

Effects of Macular Carotenoids on Eye, Brain, and Body



James M. Stringham, Ph.D.

Visual Performance Laboratory
Duke Eye Center
Duke University Medical School
Department of Ophthalmology

james.stringham@duke.edu



Disclosures

- Paid speaker for Abbott Nutrition
- Paid speaker for Industrial Organica
- Paid speaker for MacuHealth
- Paid speaker for Stauber USA

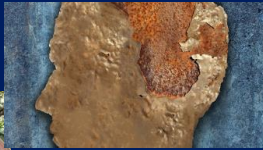
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2

The Oxygen Paradox

Although indispensable for life, oxygen can be toxic.

- Reactive oxygen species (e.g. singlet oxygen, superoxide radicals)
- Oxidative stress



Oxidation, sped along by an electrolyte (salt)

3

The "Rusty Pipe Wrench Experiment"



4

The "Rusty Pipe Wrench Experiment"



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The "Rusty Pipe Wrench Experiment"



6

Lutein, Zeaxanthin, & Mesozeaxanthin

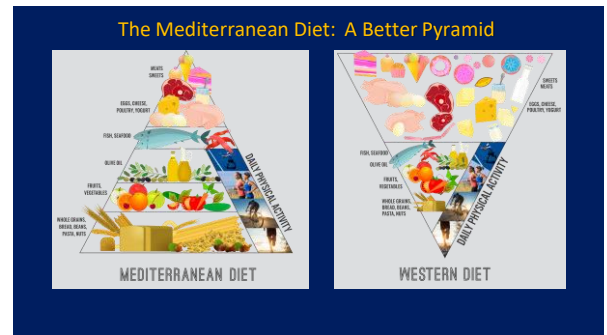
- **Carotenoids**
 - Pigments that give fruits and vegetables their color
- Exceptional antioxidants
 - *Xanthophyll* carotenoids capable of *triplet excitation transfer*
 - Can quench free-radical oxygen, regenerate
- Lutein, zeaxanthin, and mesozeaxanthin appear yellow-orange...absorb harmful blue light (see figure on right)
- Combine to form "macular pigment" in the retina



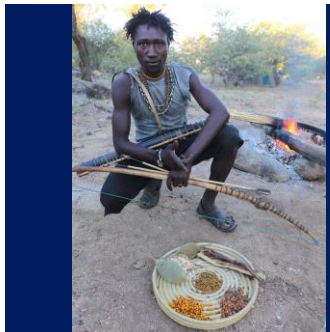
Macula lutea ("yellow spot")

- MPOD ranges from 0 to 1.65 OD
 - Can reach extremely high concentration
- The average American does not consume enough leafy-greens (e.g. kale, spinach, broccoli) to raise MPOD to meaningful levels (NHANES, 2013-2014).
 - Average American = 0.30 MPOD
 - Significantly improved ocular health / visual performance seen at values of 0.70 and beyond

7



8



The Hadza tribe (northern Tanzania)

- One of the few remaining hunter-gatherer societies on earth.
- Microbiome is exceptionally diverse (Schnorr et al. 2014)
- The majority of the annual Hadza diet (~70% of kilocalories) comes from plant foods.
- Birds, small, medium and large-sized game meat comprise ~30% of the annual diet
- The human gastrointestinal tract is increasingly recognized as the gateway to pathogenic, metabolic and immunologic diseases
- Hadza have relatively low rates of infectious disease, metabolic disease and nutritional deficiencies compared to all other human populations

9

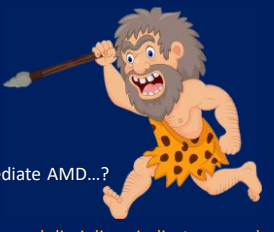
Emerging from the "Stone Age" of Macular Pigment Research

Antioxidants!

Blue-light filtration!

Protect against AMD!

...only after diagnosis of intermediate AMD...?



Convergent new research from several disciplines indicates complex, significant benefits of high L, Z, and MZ. **Across the lifespan.**

10

Where we started: Higher dietary intake of carotenoids, higher MPOD reduces risk for developing AMD

Original Contributions

Dietary Carotenoids, Vitamins A, C, and E, and Advanced Age-Related Macular Degeneration

Johnson et al. 2001; Johnson et al. 2002; Johnson et al. 2003; Johnson et al. 2004; Johnson et al. 2005; Johnson et al. 2006; Johnson et al. 2007; Johnson et al. 2008; Johnson et al. 2009; Johnson et al. 2010; Johnson et al. 2011; Johnson et al. 2012; Johnson et al. 2013; Johnson et al. 2014; Johnson et al. 2015; Johnson et al. 2016; Johnson et al. 2017; Johnson et al. 2018; Johnson et al. 2019; Johnson et al. 2020

- A higher dietary intake of carotenoids associated with a lower risk for AMD.
- Those in the highest quintile of carotenoid intake had a **43% lower risk** for AMD.
- Specifically, higher frequency of intake of spinach or collard greens was associated with a substantially lower risk for AMD.

