Positron Emission Tomography: UBC/TRIUMF

V Sossi
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Physics and Astronomy Dept.
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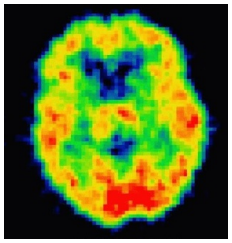
a place of mind

PET program at UBC/TRIUMF (background)

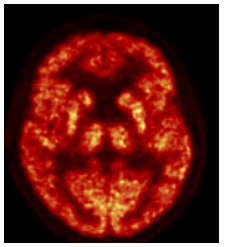
Established in ~ 1980: collaboration between UBC- PPRC (Drs. Brian Pate, D Calne) and TRIUMF (Dr. E. Vogt)

First human scanner built at TRIUMF



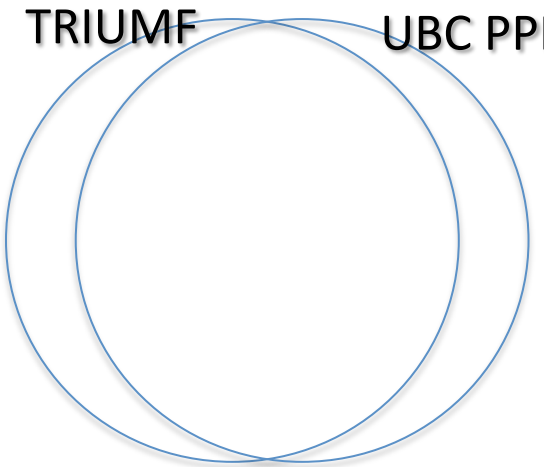
Next human (brain) PET (~commercial) scanners **(**ECAT 953B**,** ***HRRT****,* *GE Advance*)

Acquired a dedicated microPET ~ 2003

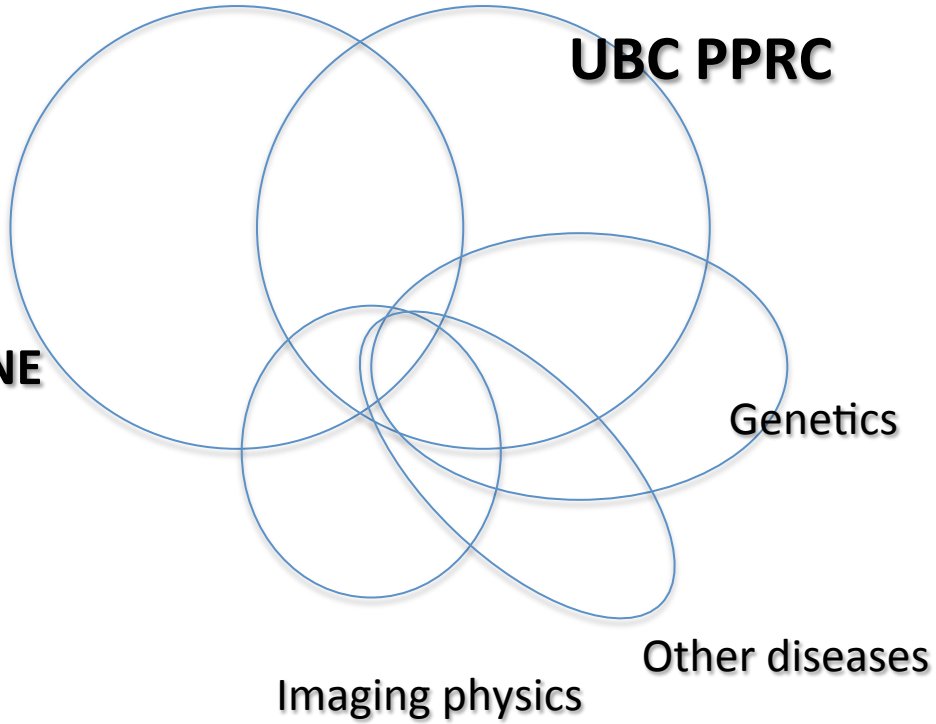


Acquired a hybrid microPET/SPECT/CT 2012

Radiochemistry/ Brain Imaging PET program as started



Today: more complex and richer



Clinical and preclinical imaging program

Radiochemistry at TRIUMF: key aspect and excellent opportunity for growth

Operational paradigm

Radiotracers produced at TRIUMF, sent through a pipeline to the UBC hospital

UBC

consummables
tracer costs
+ 2 production chemists

Imaging programs

- Human scanners (GE Advance, HRRT)
- MicroPET imaging (Focus 120, at UBC) + microPET/SPECT/CT Milabs Vector (at CCM)
- Physics/Instrumentation/Modelling

Imaging programs

Medical research focus :

- **movement disorders** – Pacific Parkinson's research centre (Director **AJ Stoessl, main source of research funding**)
- mood disorders (L Yatham)
- dementia (R Hsiung, H Feldman)

Imaging physics

- PET Quantification algorithms
- Kinetic modeling
- PET/MRI image analysis methods

Radiochemistry

12 tracers routinely produced

Tracers routinely used

- Dopaminergic
  - ^{18}F-fluorodopa
  - ^{11}C-dyhydrotetrabenazine
  - ^{11}C-methylphenidate
  - ^{11}C-raclopride
  - ^{11}C-schering
- Serotonergic
  - ^{11}C-DASB
  - ^{18}F-setoperone
- Noradrenergic
  - ^{11}C-MRB
  - ^{11}C-Yohimbine
- Cholinergic
  - ^{11}C-PMP
- Plaque detection
  - ^{11}C-PIB
- Inflammation
  - ^{11}C-PBR28
- Energy metabolism
  - ^{18}F-FDG

Parkinson's research

- **Origin**: imaging of subjects at risk- LRRK2 + RBD

dopaminergic, serotonergic and cholinergic system + inflammation (MJFF, CIHR, Cundill, Parf)

