Effects of Macular Carotenoids on Eye, Brain, and Body

Duke Eye Center

James M. Stringham, Ph.D.
Visual Performance Laboratory
Duke Eye Center
Duke University Medical School
Department of Ophthalmology
james.stringham@duke.edu

visual performance laboratory

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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)

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The "Rusty Pipe Wrench Experiment"

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The "Rusty Pipe Wrench Experiment"

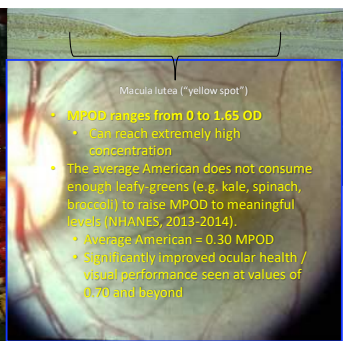
4

The "Rusty Pipe Wrench Experiment"

5

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



- **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

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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

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Emerging from the "Stone Age" of Macular Carotenoid 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.

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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

Seddon et al. 1994

- 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.

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

Mares et al. 2011, CAREDS study

- 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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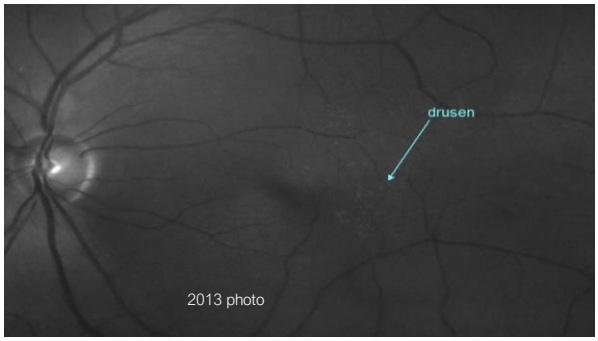

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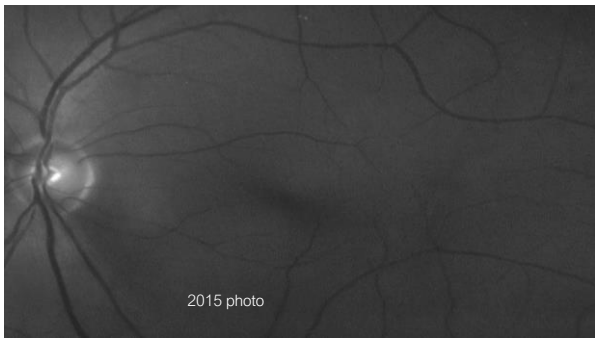

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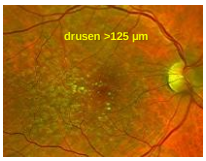
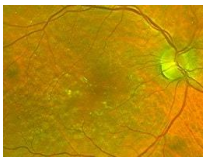
Reduction of drusen in AMD

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

Intermediate AMD

Reduced drusen





9/22/17

10/18/18

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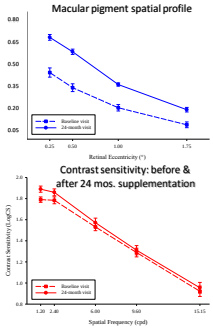
Visual performance in early-stage AMD patients:

2-year L, Z, MZ supplementation trial

- 75% of 98 patients' visual performance improved
  - 23 of 25 parameters of visual performance shown to improve over two years
    - Contrast sensitivity (see bottom figure on right), reading speed, glare disability all improved significantly
  - Only 2 patients in entire sample progressed along AREDS severity scale (only 1 step more severe).
    - Response to supplementation was very strong, promising



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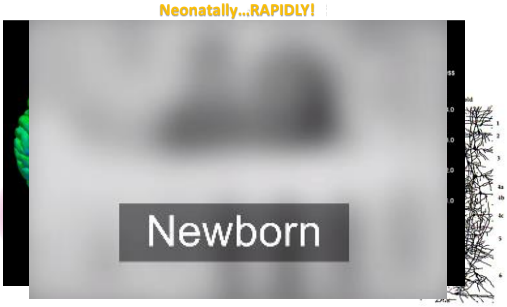
Brain Growth and Synaptogenesis Continue Throughout Pregnancy, and Neonatally…RAPIDLY!



