PET studies in Parkinson's Disease Dyskinesias and Dementia

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MD(Res) Thesis

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ABSTRACT

Parkinson's disease is the second most common neurodegenerative disease in the world. The initial motor symptoms are well controlled with replacement therapy with levodopa. Slowly over time the patients run into problems both due to the inexorable progression of the disease and also due to complications of the drugs itself. The two most common disabling complications that are difficult to treat are levodopa-induced-dyskinesias and dementia. Although there have been extensive research, the pathophysiology of both these conditions are still unclear. Unsurprisingly treatment options are limited for both these conditions.

From the dyskinesia research, studies with animal models of Parkinsonism have shown abnormalities in glutamate neurotransmission but the role of glutamate in causing dyskinesias in PD patients in still unclear. Using a novel PET tracer [11C]CNS-5161 we demonstrated in vivo an increased activity of NMDA-glutamate receptors specifically in the motor areas when levodopa was administered to dyskinetic PD patients. On the other hand non-dyskinetic PD patients had the opposite effect i.e. reduction of glutamate channel opening with levodopa administration. Our study implicates glutamate overactivity to be a major factor in causing LID and supports the use of anti-glutamate agents in PD dyskinesias.

In PD Dementia patients the pathophysiological basis of the disease is still unknown. Concomitant AD type amyloid pathology, cortical Lewy disease , inflammation and biochemical neurotransmitter defects have all been thought to cause the disease. Using specific PET tracers, [11C]-PIB which bind to amyloid , [11C]-PK11195 which bind to activated microglia associated with inflammation and [18F] FDG which measure neuronal dysfunction we showed increased cortical microglial activation and glucose utilisation in both PDD and PD patients but more so in PDD patients implying ongoing disease activity with inflammation playing an important role relatively early in the disease. The conspicuous absence of [11C]-PIB uptake in the majority of PD patients makes amyloid pathology quite unlikely in causing the disease. Our study favours treatment strategies to reduce microglial activation relatively early in the disease compared to anti-amyloid therapy in PDD.

Thus this research provides a pathophysiological basis for both PD dyskinesias and dementia and does open up avenues for further treatment strategies.

Declaration of Originality

This work has been done by myself under the supervision of Professor Brooks.

There are two studies and my contribution is clearly delineated in the following page

All other work mentioned in this thesis have been appropriately referenced.

MY CONTRIBUTION TO THE TWO STUDIES IN THIS RESEARCH

1. GLUTAMATE NEUROTRANSMISSION IN LEVODOPA-INDUCED DYSKINESIA STUDY

A. Recruitment of all 18 patients from clinics
   8 PD LID (Parkinson's disease and dyskinesias)
   10 PD NLID (Parkinson's disease without dyskinesias)
   2 healthy volunteers

B. Consent and clinical assessment

C. Scanning of each of the 8 PD LID patients (One MRI Brain and Two [11C]CNS5161 PET scans – One 'off' and one 'on' levodopa)
   Scanning of each of the 10 PD NLID patients (One MRI Brain and Two [11C]CNS5161 PET scans – One 'off' and one 'on' scan). Three PD NLID withdrew consent and so had the MRI and 'off' scans only.
   Scanning of two healthy volunteers (One MRI Brain and one PET scan each).

D. Analysis of all scans upto the end of kinetic modelling stage with determination of the rate constants, Binding potential and Volume of distribution.
   (Rank-Shaping regularization of exponential spectral analysis (RS ESA) was done by Subrata Bose in our group).

2. PARKINSON'S DISEASE DEMENTIA STUDY

A. Recruitment of 9 Parkinson's disease dementia patients (PDD) from clinics
B. Consent and clinical assessment
C. Neuropsychology assessment
D. Scanning of each of the 9 PDD patients
   One MRI Brain, and three PET scans each – (one [11C] PIB, one [18]F FDG and one [11C] PK11195)
E. Analysis of all scans upto Region of interest analysis.
F. Non-demented PD patients and contorls were studied by Dr P Edison in our group.

ACKNOWLEDGEMENT

The work of this MD thesis was done in the Department of Neurosciences, Cyclotron Building, Imperial College London.

First I would like to thank Professor Brooks for all his patience, support and guidance during the entire period of this research. Without his guidance this research would have been directionless. In addition to steering this research project he acknowledged my aspirations and helped me build my career accordingly.

The Department itself is world renowned for good quality research in Neurosciences and PET and I am proud to have worked here.

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I would like to take this opportunity to thank Dr Alexander Hammers for his help and guidance in this work. A special word of thanks to Nicola Pavese in our department for his support in helping me write up the thesis. Also a big thank you to Dr Paul Edison for his help. I would take this opportunity to thank the staff at the PET centre , Andy, Hope, Andreanna, and James for their help. I am extremely indebted to my patients for taking part in the study and lending support to research in Parkinson's disease.

Lastly, I cannot do without mentioning my family without whose help I could not have completed the work. I dedicate this work to my mother for her help and support for my research but could not see the end as she succumbed to a sudden stroke at a crucial stage of this work.

I would also express my gratitude to my wife, Julekha for her endurance in helping me to write up the thesis. I would also thank my dad for his courage in putting me back at work after my mother's demise. And the last but not the least my two daughters', Zayna and Zoeya, to allowing papa to be away from them and finish this work.

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. It is a slowly progressive disease and is a leading cause of disability suffering worldwide. Parkinson's disease is named after James Parkinson who gave the first detailed description of the disease in "An Essay on the Shaking Palsy" in 1817. The initial presentation is usually with a motor disorder of bradykinesia, rigidity, tremor and postural instability. It was not until the second half of the twentieth century that the pathological basis of this disease came to light. The loss of the pigmented dopaminergic neurons of the substantia nigra pars compacta was thought to be the neuropathological hallmark of Parkinson's disease and this led to the discovery of Dopamine replacement therapy with levodopa . It was a revolutionary drug as it improved the motor symptoms dramatically. Since its introduction in the late 1960s, levodopa has been the most widely used and most effective drug for the symptomatic therapy of Parkinson's disease.

However the benefits of this drug are short-lived and chronic treatment leads to complications of involuntary movements termed 'dyskinesias'. One hand the underlying disease progresses relentlessly leading to further dopaminergic neuronal cell death with consequent increased need of dopamine and on the other hand replacement therapy with levodopa leads to even more problems. All other treatment options with drugs and surgery either have significant side effects or are invasive.

Another long-term complication of Parkinson's disease is dementia. This is a major non-motor complication unlike dyskinesia and is not responsive to levodopa treatment. Most importantly, these PDD patients have a significantly high morbidity and mortality compared to PD patients without dementia.

Both these complications, dyskinesias and dementia, are very disabling for PD patients and frustratingly the treatment options are very limited. Over the last two decades a number of areas of research have been done in both dementia and dyskinesias but with very little concrete answers.

From the research done in PD dyskinesias, animal studies in rodents and primates there has been increasing evidence that non-dopaminergic mechanisms are involved in the pathophysiology of dyskinesias. In particular abnormal glutamate neurotransmission have

been implicated by a number of studies. Using a novel tracer [11C] CNS 5161 PET it is possible to study the glutamate receptor function. One aim of this dissertation is to investigate glutamate neurotransmission in PD and study its significance in the causation of LID.

From the research in PD dementia a number of post-mortem studies have found Alzheimer's type amyloid deposition in PDD brains. Moreover studies in Alzheimer's disease have shown that amyloid plaques can be imaged with a special tracer. In addition abnormal glucose metabolism and inflammatory changes have also shown to be in Alzheimer's disease and also in Parkinson's disease without dementia. These studies have been made possible by the use of various PET tracers that specifically look at these processes. I also aim to find whether amyloid load is high in Parkinson's disease dementia and whether there is abnormal glucose metabolism and inflammation are present in PDD.

The aims of this dissertation are to

(a) Study the glutamate and adenosine binding in PD LIDs using two novel PET tracers [11C] CNS 5161 and [11C] SCH442416 which bind to the receptors of the above chemicals respectively.

(b) Using PET to look at the amyloid binding in PDD and correlate it with glucose metabolism and inflammation in the same areas.

1.1.1 POSITRON EMISSION TOMOGRAPHY (PET)

1.1.2.1 INTRODUCTION

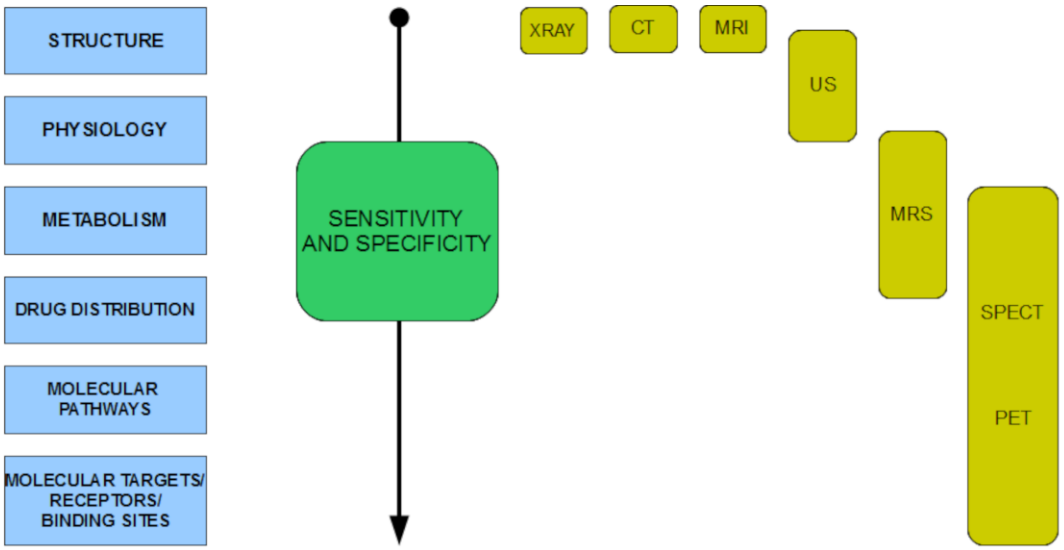
PET is a powerful and versatile imaging tool which allows in vivo examination of brain functions. It has made invaluable contribution to neuroscience research by giving us not only functional information but also quantitative data of cerebral blood flow, metabolism, and receptor binding. PET science has now gone beyond the boundaries of being used only in the research context. Its use has overflowed into the clinical domain and is being increasingly used to help with the diagnosis, monitoring and assessing response to treatment of a number of neurological conditions. But it's use in clinical neuroscience is restricted compared to oncology because of the high costs and need of enormous support facilities of having a cyclotron, PET scanner and radiochemical laboratories.

PET provides unbiased in vivo measurement of local tracer activity at a very high sensitivity. This unique property is of this form of imaging gives a distinct and crucial advantage over the others. When PET was introduced in medicine the first organ of major interest was the brain. Since then brain PET imaging has been recognised as a powerful and versatile tool in research whereas it's potential for clinical use as a diagnostic tool remains unexploited. Brain PET has been classified as a method of functional imaging. In this area it faces a tough competition from SPECT and firm which are less expensive and easily available. PET is not only functional but also quantitative. It provides measurement of physiological parameters locally in the brain tissue at a spatial resolution far beyond the capabilities of other techniques. Hence it's enormous success in the research field. Although functional changes that precede structural damage can be best demonstrated by PET it is important to note that these changes are subtle and does depend upon the physiological state of the brain during the time of the actual study. However when combined with a specific and detailed clinical assessment this form of imaging can yield extremely valuable information.

PET can measure local physiological processes. It can cerebral blood flow and energy metabolism which are the basis for using 18F-flouro-2-deoxy-D-glucose (FDG) and 15[O]-water.

