Dietary Pattern and Health Relevant Outcomes (Animal Models)

Psychosocial Stress and Diet Composition Effects on Health and Aging in Nonhuman Primates

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I will be playing the following roles during this talk

Carol Shively, PhD
WFUSM

Brett Frye, PhD
Emory and Henry College, and WFUSM

Jacob Negrey, PhD
University of Arizona

Shively et al., 2023

Funding Provided by: NIH R01HL087103 (CAS), NIH RF1AG058829 (CAS)

Take home messages

- Diet composition has far-reaching effects on health.
- Adverse effects of psychosocial stress may be amplified by an unhealthy diet.
- Social isolation in older individuals may be mediated by neurobiological factors that are also affected by diet.

Long-tailed macaques respond to Western diets like humans

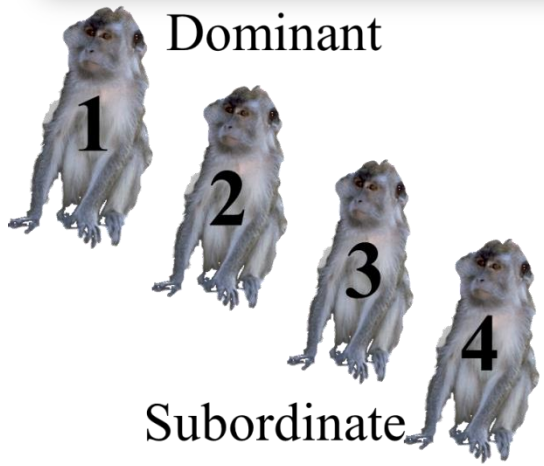
- ***Atherosclerosis[1]***
- ***Elevated sympathetic activity[2]***
- ***Blunted HR responses to acute stress[2]***
- ***Elevated cortisol reactivity[2]***
- ***Increased body fat & insulin resistance[3]***
- ***Hepatosteatosis[3]***

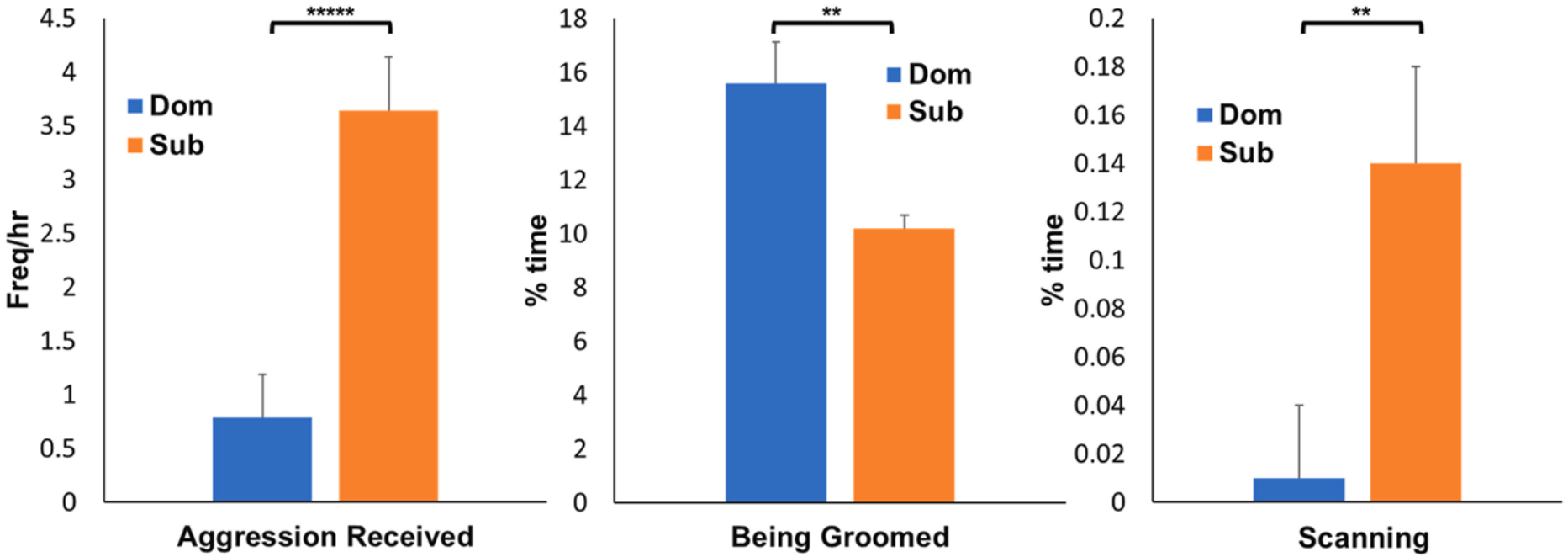
Cynomolgus macaque aka long-tailed macaque (*Macaca fascicularis*)

[1]Bond et al. 1980 PMC1903666; [2]Shively et al. 2020. DOI: 10.1016/j.ynstr.2020.100254
[3]Shively et al. 2019. DOI: 10.1002/oby.22436;

Monkeys' social environments can be stressful.

