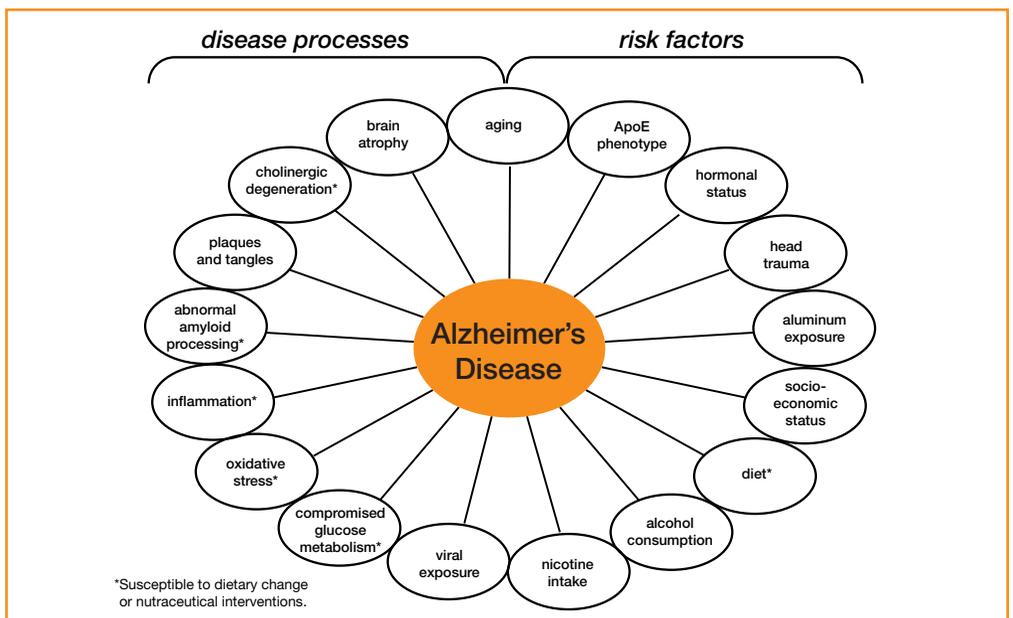


# Neurocognitive and Mood Effects of Nutrition and Nutraceuticals

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Cognitive processes involve multiple mechanisms that interact in complex and possibly idiosyncratic ways. This complexity likely underlies the general lack of meaningful impact of monopharmacological (or “magic bullet”) approaches to brain dysfunction, including cognitive decline and dementia. For example, the cholinesterase inhibitors used in the treatment of Alzheimer’s disease (AD) have a narrow therapeutic window and are effective only at certain stages of the disorder. This is perhaps unsurprising considering that the onset and progression of AD are influenced by numerous other processes, as well as cholinergic degeneration.

AD is a product of a pathological cascade, involving progressively accelerating neurotoxic interactions between oxidative stress, inflammatory responses, compromised hormonal pathology, compromised cerebral metabolism, neurofibrillary tangle generation, and  $\beta$ -amyloid deposition, among other processes, which include cholinergic degeneration (Fig 1).



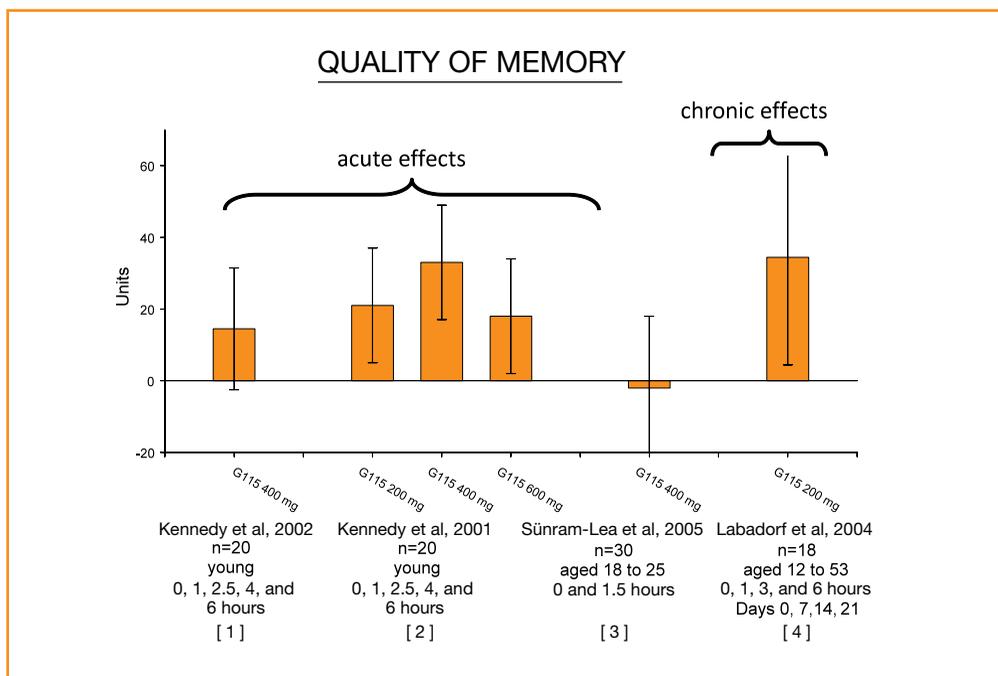
**Fig 1. Processes involved in the risk and etiology of Alzheimer’s disease, with many also implicated in nonpathological aging.**