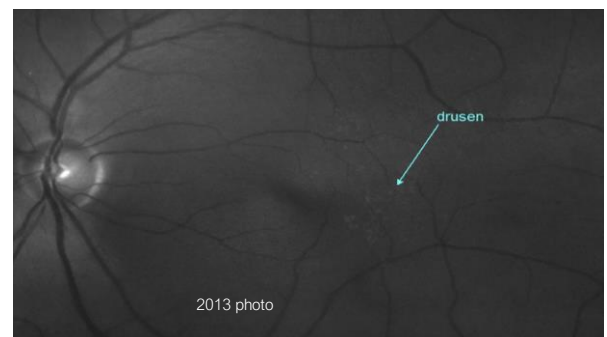
Original Contributions

Healthy Lifestyles Related to Subsequent Prevalence of Age-Related Macular Degeneration

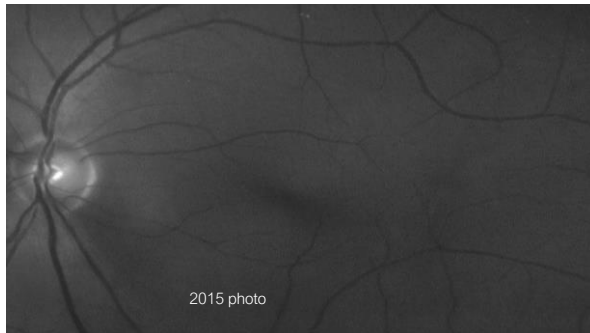
Johnson et al. 2001; Johnson et al. 2002; Johnson et al. 2003; Johnson et al. 2004; Johnson et al. 2005; Johnson et al. 2006; Johnson et al. 2007; Johnson et al. 2008; Johnson et al. 2009; Johnson et al. 2010; Johnson et al. 2011; Johnson et al. 2012; Johnson et al. 2013; Johnson et al. 2014; Johnson et al. 2015; Johnson et al. 2016; Johnson et al. 2017; Johnson et al. 2018; Johnson et al. 2019; Johnson et al. 2020

- Women whose diets scored in the highest quintile compared with the lowest quintile had **46% lower odds** for early AMD.
- Women in the highest quintile of physical activity had **54% lower odds** for early AMD.
- Having a combination of 3 healthy behaviors (healthy diet, physical activity, and not smoking) was associated with **71% lower odds** for AMD

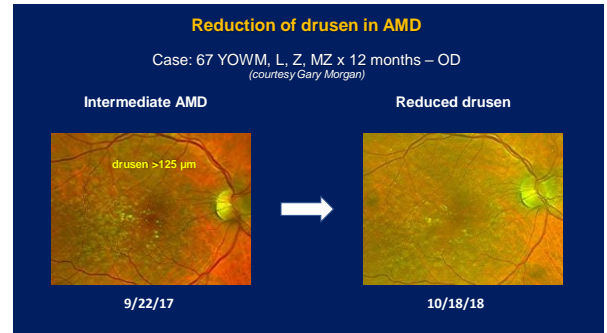
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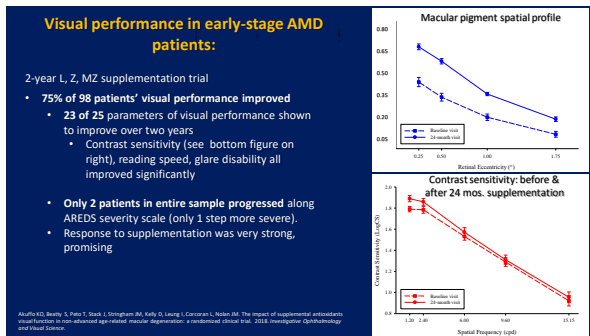
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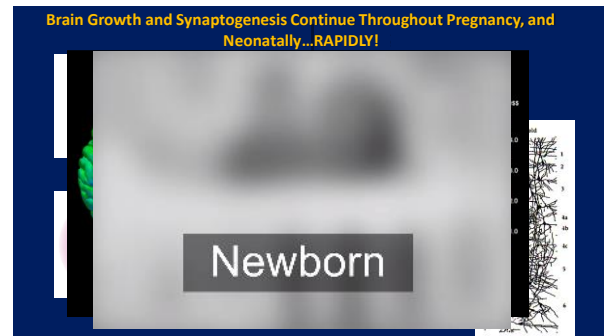
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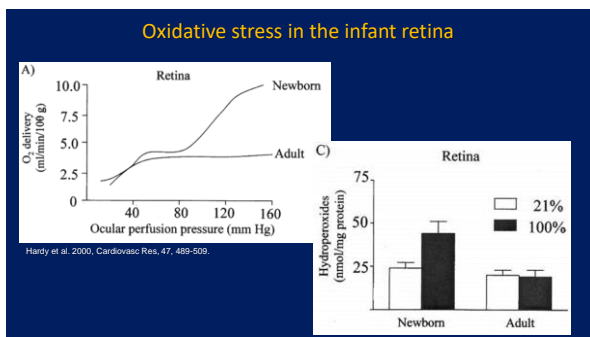
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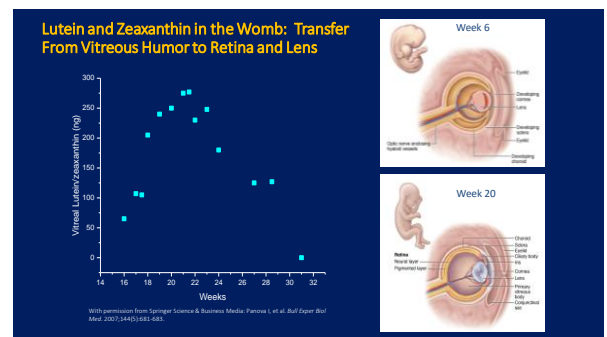
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16

