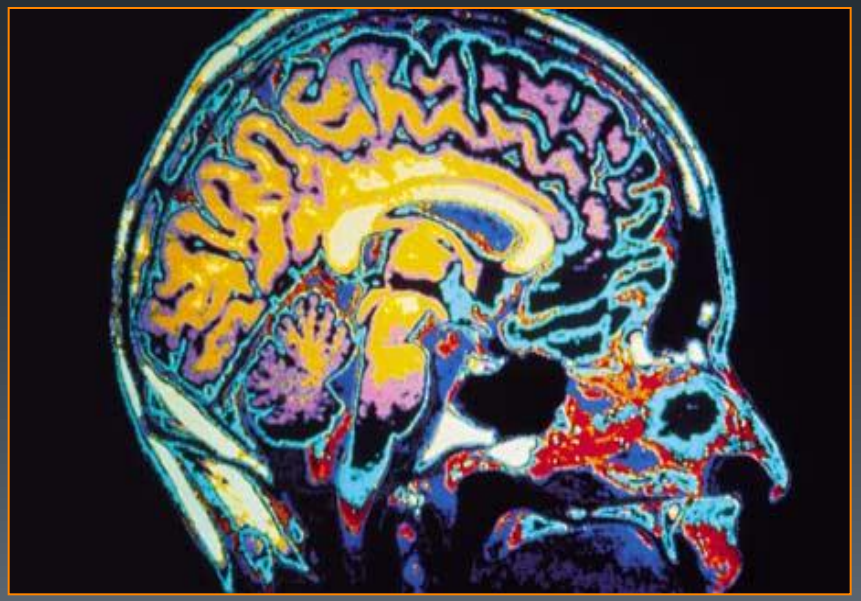
Brain microstructural changes associated with cognitive performance in MS patients



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Supervised by Dr.Miron Shmuel, SMC, Sheba

Background

- Multiple Sclerosis (MS) is an inflammatory disease in which the myelin sheaths around the axons in the brain and spinal cord are damaged, leading to demyelination and scarring.

- MS is characterized by white matter (WM) and grey matter (GM) structural damage, and a progressive decline in cognitive performance and physical impairment.

- The performance of cognitive tasks engages a complex network of brain regions, which integrate the data by using the white matter (WM) fiber tracts.

Background

- Diffusion tensor imaging (DTI) is an MRI method with high sensitivity to detect brain microstructural changes in GM regions and WM tracts.

- Voxel based morphometry (VBM) is a neuroimaging analysis technique that allows investigation of focal differences in brain anatomy, using the statistical approach of statistical parametric mapping.

Motivation!

- “MS causes widespread tissue damage in normal-appearing white matter of the brain and spinal cord, whose extent and severity is more strictly associated to the clinical manifestations of the diseases than the extent of focal pathology.

  Discrete, macroscopic lesions are just the tip of the iceberg of MS Pathology”

J Neurol (2005) 252 [Suppl 5]: V/16–V/24
DOI 10.1007/s00415-005-5004-5

Massimo Filippi
Maria Assunta Rocca

MRI evidence for multiple sclerosis as a diffuse disease of the central nervous system

Objective

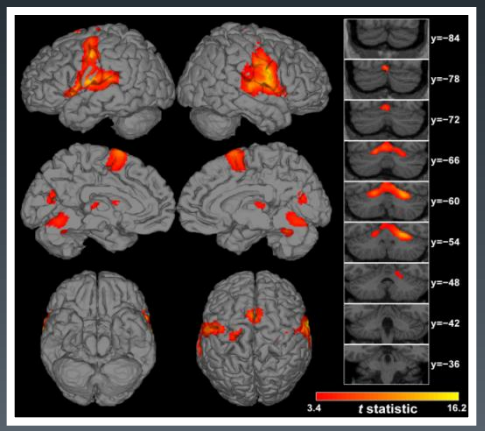
- Identify brain microstructural changes in white matter and grey matter in correlation with cognitive performance and clinical parameters of RRMS patients.

Cognitive tests:
MCCT, EDSS

MRI sequences:
T1, T2, Flair, DTI

Structural brain maps: FA, ADC, Lambda1/2/3/r (DIVA)

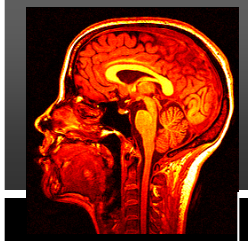
Correlation: cognitive performance vs. structural brain maps
Voxel Based Analysis (SPM8)



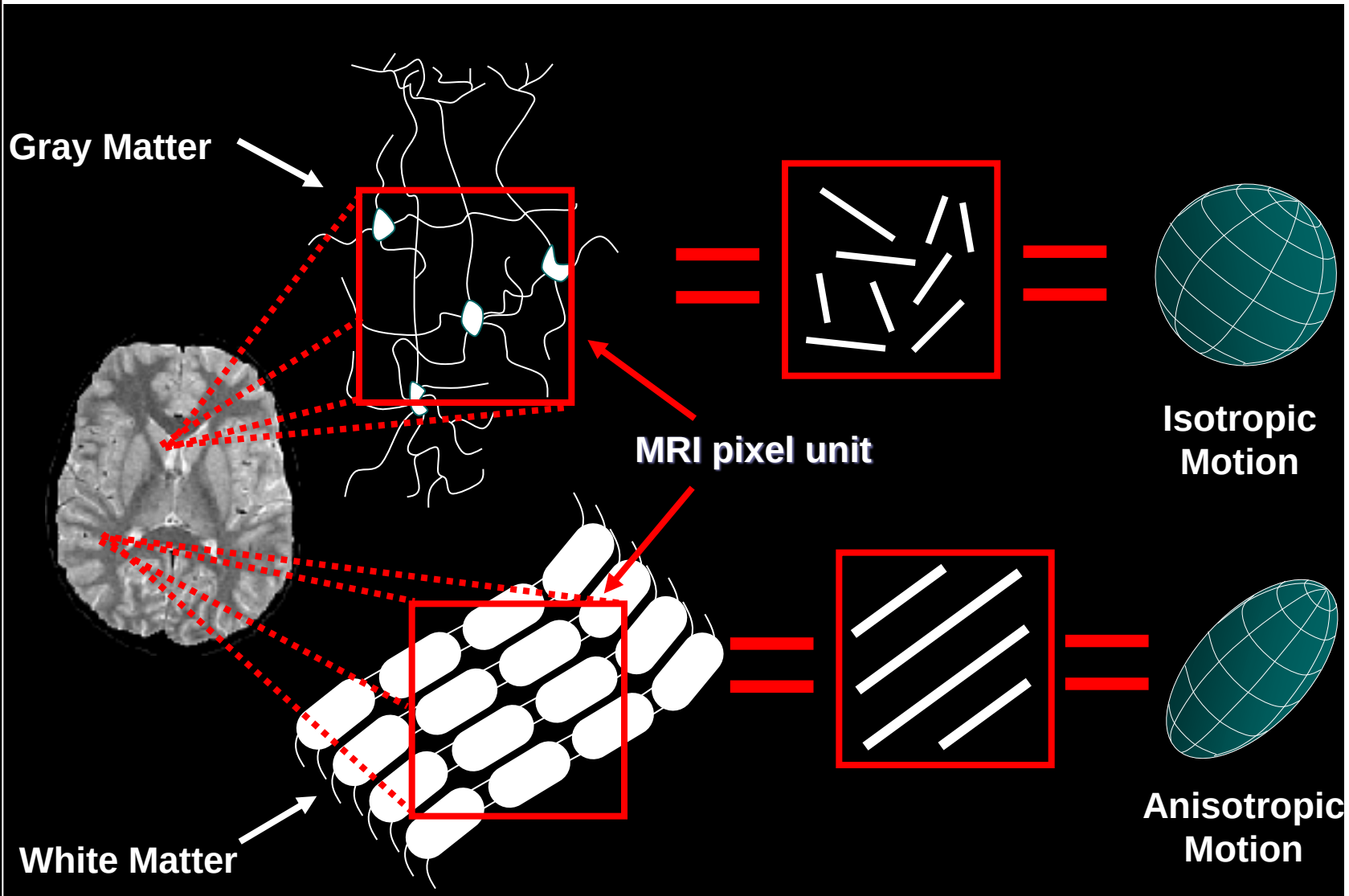
Result: Recognition of Brain Areas in which significant corr. btw FA/ADC and cognitive performance were found