- ***Macaques organized by social status hierarchies***
- ***Social status is stable over time***
- ***Subordinates appear stressed relative to dominants***





[1]*Shively et al. 2020. DOI: 10.1016/j.ynstr.2020.100254*

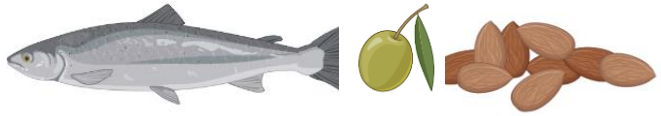
Diet Composition Effects on Social Isolation and Anxiety in Cynomolgus Monkeys

Trial Design

n=38 Females
Lab Chow Diet
Social Groups n=4-5

Western Diet (N=21)
11 dominant, 10 subordinate

Mediterranean Diet (N=17)
10 dominant, 7 subordinate



Pretreatment → Dietary Intervention

7 months

HPA function
ANS function
NeuroMRI
Social behavior (6 wks)
Ovarian function (6 wks)

31 months (~9 year followup in humans)

HPA function at 12, 29 mos
ANS function at 12, 29 mos
Social behavior for 24 mos
Ovarian function for 12 mos

Monocyte gene expression at 15 mos
NeuroMRI at 29 mos
Brain seqRNA at study end

Diet Compositions

Not like human or natural NHP diet

Diet Composition	Human		Nonhuman Primate		
	WEST	MED	WEST	MED	Lab Chow[7]
	% of Calories	% of Calories	% of Calories	% of Calories	% of Calories
Protein	15[1]	17[2]	16[1]	16[2]	**18**
Carbohydrate	51[1]	51[2]	54[1]	54[2]	**69**
Fat	33[1]	32[2]	31[1]	31[2]	**13**
	% of Total Fats		% of Total Fats		
Saturated	**33[1]**	21[2]	**36[1]**	21[2]	**26**
Monounsaturated	36[1]	**56[2]**	36[1]	**57[2]**	**28**
Polyunsaturated	24[1]	15[2]	26[1]	20[2]	**32**
ω6:ω3 Fatty Acids	**15:1[5]**	**2.1-3:1[6]**	**14.8:1[5]**	**2.9:1[6]**	**12:1**
Cholesterol mg/Cal[8]	0.13[1]	0.16[2]	0.16[1]	0.15[2]	**trace**
Fiber g/Cal	0.01[1]	0.03[3]	0.02[1]	0.04[3]	**0.01**
Sodium mg/Cal	**1.7 [1,4]**	**1.3[2,3]**	**1.7[1,4]**	**1.0 [2,3]**	**0.25**

*WEST & MED diet formulated in the Wake Forest Primate Diet Lab

Major Ingredient Differences

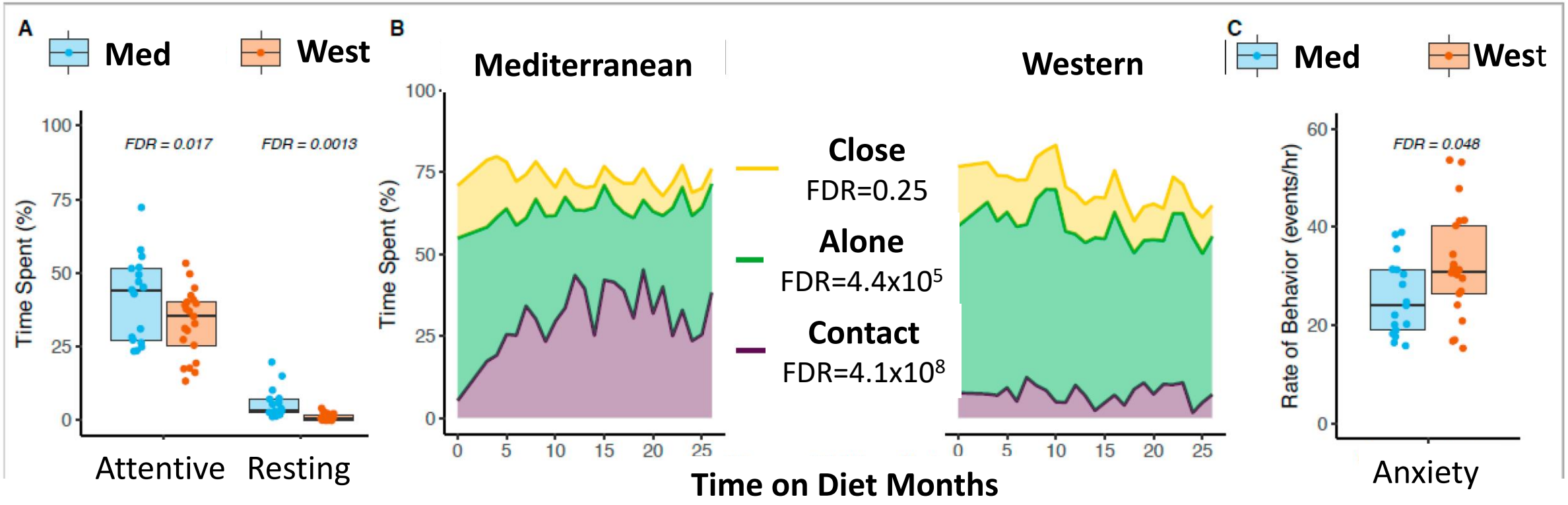
Fats	Lard	Olive oil
	Beef tallow	Fish oil
	Butter	Walnuts
	Cholesterol	Egg
Protein		Fish meal
		Bean flour
	Casein	black/garbanzo
	Whey	Wheat flour
Carbs	High fructose corn syrup	Tomato paste
		Applesauce
	Sucrose	Banana

1. USDA 2014,women 40-49 from NHANES; 2. Bedard 2012; 3. Kafatos 2000; 4. Powles 2013; 5. Simopoulos 2006; 6. Cordain 2005; 7. LabDiet Chemical Comp. Diet 5037/8; 8. ~256 mg or 1.3 eggs/day