Molecular techniques are now not limited to the test tube and have made their way into the domain of PET imaging. Many PET tracers bind specifically to certain receptors or

metabolised by specific enzymes and therefore are well suited for quantifying their activity and local expression. In the cyclotron facility, positron emitting radionuclides are incorporated into naturally occurring chemicals, metabolites, pharmaceuticals, or analogs of such compounds. The regional distribution of the positron-emitting compound is recorded by PET as a function of time after tracer administration. By simultaneously measuring radioactivity concentrations in arterial blood and in brain, the dynamic PET recording can be converted into a parametric image, in which the magnitude of physiological variables in each image element (voxel) is calculated by means of appropriate tracer kinetic modelling methods. The studies in the present thesis focused on Parkinson's disease dyskinesias and dementia and hence the focus will be in the imaging techniques for these conditions after going through few basic concepts in PET.

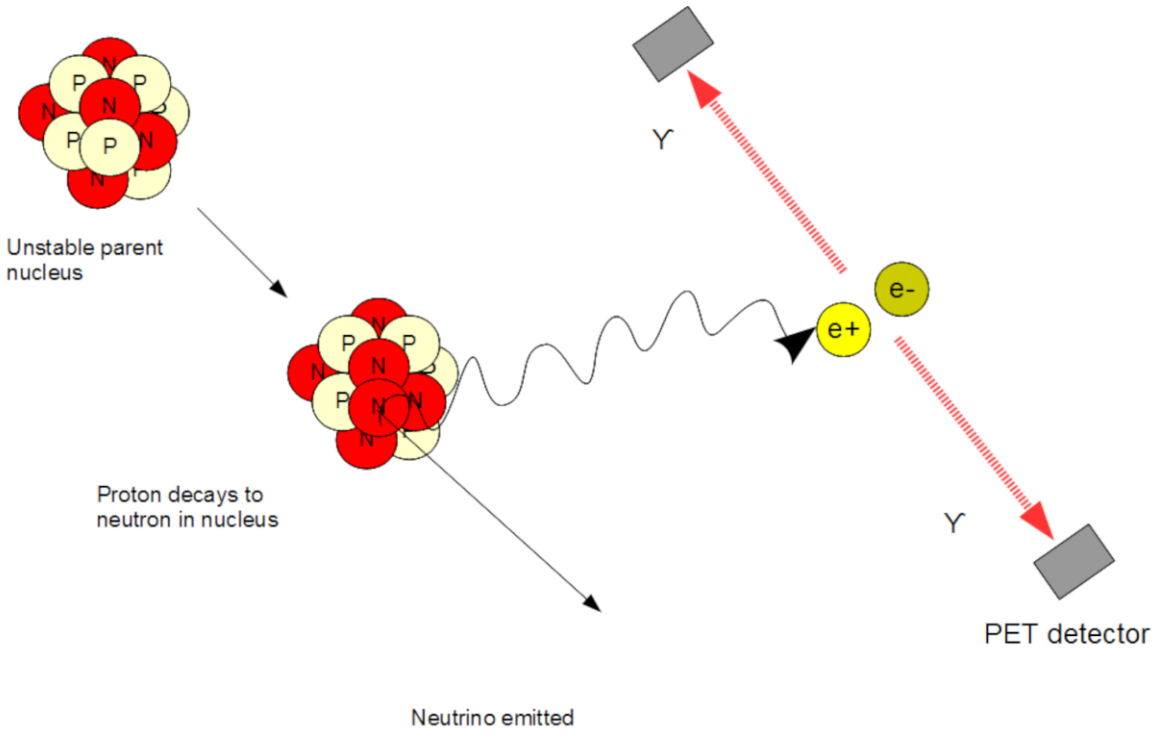


Spectrum of medical imaging. The sensitivity range covers from millimolar (top) to picomolar (bottom). X-ray, CT and MRI give accurate structural information with high resolution. Nuclear imaging techniques (PET and SPECT) have lower resolution but offer pharmacokinetic and pharmacodynamic information.CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound imaging; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; SPECT, single photon emission computerized tomography. Adapted from: Price, P; PET as a potential tool for imaging molecular mechanisms of oncology in man; Trends Mol. Med; 2001, 7(10): 442-446.

The positron is the anti-particle of electron and its charge is positive. Positrons are emitted from unstable nuclei which are proton-rich. The spontaneous decay of a positron emitter produces a positron, which travels a certain distance (depending on its energy) to finally react with one electron of a surrounding atom. This process is called annihilation; as a result, two gamma rays are emitted (511 keV each, emitted at 180º to each other, see Figure below). The generation of these gamma rays is the basis of positron emission tomography. When a tracer containing a positron emitter is administered to an organism, the high-energy gamma rays

produced, which have a high penetration power, escape from the body and are detected by scintillation crystals.

Scintillation is a process by which the energy deposited by the gamma ray is converted to optical photons. These scintillation photons are collected at the rear base of the crystal and then converted to an electrical signal and amplified by the photomultiplier tubes.



Positron annihilation reaction

Diagram to show a Positron annihilation reaction - A positron(e+) and a neutrino ν_e are emitted from the nucleus by the β+ decay

Picture of the ECAT+ scanner with the flat panel removed

The state of the art positron camera is a complex radiation detection technology product combined with a relative large computing power for data acquisition and image reconstruction.

The basic detector in a modern PET camera is a BGO detector block divided into 8x8 sub-detectors and read out by 4 photomultiplier tubes (PMT). By adding and subtracting the individual signals of the PMT's the scintillating sub-detector in the BGO block can be identified.

Around 70 blocks will form a ring and 4 of these rings can be added to get an axial field of view of approximately 15-16 cm. In this way 31-63 planes are imaged simultaneously with a spatial resolution of 4-7 mm FWHM depending on the specific design of the tomograph. The septa between the adjacent sub-detector rings can also be retracted creating a much higher sensitivity in this 3-D mode at the cost of a larger scatter fraction. With the present generation of positron cameras the singles count rates that can be managed are in the order of over 50,000,000 counts per second resulting in coincidence count rates of over 500,000 per second.

1.1.2.2 BASIC CONCEPTS OF POSITRON EMISSION TOMOGRAPHY

SPATIAL RESOLUTION :

The spatial resolution depends on the actual detection of the exact LOR along which a positron emitting radionucleotide can be found. The spatial resolution depends upon the Positron range, non-colinearity, crystal dimensions and block effects.

a) Range

The range of the emitted positrons is different for each radionuclides.The maximum energy of the positron emitted is typical for each radioisotope. Since the surplus in energy has to be divided between the positron and the neutrino there is a continuous energy spectrum for the positron up to the maximum energy. The mean energy of the positron is roughly 40% of the maximum energy. So there is always a finite distance between the place of decay and place of annihilation. For a radionuclide like 18F, with a low maximum energy of 0.635 MeV, the maximum positron range in tissue (water) is 2.3 mm. The mean range in water is 0.6 mm. Nearly all other positron emitting radionuclides have a larger maximum energy. It is the direct distance travelled by the positron from the decaying atom to the location of the annihilation event. The range is directly proportional to the energy of each emitted positron. As shown in the graph 18F and 11C are at the lower end of the spectrum of ranges. The mean range may vary by millimetres but it may be enough to cause a significant error in the resolution. For 18F contribution of positron range to spatial resolution is ~ 0.15 mm

b) Non-colinearity

Non-colinearity is independent of the PET radionuclide. The two annihilation photons may deviate from the LOR depending on their momentum as shown in the diagram. The magnitude of error increases linearly with the diameter of the scanner.

c) Crystal dimensions

The crystals used to detect the incident gamma rays have unique properties that can alter the resolution of the PET scanner. A better resolution is possible with crystals having these characteristics

- Higher density
- Higher atomic number
- Shorter decay time
- Higher light output
- Good energy resolution

d) Block effects depend on

Multicrystal response

Two uncorrelated photons are contemporarily detected in two crystals

Scatter inside crystals

The incoming photon is scattered in neighbouring scintillators

Crystal dimensions and depth of interaction

A photon may not be confined and lose its energy also in neighbouring crystals

Spatial resolution is measured as Full width half maximum (FWHM)

$$FWHM = k_R \sqrt{FWHM_D^2 + FWHM_N^2 + FWHM_P^2 + FWHM_B^2}$$

$FWHM_N$ = Non-colinearity ~ 1 - 2 mm

$FWHM_D$ = Finite dimensions of the crystal ~ 2 - 4 mm

$FWHM_P$ = Positron range ~ 0.5 – 2 mm

$FWHM_B$ = Block effects ~ 2- 3 mm

Characteristics of the scanner used in this research

System	Det	Axial (cm)	Res (mm)	Sens-2D (kcps/kBq/ml)	Sens 3D
ECAT HR+	BGO	15.5	4.6	5.4	24.3

The imaging volume is surrounded by a ring (commonly a series of rings) of detectors which consist of scintillating crystals coupled to photomultiplier tubes (PMTs). With all PMTs connected to an annihilation coincidence detection circuit, an annihilation event is endorsed if two detectors provide signals within a set coincidence time window. For conventional scanners based on bismuth germanate (BGO) scintillators, a typical time window is 12 ns (Bushberg et al., 2002) . This length in window is due to a long light decay, which has been surpassed by a new candidate:LSO (with a decay time 7x shorter and 4x light output).

Dead time

In PET systems there is a minimum amount of time that the system takes to process one piece of information before going onto the other. This is known as the 'dead' time.Since radioactive decay processes are random it is likely that successive events will occur and these may not be detected by the system. The dead time will vary between different systems according to their design and architecture. There are different sources of dead time. One is the integration time that is the time spent in integrating the charge from the photomultiplier tubes. So there may be a pulse pile up if the new photon deposits energy in the detector crystal while the charge from the previous event is being integrated. This might lead to either a rejection of both events or an altered summation of both. There is also a 'reset' time when the sub-system is unable to accept any further information. Multiple coincidences occurring at the same time window may be rejected contributing to the dead time. Processing the coincidence may also take time during which no new coincidences will be registered leading to increases in the dead time.

Dead time measurement for a particular scanner can be done by linear extrapolation from the data of repeated count rate measurements of simple, prompts and randoms with a decaying source. The simplest technique for dead time correction is by creating a look-up table of dead time correction factors. But, dynamic spatial variations in source distribution in the subsets of the scanner preclude the use of this method. Therefore, other sophisticated methods have been implemented. Dead time correction is done in practice by schemes

measuring for each sub-system where the "live time" = (acquisition time x [1- fractional dead time]).

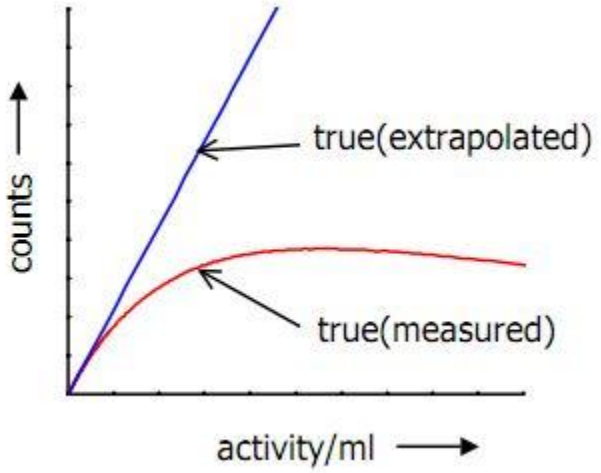


Diagram to show a method of measuring dead time

$\%\ DT = (1 - T / T_{extrap}) \times 100$

% DT : percent dead time

T : measured true events

T_{extrap} : extrapolated true events from low count rate data

NOISE EQUIVALENT COUNT RATE

NEC is the overall ability of the scanner to detect the true events count rate. It defines the true count rate by accounting for the additional noise from scatter and random events.