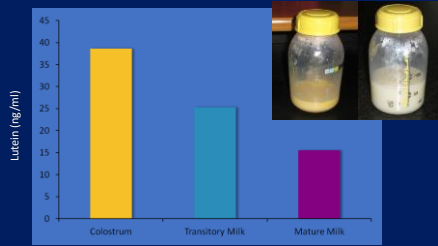


17



18

After baby is born...why is colostrum yellow...?

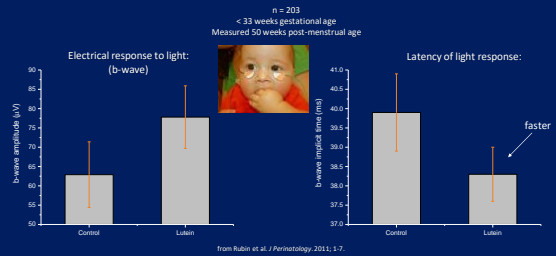


Marini C, Schwenger F. *Ann Nutr Metab*. 2001;45:82-85.

19

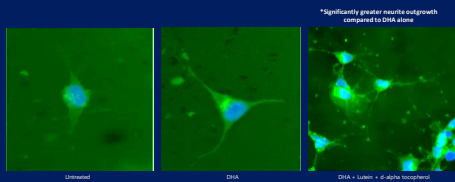
EARLY Functional Vision Benefits

Premature infants consuming lutein-supplemented formula exhibit signs of enhanced neural development in the retina



20

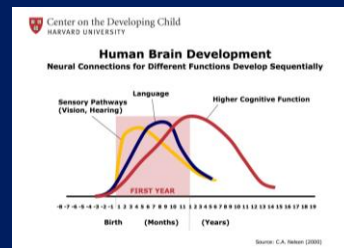
Effect of Lutein, Vitamin E (RRR- α -Tocopherol), and DHA on *in vitro* neuronal development



Naharika et al. *Contemp and Systemic Effects of the Effects of Neurodevelopment and the Role of Lutein, Vitamin E, and DHA in the Development of the Brain*. *Journal of Neurology*. November 9, 2019, San Diego, CA.

21

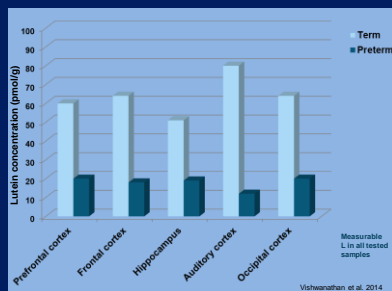
Peak of synaptogenesis (i.e. "wiring up") of the brain. 700 per second!!!



*This critical window opens once in a lifetime. Once it closes, it does not re-open. To optimize neural development, early nutritional intervention is key.

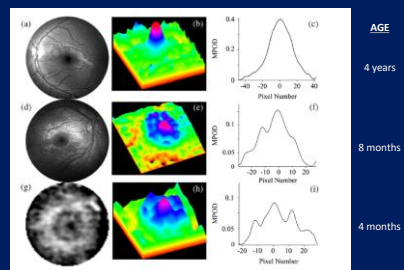
22

Lutein in the brain of term vs. preterm infants



23

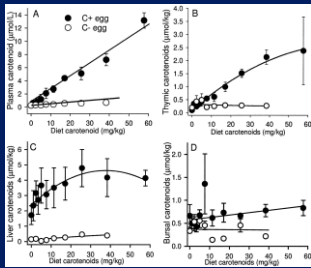
Infants and children accumulate the macular carotenoids in their retinas (macular pigment):



From Sharifzadeh et al. (2013). *Journal of Biomedical Optics*. 18(11), 116001.

24

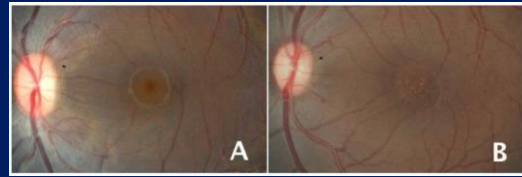
Tissue uptake of carotenoids in growing chickens is related to carotenoid exposure during embryonic development



Koussas E.A. et al. J. Nutr. 2003;133:1132-1138

25

Early diet matters: lutein and zeaxanthin-fed monkey vs. diet devoid of carotenoids



Normal diet (including lutein + zeaxanthin)

Early diet devoid of lutein + zeaxanthin

From Erdman et al. (2015)

26

Macular Carotenoids & Visual Performance

27

What is Visual Performance?

Acuity...?

