

# **Alterations in brain connectivity following supplementation with a putative caloric restriction mimetic blend of nutrients and phytochemicals**

## **INTRODUCTION/BACKGROUND**

Caloric restriction (CR) without malnutrition has been consistently shown to increase longevity and lifespan in a broad range of species. Recent studies in a rhesus monkeys have demonstrated that brain atrophy, a characteristic of human aging, is attenuated by CR (1). These findings are translationally relevant since CR has been associated with improvements in working memory, executive function and cognitive function in elderly humans (2). Thus, there is an unmet need for nutritional supplements, which can mimic the biological effects of CR, without the need for calorie or energy limitations. In an effort to meet this need, a formula consisting of ingredients selected on the basis of producing gene expression changes in mouse tissue that were similar to those seen with CR was designed. The purpose of the present study was to investigate the effects of the blend of nutrients and phytochemicals on brain connectivity in situ in humans assessed by fMRI.

## **METHODS**

### **Study Design**

This was a double-blind, placebo-controlled study where N=60 healthy subjects ranging in age from 40-60 were randomly assigned to 1 of 2 groups: Supplemented group or Placebo group. Each group consisted of 30 subjects (15 men and 15 women). Subjects consumed the supplement (or placebo) for a forty-two day period. A comprehensive imaging protocol was administered at baseline and after 6 weeks of supplementation. Total scanning time for each session was approximately 90 minutes.

### **Nutrient blend**

EPA+DHA ultra-pure fish oil concentrate, resveratrol (from *Polygonum cuspidatum* root), quercetin (from *Dimorphandra mollis* fruit extract), purple corn (*Zea mays L.*) cob extract, rosemary (*Rosmarinus officinalis L.*) leaf extract, citrus bioflavonoids (naringin and hesperidin), coenzyme Q<sub>10</sub>, alpha lipoic acid, astaxanthin (a carotenoid from *Haematococcus pluvialis* algae), lycopene (a carotenoid), lutein (a carotenoid from Marigold flower (*Tagetes erecta*)), vitamin D<sub>3</sub> (as cholecalciferol), vitamin K<sub>2</sub> (as menaquinone-7), and d-limonene (from *citrus sinensis* peel oil).

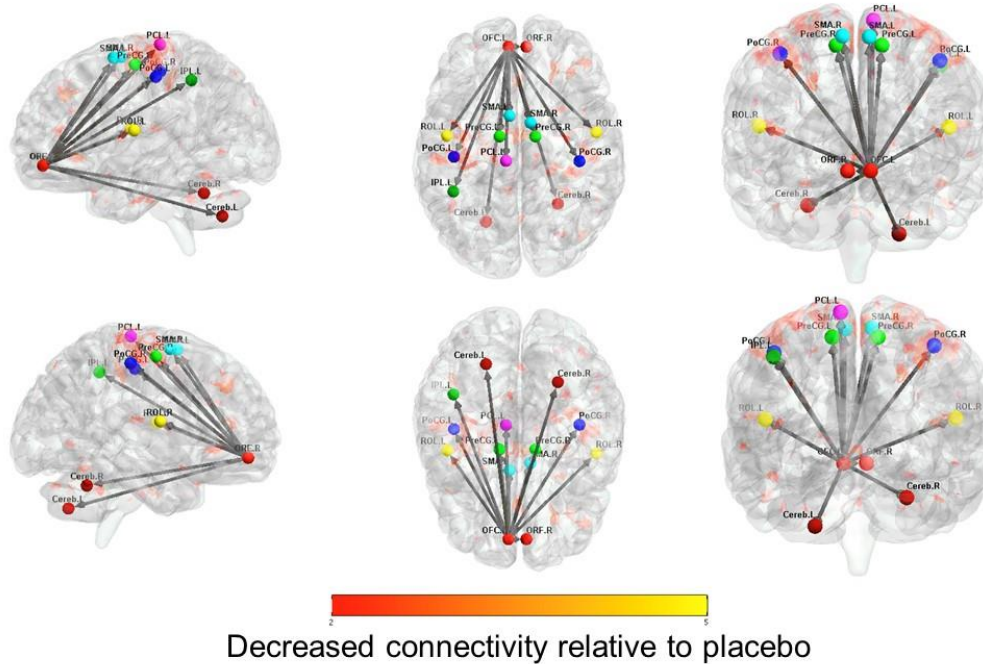
### **Magnetic Resonance Imaging (functional MRI).**