RANDOMS AND SCATTERS

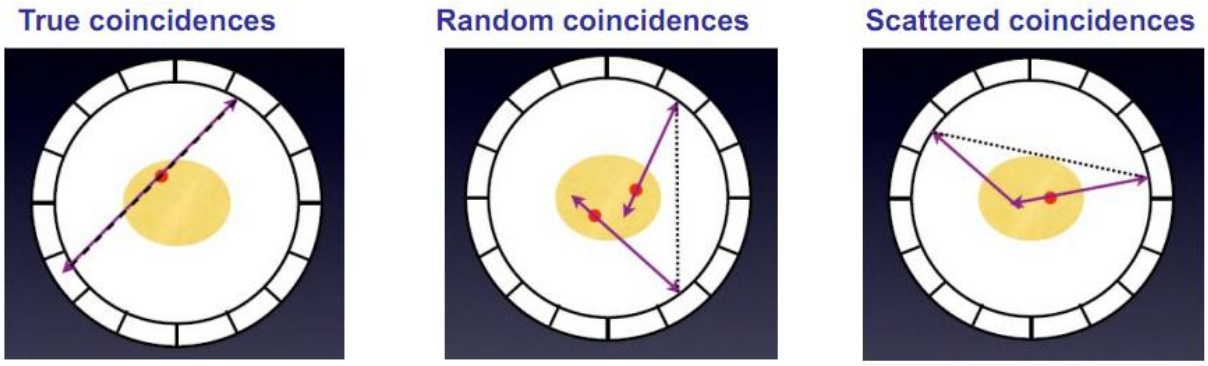
True coincidences occur when both photons from an annihilation event are detected by detectors in coincidence, neither photon undergoes any form of interaction prior to detection, and no other event is detected within the coincidence time-window.

A scattered coincidence is one in which at least one of the detected photons has undergone at least one Compton scattering event prior to detection. This results in incorrect positioning of

the coincidence line. They add statistical noise to the signal. The number of scattered events detected depends on the volume and attenuation characteristics of the object being imaged, and on the geometry of the camera.

Random coincidences occur when two gamma rays from two different annihilation reactions are detected by a detector pair. As with scattered events, the number of random coincidences detected also depends on the volume and attenuation characteristics of the object being imaged, and on the geometry of the camera. Random coincidences also add statistical noise to the data.

In 3D mode the amount of scatter in the signal can become extremely large (Cherry et al 1991, Badawi et al 1996), and accurate scatter correction methods are required.



Attenuation correction

Attenuation is the loss of detection of true coincidence events because of their absorption in the body or due to their scattering out of the detector field of view.

The detected photon pairs are less than the emitted ones due to absorption along the flight. By using an external positron source the individual attenuation can be measured. From a blank scan and a transmission scan an attenuation map can be calculated.

The transmission scan can be performed by external sources because of the coincidence measurement the measured attenuation is independent of the position of the source. To correct for attenuation a transmission scan is performed with the patient in the scanner prior to injection of the radiotracer. Rotating 68Ge/68Ga annihilation source of half life 270 d. can be used as the positron emitting source for the transmission scan which lasts10 minutes. The count rate is measured for all possible lines of response (LOR), the line along which the coincidence event occurred. A blank scan is performed on a daily basis prior to any patient

scans, and the ratio of blank counts to the transmission counts is yields a correction factor which can be applied to each line of response.

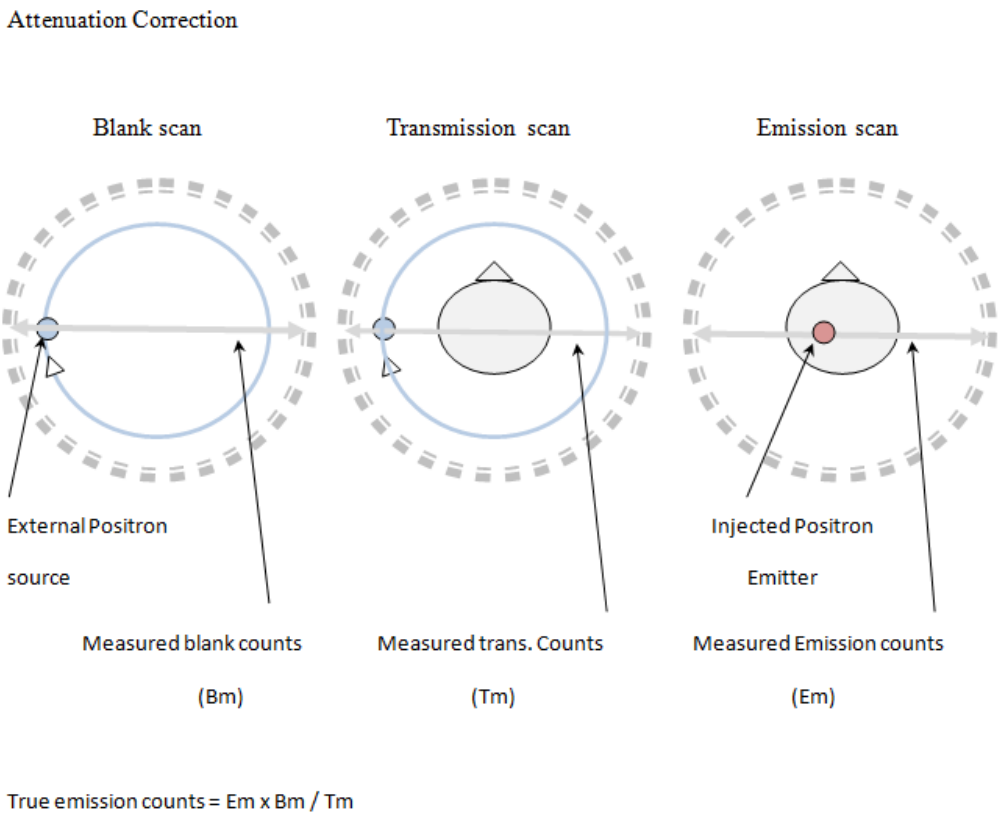


Image reconstruction

Corrections for the above are integrated into reconstruction procedures with reasonable accuracy.

The basis for data normalization is provided by acquisition of a very large number of events from a phantom filled with radioactivity. The attenuation correction for each LOR is constant and can be estimated directly by thresholding to determine the head contour or by fitting transaxial ellipses to the head, which yields reasonable results in brain scanning.

Image reconstruction can be achieved by two approaches- analytical and iterative.

Analytical

Analytical approach is by filtered back projection which is essentially inverting the physical process of projection of the original events into LOR's. It is commonly implemented by the use of Fournier transforms and filtering in frequency space. A more advanced and accurate

technique is Fournier rebinning (FORE) with its relative algorithms which is more appropriate for 3D image processing. Filtered back projection is a linear method of image reconstruction.

Iterative processing

A commonly used algorithm is called ordered subsets expectation maximization (OSEM). OSEM is a non-linear form of image reconstruction. Prior anatomical information with MRI is used to sharpen contrasts between anatomical compartments. Image noise typically increases during iterations together with improvements in image contrast, and can lead to degradation of the quality of image reconstruction. Analysis of statistical image properties may help to optimise the signal-to-noise ratio in reconstructed images (Buvat et al., 2002). Iterative reconstruction can optimize spatial resolution by implementing a statistical maximum a posteriori probability algorithm (MAP) without an increase in noise (Chatziioannou et al., 2000) .

Motion detection and correction

Head motion is a practical problem for even normal volunteers when scanned for long times as in our case for 60 - 90 minutes. It reduces image resolution and correction of this problem is essential in high resolution studies. There are several software packages providing motion correction for coregistration of multiple frames in kinetic and functional activation studies (Bloomfield et al.,2003).

Spatial Normalization

Spatial normalisation is a process of matching individual brain anatomy to a template. Brain atlases based on CT or MRI obtained from normal subjects and registering them in a common co-ordinate space have been developed by several groups. As there are significant differences amongst individual groups it is preferable to have atlases based on multiple subjects rather than single ones. Automatic matching of individual brains to atlas templates is usually achieved by coregistration procedures that allow for translation and rotation (defined

by six independent transformation parameters) , scaling along three dimensional axes (adding three more parameters) and also allowing for linear distortion (affine transformation with 12 more parameters). Non-linear transformations can also be applied to improve coregistration of cortical landmarks (Grachev et al.,1999). A standard brain that is close to the Talairach brain atlas and coordinate system was generated from 305 normal MRI brain scans at the Montreal Neurological institute (MNI). It has then been accepted internationally and is known as the MNI standard brain and can be used as a template on spatially normalised brains.

Standardized uptake rate (SUV)

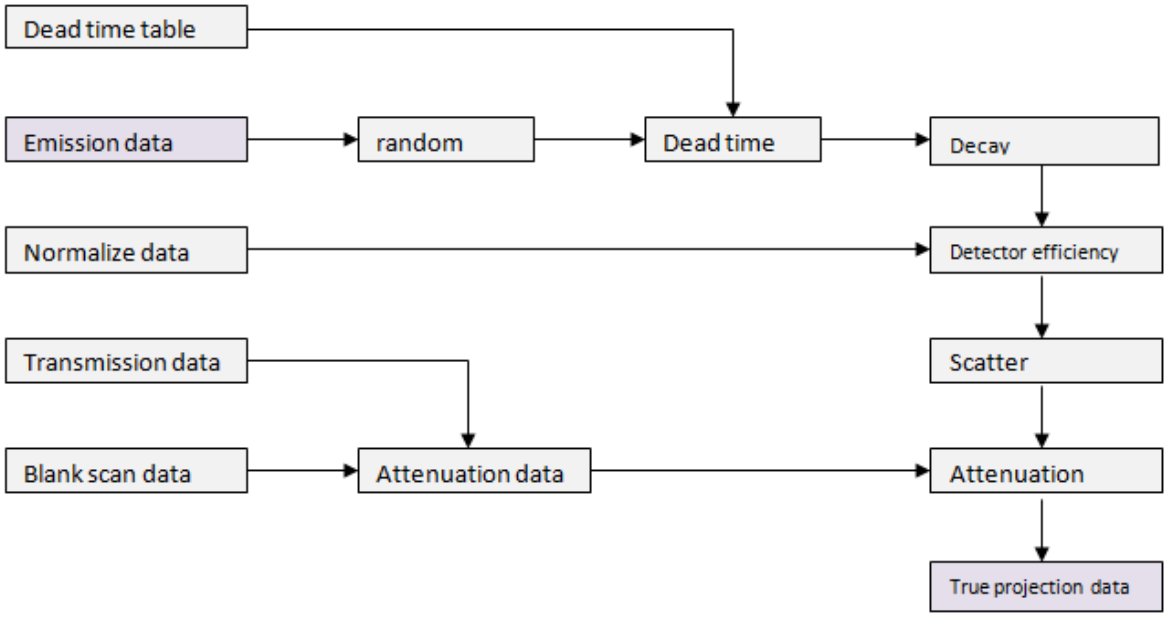
SUV, (also referred to as the dose uptake ratio, DUR) is a widely used, simple PET quantifier, calculated as a ratio of tissue radioactivity concentration (e.g. in units kBq/ml or µCi/g) at time T, C_{PET} (T) and injected dose (e.g. in units MBq or µCi/g) at the time of injection divided by body weight (kg).