Behaviors Altered by Diet Composition

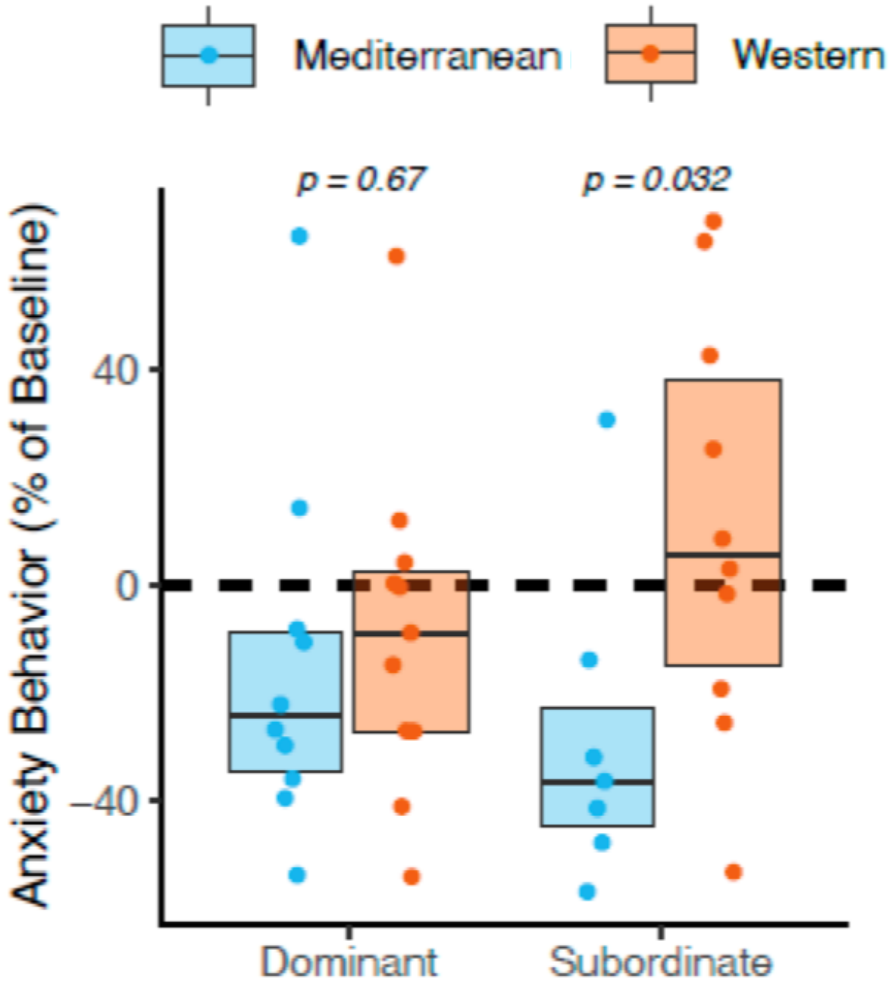
- **Med Group: More Attentive, Relaxed, Body Contact**
- **West Group: More Isolated and anxious**

Close	Within arm's reach of another monkey
Alone	Out of reach of another monkey
Contact	In physical contact with another monkey



Johnson et al. 2022, DOI: 10.3390/nu14142852

Social Status Altered Diet Effects on Anxiety



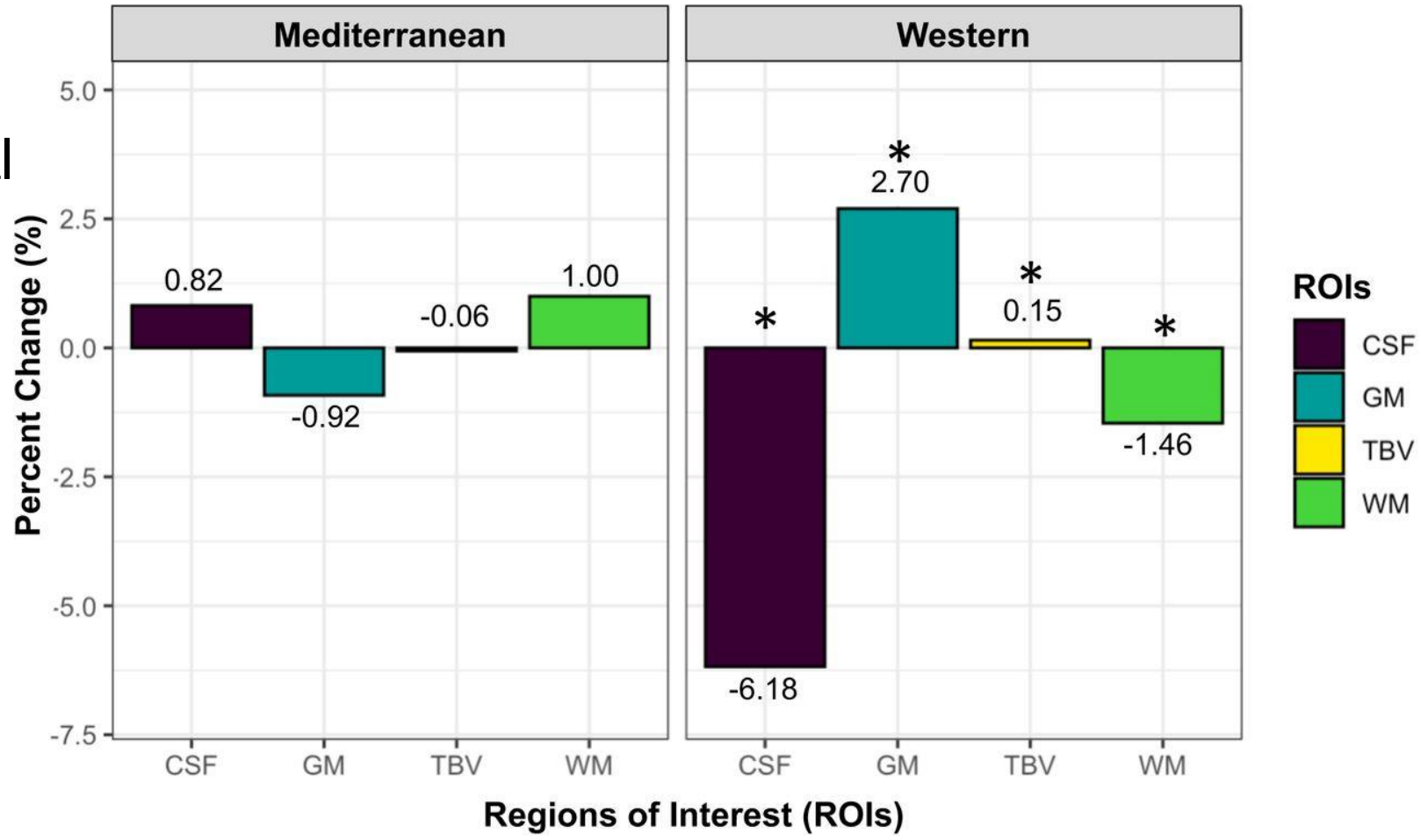
Subordinate status (high stress) interacted with Western diet to increase anxiety

