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Investigating multiple sclerosis using advanced MRI

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Melbourne Brain Centre Imaging Unit

BHAVI MS Symposium June 2023

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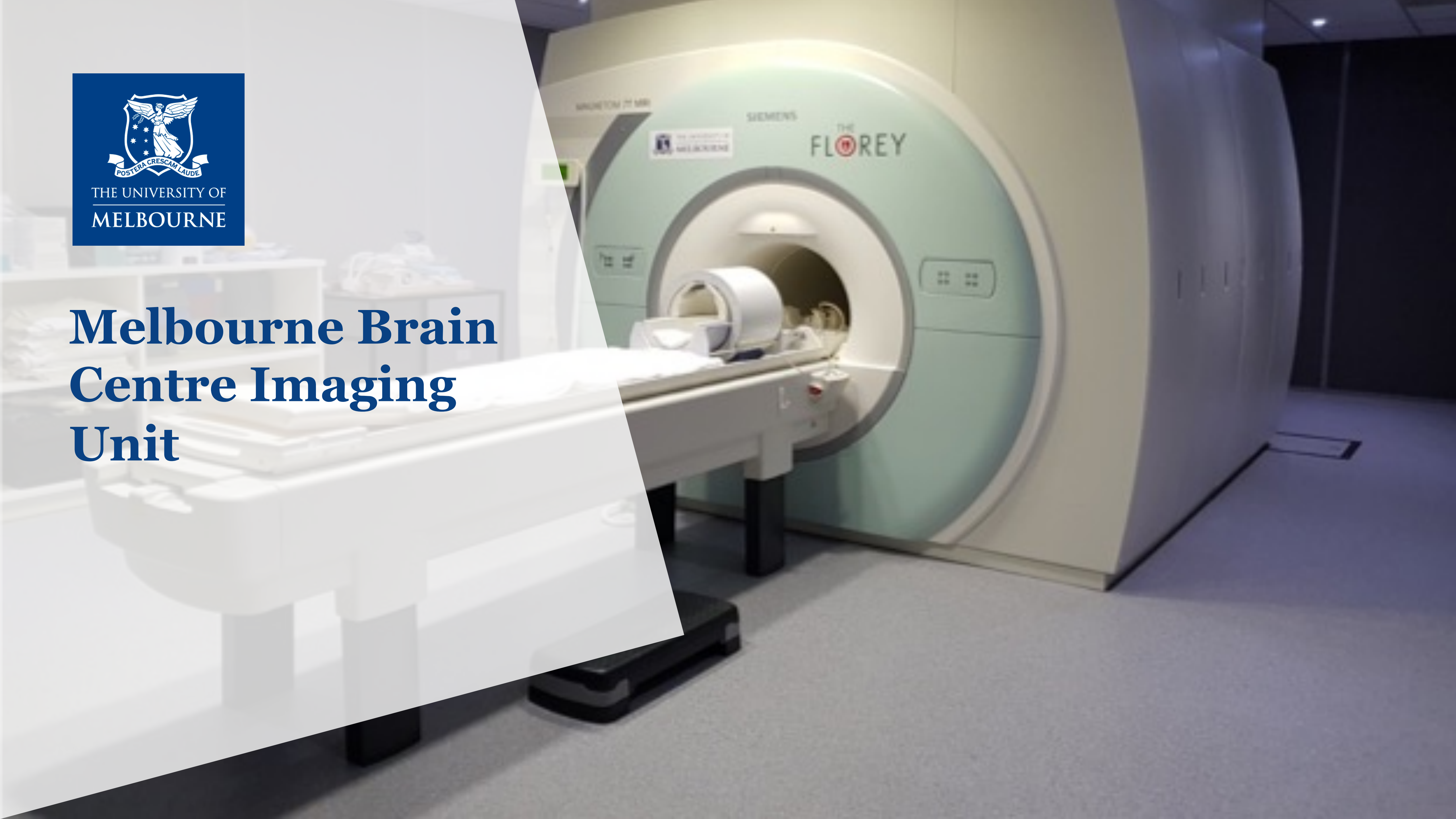
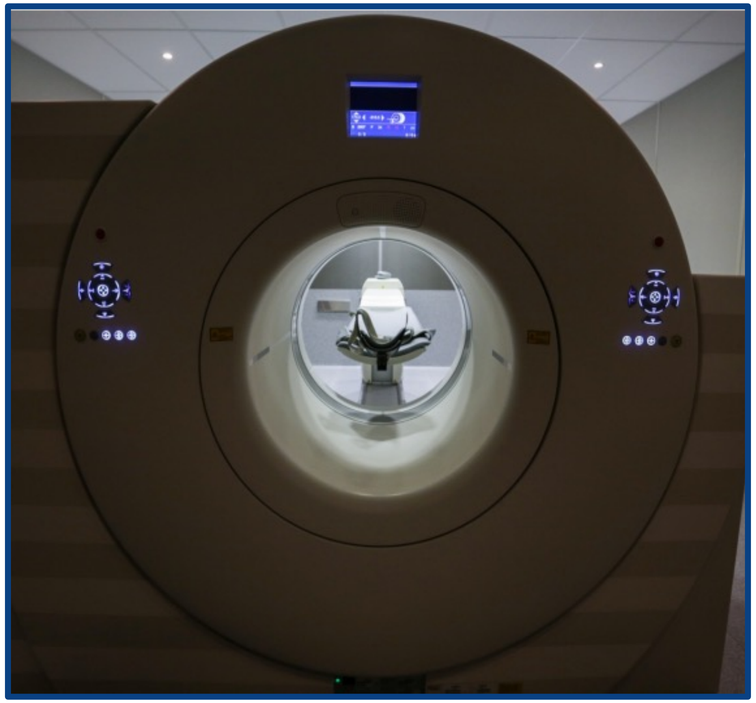


Our facility houses and operates

Positron Emission Tomography - Computed Tomography (PET-CT)

Ultra-high field Magnetic Resonance Imaging (7 Tesla MRI)

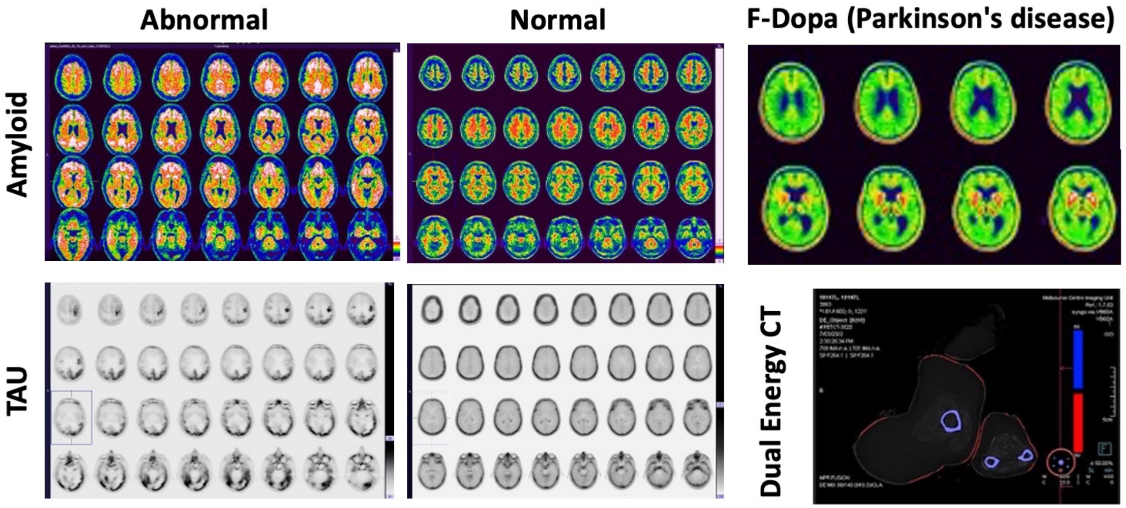


PET-CT Siemens VISION EDGE 600

- High sensitivity and resolution PET tracer 3D measurement available for:
  - ^{18}F Amyloid in Alzheimer's
  - ^{18}F TAU in CTE in Athletes
  - ^{18}F FDOPA in Parkinson's
  - ^{18}F AV133 in long COVID
  - ^{22}Na for Plants sciences
- Raw data storage
- Dual energy Low dose CT
- CT for material science, digitising museum artefacts, and 3D Printing

CT of mummified Egyptian boy

PET-CT imaging of the brain



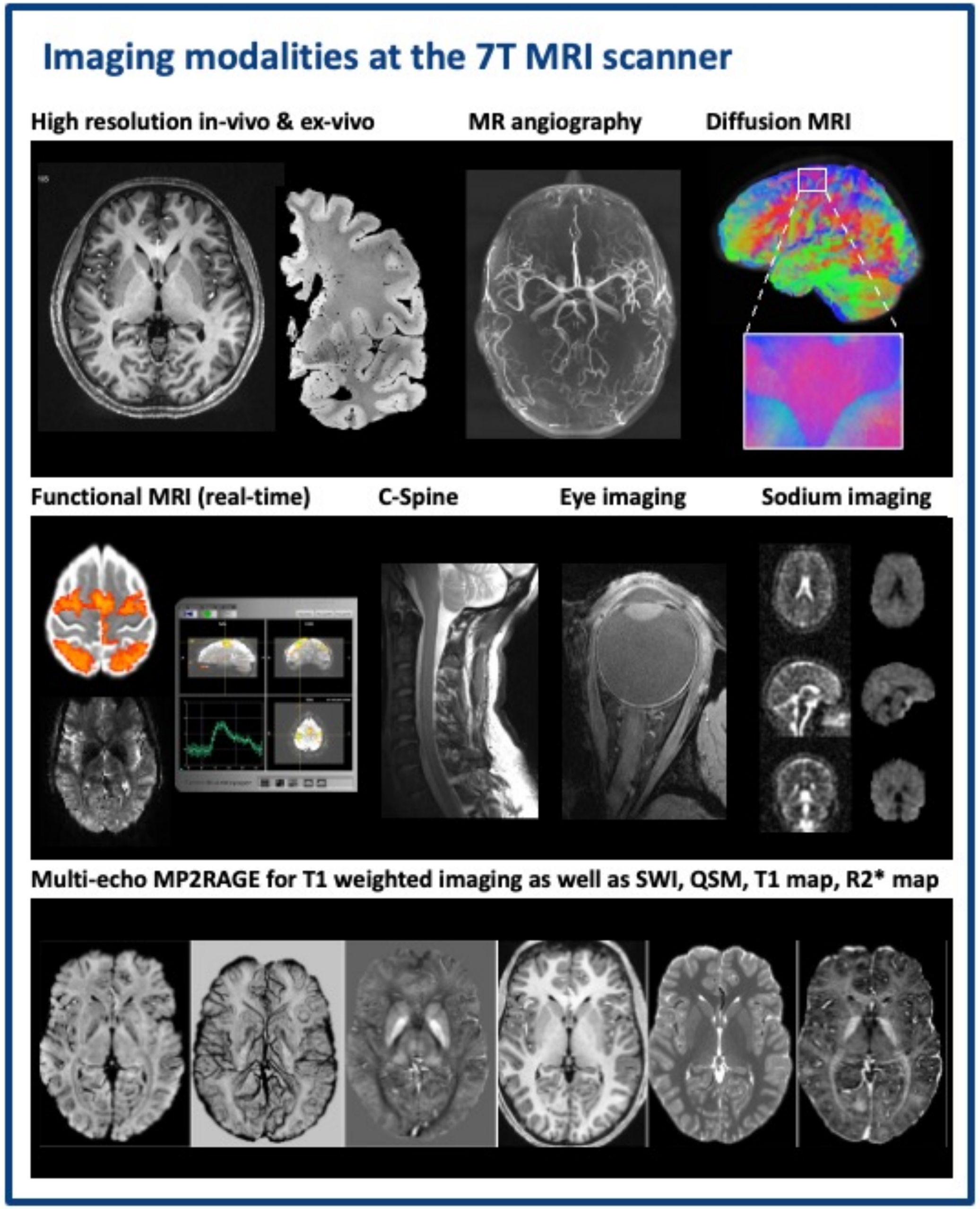
Our facility houses and operates

Positron Emission Tomography - Computed Tomography (PET-CT)

Ultra-high field Magnetic Resonance Imaging (7 Tesla MRI)

Siemens Magnetom 7T plus VE12U: hardware & software

- Head coil: Single-channel transmit & 32-channel receive parallel 8-channel transmit & 32-channel receive (Nova Medical)
- Eye coil (MRI Tools 1Tx/6Rx)
- Cervical Spine coil (Rapid 1Tx/8Rx)
- Sodium coil (QED 1Tx/1Rx dual tuned H/Na)
- Modular coils: carotids, spine & cardiac (MRI Tools 1Tx/4Rx per module)
- Physiological monitoring pulse & respiration
- FMRI response button boxes (Cedris lumina 2x2, 2x4)
- Skin conductance recording
- MRI Compatible LED monitor 120Hz
- Headphones for ear protection and audio communication
- MRI compatible glasses (+6 to –6 dioptre correction)
- AD instruments: GSR amp & Neuro amp
- Real-time fMRI neurofeedback (Turbo Brain Voyager)
- Eye tracking (EyeLink)



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Multiple sclerosis

Damage in the brain and spinal cord in MS

1) Lesions – typical hallmark

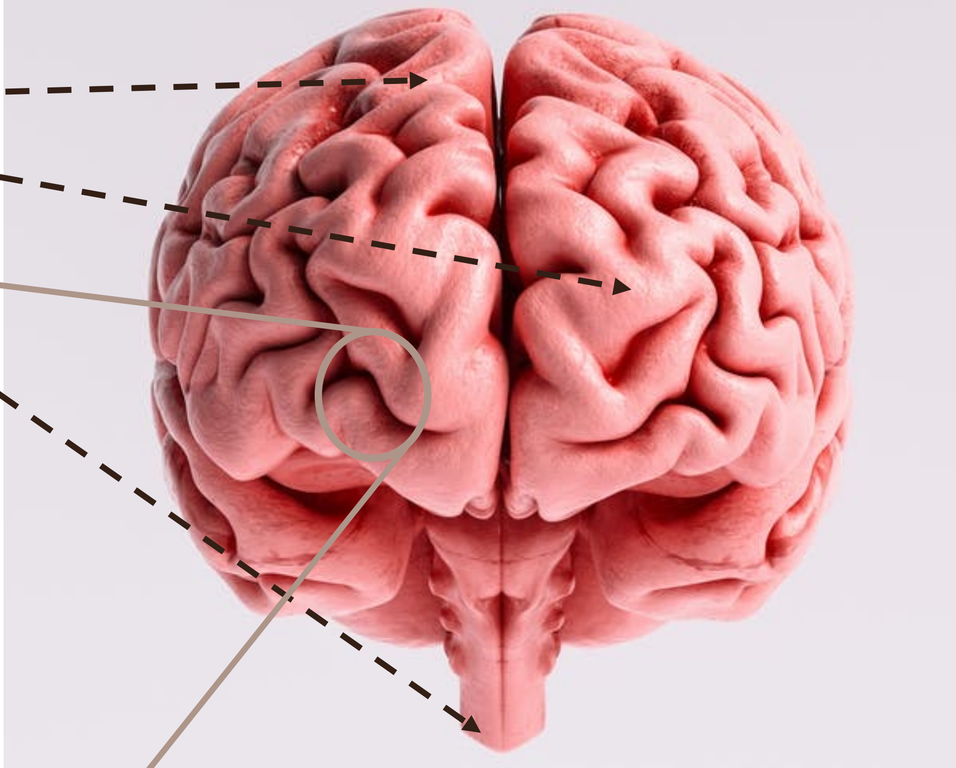
Inflammation

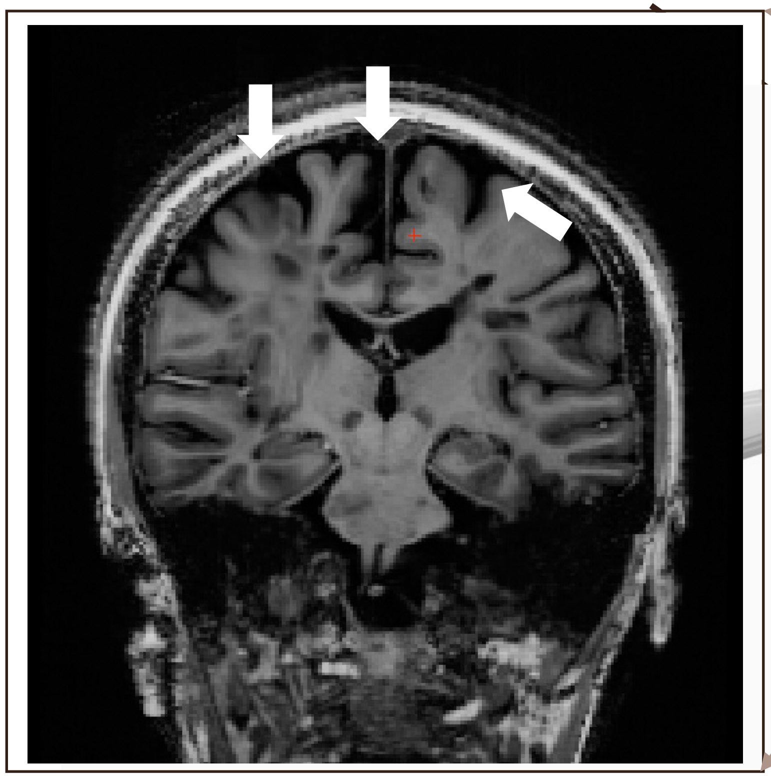
Demyelination

2) Atrophy

Degeneration / shrinkage of

brain tissue

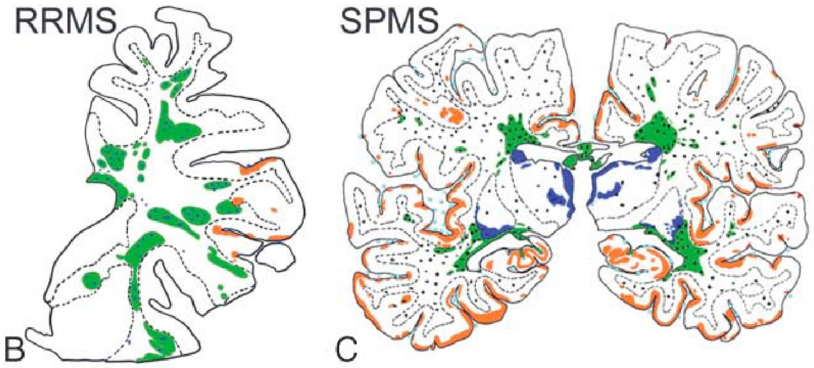




https://www.powerofpositivity.com/stress-can-shrink-your-brain/
https://theconversation.com/how-coronavirus-affects-the-brain-141100

