

Diet, Aging, and Menopause: Effects on Alzheimer's Pathology

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BACKGROUND DEFINITIONS

Calorie Restriction: Limiting the number of calories to below baseline intake, based on age, sex, and weight. Importantly, lowering to a level which avoids malnutrition. Most studies calorie restrict between 10% and 40%.

Western Style Diet (WSD): In most developed countries, people eat higher amounts of fats and sugar than recommended. In order to model this, we give animals diets containing higher percentages of fats and sugars than their standard diet counterparts.

Prefrontal Cortex (PFC): An area in the front of the brain, one of the last evolutionarily and developmentally to mature. PFC is responsible for higher order processes such as emotional regulation, decision making, logical thinking, and personality.

Rhesus macaque: A non-human primate commonly used in biomedical research, due to similarities in genetics, development, aging, physiology, social behaviors, and more.

Menopause: A state of reproductive senescence resulting from depletion of ovarian follicles, clinically defined as 12 months sans menstrual period. Human and non-human primates undergo menopause.

Estropause: A state of reproductive senescence resulting from elevated levels of sex hormones, such that animals do not cycle anymore. Rodents undergo estropause.

Alzheimer's Disease: The most common dementia in the United States. The cause is unknown, there is no cure, and it is a progressive disease that ends in death. As far as we know, only humans get Alzheimer's.

Amyloid beta: A protein which occurs naturally in the human and monkey brain. As aging occurs, this protein begins to aggregate in the brain, forming plaques. While we do not know what role they play in the disease, these plaques are necessary for a postmortem Alzheimer's disease diagnosis.

CALORIE RESTRICTION DATA

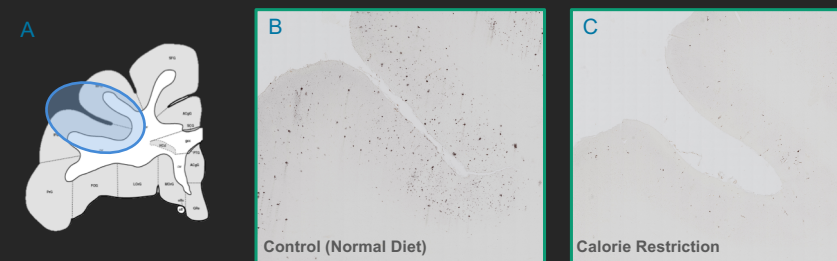


Figure 1: Using a method called immunohistochemistry, amyloid beta in the PFC of rhesus macaques is stained. (A) Coronal section from a rhesus macaque brain atlas, showing the area of analysis for this study. Above, examples of (B) a normal aged monkey and (C) a monkey of the same sex and age which was calorie restricted by 30% from middle age until natural death.

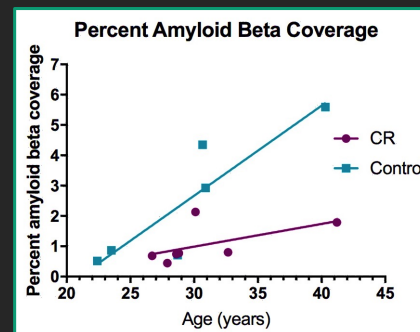


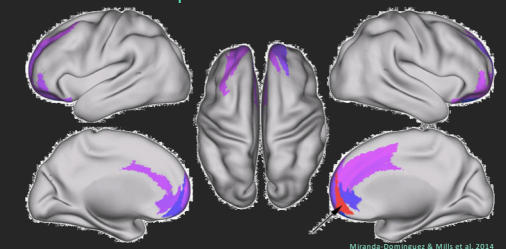
Figure 2: The effect of age and caloric restriction on PFC percent area covered by amyloid beta. Linear regressions were calculated for both diet groups to determine how age affects amount of amyloid beta (measured by average percent area coverage). For control animals, a significant regression was found ($F(1,4)=15.39, p=0.02$) with an R^2 of 0.79. For CR animals, a regression was found ($F(1,5)=2.51, p=0.17$) with an R^2 of 0.33. When averaged rostrally through caudally across the PFC, CR diet attenuates formation of amyloid beta plaques along the primary sulcus, even during the very late stages of aging.

FUTURE RESEARCH

How do diet and menopause interact?

Using surgically menopausal monkeys (ovaries are removed to induce a lack of naturally circulating sex hormones), we will look at effects of estrogen replacement timing in a clinically relevant WSD model. Many women begin estrogen therapy at the onset of menopause, while many choose to wait. What are the brain effects of each?

Macaque Default Mode Network



Group	Estrogen Replacement	Estrogen Timing	Diet
Control	X	X	WSD
Immediate E	Yes	Immediately after surgery	WSD
Delayed E	Yes	2 years after surgery	WSD

In this cohort, we look at functional magnetic resonance brain imaging (fMRI) across 4 years, as well as use immunohistochemistry to observe physical postmortem brains of the animals.

SUPPORT

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