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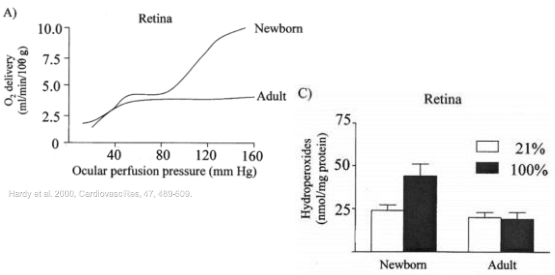
Oxidative stress in the infant retina



Hardy et al. 2000, Cardiovascular Res, 47, 489-509.

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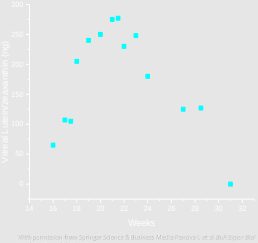
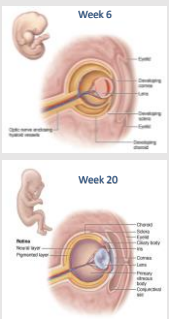
Lutein and Zeaxanthin in the Womb: Transfer From Vitreous Humor to Retina and Lens





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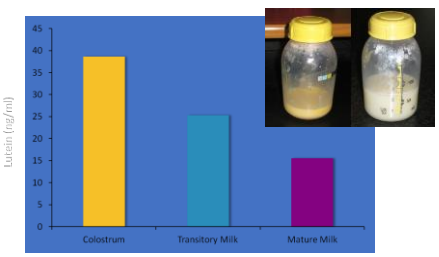
After baby is born…why is colostrum yellow…?



Macias C, Schweigert FJ. Ann Nutr Metab. 2001;45:82-85.

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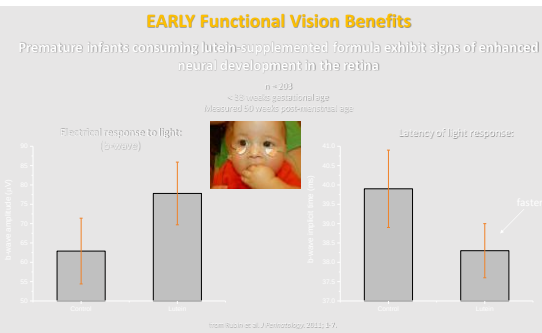
EARLY Functional Vision Benefits

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



from Rubin et al. J Perinatology 2011; 1-7.

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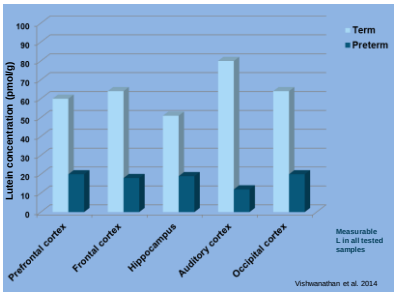
Lutein in the brain of term vs. preterm infants



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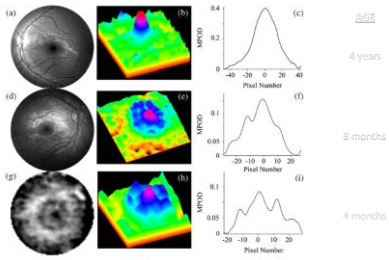
Infants and children accumulate the macular carotenoids in their retinas (macular pigment):



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

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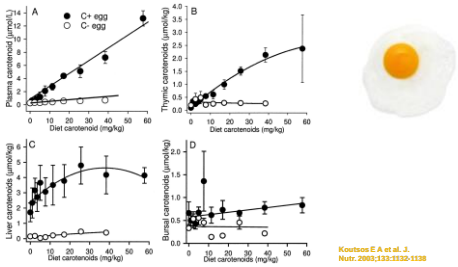
Tissue uptake of carotenoids in growing chickens is related to carotenoid exposure *during embryonic development*



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

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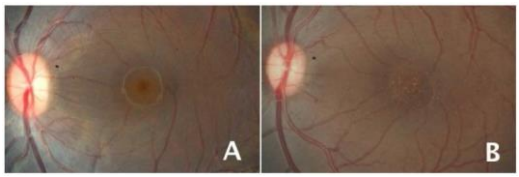
Early diet matters: lutein and zeaxanthin-fed monkey vs. diet devoid of carotenoids



Normal diet (including lutein + zeaxanthin) | Early diet devoid of lutein + zeaxanthin

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Why Do We Accumulate Macular Carotenoids?