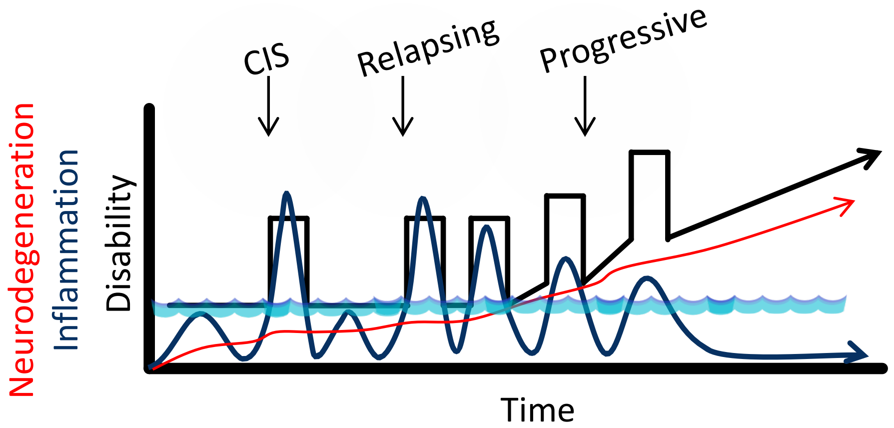
Symptoms of MS

White and grey matter pathology[1]

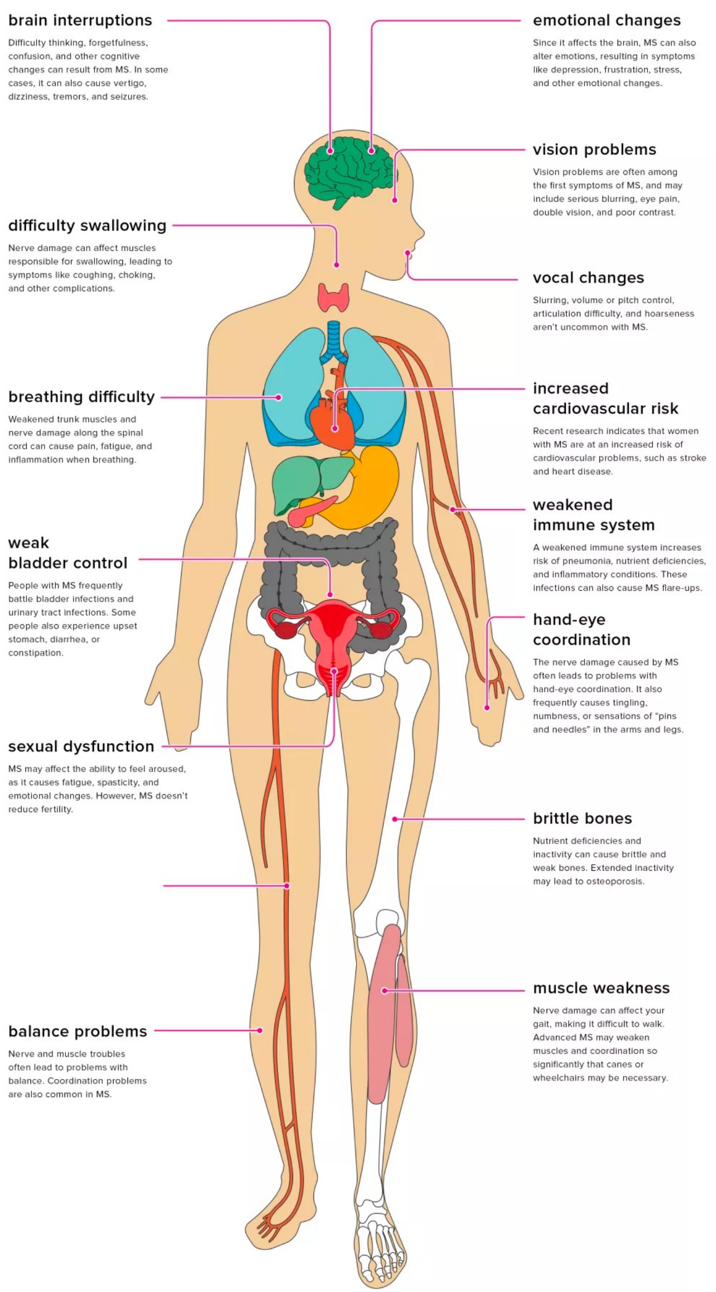


Demyelination in white matter - Demyelination in cortex

Clinical course



Multifocal, widespread and heterogeneous character of pathological processes + clinical course variable



Kutzelnigg et al. 2005; Image https://www.healthline.com/health/multiple-sclerosis/effects-on-the-body

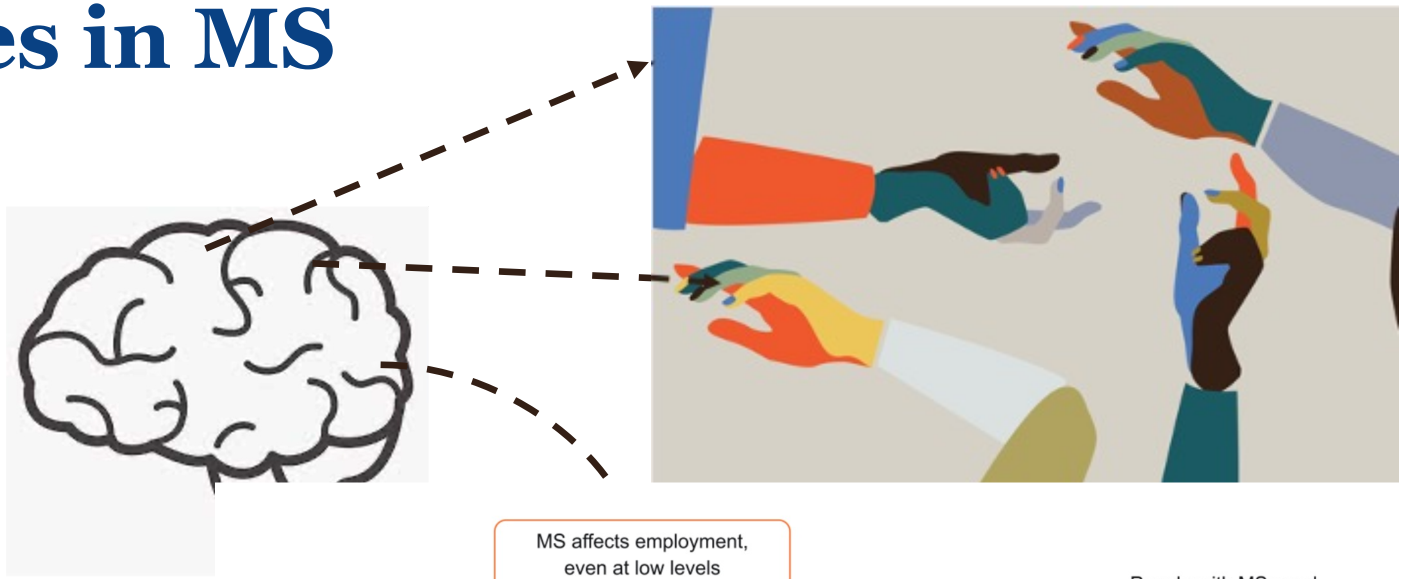
Motor disabilities in MS

Motor impairments are very common

Symptoms[4]

- Balance
- Walking
- Coordination
- Muscle weakness
- Spasticity
  abnormal muscle tightness due to prolonged muscle contraction
- Tremor
  involuntary, rhythmic muscle contraction
- Clumsiness

Impact on quality of life and independence



[1]Souza et al., 2010, Johansson et al., 2007; Image - Giovannoni et al. 2016

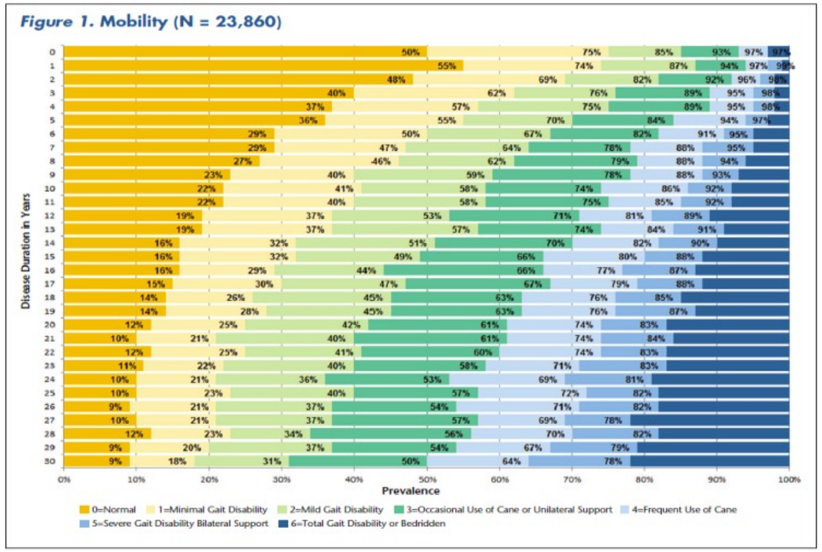
Motor disability in MS

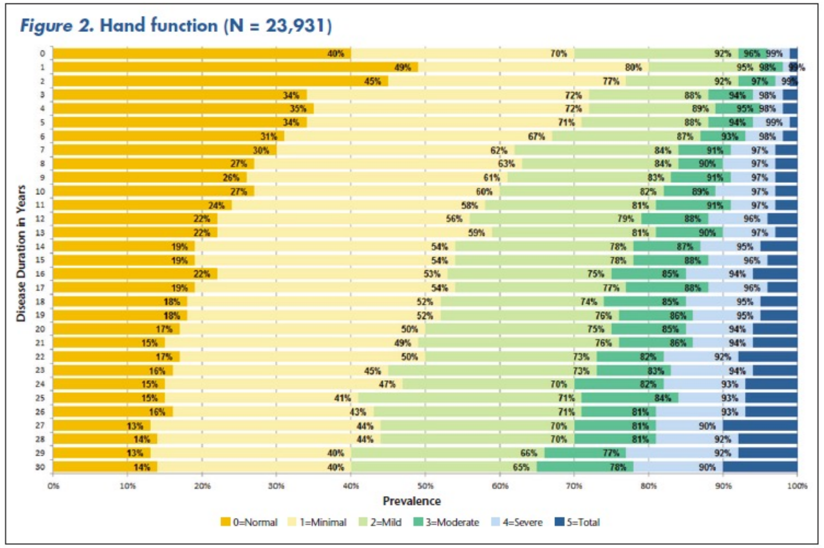
- **MS leads to progressive loss of both upper and lower[1]**
  - Up till 85% experience within 10 -15 years walking problems[2]
  - 60% within first year impaired hand function[3]

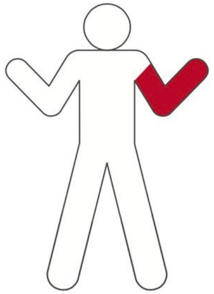
- **Though, most previous research focussed**
  - on overall disability
    - EDSS – clinical rating scale
    - weighted towards mobility
    - other subscales cognition, bowel bladder etc

- **Upper limb disability especially understudied**
  - Presents early on
  - Self-reported as impairing and restricting by more than 50%[2]

- **Limited correlation between limbs[4]**



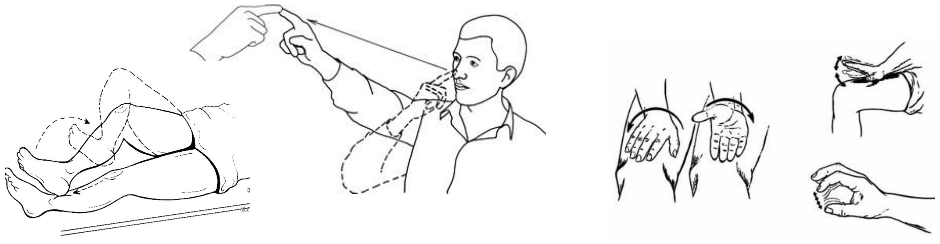




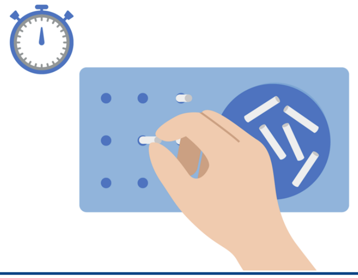
[1]Bertoni 2015; [2]Kister et al. 2013; [3]Johansson et al., 2007; [4]Coghe et al. 2019

Measuring motor impairments

1. Simple tests



3. 9-Hole Peg Test (9-HPT)



4. Timed 25 Foot Walk (T25FW)

2. Expanded Disability Statis Scale (EDSS)

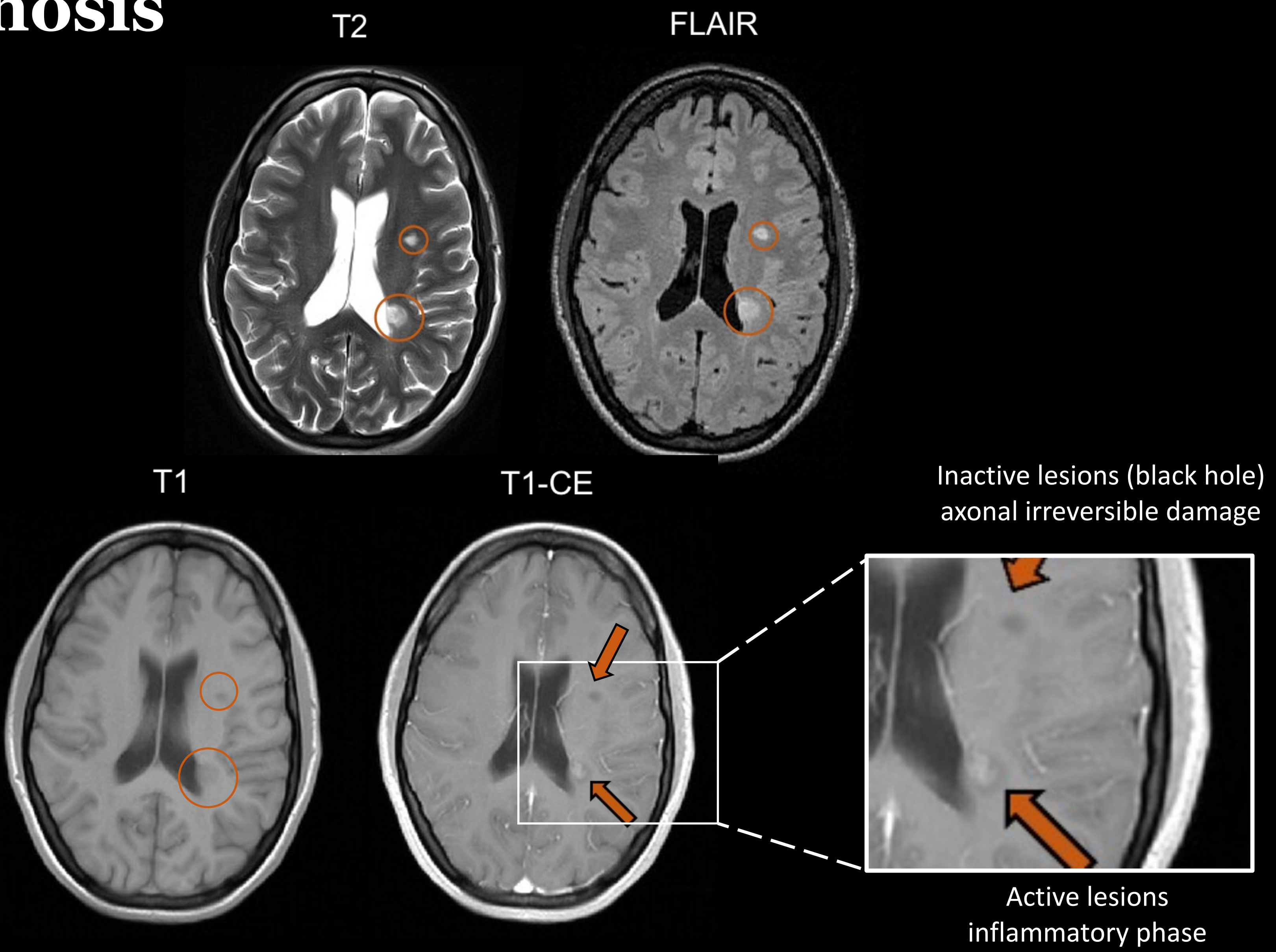
- used clinic & research
- 8 functional subsystems
- overall disability (weighted to mobility)

5. Laboratory gait analysis

MRI and diagnosis

Diagnosis Criteria

- Clinical observations
- Oligoclonal bands in the cerebrospinal fluid
- MRI – dissemination of lesions
  - In time
  - In space (1 or > in at least 2 areas)
    - periventricular
    - juxtacortical
    - Infratentorial (cerebellum)
    - spinal cord



<u>Conventional MRI</u>

- Diagnosis
- Monitoring disease progression
- Clinical trails (outcome lesions, relapses)

Classical hallmark – WM lesions

Imaging

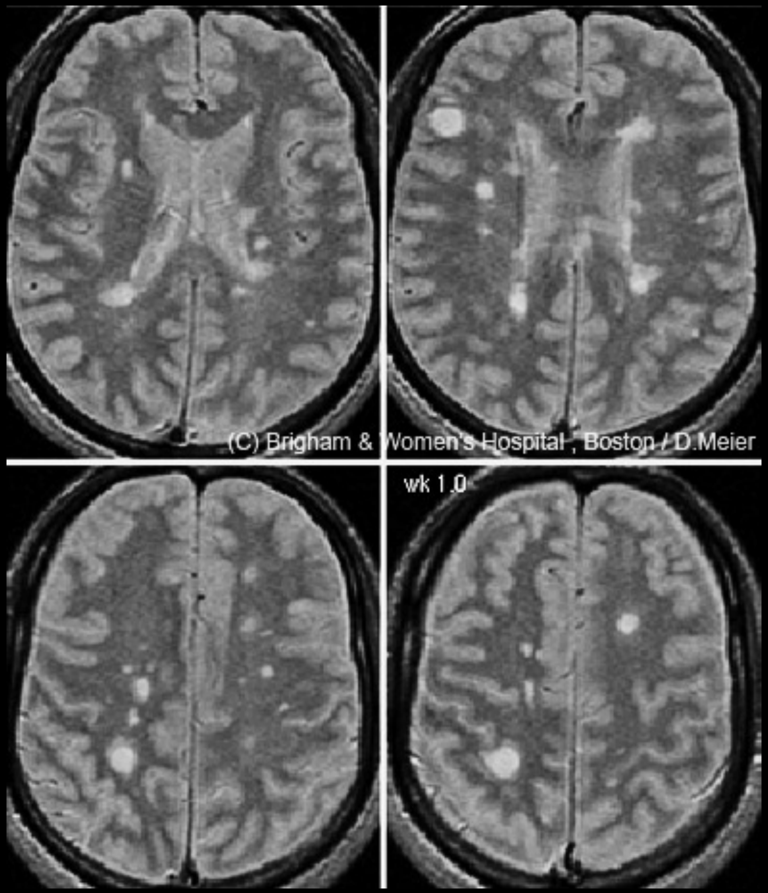
Classical hallmark of MS: white matter lesions