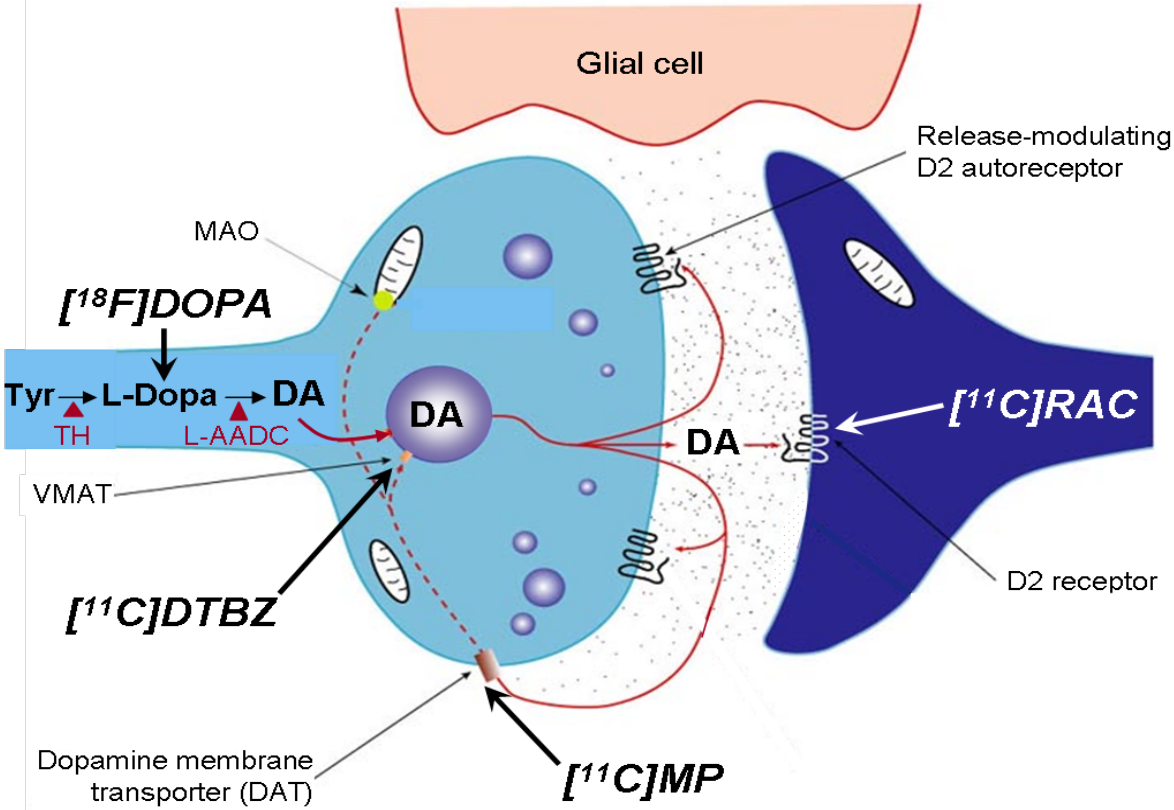
Overlap syndrome (Parf)

- **Treatment related complications** (CIHR)
  psychiatric complications
  role of the serotonergic system

Effect of **exercise** on disease progression (Cundill)

- Use disease to better understand **normal brain function**

MULTI-TRACER PET

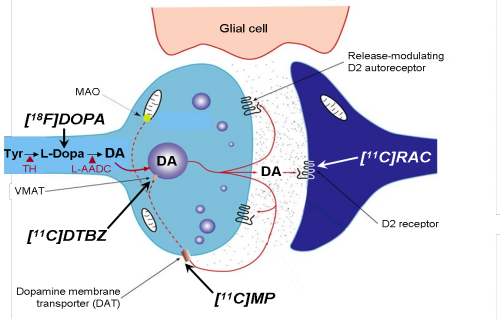


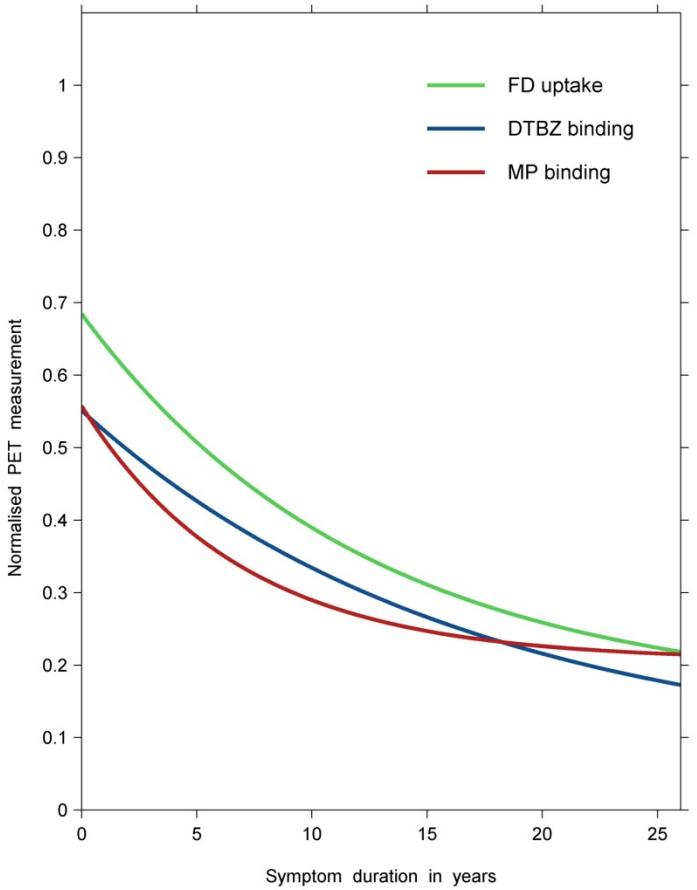
Longitudinal changes in striatal dopamine processing in the progression of Parkinson's disease: evidence of failure of compensatory changes

Early disease: upregulation of dopamine synthesis and downregulation of DAT in the putamen in the early stage of PD.

Late disease stage: The age-normalized tracer values of the different markers tend to approach one other in the late disease stage when the rate of decline in all PET measurements was similar in the putamen.

Breakdown of compensatory mechanisms in the putamen could contribute to the worsening motor symptoms in the advanced stage.





Nandhagopal et al., Brain 2011

VIEWS & REVIEWS

Parkinson disease, 10 years after its genetic revolution

Multiple clues to a complex disorder

Christine Klein, MD
Michael G. Schlossmacher, MD

Neurology® 2007;69:2093-2104

~ 10% of PD is of genetic origin

Table Different monogenic forms of parkinsonism

Acronym	Mode of inheritance	Locus	Gene/protein	Mutations
Monogenic	confirmed			
PARK1/PARK4	Autosomal dominant	4q21-q23	*SNCA*/α-synuclein	3 missense mutations,[9,135,136] whole gene duplications/ triplications in <10 families[10,12]
PARK8	Autosomal dominant	12q12	*LRRK2*/dardarin	>50 variants, >16 of them pathogenic[124]
PARK2	Autosomal recessive	6q25.2-q27	*Parkin*	>100 different mutations (gene dosage alterations and small sequence changes)[53,58]
PARK6	Autosomal recessive	1p35-p36	*PINK1*	40 small sequence change,[71] rarely large deletions[137]
PARK7	Autosomal recessive	1p36	*DJ-1*	10 mutations (point mutations and large deletions)[67,138]
PARK9	Autosomal recessive	1p36	*ATP13A2*	3 different mutations that lead to premature protein truncation[68]
Monogenic	single cases			
PARK5	Autosomal dominant	4p14	*UCHL1* /ubiquitincarboxyterminalhydrolase I	1 mutation found in single family[139]
PARK13	Unknown	2p12	*Omi/HtrA2*	1 point mutation in four families; 1 disease-associated variant[140]
Not assigned	Unknown	5q23.1-q23.3	*Synphilin-1*	1 missense mutation in two patients[141]
Not assigned	Unknown	2q22-q23	*NR4A2/Nurr1*	3 different mutations, 1 of them in coding region[142,143]
Not assigned	Unknown	15q25	*POLG*/DNA polymerase γ	1 family with compound heterozygous mutations[144]

