
How are these facts related to LO1???

The Chaim Sheba Medical Center | TEL AVIV UNIVERSITY

4.7.14

Subtle BBB Permeability and Angiogenesis in Parkinson-Disease(PD) patients, suffering from Levodopa Induced Dyskinesia(LID)

Segal Ofir, 5'th Year Medical Student, 6-Years program

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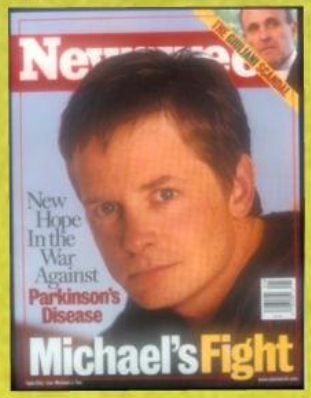
Epidemiology of Parkinson's Disease

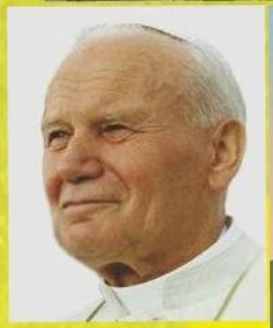
The second most common neurodegenerative disorder after Alzheimer´s disease (AD).

Affecting 1-2 % of the general population over the age of 65 years.








Parkinson's Disease

- A multisystemic disease causing **motor symptoms** and **nonmotor symptoms**, including: autonomic dysfunction, neuropsychiatric problems, and sensory symptoms.

-The motor symptoms result from the death of dopamine-generating cells in the substantia nigra

-In this lecture we'll focus on the motor symptoms of PD

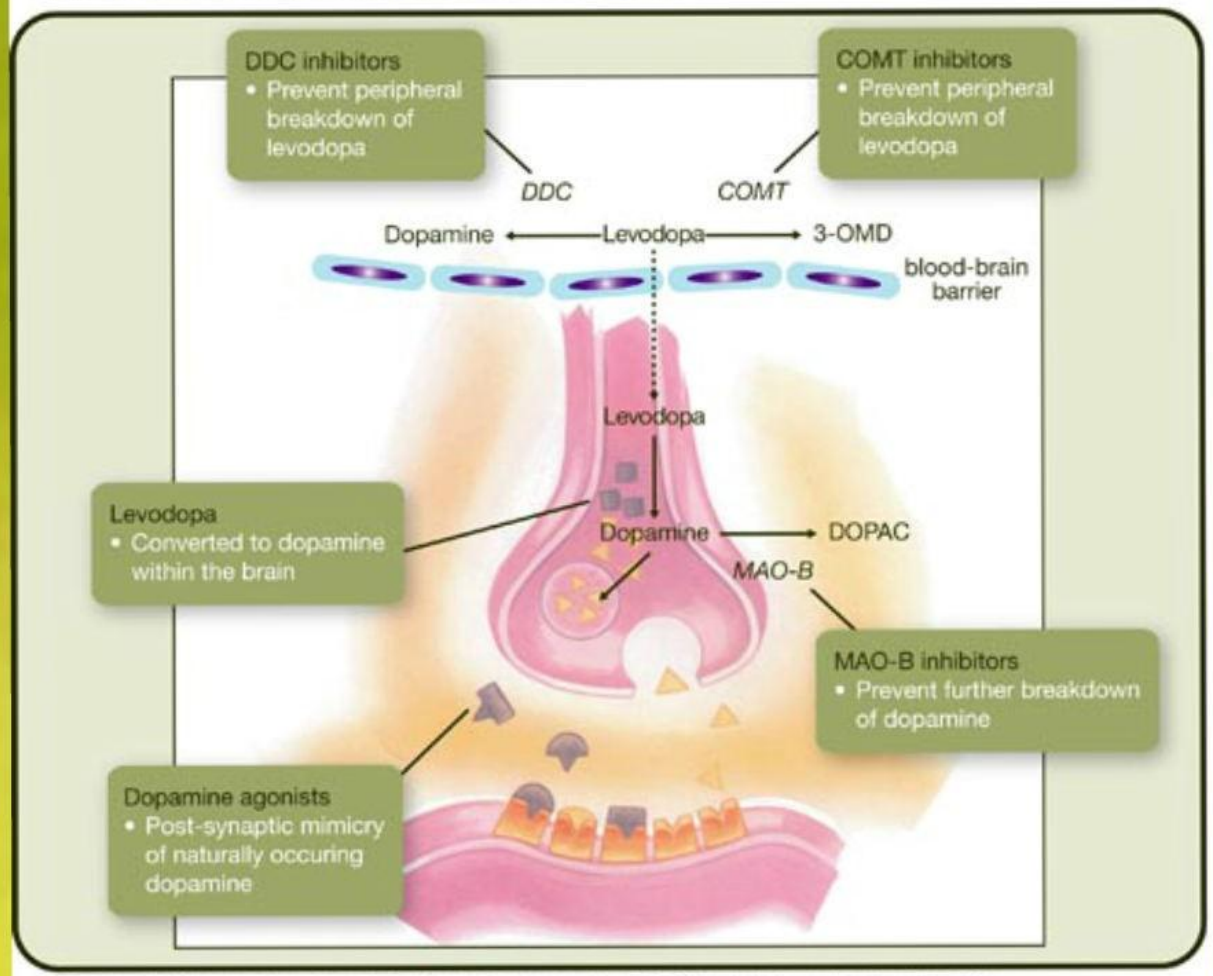
Three cardinal motor symptoms in PD:

1. Resting tremor

2. Bradykinesia (slowness of movements)

3. Muscle rigidity

Figure 14. Mode of action of anti-parkinsonian therapies



COMT=catechol-O-methyltransferase; DDC=dopa decarboxylase; DOPAC=dihydroxyphenylacetic acid; MOA-B=monoamine oxidase-B; 3-OMD=3-O-methyldopa

- There are several groups of anti-parkinsonian therapy which elevate the dopamine levels in the brain.
- **The gold standard, and most effective treatment for the motor symptoms of PD is L-Dopa (Dopamine precursor).**
- Sooner or later all patients are treated with L-Dopa.
- Dopamine doesn't cross BBB, L-Dopa does.

The limitations of L-Dopa therapy

Short term side effects- nausea, somnolence etc

Long-term motor complications:

1. motor fluctuations
2. L-Dopa-induced dyskinesia

Motor fluctuations:

-Within 5 years of L-Dopa treatment ~50% of patients develop motor fluctuations in response to medication .

(sweet and McDowell 1975; Dupont et al., 1996)

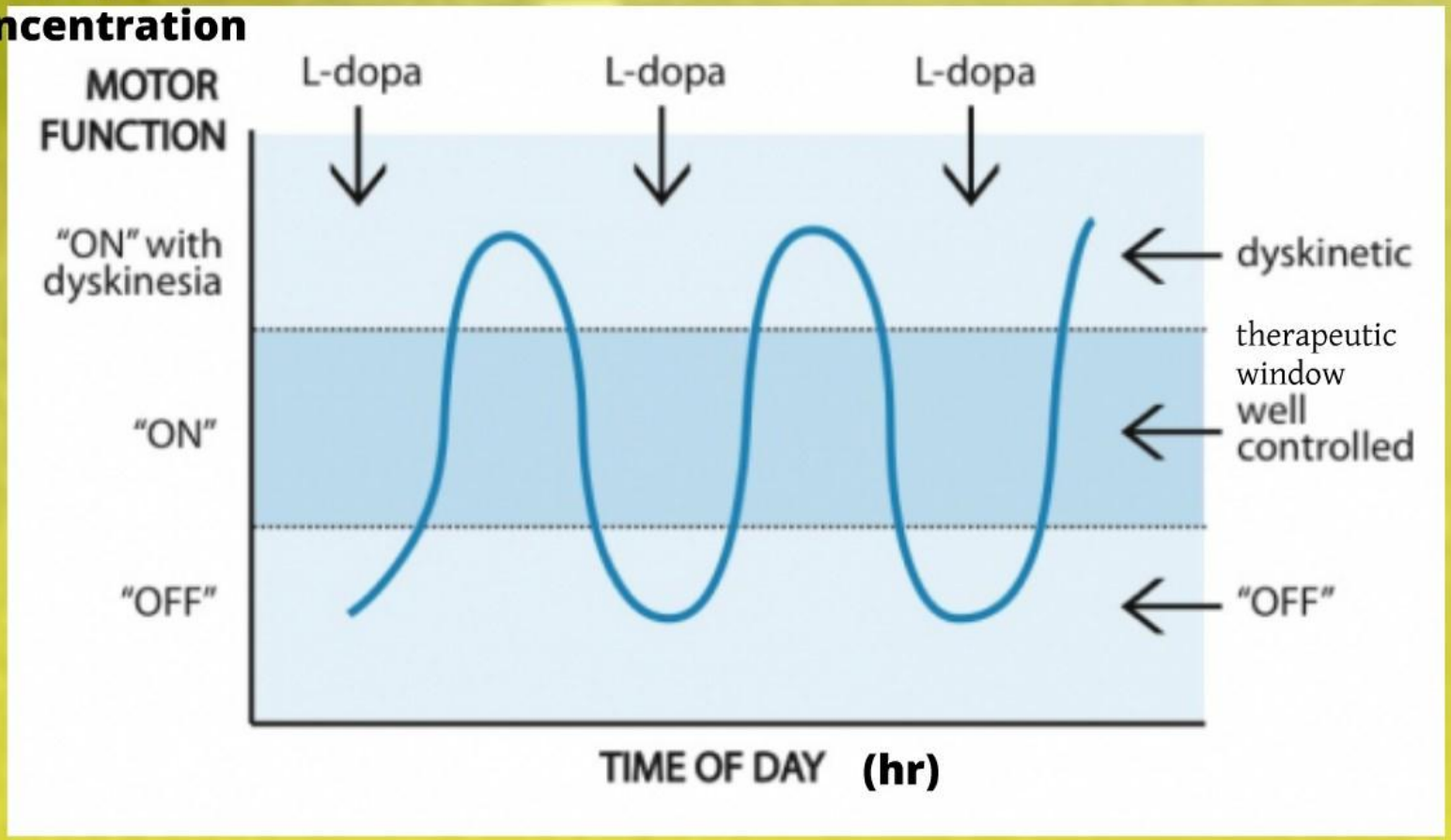
-**"off" state:** No response to medication and significant Parkinsonian motor symptoms (rigidity, bradykinesia etc)

