

**Myotonic Dystrophy Foundation Annual Meeting
San Francisco, CA August 17-18, 2012**

The Brain: Cognitive Function and DM

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Disclosures

- Athena Diagnostics – royalties/patent licensure for myotonic dystrophy type 2 and ataxia genetic testing
- Grants from
 - PTC Therapeutics, GSK Pharmaceuticals, Genzyme
 - NIH, MDA, National Ataxia Foundation

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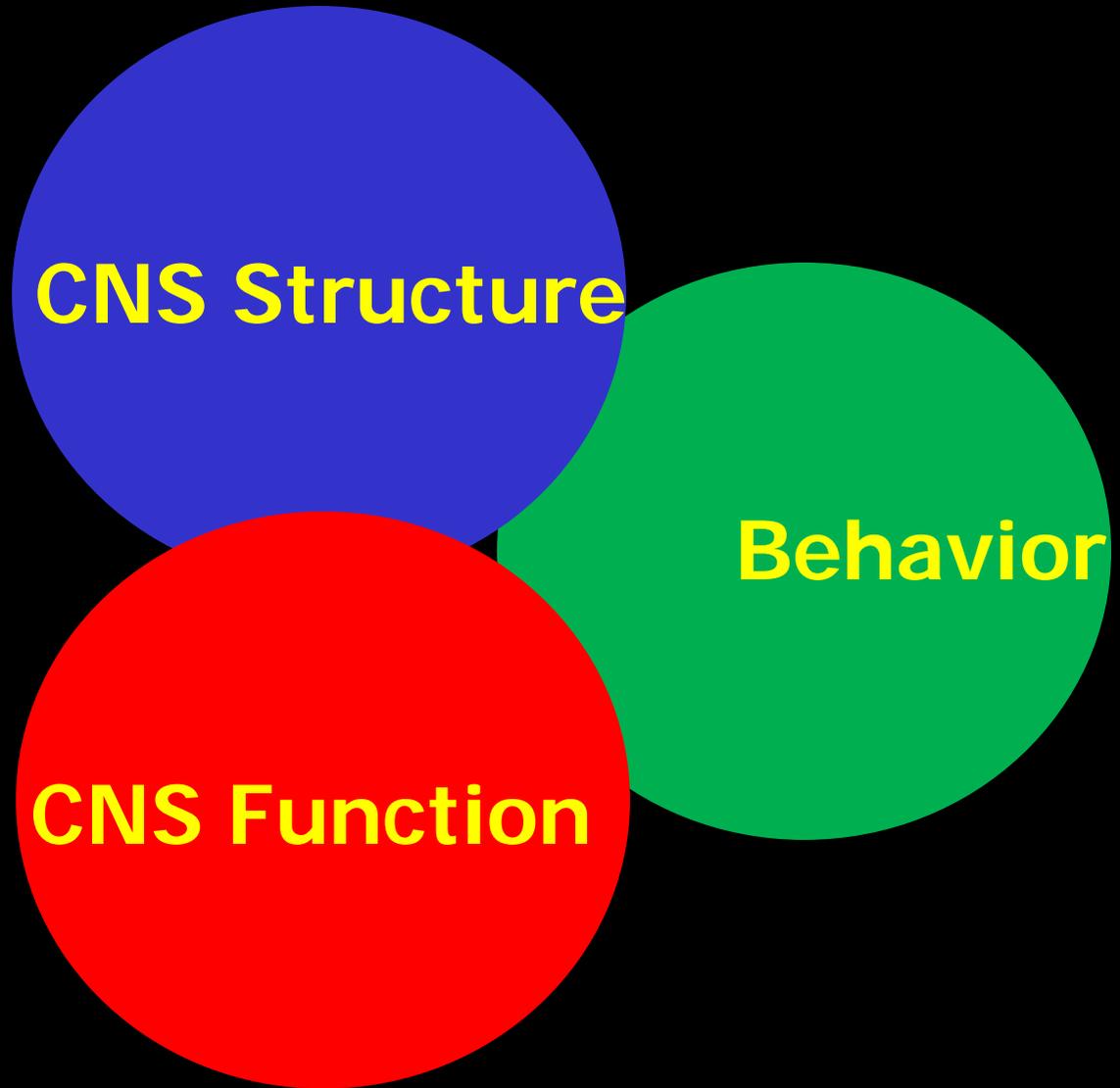
DM1 & DM2 Patients and
Families



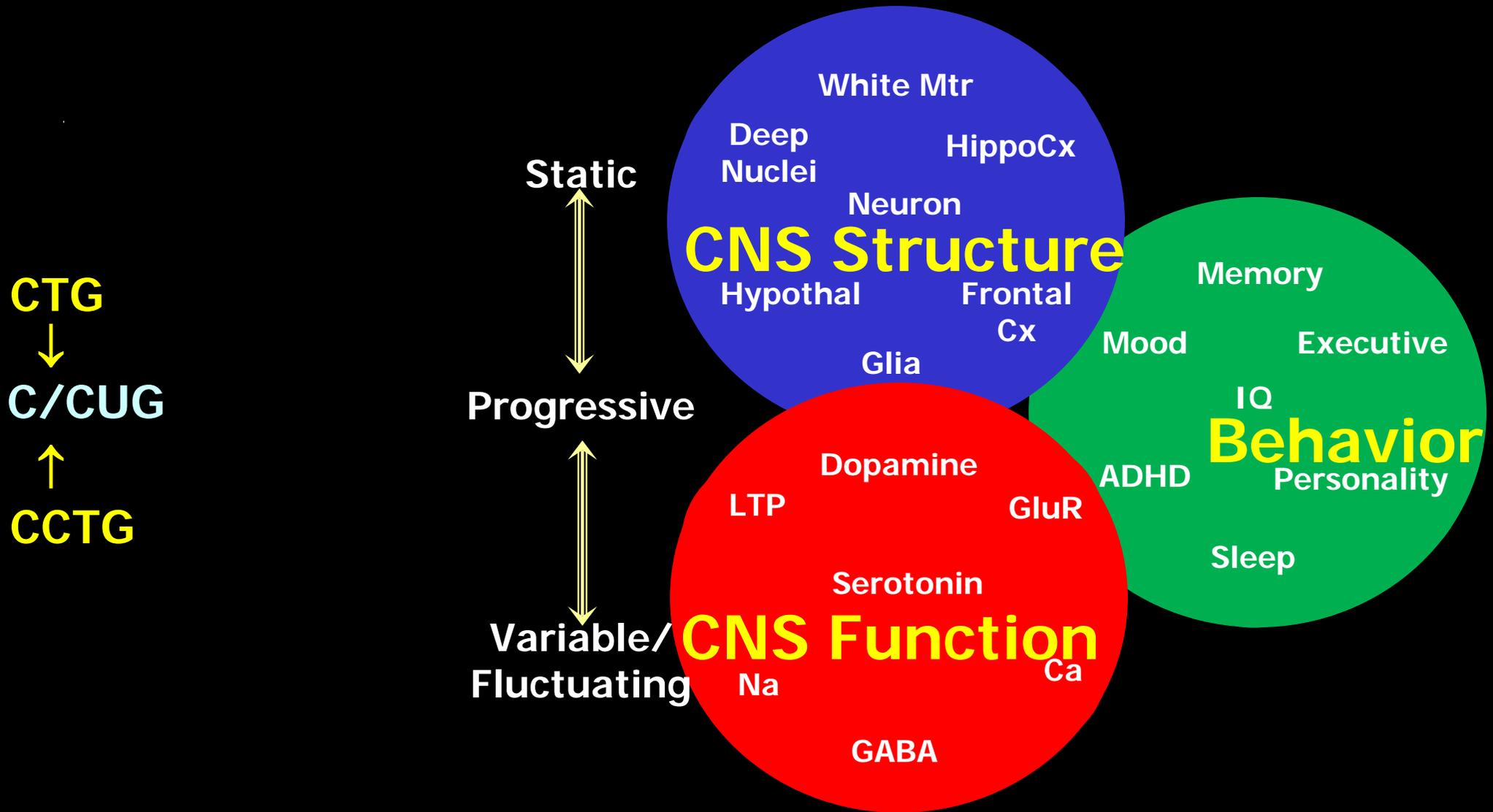
Overview

- What cognitive and behavioral changes are seen in DM?
- What is the time course and cause of these changes?
- What are the underlying mechanisms leading to CNS change?
- What treatments are or will be available?
- What can you do to help conquer CNS effects of DM?

CNS Effects of Myotonic Dystrophy



CNS is not Liver



So what cognitive change occurs in DM?

What Clinical CNS Changes occur DM?

