Visual, Auditory, and Somatosensory Impairment in Neurodegenerative Disorders

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Disclosures

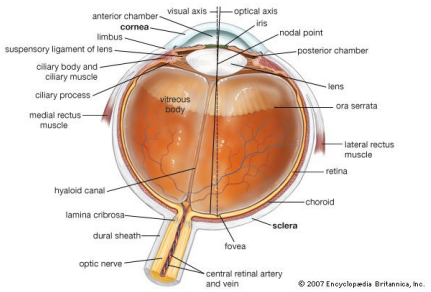
- Speaking, consulting, advisory board activities from Biogen, Genzyme, Novartis, Genentech, Bristol Myers Squibb, and EMD Serono

Objective

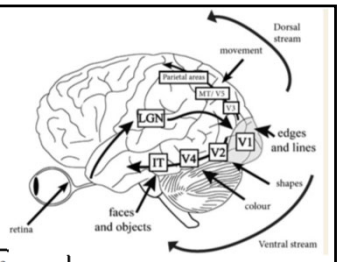
- Brief review of anatomy of visual, auditory and somatosensory systems
- Discuss how these three systems are impacted by the neurodegenerative diseases of MS, PD, and AD.

Visual System

- Visual Acuity and Contrast Sensitivity
  - Eye Disorders – Cataracts, Retinal Detachment, Glaucoma
  - Optic Nerve – inflammation
- Visual Cortex
  - Visual spatial cognition
  - Hallucinations
- Oculomotor Control
  - Double Vision
  - Saccadic and smooth pursuit dysfunction



Visual Spatial Impairment in Neurodegenerative Disorders



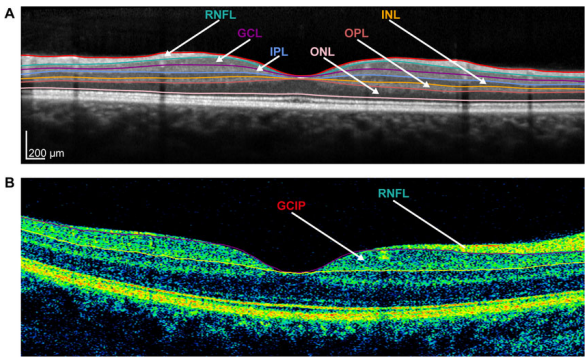
Typical Constellation of Visual Spatial Impairments in the Early Stages of Neurodegenerative Diseases

	Bottom-up / top-down	Dorsal / ventral	Allocentric / egocentric
Alzheimer's disease	Bottom-up most patients, although some patients show top-down	Both are often affected	Allocentric
Posterior cortical atrophy	Bottom-up, all patients	Dorsal more than ventral, although both are affected with disease progression	Patients cannot use either frame of reference well due to severe bottom-up impairments
Parkinson's disease	Top-down	Dorsal	Egocentric
Lewy body dementias	Both, nearly all patients	Both, nearly all patients	Unknown, likely both in most patients
Corticobasal syndrome	Variable, top-down likely more common but in some patients bottom-up can be prominent, as discussed in text	When visual spatial processing is affected, dorsal impairments are usually more severe	Unknown, likely egocentric
Progressive supranuclear palsy	Top-down attentional impairment is common	Patients have difficulty orienting spatial attention, but cortical dorsal / ventral streams are usually intact	Unknown, likely egocentric
Behavioral variant frontotemporal dementia	Top-down, most patients, although in early stages no visual spatial impairment may be evident	Not impaired	Unknown, may vary with pathologic subtypes
Semantic dementia and Progressive nonfluent aphasia	Not impaired	Neither impaired early, although SD may affect ventral stream processing with disease progression	Not impaired