Investigating mechanisms underlying LRRK2 mutation-related PD - collaboration with genetics (*M Farrer, UBC CERC Genetics*)

Imaged over 60 subjects with LRRK2 mutations

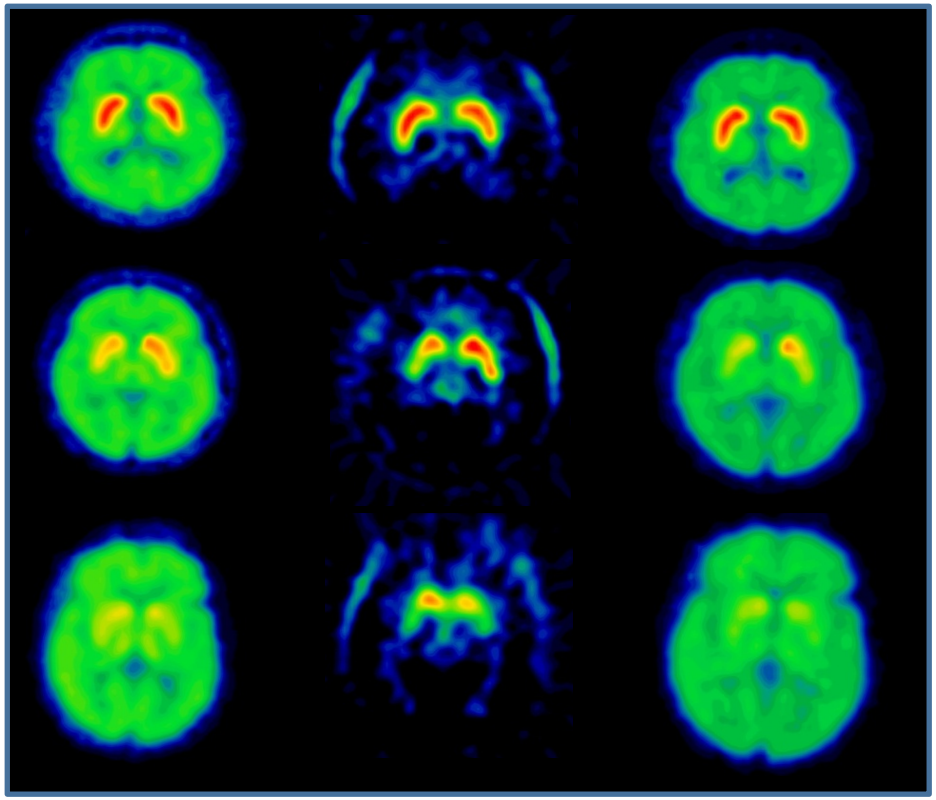
Collaboration with

- US (Mayo Clinic - Z Wszolek)
- Norway (J Aasly)
- Japan

Control

Asymptomatic

Affected

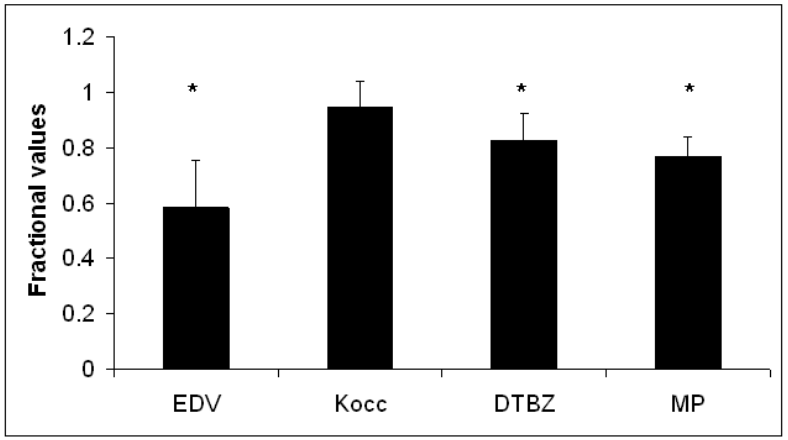


VMAT2 F-DOPA DAT

Dopaminergic deficit observable with PET

Nandhagopal *et al.*, *Neurology*, 2008
Nandhagopal *et al.*, *Neurology*, 2011

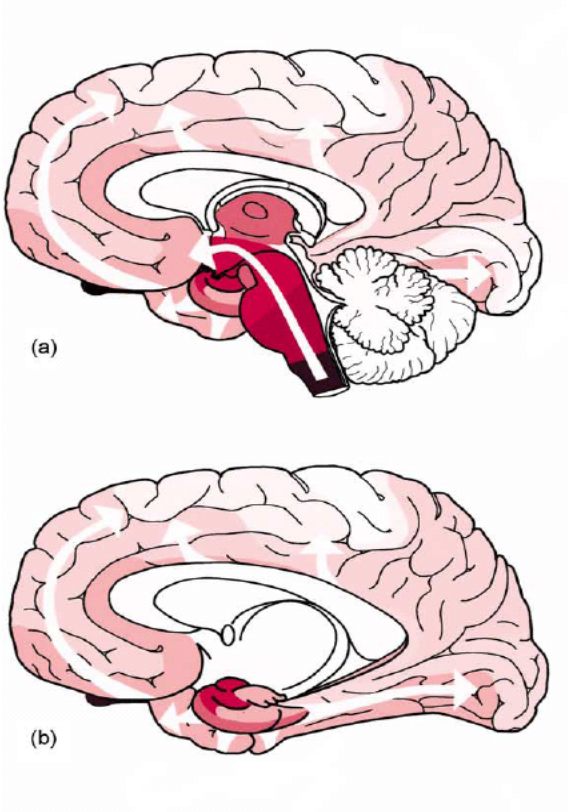
Dopamine turnover (1/EDV) appears to be most affected