- **Neuropsychological Abnormalities**
 - **Autistic Spectrum Disorder** – (Ekstrom...Wentz, Am J Med Gen, 2008)
 - **Attention Deficit** - (Douniol ...Guile, Dev Med Child Neurol, 2012)
 - **Developmental cognitive impairment** (Wozniak, NMDisorders, 2012)
 - **Executive function loss** (DM1/DM2 – Meola, Neurology, 1999)
 - **Avoidant personality** (Winblad, NMDisorders, 2005).
 - **Progressive loss of executive function** (Modoni, JNeurol, 2008)
- **Central motor function**
 - **Parkinsonism** (Sansone, JNNP, 2006)
- **Sleep Control**
 - **Sleep related ventilatory dysfunction**
 - **Central Hypersomnia** (Ciafaloni, Neurology, 2008)
- **Episodic encephalopathy? Seizures?**
- **Personal, Familial, Societal Impact of DM** (Gagnon, JRehab Med, 2007))

**So what multisystemic features
contribute to DM CNS change?**

DM1 Phenotype



Localization

Skeletal Muscle

Brain

Heart

Eye

Endocrine

Gut

Skin

Blood

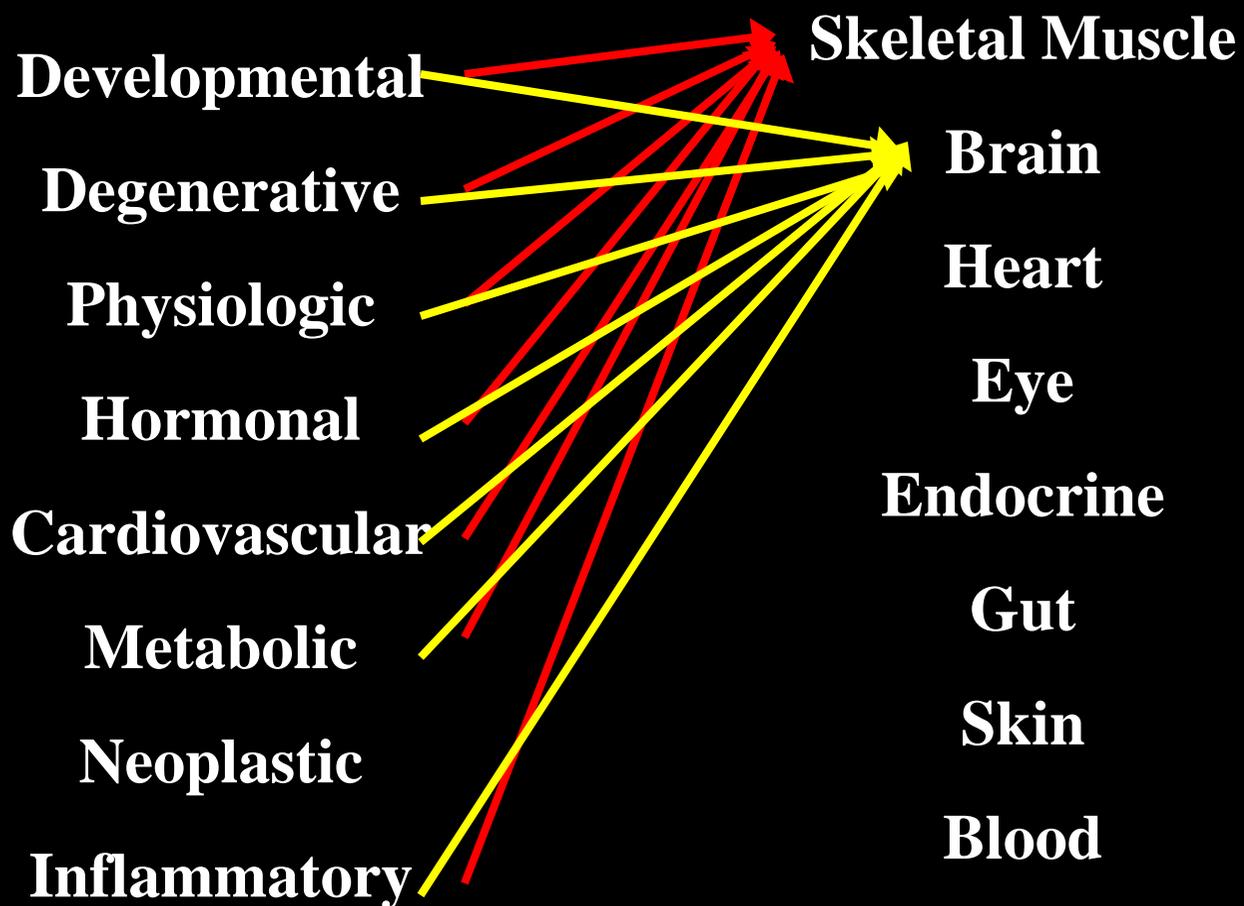
How do DM Muscle changes inform us about DM CNS changes?

DM1 Phenotype



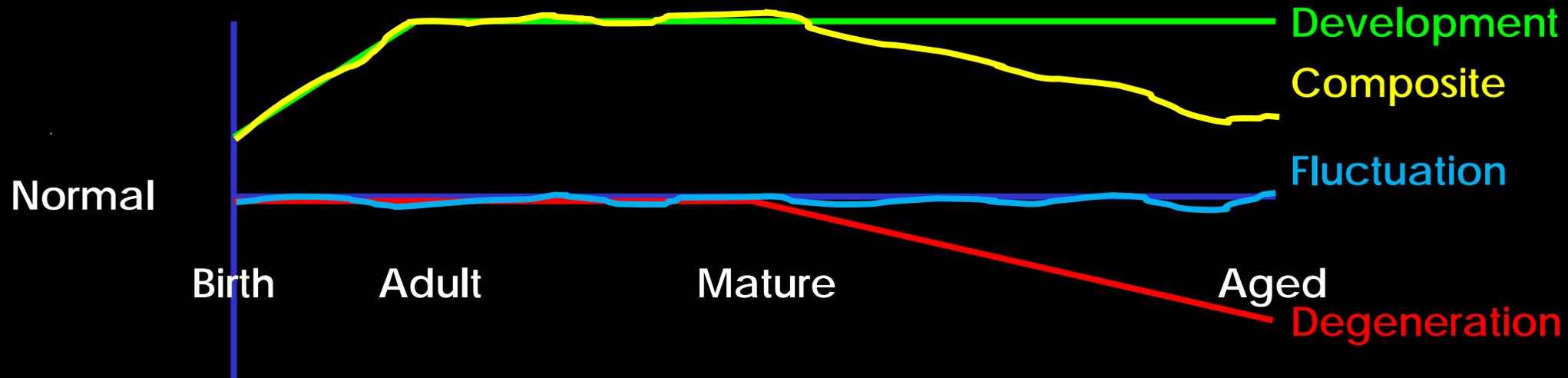
Pathological Mechanism

Localization

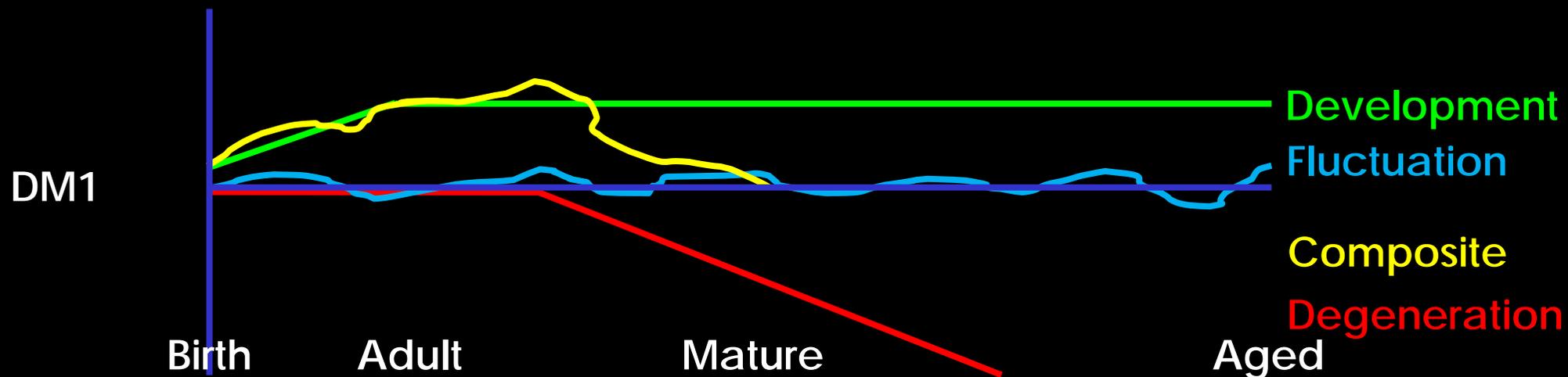


How does DM time course affect understanding, investigation and treatment?