Visual Performance

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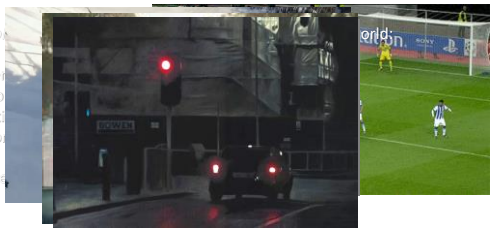
What is Visual Performance?

Acuity…?
Vision is a co

1. Speed: Te
   a. Reactio
   b. Predicti
   c. Decisio
2. Contrast se
3. Glare



4. Visual adaptation (photopigment kinetics)

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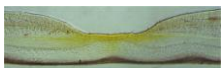
Macular pigment and Visual Performance



How? 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

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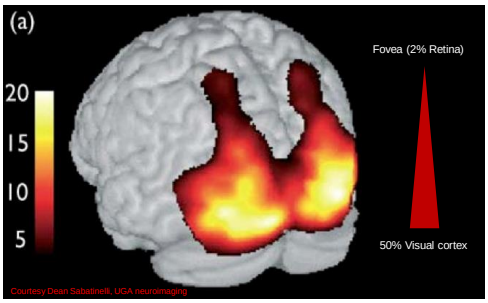
Brain activation (fMRI) while processing a simple foveal stimulus:



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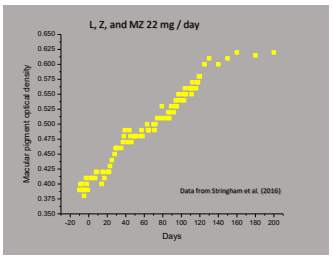
Retinal response to supplementation with L, Z, and MZ:



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

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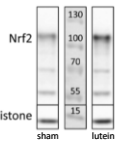
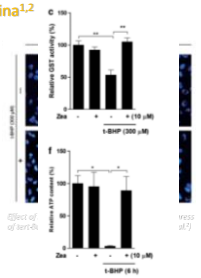
The Nrf2 pathway: Lutein and Zeaxanthin Enhance Expression of Genes that Significantly Benefit the Retina[1,2]

- 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.)



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

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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!

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Visual Performance in the Real World

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

Owsley & Sloane (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.

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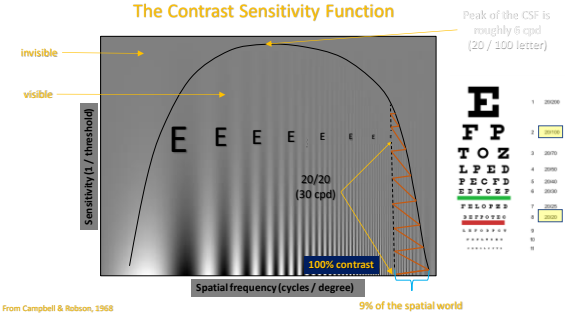
The Contrast Sensitivity Function



From Campbell & Robson, 1968

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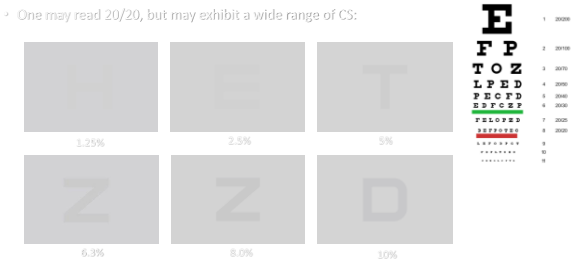
Contrast Sensitivity vs. Visual Acuity

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



Courtesy Mark Roark, OD

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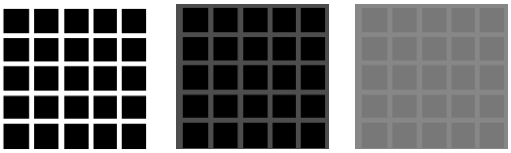
High MPOD leads to enhanced neurophysiology, improved contrast sensitivity:



Hermann grid illusion
(Ludimar Hermann, 1870)