Possin 2010,
Weil et al, 2016

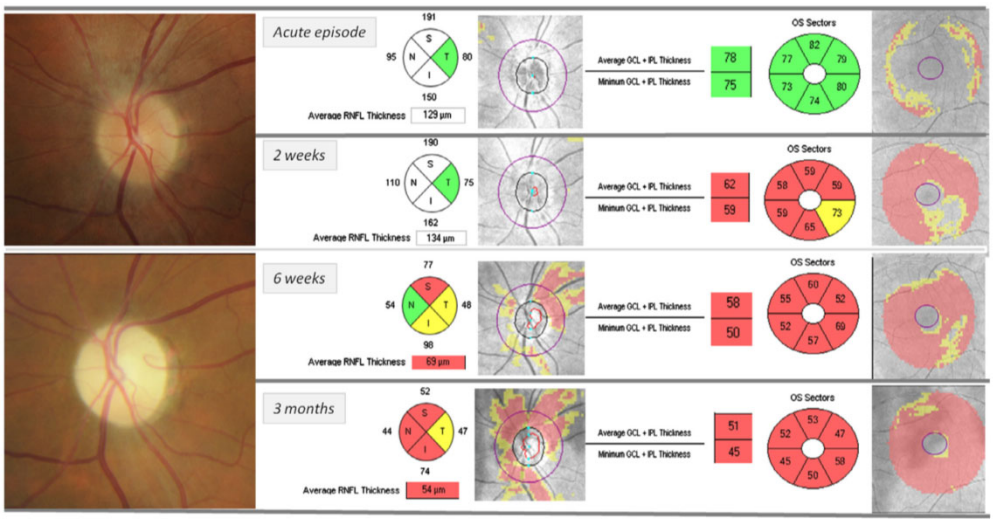
Optical Coherence Tomography - OCT

- Non-invasive study using near infrared light waves to provide cross-sectional images of retina
- Identify neuroaxonal injury, surrogate for neurodegenerative diseases
- AD, PD, HD, MSA, SCA, spastic paraparesis, MS, etc
  - Retinal nerve fiber layer – axonal loss
  - Ganglion cell-inner plexiform layer – neuronal damage



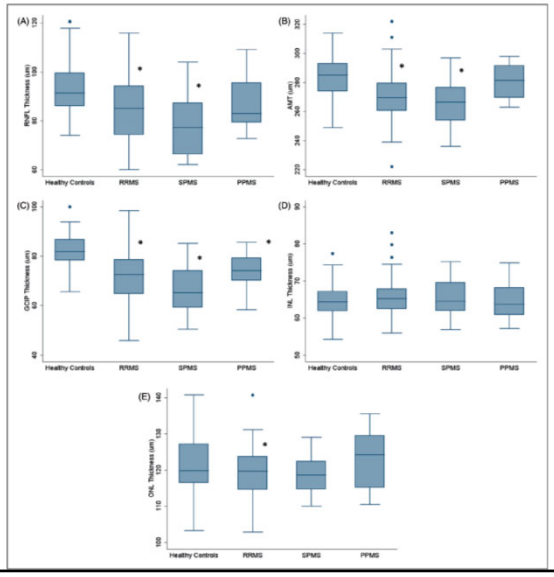
Oberwahrenbrock et al, 2015

Acute Optic Neuritis



Rebolleda et al, 2015

RNFL and GCIP thinning in MS subtypes



Saidha et al, 2011

AD and Vision Loss

- Postmortem studies in AD showed substantial loss of retinal ganglion cell
- Amyloid-beta deposits occur in retina of patients with AD
- RNFL and GC-IP thinning in patients with AD, associated with brain atrophy on MRI
- In a study of 3289 individuals (mean age 68.9, 57% women).
  - 1.2% had dementia
  - 37% higher risk of dementia in those with thinner GC-IPL
  - Thinner RNFL at baseline associated with 44% higher risk of dementia, and 43% higher risk of AD

Mutlu et al, 2018

RNFL thinning associated with future cognitive decline

- UK Biobank prospective study
- 32,038 participants, mean age 56.0, 53.6% women
- Exclude eye disease, vision loss, history of ocular or neurological disease, or diabetes
- Thinnest RNFL quintile 11% more likely to fail 1 cognitive test at baseline
- Follow up cognitive testing in 1251 participants, 3 years later
- Those with 2 thinnest quintiles were twice as likely to have at least 1 worse test score at follow-up

Figure 1. Proportion of UK Biobank Participants Exhibiting a Cognitive Deficit at Baseline Testing

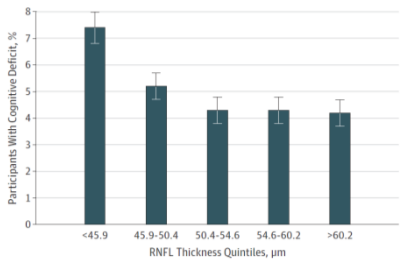
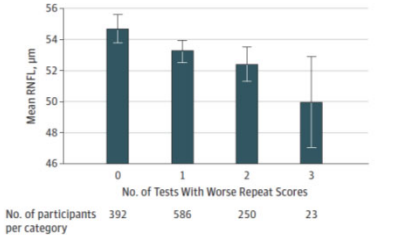


Figure 2. Proportion of UK Biobank Participants Exhibiting a Decline in Cognitive Function on Repeat Assessment