Diffusion Tensor Imaging

- An MRI sequence tailored to evaluate water molecules' movement in the brain.
- What DTI measures by numbers = reflects the micro-structure of brain tissue
- Image intensities inversely related to the relative mobility of water molecules in tissue and the direction of the motion
  - White matter: Diffusion is restricted $\Rightarrow$ anisotropic
  - Gray matter: Diffusion is unrestricted $\Rightarrow$ isotropic

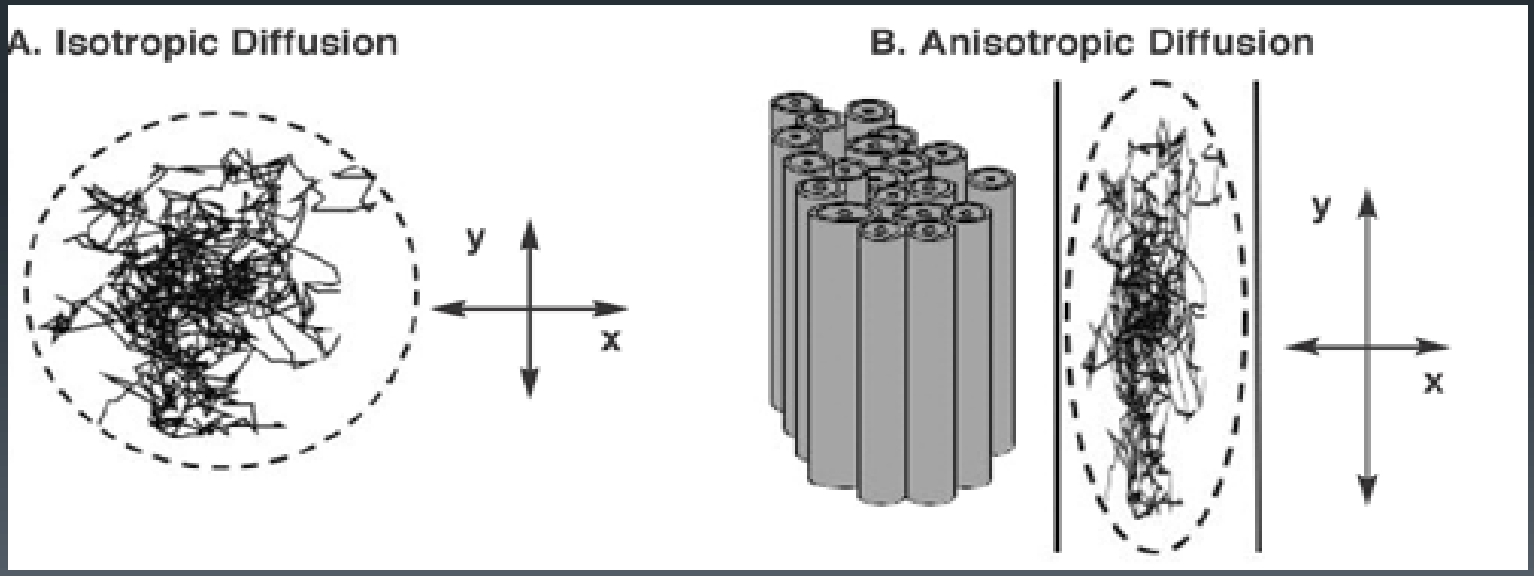


DTI : it depends on microstructure



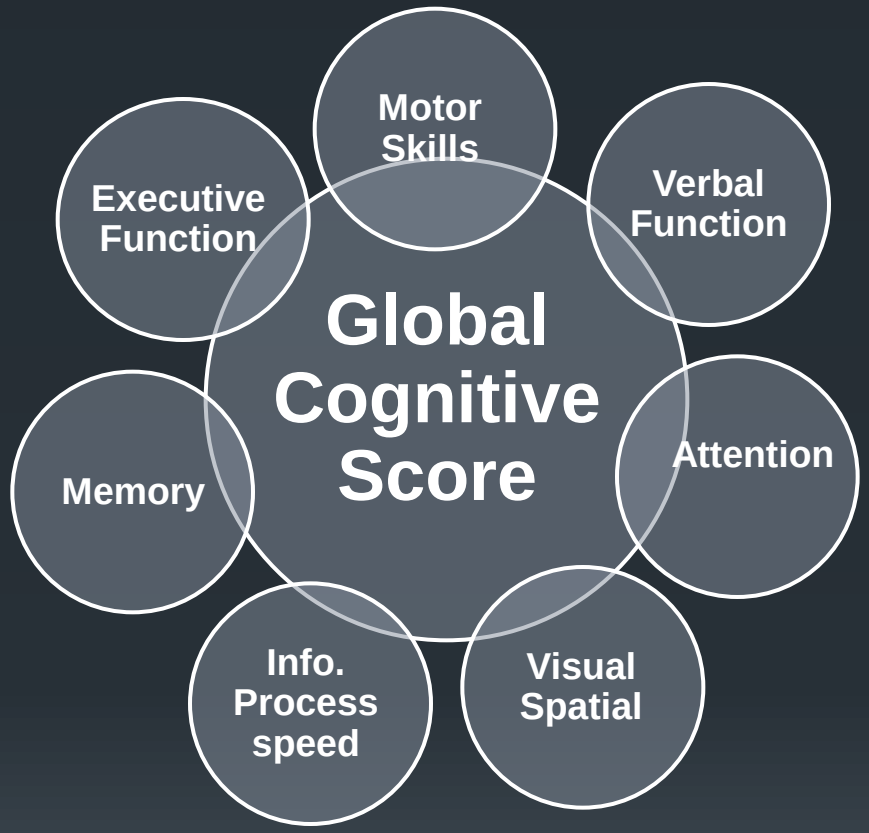
DTI's indices

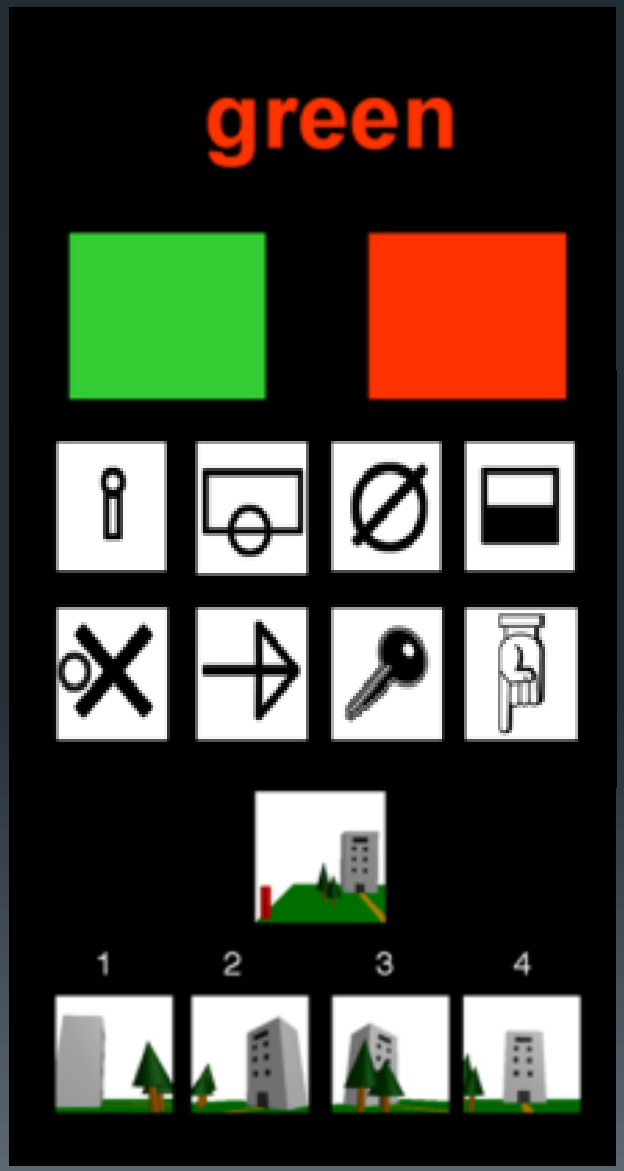
- The amount of diffusion occurring in one voxel of a MRI image is termed the Apparent Diffusion Coefficient (ADC) or Mean Diffusivity (MD).
