Functional Imaging studies in PD

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ISRAEL
Isoflupane binds to DaT on nigrostriatal neurons

**Autoradiograph**

**(in vitro)**

**DaTSCAN™**

**(in vivo)**

- Pre-synaptic neuron
- ioflupane
- Dopamine
- Dopamine receptor
- Post-synaptic neuron

**Density**

- Low
- High

**Caudate**

**Putamen**

Axial section adapted from: Gunther et al., 1997 *Nuc Med Biol.*

FDA briefing document 2009
http://www.fda.gov/downloads
Changes in the DA system in PD

There are three major approaches to studying the integrity of presynaptic DA function:


2) Binding to the plasmalemmal dopamine transporter (DAT) assessed using a large variety 11C and 18F labeled tropane (cocaine-like) derivatives or with 11C d-threo methylphenidate (MP) and also a number of gamma-emitting analogs that can be analyzed using single photon emission computed tomography (SPECT).

3) Fluoro-l-dopa (FD), which is sensitive to and provides a measure of the rate of aromatic acid decarboxylation and also storage of fluorodopamine in synaptic vesicles.
As expected all of these tracers show similar change in PD. These consist of a substantial loss of **striatal DA innervation** that is **asymmetric** with a characteristic **rostral-caudal gradient**, such that the **posterior putamen** is most severely affected and the caudate is relatively spared.
Such changes are seen in the clinically unaffected striatum in patients with early unilateral disease and may also be seen in subjects who are clinically unaffected but who have a high risk to develop PD based on genetic mutations or exposure to DA neurotoxins. Although there is a close relationship by PET (or SPECT) and clinical measures of disease severity there is sufficient discordance that imaging cannot be used as a biomarker.
Substantia nigra: loss of dopaminergic cell bodies

Isoflupane binds to DaT on nigrostriatal neurons

**Autoradiograph**
*in vitro*

- **Density**
  - Low
  - High

**DaTSCAN™**
*in vivo*

Axial section
adapted from: Gunther et al., 1997 *Nuc Med Biol.*

FDA briefing document 2009
http://www.fda.gov/downloads
Geometric VOI
Healthy control
Early Parkinson
Advanced Parkinson

Anatomical ROI
Lancet Neurol 2009; 8: 1128-39
Male, 58 y
UPDRS: 3
MoCA: 30
Non-motor symptoms: 2
Smell identification: 32

Female, 59 y
DAT – SPECT in PD

Parkinson’s disease (PD)

High res. anatomical MR image  DAT scan of A healthy subject  DAT scan of a patients with PD
Striatal Dopamine Transporter Binding (DAT-Scan)

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Eisensehr et al., Sleep 2003, Eisensehr et al., Brain 2000
פיתוח אמצעי אבחון רגישים
ליזיהו מחלת פרקינסון בשלבים מוקדמים
שנים ממועד אבחון המחלה
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מתדרדרות בתפקוד המוחי
בדיקה נוירולוגית
הדמייה
סמינס ביוכימיים
וחירום
הפרקינסון
Tokuda 2010
מנוזל השדרה
The blue space and arrows represents the cerebrospinal fluid.
F-dopa PET in early-asymmetrical PD

Clinically unilateral PD
H&Y I; n=8  tremor +,
6 bradykinesia
% depletion vs controls

18%  54%
12%  34%

8 Controls
THE TIME AT WHICH SYMPTOMS APPEAR VARIES BETWEEN INDIVIDUALS.

Healthy  Pre diagnosis??  Diagnosed with PD
מסומן המסמך את קצות הנוירונים הדופמינרגים DOPA עם PET שלהולה פרקינסון חד צדדי

MRI  Control  Hemi-Parkinson
Neuroimaging – e.g., CALM-PD; REAL-PET

At the time of diagnosis
$^{11}$C-WAY 100635 PET 5-HT1A binding in 51 y.o. healthy control and 53 y.o. PD patient
DOPAMINE TRANSPORTER (DAT) SPECT CAN REFLECT DOPAMINERGIC DENERVATION OF THE STRIATUM

Healthy

Asymptomatic mutation carrier

Parkinson patient
G2019S-\textit{LRRK2} mutation carriers use the brain differently to solve motor imagery problems.
DaT Scans
DaT SPECT - VOI analysis

Anterior
Middle
Posterior
**Differences between asymptomatic carriers and non-carriers**

**DaT SPECT VOI analysis**

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Legend:
- **NMC**
- **NC**
- **PD**
Quantification of DaT uptake using VBM analysis

$p<0.05$; Corrected for multiple comparison

LC = First-degree relatives, carriers
NC = First-degree relatives, non carriers

Non Carriers $> \text{carriers}$

Artzi et al. in preparation
Thank you