Sossi et al. *Mov Disorders 2010*

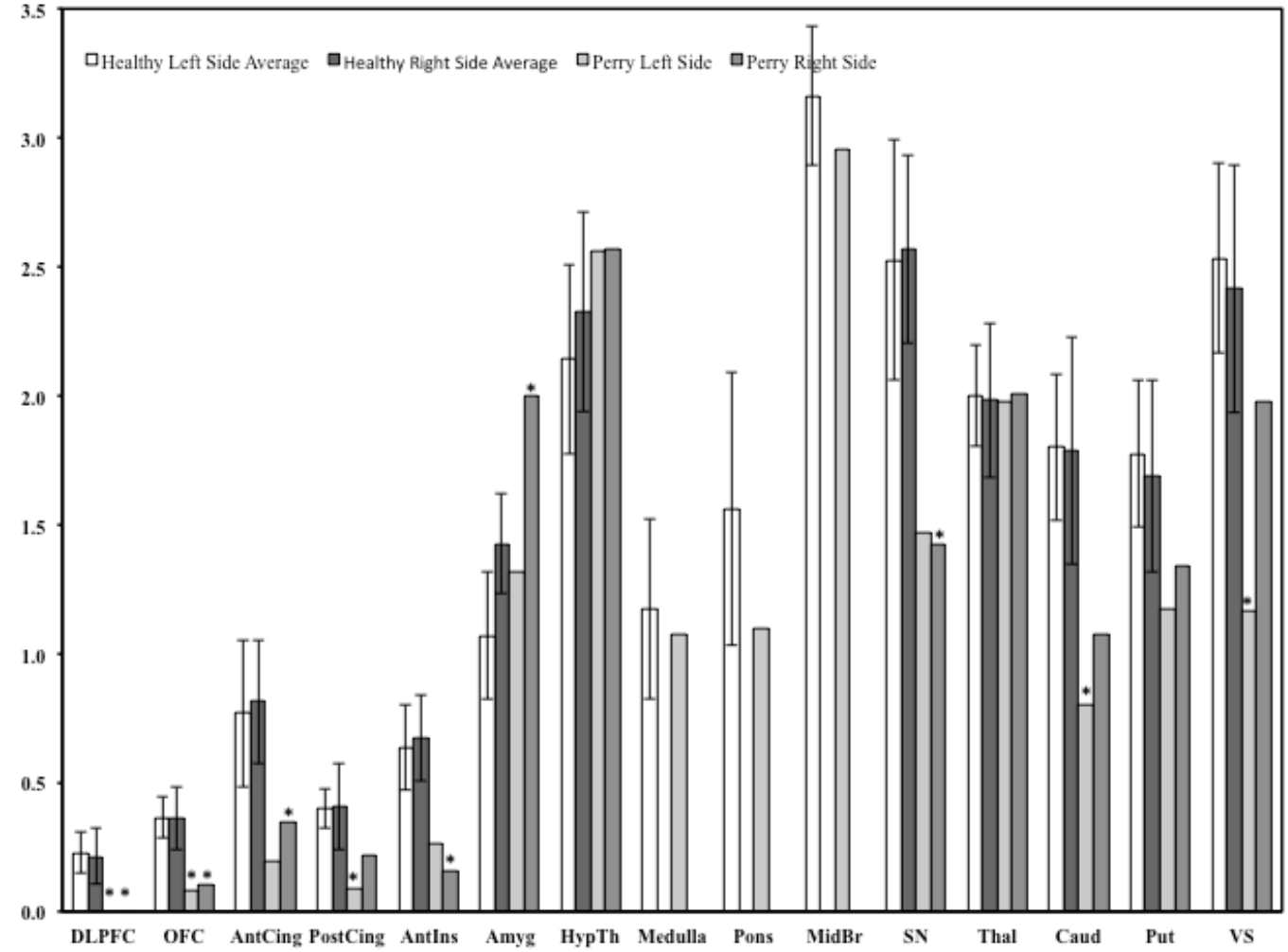
Braak: is PD a motor disorder?

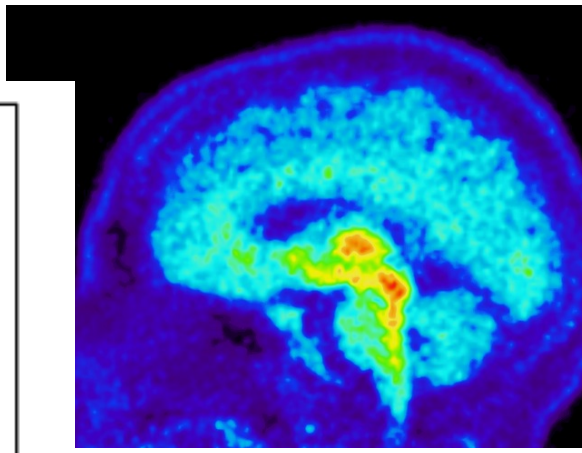
- Olfactory
- Depression
- Sleep Disorders
- Autonomic

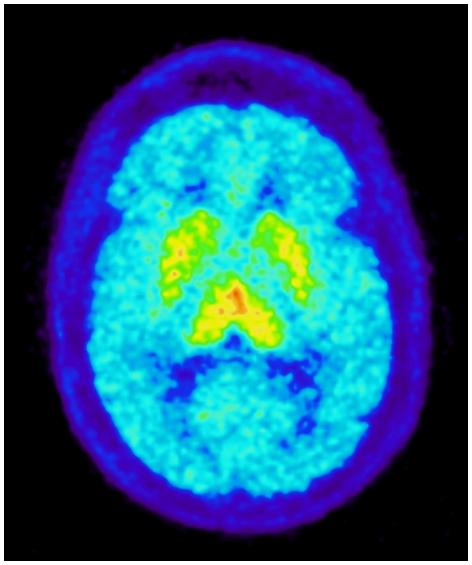


Does it even start in the brain?