- The non-uniformity of diffusion with direction is usual described by the term Fractional Anisotropy (FA).

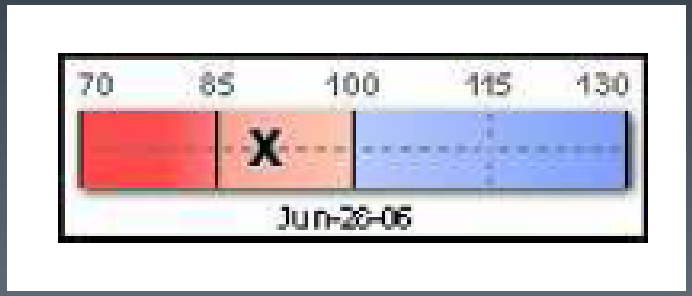


Cognitive tests

MCCT: Mindstream Computerized Cognitive TEST







NeuroTrax®

Cognitive tests:
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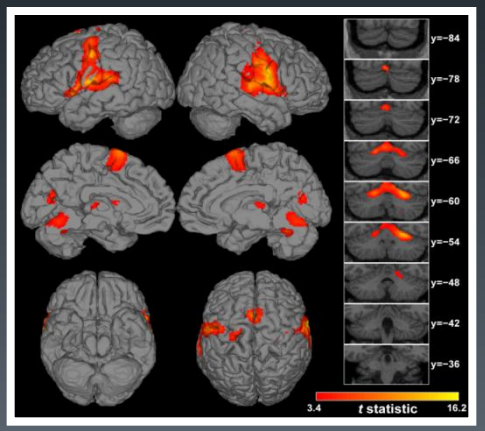
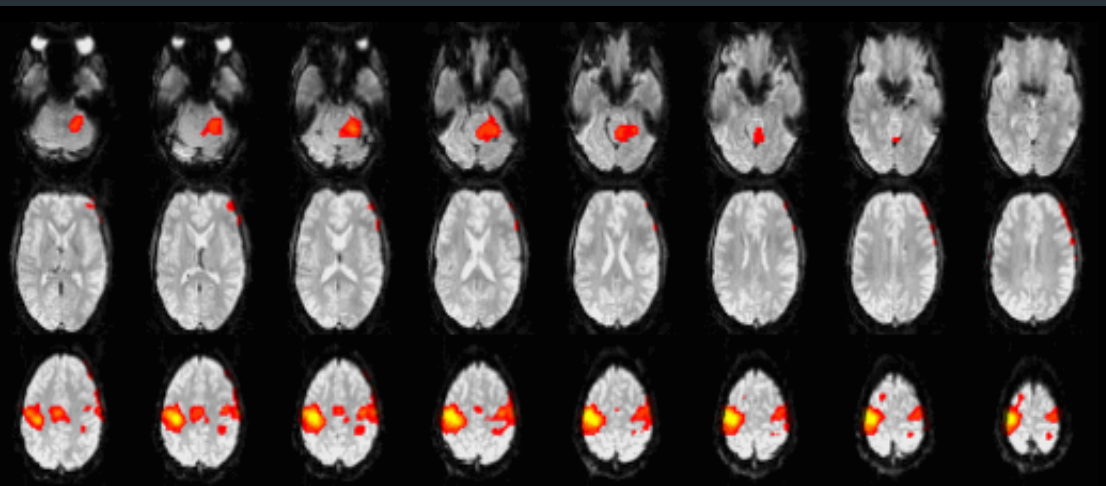


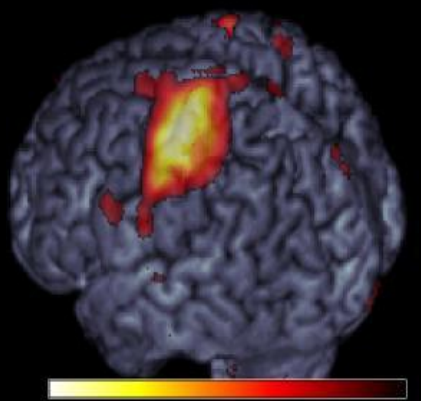
Result: Recognition of Brain Areas in which significant corr. btw FA/ADC and cognitive performance were found

Voxel Based Analysis

- Neuroimaging analysis technique that allows investigation of focal differences in brain anatomy.
- We can refer to the numerical properties of every voxel in the brain.