Ko et al, 2018

Retinal changes in PD

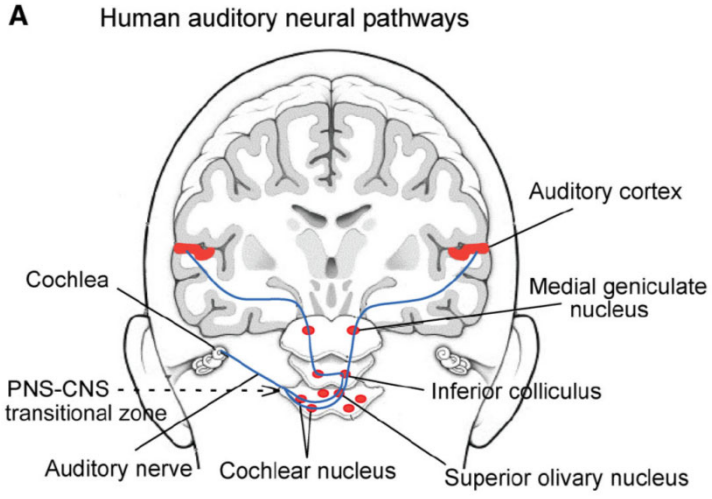
- Retinal cells have high concentration of dopamine
- Deposition of alpha-synuclein in retinal ganglion cells in clinicopathology studies
- Thinning of RNFL and GCIP layer observed
- No significant correlation to disease severity or duration

Pathophysiological changes in the retinal layers in Parkinson's disease: Insight from OCT studies.

Observation	Interpretation
Thinning of the inner retinal layers which contain the dopaminergic amacrine cells [22–25,31,32,36,40,46,54–57]	Dopaminergic depletion [5]
Thicker outer plexiform layer [23,36,43]	Alpha synuclein deposition [80,81]
Thinner outer nuclear layer and photoreceptor layer [45]	Dopamine deficiency
Decreased thickness of temporal RNFL [25–27,36]	Mitochondrial toxicity [27]
Changes in the thickness of choroid and retinal vessel diameter [12,40,75–77]	Vascular disturbances

Mailankody et al, 2019

Auditory System



Jafari et al, 2020

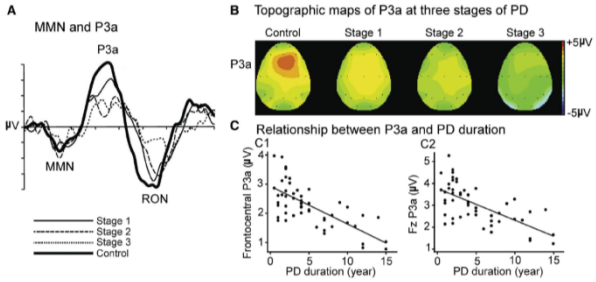
Hearing Loss and Dementia

Sherard Audiology, Johnson et al, 2021

Syndrome	Core clinical features	Key auditory symptoms	Auditory deficits[a]	Proposed auditory diagnostic test[b]	Pathological neuroanatomy[c]
Alzheimer's disease					
Typical	Episodic/topographical memory loss, parietal deficits	Difficulty tracking sound sources/information in busy acoustic environments, auditory disorientation, difficulty understanding less familiar accents, auditory agnosia, increased sound sensitivity	Scene analysis, localization, attention, melody contour, accents, environmental sound recognition, working memory	Auditory stream separation, sound localization/motion detection[i], DLT[1,2,3,4]	Posterior cingulate, precuneus, lateral temporo-parietal cortex
PCA[d]	Visuo-perceptual/visuo-spatial, other parietal deficits	Similar or more severe than typical AD	More severe involvement of auditory scene /spatial processing	Auditory stream separation, sound localization/motion detection[i,2,5,j]	
LPA[d]	Anomia, phonological and verbal working memory deficits	Similar or more severe than typical AD	Phoneme perception, prosody perception, working memory	Phoneme discrimination[j,6]	
LBD[e]	Fluctuating alertness/attention/executive deficits, visuo-perceptual deficits, visual hallucinations, REM sleep behaviour disorder, parkinsonism	Auditory hallucinations	Pure tone detection, complex tone perception, auditory scene analysis, rhythm perception, speech loudness perception	Sinewave speech comprehension[k,7,8]	Cortico-subcortical circuits
FTD					
nfvPPA	Speech production deficits, agrammatism	Agnosia for environmental sounds/accents, word deafness[f]	Pure tone detection, perception of pitch interval/timbre/rhythm/prosody, accent comprehension	Temporal pattern discrimination[9]	Peri-Sylvian networks, prefrontal cortex
svPPA	Anomia and vocabulary loss, visual agnosias, behavioural changes similar to bvFTD	Musicophilia/sound aversion[g], tinnitus, phonagnosia/nonverbal sound agnosia	Environmental sound/voice recognition, emotional recognition/reactivity, hedonic valuation, integration of semantic/affective information	Environmental sound recognition[10]	Auditory/multimodal association cortex in anterior temporal lobe, orbitofrontal cortex, insula
bvFTD	Socio-emotional, executive dysfunction with disinhibition, apathy, loss of empathy, obsessions and rituals, dietary and other behavioural abnormalities	Sound aversion/musicophilia[g], phonagnosia[h]	Emotional recognition/reactivity, hedonic valuation, voice recognition[f], integration of semantic/affective information	Vocal emotion recognition[11]	Auditory/multimodal association cortex in anterior temporal lobe, orbitofrontal cortex, insula, anterior cingulate, striatal circuits

