Flavanol-rich food for thought

Judy Pa & Adam Gazzaley

A randomized clinical trial in older adults shows that high dietary intake of cocoa flavanols enhances memory performance on an object-recognition task and neural activity as assessed by functional magnetic resonance imaging in the dentate gyrus of the hippocampus, a region that is critical for learning and memory.

It seems that 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. Although 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 determine 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 in which 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 found that older adults who consumed a high-flavanol diet for 12 weeks exhibited improved memory performance and greater cerebral blood volume in the right dentate gyrus compared with individuals on a low-flavanol diet. Importantly, they observed a significant correlation between enhanced cerebral blood volume in the dentate gyrus and enhanced performance on the Modified Benton (ModBent) test, an object-recognition memory task. That is, change in neural function tracked change in cognitive function.

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Alongside a large body of published work[2,3], the authors conducted a series of preparatory experiments to validate their tools and guide the trial design. They needed a task that would selectively activate the dentate gyrus to be used as an outcome measure. Leveraging data from animal and human studies, the authors targeted pattern separation, the process of distinguishing between very similar stimuli from memory, as represented by neurons in the dentate gyrus[4]. Adapting principles from an established memory test[5], they created the computerized ModBent test, a challenging visual memory recognition task (**Fig. 1**). To demonstrate that the ModBent task was specific to dentate gyrus function and not to other memory regions, the authors performed a double-dissociation study of the ModBent and a memory retention task in healthy young adults. They confirmed that the ModBent test selectively activated the dentate gyrus, whereas the memory retention task selectively activated the entorhinal cortex.

To identify the precise site of age-related neural dysfunction in the dentate gyrus, the authors conducted a study in healthy 21- to 65-year-old individuals and found that performance on the ModBent waned with age. Once the ModBent was validated as being specific to the dentate gyrus and sensitive to age, the authors created two distinct versions of the test to be used for assessment at the beginning and end of 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]. Although 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 accounted 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.

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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.

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 one to speculate 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 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 that are important for maintaining a healthy brain, such as diet and exercise recommendations. The present study certainly moves this discussion along in a positive way, but uncertainties as to 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 targeted 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.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Reading dendritic activity with gap junctions

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Patch-clamp recordings and imaging in retina show that electrical synapses between dendrites of neighboring ganglion cells transform spatial patterns of light activated synaptic input into a temporal population code.

Spikes emitted by certain types of retinal ganglion cells have long been known to exhibit a remarkable level of synchrony[1]. However, the origin and role of these fine-scale temporal correlations have remained elusive. The dendrites of several neuronal subtypes are innervated by both electrical and chemical synapses, and such dual innervation is particularly prevalent in the retina. But the manner in which electrical and chemical synaptic inputs interact in dendrites and contribute to information processing is poorly understood. Previous studies have provided insights into parts of this complex puzzle, either by focusing on the synaptic and dendritic mechanisms or by concentrating on how sensory information is encoded by neuronal firing. In an elegant study in this issue of *Nature Neuroscience*, Trenholm *et al.*[2] provide a compelling account of how electrical and chemical synapses interact with nonlinear dendritic conductances in electrically coupled, direction-selective retinal ganglion cells (cDSGCs) and elucidate how these mechanisms work in concert to help convert local changes in light intensity into synchronized spikes across the local cDSGC population.

How did the authors link synaptic and dendritic mechanisms with sensory coding so effectively? Three key factors stand out. First, they chose a powerful model system for dissecting the mechanisms that give rise to the encoding of sensory information. The flat-mount retina preparation provides direct access to an intact sensory processing circuit in which responses to physiological input (light) can be directly measured and manipulated using patch-clamp recording, two-photon imaging and pharmacological approaches. Second, the authors took advantage of a transgenic line (*Hb9-eGFP*) that expresses

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