- No need to define ROI!



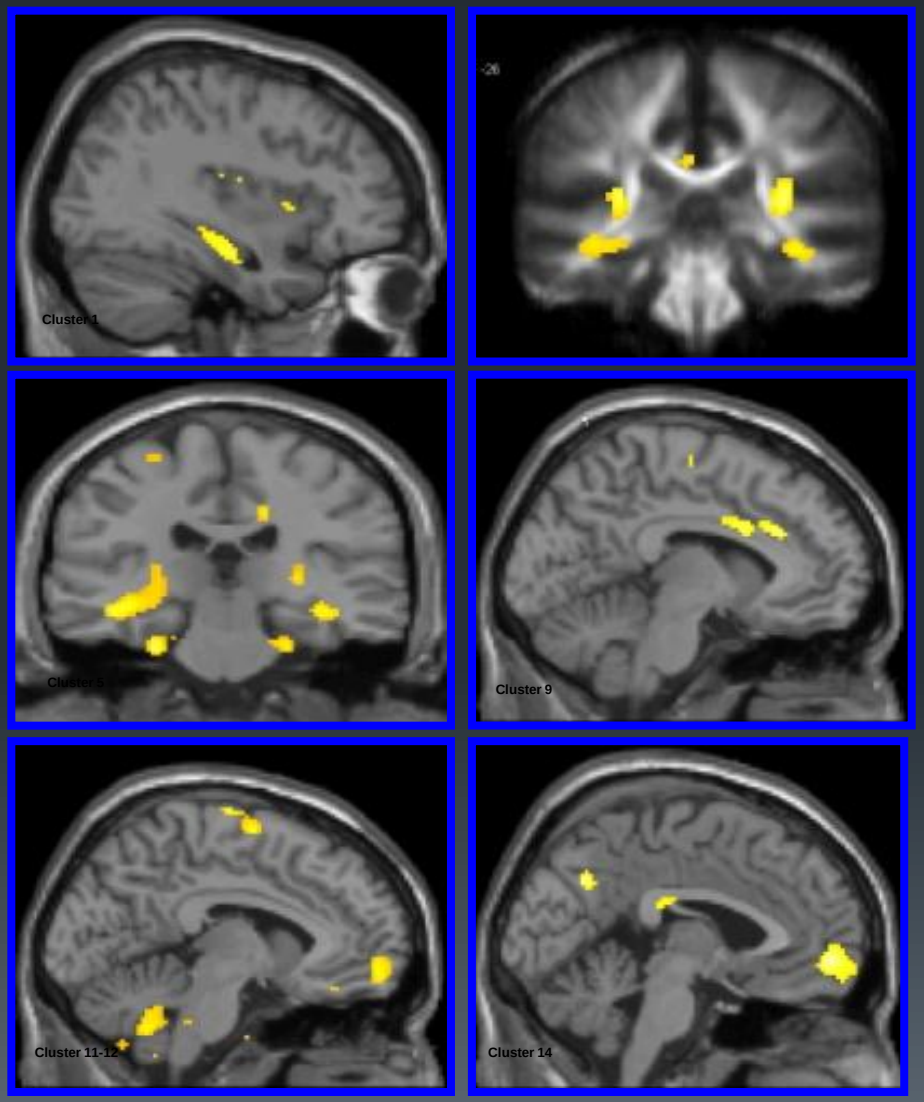


Statistics with SPM (Statistical Parametric Mapping)

- Different Designs: One-sample t-test
  Two-Sample T-test
  Multiple Regression
  Full Factorial
  Flexible Factorial…

- Correction for multiple comparisons (FWE)

Clusters - in anatomical context



Materials and Methods

Subjects

60 subjects with relapsing-remitting MS

Evaluation of:

1. Neurological disability (EDSS)

2. Cognitive performance - MCCT computerized battery of cognitive tests

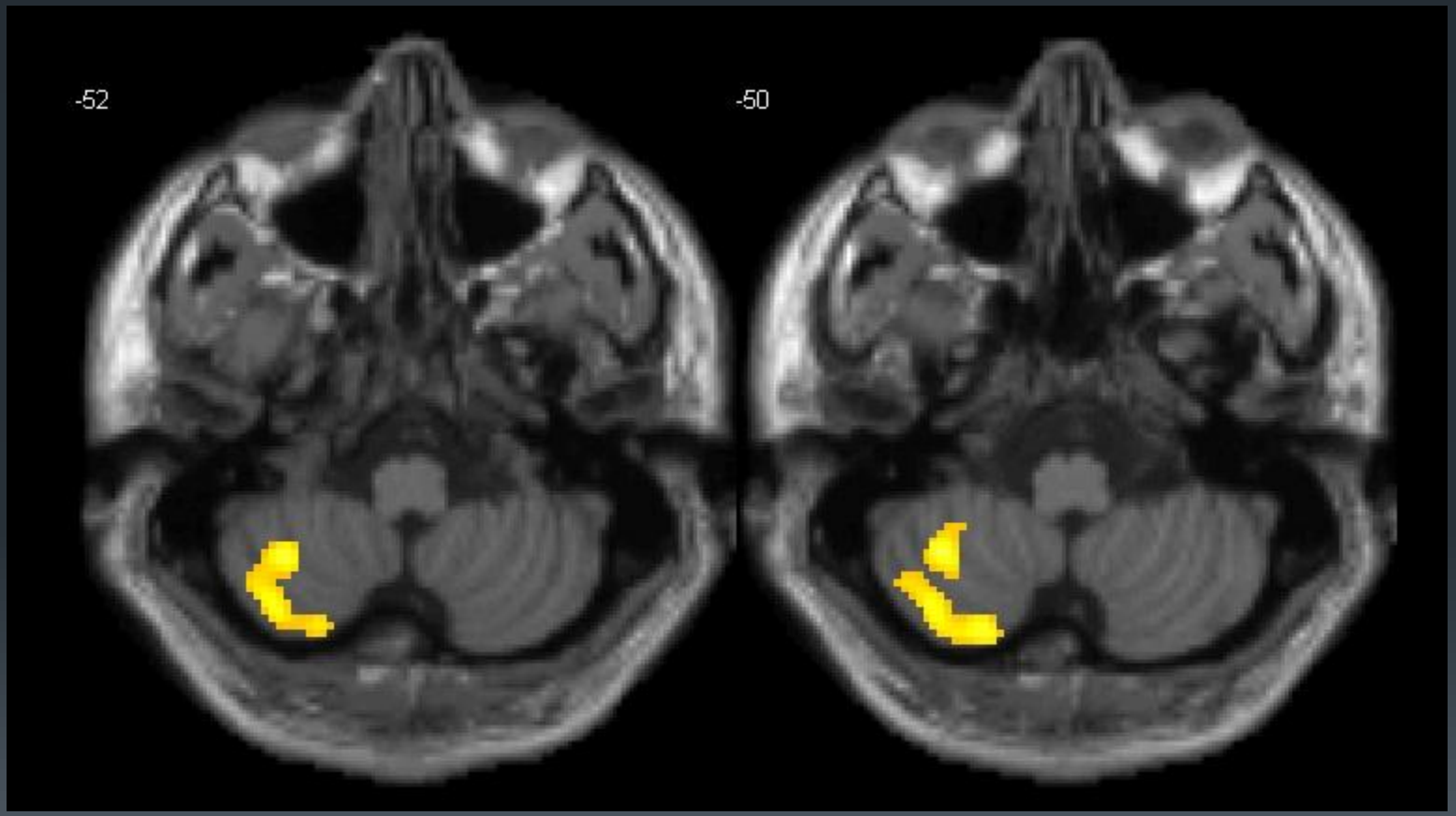
3. MRI + DTI on a 3T (GE) scanner (within 6 months of cognitive tests)