Vision is a complex process

1. Speed: Temporal resolution
 - a. Reaction time
 - b. Prediction
 - c. Decision

2. Contrast sensitivity

3. Glare

4. Visual adaptation (photopigment kinetics)



28

Macular pigment and Visual Performance

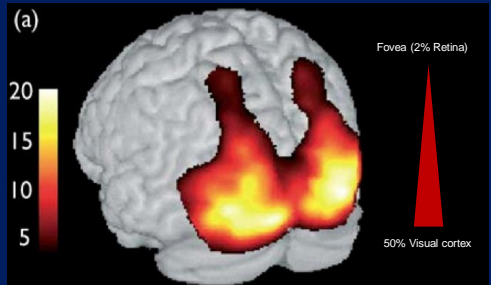


How is vision improved? At least four ways:

1. Healthy tissue
 - Lower oxidative stress, inflammation allows tissues to function more efficiently
2. Epigenetics
 - Endogenous antioxidant / physiological enhancement systems "switched on" in presence of L, Z, MZ
3. Light filtration
 - Glare effects (visual discomfort, disability glare, photostress recovery)
4. Physiology (neurophysiology)
 - Contrast sensitivity, visual processing speed, enhanced visual cycle kinetics

29

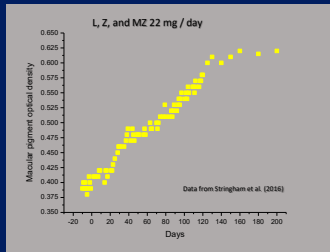
Brain activation (fMRI) while processing a simple foveal stimulus:



Courtesy Dean Sabatinelli, UGA neuroimaging

30

Retinal response to supplementation with L, Z, and MZ:

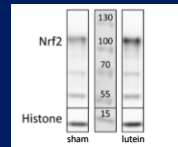


Consistent consumption of at least 12 mg / day of L / Z / MZ significantly increases MPOD (usually within 6 months)

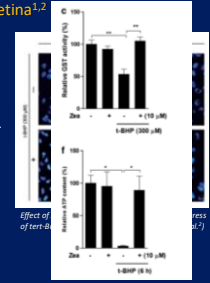
31

The Nrf2 pathway: Lutein and Zeaxanthin Enhance Expression of Genes that Significantly Benefit the Retina^{1,2}

- **Nrf2**: Regulates the transcription of genes that process and eliminate carcinogens and toxins as well as the transcription of many genes with direct or indirect antioxidant effects (e.g., glutathione, superoxide dismutase, and catalase).
- Prevent cell death
- Enhance neurophysiological performance (ATP ↑)
- Upregulated transcription levels ranged from **1.3 to 4.5 fold**.



Effect of lutein on Nrf2 activation (from Frede et al.¹)



Z / MZ enhances glutathione transferase activity (top), and raises cellular ATP levels (bottom)

32

Visual Acuity is One Aspect of Visual Performance



1862: Dutch ophthalmologist Herman Snellen developed the Snellen chart to study visual acuity.

Visual acuity is a resolution task, determined primarily by the optics of the eye.

- It has become the basis for the judgment of visual performance.



Visual acuity testing is like auditory testing with a **single intensity level** across frequencies!



33

Visual Performance in the Real World

Contrast sensitivity, acuity, and the perception of 'real-world' targets

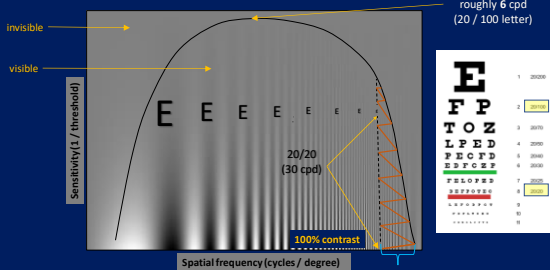
OWSLEY, SLOANE, AND WATKINS (1987): Contrast sensitivity at middle and low spatial frequencies (e.g. 6 cpd) was significant predictor of real-world object detection and identification. *Faces, road signs, basic objects*.

- CS determined to be a better predictor of performance than age!
- VA was not a significant contributor to real-world visual performance.



34

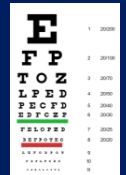
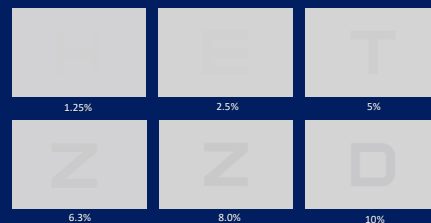
The Contrast Sensitivity Function



From Campbell & Robson, 1968

Contrast Sensitivity vs. Visual Acuity

- One may read 20/20, but may exhibit a wide range of CS:



Courtesy Mark Roark, OD

35

36

High MPOD leads to enhanced neurophysiology, improved contrast sensitivity:

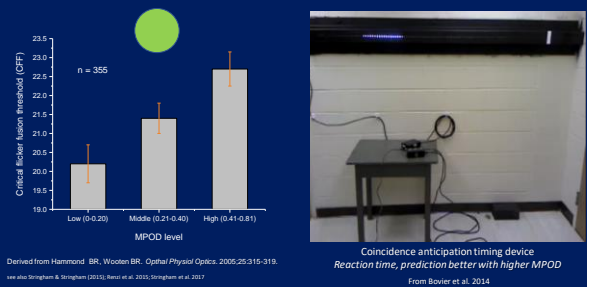


Hermann grid illusion
(Ludimar Hermann, 1870)