-**"on" state:** Good response to medication and fewer parkinsonian motor symptoms.

Fluctuation between "On" and "Off" state is very rapid

Motor fluctuations:

L-Dopa plasma concentration



Dyskinesia = Involuntary, hyperkinetic movements, including chorea, dystonia, and athetosis .

- LID occur in 35-40% of PD patients, 4-6 years after L-DOPA treatment, and 90% after 9 years!

Once established, LID is difficult to treat, and almost impossible to get rid of!

Pathophysiology of LID

-The mechanism of LID is complex, and has to do with non-physiological pulsatile stimulation of the post-synaptic receptors by dopamine.

-The neuronal mechanism which causes LID also has to do with an abnormal neuroplastic changes in the basal ganglia .

-Brain plasticity is not limited to neurons, but also involves changes in asrocytes and microvascular cells forming "neurovascular unit"

parkinson gait ON\OFF L-Dopa

Pathological angiogenesis in the brain :

-Occurs in several conditions:

* locally increased metabolic demands(tumors)

* response to injury(ischemia, trauma etc.)

- Causes dysfunction of the BBB

The factor that regulates this angiogenesis is VEGF!

VASCULAR ENDOTHELIAL GROWTH FACTOR - VEGF

- Signal protein
- Vasculogenesis and angiogenesis
- Upregulated following traumatic injury, ischemia

protective:

Increasing tissue vascularization

destructive:

induces BBB leakage and inflammation

Study goals

- Broaden our understanding of the pathophysiology of LID

- Identify imaging and blood biomarkers for LID.

How ?

- It has been proposed in the literature that LID is related to BBB dysfunction and pathological angiogenesis.

- First In-vivo study on humans, using special neuroimaging methods , investigating angiogenesis, BBB permeability and volumetric measurements in PD patients suffering from LID .

Study question:

Are pathological angiogenesis and BBB disruption, related to LID development in L-Dopa treated PD patients?

Dr.Yael Mardor's group, Advanced Technology Center, has recently developed MRI-based vessels function maps that enable real -time depiction of subtle BBB abnormalities in humans.

- **High sensitivity to BBB disruption**
- **High spatial resolution**

How can this increased sensitivity be achieved?

How can this increased sensitivity be achieved?

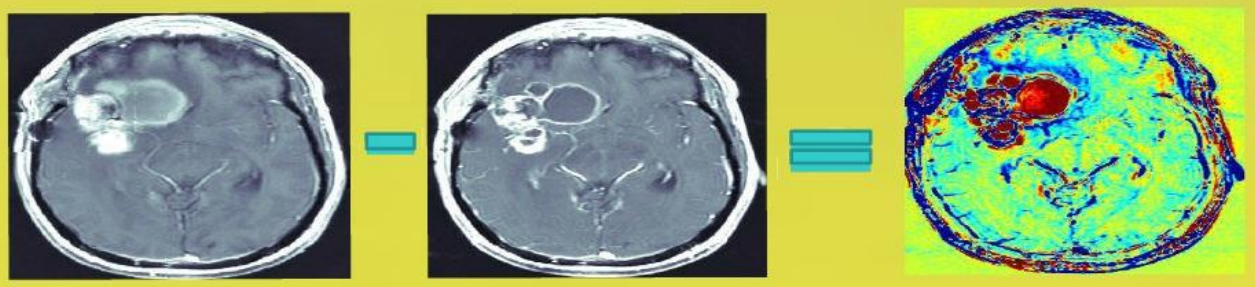
Delayed Contrast Extravasation MRI:

Method

Acquire 2 series of T1-MRI 2 & 75 min post contrast injection

Subtract the early (2 min) images from the late (75 min) images

75 min Gd | 2 min Gd | TRAM



Blue = tumor tissue , efficient Gd clearance at 75 min

Red = non tumor tissue, Gd accumulation at 75 min

Our Study population-at first

Inclusion:

- 20 PD patients aged 30-70(today- 30 patients)
- L-dopa treatment for more than 2 years
- 2 PD patients groups

with LID
(minimum 1 year)

without LID

Exclusion criteria:

- History of cranial injury
- Abnormal renal function(creatinine)
- Severe tremor or dyskinesia
- Dementia
- MRI contraindications

Matching

Couples matching (from the LID and nonLID groups) according to:

age, gender, duration of PD, duration of L-dopa treatment.