Patient characteristics

- 60 subjects
- 17 M, 43 F
- Age: 21-46 (Mean: 34±5.6)
- Disease Duration: 1-10.6 (Mean 5.2)
- EDSS: 0-6.5 (Mean 2 ±1.7)

Results

FA versus Executive function



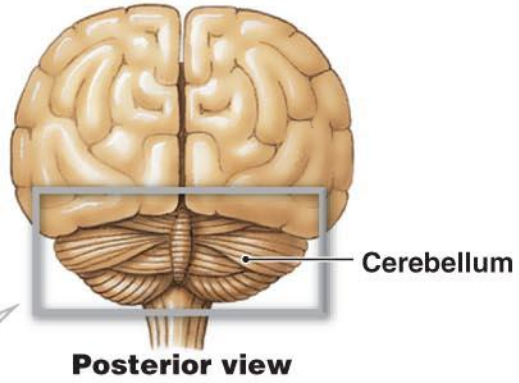
Cerebellum (“Little brain”)

- **Gross Anatomy**:
- Located in the bottom of the brain, underneath the cerebral cortex and behind the pons,
- Divided into two hemispheres united in the midline by the vermis.
- Its’ connections with other parts of the brain travel through the cerebellar peduncles

- It contains more neurons than the rest of the brain all put together.
- It receives nearly 200 million input fibers.

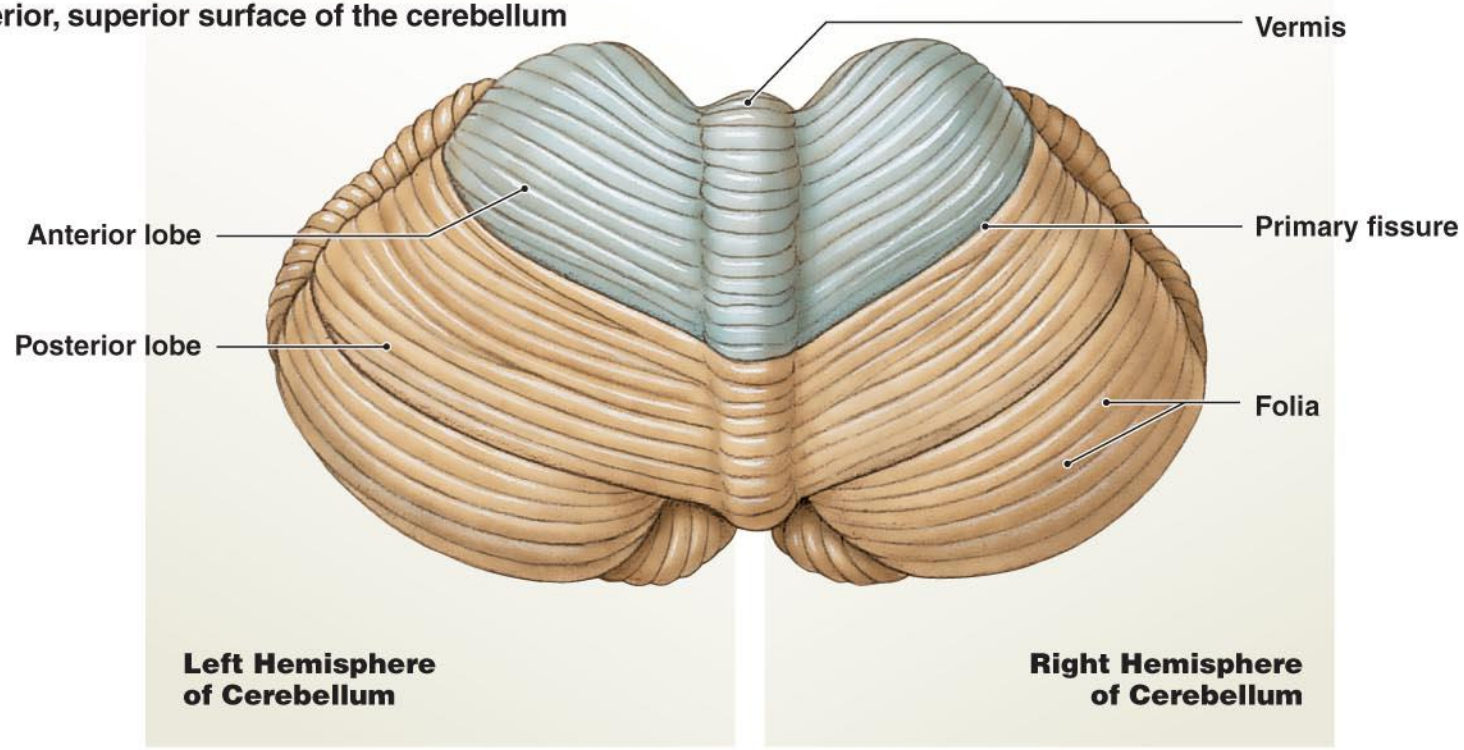
Sub-divisions

- The cerebellum consists of a tightly folded and crumpled layer of cortex, with white matter underneath and several deep nuclei embedded in the white matter.
- At the microscopic level, each part of the cortex consists of the same small set of neuronal elements, laid out in a highly stereotyped geometry
- Divided into 3 lobes:
  - Anterior lobe (above the primary fissure)
  - Posterior lobe (below the primary fissure)
  - Folluculonodular lobe (below the posterior fissure)