- Important diagnosis and progression
- Relation between lesion load and clinical disability is moderate

Clinical-radiological paradox

- Relapsing-remitting MS
- Over a year clinically stable

<u>Look beyond WM lesions and conventional MRI sequences</u>



http://www.msdiscovery.org/news/news_synthesis/322-more-meets-eye

Imaging

Besides white matter lesions (T1 / T2 / FLAIR)

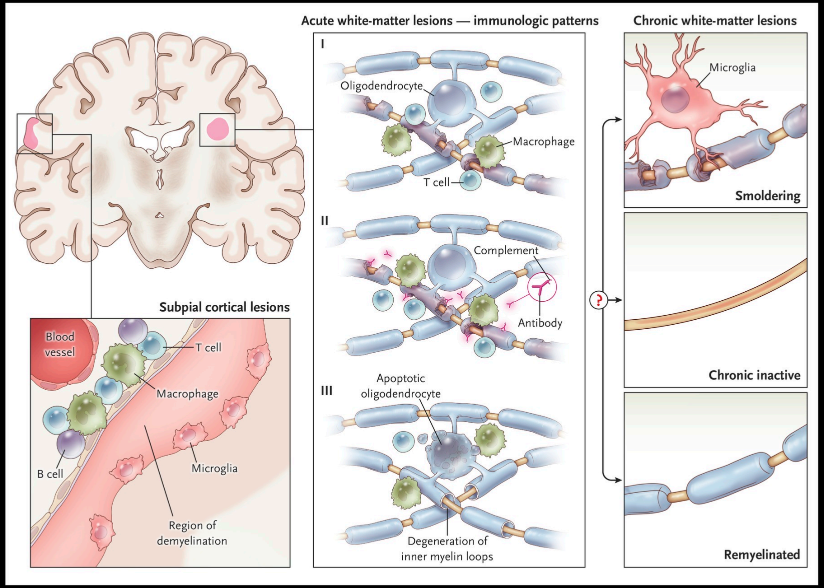
grey matter lesions (DIR, SPIR)

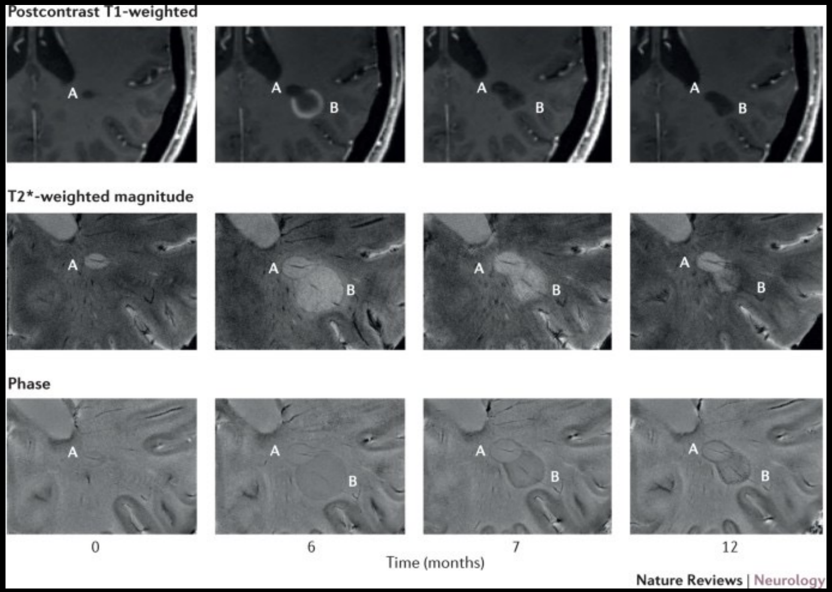
Types of lesions

- Active: different patterns
- Chronic lesions
  - Chronic inactive
  - Remyelination
  - Chronic active = smouldering (T2*, Phase, QSM)

Besides conventional MRI → **7T and advanced MRI techniques**

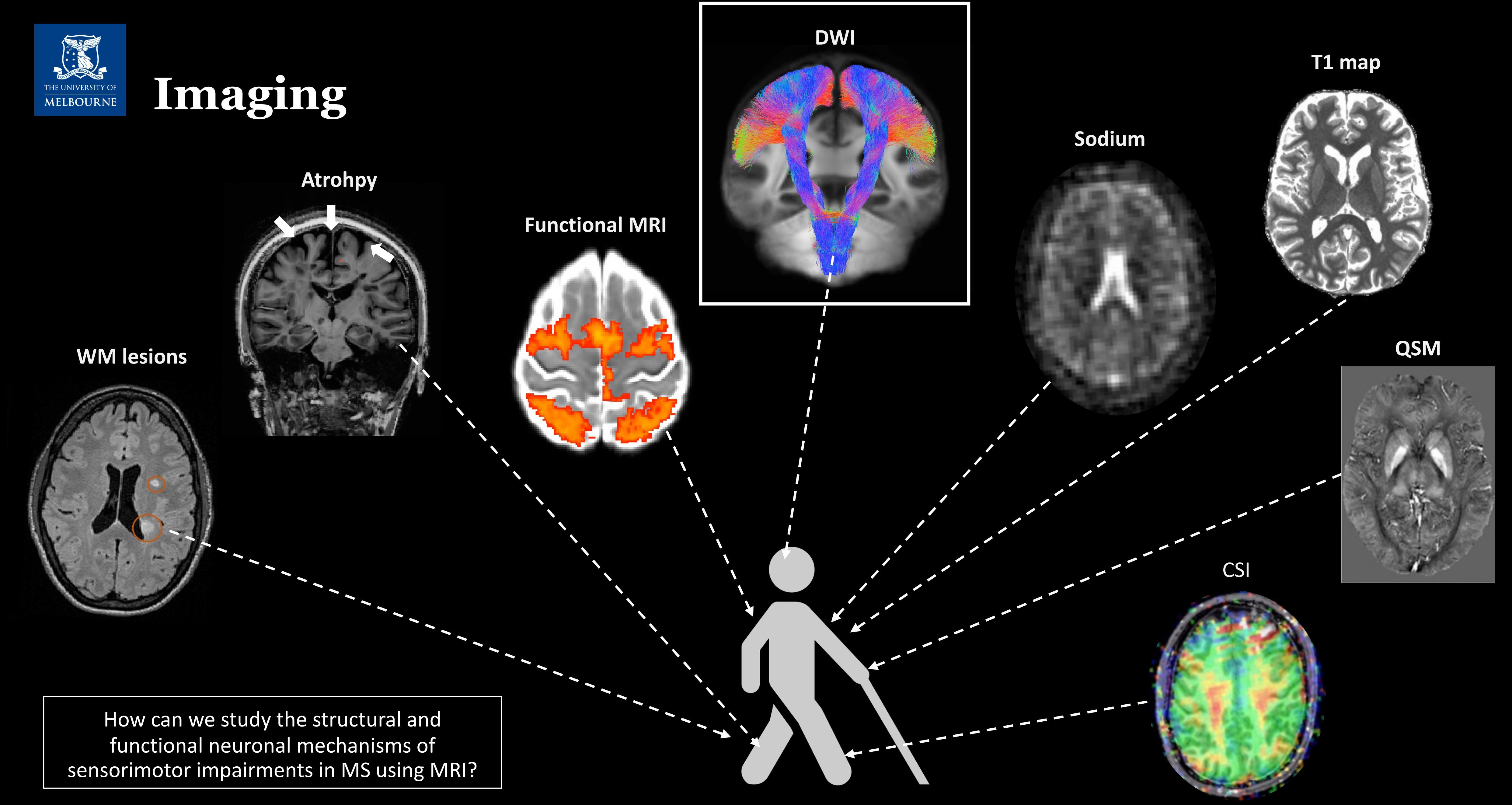
- Different types of lesions (smouldering)
- central vein (diagnosis)





Absinta et al., 2016; Reich et al., 2018

Imaging



How can we study the structural and functional neuronal mechanisms of sensorimotor impairments in MS using MRI?

http://www.msdiscovery.org/news/news_synthesis/322-more-meets-eye

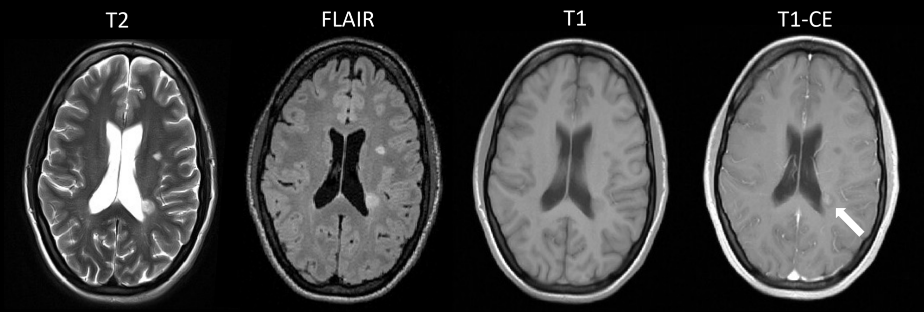
Axonal loss in major motor tracts is associated with impaired motor performance in minimally disabled MS patients

Strik et al – Brain Communications - 2021

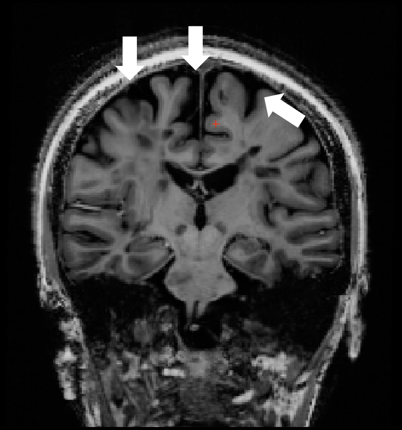
The microstructural changes in the brain

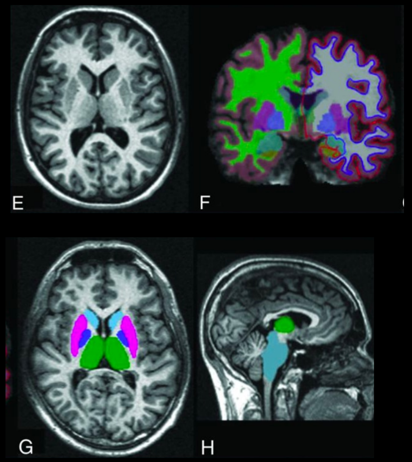
Conventional imaging

Lesions relates moderately to disability

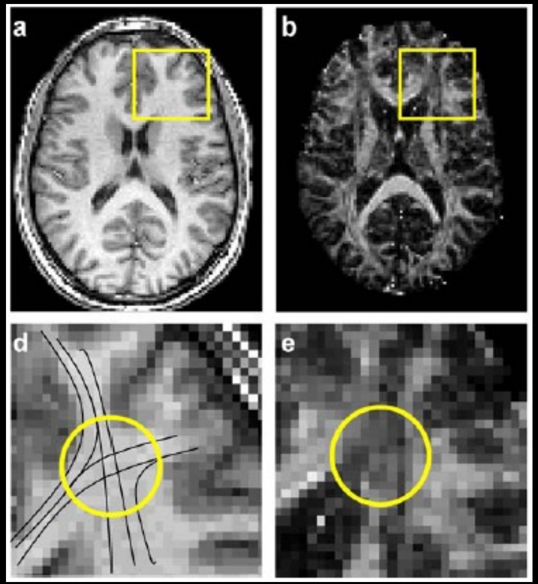


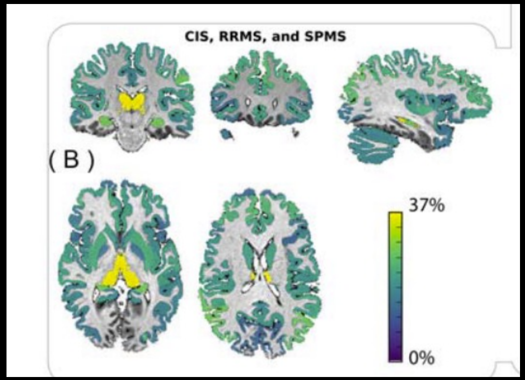
Atrophy



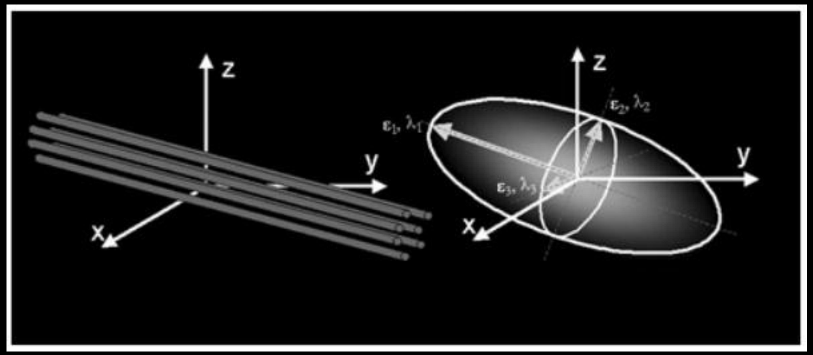


Diffusion Tensor Imaging





transfer of water molecules is described with a tensor

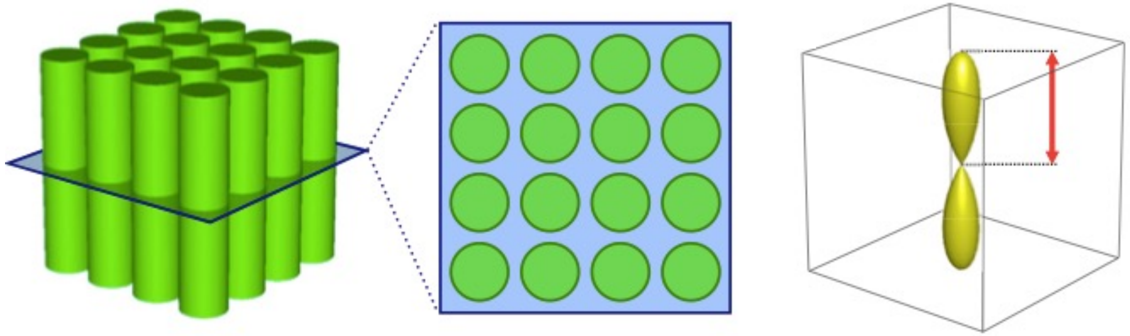


Limitations

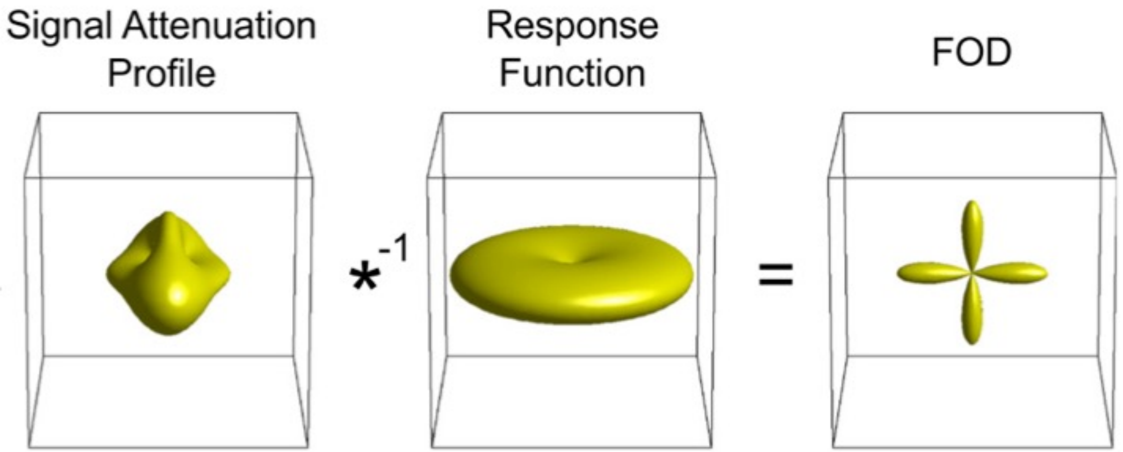
- Assumes single fibre population
- Many voxels contain partial volume fraction of 2 or more fibre populations
- Crossing fibers in 90% WM voxels[2]

[1]Eshagi et al 2018; [2]Jeurissen et al., 2010; Assaf et al (2008); Alexander et al. (2007)

Constrained spherical deconvolution



FOD



Sensitive to white matter axonal degeneration

Provide estimation of distribution of fibers in each voxel (FOD)

Raffelt et al (2012); Raffelt et al (2015)

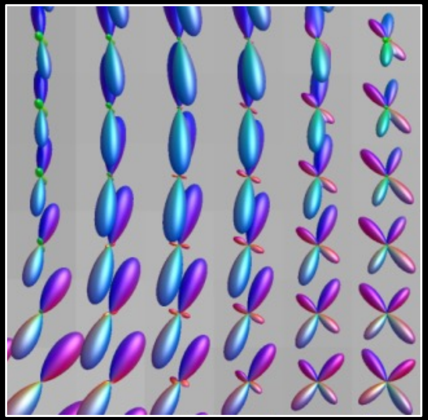
Fibre-specific measures

Fixel = fibre population within a voxel

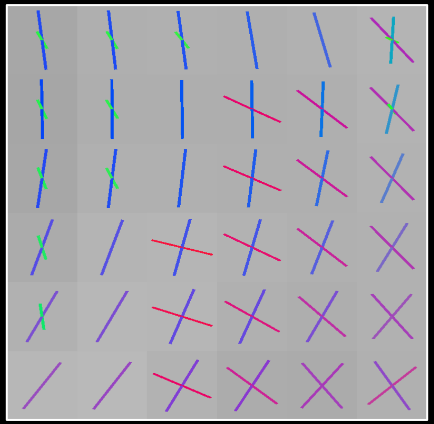
Fixel-specific measures:

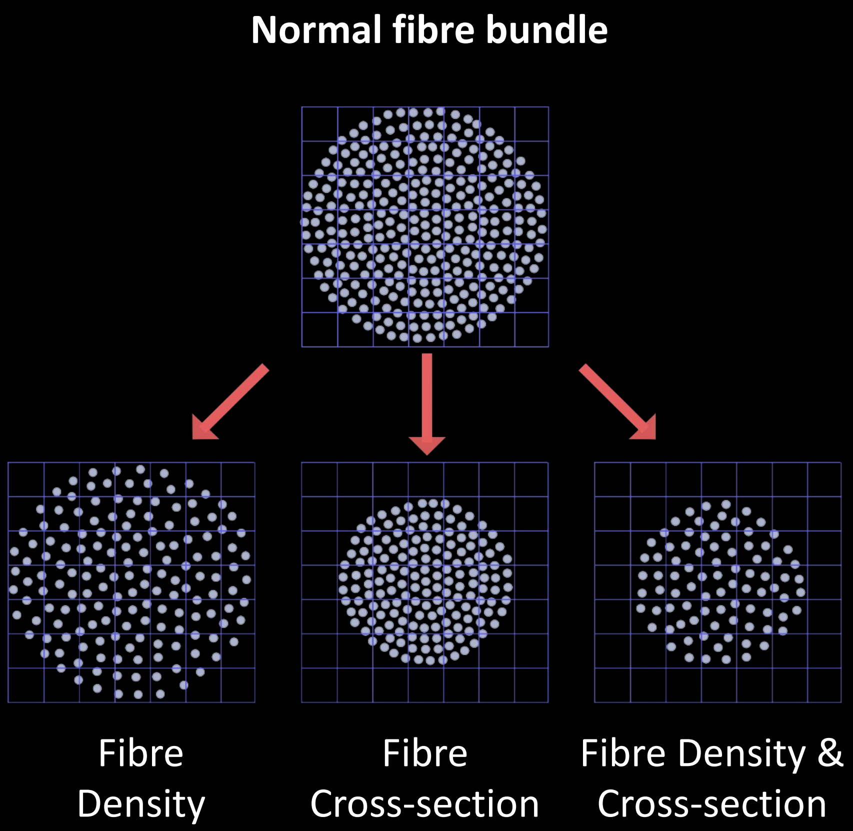
- Fibre density (FD)
- Fibre cross-section (FC)
- Fibre density and cross-section (FDC)

FOD



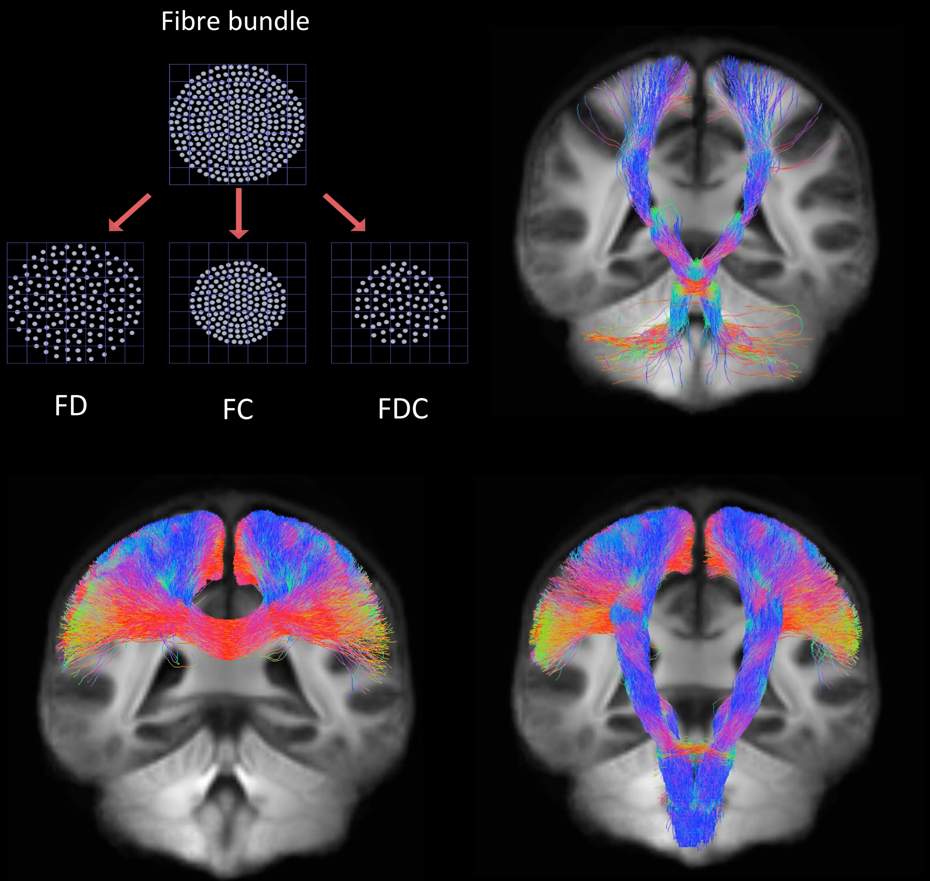
Fixels





Raffelt et al. 2017

Compare degree of axonal degeneration of motor tracts to motor performance using novel axonal markers



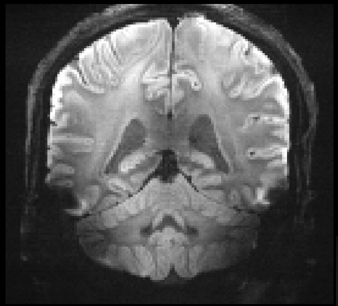
Methods

Participants

- 28 MS patients no to minimal disability (EDSS <4, pyramidal & cerebellar function ≤2)
- 17 healthy controls

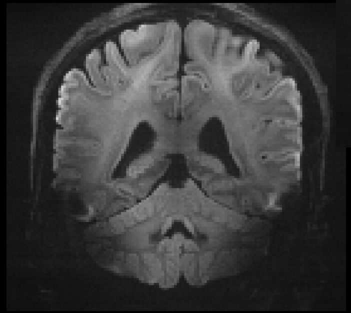
Ultra-high field MRI (7T)

- Whole body Magnetom 7T MRI (Siemens, Erlangen, Germany), combined single-channel transmit & 32-channel receive head coil (Nova Medical, Wilmington MA, USA)
- Comprehensive study
  - Resting-state fMRI (TR=0.8 , 1.6 mm iso)
  - Task fMRI - force matching task (TR= 1.7, 1.24 mm iso)
  - QSM (9 echoes, 0.75 mm)
  - Structural (0.9 mm iso)
  - **Diffusion (multi-slice 2D spin-echo EPI sequence (CMRR, University of Minnesota)** [1]



b=1000 s/mm2

b=3000 s/mm2



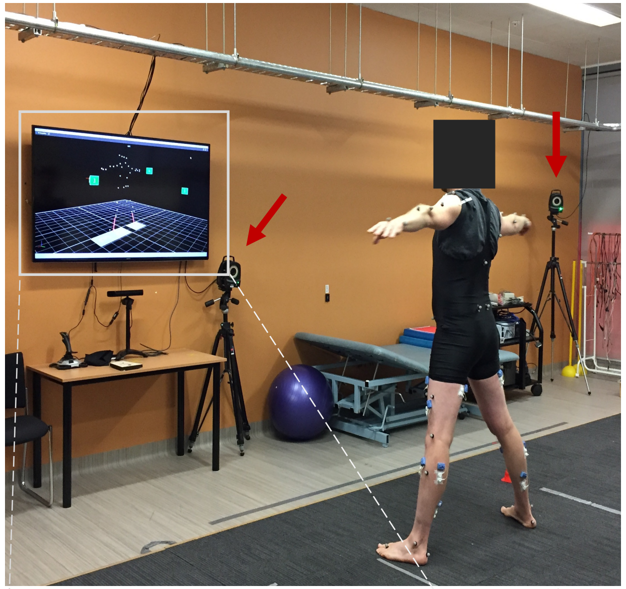
b=2000 s/mm2

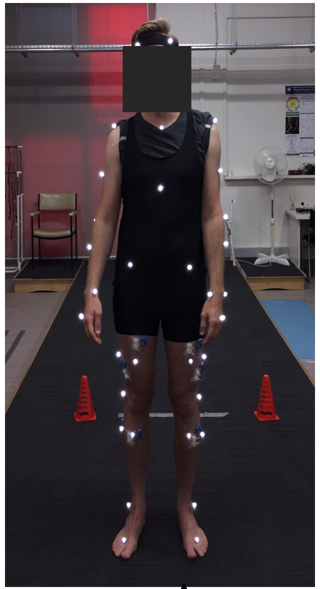
Coverage	TR	TE	MB	Acceleration GRAPPA	slices	Reso	b-shells	Directions	B0 images PA	Time
Whole brain	7000 ms	74.4 ms	2	3	128	1.24 mm iso	1000 s/mm^2 2000 s/mm^2 3000 s/mm^2	103	6	13 mins

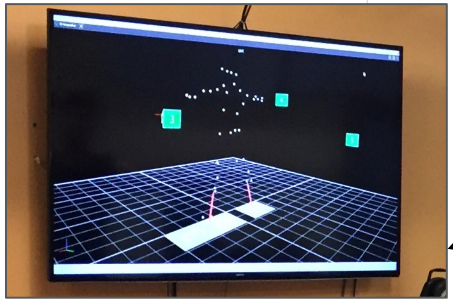
[1]VU et al. (2015). High resolution whole brain diffusion imaging at 7T for the Human Connectome Project.

Motor performance

3D video tracking gait assessment (Prof Mary Galea and Dr Eduardo Cofré Lizama)



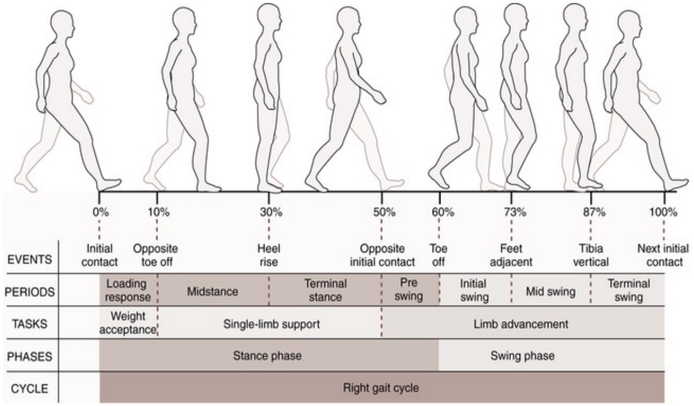




Reflective markers on specific body landmarks

3D model

Walkway

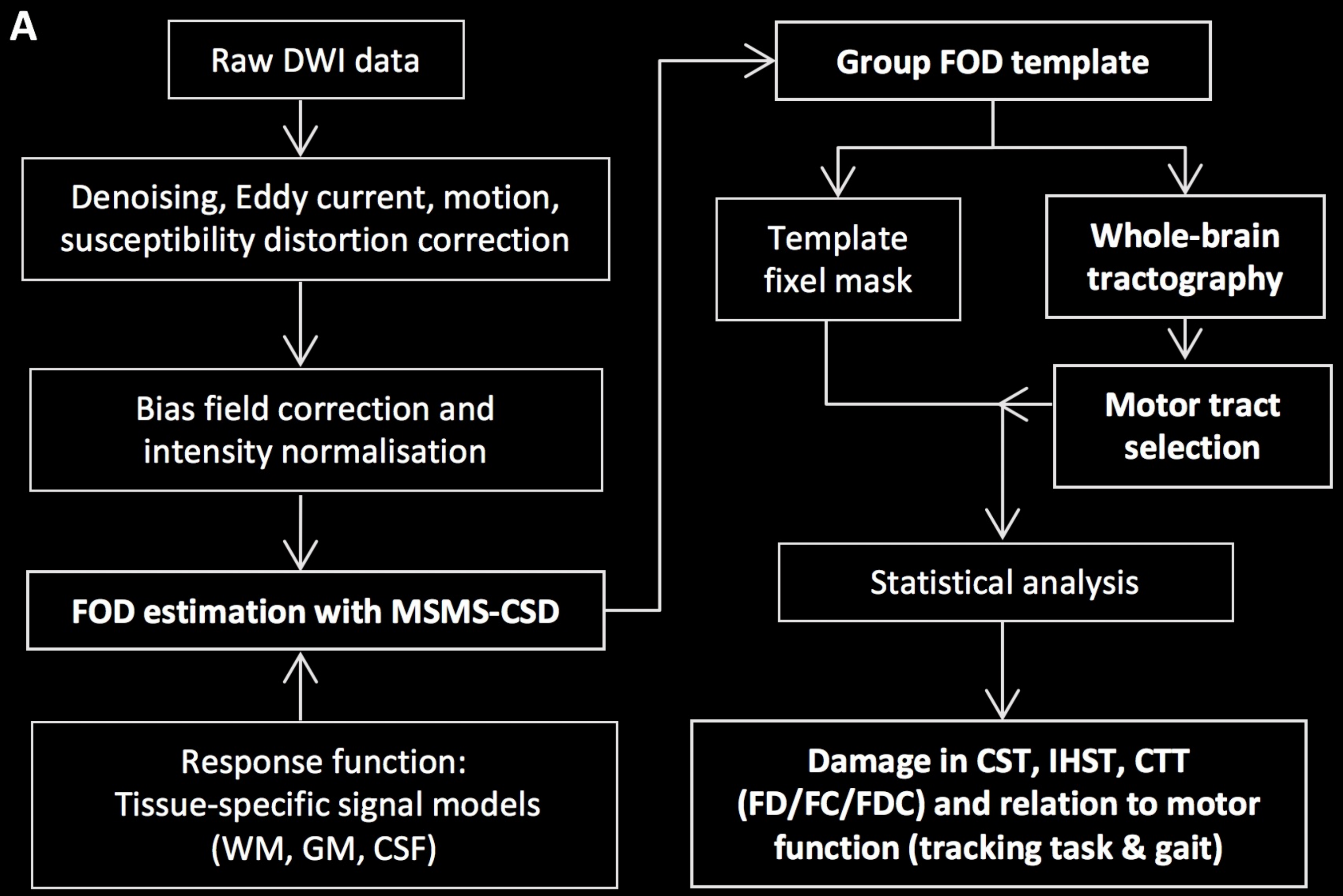


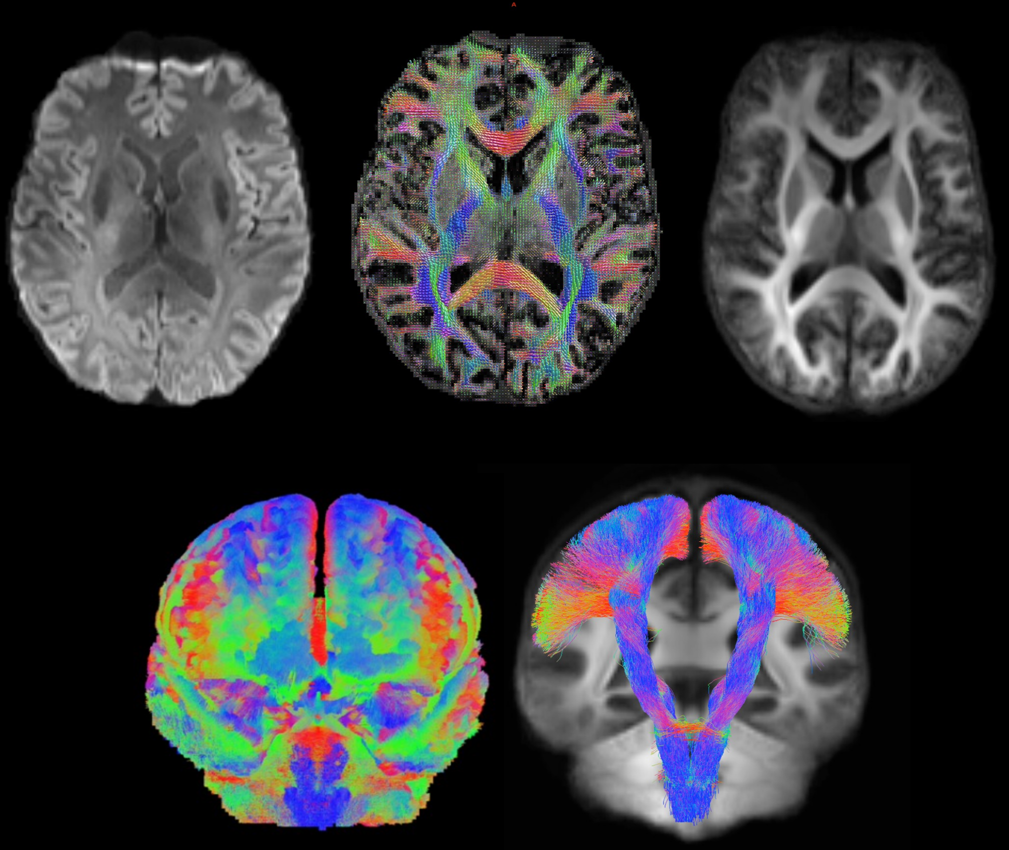
Stance, Stride length, Step width, Single support, Double support

Upper performance during MRI task

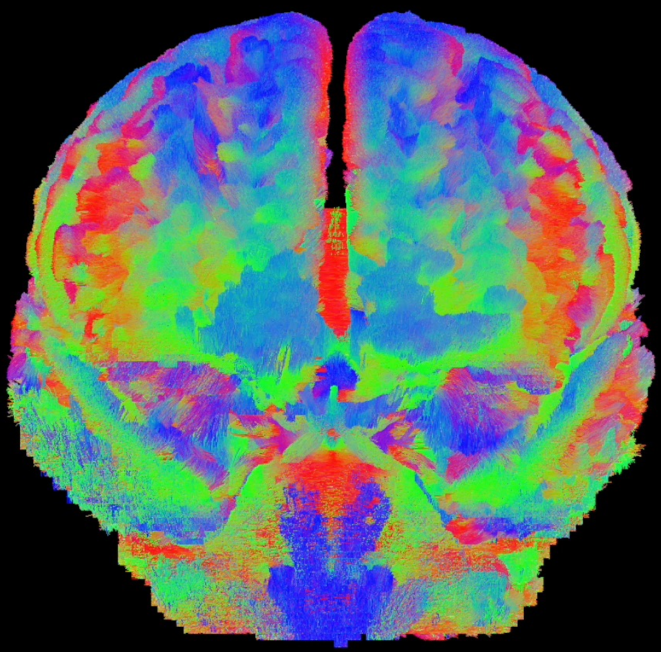
Neumann: Kinesiology of the musculoskeletal system: foundations for physical rehabilitations

Pre-processing pipeline - multi-shell multi-tissue CSD (MRtrix3)