Stringham et al. 2017; Nolan et al. 2016; Wolf-Schwartbach et al. 2015; Stringham et al. 2011

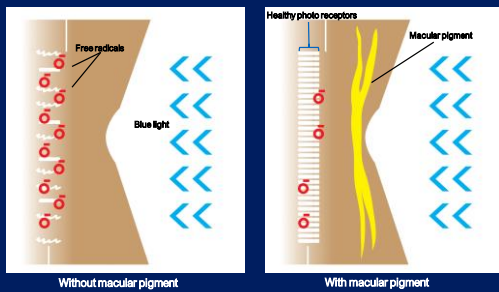
37

Visual Performance: MPOD is related to faster visual processing

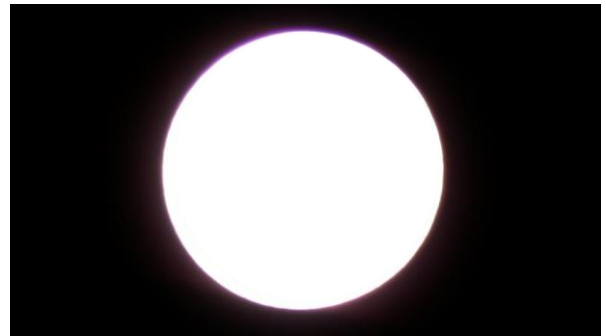


38

Blue light filtration = reduced oxidative stress:



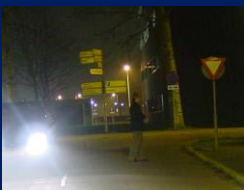
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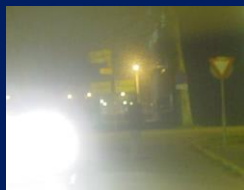
40

High vs. Low MPOD: Glare Disability Reduced

High MPOD



Low MPOD



Stringham & Hammond. *Optom Vision Sci*. 2008;85(8):88; Hammond et al. *Invest Ophthalmol Vis Sci*. 2014;55(12):8583-9; Nolan et al. (2016); Stringham et al. (2016)

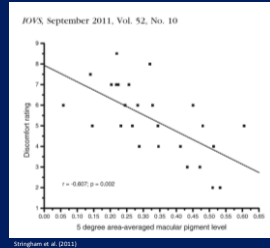
41

Light scatter from glare can give the impression of poor visual acuity:



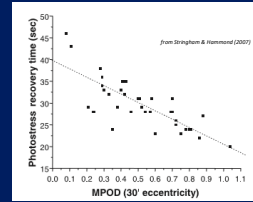
42

Effects in Glare: Higher MPOD = Lower Visual Discomfort



43

Photostress recovery and the "fatigue function"



- MPOD is related to photostress recovery time
- Increases in MPOD via supplementation with L, Z, and MZ significantly reduce PSRT*

See also Stringham & Hammond, 2008; Palayya et al. 2013; *Hammond et al. 2014; Stringham et al. 2016

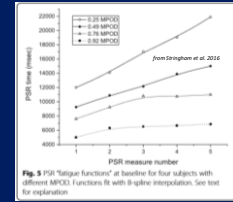


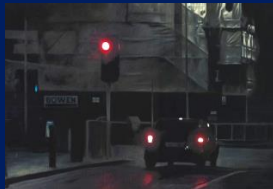
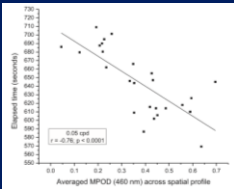
Fig. 5 PSRT "fatigue functions" at baseline for four subjects with different MPOD. Functions fit with 8-spline interpolation. See text for explanation.

Repeated exposures of a bright flash of light reveal fatigue in photostress recovery for those with low MPOD

44

MPOD Associated With Better Vision in Dim Light, Faster Dark Adaptation

Suggests increased visual cycle efficiency promoted by MCs



*Stringham & Hammond, 2008; Hammond et al. 1998; Palayya et al. 2013; Hammond et al. 2014; Stringham et al. 2016

45

Full circle: Macular Carotenoids and AMD

Case: 67 YOWM, L, Z, MZ x 12 months – OD
(courtesy Gary Morgan)

Intermediate AMD



9/22/17

Reduced drusen



10/18/18

46

OCT:

Although improved over the previous year, there are clear signs of drusen, and intermediate AMD.