Structural features of the cerebellum

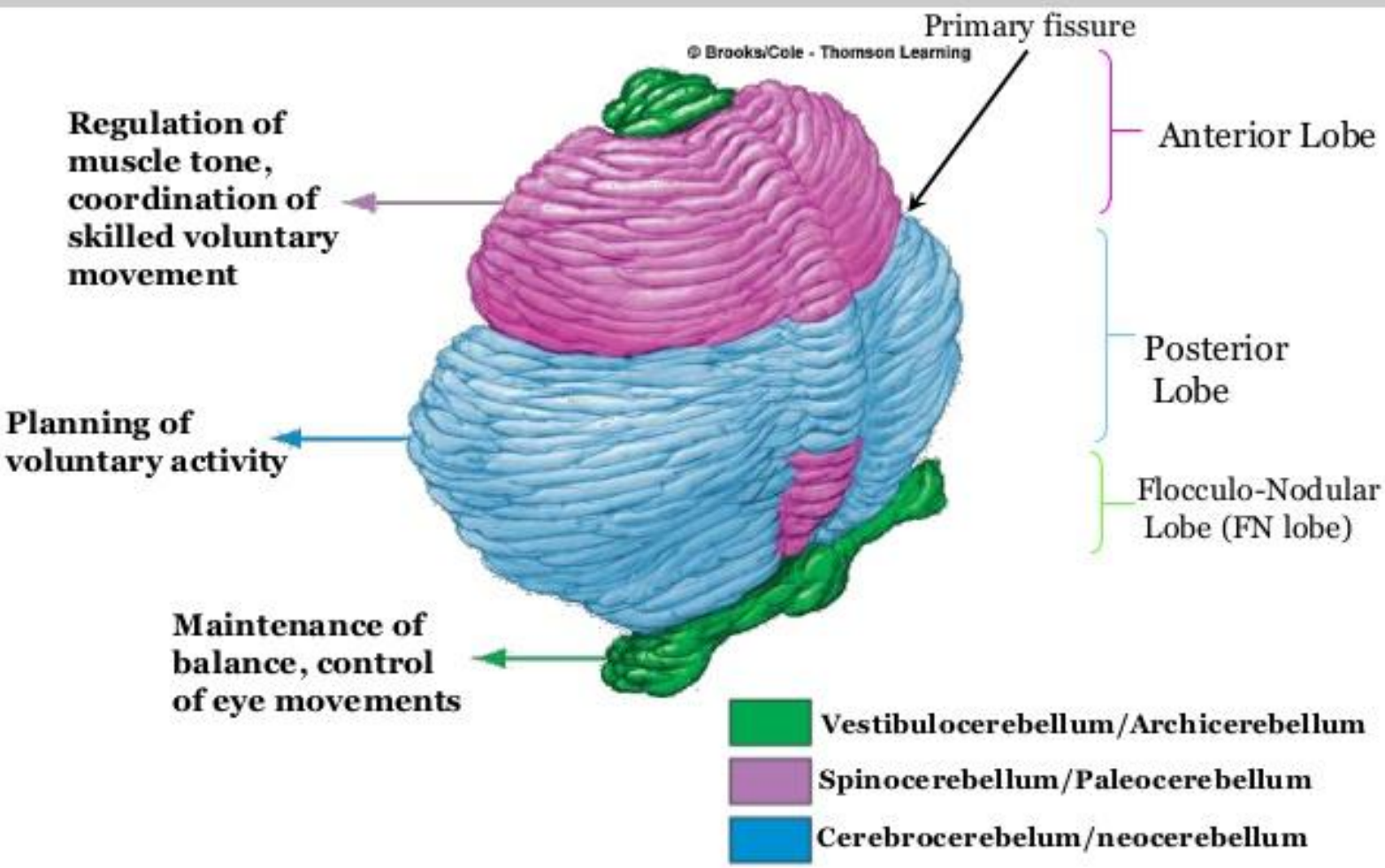
The posterior, superior surface of the cerebellum



The Cerebellum – White and Gray Matter

(d) Coronal section, posterior view

Functional and phylogenetic subdivision



Another subdivision…

Functional and phylogenetic Role

Phylogenetic denomination	Anatomical parts	Role
Vestibulocerebellum *(Archicerebellum)*	Flocculonodular lobe (+ adjacent vermis)	Regulates balance and eye movements.
Spinocerebellum *(Paleocerebellum)*	Vermis and intermediate parts of the hemispheres ("paravermis")	regulates body & limb movements. The spino cerebellum is able to elaborate proprioceptive input in order to anticipate the future position of a body part during the course of a movement.
Cerebrocerebellum *(Neocerebellum)*	Middle portion of the vermis & Lateral parts of the hemispheres	involved in planning & initiation of movement.It has purely cognitive functions as well.

The cerebellum's functions:

- Motor functions:
  - Dysmetria (incoordination of the limbs)
  - Ataxia (wide based, unsteady, lurching gate)
  - Dysarthria (speech impairment)
  - Nystagmus (disturbance of eye movement)

  - Midline lesions are characteristically associated with truncal ataxia, and lesions of the cerebellar hemispheres produce incoordination in the ipsilateral limb.

- Non-motor functions?!

The Cerebellum's role…

- Greek anatomist, Erasistratos (310-250 BC) was at the opinion that there is a relation between the size of the cerebellum and the running speed of animals.

- Franz Joseph Gall (1838) on the cerebellum:

> ''The lady of whom I have spoken above (…) has a large and beautiful head like a man, and she possesses distinguished talents; but the nape of her neck has very little breadth under the ears, which indicates a small development of the cerebellum. I have hitherto found this conformation in all persons in whom the instinct of reproduction was naturally feeble'' (p. 24).

\Language, cognition and the cerebellum: Grappling with an enigma; *Alan Beaton and Peter Marien, Elsevier 2010*

- Luciani (1891) described three symptoms of cerebellar defect: **atonia, asthenia and astasia**.

- Babinsky (1902) coined the term '**disdiadochokinesis**': Inability to execute rapidly alternating movements.

- Holmes (1917) described the effects of gunshot wounds in 21 victims of the WWI as '**decomposition of movement**'.

- Leiner (1989), wrote: "cerebellar connections to prefrontal cortex enable the cerebellum to "improve" mental skills. Connections to Broca's are enable it to "improve" language skills and connections to motor cortex enable the cerebellum to "improve" motor skills."

- Weisenburg, (1927): "Perhaps there is no subject in neurology today about which there is more controversy than the function of the cerebellum"

Brain (1998), **121**, 561–579

The cerebellar cognitive affective syndrome

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- 20 patients (12M 8 W)
- 13p – Stroke; 3p - post infectious cerebellitis, 3p - cerebellar cortical atrophy and 1p- midline cerebellar tumor resected.
- Study included: comprehensive medical evaluation, neurological examination and bedside mental state testing, as well as MRI and EEG.

Cerebellar cognitive affective syndrome (Schmahmmann & Sherman)

- Disturbances of executive function. This includes deficient planning, set-shifting, abstract reasoning, working memory, and decreased verbal fluency.
- Impaired spatial cognition, including visuospatial disorganization and impaired visuospatial memory.
- Personality change, characterized by flattening or blunting of affect, and disinhibited or inappropriate behavior.
- Linguistic difficulties, including dysprosodia, agrammatism and mild anomia.

