

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



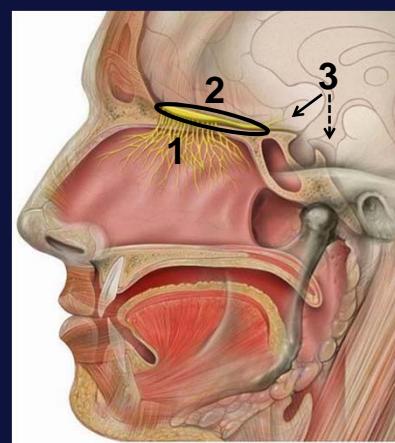
Albert Joseph

*\*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 19<sup>th</sup> 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.

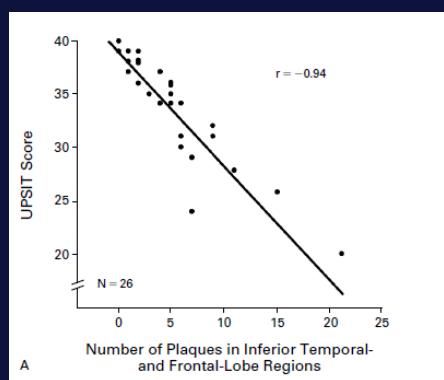
Gowers, *A Manual of Diseases of the Nervous System*, 1886



## 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  
MRI lesion burden in olfactory brain  
α

- 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

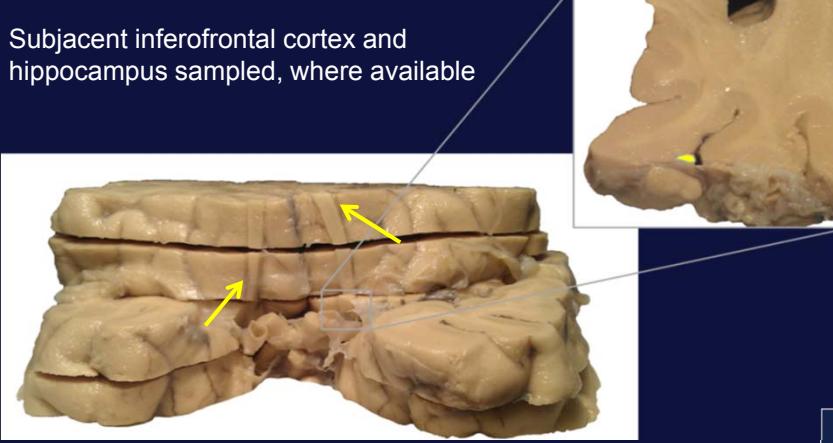
(n=8)



## Olfactory Pathology in Demyelinating Diseases

### Materials and Methods

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



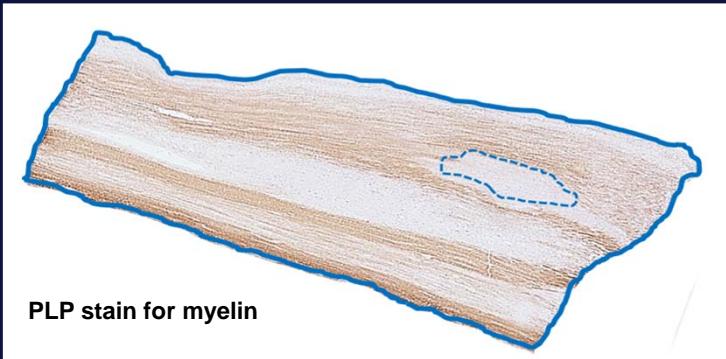
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## Olfactory Pathology in Demyelinating Diseases

### Materials and Methods

#### Demyelination

- Areas of DM quantified and related to total sampled area



PLP stain for myelin

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## Olfactory Pathology in Demyelinating Diseases

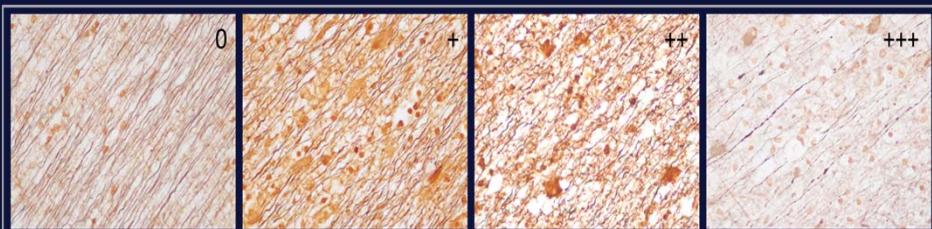
### Materials and Methods

#### 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*



## Olfactory Pathology in Demyelinating Diseases

### Results

#### Cohort

Demographics	Disease				
	Control	MS	NMO	ADEM	HSE
Gender	F:5, M:3	F:11, M:6	F:3, M:0	F:3, M:4	F:0, M:3
Age (yrs)	63.0 (52-77)	53.4 (25-76)	39.3 (18-64)	25.4 (10-39)	36.0 (18-47)
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
					76.3 (73-80)