Typically, this kind of situation results in severely impaired dark adaptation



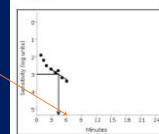
47

Case: 10/18/2018, L, Z, MZ x 12 months – Dark Adaptation

Dark Adaptation Test Results

DOB: 01-27-1951; Patient ID: 40127

Test Eye: Right
Test Date: 10-18-2018 10:33
Age at Test: 67
Protocol: Rapid Test
Pupil Size: 4.00 mm
Prescription: ---
Trial Lens: ---



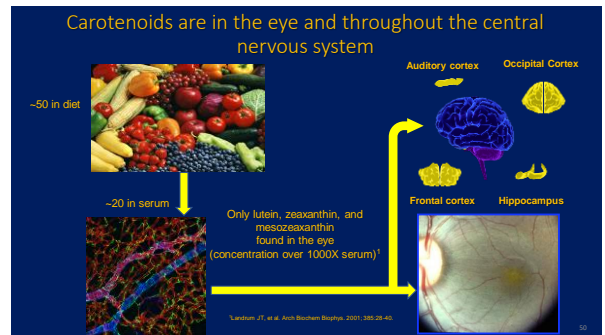
Rod Intercept is 4.36 minutes.
Fixation Error Rate is 0%.

Comments: AMD Maculopathy for 1 yr

48

Systemic & Cognitive Findings: Young, Healthy Individuals

49

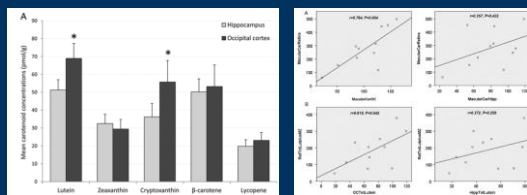


50

Relationship Between Carotenoids in the Eye and the Brain

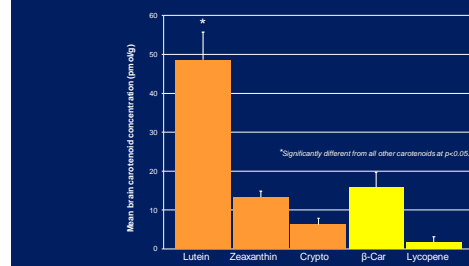
Macular pigment carotenoids in the retina and occipital cortex are related in humans

2016



51

Carotenoid concentration in the brain (mean of 4 brain regions; age 0-1 yrs)

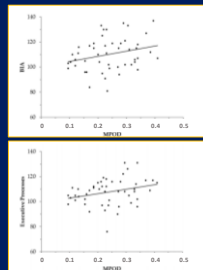


Vishwanathan R, et al. Acta Biologica Cracoviensia 2011;163 (suppl 1): Abstract 1.23

52

Pre-adolescent children (7-13 yrs.): Relationship between MPOD and Intellectual Ability / Executive Processes

- On average, children with higher MPOD:
 - Exhibit higher intellectual ability ($r = 0.268$; $p < 0.05$)
 - Verbal comprehension, concept formation, and visual matching
- Score higher on tests of executive functioning ($r = 0.288$; $p < 0.05$)
 - Higher-order cognitive abilities, including goal-directed behavior, planning, judgment, reasoning, and problem solving.



53



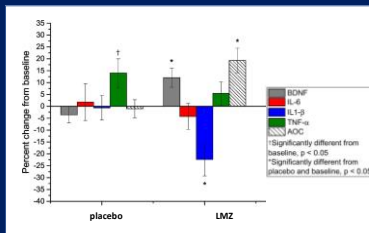
New data:

- Does macular carotenoid supplementation improve cognitive performance in **young, healthy adults (18-25 yrs)** in **6 months'** time?
 - If so, are the effects related to changes in inflammatory / oxidative stress / neuroplasticity parameters, or MPOD?

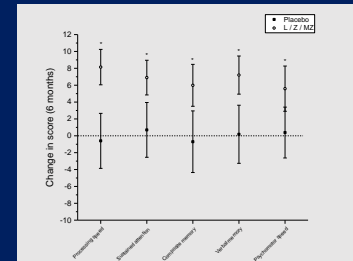
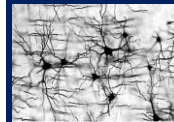


54

Results: Cytokines, BDNF, and antioxidant capacity



Cognitive Effects:



55

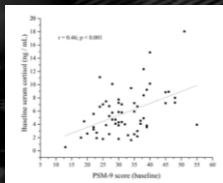
56

Supplementation with macular carotenoids reduces psychological stress, serum cortisol, and sub-optimal symptoms of physical and emotional health in young adults

Nicole Trezza Stringham ^{1,2,3,4}, Philip V. Holmes ^{1,2,3,4}, James M. Stringham ^{1,2,3,4}

¹Neuroscience Research Program, Biomedical and Health Sciences Institute, University of Georgia, Athens, GA 30602, USA; ²Department of Psychology, University of Georgia, Athens, GA 30602, USA

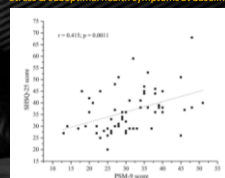
Stress & Cortisol relationship at baseline:



Benton (2012): Given the complexity and metabolic demands of the brain, signs of subclinical nutrient deficiency will manifest first as "disruption of normal brain functioning"

1-year study, supplementation with L, Z, and MZ Goal: Determine whether supplementation influences blood cortisol, psychological stress, and symptoms of emotional health.

Stress & suboptimal health symptoms at baseline:



A study on psychological stress. Hmm...where to find research participants?

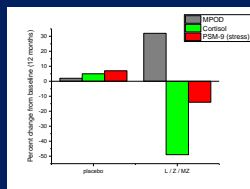


College students!!