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

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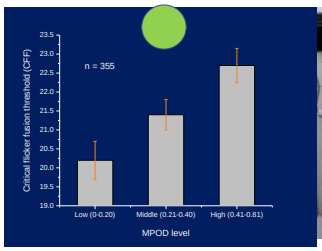
Visual Performance: MPOD is related to faster visual processing



Derived from Hammond BR, Wooten BR. *Optical Physiol Optics*. 2005;25:315-319.

see also Stringham & Stringham (2013); Reed et al. 2015; Stringham et al. 2017

Coincidence anticipation timing device
Reaction time, prediction better with higher MPOD
From Bovier et al. 2014

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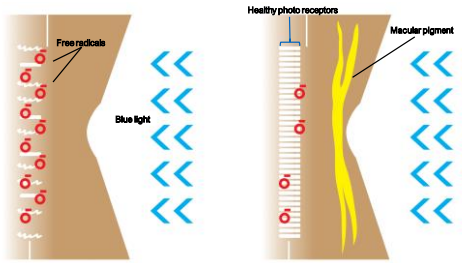
Blue light filtration = reduced oxidative stress:



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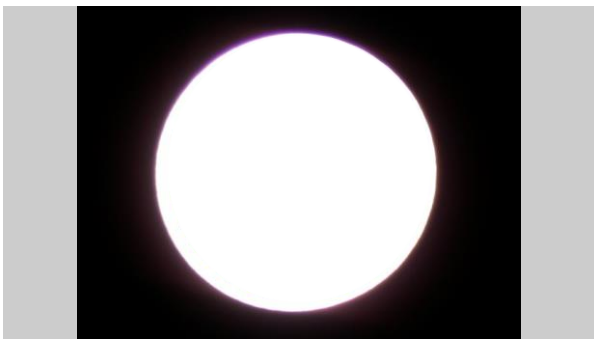

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High vs. Low MPOD: Glare Disability Reduced

High MPOD

Low MPOD

Stringham & Hammond. Optom Vision Sci. 2008;85:82-88; Hammond et al. Invest Ophthalmol Vis Sci. 2014;55(12):8583-9.; Nolan et al. (2016); Stringham et al. (2016)

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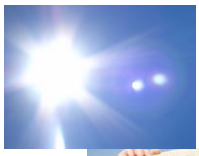
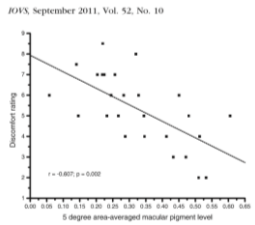
Effects in **Glare**: Higher MPOD = Lower Visual Discomfort





Stringham et al. (2011)

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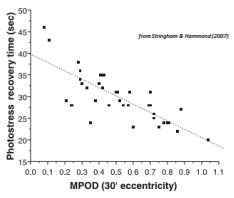
Photostress recovery and the "fatigue function"



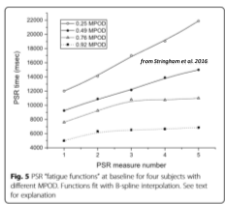


Fig. 5 PSR "fatigue functions" at baseline for four subjects with different MPOD. Functions fit with B-spline interpolation. See text for explanation.

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

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

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

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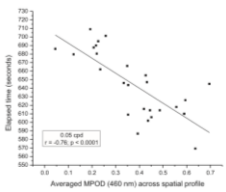
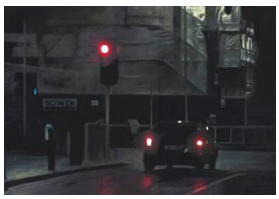
MPOD Associated With Better Vision in Dim Light, Faster Dark Adaptation





Stringham et al. 2015

*Stringham & Hammond, 2008; Hammond et al. 1996; Putnys et al. 2013; Hammond et al. 2014; Stringham et al. 2016

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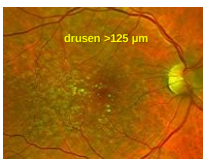
Full circle: Macular Carotenoids and AMD

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

Intermediate AMD



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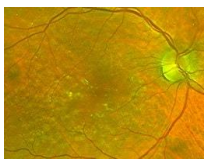
Reduced drusen



10/18/18

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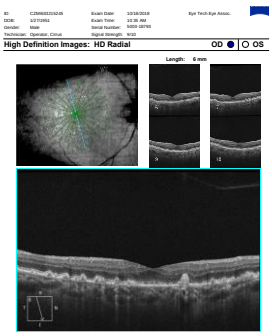
OCT:

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



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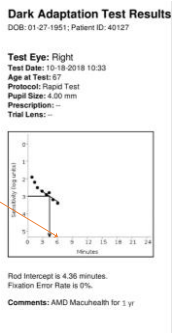
Case: 10/18/2018, L, Z, MZ x 12 months – Dark Adaptation

6 minutes is considered the point of DA impairment



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Systemic & Cognitive Findings: Young, Healthy Individuals

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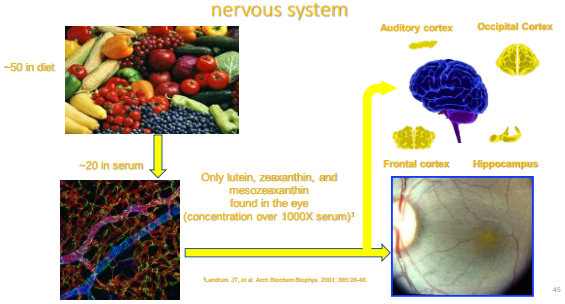
Carotenoids are in the eye and throughout the central nervous system



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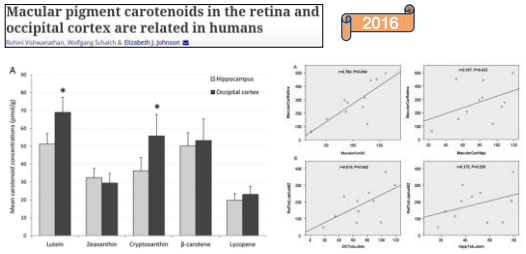
Relationship Between Carotenoids in the Eye and the Brain



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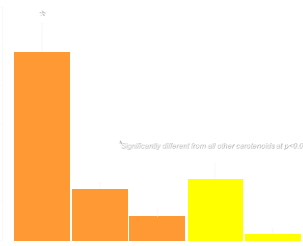
Carotenoid concentration in the brain (mean of 4 brain regions; age 0-1 yrs)



Vishwanathan R, et al. *Acta Biologica Cracoviensia*2011;153 (suppl 1)..Abstract 1.23

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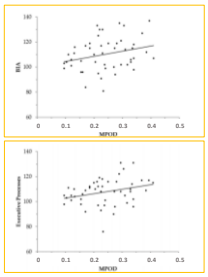
Pre-adolescent children (7-13 yrs.): Relationship between MPOD and Intellectual Ability / Executive Processes

- 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.



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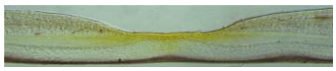
New data:

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



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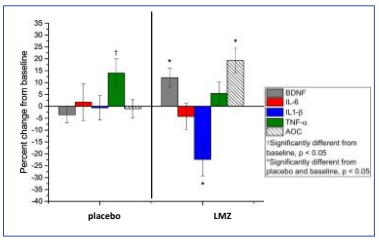
Results: Cytokines, BDNF, and antioxidant capacity



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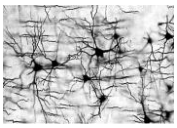
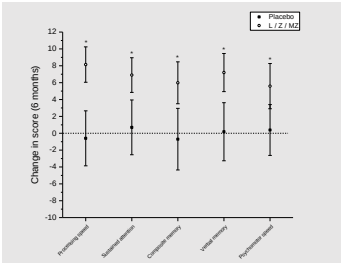


Cognitive Effects:



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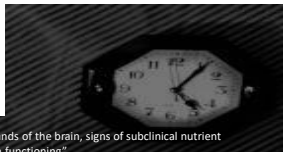
Supplementation with macular carotenoids reduces psychological stress, serum cortisol, and sub-optimal symptoms of physical and emotional health in young adults

Nicole Tressa Stringham, Philip V. Holmes, James M. Stringham



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.

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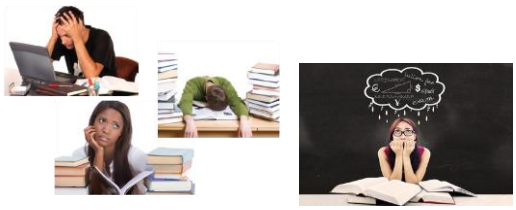
A study on psychological stress. Hmm…where to find research participants?