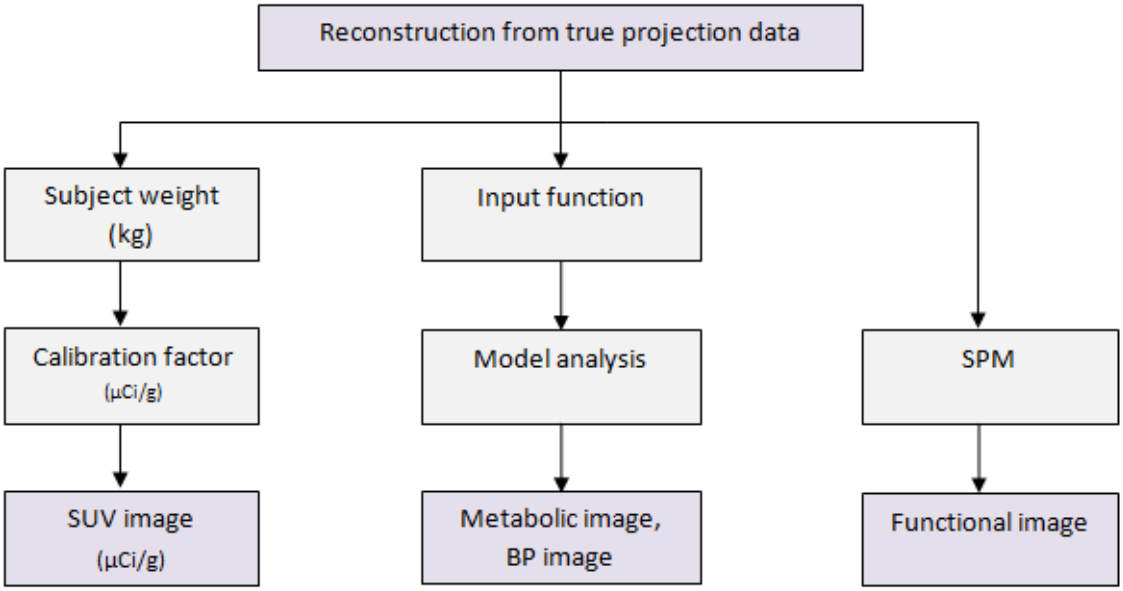
$$SUV_{bw} = \frac{C_{PET}(T)}{\text{Injected dose} / \text{weight}}$$

Instead of body weight, the injected dose may also be corrected by the lean body mass, or body surface area (BSA)

Advantages - Calculation is simple and does not require blood monitoring
Disadvantages- Use for quantitative studies is limited because of major sources of variability and unpredictability (Hamberg et al., 1994; Keyes 1995)

Short algorithm for the acquisition of PET data





Physiological modelling

Quantitative measurement of local tracer activity is done by mathematical modelling of tracer transfer between compartments. These are done to relate local tracer activity to physiological and biochemical procedures. Quantitative models usually require data on the arterial tracer concentration that is available to the brain for uptake – input function. This is done by continuous arterial blood sampling. This includes insertion of an arterial cannula in the radial artery. Blood samples of tracers with low peripheral extraction, such as FDG, can be sampled from a heated dorsal hand vein which provides tracer concentrations close to the arterial ones but in a much less invasive way.

Tracer concentration within each compartment are denoted by Cx where x denotes the compartment (commonly used indices are a: arterial, v: venous). The speed of transfer between compartments are described by transfer rate constants Ki.

K1

It is a composite rate constant which incorporates f1, the flow of plasma to and fro the capillary bed, the passage across the blood-brain-barrier and the concentration profile of the tracer in the capillaries. k 2 is also related to blood flow in the same way as K1. It is reasonable to assume that the ratio of K1/k2 is insensitive to blood flow and also that it is regionally constant.

k 3 incorporates the concentration of available binding sites and depends on the local BMAX of the receptor and the concentration and affinity of competing exogenous and endogenous ligands.

k4 is the dissociation rate constant of the receptor – ligand complex.

Total Volume of Distribution V_D is not affected by the blood flow and can be linearly related to BP as shown below.

$V_{D\,(F)} = \frac{K1}{k2}$

$V_{D\,(F+NS)} = \frac{K1}{k2}(1 + \frac{k5}{k6})$

$V_{D\,(total)} = \frac{\boldsymbol{K1}}{\boldsymbol{k2}}\left(\mathbf{1} + \frac{\boldsymbol{k3}}{\boldsymbol{k4}} + \frac{\boldsymbol{k5}}{\boldsymbol{k6}}\right)$

$V_{D\,(total)} = \mathbf{V_D}_{\,(F + NS)}\,(1 + f_2\,\mathbf{BP})$

$$f_2\,BP = \frac{\mathbf{V_D}_{\,(total)}}{\mathbf{V_D}_{\,(F + NS)}} - 1$$

Plasma Input Models

Plasma input models in PET are often treated as a gold standard (Kety and Schmidt et al.,1948; Mintun et al., 1984). The impulse response function is a sum of exponentials, with the rate of delivery from the plasma, K_1, given by the initial value of the impulse response function. For reversible tissue kinetics the total volume of distribution, VD, is given by the integral of the impulse response function.

For irreversible tissue kinetics the irreversible uptake rate constant from plasma, K_I, is given by the final value of the impulse response function. It may be noted that the final value of the impulse response function is equal to the limiting slope of a Patlak plot (Patlak et al., 1983). This result, as with the Patlak analysis, is independent of the number of intermediate reversible tissue compartments.

Reference Tissue Input Models

Reference tissue models have the advantage that no blood measurements are required and parameters are derived purely from the tomographic tissue data. For reference tissue input models the general form of the impulse response function (IRF) is a sum of exponentials plus a delta function term. When there is no significant blood volume contribution to either the target or reference tissue, the coefficient of the delta function is equal to the relative delivery of tracer to the target versus the reference tissue . For reversible models in both the reference and the target tissues the integral of the impulse response function is equal to $\frac{VD}{V'D}$. If the target tissue is irreversible and the reference tissue is reversible, the normalised irreversible uptake rate constant from plasma , $\frac{KI}{V'D}$, is given by the final value of the IRF. If both the target and and reference tissues are irreversible then the ratio of the uptake rate constants between the target and reference , $\frac{KI}{K'I}$, is given by the integral of the IRF.

There are few similarities between the reference tissue models and plasma input models but the most important is to note that, the integral of the IRF is the VD (volume of distribution) in the input function models whereas for the reference tissue models it is the relative volume of distribution $\frac{VD}{V'D}$.

BP (Binding Potential)

The original definition of binding potential was introduced by Mintun (1984) as the ratio of B_{max} (the maximum concentration of available receptor sites) to the apparent K_D (affinity) of the free radioligand.

$$BP = \frac{k_3}{k_4}$$

One tissue compartment model

K1 is the speed of transfer of the tracer from blood to the brain tissue which depends on the property of the transport process and the concentration of the tracer in the arterial blood Ca (t) which is the input function. It is important to note here that it is the input function of the plasma which is important and the tracer is not usually taken up by the red cells and if it is taken up it does not transfer it to the brain tissue. Plasma input function is determined by centrifugation of the blood sample immediately. From blood to brain tissue the actual tracer transfer is calculated by the product of k_i and C_a (t). The same is true for reverse transport which is the product of k_2 and Ct (t) (tracer concentration in tissue).

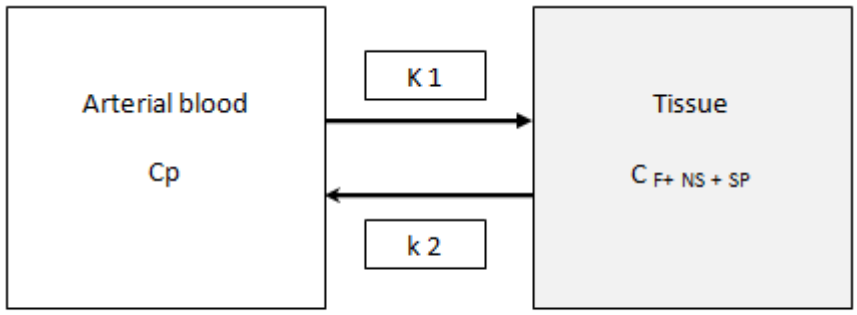
$$\frac{dCt}{dt} = k1.Ca - k2.Ct$$

The simplest compartmental model is the model which has only one tissue compartment. The most popular application of the single-tissue compartment is blood flow measurement by ^{15} [O] labeled water and PET based on the Fick principle (Kety et al., 1951).

The single-tissue compartmental model is sometimes enough for many radioligands to describe their kinetics. The neuroreceptor ligand actually behaves under the two or three

tissue compartmental model; however, practically one tissue compartmental model is sufficient to describe the kinetics of the ligand in some cases.

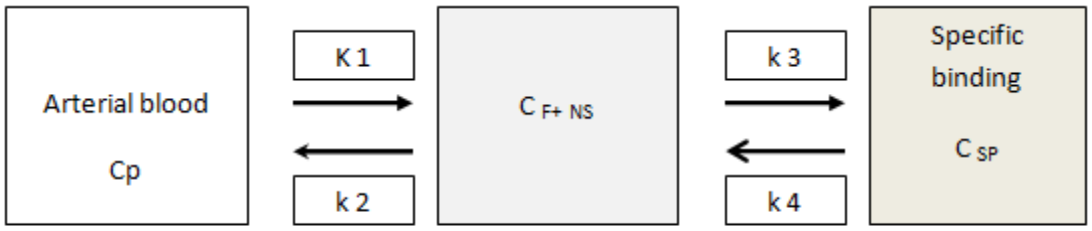
(Koeppe et al., 1991; Watabe et al., 2000)



One tissue compartmental model

VD = $\frac{K1}{k2}$

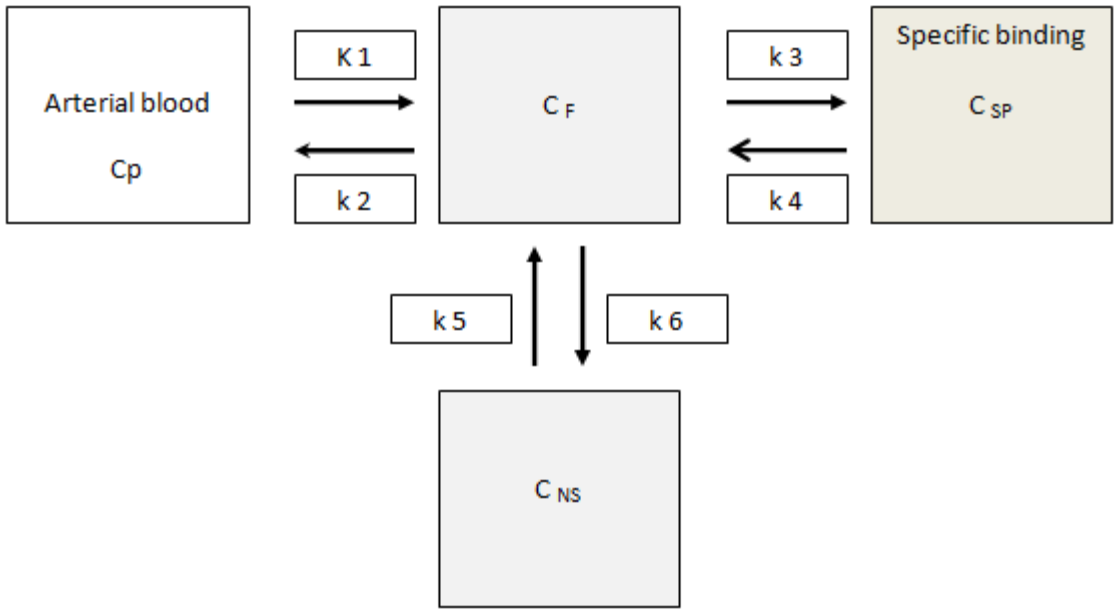
The two tissue compartmental model fits many radioligand tracers well. [^{18}F]FDG is a typical example of the two tissue compartmental model. For many neuroreceptor radioligands, rapid equilibrium between the nonspecific-binding and free compartments can be assumed and the two tissue compartmental model is enough to interpret the kinetics of the ligand (Watabe et al.,2006).