## Neurocognitive and Mood Effects of Nutrition and Nutraceuticals

Nutrients and extracts from botanical sources may offer a more promising approach by affecting multiple systems. Unlike mainstream pharmacological agents, nutrients and extracts from botanical sources may contain many active components. It appears that certain plants have evolved with a combination of properties which, in concert, may affect multiple neuronal, metabolic, and hormonal systems with direct effects on cognitive processes. In addition, numerous indirect physiological processes impinge on neurocognitive function (eg, glycemic control, vascular function, oxidative stress, inflammation, and psychological stress), all of which are possible to modify by appropriate dietary change.

Over the past decade or so, great progress has occurred in evaluating the efficacy of specific nutritional interventions, including dietary supplements, in the context of cognitive enhancement. Research on the biobehavioral effects of herbal extracts have included, but are not restricted to, randomized controlled trials using species of ginseng, *Melissa officinalis*, species of salvia (sage), *Ginkgo biloba*, valerian, guarana, ginkgo-phosphatidylserine, cocoa polyphenols, *Bacopa monnieri*, Pycnogenol®, Enzogenol®, tea catechins, soy isoflavones, and curcumin. This paper will use ginseng and *M officinalis* as examples.

For millennia, ginseng has seen use in traditional medicine systems and often is marketed as a “pick-me-up.” This and other properties relevant to neurocognitive function usually are ascribed to the ginsenosides, terpenoid saponins found only in ginseng. G115 is a standardized extract with an invariant 4% ginsenoside content. Several clinical trials have shown that G115 can acutely improve cognitive function and, in particular, memory (Fig 2).



**Fig 2. Effects of a standardized extract of Panax (G115) ginseng on an aggregate memory score in four studies.**<sup>1-4</sup> Bars represent improvement compared with placebo, with 95% confidence intervals.

Figure courtesy of Keith Wesnes, PhD, Bracket, UK; Swinburne University, Australia.

Like other nutraceuticals, ginseng can improve mood and cognitive function during heavily loaded cognitive processing (six repeated 10-minute cycles of serial subtractions and a vigilance/working memory task),<sup>5</sup> specifically improving Serial Sevens performance and reducing mental fatigue. More recent work has shown that an extract of American ginseng (*Panax quinquefolius*), which has a different ginsenoside profile, has replicable positive effects on working memory.<sup>6</sup>