Johnson et al. 2022, DOI: 10.3390/nu14142852

Diet Composition Effects on Alzheimer's Disease-Related Neuroanatomy

Over Time in Middle-Age:

- **WEST:** Changes global brain volumes
- **MED:** Global Brain Volumes Stable

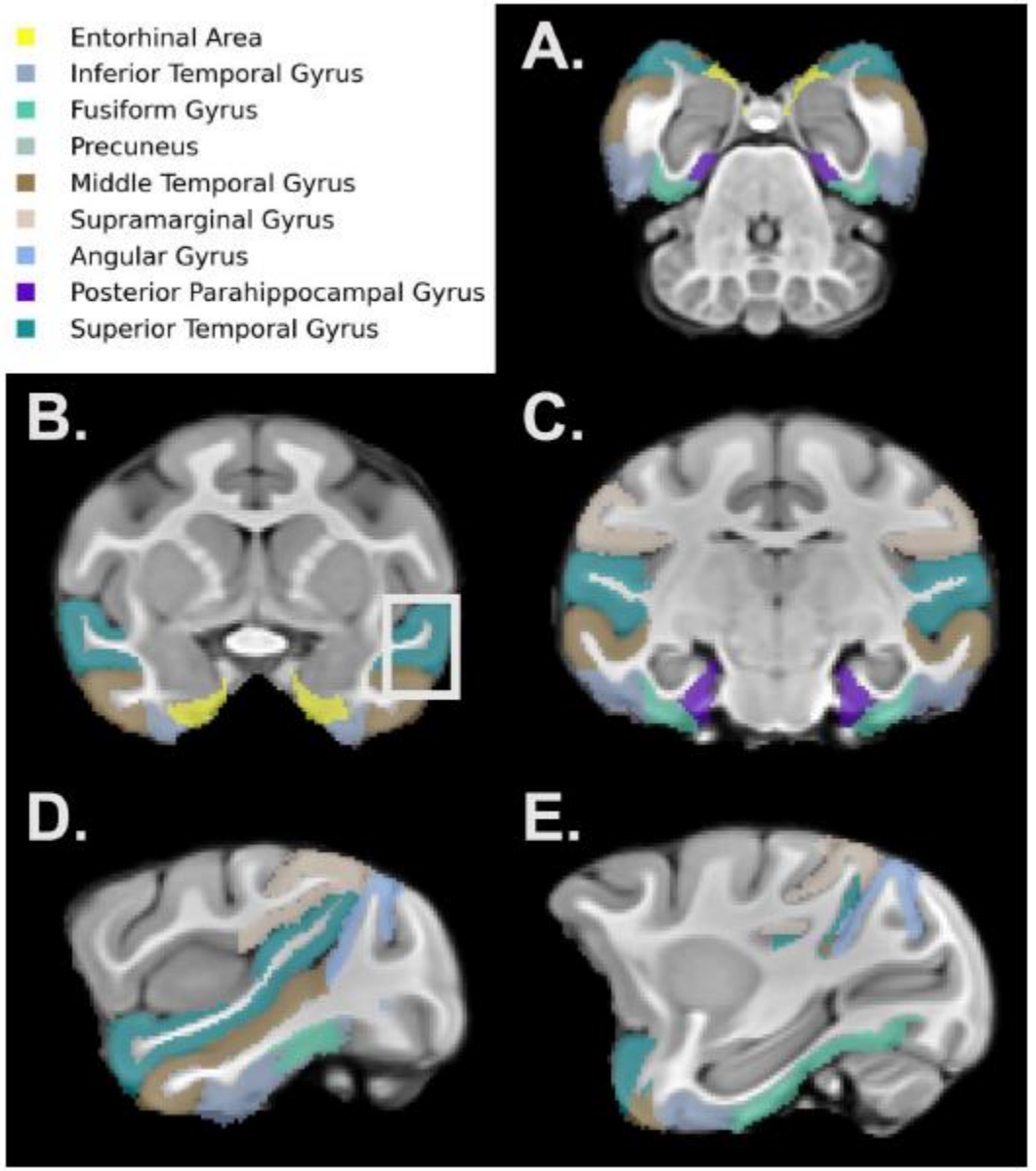


Frye et al 2021
Alzheimer's & Dementia

Construction of NHP AD-related Meta-ROI

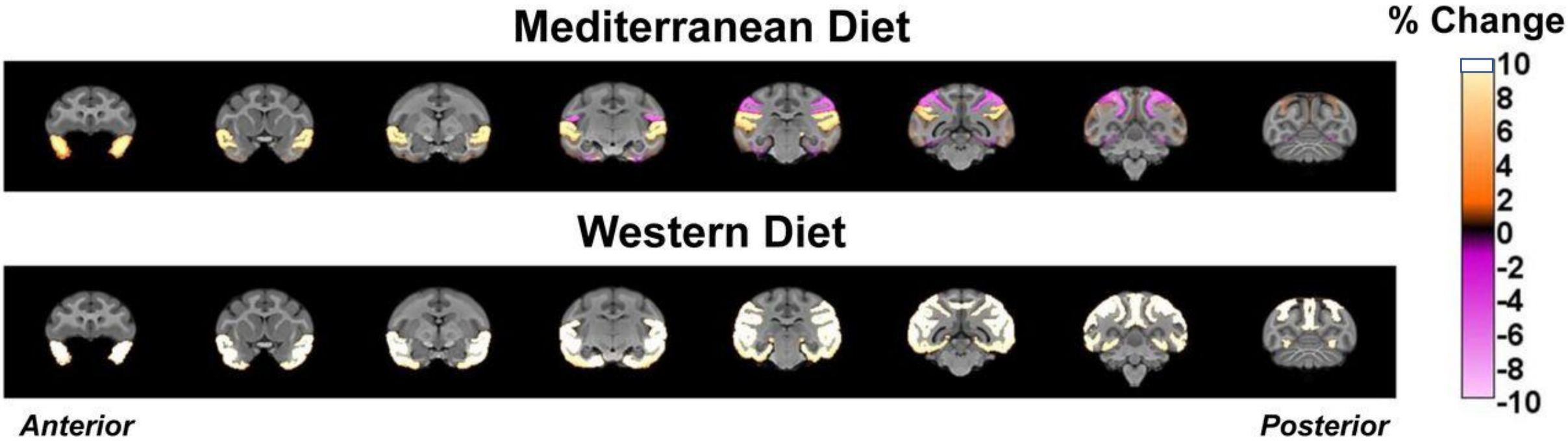
Parcellation map of macaque brain regions included used to construct NHP Alzheimer's disease-related thickness and volume Meta-ROIs (regions of