Serotonergic system in PD (^{11}C-DASB) Perry subject

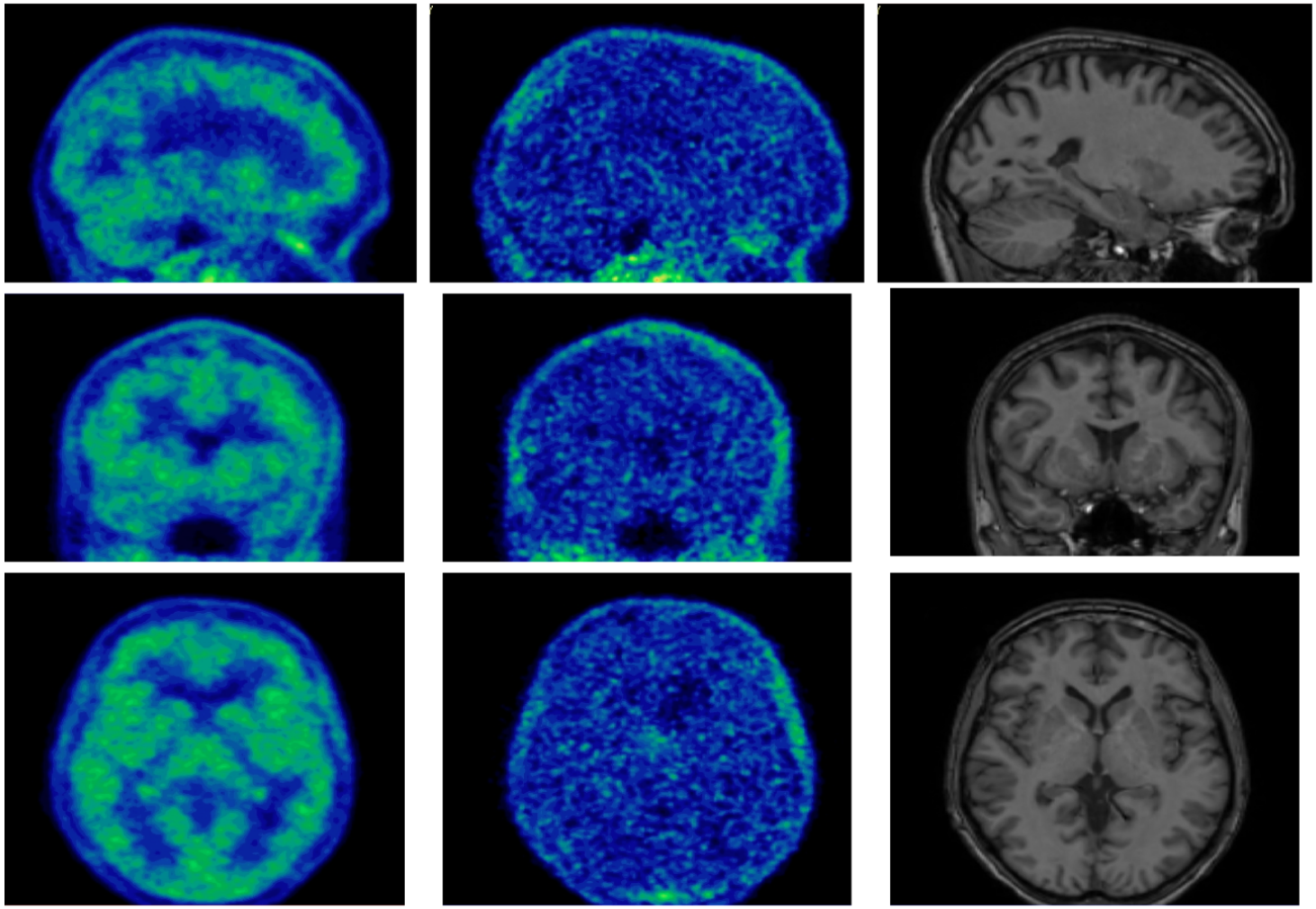






A Cavalho, submitted

Inflammation – ^{11}C-PBR 28



Minutes 0-60 Minutes 60-90 MRI

Dementia

FTD, Mixed dementia (I Mackenzie, R Hsiung)

Vascular dementia (T Lui-Ambrose)

Part of 3 large scale clinical trials

ADNI-GO
Tau-RX *(Efficacy of Tau-RX treatment for AD)*
DIAN

Novel direction being implemented

Traumatic brain injury

tau-imaging tracer PBB3

phenyl/pyridinyl-butadienyl-benzothiazoles/benzothiazoliums
(Maruyama et al Neuron 2013)

Application submitted to GE-NFL

Preclinical imaging

Animal models (CIHR,MJFF)

Rodent

Treatment – imaging interaction

LRRK2 – G2019S

Characterization of the dopaminergic system

Role of inflammatory triggers

Preclinical imaging – Neurodegeneration

Interaction between treatment (pramipexole, levodopa) and imaging markers

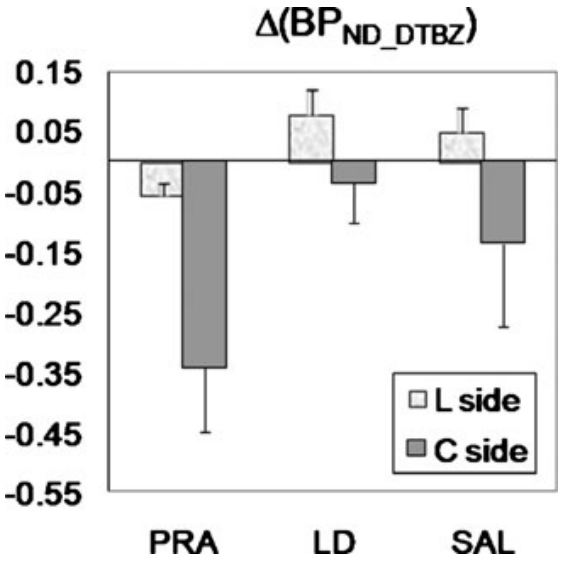


Fig. 1 Changes in BP_{ND_DTBZ} [BP_{ND_DTBZ} (post-treatment) − BP_{ND_DTBZ} (pre-treatment)] for the three treatment groups, pramipexole (*PRA*), levodopa (*LD*), and saline (*SAL*). *Bars* represent standard errors. In the figure, changes are shown for each treatment group separately and are not adjusted for the predicted values (see text)

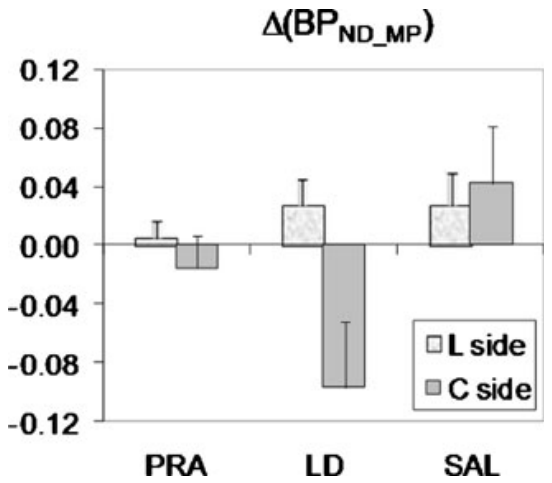
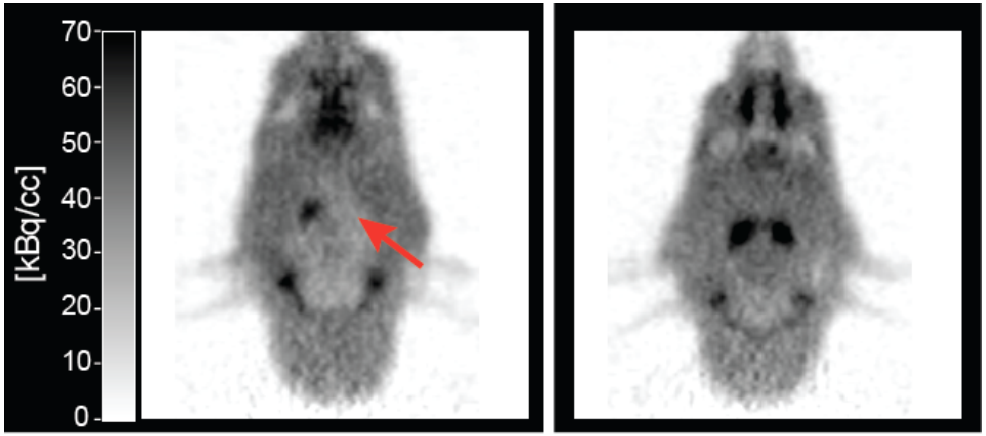