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Study Methods- at first

- Assessment of BBB permeability and pathological angiogenesis with "Delayed Contrast Extravasation MRI" using SPM. Creating 2D **Qualitative** maps.
- Volumetric measurements-regions of interest(ROI) manual segmentation using SPM.
- Measuring VEGF levels in the patient's serum
- Clinical evaluation of the motor symptoms of PD, and severity of dyskinesia: UPDRS score\AIMS score

Preliminary results and problems along the way-

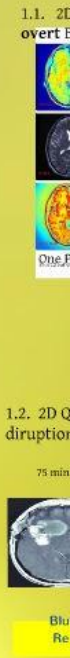
first problem:

BBB permeability assessment:

1.1. **2D Qualitative maps- had shown no significant overt BBB permeability in the dyskinetic group.**

1.2. 2D Qualitative maps usually discover "significant" BBB disruption as in tumors\stroke, where there is a "lesion".

1.3. No statistical analysis can be done for BBB permeability (as the data is qualitative and not quantitative).



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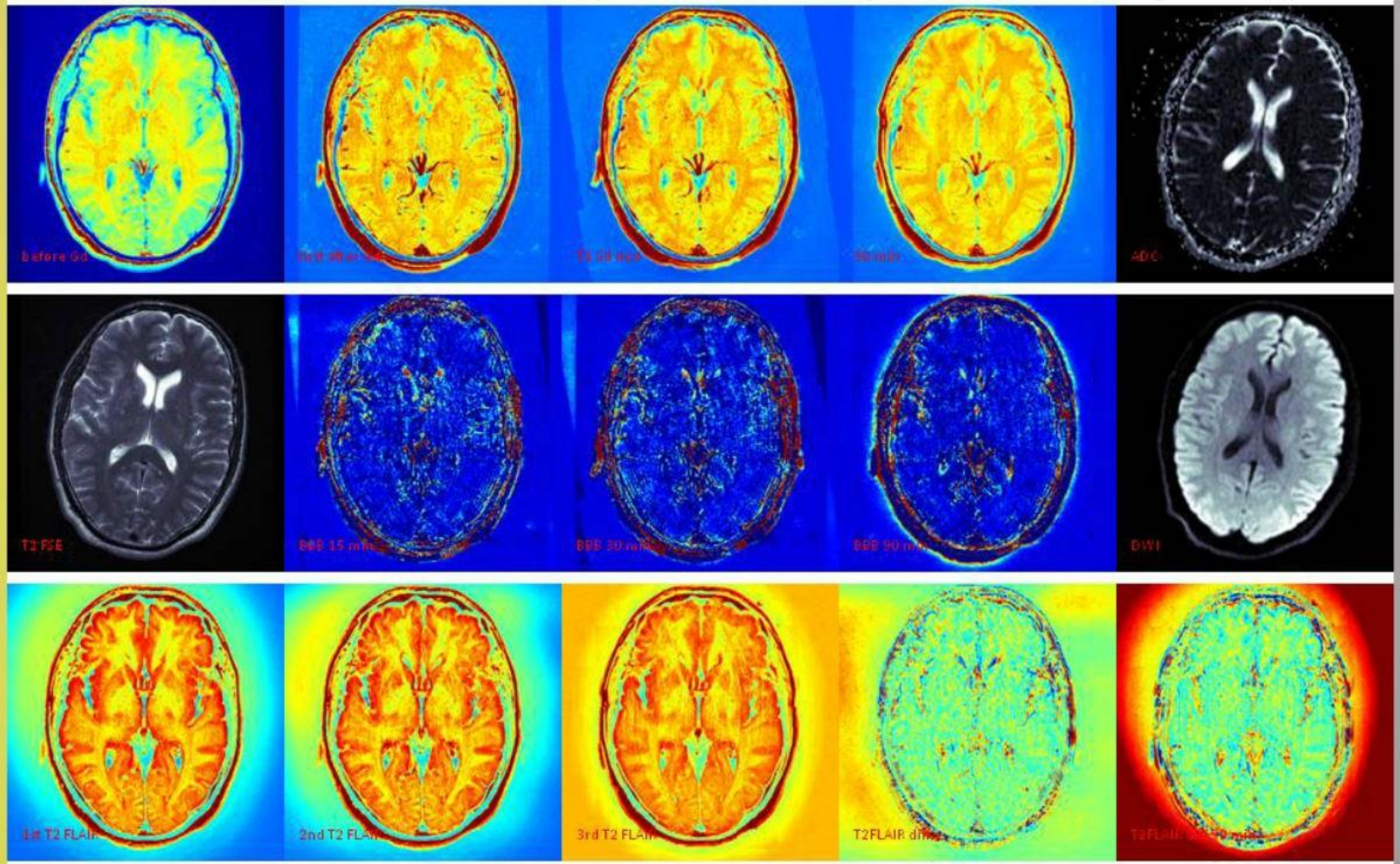