Two tissue or three compartmental model

Two tissue or three compartment model (Reversible). This model consists of plasma, free ligand plus non-specific binding in tissue and specific binding and rate constants k1- k4.

$$VD = \frac{K1}{k2}\left(1 + \frac{k3}{k4}\right)$$



Three tissue or four compartmental model

Three tissue compartmental model or four compartment model (reversible). This consists of plasma, free ligand in tissue, specific binding and non-specific binding and six-rate constants (k1 – k6).

$$VD = \frac{K1}{k2}\left(1 + \frac{k3}{k4} + \frac{k5}{k6}\right)$$

To simplify the complex equation in the three compartment model the C_F and the C_{NS} are often combined together into one compartment on the basis of the assumption that the equilibrium between the free and non-specific bound tracer is faster compared to the kinetics of the specific binding. The free fraction (f2) therefore is the fraction of the total tracer (i.e. in C_F & C_{NS}) in the free state.

Similarly the equilibrium between the free tracer in the plasma and the tracer bound to the plasma proteins is also rapid. The fraction of the total free tracer in the plasma is denoted as 'f1'. Also important to note is that both K1 and k2 are dependent on the blood flow and permeabilily across the blood-brain-barrier (Frey et al., 1987; Gjedde and Wong et al., 1990).

Distribution of volume (V_T)

The distribution of volume of a radioactive tracer is a factor by which the volume of the tissue of interest would need to change to maintain the same mass of tracer in the tissue but at a concentration equal to that in the arterial plasma. In simpler words it is the ratio of the tissue concentration to the plasma concentration at equilibrium state. At equilibrium state there is no net transfer of the tracer in between the tissue and blood compartment (Frankle et al., 2005).

For the three compartment models

$V_{(F + NS)} = \frac{C_{(F + NS)}}{f_1 C_P}$

Also $V_{(F + NS)} = \frac{K_1}{f_1 k_2}$

$V_{SP} = \frac{C_{SP}}{f_1 C_p}$

Also $V_{SP} = \frac{K_1 k_3}{f_1 k_2 k_4}$

The total distribution of volume V_T is the total of $V_{(F + NS)}$ + $\mathbf{V_{SP}}$

$V_T = \frac{K_1}{f_1 k_2}\left(1 + \frac{k_3}{k_4}\right) = \frac{K_1}{f_1 k_2}\left(1 + \frac{B_{MAX}}{K_D}\right)$

(Frankle et al., 2005)

In a receptor-free tissue (i.e. reference region) DV= $\frac{K_1}{k_2}$. The distribution volume ratio of receptor containing and receptor free regions is, assuming that K1/k2 is equal in both regions.

DVR = $1 + \frac{B_{MAX}}{K_D}$ = 1 + BP

Unlike DV , the DVR has more applications, since it correlates with the concentration of available receptors (binding potential BP) and is not dependent on the non-specific binding in tissue or binding to plasma proteins,

If the metabolite corrected plasma data is available the DV's can be calculated as described above from the region of interest and from reference region and then the ratio DVR can be calculated (Logan et al., 1990)

Irreversible tissue compartmental model

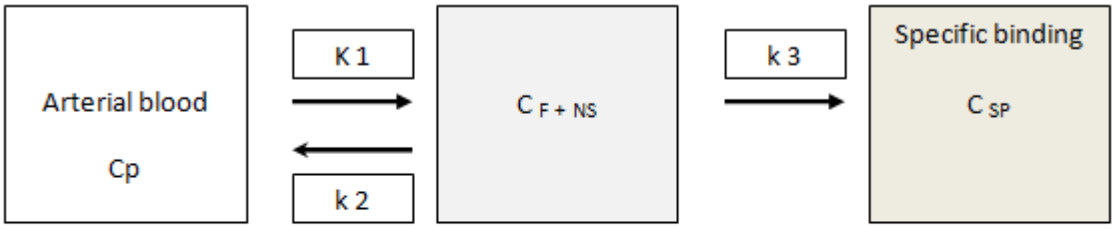


Figure showing an irreversible two tissue model

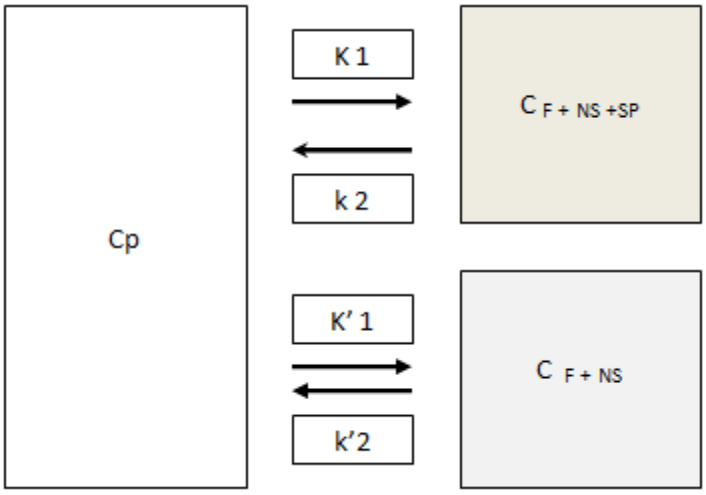
$$K_I = \frac{K1\ k3}{k2+k3}$$

Reference tissue input models

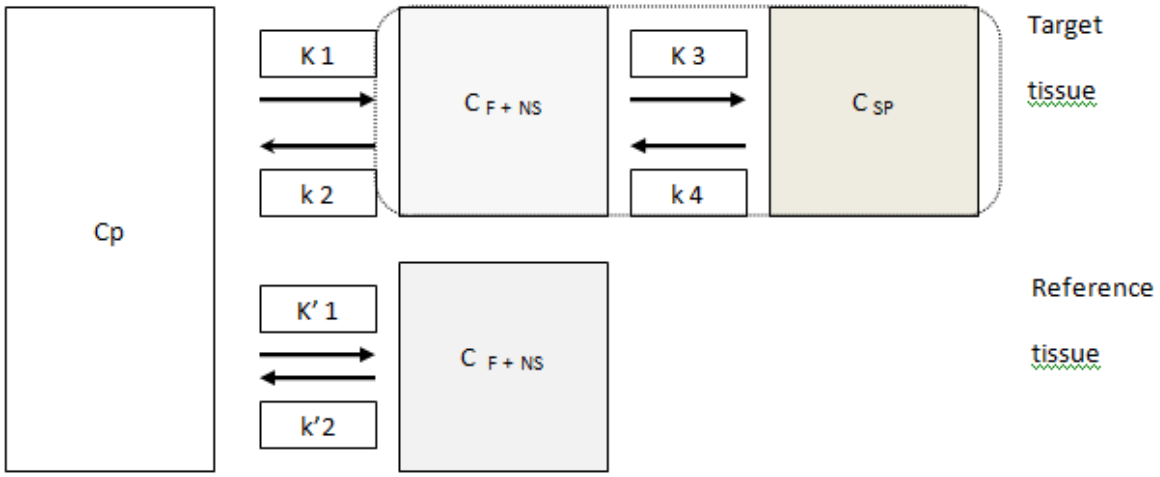
Many radioligands for neuroreceptor studies use the reference tissue model (Lammertsma. 1996) or its extensions (Edres et al., 2003). These are primarily to avoid the invasive arterial monitoring. The downside being more assumptions compared to the ones using arterial blood monitoring. For example, the existence of the specific binding in the reference region result in an underestimation of specific binding in the target region (Watabe et al., 2006). The target region and the reference region have the same plasma input function. It uses the C′f , time activity curve of the reference region as an indirect input function.

Simple reference tissue input model

Lammerstma and Hume et al., 1996

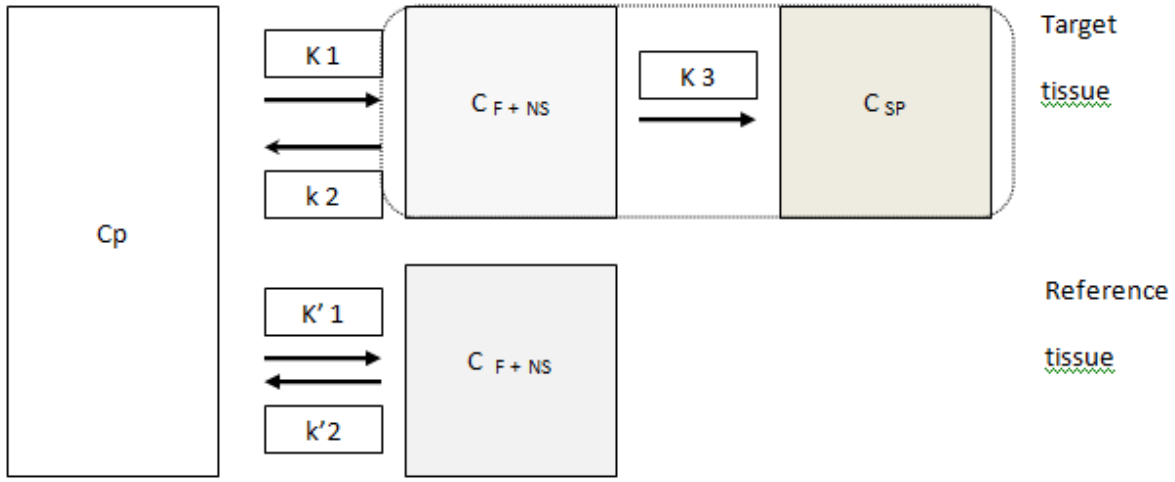


Full reference tissue model



BP . f2 = $\frac{\frac{K1}{k2}\left(1+\frac{k3}{k4}\right)}{\frac{K'1}{k'2}} - 1$

Irreversible reference tissue model



$$\frac{KI}{VD} = \frac{\frac{K1\ k3}{k2+k3}}{\frac{K'1}{k'2}}$$

Non- compartmental models

There are several methods of analysis of PET data which do not require assumption of the number of compartments. Instead, they estimate the macro parameters such as the distribution volume based on common properties among the compartmental models. Graphical approaches by (Patlak et al., 1983) and (Logan et al., 1990) estimate the macro parameter by graphically fitting a straight line to the transformed experimental data. Graphical methods can be applied to both reversible and irreversibly binding tracers. They provide considerable ease of computation compared to the optimization of individual model parameters in the solution of the differential equations generally used to describe the binding of tracers (Logan et al.,2000). Patlak plot should be applied for irreversible tracer and Logan plot for reversible tracer (Watabe et al., 2006).

Spectral analysis (Cunnigham et al.,1993; Murase et al., 2003), assumes that the observed PET data can be described by sets of exponentials as IRF and employs non-negative least

squares fitting to estimate exponential basis functions. The spectral analysis also supplies information on the number of compartments.

The basis pursuit denoising (Gunn et al., 2002) extends the concept of the spectral analysis and permits negative coefficient for the basis functions, facilitating adaptation for the reference tissue model.

Rank-shaping regularization of exponential spectral analysis (RS ESA)

ESA process uses a non negative algorithm and does not need a defined compartmental structure. Howebver the disadvantage is that it cannot be used for reference region modeling because of its positivity constraints. Within Spectal analysis, RS ESA is an Bayesian development which does take into account the negative frequencies which would have been otherwise discarded. therefore, it can be be used with a reference input (Turkheimer et al., 2003, 2007). RS-ESA bridges the gap between the reliability of the estimates obtained by compartmental models and the flexibility of SA that is computed from non-compartmental models.