- => General lowering of overall intellectual function

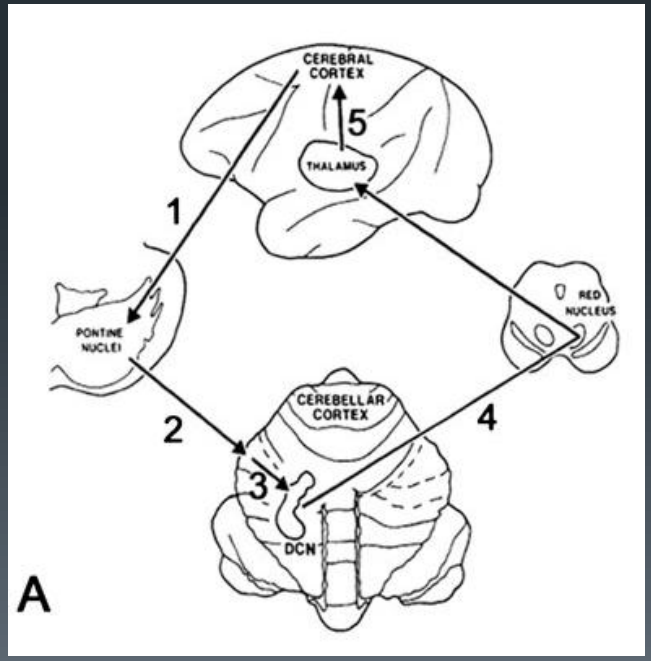
The responsible neural circuit

- Disturbances of:
  - Executive function – prefrontal cortex
  - Visuospatial deficits – parietal lobe
  - decreased verbal fluency and linguistic processing- frontal/temporal lobe
  - impaired visuospatial sequencing - right temporal lobe
  - Changes in affect and motivation- limbic related regions in the cingulate and parahippocampal gyri and frontal lobe.

The presence of these cognitive deficits in patients with cerebellar lesions can be better understood when viewed in light of the anatomical connections linking the cerebral association areas and paralimbic regions with the cerebellum.

The responsible neural circuit

- 2 stage feedforward system:
  - Cerbral cortex → Corticoponitine → pons → pontocerebellar → Cerebellar cortex
- 2 stage feedback system:
  - Cerebellar cortex → cerebellothallamic →Thalamus → thalamocortical → Cereal cortex



- Anatomical studies revealed cognitive areas in the cerebral cortex which project to the cerebellum include: posterior parietal cortex (spatial awareness), areas of the superior temporal gyrus (language), the posterior parahippocampal areas (spatial memory), the visual association areas in the parastriate cortices (higher-order visual processing), and the prefrontal cortex (complex reasoning, judgment attention, and working memory). There are also projections from the cingulate gyrus to the pons.

- The cerebellum has also been shown to connect brainstem nuclei to the limbic system

- The organization of these anatomical pathways helps clarify the role the cerebellum plays in motor as well as non-motor functions.

- The connection with the limbic system presumably underlies the affective symptoms of pathology in the cerebellum.

‘Dysmetria of thought’

- “ ‘Dysmetria of thought’ is the concept that we proposed as the fundamental mechanism underlying disorders of intellect and emotion resulting from cerebellar dysfunction...In this view, the cerebellum detects, prevents, and corrects mismatches between intended outcome and perceived outcome of the organism’s interaction with the environment. In the same way as the cerebellum regulates the rate, force, rhythm, and accuracy of movements, so might it regulate the speed, capacity, consistency, and appropriateness of mental or cognitive processes. In this model, the cerebellar contribution to cognition is one of modulation rather than generation.”

Dysmetria of thought: clinical consequences of cerebellar dysfunction on cognition and affect , *Trends in Cognitive Sciences*, *Jeremy D. Schmahmann, 1998*

Back to our results…

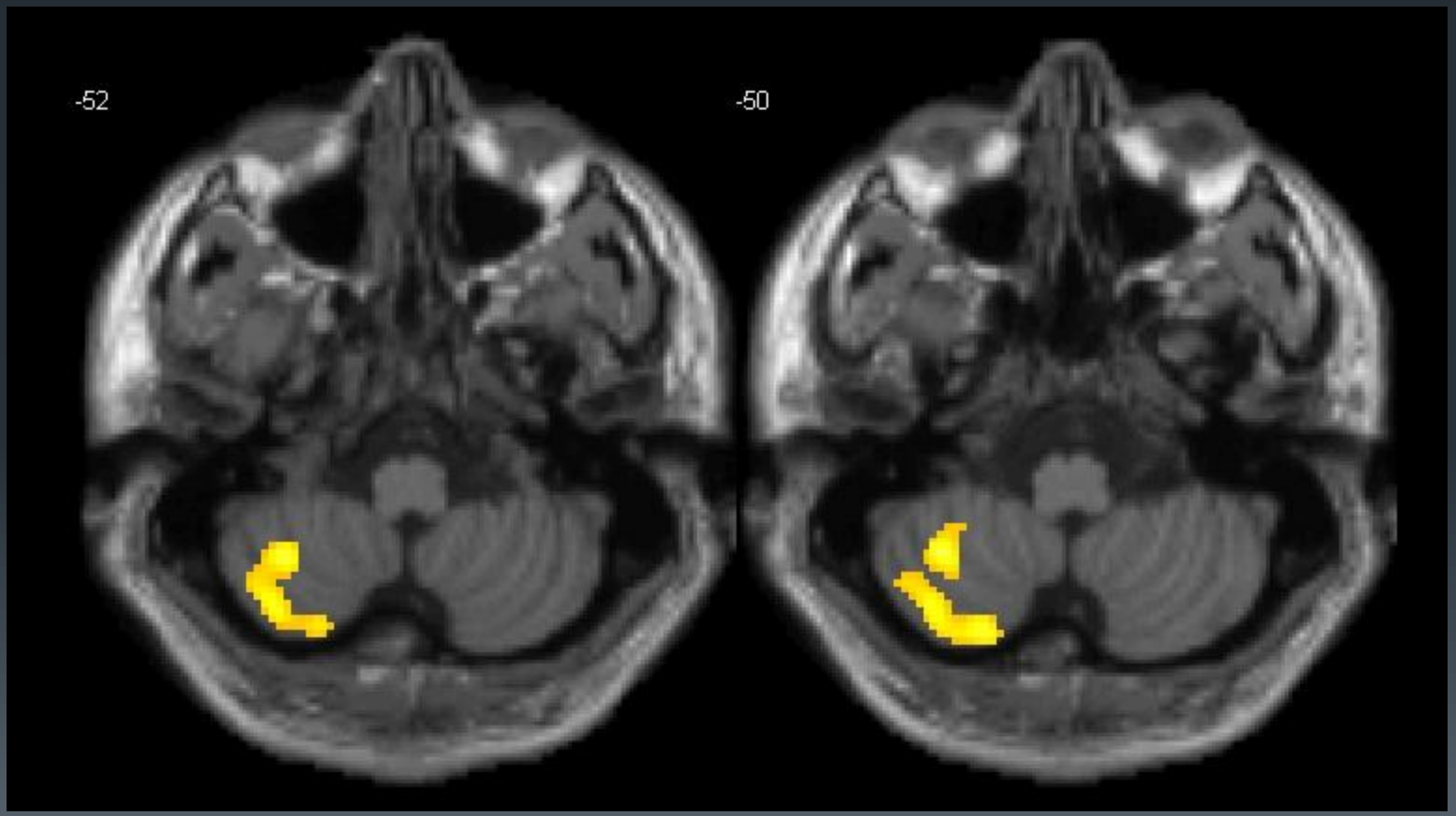
Executive function

- Management (regulation, control) of cognitive processes, including working memory. reasoning, task flexibility and problem solving as well as planning and execution.