One Patient with LID

Slice 12 out of 24

n=23. LID=9 . nonLID=14

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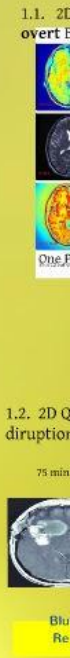

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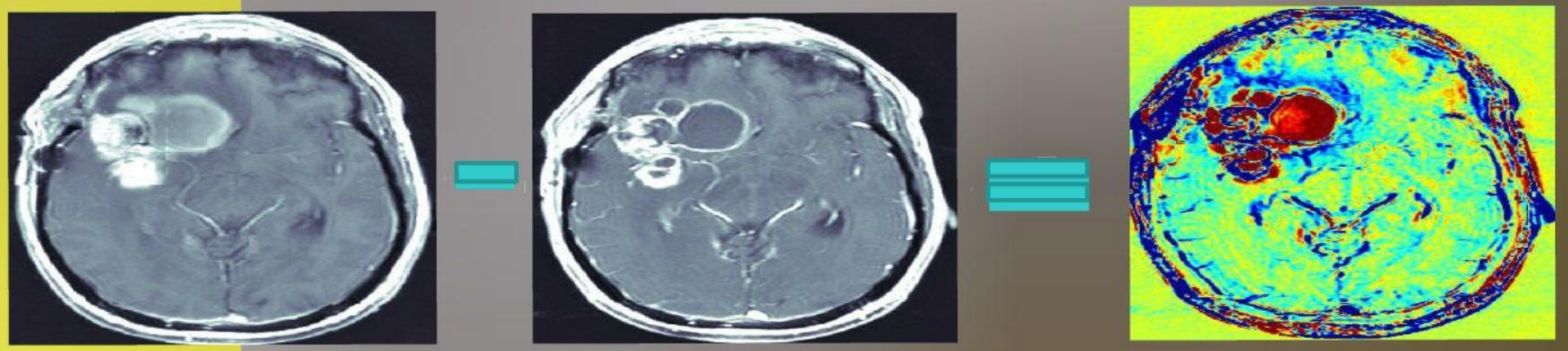
75 min Gd

2 min Gd

TRAM



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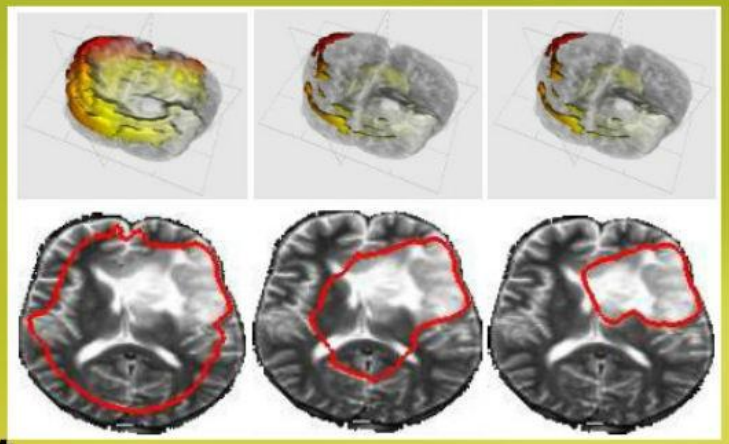
Second problem:

Volumetric measurements-manual segmentation:

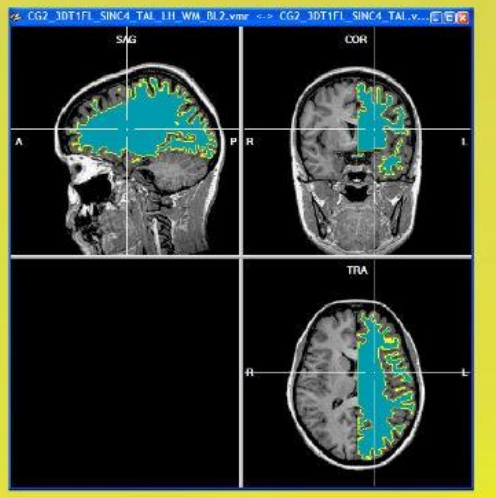


2.1. Less accurate.

2.2. Operator dependant.

2.3. Time consuming.

2.4. Good for brain lesions, bad for anatomy!



Suddenly I tought-

Why not creating an automatic 3D- whole brain segmentation??