Whereas Reference tissue modeling approaches such as STRM and Reference tissue Logan plot are used for monocompartmental reference regions, RS ESA can be useful in situations where the refernce region is multicompartmental (Turkheimer et al., 2012).

RS-ESA can be estimated using it's implementation in CLICKFIT, an in-house software toolbox for Matlab (version 6.5, The Mathworks, Natick, MA, USA).(Turkheimer et al., 2012)

Abbreviations used in this chapter:

VD= Total volume of distribution of the target tissue (mL plasma).(mL tissue) $^{-1}$

V_T = Total distribution of volume

K1 = Plasma to brain transport constant (mL plasma).min−1(mL tissue). $^{-1}$

BP = Binding potential (mL plasma).(mL tissue) $^{-1}$

BP.f2 = Product of binding potential and the tissue 'free fraction' Unitless

KI = Irreversible uptake rate constant from plasma for target tissue (mL plasma).min^{-1} (mLtissue). $^{-1}$

k2 = Brain to plasma transport constant min^{-1}

k3 = First order association rate constant for specific binding min^{-1}

k4 = Dissociation rate constant for specific binding min^{-1}

k5 = Association rate constant for non-specific binding min^{-1}

k6 = Dissociation rate constant for non-specific binding min^{-1}

1.1.2.3 PET ISOTOPES

Most commonly used isotopes are carbon-11, nitrogen-13, fluorine-18 and oxygen-15. Fluorine-18 has a small positron range and its half-life is relatively long (109.8 min) allowing the preparation of complex molecules with acceptable radiochemical yields. Isotopes like Carbon-11 because of their shorter half-lives need to have a cyclotron on-site. Carbon-11 can be obtained from a cyclotron in different chemical forms, depending on the irradiated material and the environment during irradiation; however, two chemical forms are, by far, the most commonly used radioactive precursors for labeling molecules: [11C]CO2 (obtained by irradiating N2/O2 mixtures) and [11C]CH4 (obtained by irradiation of N2/H2 mixtures). Nitrogen-13 is obtained by irradiation of water solutions and is usually produced as $[13N]NH4^{+}$ after irradiation of diluted ethanol aqueous solutions.

Radionuclide	Half-life (min)	Specific activity (Ci/mmol) x 10^6	Decay mode	Decay Product	Max. Energy (MeV)	Most Probable Energy (MeV)	Max. Range (mm)
Fluorine-18	109.8	1.71	97 % β^+ 3 % EC	Oxygen-18	0.69	0.202	2.4
Carbon-11	20.4	9.22	100 % β^+	Boron-11	0.96	0.326	4.1
Nitrogen-13	9.98	18.9	100 % β^+	Carbon-13	1.19	0.432	5.4
Oxygen-15	2.05	90.8	100 % β^+	Nitrogen-15	1.70	0.650	8.0

Table showing the Physical characteristics of fluorine-18, carbon-11, nitrogen-13 and oxygen-15. EC: Electronic capture. Adapted from: Welch, M.J; Redvanly, C.S; Handbook of radiopharmaceuticals: Radiochemistry and applications; Wiley, 2005.

A radiotracer can be defined as a substance containing a radioactive atom to allow easier detection and measurement. The physical properties of the radiotracer attributed by the radioactive atom while the biological profile is determined by the chemical structure of the molecule attached to the radioisotope.

An ideal PET radioligand needs to have a selected criteria which includes

- high selectivity
- high affinity
- minimal lipophilicity
- good blood-brain-barrier penetration
- insignificant metabolism
- lack of pharmacological effect
- safe
- amenability to labelling

Quality requirements for radiotracers

This includes radionuclidic purity (absence of contamination by other nucleotides), chemical purity (absence of toxic organic solvents) and radiochemical purity. The pharmacological quality encompasses sterility, apyrogenicity and, a stable pH and osmolaltiy. If all these quality requirements are fulfilled then the chances of side-effects related to tracer injection will be extremely rare.

Specific activity

This parameter is critical for the accurate measurement of saturable biochemical processes. It indicates the amount of labelled pharmaceutical relative to the total amount of pharmacologically active (labelled and unlabeled) pharmaceutical (Hume et al.,1998). For most radiotracers measuring metabolism a specific radioactivity of at least 10 GBq/µmol is considered standard. For higher affinity receptor ligands this may not be sufficient as even small amount of the binding drug may occupy a major proportion of the receptors leaving very little for the labeled drug.

1.1.2 CLINICAL CONSIDERATIONS : EXTENT OF THE PROBLEM

Parkinson's disease is the second most common neurodegenerative disease. It is associated with a significant morbidity and mortality . After fifteen years of disease duration, more than 70 % would have died and half of those surviving would require nursing home care (Hely et al., 2005).

Disease Progression and effect of levodopa

Annual rates of deterioration in UPDRS scores in untreated PD as extrapolated from multiple randomized controlled intervention trials, are between 8- 10 points for the total UPDRS score and 5 - 6 points for the motor section of this scale (Poewe et al.,2009). The mean deterioration of motor and disability scores ranged from 2.4 to 7.4% of the maximum possible score per year (Schrag et al., 2007).

But with levodopa treatment there is a degree of improvement particularly in the early phases of the disease. One group found an annual decrease of UPDRS motor scores of 3.3 score points in 145 levodopa treated PD patients (Schrag et al., 2007). One year follow up data showed that the improvement in motor scores were 5.1% in the patients who were at the early stage of the disease (Hoehn and Yahr, 1–2.5) compared to a meagre 0.35% for those in the later stage (Hoehn and Yahr stage 3–5) (Schrag et al., 2007). Earlier studies have also described faster rates of decline of UPDRS motor scores in the first versus later years of disease. (Bonnet et al., 1987; Lee et al., 1994). Although this may well represent ceiling effects of the UPDRS, faster progression of motor impairment in early versus later years would seem consistent with pathological reports on exponential declines of nigral cell counts in PD over time. (Greffard et al.,2006; Fearnley et al.,1991).

Mortality in PD

In their seminal article, Hoehn and Yahr found an excess mortality in PD patients over the age-matched normal population of about three-fold and concluded that "…the state of parkinsonism severely limits life expectancy." (Hoehn et al.,1967). Most studies in the post-levodopa era have found a little improvement but mortality ratios were still high, ranging between 1.5 and 2.5 (Poewe et al.,1986).

These studies show the extent and course of Parkinson's disease. It also shows that levodopa treatment brings some improvement in the symptoms but the underlying pathology continues.

Complications of levodopa - dyskinesias

In the late 1960's Yahr et al. wrote that chronic levodopa treatment led two common motor complications, namely fluctuations and levodopa-induced dyskinesias (Yahr et al., 1968). Since then a number of clinical studies were undertaken to show the epidemiology and to some extent the predisposing features of such complications. The dyskinesias could be best predicted by duration of treatment (Miyawaki et al., 1997 , Schrag and Quinn, 2000). However, other predisposing factors include shorter time from symptom onset to initiation of levodopa , younger age of onset (Kostic et al., 1991; Schrag and Quinn et al.,2000) , longer disease duration, greater disease severity (Lesser et al., 1979; Tanner, 1996; Parkinson Study Group, 1996) and higher doses of levodopa (Barbeau, 1969; Lees and Stern et al., 1981; Tanner et al., 1985) .

In a study by Schrag and Quinn, a third of the patients receiving levodopa developed dyskinesias. (Schrag and Quinn,2000). It has been estimated that after initiation of treatment with levodopa about 10% of patients per year develop motor complications (Marsden and Parkes, 1977), and about 50% suffer these complications after 5 years of treatment (Sweet and McDowell, 1975; Dupont et al et al., 1996 ; Lang and Lozano, 1998). Rates of these complications on levodopa treatment reported in the literature vary greatly, ranging from 0 to 66% developing dyskinesias during the first year of treatment (Barbeau, 1969; Brannan and Yahr, 1995), 30% within 2 years (Parkinson Study Group, 1996), 19 to 80% of patients experiencing fluctuations after 5 or 6 years of treatment with levodopa (Poewe et al et al., 1986; Brannan and Yahr, 1995) and upto 90% (Rascol et al., 2000). Peak-dose dyskinesias were present in 11% of patients with a treatment duration of 5 years or less, 32% with a treatment duration of 6–9 years, and 89% of patients with a treatment duration of 10 or more years. (Schrag and Quinn, 2000). Similar results of have been published by of about 50 series of around 4000 patients in a cumulative study (Table below) (Ahlskog and Muenter, 2001). Of them few had reported 90 % dyskinesias in more than nine years of treatment with Levodopa (Hoehn et al.,1983; Cedarbaum et al.,1991)

Years of levodopa treatment	7 – 12 months	13 – 24 months	2.5 – 3.5 years	4 -6 years	9 – 15+ years
Weighted by N in each series (%)	7.0	28.7	26.9	36.2	87.8

Table - Dyskinesias: Median percent of levodopa-treated Parkinson's disease (PD) patients who experienced dyskinesias after defined intervals of therapy (Ahlskog and Muenter , 2001)

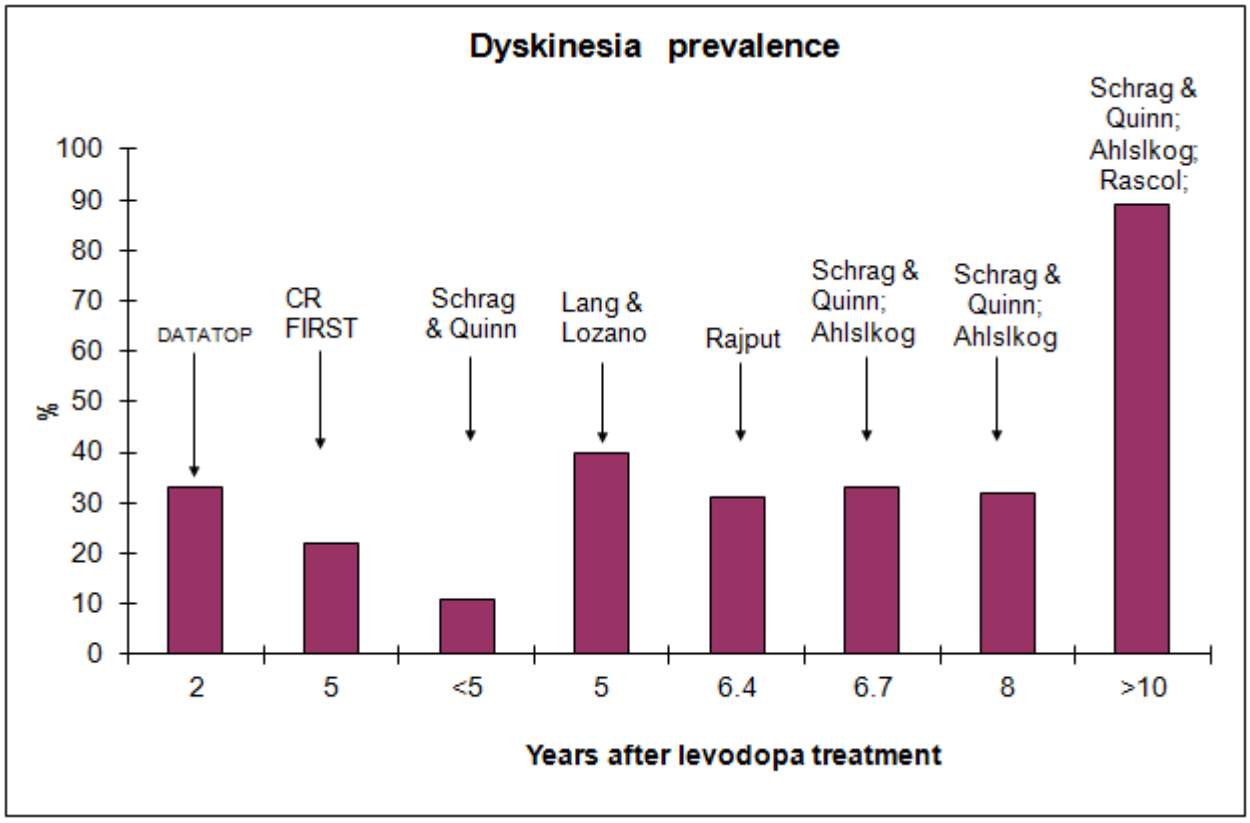


Figure 1.1.2 Showing the prevalence of LID from different studies

The mean time from symptom onset to development of fluctuations, as reported by the patients, was 6.5 (SD = 4.1) years and development of dyskinesias was 6.7 (SD = 3.1) years (Schrag and Quinn ,2000). Longer term follow up studies showed an initial benefit was followed by a plateau of about 3 years and then a further period of decrease in function, occurring more rapidly in the later phases (Barbeau ,1969). A very similar result has been reported after 40 years by Lopez et al., 2010