Auditory Dysfunction in PD

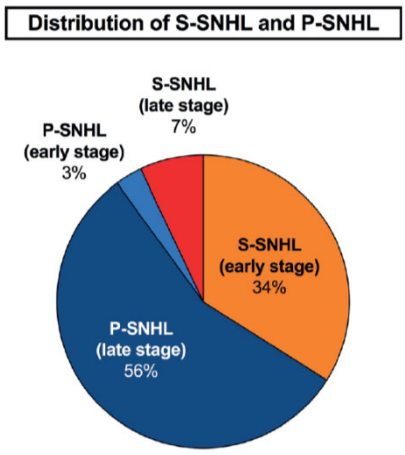
- Hearing dysfunction more prevalent in early onset PD than late onset PD
- Elderly with hearing loss have higher incidence of PD
- Nonmotor feature of PD
  - Dopamine system contributes to temporal processing of auditory information
  - Dopamine modulates GABA/glutamate effects on auditory processing
  - Alpha synuclein dysfunction
    - Alpha synuclein is expressed in cochlea, early hearing loss in alpha-synuclein deficient mice

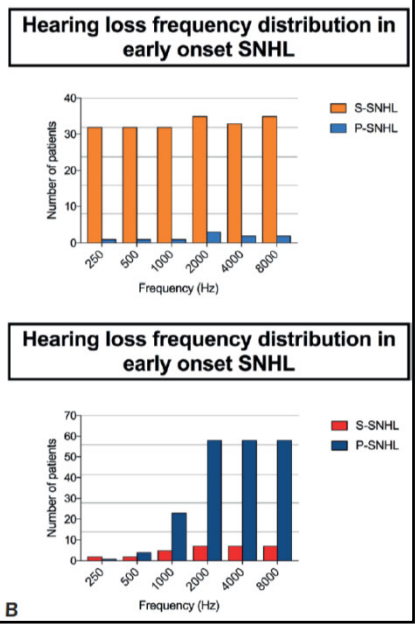


Jafari et al, 2020

Hearing Loss and MS

- Systemic Review
- 47 articles
  - 29 case reports
- 1533 patients
- 25% had SNHL
  - S-SNHL 69% (17% overall)
  - P-SNHL 31% (8% overall)

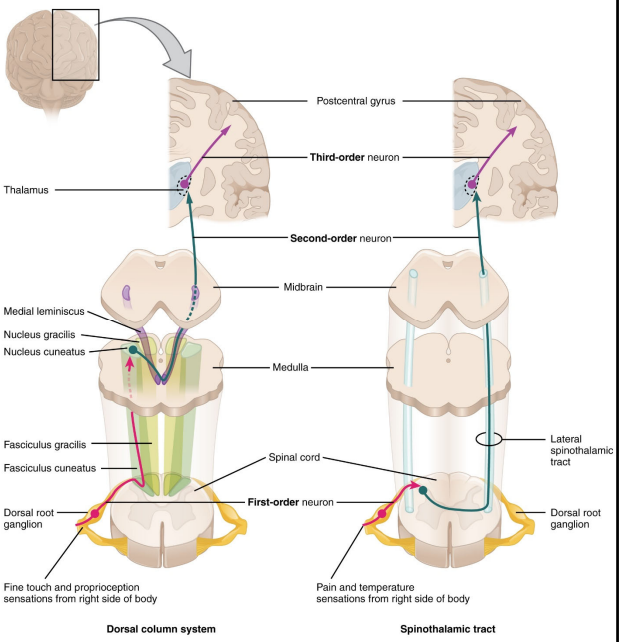




Di Stadio et al, 2018

Somatosensory System

- 2 ascending tracts
  - Fine touch, proprioception - DCML
  - Pain and temperature - ALS
- Alterations
  - Gait and balance
    - Fall risk
  - Pain and paresthesia
- Peripheral nerves