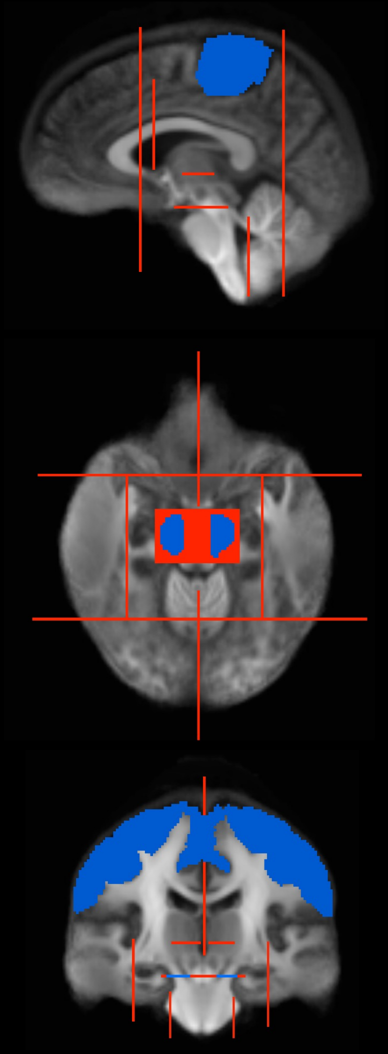


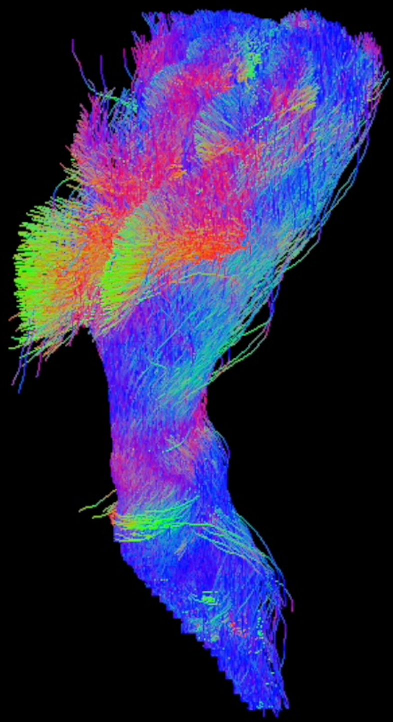


Whole brain tractography and motor tracts



whole brain probabilistic fibre tractography
(20 million seeds randomly assigned)

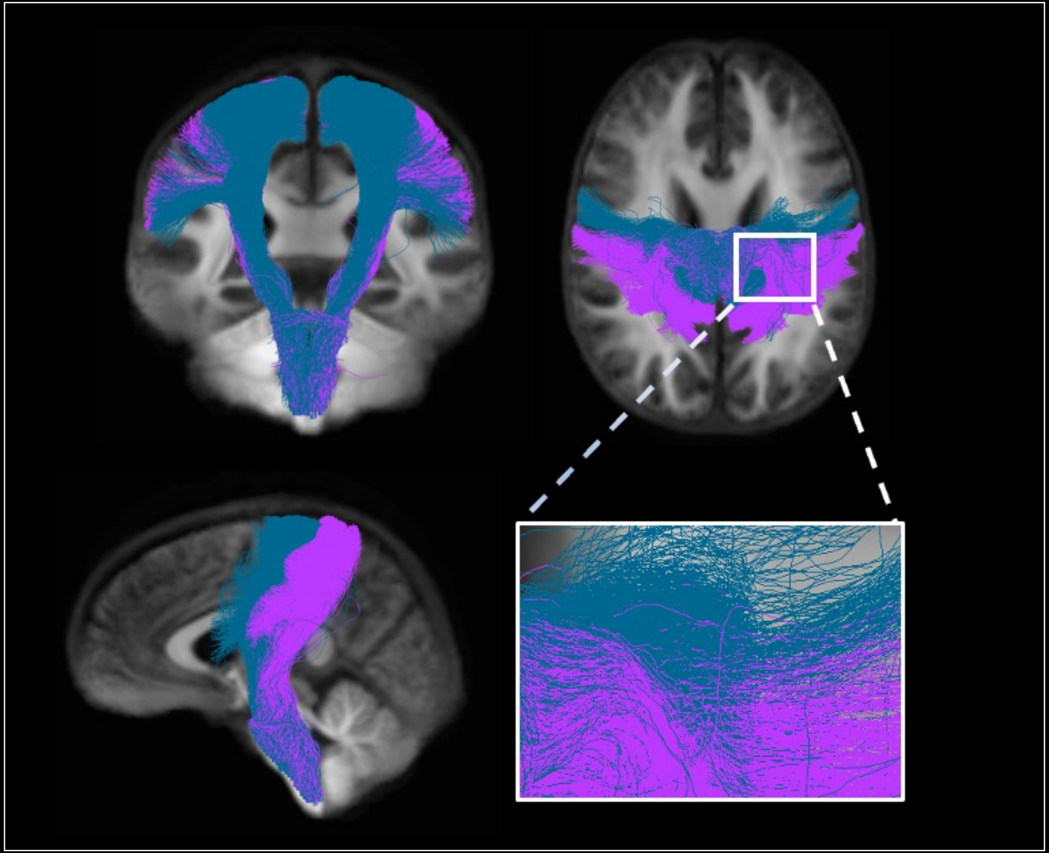




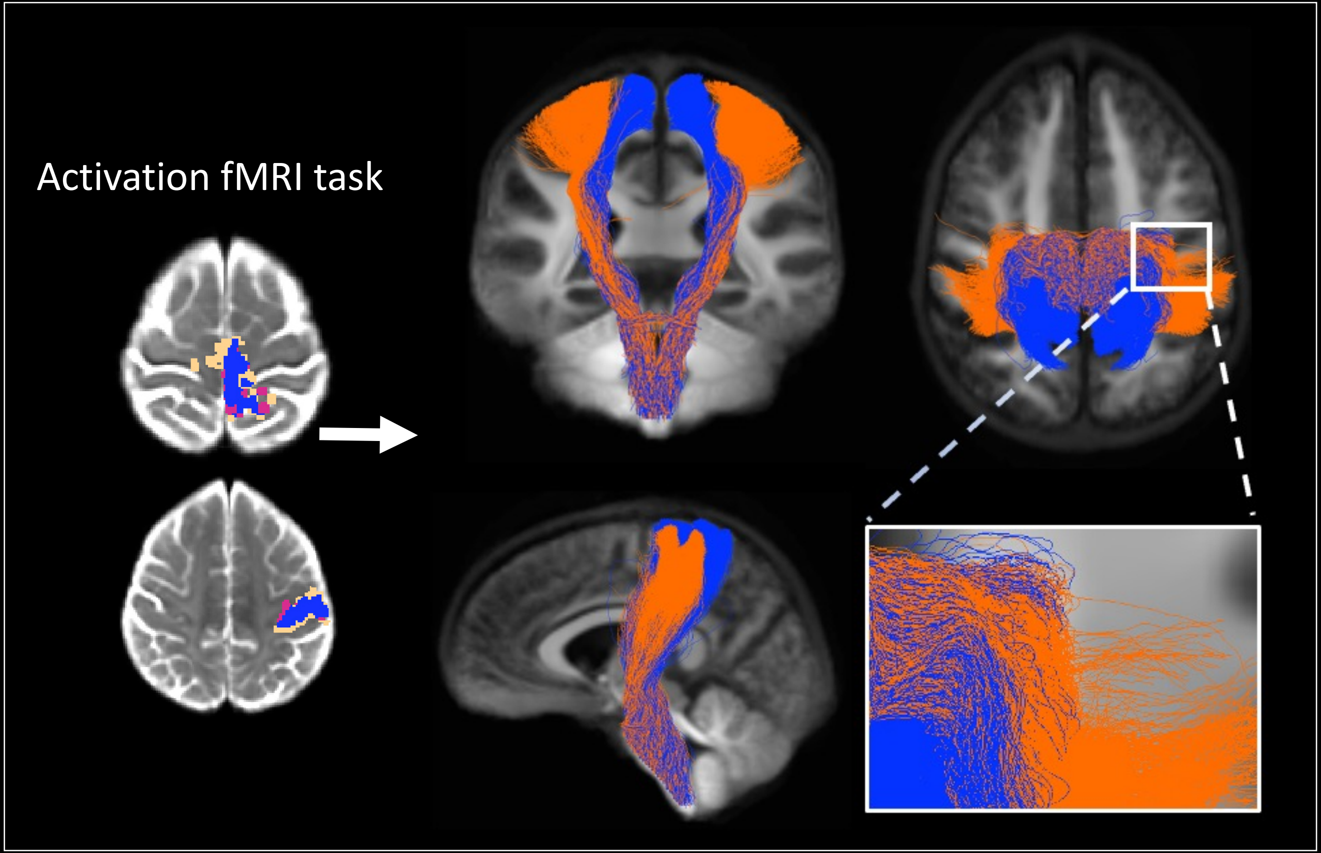
Corticospinal tracts = main motor tract

The corticospinal tracts: subdivide into different tracts

1. Primary motor & somatosensory tracts



2. Upper limb and lower limb tracts



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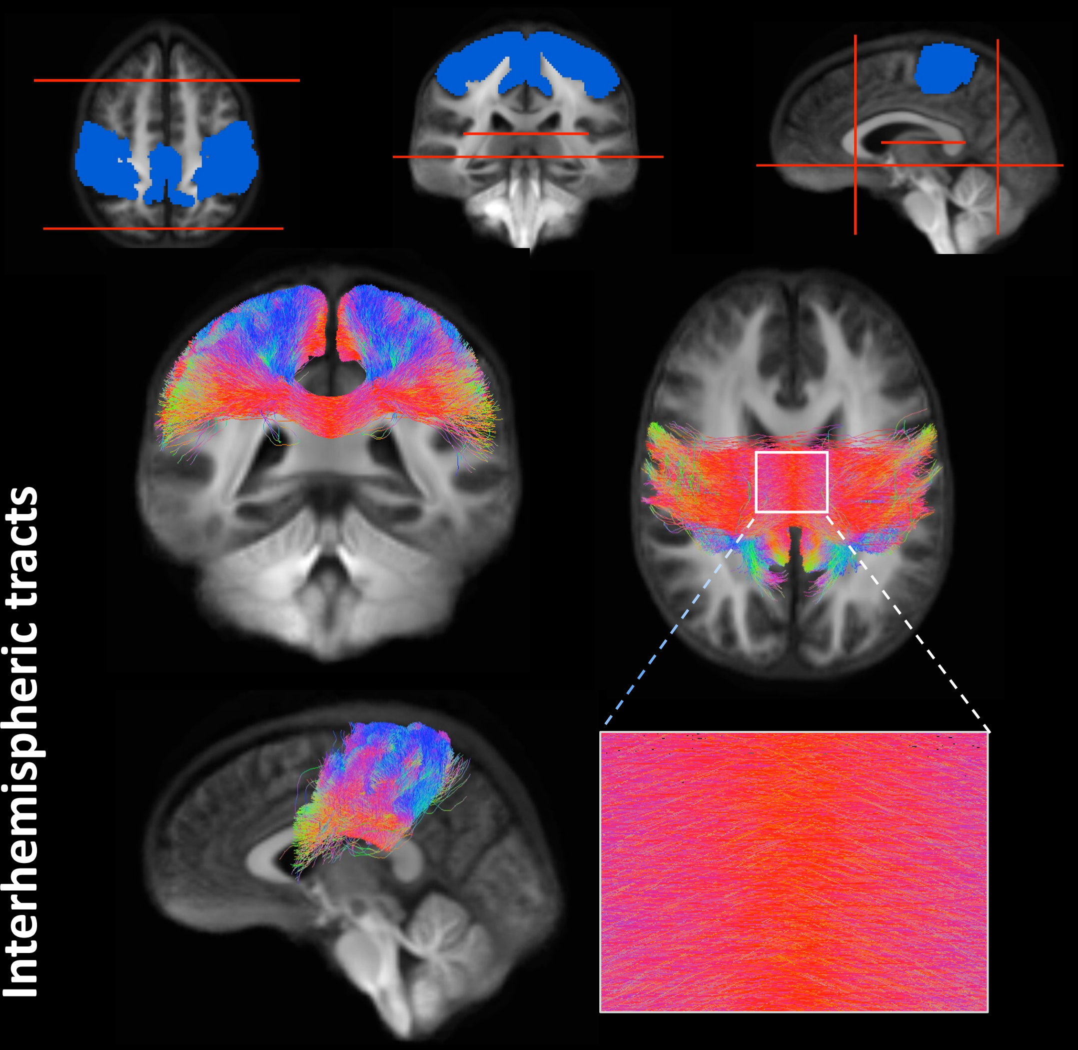
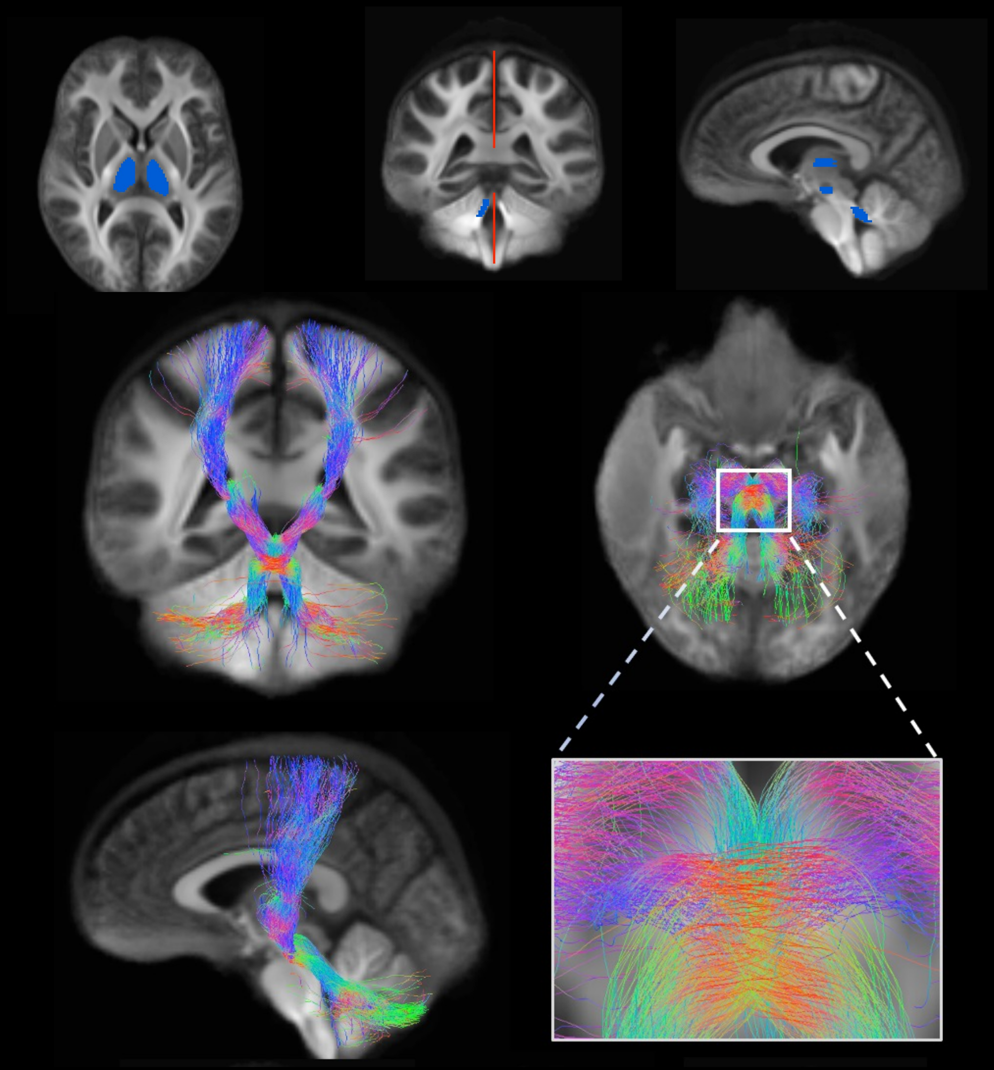
The interhemispheric tracts and cerebello-thalamic tracts