interest): regions that maximally discriminate cognitively normal from MCI/AD in humans

Schwartz et al., 2016 Neuroimage: Clinical



Frye et al 2021
Alzheimer's & Dementia

WEST Diet Increased Cortical Thickness of NHP AD-Signature Meta-ROI



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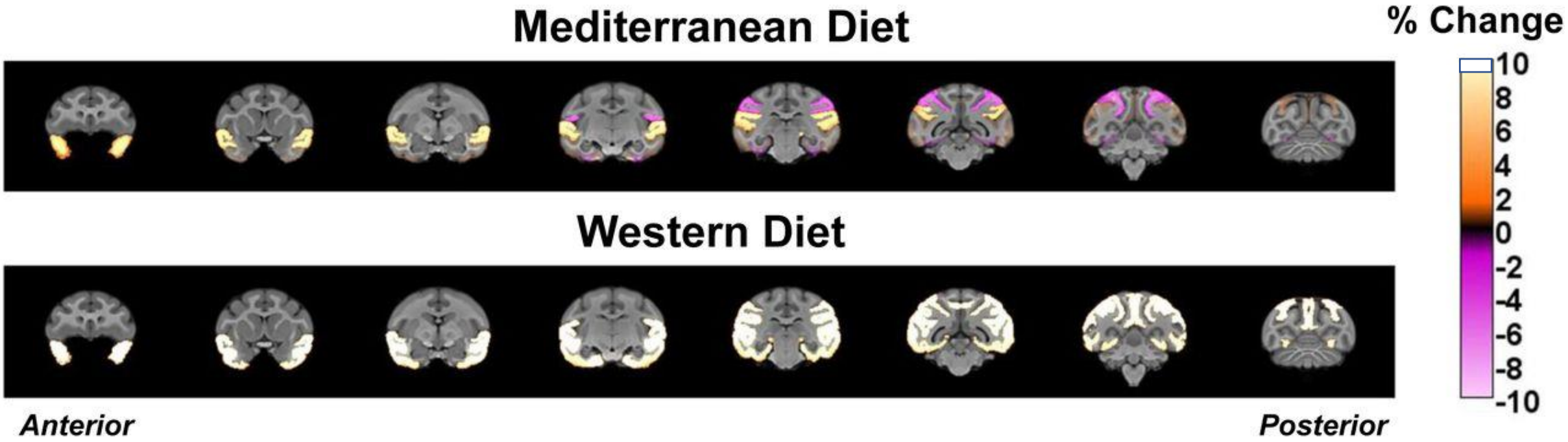


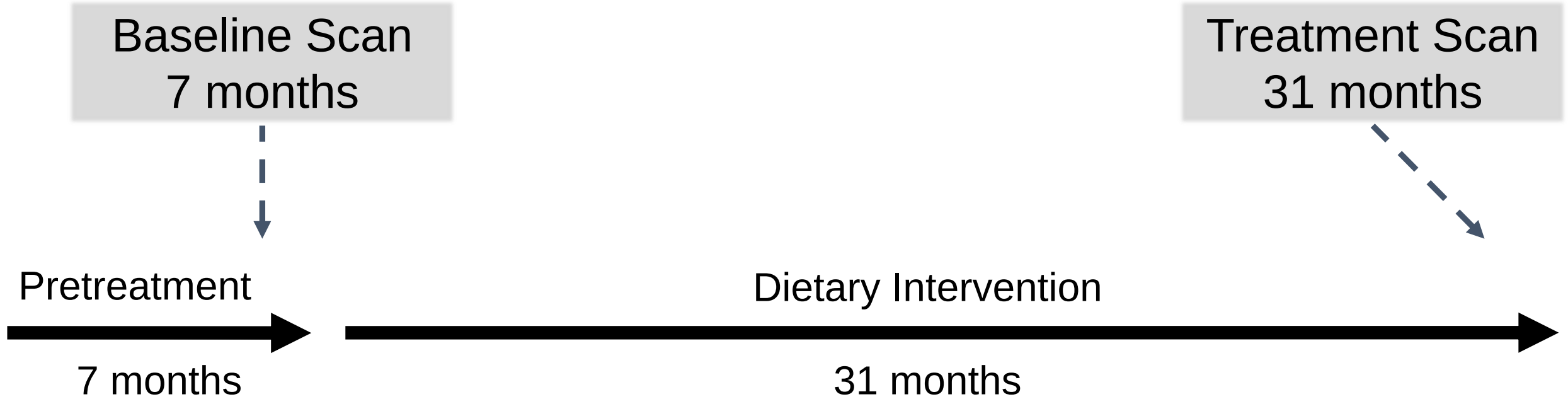
ADNI reported a two-phased longitudinal preclinical AD pattern in which increased cortical thickening was followed by cortical thinning (Pergueroles et al., 2017)