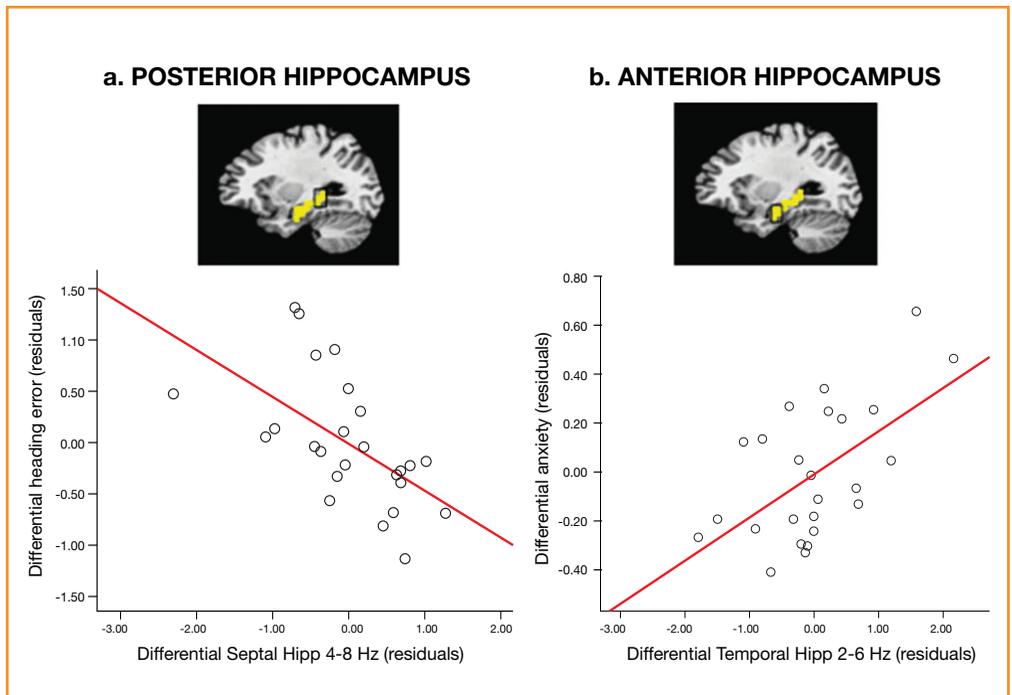
In order to put these findings into perspective, effect sizes of ginseng were compared with those associated with the pharmacological cognitive enhancer du jour, namely modafinil.<sup>7</sup> The largest effect size in the healthy human modafinil literature was 0.77 (Cohen's d for visuospatial working memory). Ginseng effects were more variable, including negative effects at some doses. Nevertheless, the highest effect sizes were 0.86 in the cognitive domain (reaction time) and 1.40 for mood (the aforementioned alleviation of mental fatigue). It is necessary to perform these comparisons in direct head-to-head clinical trials. However, they imply that polypharmacological approaches to cognitive enhancement may prove at least as fruitful as traditional pharmacological drug-discovery pipelines.

## Neurocognitive and Mood Effects of Nutrition and Nutraceuticals

Other studies have focused on the mood effects of natural products. One example is *M officinalis* (lemon balm), with the plant and extracts thereof long considered as anxiolytic agents. In one study, the effects of two doses of a standardized extract of *M officinalis* on mood changes during a multitasking battery were evaluated. Subjects simultaneously performed four cognitive tasks with snapshots of mood taken immediately before and after the stressor.<sup>8</sup> The findings showed that compared with placebo, lemon balm was associated with decreased self-rated alertness and increased calmness during the stressor in a dose-dependent manner.

More recently this field has drawn on methodologies from the neuroimaging discipline. One such method is magnetoencephalography (MEG), which measures changes in magnetic fields associated with postsynaptic potentials. MEG has the advantage of other imaging techniques in that it has both extremely good spatial and temporal resolution. One exciting application is the use of a virtual water maze, which mimics the classic rodent Morris water maze (MWM). In the MWM, an animal finds a submerged platform in a large tank of opaque liquid using environmental or allocentric cues, which is a prototypical hippocampal task.

In the virtual version, humans navigate their way through a virtual pool to find a platform while in the MEG scanner. Like its rodent predecessor, successful completion of the task is dependent on hippocampal function<sup>9</sup> and specifically on the hippocampal theta waveform. More recently it was demonstrated that, during a version of the task where some trials were associated with electric shock, subfields of the hippocampus responded differentially to cognitive performance and anxiety,<sup>10</sup> with activity in the posterior third predicting cognitive performance and the anterior third associated with affect (Fig 3). These findings suggest the possibility of measurable and modifiable neural markers for cognition and mood, which may complement more established measures.



**Fig 3. Differential association between hippocampal region-of-interest (ROI) theta and navigation performance and anxiety level.**<sup>10</sup> Partial regression plots (with least square lines) show relationships between differential left hippocampal ROI high theta (4-8 Hz) and differential heading error (a), and between differential left hippocampal ROI low theta (2-6 Hz) and differential anxiety in the hidden platform condition (b).

**Source:** Cornwell BR et al. Distinct contributions of human hippocampal theta to spatial cognition and anxiety. *Hippocampus*. 2012;22(9):1848-1859. Reprinted by permission of John Wiley and Sons. Figure courtesy of Brian Cornwell, PhD, Swinburne University, Australia.

This work is in its infancy, but may uncover promising candidates with which to optimize day-to-day cognitive functioning, to maintain psychological well-being throughout life, and even to treat conditions where mental function becomes fragile, including dementias. However, it is important not to fall into the trap of attempting to mimic classic drug development pipelines. Specifically, nutrition interventions may rely on synergistic interaction between components, such that efficacy is possibly reduced by attempting to isolate individual active components.

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