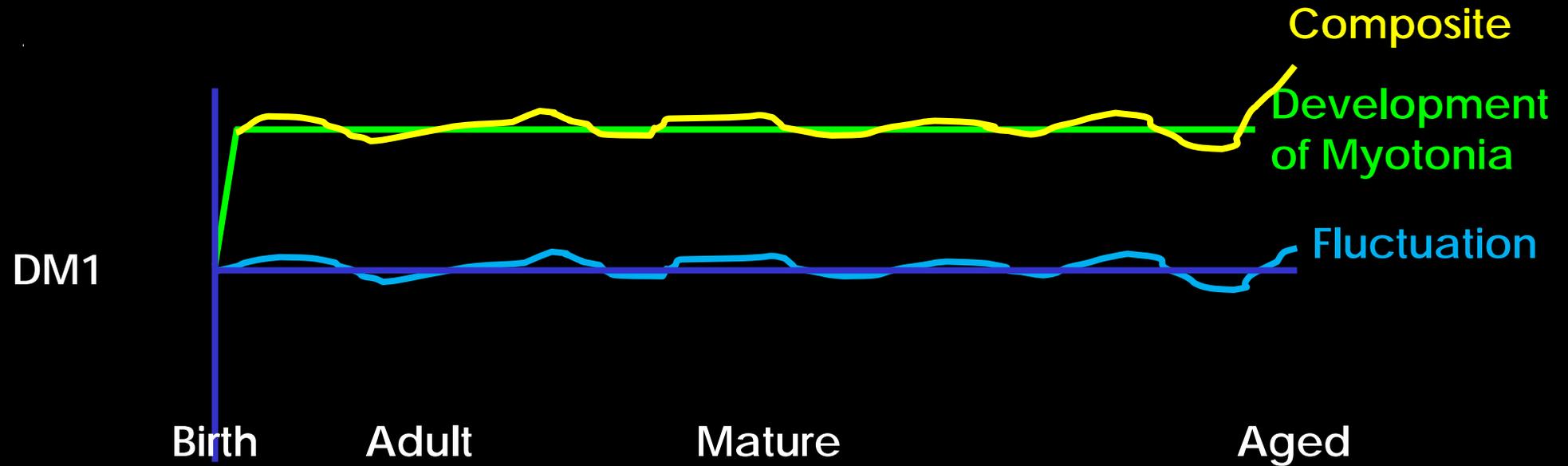
Time course of strength in Ctrl v DM1?



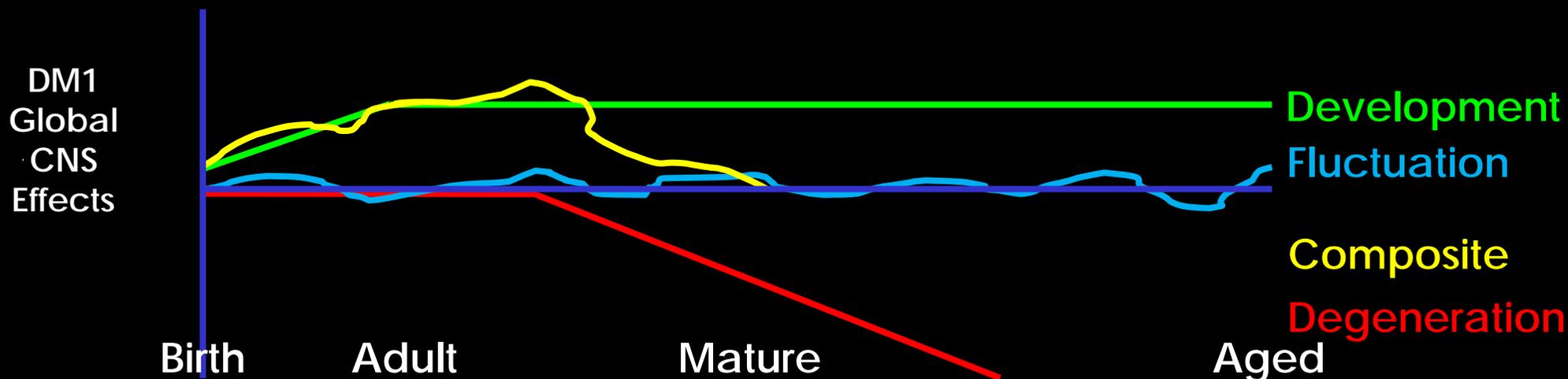
Fluctuation includes Δ in: stamina, sleepiness, pain, systemic disease



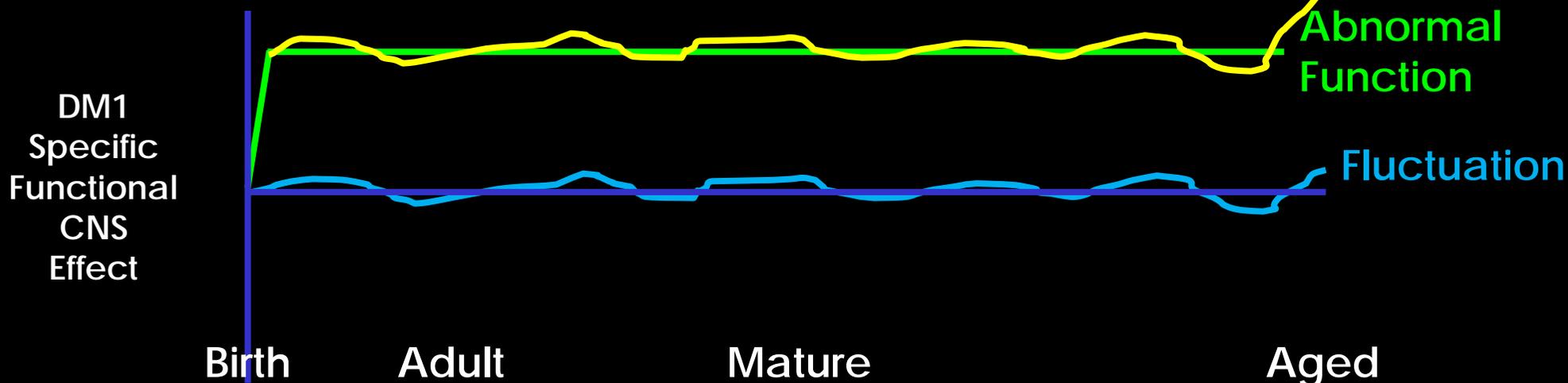
Time course of myotonia in DM1?



Time course of DM1 CNS Effects



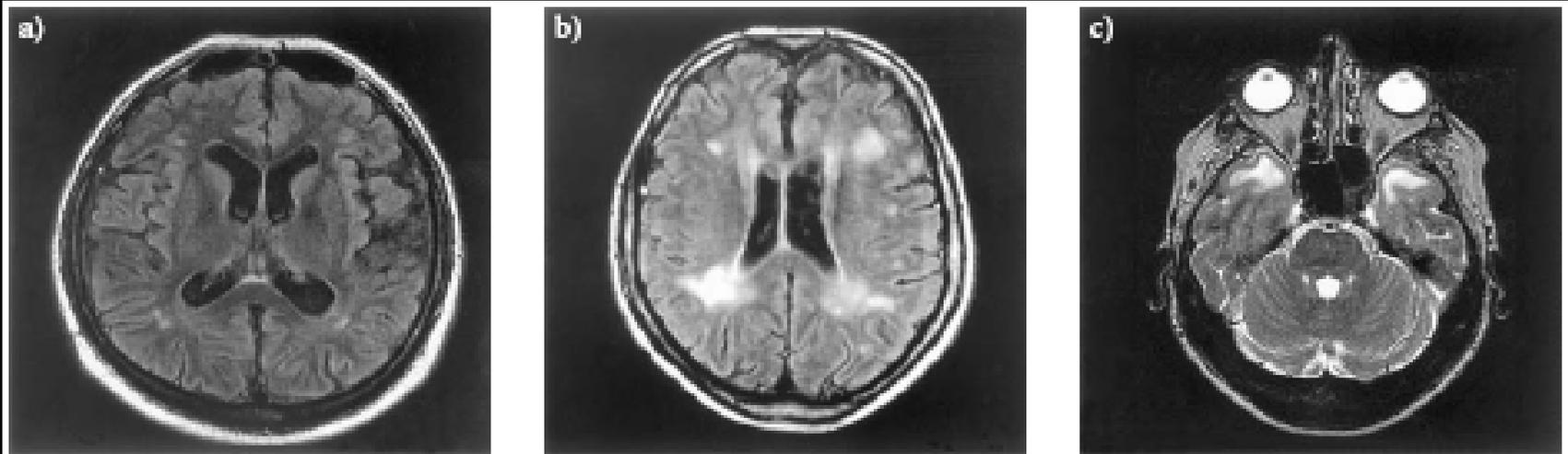
Fluctuation includes Δ in: stamina, sleepiness, pain, systemic disease
Composite