who observed a significant improvement in UPDRS scores during the first year, then a progressive decline, more evident after the third year. Motor complications increased after the third to fourth year from about 50 % to 85 % at the end of the survey (tenth year). Yet another clinicopathological study by Rajput reported a 9.8 year old follow-up of 42 patients receiving on an average a meagre 500mg /day of levodopa had motor complications in 71.4 % of the cases most commonly dyskinesias in 62% after 6.4 years of treatment (Rajput et al 2002).
In a 6 year follow up study with suboptimal doses of levodopa (less than 500mg/ day) (Poewe et al.,1988) still found 54% patients having dyskinesias proving that additional mechanisms other than high doses of levodopa are likely to be involved in causation of LID.
Also important to note is that poor or moderate response to levodopa was associated with lower quality of life in patients with a disease duration of $\leq$5 years or $\geq$ 10 years (Schrag and Quinn, 2000).

What is striking from the clinical point of view is a distinct pattern of good response to levodopa , followed by a plateau period of gradual decline and then complications of LID catapulted to a significantly high level from around the fourth to seventh year onwards and this is being reproduced by different studies over and over again.

Expression of dyskinesias

Dyskinesias are broadly divided into two types. The 'on' type is when levodopa is exerting its antiparkinsonian effect and this includes peak dose chorea, peak dose dystonia and diphasic type . The 'off' type is when the anti parkinsonian effect of the drug is no longer active and this type include off dystonia. Peak dose dyskinesias are the most common type. These are usually choreiform and tend to be less disabling and less painful. Dyskinesias typically occur in association with high concentrations of levodopa in the plasma and at a time when the maximum benefit of the drug happens. Diphasic dyskinesias on the other hand can appear at or just before the onset of the on response, disappear during the on period and re-emerge as the off period begins (Olanow,2009). These are typically comprised of large amplitude stereotypic, rhythmic, and repetitive movements that usually predominate in lower

limbs, tend to be dystonic or ballistic and sometimes painful, while peak dose dyskinesias involve more the upper limbs, have a choreic phenotype. Patients can also experience off-period dystonia's which are usually localised in the legs or commonly toes (Vidialhet et al.,1999). These are usually painful. It is important to note that in all forms of 'on' LID the key abnormality in the basal ganglia circuitry is enhanced direct pathway related inhibitory influence on the GPi and SNr (Brotchie , 2005).

LID and Parkinsonian motor signs do not always start in the same body region (Fabbrini et al., 2009) unlike other reports (Mones et al.,1971; Horstink et al.,1990,Vidailhet et al.,1997; Poewe 1998; Grandas et al.,1999).This finding could reflect that the pathophysiology of LID may be different to PD and could include mechanisms in adddition to loss of nigrostriatal dopaminergic neurons (Fabbrini et al., 2009).

1.1.3 BASAL GANGLIA ANATOMICAL AND FUNCTIONAL ORGANISATION

Basal ganglia are a group of interconnected nuclei located at the base of the cerebral hemispheres. The parts belong to the forebrain, diencephalon and the midbrain. The nuclei comprise of the striatum (caudate and putamen), the globus pallidus externa (GPe) and pars interna GPi, subthalamic nucleus and the substantia nigra ((pars compacta (SNc) and pars reticulata (SNr)). As shown in the diagram

The classic box and arrow basal ganglia model (Crossman 1987; Albin et al.,1989; DeLong et al.,1990) proposes a motor circuit with two output nuclei GPi and SNr and two input nuclei the striatum and STN. Along with these there are two intrinsic structures GPe and SNc.

Although some uncertainty remains regarding the degree of segregation between circuits and whether the circuits are truly closed or partially open, the overall scheme has been accepted by most researchers and has provided a framework for understanding the diverse behavioural disturbances clinically evident in disorders of the basal ganglia and a rational basis for new surgical treatments for some of these disorders (Delong et al., 2007) .

The striatum and SNc receive topographically organised input from the cerebral cortex whereas the two output nuclei feed the information back to the cortex via the thalamus. There is a clear consensus in considering that input to the basal ganglia from different cortical areas terminates within specific basal ganglia territories, which are connected to similarly specific portions of the thalamus. These thalamic nuclei in turn feedback to the specific areas in the cortex from where the cycle originated (Alexander et al., 1986; Kelly and Strick, 2004; DeLong and Wichmann, 2007).

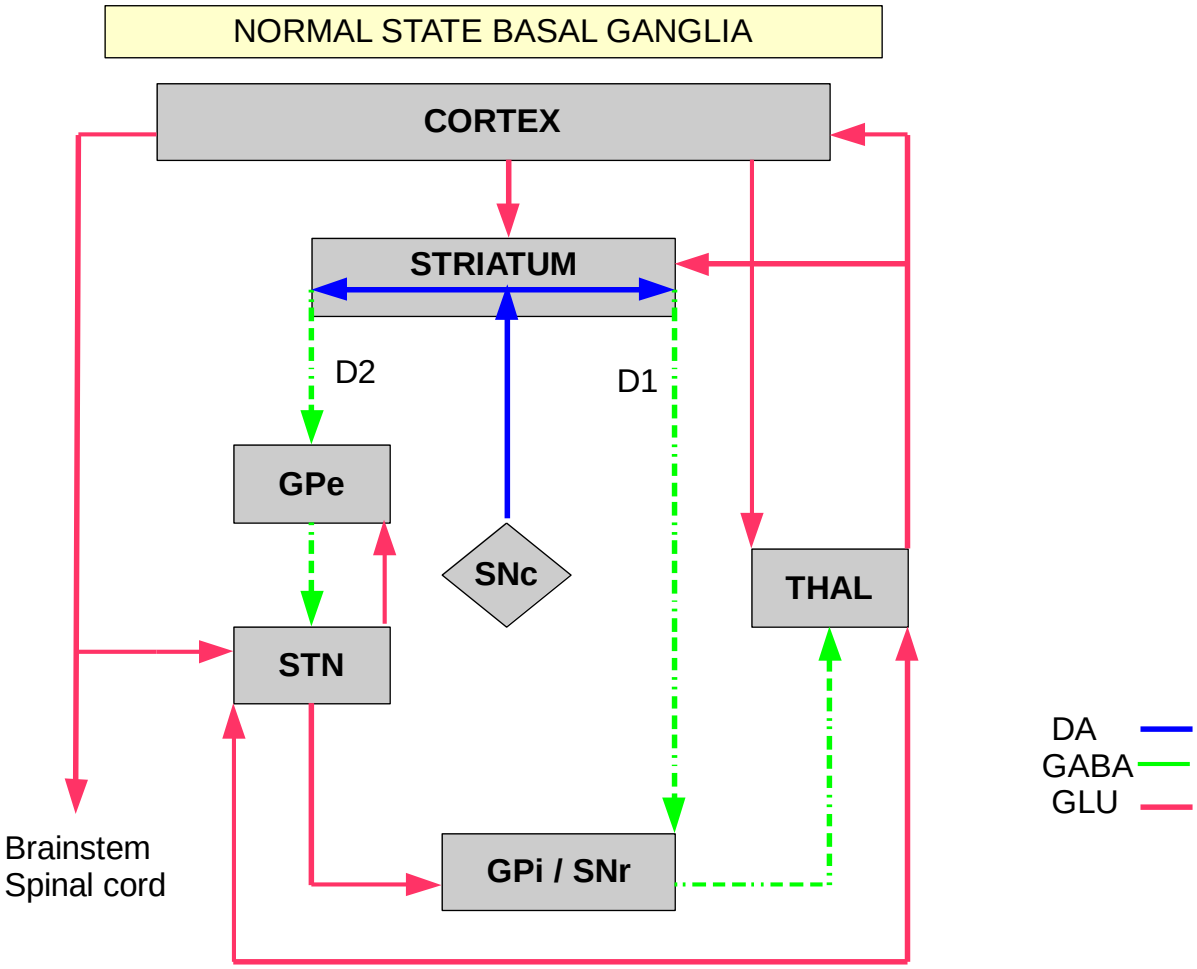
The striatum receives massive cortical excitatory inputs and is densely innervated by dopamine from the SNc. Additional input to the striatal direct pathway neurons comes from the intralaminar nuclei of the thalamus (i.e. the centromedian and parafascicular nuclei)

In the striatum, the major neuronal population is represented by medium spiny neurons (MSNs), accounting for almost 95% of total striatal cells (Kemp and Powell, 1971). MSNs use ɣ-amino-butyric acid (GABA) as a inhibitory neurotransmitter