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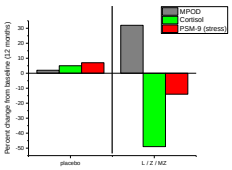
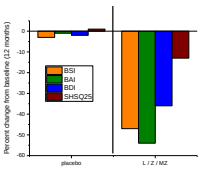
Effects: 12 months later





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
- BDA
- SHSQ-25

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

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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

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Carotenoids in the Brain Preserve Cognitive Performance

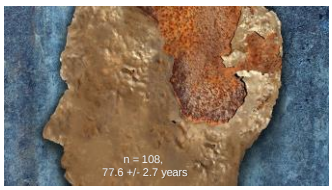
MPOD significantly associated with:

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

Cognitive function measures	Serum L + Z	MPOD
3MS	~0.111	0.269*
SRT: learn	0.067	0.263*
SRT: delayed recall	0.062	0.223*
Reaction time	0.062	~0.059
Verbal fluency	~0.2*	0.249*
Digit-symbol substitution task	~0.016	0.249*
Box drawing task	~0.097	0.154
Pattern comparison task	~0.127	0.195*

3MS, Teng Modified Mini-Mental State Examination; SRT, Buschke Selective Reminder Test.
*P ≤ 0.05.

Vishwanathan et al. 2014, Age and Ageing; 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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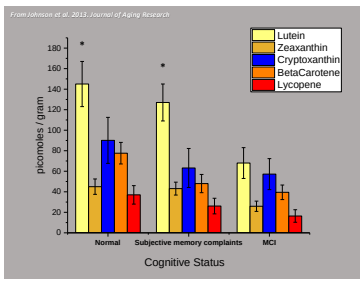
Carotenoid concentrations in the brain, for those 80 – 107 years old, as a function of cognitive status:

From Johnson et al. 2013; Journal of Aging Research



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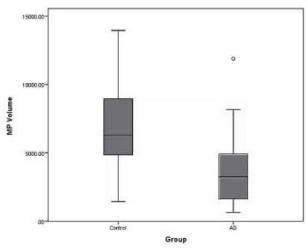
Macular Carotenoid Status in Early-Stage Alzheimer's Disease Patients:

(from Nolan et al. 2015)

Early – stage Alzheimer's disease patients have significantly lower MPOD, compared to matched normal controls



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

Nolan JM et al. 2018

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

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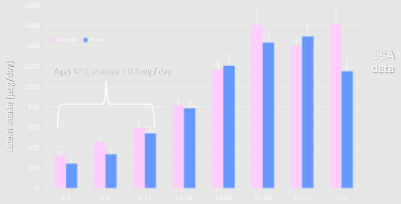
Why do we see such dramatic effects on visual and cognitive performance?

The American diet…not so good. Overall, significantly lower MPOD compared to other nations (e.g. Japan) who consume significantly more leafy green vegetables.



X 10 USA adult levels

Japan

NHANES 2013-2014 database

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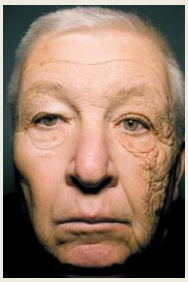
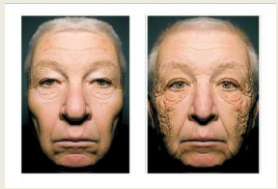
A metaphor: Effects of UV / blue light damage on skin





The gentleman pictured was a truck driver for 39 years. The left half of his face (nearest sun exposure; he often drove with his window open) is markedly more aged than the right half). The point here is that we can see effects of cumulative oxidative damage on the skin. The same process, however, occurs within the body – in places like the eye and brain – where we cannot see it…often until it is too late.

Image: www.boston.com

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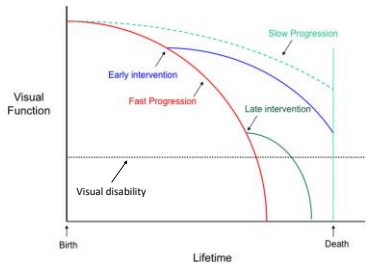
"Getting out in front of" age-related visual problems:



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We can do better than this:

"…stick a needle in my eye?!"

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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

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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 Roark*

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