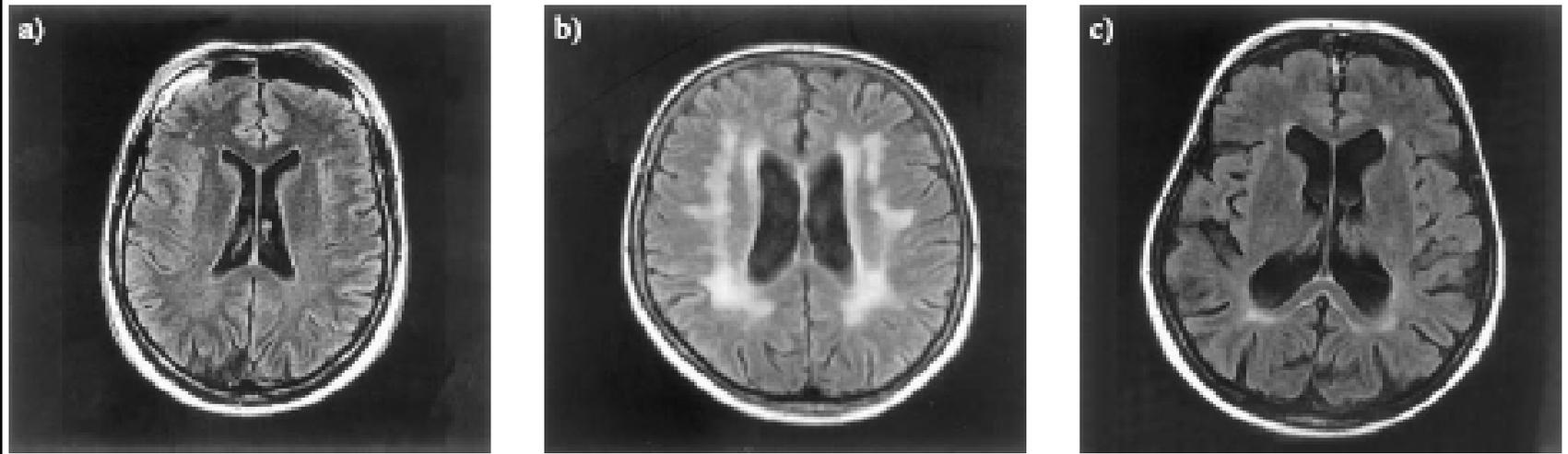
What are structural CNS changes in DM?

Structural MRI Changes in DM

DM1

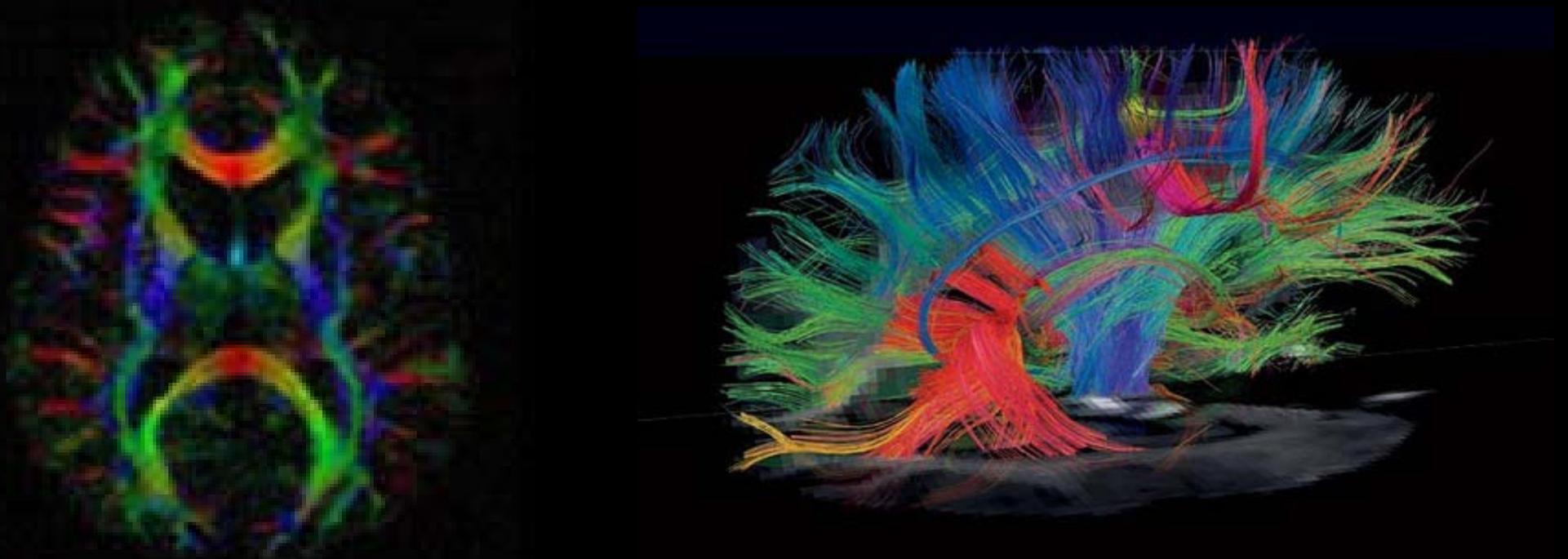


DM2

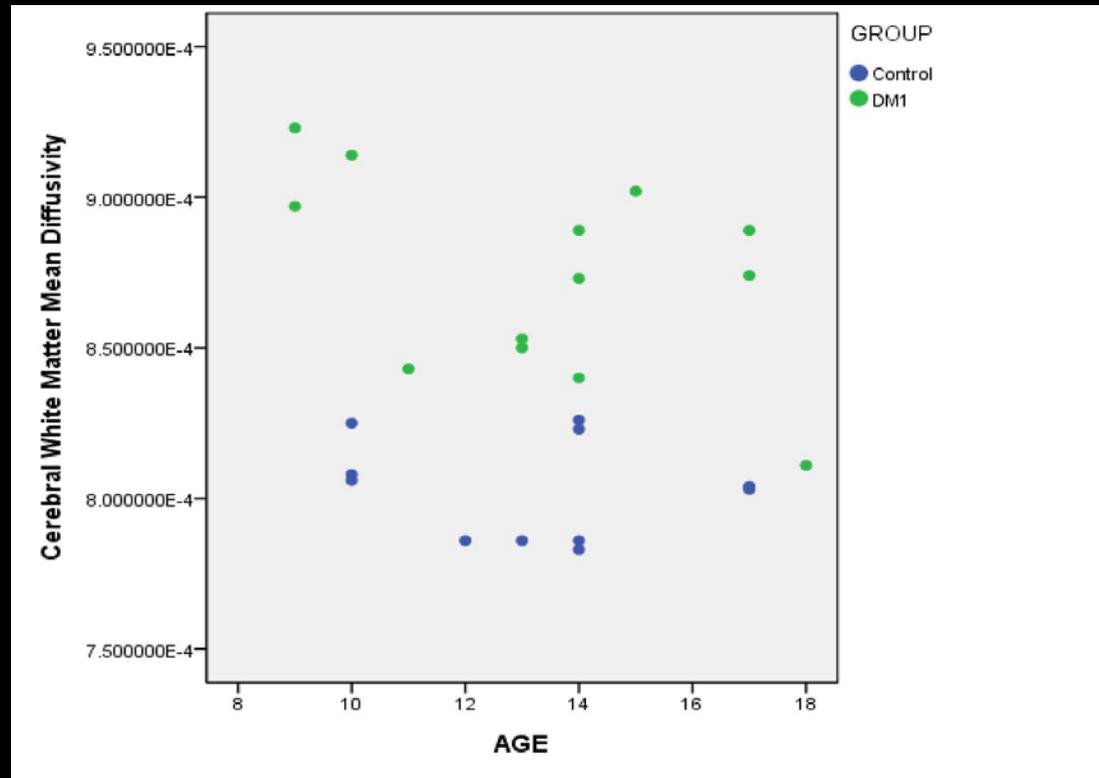


Kornblum, et al, J. Neurol, 2004

Diffusion Tensor Imaging (DTI)

