

Right under our noses: olfactory pathology in central nervous system demyelinating diseases



Albert Joseph

**Presenter has no disclosures*

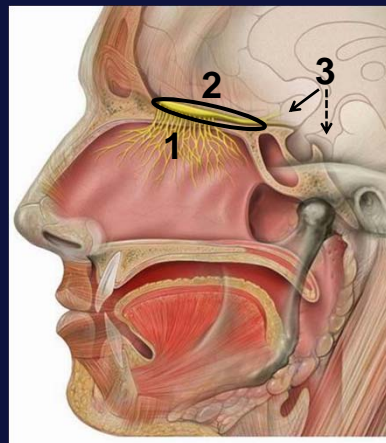
Olfactory Pathology in Demyelinating Diseases

Background

- Olfactory dysfunction is a common feature in multiple sclerosis (MS)
 - 20-50% of patients exhibit olfactory deficits on testing
(Pinching et al., 1977; Hawkes et al., 1997; Doty et al., 1997; Lutterotti et al., 2011; Rolet et al., 2013)

- Olfactory anatomy:
 1. Olfactory neuroepithelium
 2. Olfactory bulb and tract
 3. Olfactory brain

- *What is the anatomic substrate for loss of smell in MS?*



Olfactory Pathology in Demyelinating Diseases

Background

- At end of 19th century → Gowers described MS pathology in detail

the nodules in the brain. The cranial nerves are often involved; for a certain distance the nerve may be grey in its entire thickness or in part. The **olfactory** optic, third, fifth, and facial nerves are those that have been **most frequently diseased**. Less commonly the roots of some of the spinal nerves are affected.

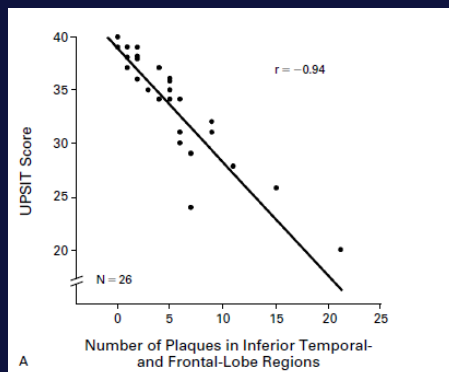
Gowers, *A Manual of Diseases of the Nervous System*, 1886



Olfactory Pathology in Demyelinating Diseases

Background

- Zimmerman and Netsky (1950) → **NO** olfactory bulb/tract DM in MS (n=8)



Doty et al., *NEJM* 1997

Olfactory loss
 α
 MRI lesion burden in olfactory brain

- Shifted search for olfactory dysfunction in olfactory brain



Olfactory Pathology in Demyelinating Diseases

Research Hypothesis

That olfactory bulb/tract are pathologically affected in MS and in other demyelinating diseases



Olfactory Pathology in Demyelinating Diseases

Case Selection

- Human autopsy cohort of pathologically confirmed cases

'Demyelinating' Diseases

Multiple sclerosis (MS) (n=17)

Neuromyelitis optica (NMO) (n=3)

Acute disseminated encephalomyelitis (ADEM) (n=7)

Neuroinflammatory Disease

Herpes Simplex Encephalitis (HSE) (n=3)

Neurodegenerative Disease

Alzheimer's Disease (AD) (n=4)

Non-neurologic Controls

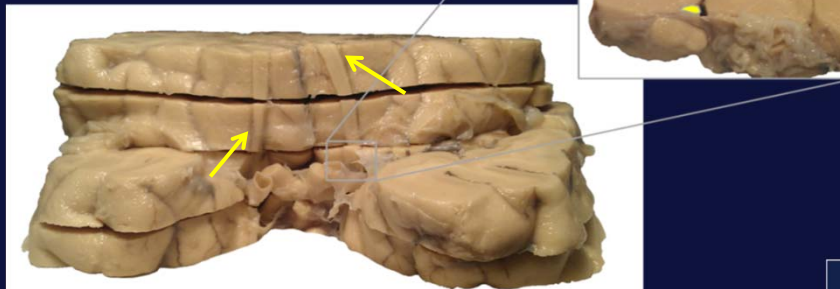
(n=8)



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Materials and Methods

- Coronally sliced brains realigned → olfactory bulbs/tracts sampled
- Subjacent inferofrontal cortex and hippocampus sampled, where available