57

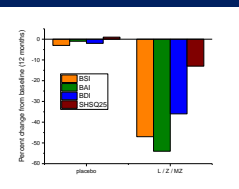
58

Effects: 12 months later



Versus placebo:

- MPOD increased significantly
- Cortisol decreased significantly (dramatically)
- Psychological stress decreased significantly



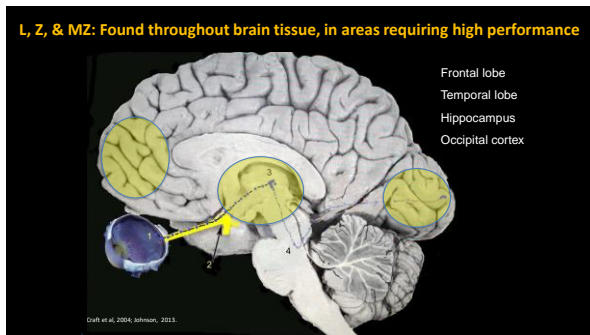
Versus placebo, symptoms of suboptimal psychological and physical health decreased significantly:

- BSI
- BAI
- BDI
- SHSQ-25

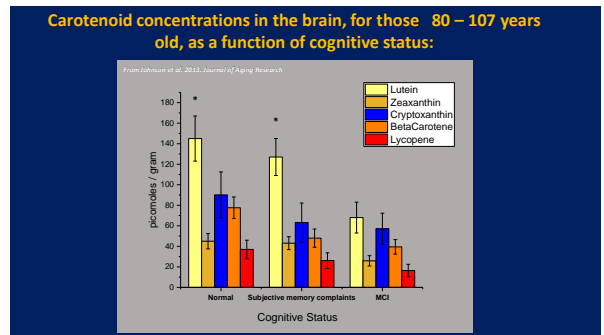
Cognitive Findings in the Elderly, Including Early Alzheimer's Disease

59

60



61



62

First evidence: Lutein and DHA improved memory, learning, and executive function in older women

- 12 mg lutein and/or 800mg DHA improved:
 - Memory scores
 - Verbal fluency
 - Rate of learning

Johnson, et al. Nutr Neurosci. 2008 Apr;11(2):75-83

63

Carotenoids in the Brain Preserve Cognitive Performance

MPOD significantly associated with:

1. Better global cognition
2. Better verbal learning and fluency
3. Better memory recall
4. Faster processing speed
5. Faster perceptual speed

n = 108, 77.6 +/- 2.7 years

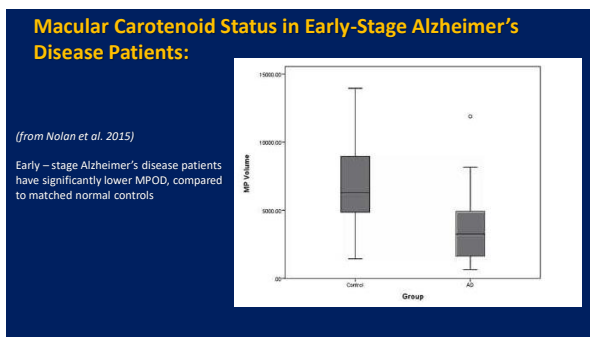
| Cognitive function measures | Serum L + Z | MPOD |
|--------------------------------|-------------|--------|
| MMSE | -0.111 | 0.260* |
| SRT: beam | 0.067 | 0.263* |
| SRT: delayed recall | 0.062 | 0.228* |
| Reaction time | 0.062 | -0.099 |
| Verbal fluency | -0.2* | 0.249* |
| Digit-symbol substitution task | -0.016 | 0.248* |
| Word naming task | -0.097 | 0.134 |
| Pattern comparison task | -0.127 | 0.197* |

MMSE, Mini-Mental State Examination; SRT, Symbolic Search; Reaction Time; *p < 0.05.

Wolfe et al. 2014, Age and Aging, 43: 271-275.

*Important point: Correlations were not determined between serum L/Z and cognition. Only retina / brain levels. Long-term accumulation in neural tissues is key.

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65

Nutritional Intervention to Prevent Alzheimer's Disease: Potential Benefits of Xanthophyll Carotenoids and Omega-3 Fatty Acids Combined

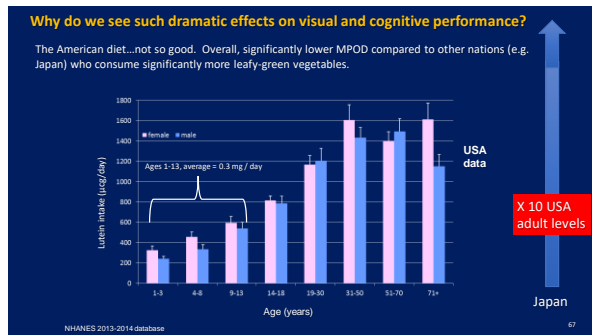
John M. Nolan, Bruce M. Nolan, Rebecca P. Nolan, Rachel M. Nolan, and John M. Nolan