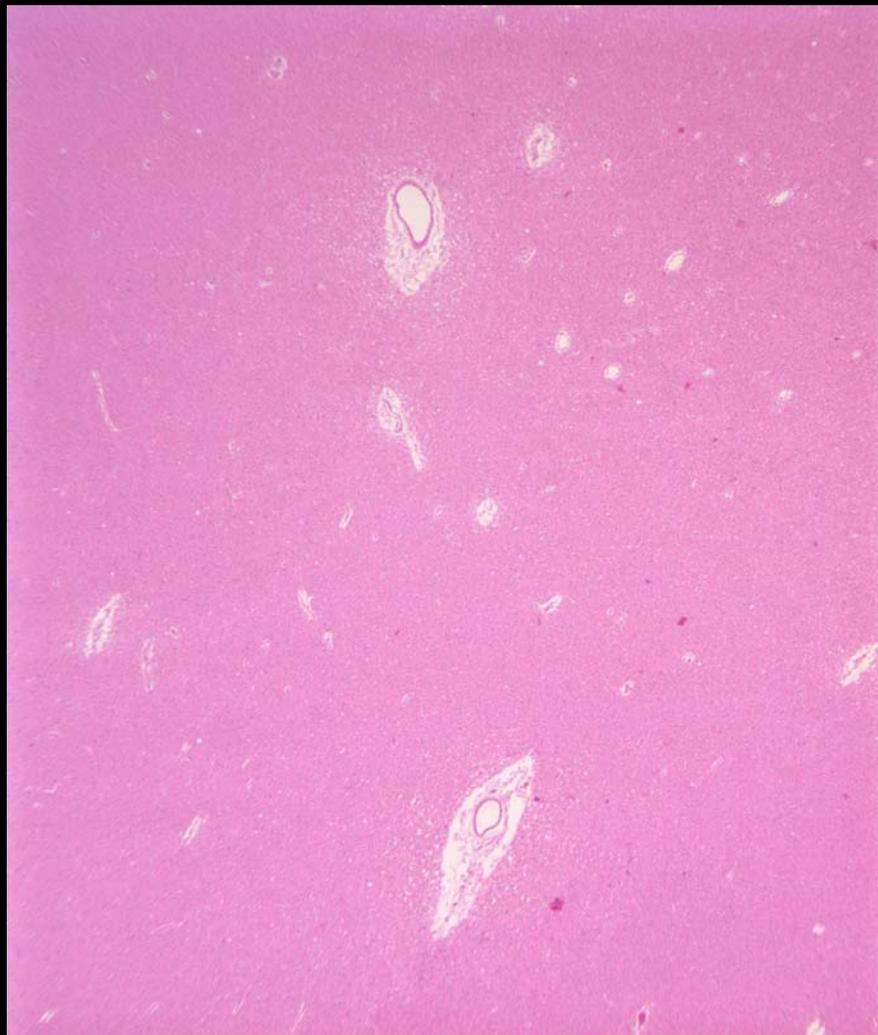


Whole cerebrum white matter DTI



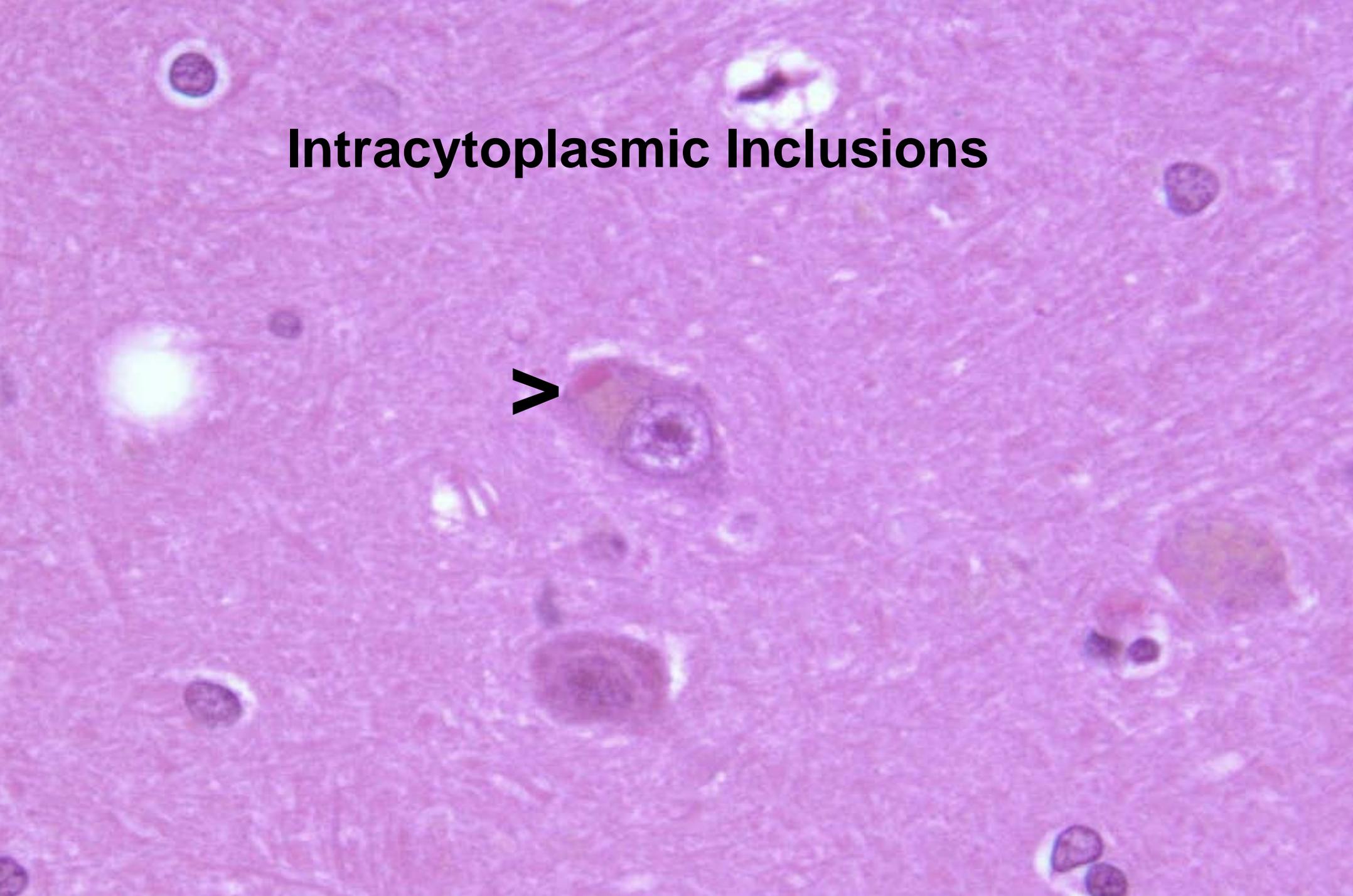
- Mean Diffusivity is significantly higher in DM1 vs. Controls
 - The differences are bilateral
 - Mean whole-brain diff: $F=41.7$, $p=.0000017$, effect size (d)=2.72, 8.4% diff
 - Mean right hemisphere diff: $F=42.1$, $p=.0000016$, effect size (d)=2.66, 8.8% diff
 - Mean left hemisphere diff: $F=39.7$, $p=.0000024$, effect size (d)=2.72, 8.0% diff
- This strongly suggests a significant abnormality in tissue organization/integrity