- **Hypothesis: thickening reflects an inflammatory process that precedes neurodegeneration and atrophy**

Regions of Interest

Global Regions
- Total Brain Volume
- Gray Matter
- White Matter
- Cerebrospinal Fluid

AD-Meta ROI
- Cortical Thicknesses (gray matter)
- Cortical Volumes (gray + white matter)



Regions of Interest

Global Regions
- Total Brain Volume
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AD-Meta ROI
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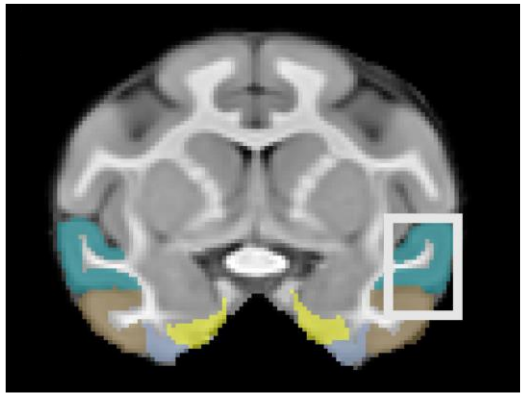
Gene Expression
- CDK14
- LFNG
- SLC3A2
- MRC2



Baseline Scan
7 months

Treatment Scan
31 months

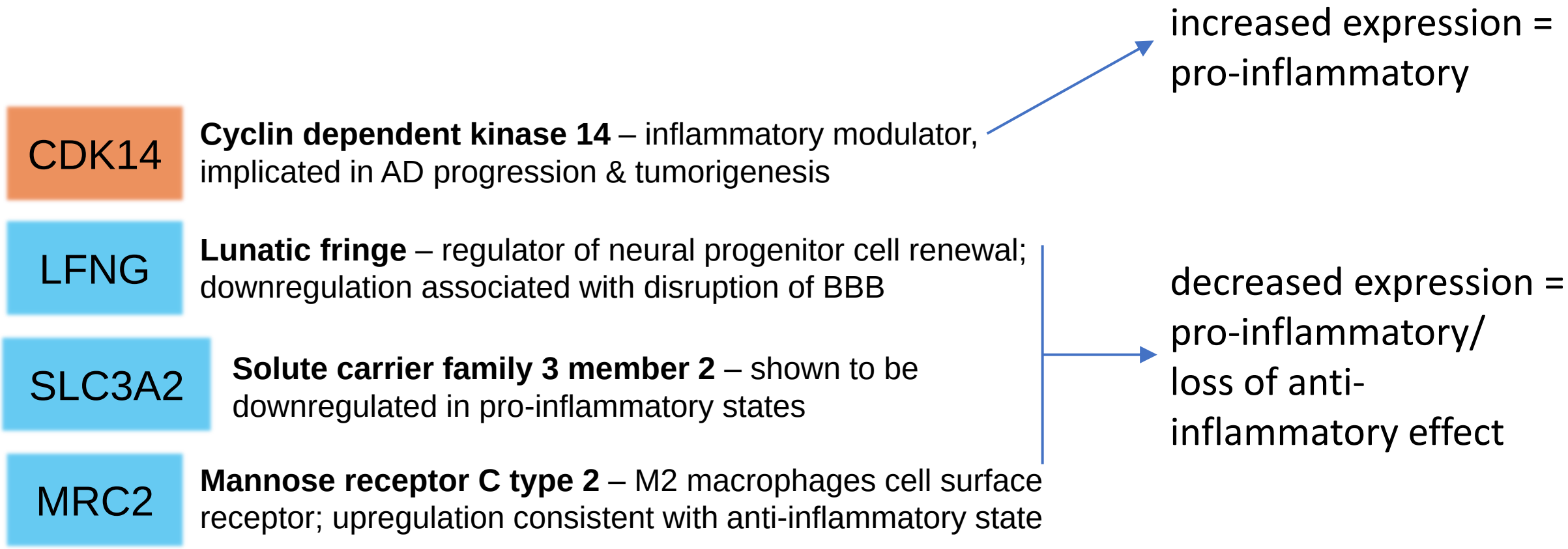
Pretreatment

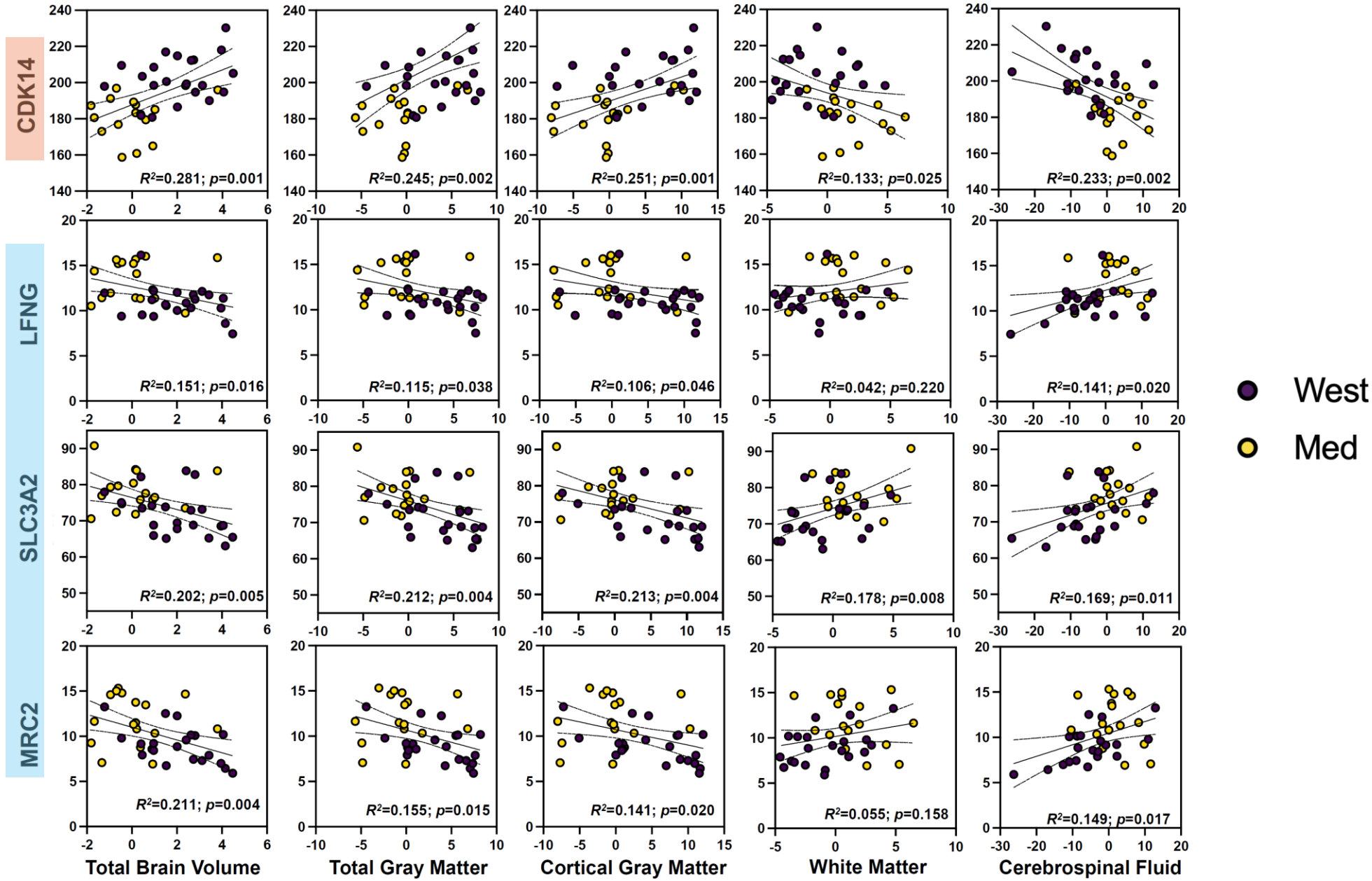
Dietary Intervention

7 months

31 months

Differentially expressed genes by diet condition

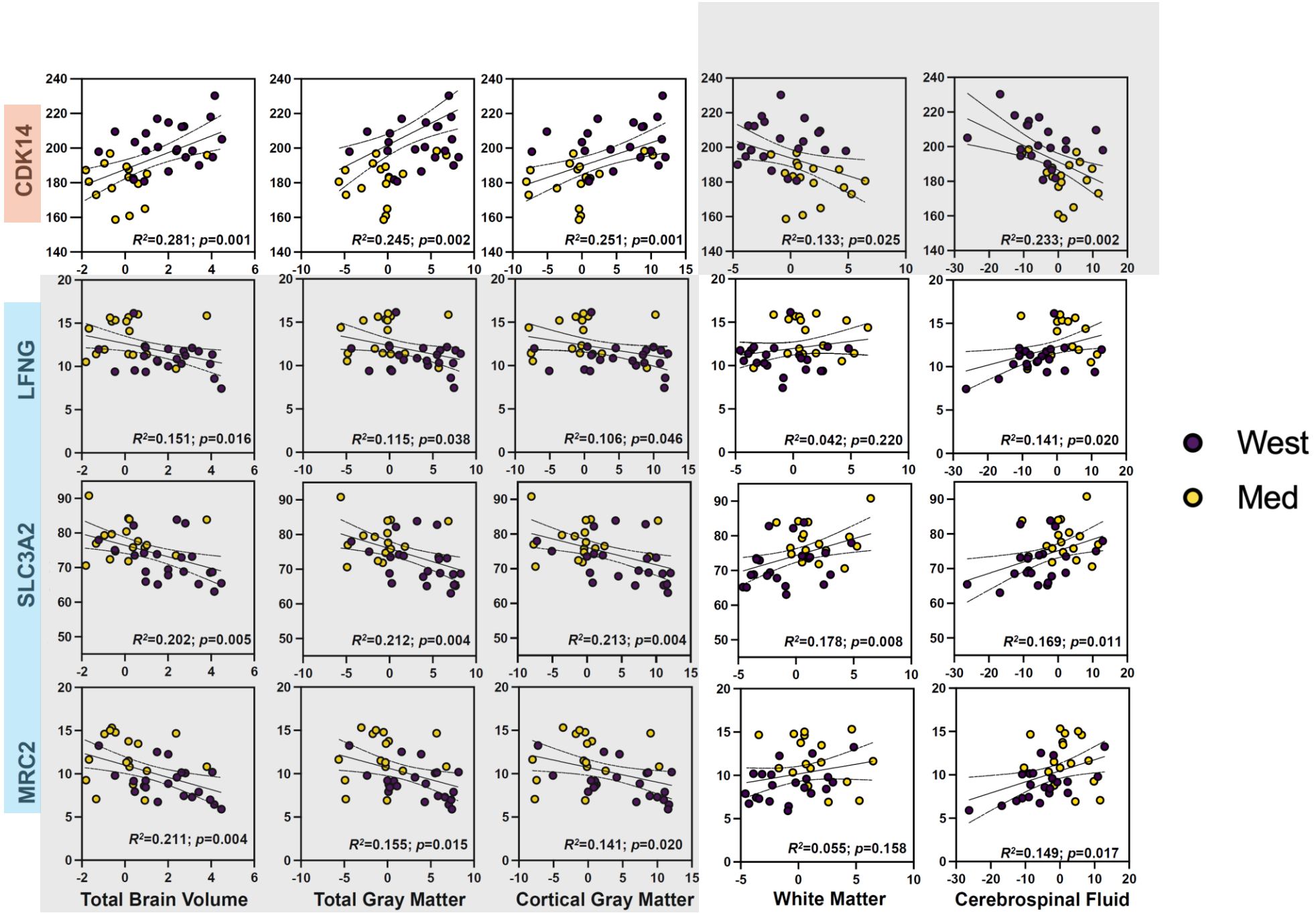




Negrey et al. submitted

+ brain volume, gray matter
