Seeing the world through rose-colored glasses: Connections between the retina and areas of the brain that control mood

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PRESENTER HAS NO FINANCIAL CONFLICTS OF INTEREST TO DISCLOSE REGARDING THIS PRESENTATION
One third of older adults with visual impairment experience increased depression and anxiety symptoms

- May lead to clinical diagnoses of anxiety or affective disorders
- A moving target: symptoms tend to fluctuate over time

(Statistics from Eramudugolla et al. 2013)
MOOD DISORDERS AND VISUAL IMPAIRMENT

Multicenter study of mental health in outpatient low-vision rehab clinics in Netherlands & Belgium (Heesterbeek and colleagues 2017)

Patient population of 50-95 year-old women & men with low or impaired vision due to macular degeneration, glaucoma, cataracts, stroke, & diabetic retinopathy

Data showed that these patients experienced TWICE the rate of subclinical depression and anxiety as similarly-aged people without visual impairment!

- 21.3% depression
- 9.5% anxiety
- Patients with macular degeneration had the most severe mood symptoms
- Prior history of mental illness did not affect these rates
Anxiety and depressive disorders are caused by deficiencies in the amount and activity of serotonin in the brain.

Serotonin is a neurotransmitter involved in regulation of mood, stress response, appetite, sleep cycle, circadian rhythms and many other processes.

Fun fact: Only 1-2% of body’s entire serotonin supply is in the brain & nervous system. The majority is in our digestive system!
Too much stress!
Decrease in brain levels of serotonin
Impaired ability of brain to cope with stress
Anxiety disorders and depression

Medications that restore brain serotonin levels treat anxiety & depression

Having impaired vision is a stressful life change!

But could more complex factors also contribute to the relationship between visual impairment, stress, and brain serotonin?
WHERE BRAIN SEROTONIN IS MADE

Most of the serotonin used by the brain is made by neurons in the **raphe nuclei** of the brainstem

- *Raphe* = “seam”
- There are several raphe nuclei, but the largest group of cells that produces the most serotonin = **dorsal raphe nucleus (DRN)**

*Bright cells = serotonergic neurons*

Images from C.Crish lab
THE SEROTONIN SUPPLY LINE

DRN and other raphe nuclei send long serotonergic axonal projections to just about everywhere in the brain...including the retina and other visual structures!

If serotonin production in the DRN is reduced or stopped there are going to be problems everywhere
RETINORAPHE PROJECTION

Bidirectional serotonergic pathway between the retina and DRN

Two major mechanisms:

1. Transmits serotonergic signals from the DRN to cells within the retina to alter visual processing
2. Transmits visual signals from the retina to the DRN to alter serotonin production
BRAIN TO THE EYES: DRN \(\rightarrow\) RETINA

There are receptors for serotonin on many cells in the retina (RGCs & amacrine).

Serotonin signaling at these receptors is shown to:

- Alter firing rate of retinal cells to facilitate dark adaptation & changes sensitivity to light (Trakhtenberg et al. 2016)
- Enhance contrast detection (Bubl et al. 2010)
- Fine-tune visual processing to speed retinal responsiveness (Lorincz et al. 2008)

= Enhance visual vigilance

Evolutionarily: when faced with a threat/stressor, enhanced vigilance or visual processing can help us detect and respond to threat (fight or flight) (Miceli et al. 2002)

Clinically: Patients with depression show reduced contrast sensitivity (Bubl et al., 2010), subtle visual processing deficits (Normann et al., 2007)
A specific subtype of retinal ganglion cells (Y-alpha RGCs) regulate serotonin production in the DRN.

Within the Y-alpha subtype, “OFF-center” RGCs that respond to decrement or offset in light (contrast detectors) have axons that directly synapse on serotonin neurons in DRN.
Mechanism of RGC control over DRN and mood

Experimental evidence from Ren et al. 2013 and Zhang et al. 2016:

Silence RGCs $\rightarrow$ reduce serotonin in DRN and increase depressive behaviors in lab mice!

Increase RGC firing rate $\rightarrow$ increase serotonin production in DRN and produce antidepressant-like effect in lab mice!

Technical note: these effects pertain specifically to the OFF-center Y-alpha RGCs. Additional regulatory effects on DRN neurons are provided by ON-center Y-alpha RGCs (Zhang et al. 2016).
Decreased visual contrast

Decreased Y-alpha OFF RGC activity

Less production of serotonin by DRN

Global deficits in brain serotonin networks

Detrimental impact on mood and other serotonin-regulated processes

Evidence: seasonal or light-induced changes in mood

Seasonal affective disorder (SAD)

- Decrease in daylight exposure during autumn can induce depressive symptoms
- Light exposure therapy can be used to effectively treat SAD
CONCLUSIONS ON MOOD AND VISION

THE BAD NEWS:

There is increased likelihood that persons with visual impairments involving compromised retinal cells will experience clinically-relevant levels of depression or anxiety.

This vulnerability may be caused by lifestyle changes due to vision loss AND/OR biological factors related to retinoraphe dysfunction.
Research indicates that:

Antidepressant medications that restore serotonin levels can be effective in correcting retina-induced deficiencies in serotonin and restoring positive mood.

Improvement in lifestyle factors such as better behavioral adaptation to vision loss, assistance with disability accommodations, and enhanced social support are associated with more positive outcomes and less depression and anxiety.
ACTIONS TO TAKE!

**Practitioners:** MONITOR MONITOR MONITOR your low vision patients for signs of mood change, depression or anxiety! Understand levels of these moods may fluctuate over time so there is a need to assess them on a regular basis.

**Patients with low vision:** Don’t feel embarrassed to tell your healthcare providers if you feel depressed or anxious, are losing interest in your daily activities, are worrying excessively or aren’t feeling quite like yourself.

Improving your outlook on life doesn’t have to depend on your eyes seeing clearly!
SELECTED RESOURCES FOR FURTHER READING ON THIS TOPIC


Trakhtenberg et al. 2016. Serotonin receptor 2C regulates neurite outgrowth and is necessary for normal retinal processing of visual information. Developmental Neurobiology, DOI 10.1002/dneu.22391