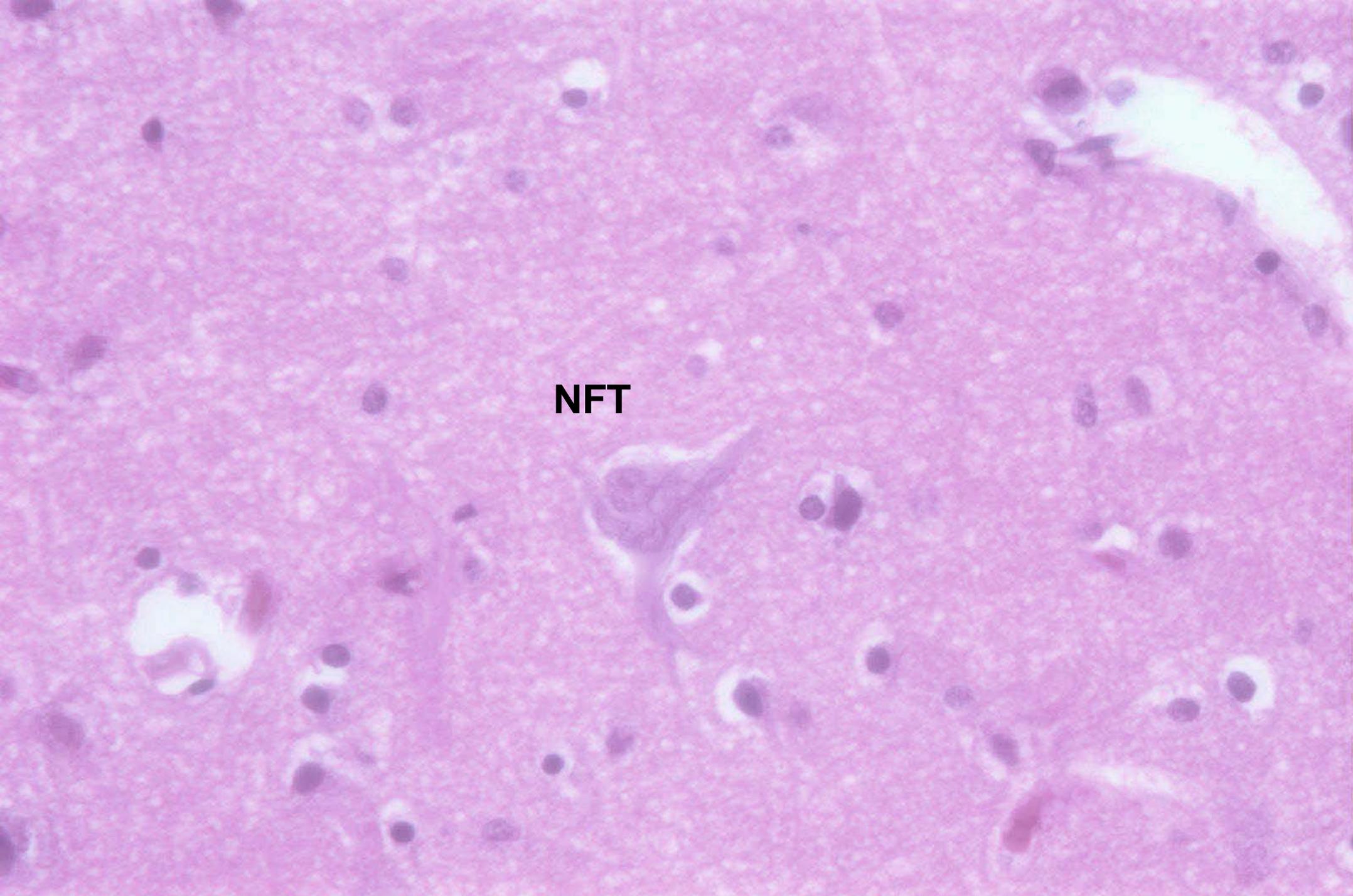
Dilated Perivascular Spaces in WM



Intracytoplasmic Inclusions

V

A light micrograph of tissue stained with hematoxylin and eosin (H&E). The image shows several cells with prominent, eosinophilic (pink) intracytoplasmic inclusions. A black arrow labeled 'V' points to one of these inclusions. The inclusions are located within the cytoplasm of the cells, often near the nucleus. The background tissue is stained pink, and the nuclei are stained purple.



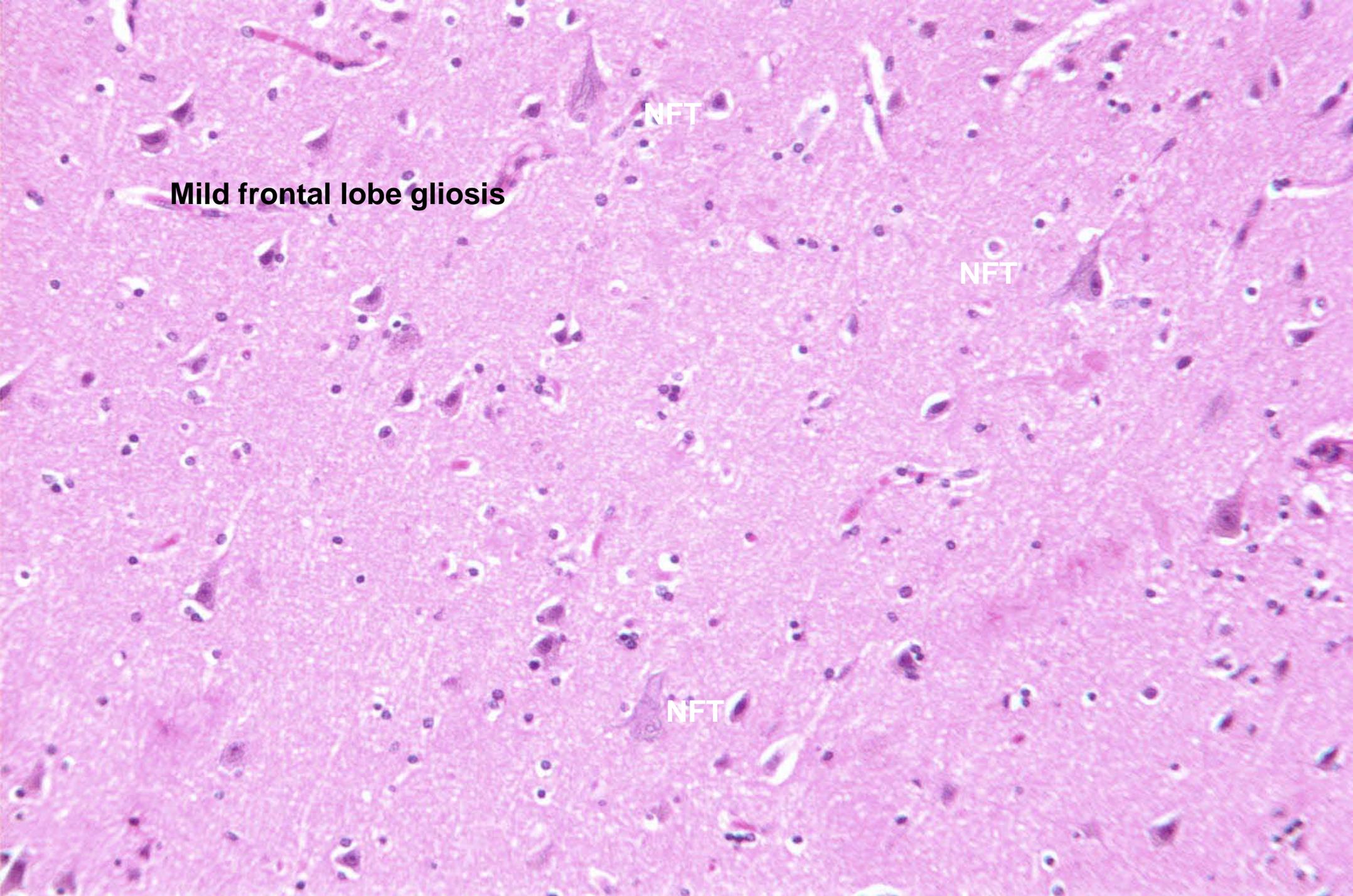
NFT

Mild frontal lobe gliosis

NFT

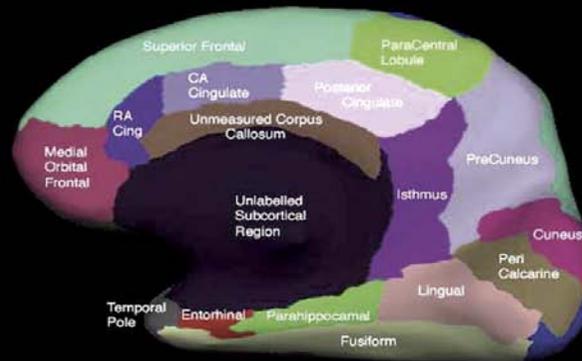
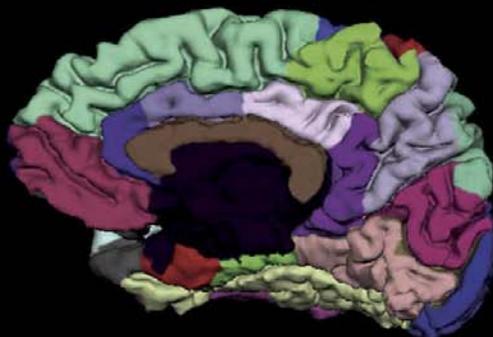
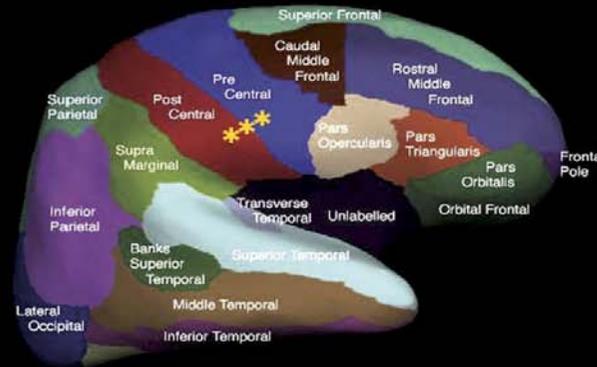
NFT

NFT



Neuropathology of DM

- **White matter rarefaction in the cerebral hemispheres**
- **Increased space around blood vessels**
- **Minimal evidence of less than normal nerve cell numbers**
- **Neurofibrillary tangles of tau proteins**
- **Protein inclusion bodies in some deep brain regions**