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



## Olfactory Pathology in Demyelinating Diseases

### Results

#### Demyelination

- Myelination pattern in olfactory bulb/tract was complex

**Control**

Grey Matter (GM)

White Matter (WM)

0/8 cases (0%)

## Olfactory Pathology in Demyelinating Diseases

### Results

#### Demyelination

MS	NMO	ADEM
 <p>GM</p>	 <p>GM</p>	 <p>GM</p>
 <p>WM</p>	 <p>WM</p>	 <p>WM</p>

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

## Olfactory Pathology in Demyelinating Diseases

### Results

#### Inflammation

**Microglial Inflammation**

Group	Parenchyma	Perivascular	Meninges
Control	~0.3	~0.2	~0.2
MS	~0.2	~0.1	~0.2
NMO	~0.3	~0.4	~0.5
ADEM	~0.9	~0.9	~0.9
HSE	~1.4	~0.4	~1.1
AD	~1.3	~0.4	~1.1

**CD3+ T-cell Inflammation**

Group	Parenchyma	Perivascular	Meninges
Control	~0.1	~0.1	~0.1
MS	~0.1	~0.05	~0.1
NMO	~0.1	~0.05	~0.4
ADEM	~0.9	~0.4	~1.1
HSE	~1.6	~0.8	~2.3
AD	~0.8	~0.4	~0.7

Legend: █ Parenchyma █ Perivascular █ Meninges

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



## Olfactory Pathology in Demyelinating Diseases

### Results

#### Inflammation (acute)

**ADEM**

Striking inflammation  
in acute neurologic diseases

**Macrophages (PG-M1)**

**T-cells (CD3+)**

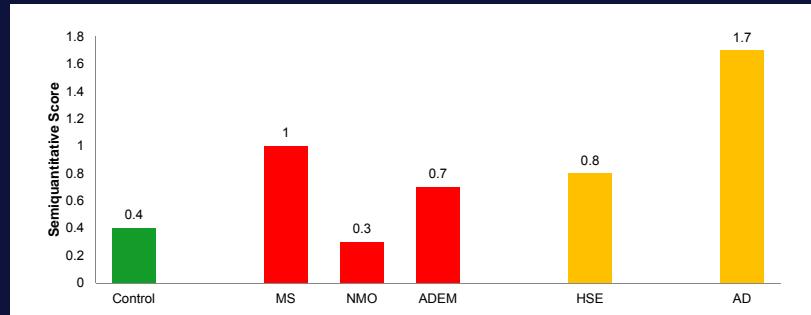
**HSE**



## Olfactory Pathology in Demyelinating Diseases

### Results

#### Axonal Loss



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



## Olfactory Pathology in Demyelinating Diseases

### Results

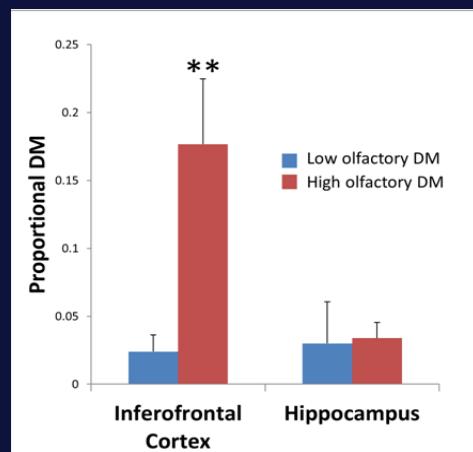
#### Relationship between olfactory and cortical demyelination

##### *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*

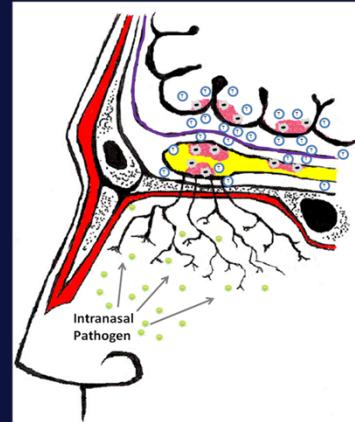
- 23 lesions from 27 hippocampal blocks from 12 cases (MS, n=7; ADEM, n=5)



## Olfactory Pathology in Demyelinating Diseases

### 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?



## Olfactory Pathology in Demyelinating Diseases

### Acknowledgements

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