Interhemispheric tracts

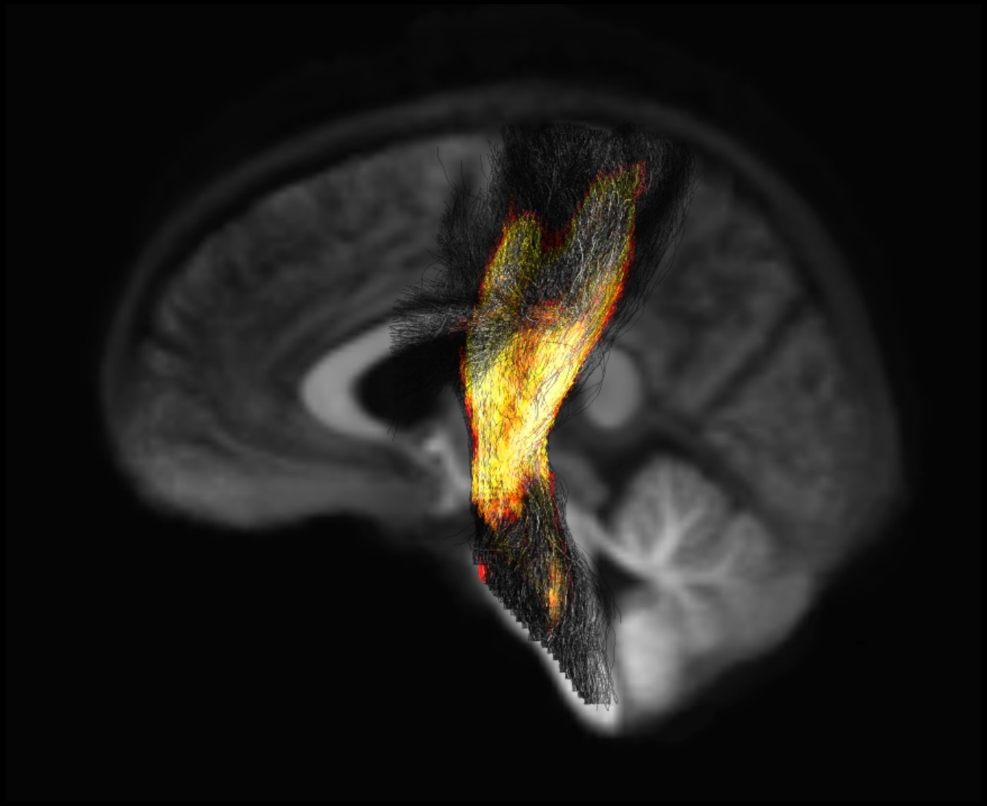


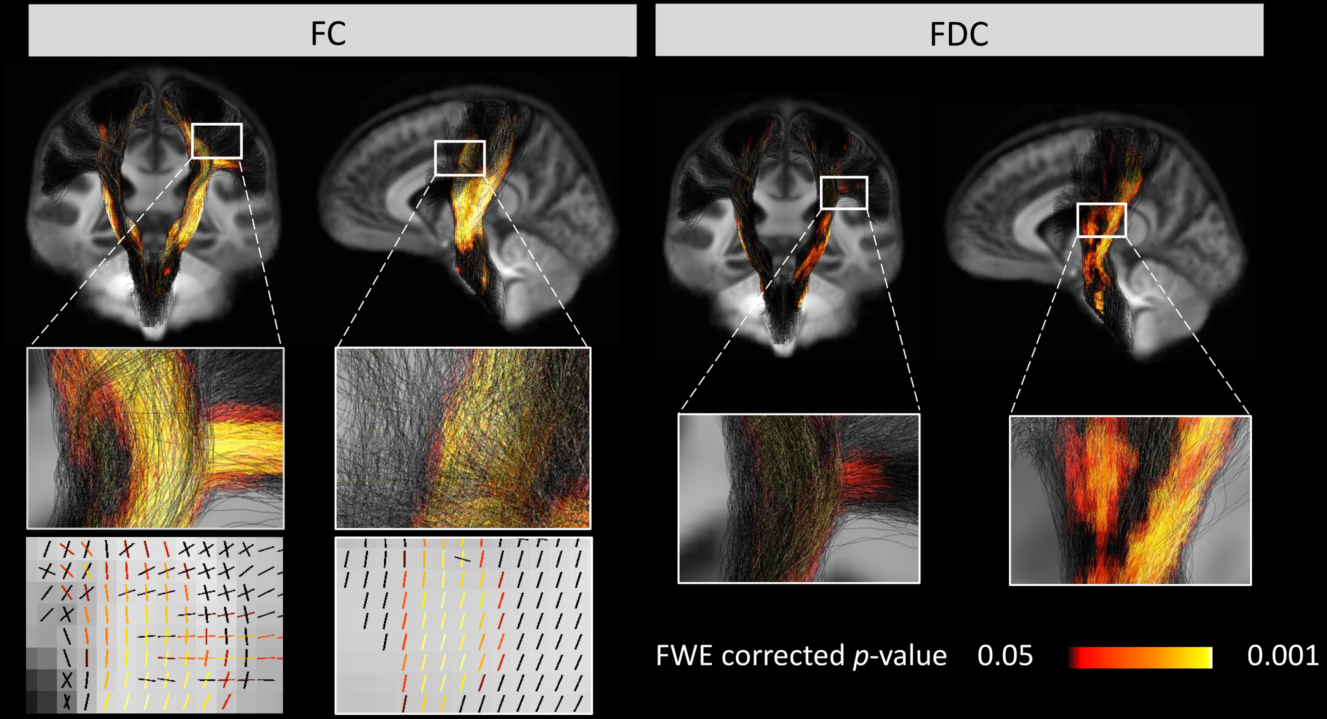
Cerebello-thalamic tracts

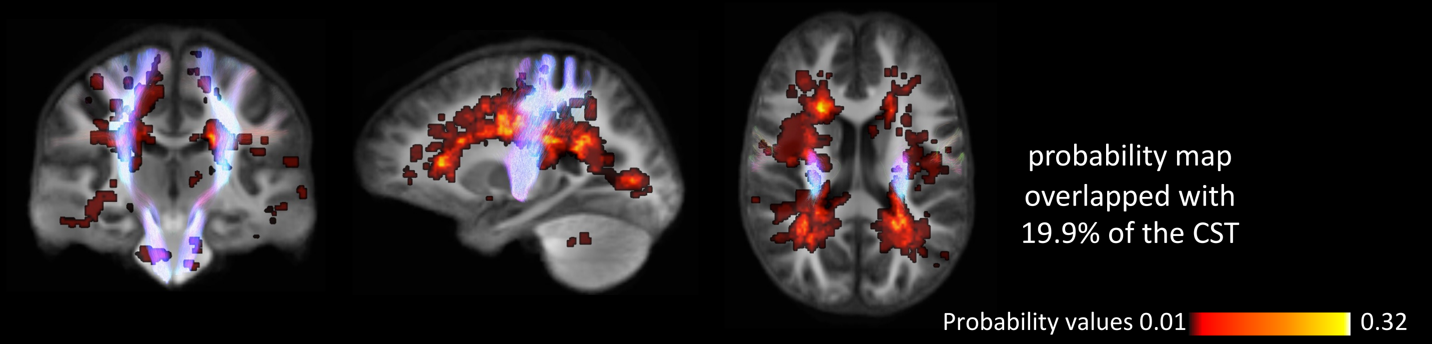


Corticospinal tracts: white matter atrophy in MS patients

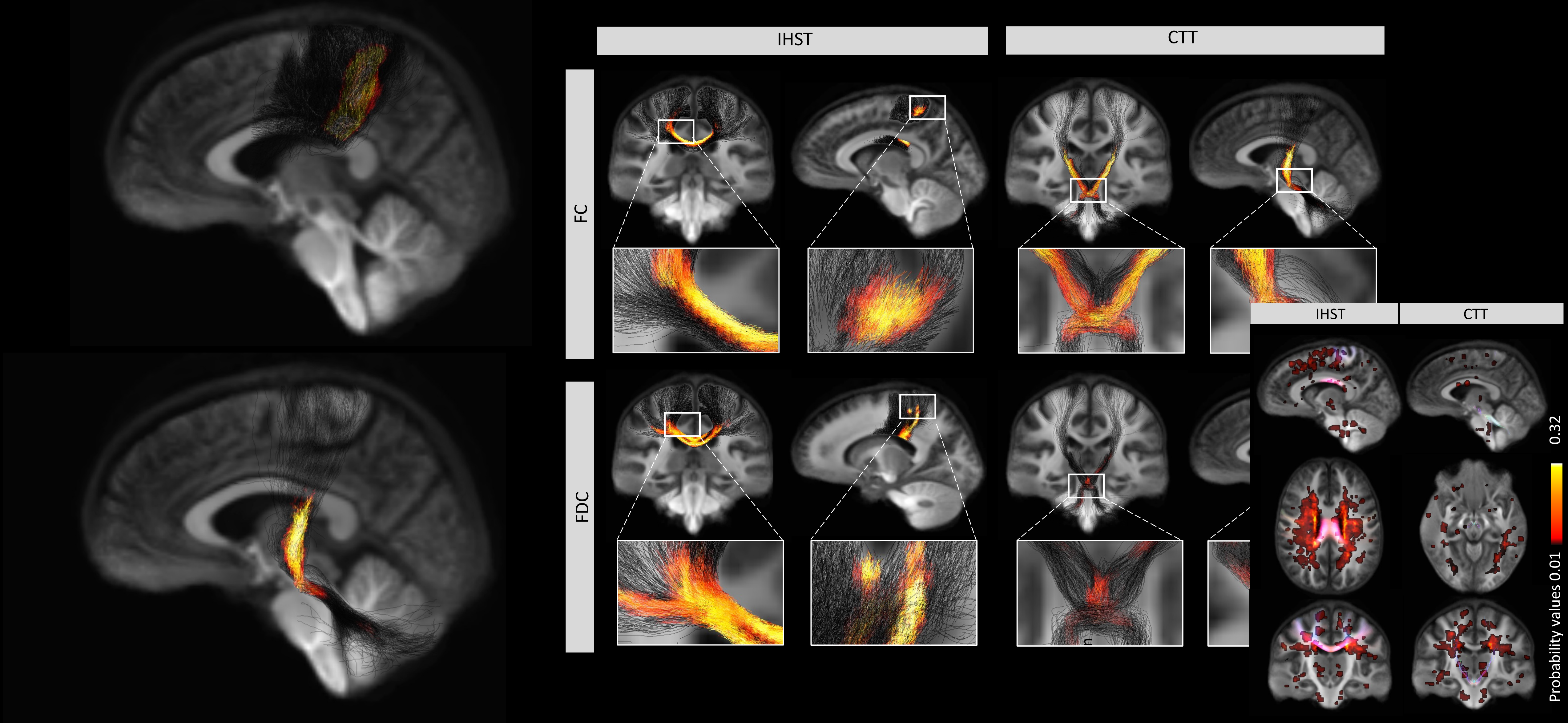
Loss of FC and FDC in early MS minimal disability







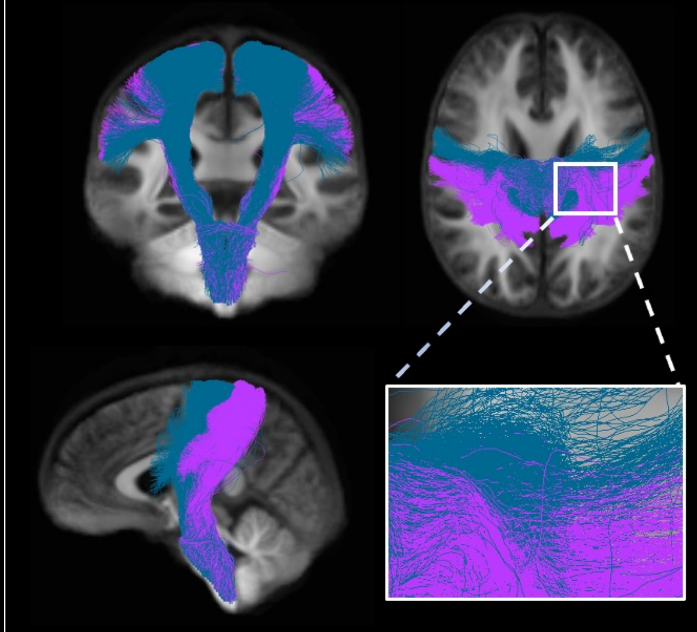
Interhemispheric and cerebello-thalamic tracts



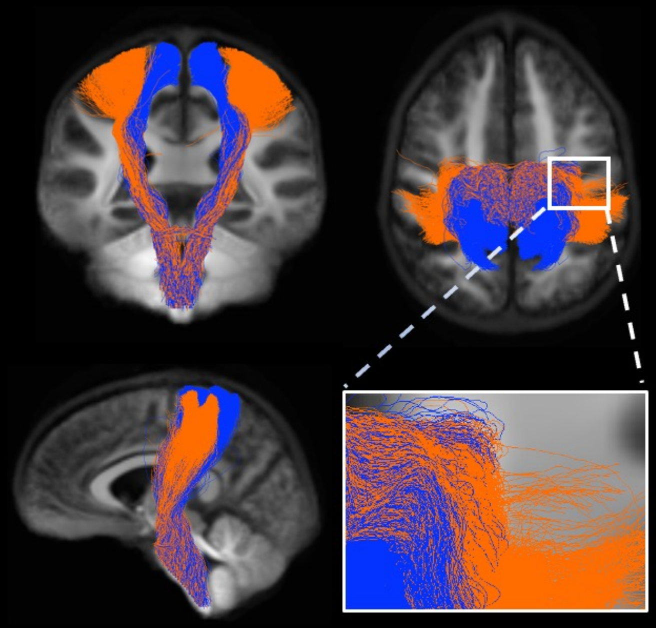
Tract specific damage

The corticospinal tract

M1 & S1



Upper and lower limb tracts

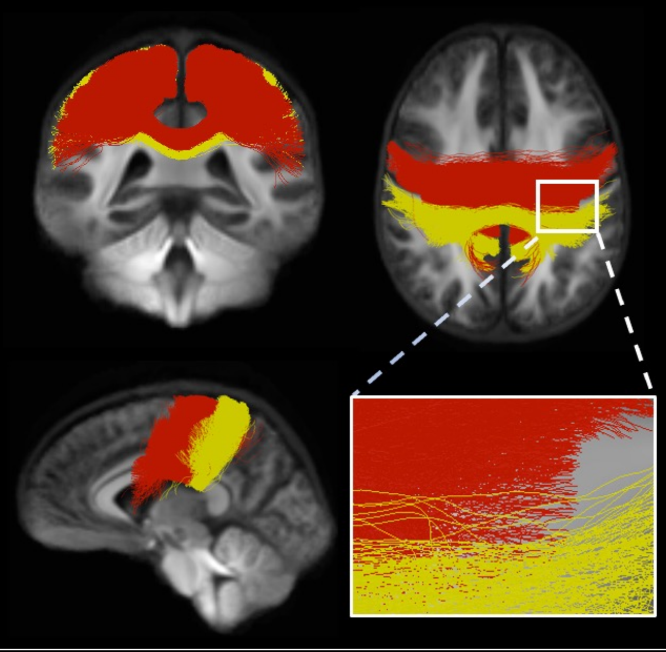


WM damage in
20.2% of M1 tracts
27.3% of S1 tracts

WM damage in
35.7% of lower limb tracts
29.7% upper limb tracts

The interhemispheric tracts

M1 and S1 interhemispheric tracts



WM damage observed in
4.6% of M1 tracts
10.9% S1 tracts

Relation to motor behavior

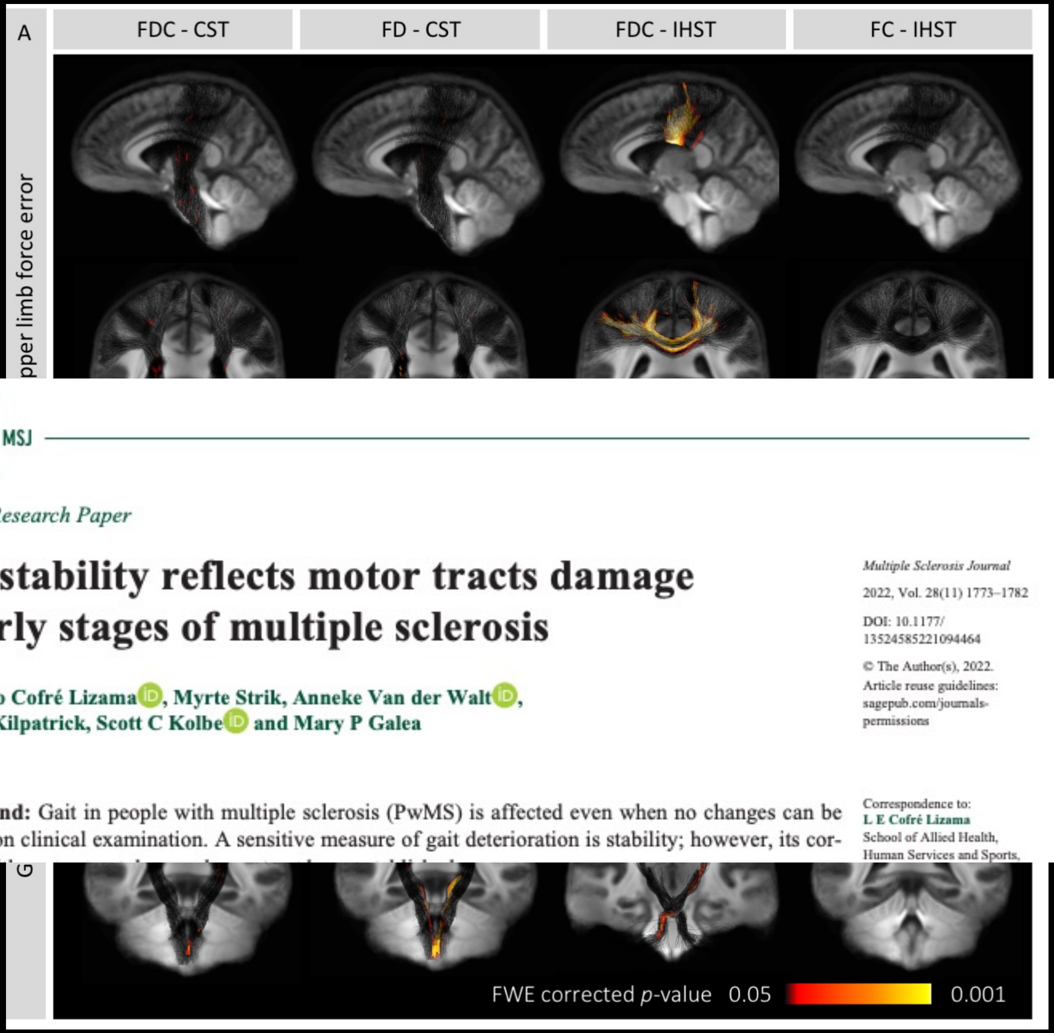
Upper limb force error (fMRI task)

- Greater upper limb force error was associated with axonal loss

Gait pattern parameters

- CST damage was associated with shorter stance and smaller step width
- Interhemispheric damage was associated with longer double support.