- white matter, CSF

- brain volume, gray matter
+ white matter, CSF



Negrey et al. submitted

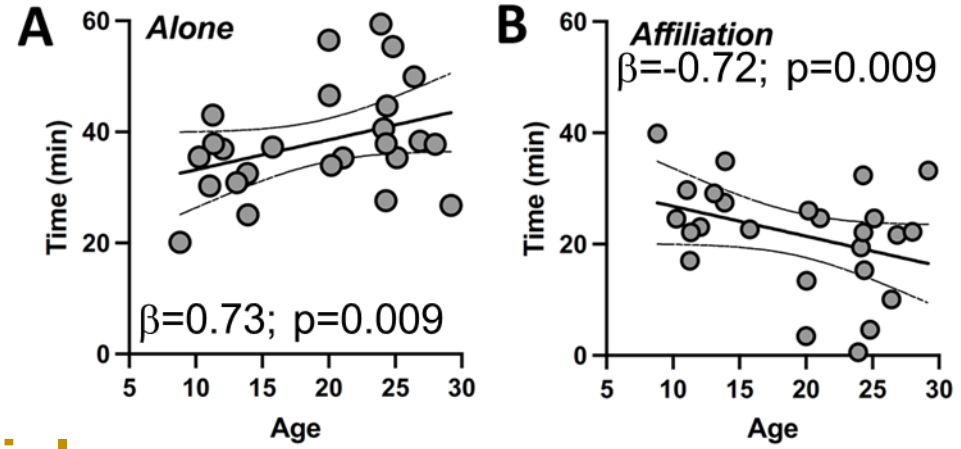
Diet effects on behavior and brain

- Western diet increases social isolation and anxiety
- Western diet is associated with increased gray matter volume and decreased white matter and CSF volume in an Alzheimer's-related "meta-region of interest"
- This increase in gray matter volume reflects a pro-inflammatory process

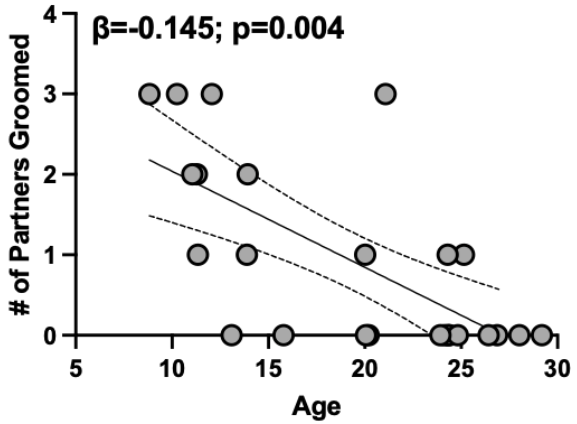
Social Isolation Increases with Age in Vervet Monkeys

Photo: Peter Chadwick

- Recorded social interactions in 25 group-living female vervets 8-29 years old
  - 60 min/monkey
- With Age:
  - Time spent alone increased
  - Time spent in affiliative behavior decreased
  - Time spent grooming others decreased
  - The number of partners groomed decreased



- **Smaller cortical thickness predicted greater social isolation 1 year later**
  - Measured AD-relevant temporoparietal cortical meta-ROI with MRI
  - Thinner cortex predicted:
  - greater social isolation (t= -2.20; p= 0.038)
  - fewer numbers of social partners (z=-2.32; p= 0.020) at 1-year follow-up



Negrey et al., 2023;
Frye et al., AAIC 2023

Conclusions

- Western diet is associated with increased social isolation and anxiety
  - Social isolation increases with age in humans and increases mortality

- Western diet is associated with an inflammatory program in a network of brain regions associated with Alzheimer's disease
  - Independently of diet manipulation, atrophy of this area is associated with social isolation in vervets - converging evidence for functional significance
  - Future direction: how do these dimensions interact with cognition

- Diet is a modifiable risk factor for adverse health outcomes and a critical variable in preclinical and clinical studies