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Flavanol-rich food for thought

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Abstract

A randomized clinical trial in older adults shows that high dietary intake of cocoa flavanols enhances memory performance and neural function in the dentate gyrus of the hippocampus, a region critical for learning and memory.

Looks like there is yet another reason to consume chocolate. As the youngest baby boomers turn 50 this year, the search for our brain's fountain of youth is intensifying. While changes in the brain and accompanying deficits in cognitive abilities are typical findings, carefully validated approaches to ameliorating age-associated declines such as memory loss remain rare. In this issue of *Nature Neuroscience*, Brickman *et al.*[1] report an elaborate series of experiments to test whether dietary flavanol, an ingredient in cocoa powder, can enhance dentate gyrus function and improve memory in healthy older adults. The dentate gyrus is a subregion of the hippocampus where new neurons are formed and is particularly vulnerable to age-related decline[2], making it a prime intervention target.

Brickman *et al.*[1] provide the first causal data in humans that high dietary intake of cocoa flavanols enhances neural function in the dentate gyrus and improves memory performance in older adults. The authors concluded that older adults who consumed a high-flavanol diet for 12 weeks exhibit improved memory performance and greater cerebral blood volume in the right dentate gyrus compared to individuals on a low-flavanol diet. To complete the story**,** they show a significant correlation between enhanced cerebral blood volume in the dentate gyrus and enhanced performance on the Modified Benton (ModBent) test, a shape-recognition memory task. That is, change in neural function tracks change in cognitive function.

Supplementing a large body of published work[2,3], they conducted a series of preparatory experiments to validate their tools and guide the trial study design. First they needed a task that selectively activates the dentate gyrus, to be used as an outcome measure. Leveraging data from animal and human studies, they targeted pattern separation, the process of distinguishing between very similar stimuli from memory, as represented by neurons in the

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dentate gyrus[4]. Adapting principles from an established memory test[5], they created the computerized ModBent test, a challenging visual memory recognition task (Figure 1). To demonstrate that the ModBent task was specific to dentate gyrus function and not other memory regions, the authors performed a double-dissociation study of the ModBent and a memory retention task in healthy young subjects. They confirmed that the ModBent test selectively activated the dentate gyrus while the memory retention task selectively activated the entorhinal cortex.

Then, to identify the precise site of age-related neural dysfunction in the dentate gyrus, the authors conducted a study in healthy individuals from 21 to 65 years old and found that performance on the ModBent waned with age. Once the test was validated as specific to the dentate gyrus and sensitive to age, they created two distinct versions of the test to be used for pre and post assessment in their trial. They continued to refine their technical approach by developing a new image-processing tool for visualizing fMRI results in three dimensions over the entire hippocampus.

Association studies have found that individuals with flavanol-rich diets have a lower risk of cognitive decline and better performance on cognitive tests[6-8]. While promising and suggestive, conclusions from correlational studies must be interpreted with caution, as they do not imply causation. A major strength of randomized clinical trials is that they permit causal interpretation of the results. Another critical feature of a trial is the inclusion of a comparison group to observe the influence of practice effects and the passing of time. In the present study, the authors found that the high-flavanol group outperformed the low-flavanol group by 630 ms on the ModBent test at follow-up, which controls for possible practice effects from repeat testing. A between-group difference of 630 ms corresponds to aging effects that occur over almost three decades[1], which is consistent with improvements reported in mice[9].

Flavanols are plant-derived nutrients that are found in many fruits, vegetables, tea, and cocoa. The benefits of flavanols have been investigated in several studies of mice and rats, including animal models of Alzheimer's disease. Flavanol consumption in animals causes increased blood flow, new blood vessel and neuron formation and increased capillary density[10,11]. The associated cognitive benefits include improved memory performance on maze tasks in animals. Strikingly, in one study of a transgenic mouse model of Alzheimer's disease, the intake of a high-flavanol diet delayed the onset of amyloid plaque formation when ingested before plaque development[12]. This tempts the idea that flavanols could be beneficial for at-risk individuals if used early.

The specific effects of flavanols on dentate gyrus structure and function are well studied in animals. For example, epicatechin, a dietary flavanol, causes increased dendritic spine density and regional metabolism in the dentate gyrus[13]. Notably, these neural effects are enhanced when combined with aerobic exercise. Brickman *et al.*[1] had planned to investigate the synergistic effects of flavanols and aerobic exercise on cerebral blood volume in the dentate gyrus, but unexpectedly, the exercise program failed. There were no differences in aerobic fitness, as measured by peak oxygen intake, between the exercise group and the no-exercise group at the end of the study. As a result, the authors were unable to test the

hypothesis that the high-flavanol diet plus aerobic exercise would have the greatest effect on cognition and dentate gyrus function. Thus, the added benefit of exercise is still unknown, but it would have important public health implications if proven successful[14].

Should this dietary supplement become part of a standard of care for older adults? Cardiologists routinely prescribe lifestyle changes for maintaining a healthy heart[15]. It seems to us that neurologists and psychiatrists should also have a list of empirically validated lifestyle considerations, such as diet and exercise recommendations that are important for maintaining a healthy brain. The present study certainly moves this discussion along in a positive way, but uncertainties of dose (how much), frequency (how often) and duration (how long) remain. 450 mg of flavanols twice a day was effective in achieving the authors' selected outcomes, but would more have shown a dose-dependent effect? Furthermore, the sustainability and long-term benefits of flavanol need to be understood. Can flavanol benefit a neurological disease, such as Alzheimer's disease or impairment caused by stroke[10]. The authors go to some lengths to distinguish the effect of flavanols on the dentate gyrus, a region selectively impacted by age-related decline, from any effect on the entorhinal cortex, a region targeted early in Alzheimer's disease[3]. However, whether cognitively normal older adults who are at risk for Alzheimer's disease may benefit from a high-flavanol diet should be explored further. Lastly, as the technology of higher field strength magnets and innovative analytical approaches continues to develop, we are eager to see how these authors and others embrace methodological opportunities to achieve higher resolution imaging of hippocampal anatomy.

The need for carefully designed randomized clinical trials with clear treatment targets is crucial. In the absence of rigorous, neuroscientific approaches aimed at target engagement and mechanisms of action, we remain in the dark as to why an intervention succeeds or fails. Future trials that couple a mechanistic understanding with clinically meaningful outcomes will produce the tastiest findings. Needless to say, the search for both pharmacological and nonpharmacological interventions to combat cognitive decline and neural loss will march on. But today, Brickman *et al.*[1] provide compelling evidence that including flavanols in your daily diet is good for the aging brain.

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Figure 1.

A computerized assessment of dentate gyrus function. Brickman *et al.*[1]. developed and validated a computerized memory test based on novel object recognition. In their trial, older adults who consumed a flavanol-rich cocoa for 12 weeks had improved memory function, which was correlated with improved cerebral blood volume.