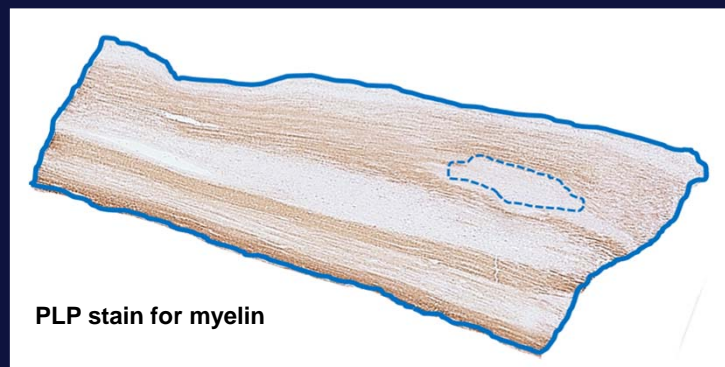


Olfactory Pathology in Demyelinating Diseases

Materials and Methods

Demyelination

- Areas of DM quantified and related to total sampled area



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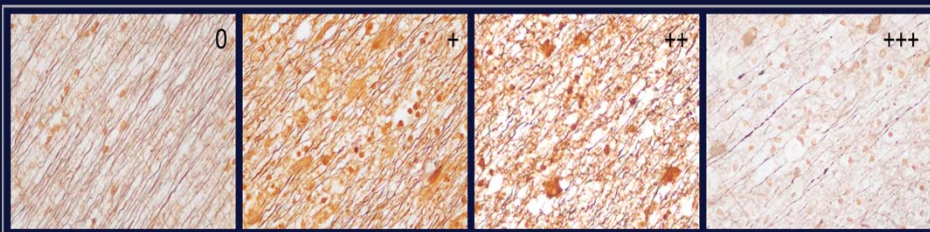
Materials and Methods

Inflammation

- T- and B-lymphocytes and macrophages/microglia scored semi-quantitatively

0 no cells/field; + 1 cell/field; ++ 2-4 cells/field; +++ > 4 cells/field

Axonal loss



Palmgren Silver stain for axons



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Results

Cohort

Demographics	Disease					
	Control	MS	NMO	ADEM	HSE	AD
Gender	F:5, M:3	F:11, M:6	F:3, M:0	F:3, M:4	F:0, M:3	F:1, M:3
Age (yrs)	63.0 (52-77)	53.4 (25-76)	39.3 (18-64)	25.4 (10-39)	36.0 (18-47)	76.3 (73-80)
Duration of Disease	N/A	8.2 yrs (4 mo-32 yrs)	8.0 yrs (1-15 yrs)	7.1 days (2-14 days)	5.0 days	10.8 yrs (8-15 yrs)

- Age and duration of disease differed significantly b/w disease groups

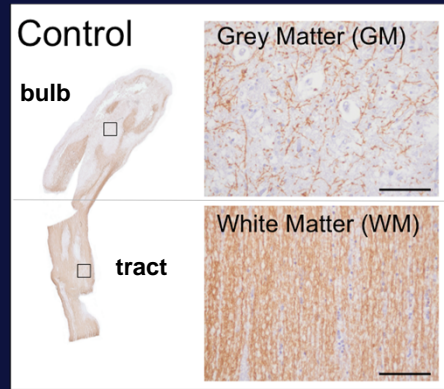


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Results

Demyelination

- Myelination pattern in olfactory bulb/tract was complex



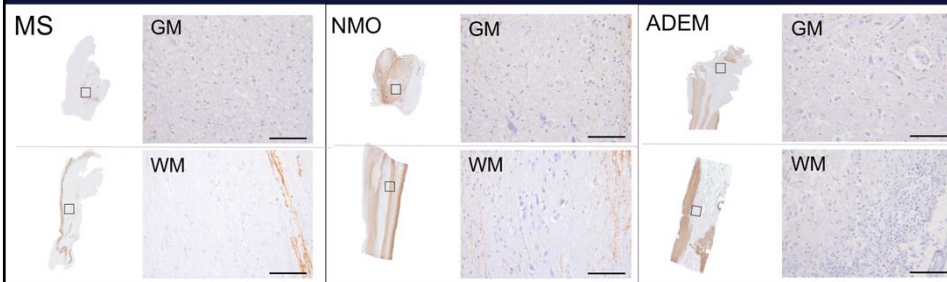
0/8 cases (0%)



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Results

Demyelination



12/17 cases (70.6%)
Proportional DM Area (18.6%)

2/3 cases (66.7%)
Proportional DM Area (2.9%)

3/7 cases (42.9%)
Proportional DM Area (3.0%)

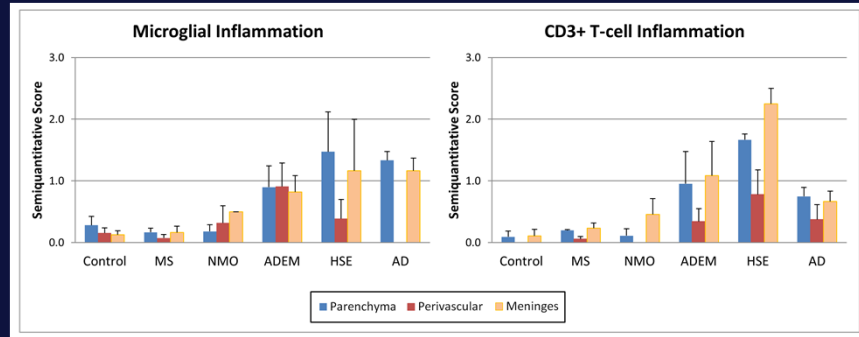
- MS / NMO plaques → all chronic; ADEM plaques → all active
- HSE, AD, and non-neurologic controls → no demyelination



