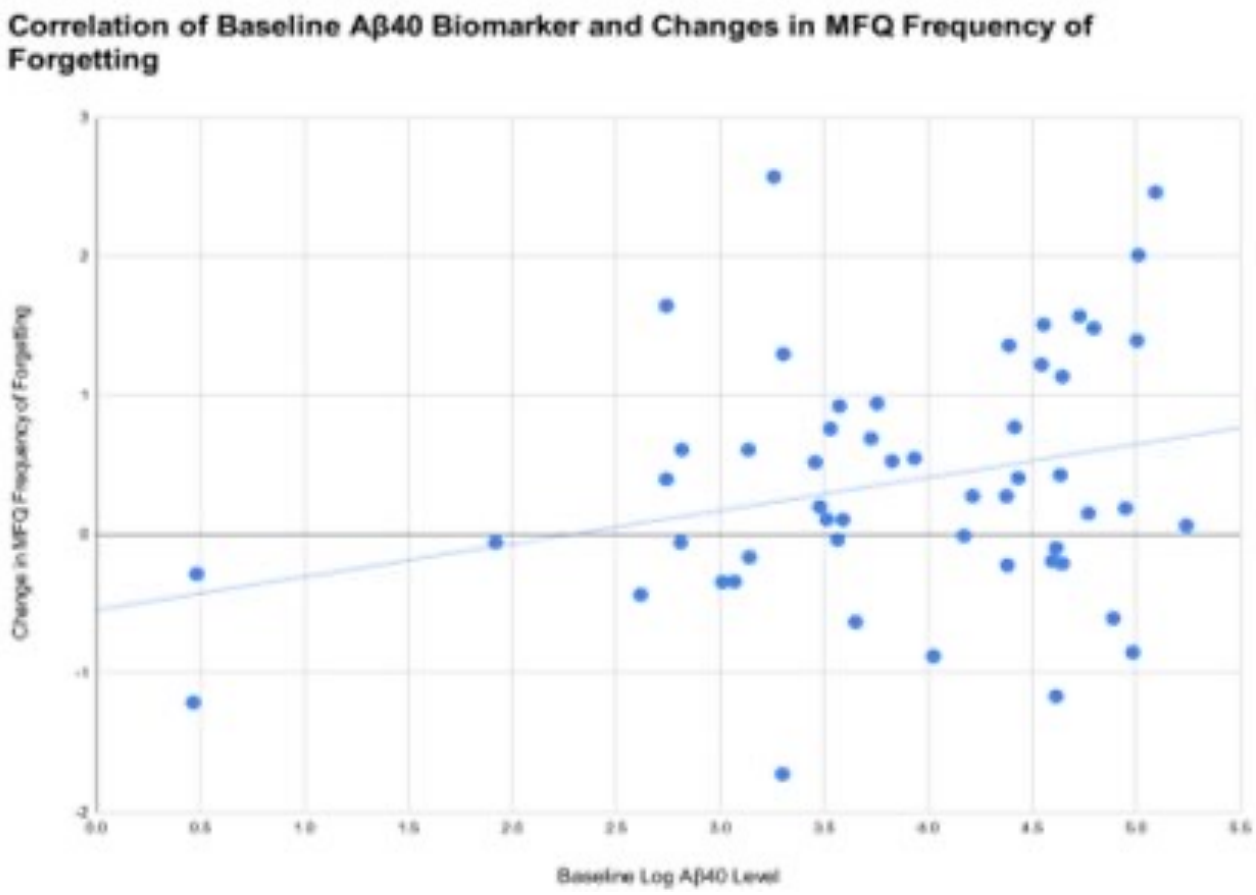
WGCNA indicates unique gene networks that are significantly correlated (* = p<0.1) with SCD, executive function, and CVRF.



High vs. Low SCD associates to regulation of inflammatory gene sets.