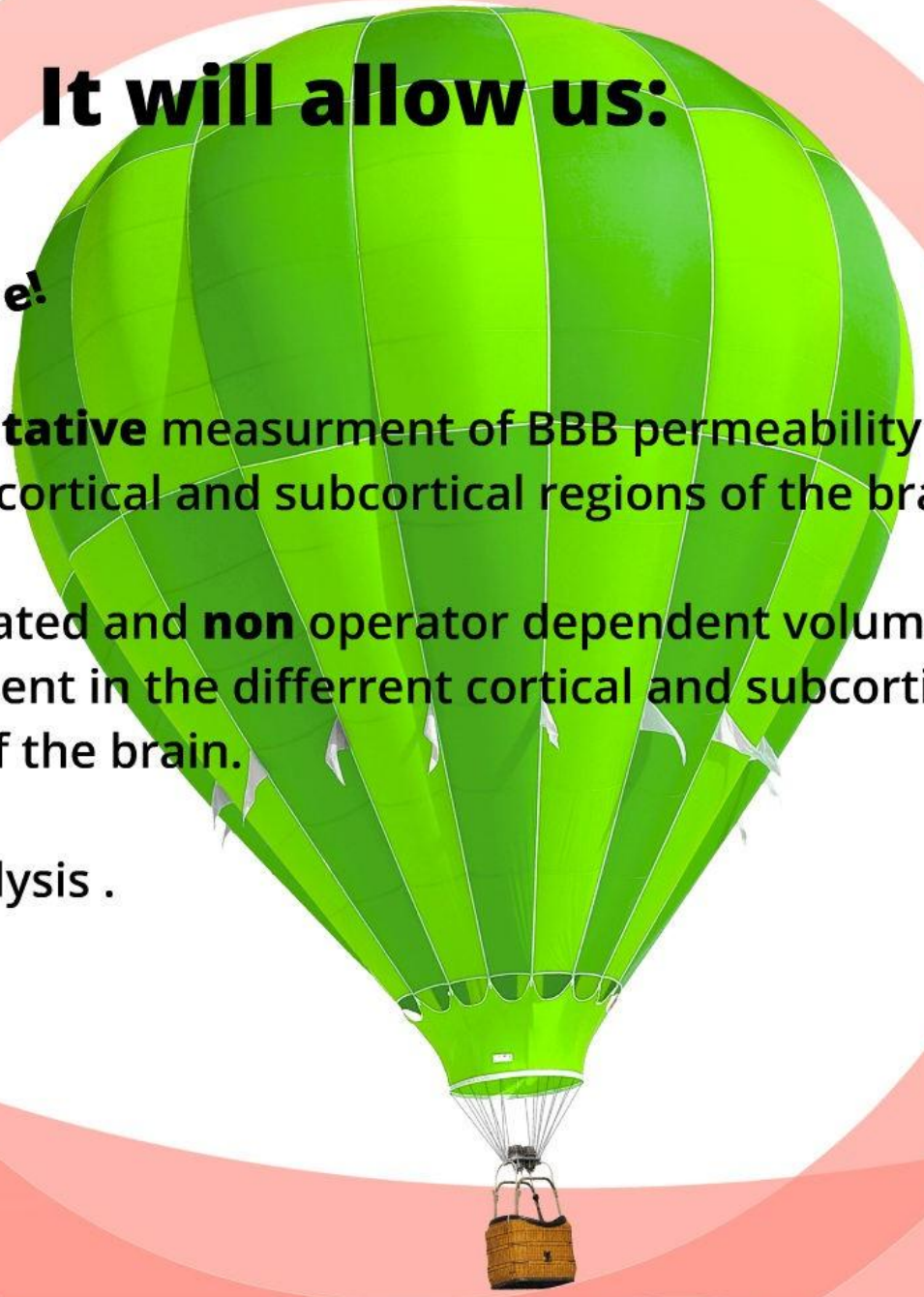
It will allow us:

More sensitive!

1. **Quantitative** measurment of BBB permeability in the different cortical and subcortical regions of the brain.

2. Automated and **non** operator dependent volumetric measurment in the differrent cortical and subcortical regions of the brain.

3. 3D analysis .