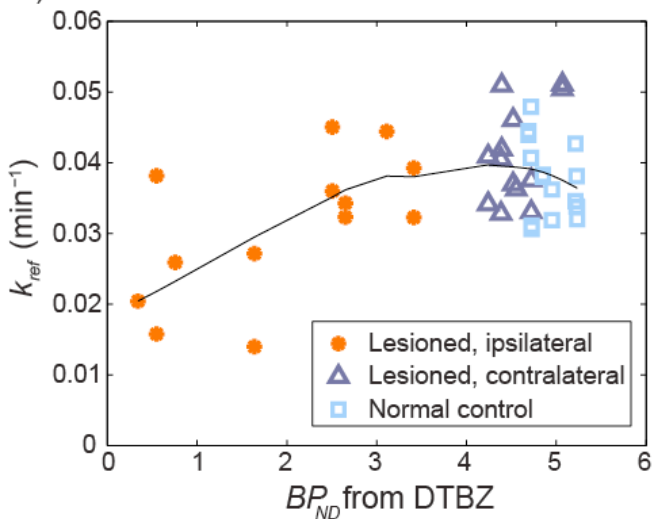
Fig. 2 Changes in BP_{ND_MP} [BP_{ND_MP} (post-treatment) − BP_{ND_MP} (pre-treatment)] for the three treatment groups, pramipexole (*PRA*), levodopa (*LD*), and saline (*SAL*) for the lesioned and control sides. *Bars* represent standard errors. In the figure, changes are shown for each treatment group separately and are not adjusted for the predicted values (see text)

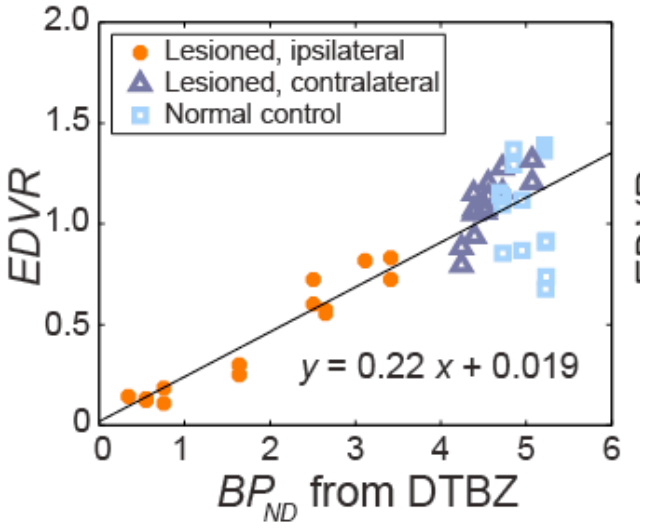
Sossi et al Eur Nucl Med Mol Imag 2010

Development of FD imaging in rats (6OHDA)



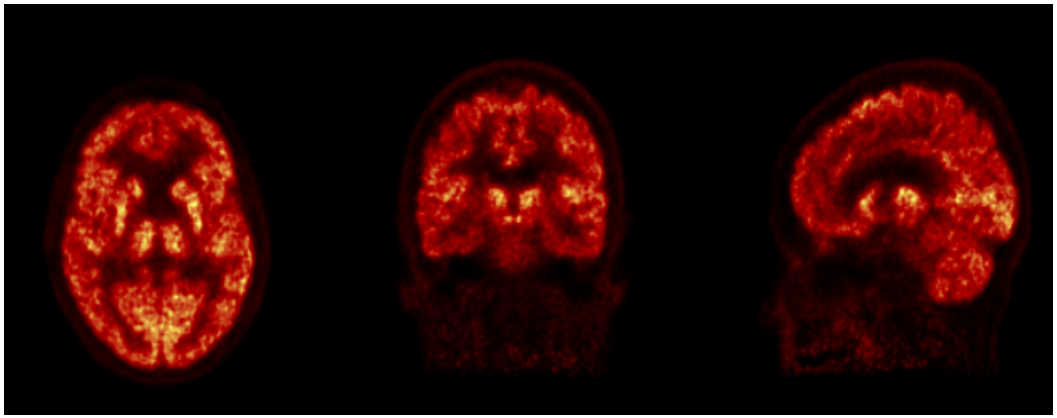
A)