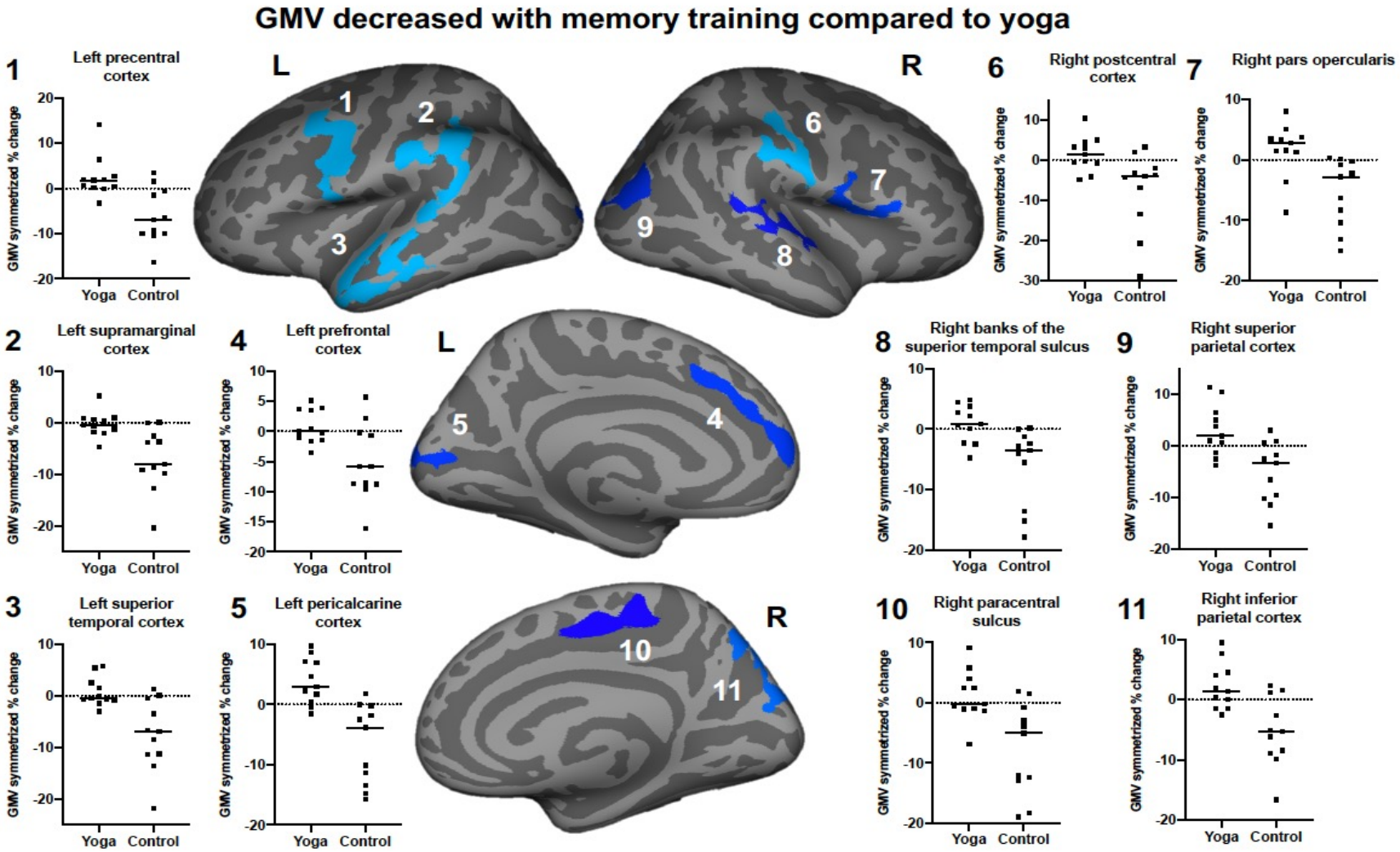
Baseline levels of Abeta40 were significantly associated with an increase in subjective memory decline (MFQ) (R=0.27; P=0.04)



An increase in Abeta40 was associated with decrease in depression (BDI) (r=-0.33; P=0.02)

Women 50+ with heart conditions and memory complaints

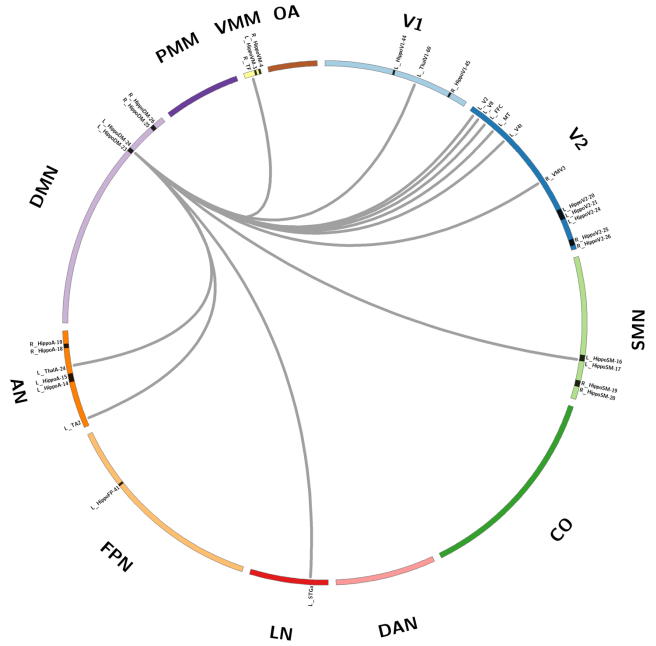
The Yoga group showed either no decline or increases in GMV the left precentral (1) and lateral occipital cortices (5) compared to **Memory training.**