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Results

Inflammation



- Olfactory bulb/tract inflammation observed in all disease groups (in parenchyma, perivascular space, meninges)



Olfactory Pathology in Demyelinating Diseases

Results

Inflammation (acute)

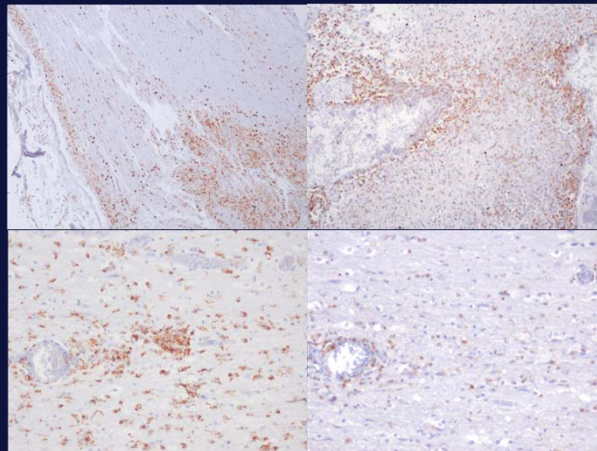
Macrophages (PG-M1)

T-cells (CD3+)

ADEM

Striking inflammation
in acute neurologic diseases

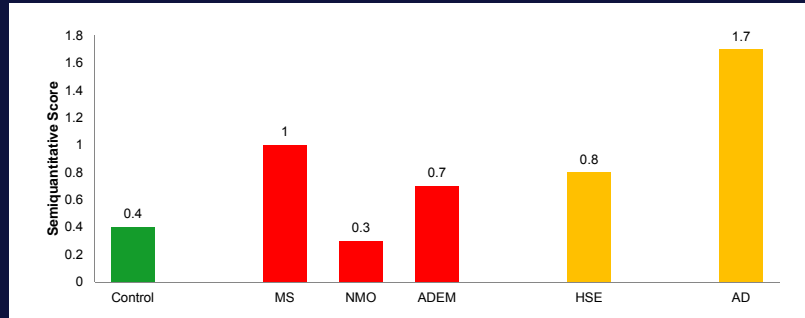
HSE



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Results

Axonal Loss



- Axonal loss was most pronounced in MS and Alzheimer's disease



Olfactory Pathology in Demyelinating Diseases

Results

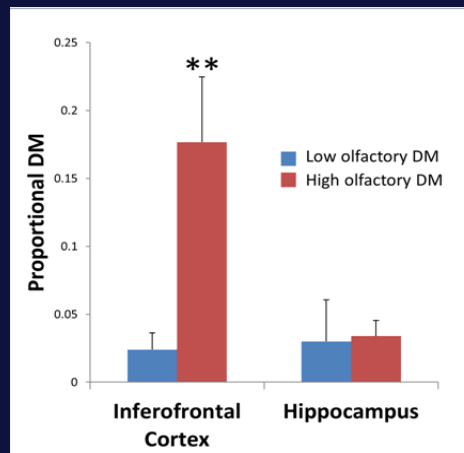
Relationship between olfactory and cortical demyelination

Inferofrontal Cortical Lesions

- 180 lesions from 73 inferofrontal cortical blocks juxtaposed to analysed olfactory bulb/tract from 22 cases (MS, n=15; ADEM, n=7)

Hippocampal Lesions

- 23 lesions from 27 hippocampal blocks from 12 cases (MS, n=7; ADEM, n=5)



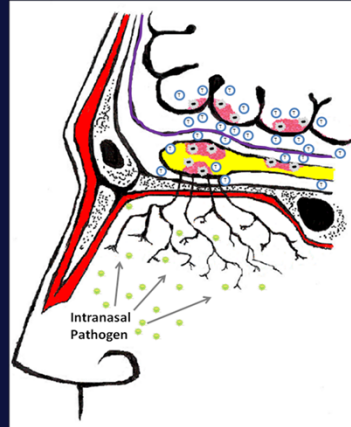
**p = 0.01



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Conclusions

- Olfactory bulb/tract demyelination:
 - frequent
 - can occur early
 - can be highly inflammatory
 - relates to subjacent cortical DM
- Alternative explanation for loss of smell in MS and other demyelinating diseases?
- Role of olfactory system in pathogenesis of demyelinating diseases?



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