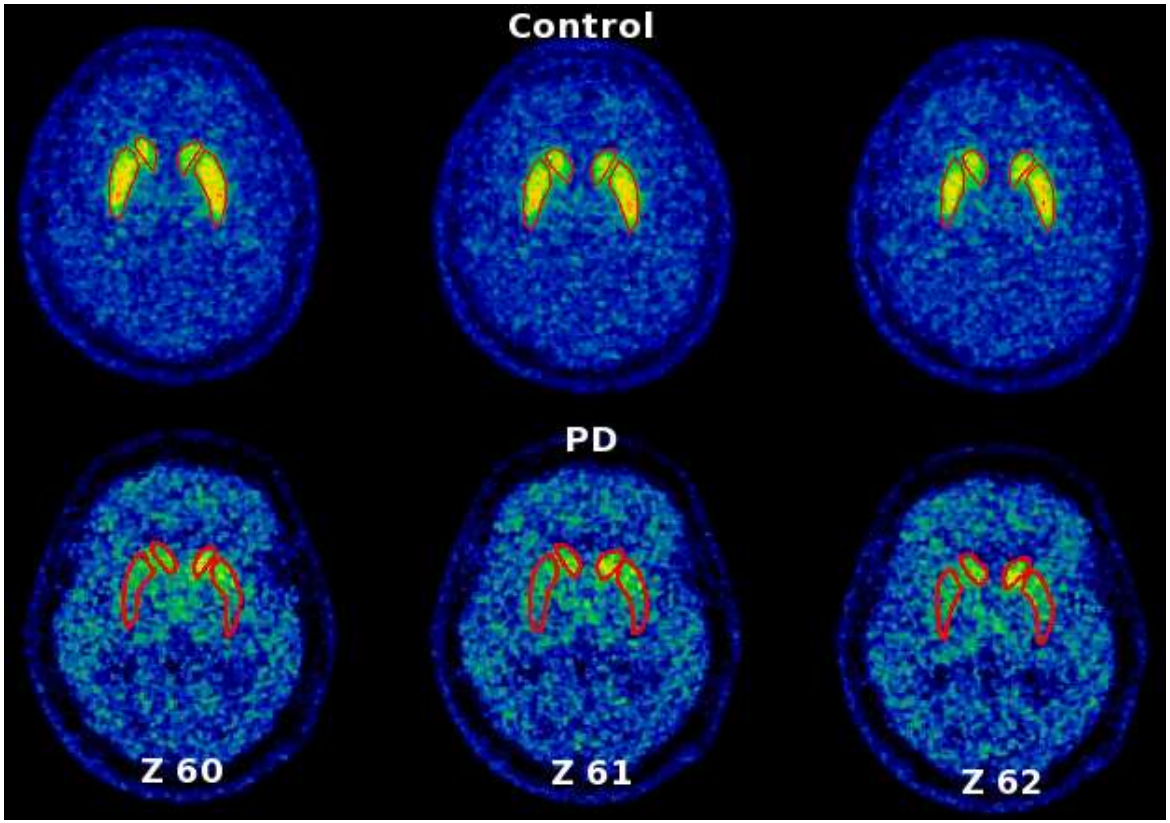
Walker et al JCBFM 2013

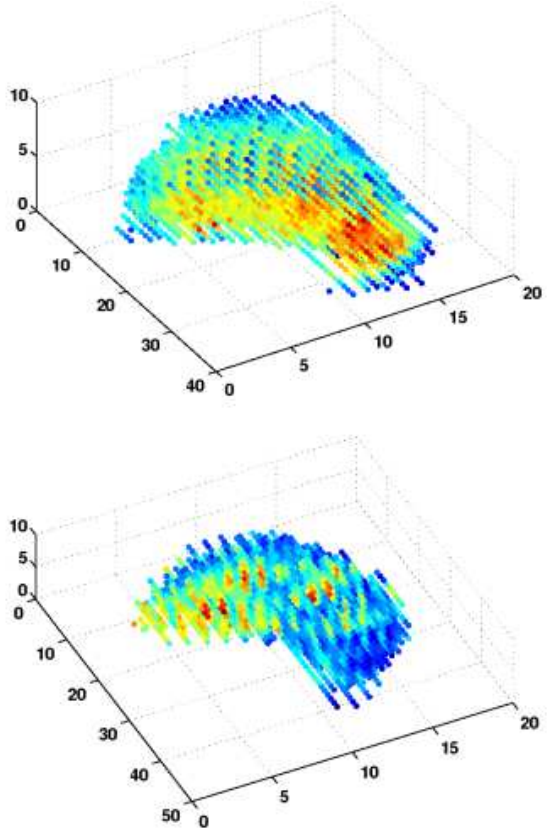
Instrumentation

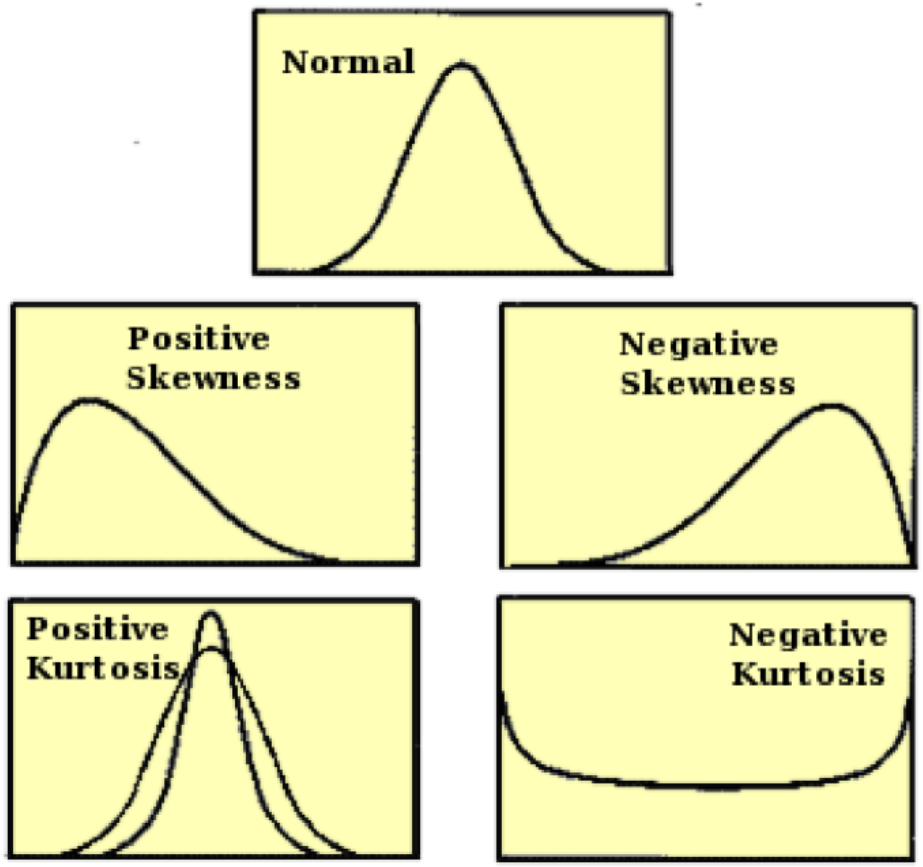


HRRT data set

MRI based shape and texture analysis of PET data – Moment invariants







Use moment invariants (MI) to describe shape.

MIs are combinations of central moments designed to be invariant to geometric changes (scale, rotation, etc).