A sensitive measure of gait deterioration is stability = Local dynamic stability (LDE; or local divergence)



MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Gait stability reflects motor tracts damage at early stages of multiple sclerosis

Multiple Sclerosis Journal
2022, Vol. 28(11) 1773–1782
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Abstract
Background: Gait in people with multiple sclerosis (PwMS) is affected even when no changes can be observed on clinical examination. A sensitive measure of gait deterioration is stability; however, its cor-

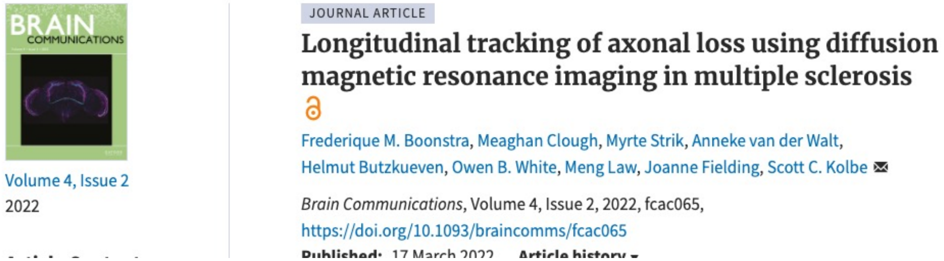
Over time

Axonal loss in 40 <u>clinically stable</u> patients over <u>1.5 years</u>

1. Fibre specific metrics
2. Retinal nerve fibre layer thickness (RNFLT)
3. Atrohpy

Fibre specific measures were

- 4 times more sensitive to change than RNFLT
- 7 times more sensitive to change than brain atrophy



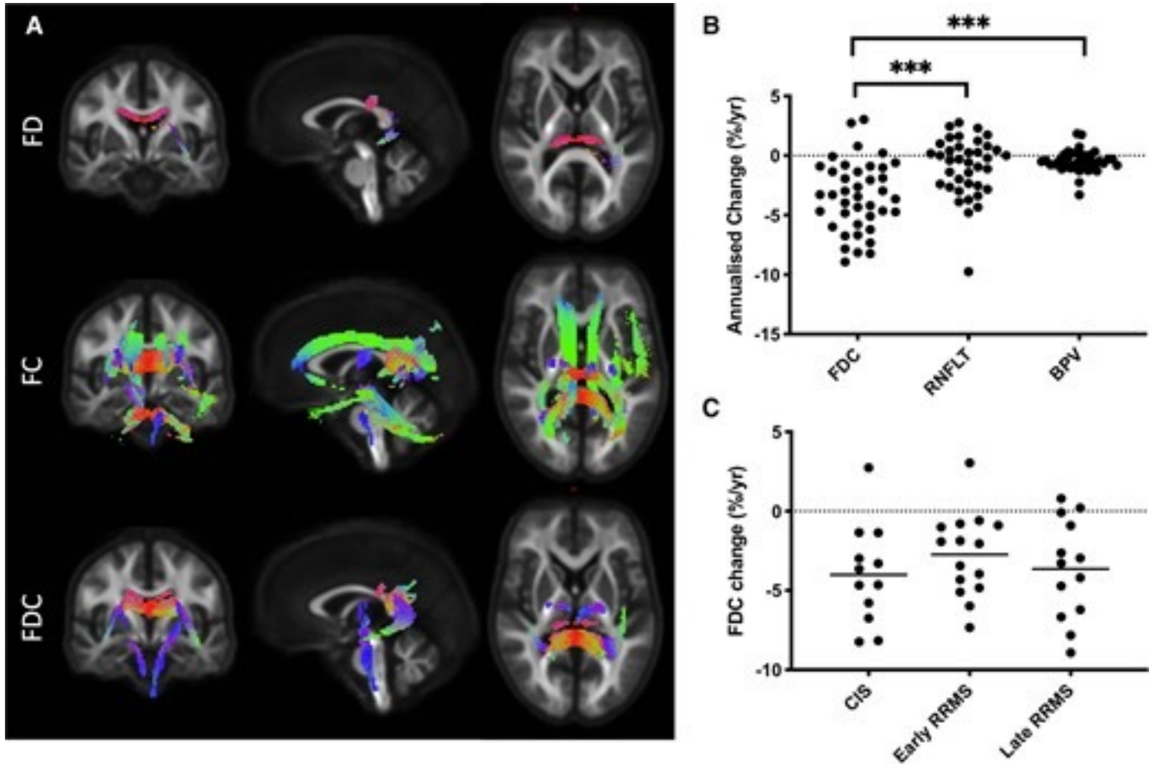
Volume 4, Issue 2
2022

JOURNAL ARTICLE

Longitudinal tracking of axonal loss using diffusion magnetic resonance imaging in multiple sclerosis

Frederique M. Boonstra, Meaghan Clough, Myrte Strik, Anneke van der Walt, Helmut Butzkueven, Owen B. White, Meng Law, Joanne Fielding, Scott C. Kolbe

Brain Communications, Volume 4, Issue 2, 2022, fcac065,
https://doi.org/10.1093/braincomms/fcac065



Boonstra et al.,Brain Communciations 2022

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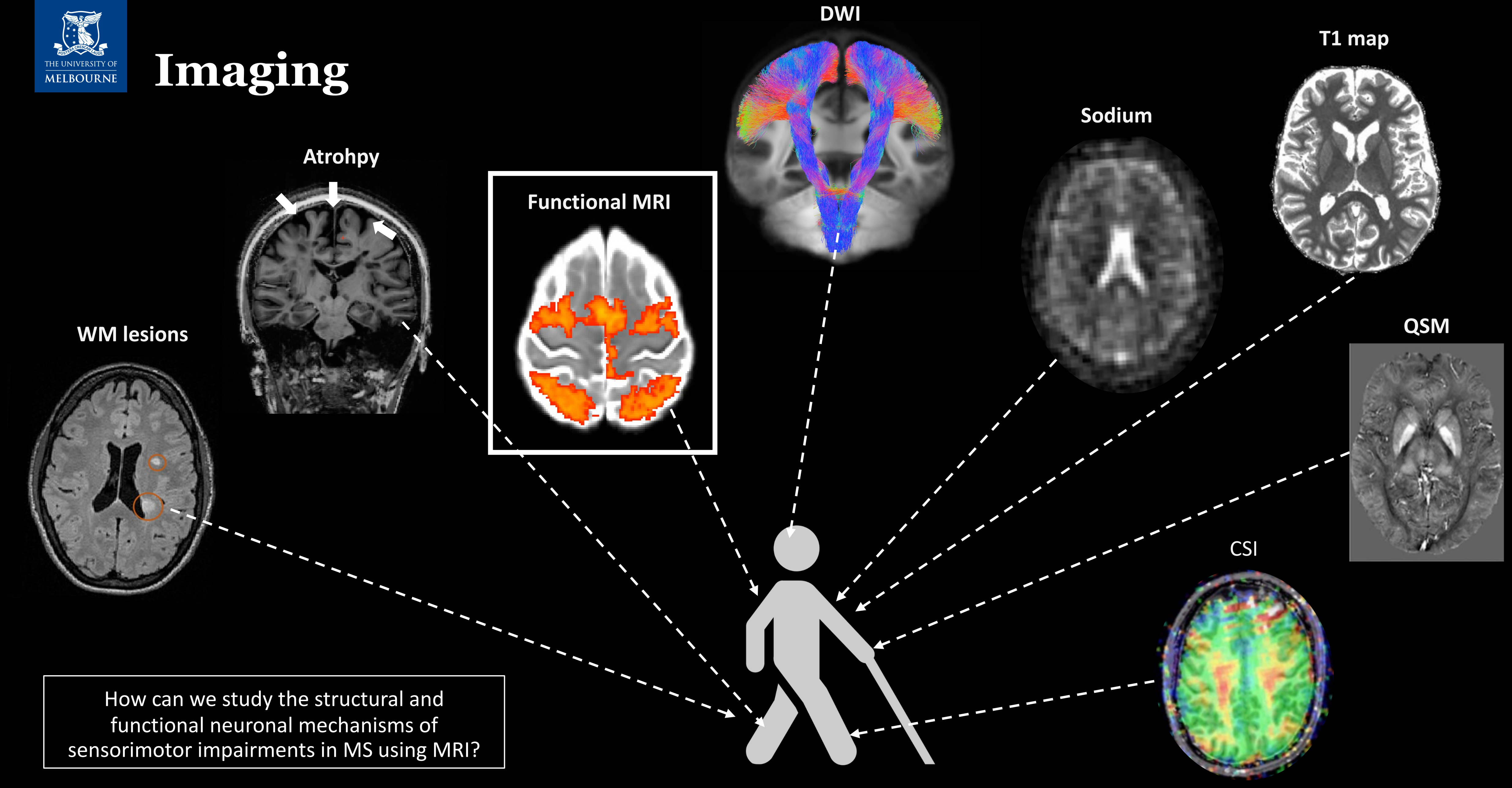
Imaging



How can we study the structural and functional neuronal mechanisms of sensorimotor impairments in MS using MRI?

http://www.msdiscovery.org/news/news_synthesis/322-more-meets-eye

Functional correlates of motor control impairments in MS: a 7T task fMRI study

Strik et al - Human Brain Mapping 2021

Background and objective

- Both upper and lower limbs are affected

- Previous fMRI task research
  - Focused predominantly on hand function[1]
  - Using simple tasks[1] --> complex sensorimotor tasks required for daily functioning

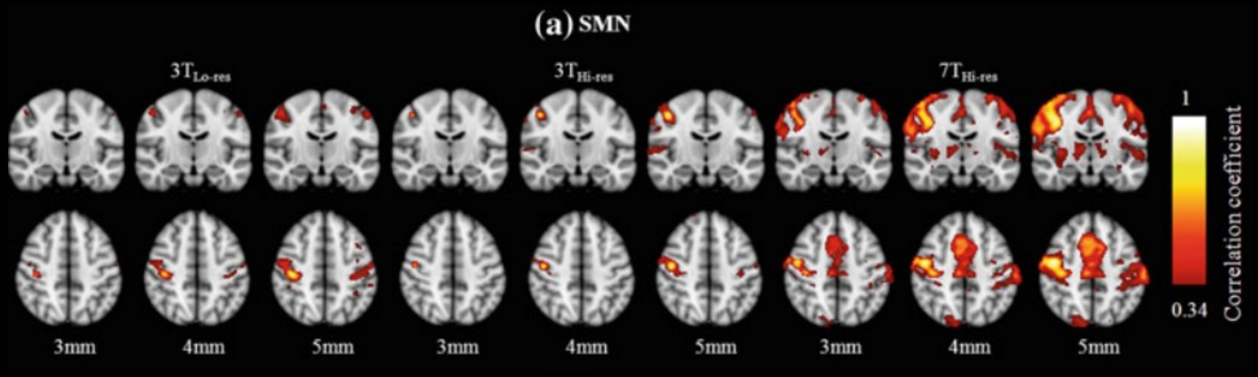
- No studies that directly compare upper and lower limb motor control using an identical task

- Use of clinical field strengths

[1]Mezzapesa et al., 2008; Rocca et al., 2003 2005

Functional imaging at higher field

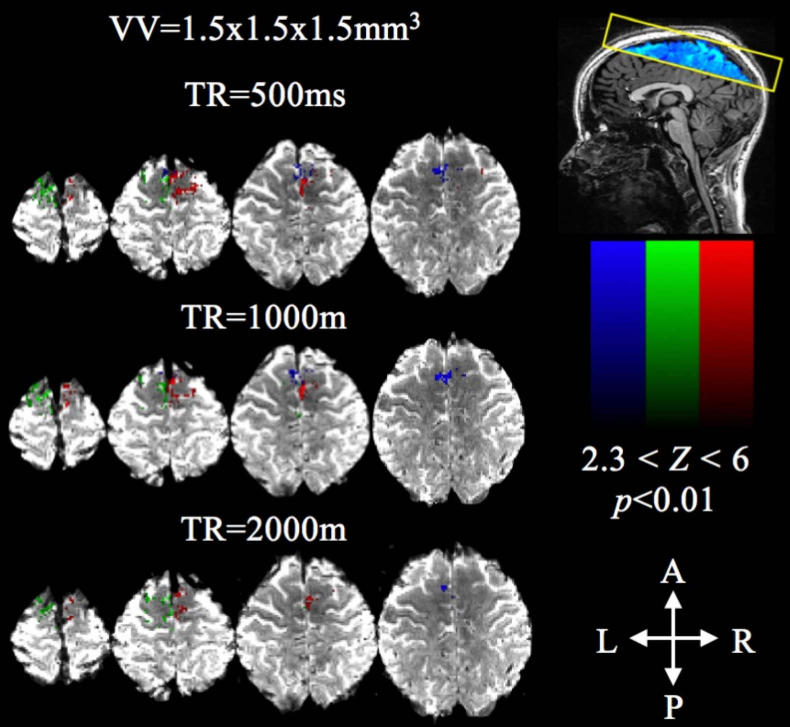
7T higher accuracy and sensitively compared to 3T *Hale et al., 2010*



3 Tesla: 96 subjects *Davey, Pujol & Harrison, 2016*

Less people, highly valuable, recruitment difficulties (disorders), $$

7 Tesla: 28 subjects *Harrison et al., in press*



Yoo, P. E., et al. (2018)

AIM:
Using 7T and complex motor task, to detect subtle activation changes underlying both limbs particularly early disability stages

Methods

Participants

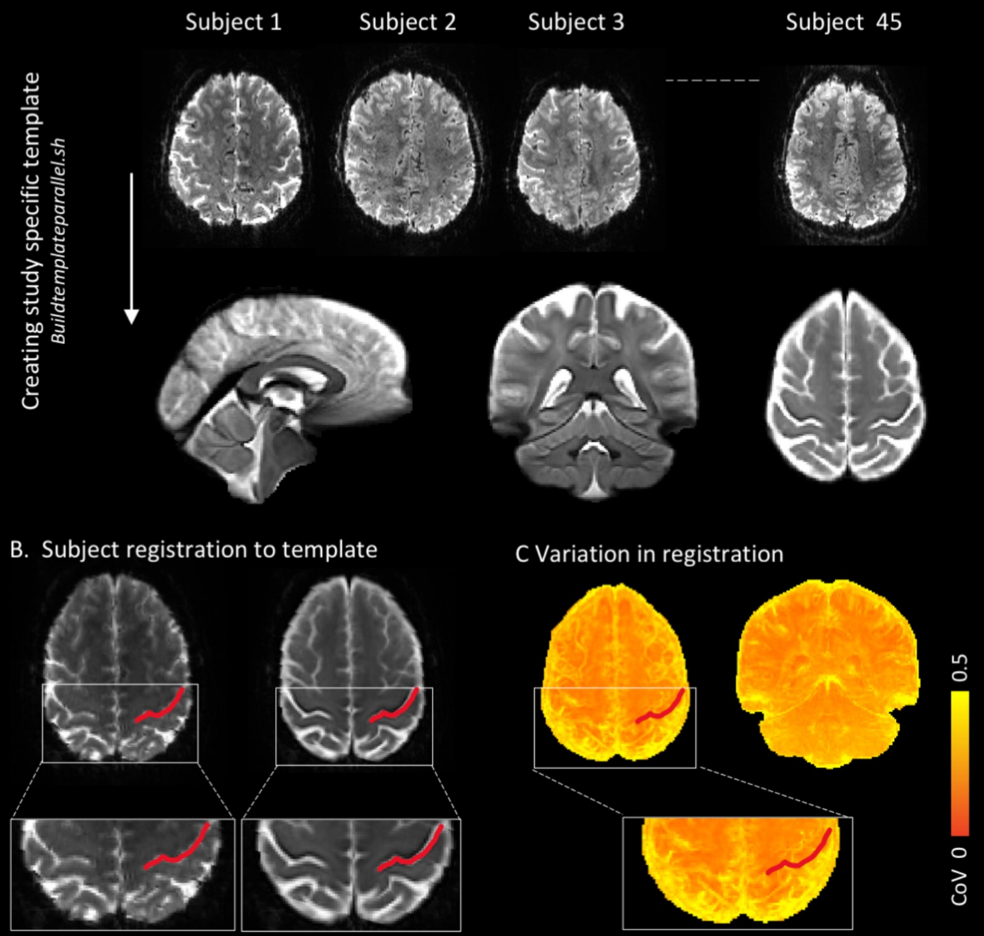
- 28 MS patients no to minimal disability (EDSS <4, pyramidal & cerebellar function ≤2)
- 17 healthy controls

Ultra-high field MRI (7T)

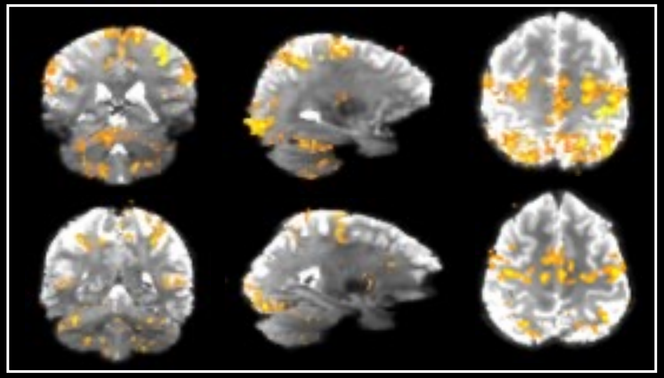
- Whole body Magnetom 7T MRI (Siemens, Erlangen, Germany), combined single-channel transmit & 32-channel receive head coil (Nova Medical, Wilmington MA, USA)

- Comprehensive study:
  - Resting-state fMRI (TR=0.8 , 1.6 mm iso)
  - QSM (9 echoes, 0.75 mm)
  - MP2RAGE (0.9 mm iso)
  - Diffusion (multi-slice 2D spin-echo EPI sequence (CMRR, University of Minnesota)

- Force matching task fMRI – 2 runs (sequence CMRR, University of Minnesota) [1]



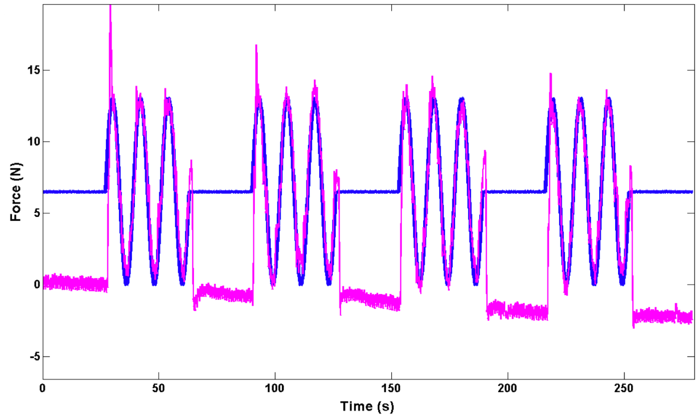
Coverage	TR	TE	MB	GRAPPA	slices	Reso	Volumes	Image matrix	Time
Whole brain	1700 ms	34.4 ms	6	2	120	1.24 mm iso	165	168 x 168	6:40



Very detailed activation patterns

[1]Moeller, et al. (2010). Multiband multislice GE-EPI at 7 tesla, with 16-fold acceleration using partial parallel imaging with application to high spatial and temporal whole-brain fMRI. **63**(5), 1144–115

Visually guided force-matching task

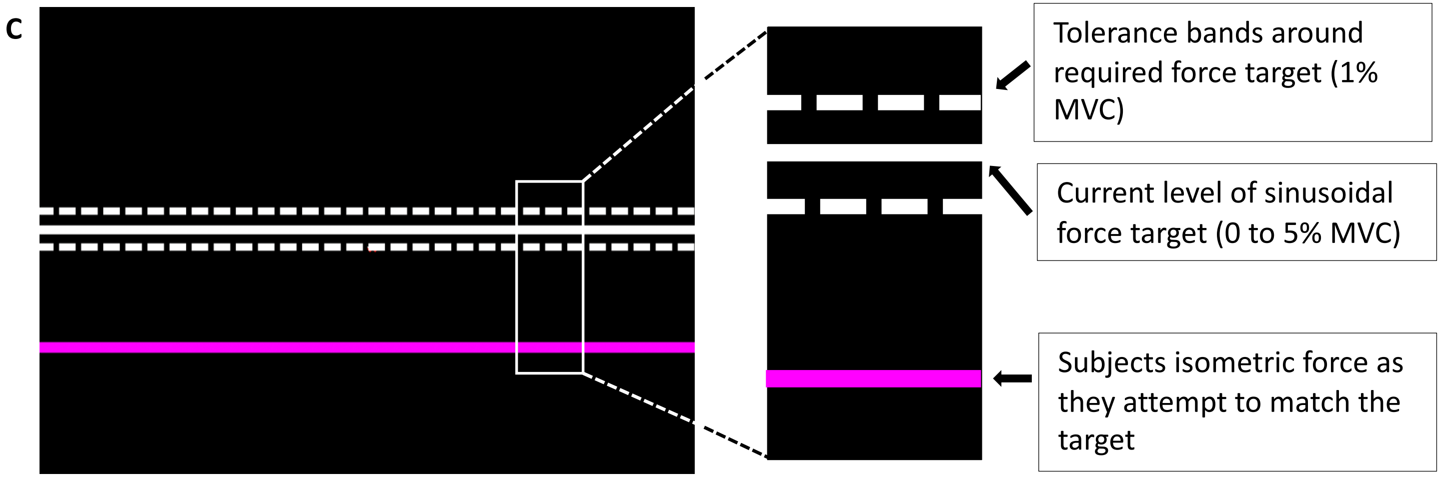


Two runs of functional MRI

- Upper limb
- Lower limb

Task[1]