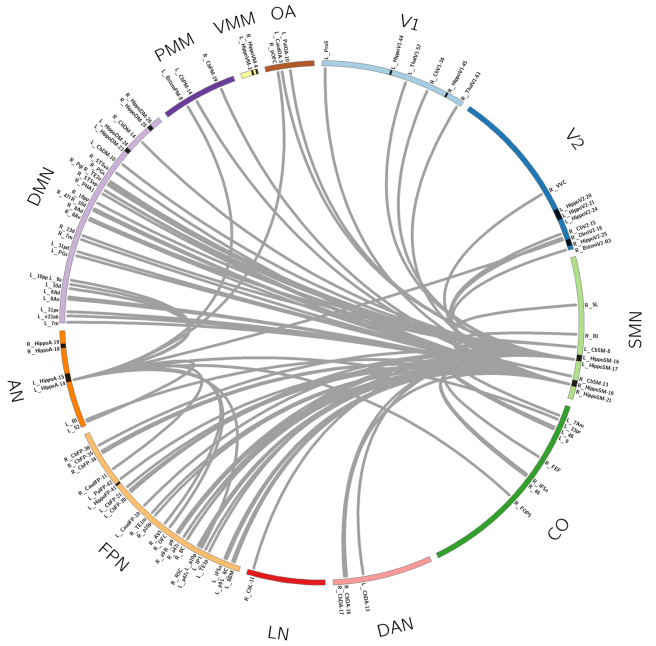
Results – Group differences in hippocampal connectivity changes

- Four hippocampal seeds showed significant differences in connectivity changes between the two groups (p<.001).
- Yoga>MET: An anterior hippocampal seed in the default mode network (DMN) showed significantly greater increases in connectivity with regions mainly in the visual system in the Yoga group than in the MET group.
- MET>Yoga: A posterior hippocampal seed in the auditory network, and two in the somatosensory network, showed significantly greater increases in connectivity with regions mainly in the DMN and frontoparietal network in the MET group than in the Yoga group.

Yoga>MET



MET>Yoga



Summary

- Postmenopausal women with cardiovascular risk factors are at high risk for SCD-MCI-AD trajectory
- YOGA improved seriousness of forgetting/SCD at 24-weeks
- SCD associates with pathways at the intersection of inflammation, mood, circadian rhythm, and cardiovascular function
- High SCD associates to increased enrichment and expression interferon/immuno-inflammatory genomic pathways
- Over 6-month follow-up, levels of aging/cognitive decline biomarker Eotaxin-1 continued to increase in MET, but not YOGA participants
- There were no group differences in AD biomarkers at baseline or at 24-week follow-up. Baseline levels of Aβ40 were associated with greater subjective memory (MFQ Frequency of Forgetting; $r = 0.27$, $p=0.04$) and anxiety. An increase in Aβ40 levels was significantly associated with a decrease in BDI ($r = -0.33$, $p=0.02$).
- **Neuroplastic effects:** neuroprtotective effects and increased anterior hippocampal connectivity
- Clinical and biological benefits to YOGA for SCD, linking changes in cognition to anti-inflammatory effects of yoga

Sponsors and collaborators

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- Collaborators:

- Linda Ercoli and Prabha Siddarth- cognitive analyses
- Katherine Narr, Lisa Kilpatrick, Beatrix Krause and Brain Mapping- fMRI
- Elaine Reed, Monica Capelletti, and Immunogenetics Center- inflammatory markers
- Steve Cole, Stan Nelson, Adrienne Grzenda, and Nelson Freimer- genetic analyses
- **Coordinators-** Michaela Milillo, Ashlyn Applegate, Raquel Hernandez, Katie Cho, Jillian Yeargin, Natalie St. Cyr, Yesenia Aguilar, Raquel Hernandez
- **Postdoctoral students**-Kelsey Laird, Beatrix Krause, Roza Vlasova, Bianca Acevedo, Amber Leaver, Anurag Pant, and Harris Eyre