- Areas known to be involved:
  - Dorsolateral prefrontal cortex
  - Anterior cingulate cortex
  - Orbitofrontal cortex

- In the MCCT batter composed out of 3 tests:
  - 1.Go-Nogo
  - 2. Stroop
  - 3. Catch game

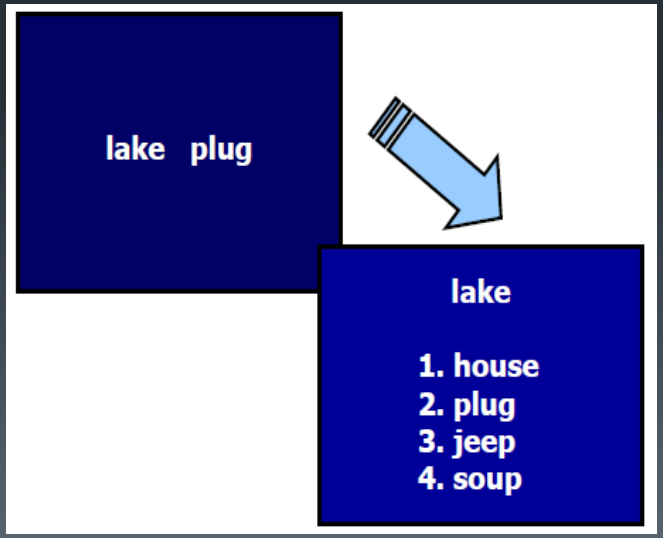
FA versus Executive function



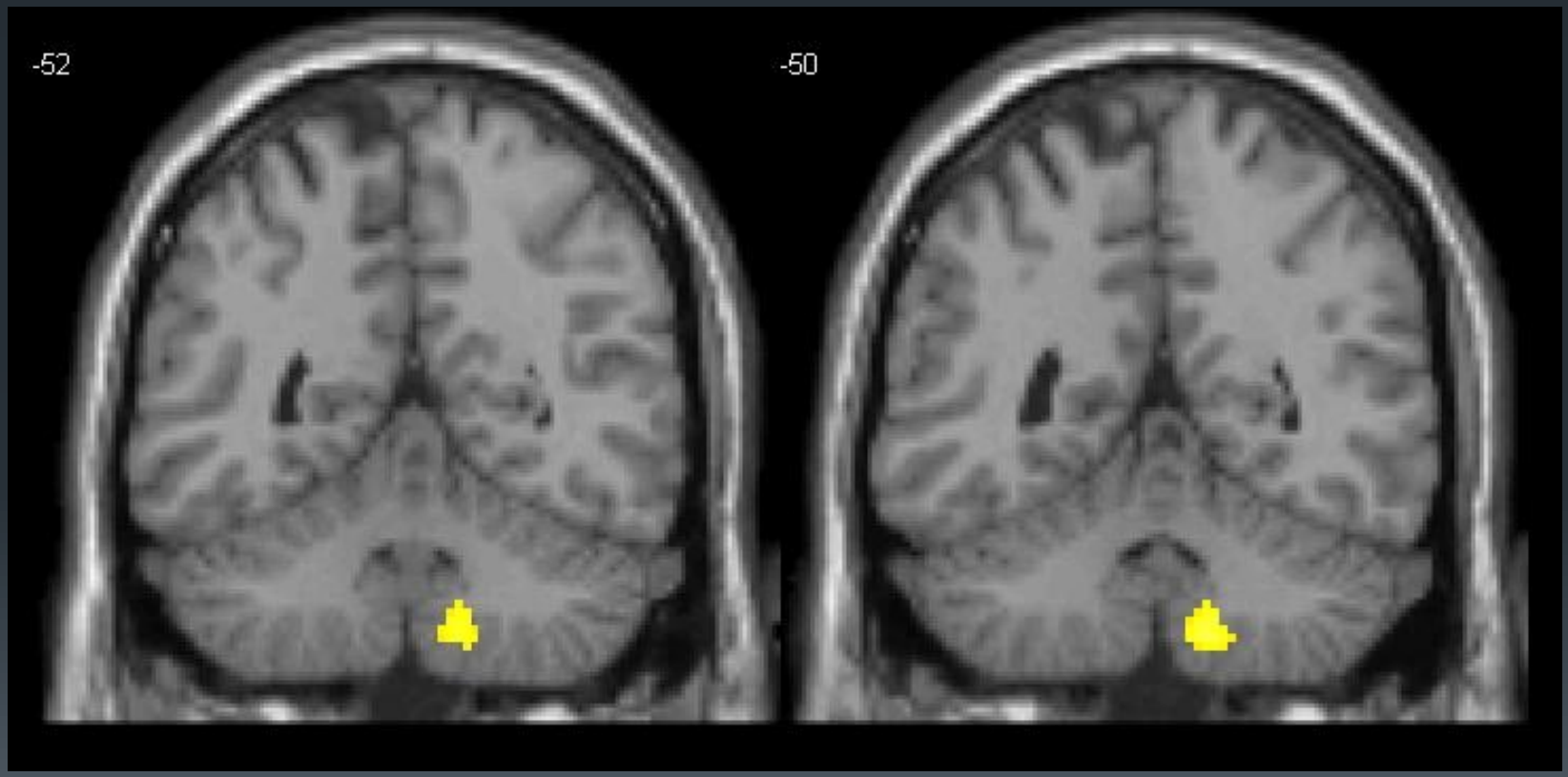
Verbal memory

- The Verbal Memory test measures immediate and delayed recognition memory for verbal paired associates. Participants are presented with 10 pairs of words to study followed by a recognition test in which they are presented with one member of a previously presented pair together with four possible alternatives for the other member of the pair

- Encoding of episodic memory:
  - Left prefrontal cortex
  - retrosplenial area of the cingulate cortex
- Retrieval from episodic memory:
  - precuneus bilaterally
  - right prefrontal cortex



FA versus Verbal memory



Conclusions so far…

- MS pathology can be detected in NAWM and NAGM.
- Thanks to Voxel Based Analysis which does not restrict an hypothesis to a ROI we can detect the involvement of new regions in cognitive tasks.
- There is a significant correlation between the cerebellum and non-motor functions as EF and verbal memory in our group of MS patients which stands in accordance to recent findings concerning the role of the cerebellum in cognition.
- There is need in further investigation of the roles of the cerebellum in cognitive tasks and the mechanism in which it coordinates with the cerebral cortex and limbic system.

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