New trial shows promise for limiting progression of AD

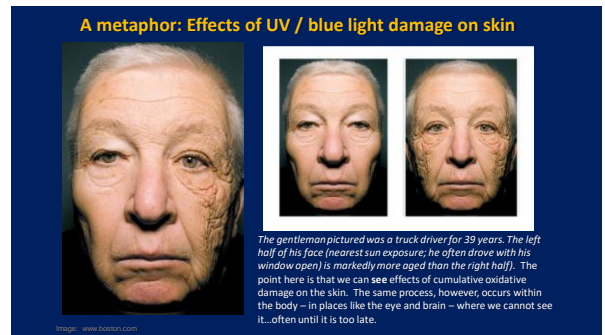
- 18-month study
- Patients with mild, moderate, and severe AD were supplemented daily with 22 mg total L, Z, MZ combined with 1 g fish oil (430 mg DHA)
- Progression of AD was significantly less for this group (p = 0.003)
 - Caregivers reported functional benefits in memory, sight, and mood
- *New study planned at Duke to confirm these results

Nolan et al. 2018

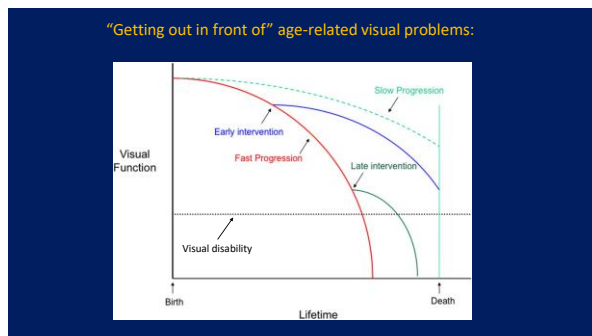
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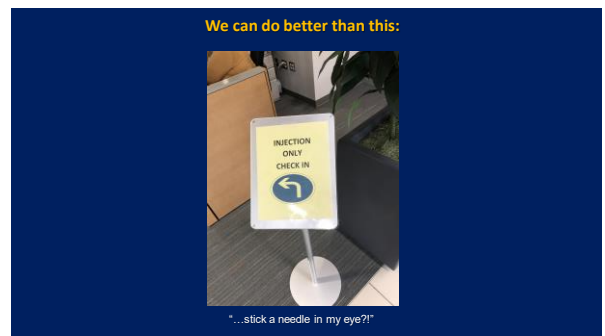
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Conclusions

The macular carotenoids have several, significant benefits across the lifespan:

- Ocular / visual development
- Visual health and performance
- Phase II (epigenetic) effects
- Cognitive health and performance
 - Across the lifespan
 - May prolong onset of age-related cognitive decline
 - May preserve function in midst of disease

...oh, and relatively high MPOD can help reduce the risk of / slow the progression of AMD!

All of these effects can facilitate a conversation about nutrition with patients

71

Acknowledgments

Collaborators

UGA: Phil Holmes

US Army Aeromedical Research Laboratory: Kevin O'Brien

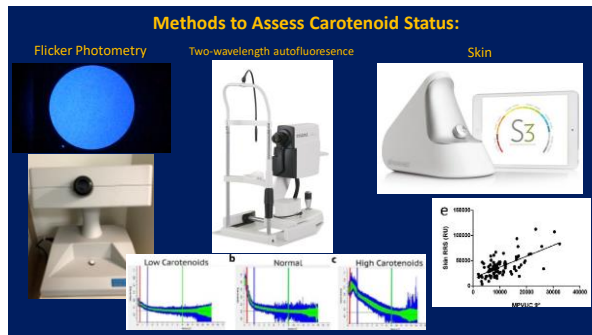
Air Force Research Laboratory: Leon McLin, Peter Smith, Paul Garcia

Duke: Felipe Medeiros, Alessandro Jammal, Tais Estrela, Eduardo Mariottoni, Carla Urata

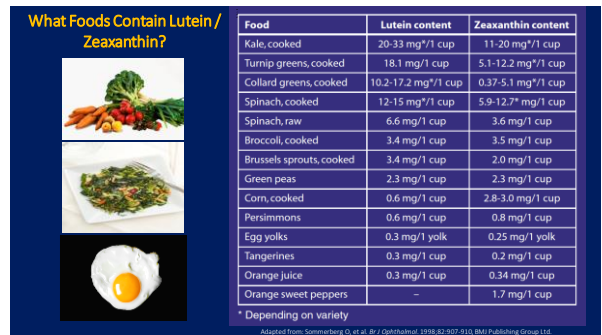
University of the Incarnate Word Optometry School: Brian Foutch

Allisonville Eye Care Center (IN): Mark Raark

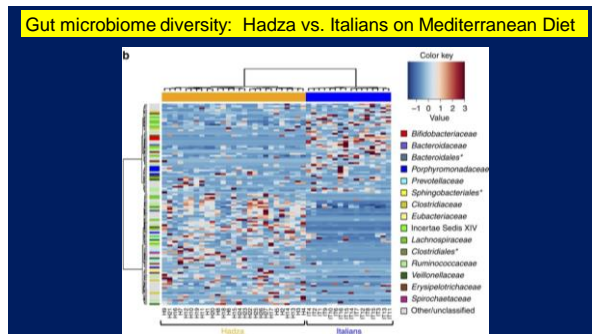
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