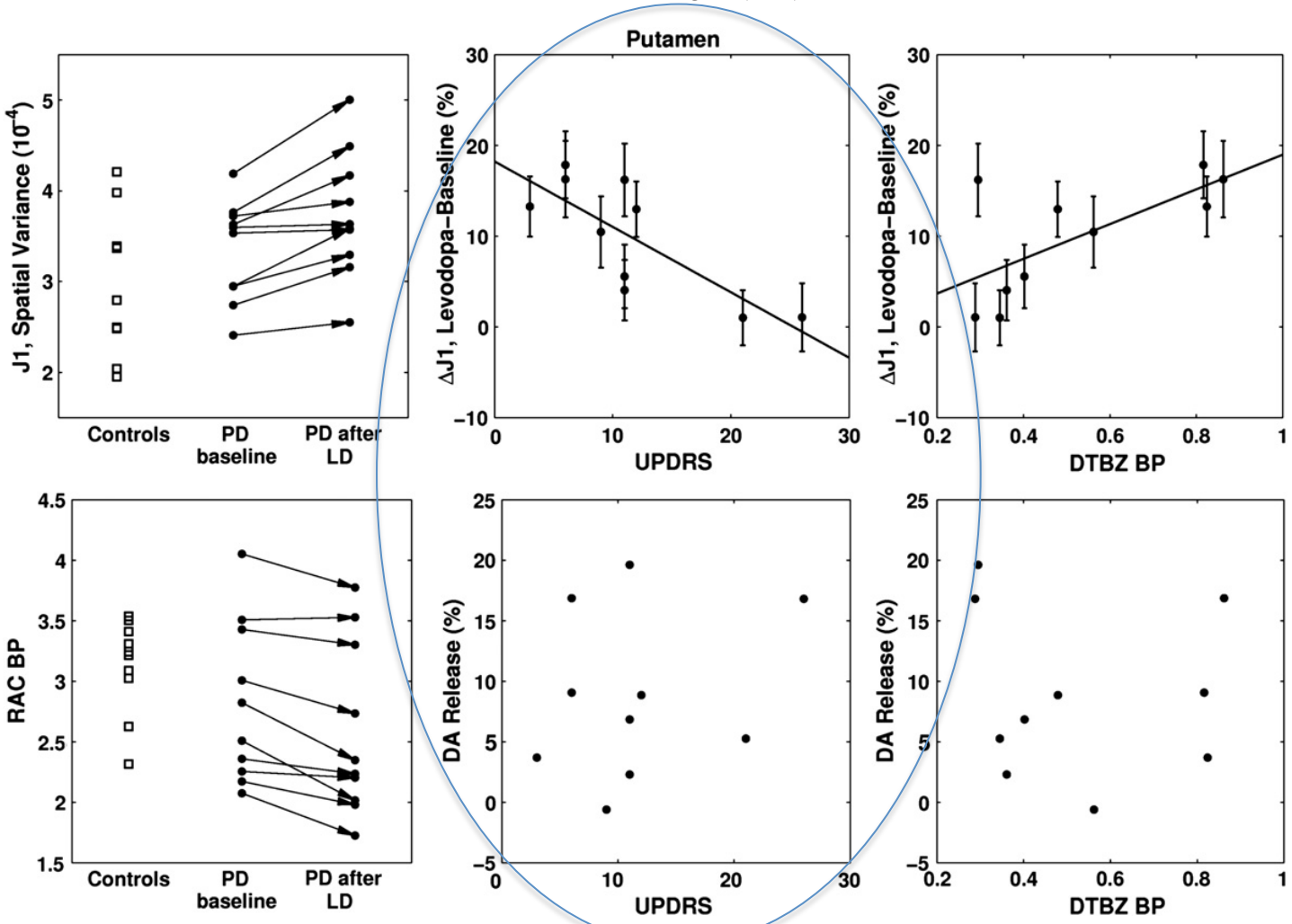


Fig. 5. Levodopa-induced changes in the putamen. Left: RAC J1 (top) and BPND (bottom) values for healthy controls, PD patients at baseline and PD after LD. Middle: levodopa-induced changes in RAC J1 (top) and DA release (bottom) as a function of UPDRS. Right: levodopa-induced change in RAC J1 (top) and DA release (bottom) as function of DTBZ BP. Values for left and right sides are shown separately. Regression results are shown in Table 4.

Gonzales et al, Neuroimage 2013

Active funded projects

1. Overlap Syndromes Resulting in Dementia / Studies of Patients with a High Genetic Risk of Developing Parkinson's Disease/ Studies on the Natural History of Sporadic and Inherited Parkinson's Disease (PI. AJ Stoessl- funding CIHR, PARF, Cundill)
2. Evolution of PD (Previously the pilot study Do Patients with Isolated REM Sleep Behaviour Disorder Without Clinical Evidence of PD have Sub-Clinical Evidence of Dopamine or Acetylcholine Dysfunction) (PI. AJ Stoessl- funding CIHR, PARF, Cundill)
3. Imaging Neuroinflammation in LRRK2 Rat Models of Parkinson's Disease. CIHR P.I. Sossi
4. Relationship between serotonergic innervation, dopaminergic deficit and levodopa induced dopamine release patters in OD treatment-related complications; a longitudinal imaging study. CIHR P.I. Sossi
5. Investigation of neuroinflammation in LRRK2 mutation carriers using positron emission tomography. MJFF P.I. Sossi
6. Clinical, pathological, genetic and biomarker studies of frontotemporal dementia. CIHR P.I. I Mackenzie
7. Multi-tracer positron emission tomography (PET) functional imaging as a tool to assess the relevance of rodent LRRK2 models to the human neurochemical phenotype associated with LRRK2 mutations related Parkinsonism. MJFF P.I. Sossi
8. Increase in dopamine turnover as a manifestation of LRRK2 mutation. MJFF P.I. Stoessl
9. Investigation of treatment related compulsive behaviours and impulse control disorders in PD *CIHR* P.I. V Sossi
10. Development and validation of a new adrenergic receptor CIHR P.I. D. Doudet
11. Role of exercise in PD Cundill Foundation P.I. Stoessl (partial funding)
12. Dian-TU study: Clinical trial on carriers of mutations causing early onset Alzheimer R Hsiung – currently in the process of site qualification
13. Tau-RX, P.I. R Hsiung
14. A PET Study of NE Transporter Occupancy and Symptom response in Depressed patients treated with Quetiapine XR AZ, P.I. L Yatham
15. Role of exercise on cognition and function in seniors with vascular cognitive impairment CIHR (P.I. Teresa Liu-Ambrose)
16. Alzheimer's Disease Neuroimaging Protocol – Grand Opportunity - ADNI-GO (P.I. R Hsiung, National Institute on Ageing)

Need for ~ 100 subjects/year and ~ 400 scans/year (300 in humans) are required to accomplish the studies

Performance – in the last 4 years:

~ 130 papers

$14.5M funding

Conclusions

- There is a strong and successful brain imaging community
  UBC considers brain-related research an area of priority
  (Brain Research Center, Center for Brain Health)

- TRIUMF is essential for radiotracer production

- TRIUMF could become a leader in novel brain-disease specific radiotracer development.

- Proximity to rodent imaging equipment facilitates interaction with industry.