Freesurfer Cortical Parcellation identifies 35+ ROIs on cortical surface

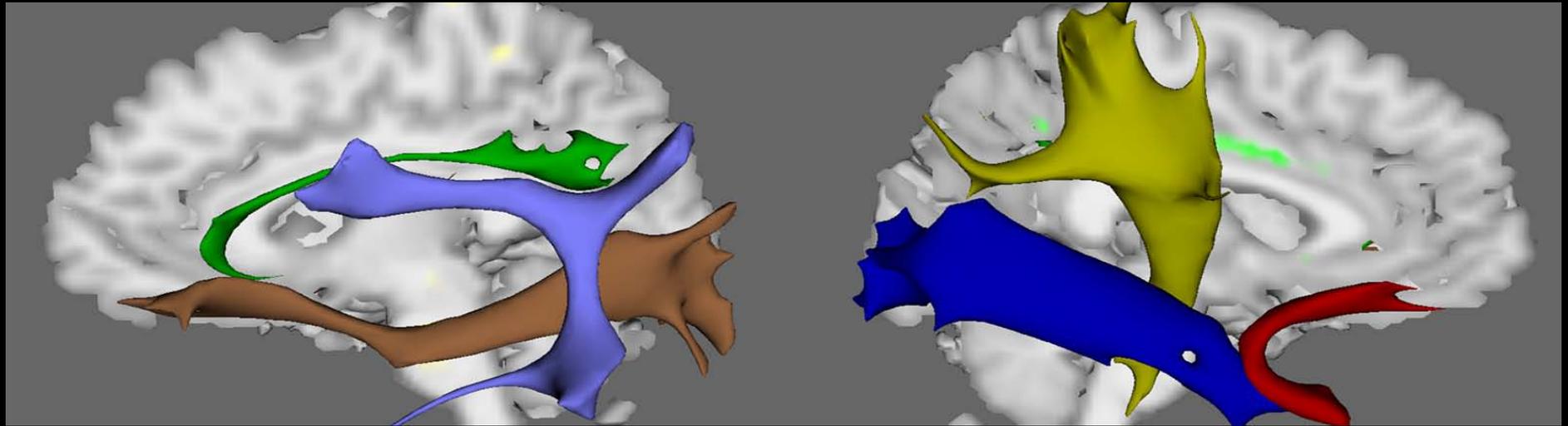
We then evaluate the white matter in close proximity to these regions

Dependent measures in these analyses are mean FA or MD within the ROI

The data clearly demonstrate that these effects are NOT regional

- **Ex: very large effects in caudal middle frontal, orbitofrontal, superior frontal, lateral frontal, inferior & superior parietal, inferior & middle temporal, lateral occipital, pre- and post-central, etc...**

Automated tract analyses: DTI



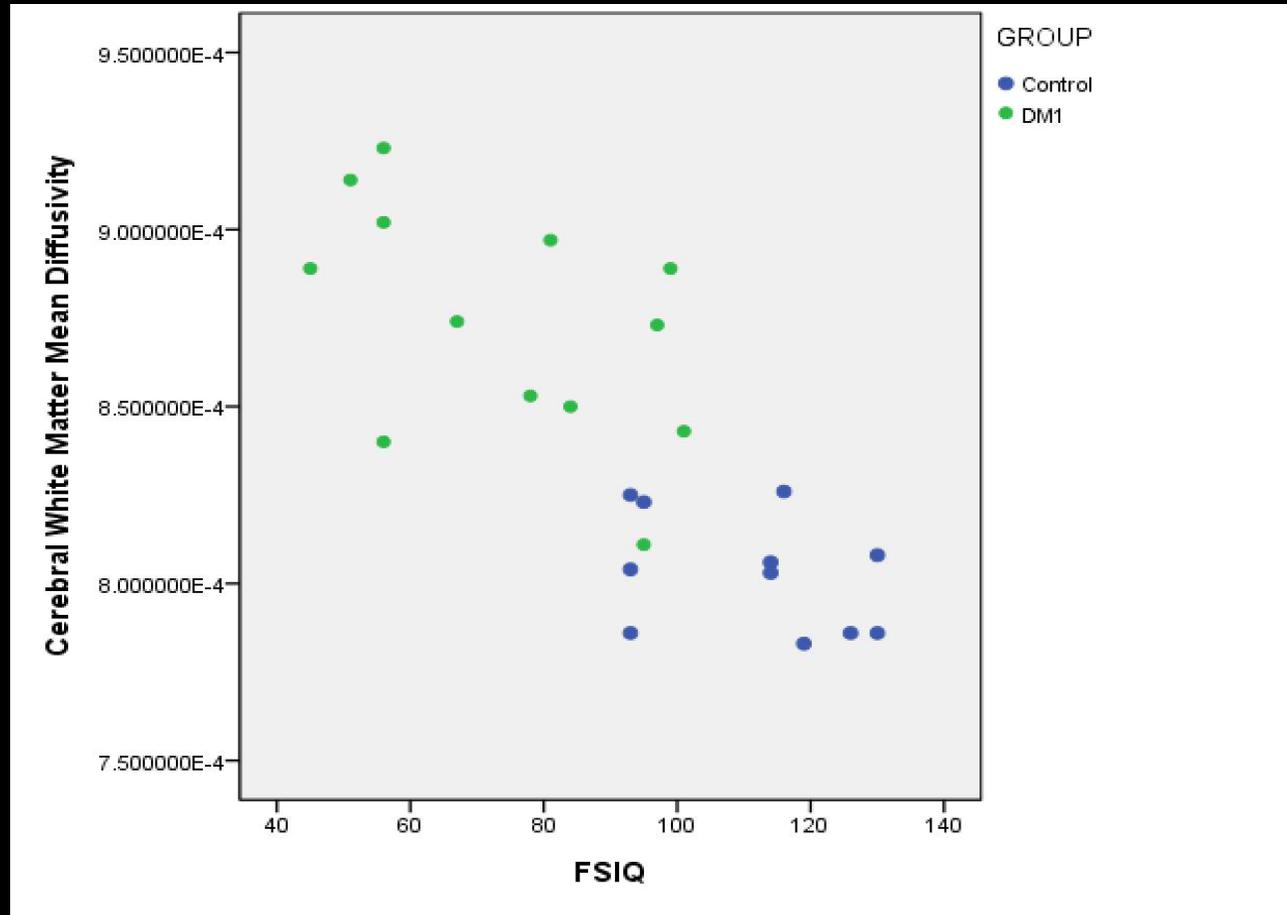
- Inferior longitudinal fasciculus (dark blue): significant; $p = .00002$
- Superior longitudinal fasciculus (light blue): significant; $p = .00001$
 - Uncinate fasciculus (red): significant; $p < .00001$
 - Occipitofrontal fasciculus (brown): significant; $p < .0001$
 - Cingulum (green): significant; $p = .00005$
 - Corticospinal tracts (yellow): significant; $p = .00012$
- Corpus callosum (not shown): all significant but splenium

CNS Functional Abnormalities in DM

Behavioral CNS Changes in DM

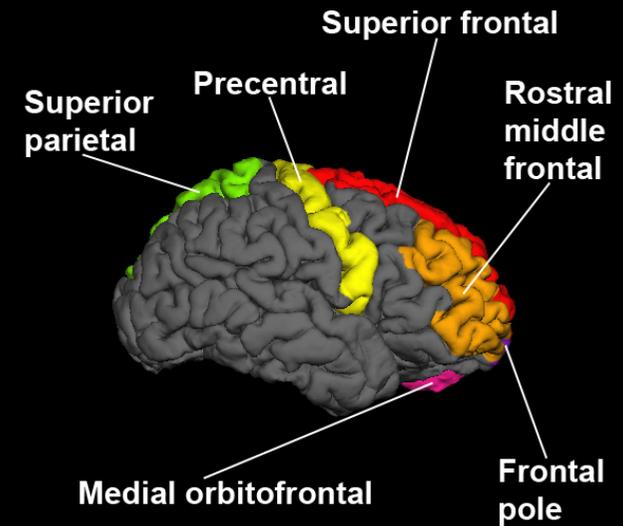
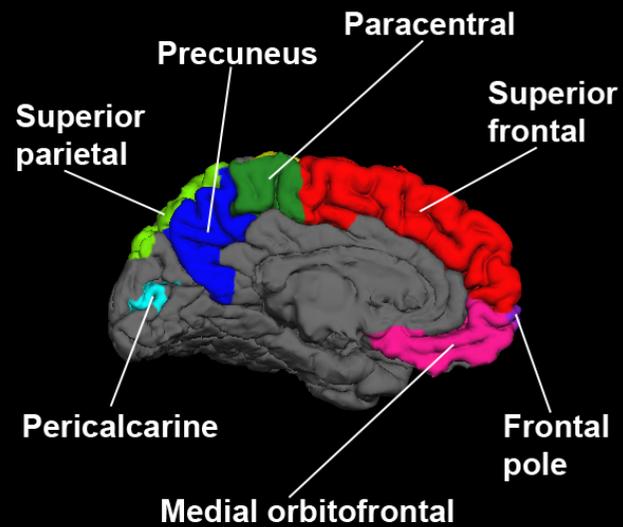
- **Neuropsychological Abnormalities**
 - Impaired DM1 cognitive abilities noted in 1913
 - Apathy or avoidant personality
 - Progressive loss of executive function
- **Central motor function**
 - Parkinsonism
- **Sleep Control**
 - Sleep related breathing issues
 - Central Hypersomnia
- **Personal, Familial and Societal Impact of DM**