- Low force contraction ankle or hand
- Cuff over dorsum foot or hold in hand
- 4 contraction blocks, 5 rest
- Complex task → Practice session



[1]Mayhew et al. 2017; Shanahan et al., 2015

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Functional motor performance measures

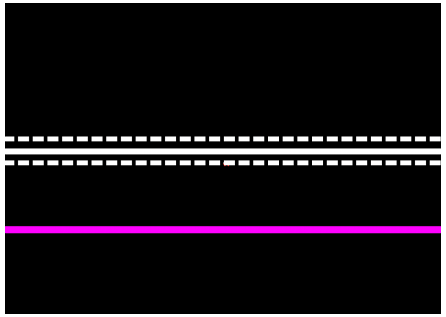
Measures of performance

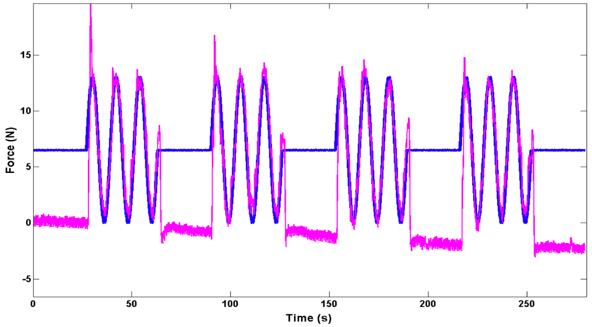
1. Lag

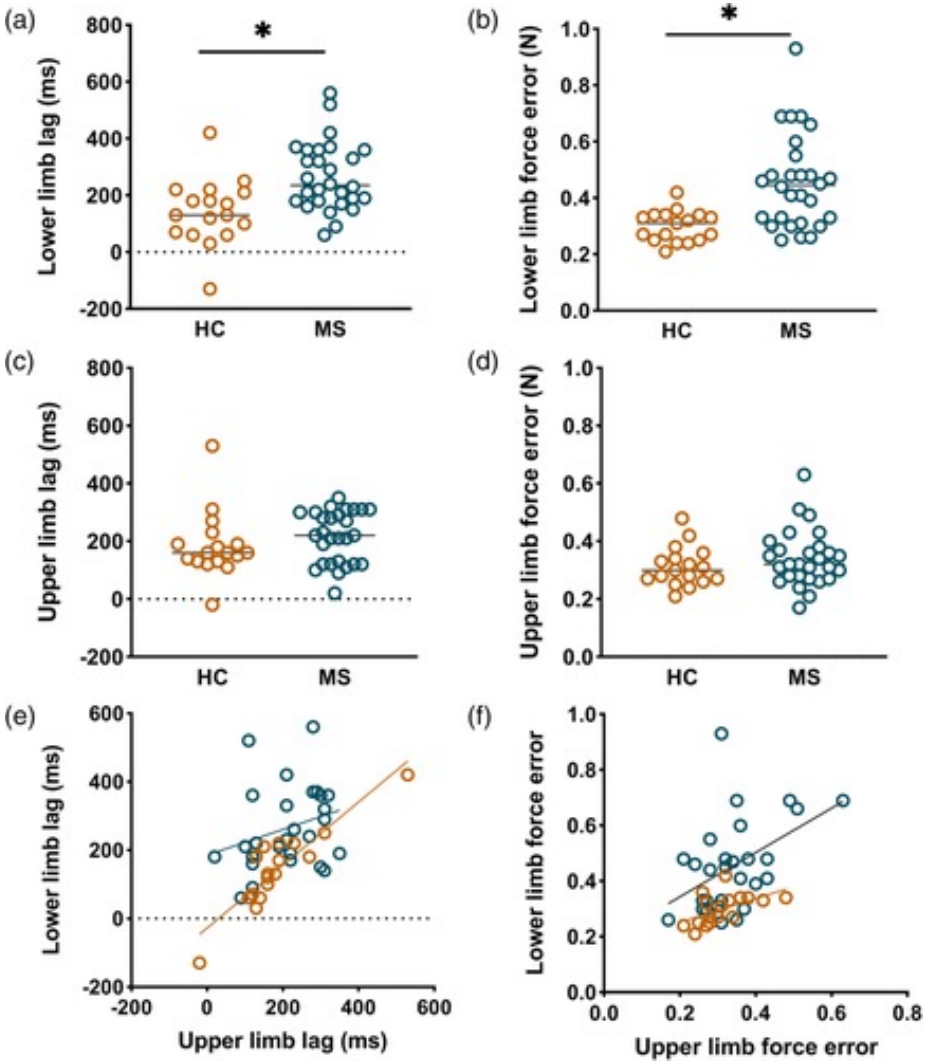
- Delay task cue and response → latency with processing speed
  - ms, cross correlation

2. Error in the force

- How accurate one is performing task → integration
  - Error in y direction, RMS (N)



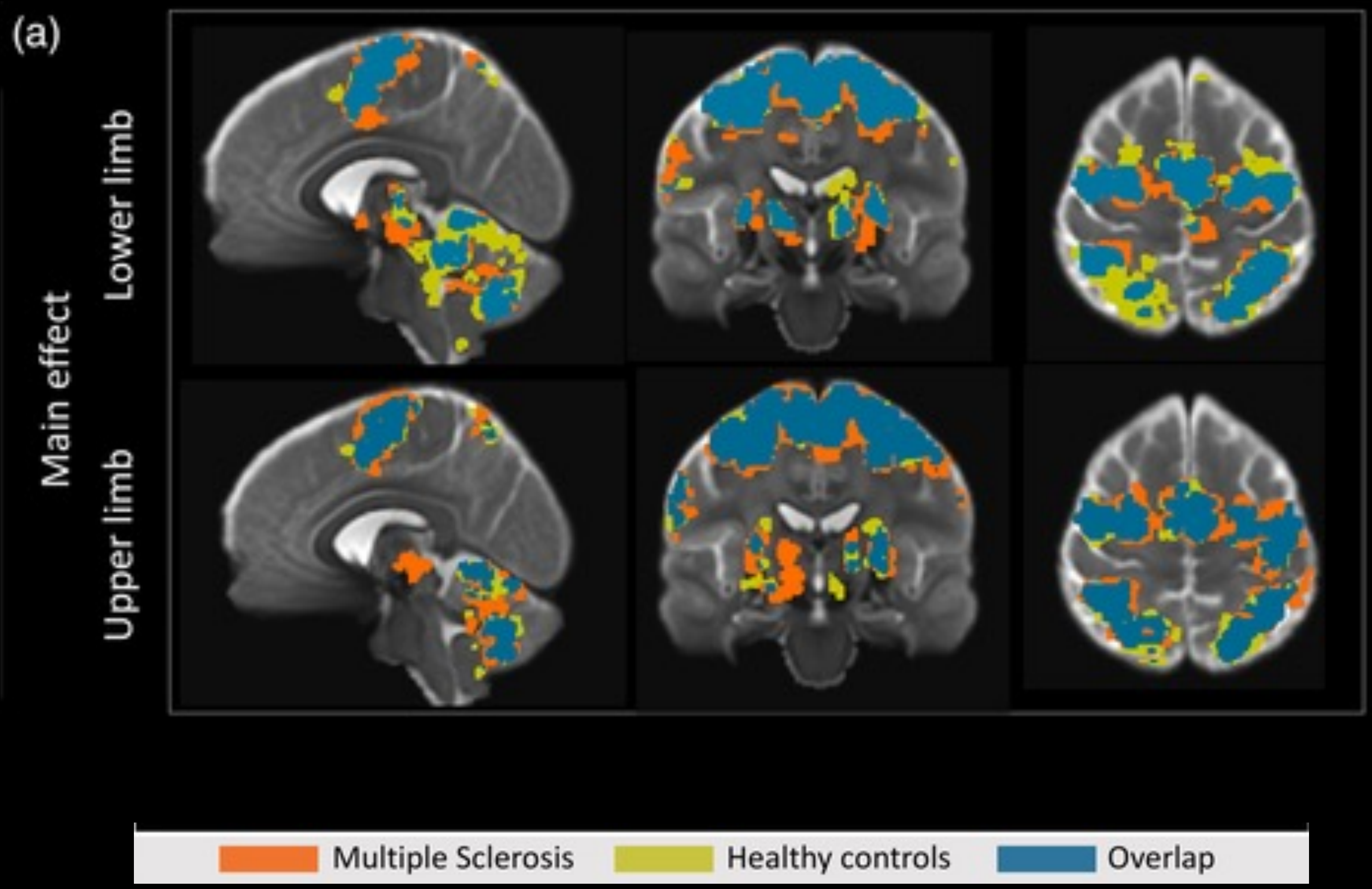




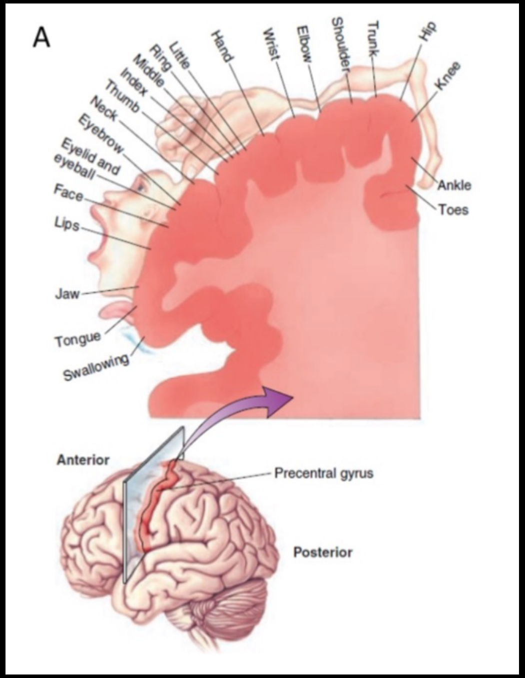
Results

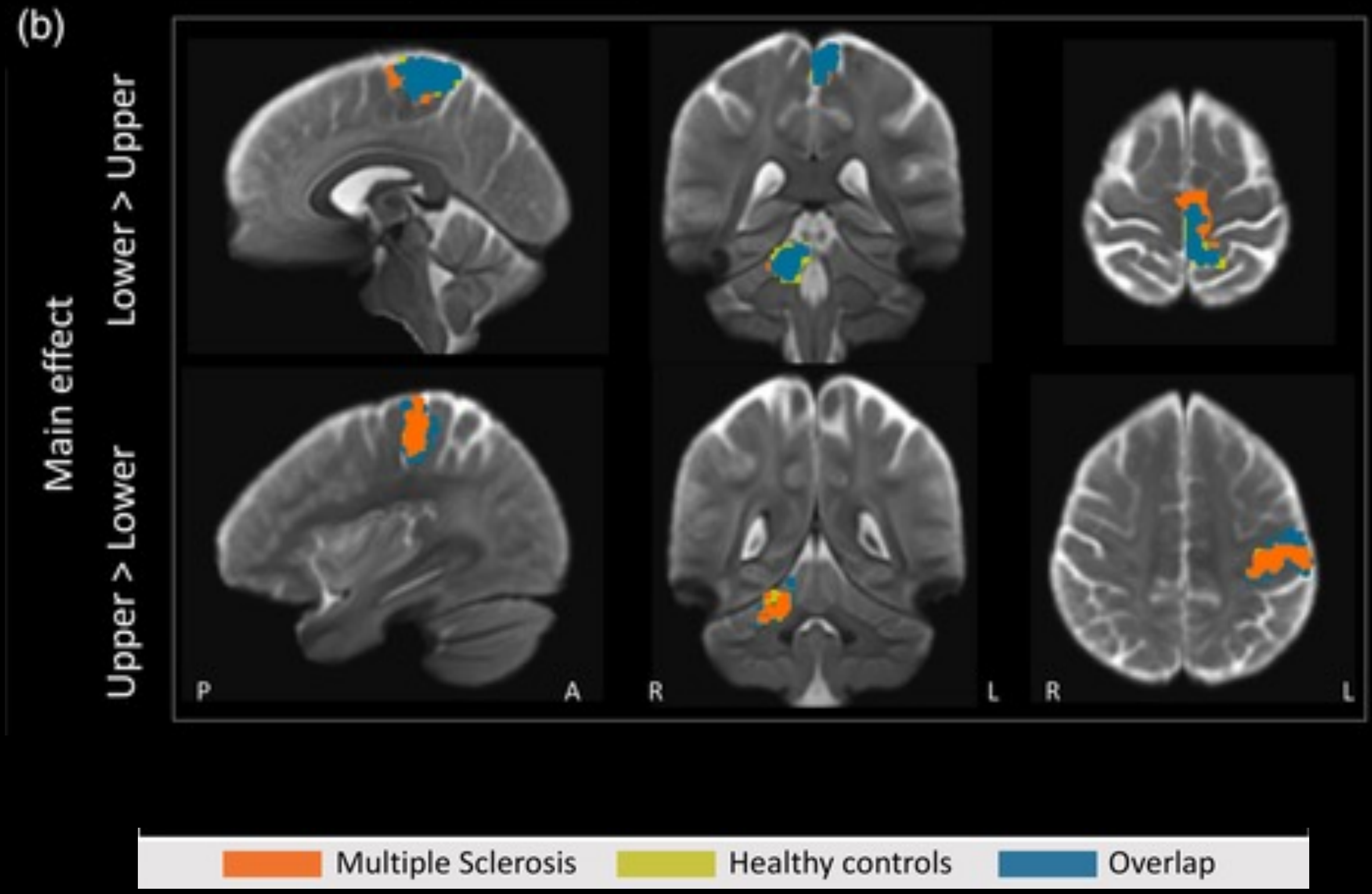
- Worse lower limb performance MS
- No difference upper limb performance
- No correlation upper and lower limb performance

Main effect upper and lower limb task



Main effect upper and lower limb task





Images copied and adapted from Neuroscience: Exploring The Brain

Motor control impairments in MS are related to dysfunctions in visuomotor integration

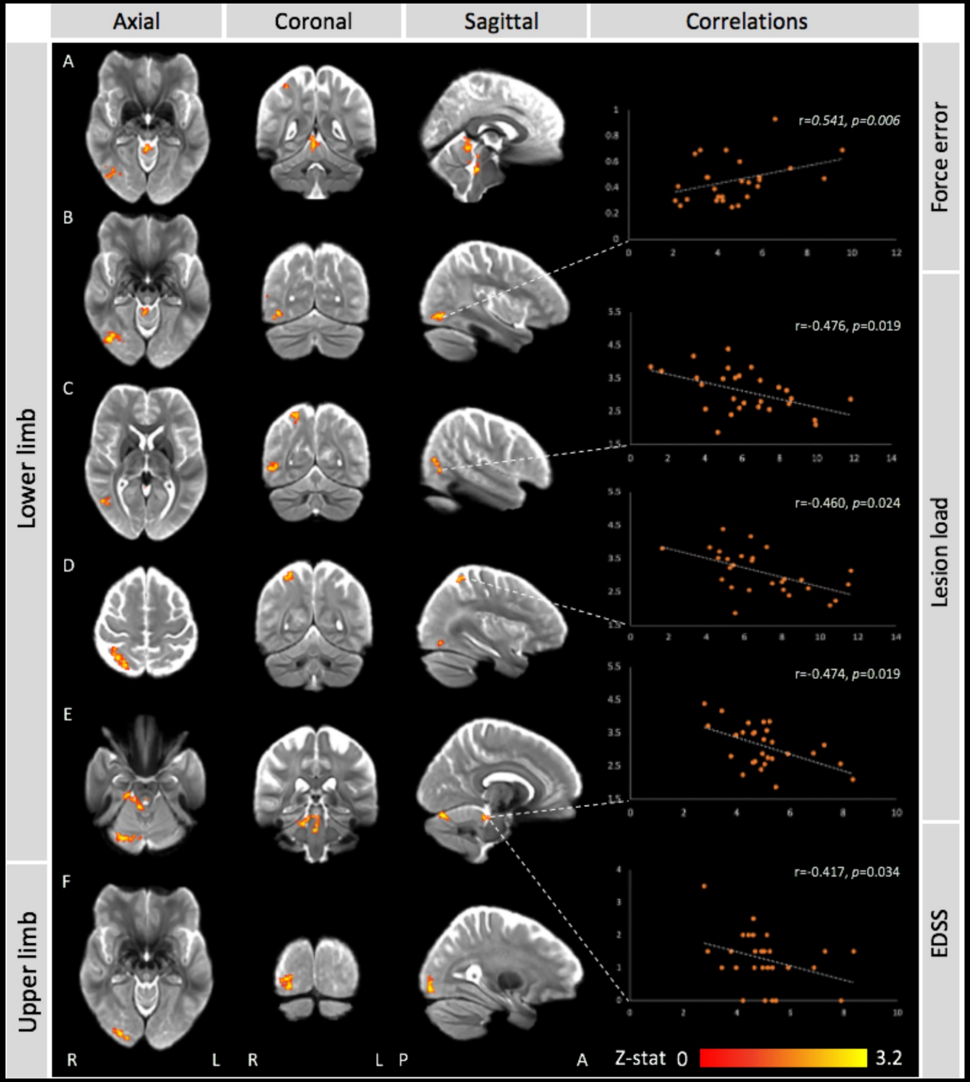
Lower activation during <u>lower limb task</u> in

- *visuomotor attention / location of objects in space / integration proprioception and vision*
- *occipital cortex (primary visual processes) and middle temporal visual area (processing of motion)*
- *Cerebellar regions involved in sensorimotor processes*

→ **Clinically relevant** (correlation to lesion load, force error, EDSS)

<u>Upper limb task</u>

- Despite no differences in upper limb task performance
- Lower inferior occipital cortical activation



Conclusions

- Minimally disabled MS patients showed during complex hand and foot tracking
  - subtle impairments in lower limb movements
  - Altered upper and lower limb brain activation
  - No correlations between upper and lower limb disabilities

- These results suggests partially divergent functional mechanisms underlying upper and lower disability progression
  - timing events?
  - different mechanisms (upper complex, other networks in the brain and spinal cord)?
  - more accurate measures needed?

- Next – longitudinal, larger cohort

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Thank you