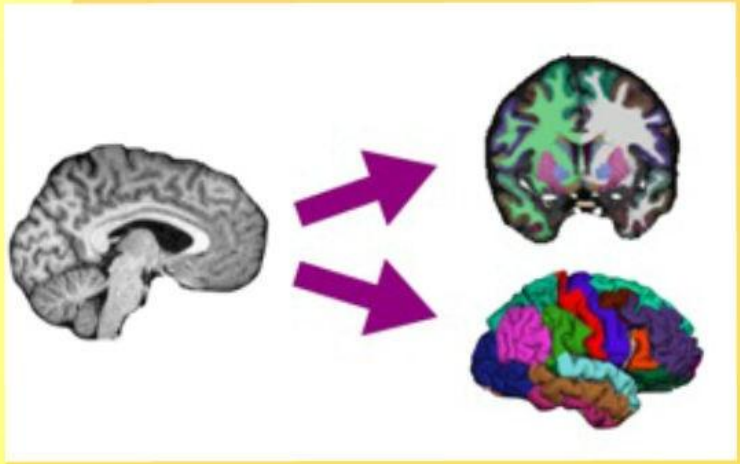


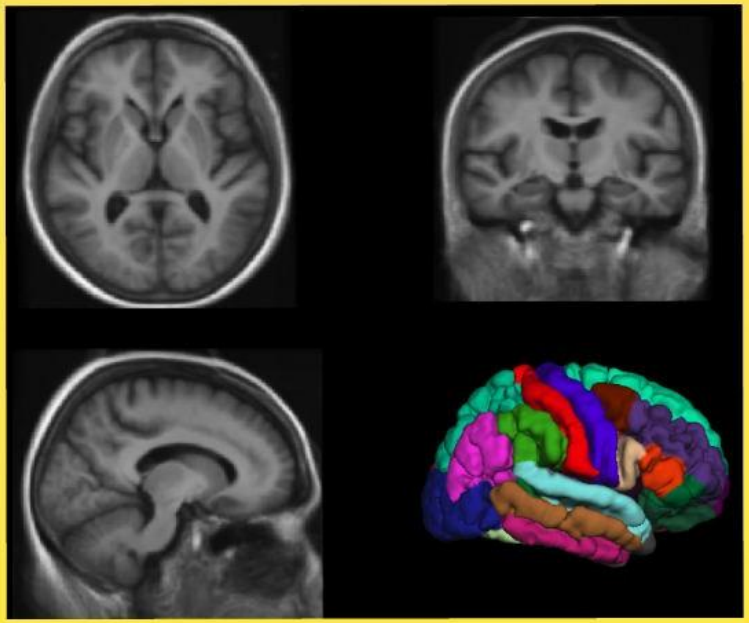
- **During the Arrow project meetings,** I've been exposed to the FreeSurfer program, used by Dr Shmuel Miron and Lior-Orbach in their research in the MS center.

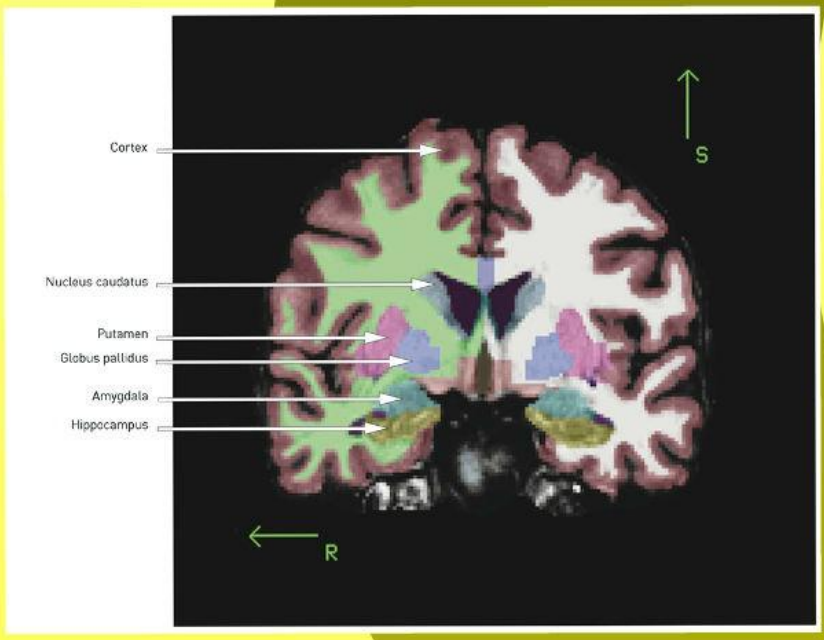
- **FreeSurfer-** contains a **fully automatic** structural imaging stream for processing cross sectional and longitudinal data.

- We've started cooperating with them using FreeSurfer .