White matter integrity is highly related to cognitive functioning

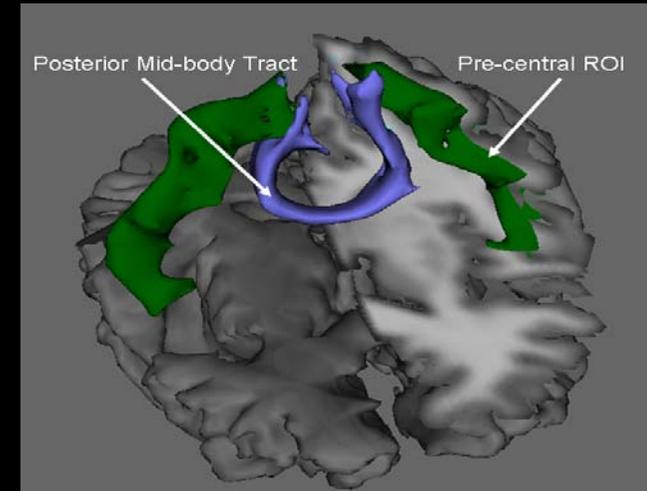
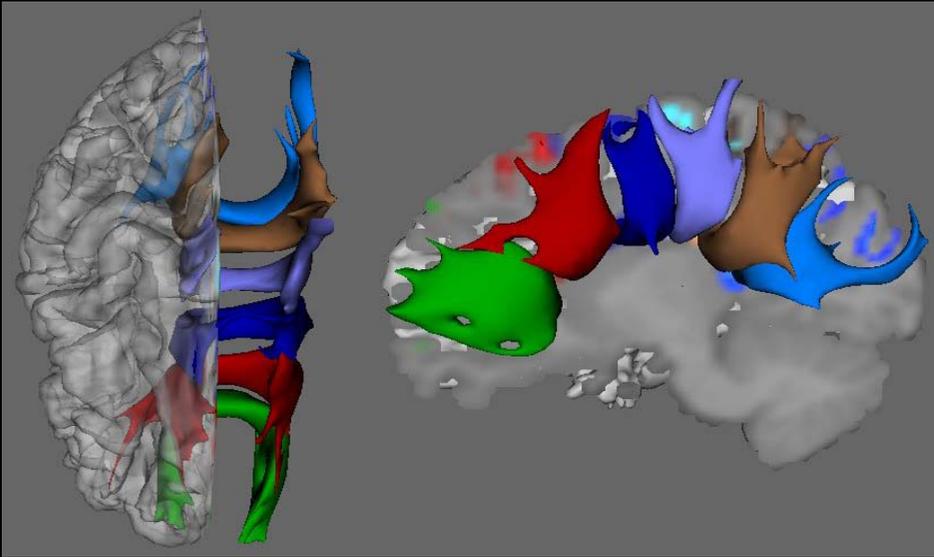


Are there functional consequences of tract abnormalities?

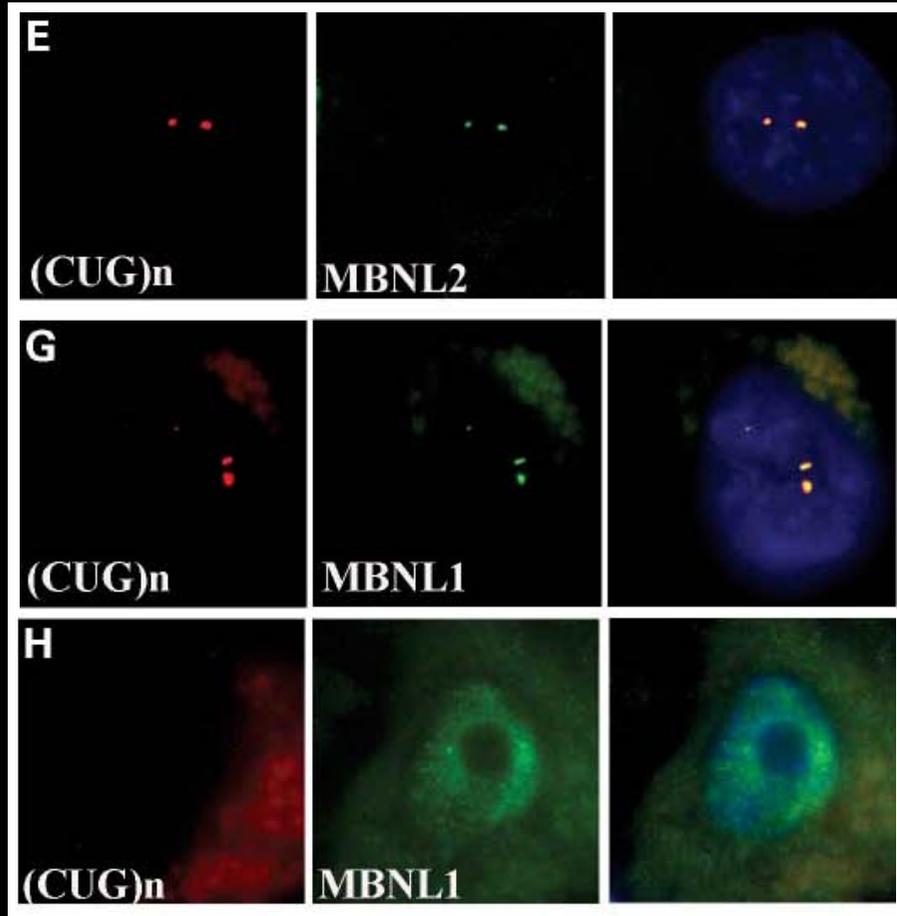
Cortical Region Partitioning



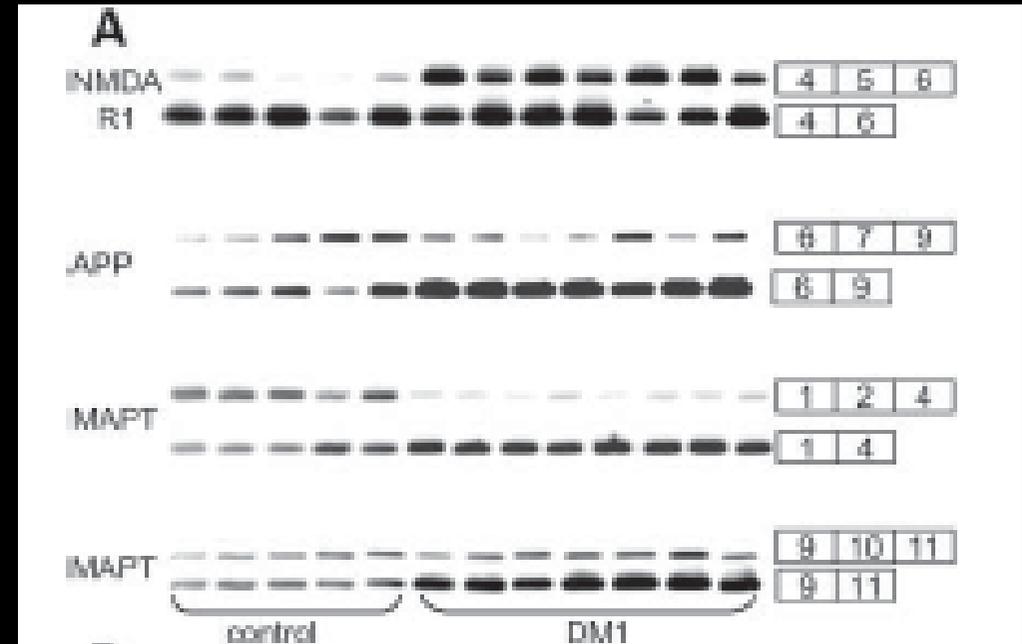
Tractography and fMRI



CNS Molecular Phenotype in DM



Jiang, et al., HMG, 2004



Jiang, et al., HMG, 2004

Conclusions

- Many of DM multisystemic features affect the CNS
- Many DM CNS deficits appear to be more functional (physiological? pharmacological?) than structural
- The same “RNA mechanism” that affects skeletal muscle affect the brain
- Minor initial deficits can grow into major problems if not addressed
- Treat what’s treatable – other organ systems, sleep deficits, attention abnormalities, mood

Conclusions

- **Much of CNS in DM is grossly normal - ? A good sign?**
- **An integrated and longitudinal explanation of function (neuropsychological, sleep, central motor control) and structure (imaging and pathology) is still needed.**
- **As Tee said more than 15 years ago:
“Functional imaging strategies in reference to autopsy findings should provide important data to characterize the brain DM phenotype”**

How You Can Help Fight DM

- **Participate in MDF**
- **Register with the National DM Registry**
- **Participate in MDA**
- **Participate in research studies**
- **Set up tissue donation from surgeries or autopsy**