Functional MRI (fMRI) examines the connectivity between brain regions. In particular, resting state connectivity can be a valuable tool to examine parameters of connectivity due to the stability of the connectivity during the resting state.

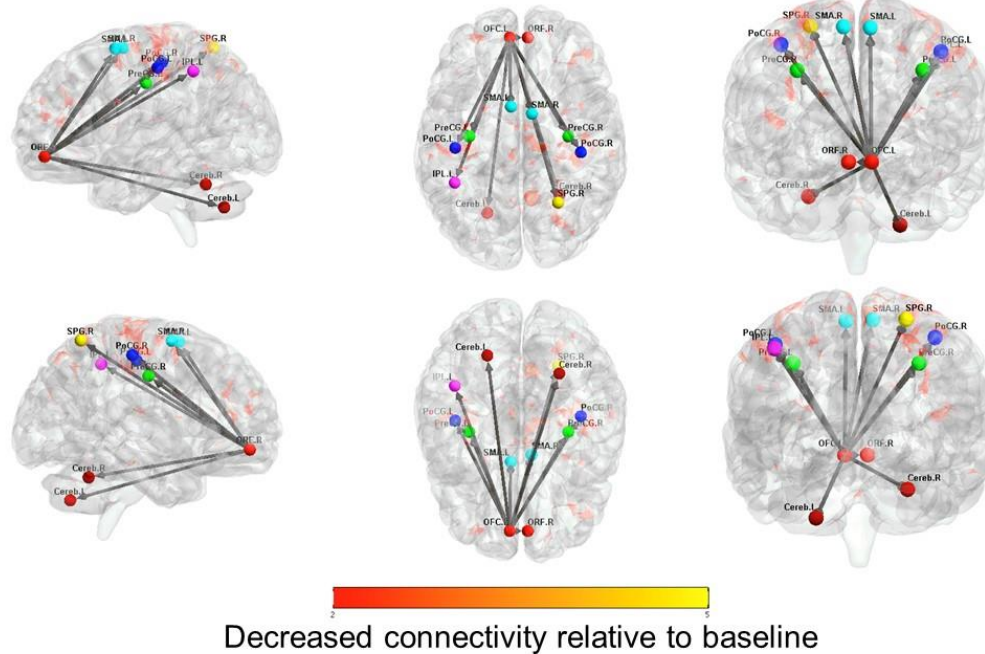
## RESULTS

The Figures below illustrate the right orbitofrontal cortex (OFC) seed region. There was a decrease in connectivity relative to baseline and relative to placebo, respectively. This reduction in connectivity allows for additional channels to exist for increased intake of new data. These findings show a significant reduced intrinsic coupling between the right OFC brain region and the clusters in precentral, paracentral, parietal, supplementary motor, precuneus, and frontal cortical regions.

Connectivity between the left Orbitofrontal (OFC) Seed Region and Other Brain Regions



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### CONCLUSIONS

The present study reveals that 6-weeks of daily supplementation of a blend of nutrients and phytochemicals, elicited positive changes in brain connectivity. To the best of our knowledge, this is the first study, which has identified fMRI effects of a putative CR mimetic in healthy middle-aged humans.

### REFERENCES

1. Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, Allison DB, Cruzen C, Simmons HA, Kemnitz JW, Weindruch R. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science*. 2009 Jul 10;325(5937):201-4.
2. Witte, A.V., et al., Caloric restriction improves memory in elderly humans. *Proc Natl Acad Sci U S A*, 2009. 106(4): p. 1255-60.