FreeSurfer- anatomical segmentation

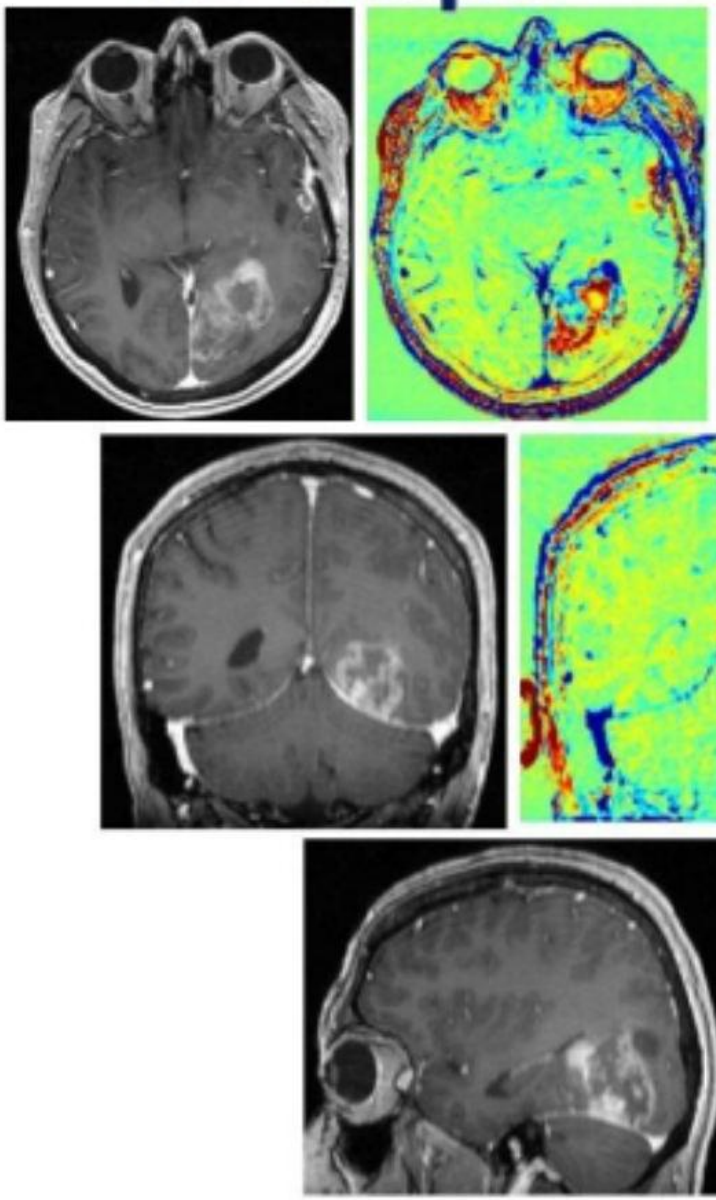




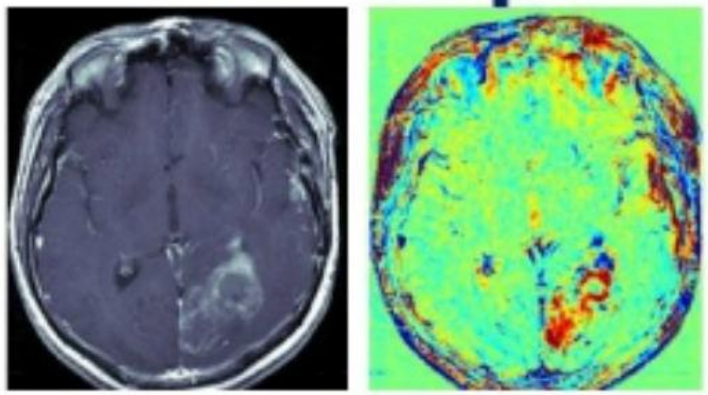


3D BBB permeability maps

FSPGR- 3D Maps



T1 SE-2D maps



Blue = Tumor

Red = non-tumor

Each patient will have :

1. Clinical scores using UPDRS\AIMS scores.
2. VEGF levels in the patient's serum.
3. Quantitative BBB permeability values in cortical and subcortical regions.
4. Volumetric measurments of cortical and subcortical regions.
5. Other MRI sequences like DTI, perfusion etc.

What have we done so far:

- ✓ 1. Already recruited 23 PD patients. 9 -nonLID, 14- LID.
  2 patients didn't finish the MRI scan.
- ✓ 2. 7 matched couples.
- ✓ 3. Qualitative 2D BBB permeability maps (n=23).
- ✓ 4. Whole brain segmentation . (n=12)
- ✓ 5. Quantitative 3D BBB permeability maps+measuring the permeability . (n=6)
- ✓ 6. Volumetric measurments . (n=5)
- ✓ 7. Blood sample for future VEGF measurments. (n=23)

What's next?

1. Finish recruiting patients.
2. Finish creating BBB maps.
3. Finish creating volumetric measurements.
4. VEGF measurement- ELISA.
5. Analyzing the data.
6. Publishing.

Acknowledgments:

I would like to thank-

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Prof. A. Achiron MD, PhD- Director, Multiple Sclerosis Center, Academic Associate Dean, Sheba Medical Center, and staff

Dr.Shmuel Miron and Lior-Orbach


THANK YOU FOR
LISTENING


GOAL!
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