https://open.oregonstate.education/aandp

Somatosensory Impairment in MS

- 82 people with MS
- 66.7% had proprioceptive impairments
- 60.8% had tactile impairments
- 44.9% had vibration impairments
- Somatosensory impairments associated with worse balance

Correlation between sensations and Expanded Disability Status Scale (EDSS), Functional Reach Test (FRT), and Timed-up and Go (TUG) test.

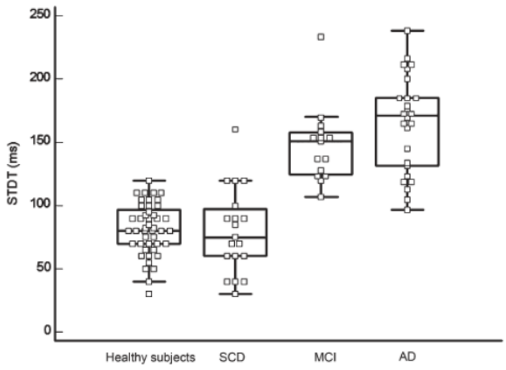
Variables	EDSS		FRT		TUG	
	r	p	r	p	r	p
Tactile Sensation						
Upper Limb	−0.31	0.012a	0.16	0.18	−0.232	0.06
Lower Limb	−0.38	0.001[a]	0.24	0.03[a]	−0.394	< 0.001[a]
Total	−0.41	0.001[a]	0.26	0.03[a]	−0.387	0.001[a]
Proprioception						
Upper Limb	−0.13	0.255	0.18	0.12	0.02	0.83
Lower Limb	−0.49	< 0.001[a]	0.34	0.002[a]	−0.43	< 0.001[a]
Total	−0.52	< 0.001[a]	0.39	0.005[a]	−0.36	0.001[a]
Vibration (seconds)						
Upper Limb	−0.13	0.256	0.29	0.009[a]	−0.06	0.6
Lower Limb	−0.46	< 0.001[a]	0.53	< 0.001[a]	−0.35	< 0.001[a]
Total	−0.39	0.001[a]	0.49	< 0.001[a]	−0.28	0.01[a]

[a] Indicates a statistically significant difference.

Jamali et al, 2017

Somatosensory impairment in AD

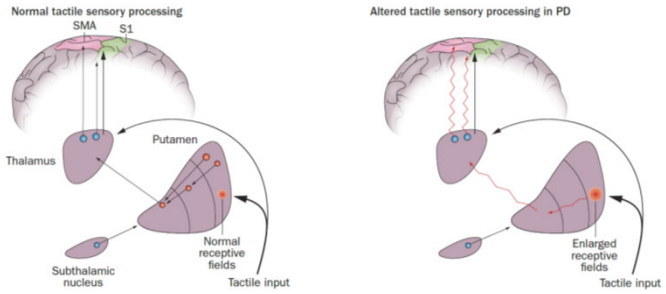
- Somatosensory temporal discrimination threshold (STDT)
- 63 patients: 28 mild-moderate AD, 116 MCI, 19 subjective cognitive deficit. 45 age-matched healthy controls
- Higher values for pts with AD and MCI than subjective cognitive subjects or healthy controls
- Values were not correlated with disease severity
- Possible dysfunction of dopaminergic pathways



D'Antonio et al, 2019

Somatosensory impairment in PD

- Disorders of perception
  - Pain – present in 30-83% patients, increased sensitivity to pain
  - Impaired position sense and limb motion
- Disorders of sensorimotor integration
  - Different activation patterns for tactile discrimination
  - Increased STDT scores
  - Trouble integrating two or more sources (vision and proprioception, object shape and texture)



Conte et al, 2013

Conclusion

- Visual impairment common in neurodegenerative diseases
  - Direct inflammation of optic nerve or deposition of abnormal proteins in retina
  - Impairments in eye movements
  - Cortical visual information processing
  - OCT surrogate marker – more data in MS and AD
- Auditory impairments
  - Auditory information processing
- Somatosensory impairments
  - Direct disruption of ascending tracts
  - Somatosensory information processing