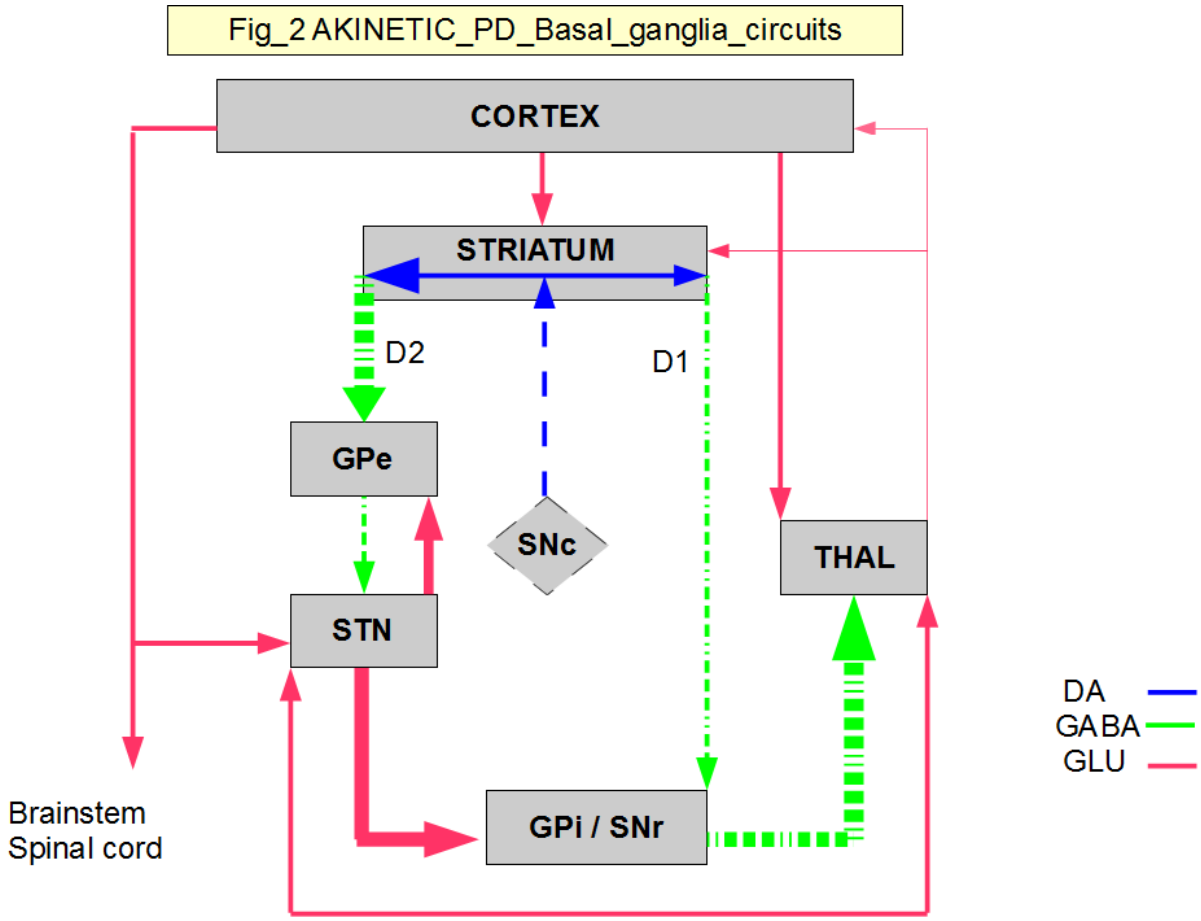
(Kita and Kitai, 1988).The striatum forms two major populations of projection neurones - the direct pathway and the indirect pathway which differ in the expression of the receptors that mediate the effect of dopamine. The striatonigral MSN's that project to the GPi and SNr express D1 receptors and form the direct pathway whereas the striatopallidal neurons projecting to the GPe and STN express D2 receptors and form the indirect pathway. The former pathway is monosynaptic, GABA ergic and is inhibitory and the latter is polysynaptic and provides a net excitatory effect. The GPi and SNr neurons give rise to GABAergic projections, which because of their high discharge rate tonically inhibit thalamocortical projection neurons in the ventral anterior, ventrolateral, and intralaminar nuclei of the thalamus, as well as brainstem neurons.

The STN is an important control structure of the basal ganglia circuits , being the only glutamatergic nucleus of the network (DeLong and Wichmann, 2007). It sends excitatory inputs to the GPe , the two output nuclei (GPi and SNr), the ventral thalamic nuclei nuclei (Nauta and Cole, 1978; Rico et al et al., 2010). It has reciprocal connections with the PPN and cerebral cortex. With inputs from the cortex and the thalamus (Wilson et al., 1983; Sadikot et al., 1992; Feger et al., 1994; Lanciego et al., 2004; Castle et al.,2005) , the STN is increasingly recognised as a prime entry point to the basal ganglia circuit probably at par with the striatum itself (Barroso-Chinea and Bezard , 2010).

In simplistic terms the tonic output arising from this circuit arising from the GPi and SNr may modulate a particular movement. Increased output from the basal ganglia circuit could express itself into less movement through inhibition of the thalamo-cortical pathway whereas decreased basal ganglia output could result in more movement by disinhibiting the these neurons (De long et al.,2007). The thalamo-cortical pathway and the basal ganglia projections can be described metaphorically as the reins of a horse. If there is increased activity arising from the circuit (i.e. more pulling force on the reins) the net effect is less movement and vice versa. The overall orchestration of movement is done by striking a balance between the direct and indirect pathway . Dopamine does this by regulating it's differential actions via D1 and D2 receptors. Kravitz et al. have very recently demonstrated the above function of direct and indirect-pathways using optogenetic approaches (Kravitz et al., 2010).


NORMAL STATE BASAL GANGLIA
CORTEX
STRIATUM
D2
D1
GPe
SNc
THAL
STN
Brainstem
Spinal cord
GPi / SNr
DA
GABA
GLU

Akinetic Parkinson's disease model

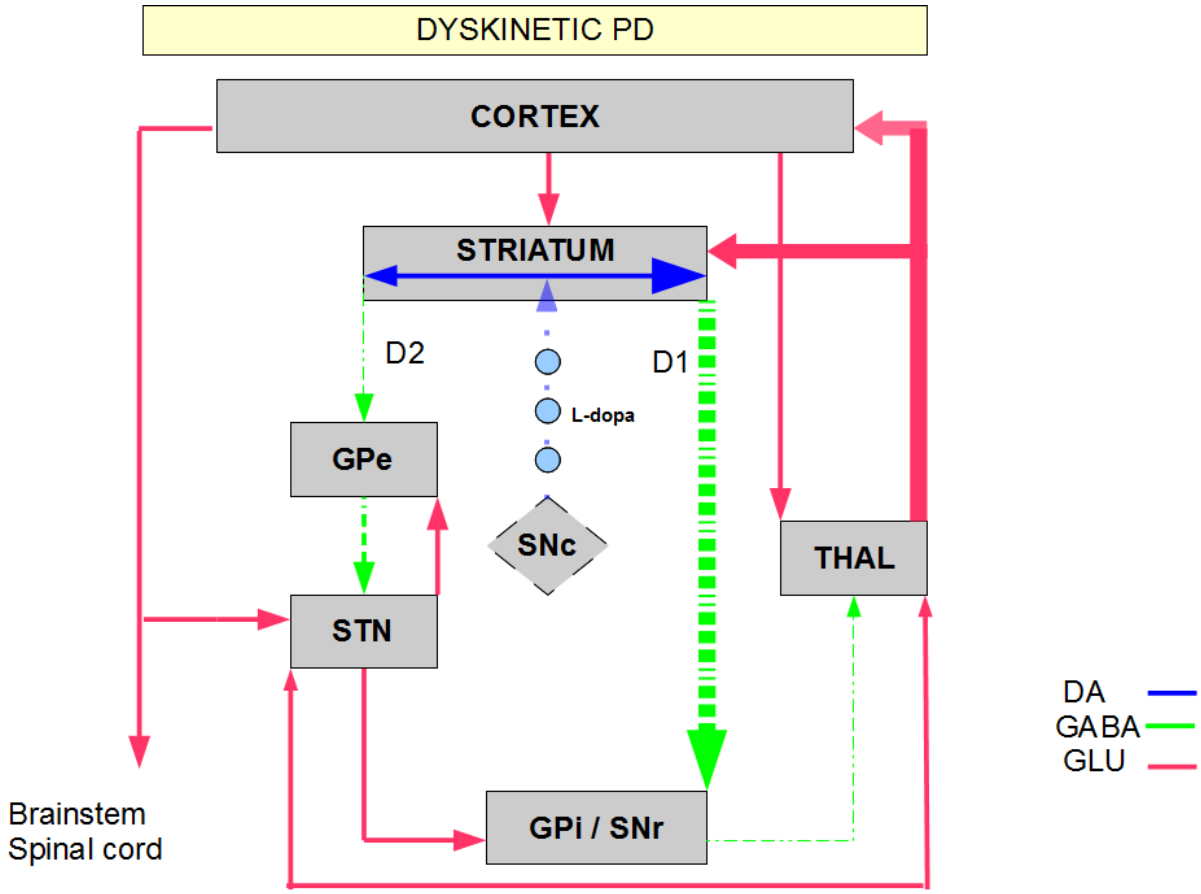


Akinetic PD

In physiological conditions, dopamine exerts a predominantly inhibitory effect on the indirect pathway and the converse is true for the direct pathway. Therefore when there is dopamine depletion, the indirect pathway is more active leading to an increased inhibition of the GABAminergic pathways to the STN which gets disinhibited and leads to increased inhibition of the thalamocortical drive resulting in less movement.

One important point to note here is that the STN has reciprocal connections with the motor cortex (Jackson and Crossman., 1981; Nambu et al., 2002; Degos et al.,2008) which keeps on the barrage of inputs to the MSN's via the corticostriatal pathway (Jellinger, 2000).

Dyskinetic PD model



Dyskinesia in PD seems to be mediated by alterations in basal ganglia activity that are the opposite of those occurring in PD (Vidailhet et al., 1999; Obeso et al., 2000; Boraud et al., 2001).The sequence of events leading to dyskinesias seem to be overactivity of the direct D1 receptor stimulation followed by excessive inhibition of the GPi activity which in turn increases the cortical drive (Wichmann and Delong et al., 1996, Bezard et al.,2001, Brotchie, 2005).

The basal ganglia circuitry model also predicts that involuntary movements would result from reduced firing in the GPi. Recording studies have demonstrated that GPi activity is reduced in monkeys and in patients with PD who have ongoing drug-induced dyskinesias(De long and Wichmann ,2007).

However, there are few important questions that this model cannot answer. For instance, lesions of the thalamus do not lead to significant bradykinesia or akinesia,and lesions of the GPi do not result in dyskinesias, as one would expect if

reduced pallidal output was sufficient to induce involuntary movements (De long and Wichmann,2007). These inconsistencies may point towards other mechanisms involved in basal ganglia function.

1.1.4 MEDIUM SPINY NEURONES (MSN)

From the basal ganglia circuitry it is known that there is an increased cortico-striatal drive resulting in dyskinesias. Medium spiny neurones at the striatum are the receiving end of these excitatory glutamatergic inputs and play a vital role in LID.

Localisation of the lesion

Recently an experimental study showed levodopa administration in the striatum but neither GP nor SnR triggered dyskinesias in rodent PD model that were already rendered dyskinetic following chronic levodopa treatment. Also interesting to note in this study is that simple addition of GABA or glutamate failed to provoke dyskinesias (Buck et al., 2010). This study illustrates that the striatum is the main structure involved in the pathogenesis of dyskinesias.

The interface between dopamine and glutamate – Medium spiny neurones (MSN) and their significance in PD and dyskinesias

The MSN is the primary cell type in the striatum, accounting for 95% of total striatal cells, and is the major target of inputs from the cortex and thalamus. These MSN's have radially projecting dendrites which are profusely populated with spines (Wilson & Groves, 1980).In rats, each MSN has approximately 5000 dendritic spines (Wickens et al., 2007). The nigro-striate dopamine axons synapse onto the striate MSN's and it is here that they converge with glutamatergic input from the thalamus and cortex. Most dopaminergic inputs are at the neck of the dendritic spine and make symmetric points of contact whereas glutamatergic synapses are made on the heads of these structures and form asymmetric contacts. This convergence of the dopaminergic and glutamatergic synapses on the MSN spine forms a ' synaptic triad' and acts like a coincidence detector by which activation of the DA terminal selectively influences the simultaneously active converging glutamatergic input at the level of individual spines (Yao et al., 2008). These dendritic spines are remarkably plastic structures and can change

their shape and number in a timescale ranging from seconds to years (Harms & Dunaevsky 2007; Chen et al., 2009). In patients and animal models of PD a marked decrease in MSN spine density has been reported (McNeill et al.,1988; Ingham et al.,1989, 1993, 1998; Arbuthnott et al., 2000; Stephens et al.,2005; Zaja-Milatovic et al.,2005; Day et al., 2006; Villalba et al.,2009) although there is still controversy whether D2 containing striato-pallidal neurones are exclusively involved (Villalba & Smith et al., 2010). Spine loss has been shown to be dependent on Cav1.3 L-type Ca2+ (Day et al., 2006).

Striatal spine pruning of MSN's in response to dopamine denervation is reversed by decortication at the M1 primary motor cortex (Garcia et al., 2010). In the same study an mGluR2/3 agonist also reversed the spine loss (Garcia et al., 2010), suggesting that glutamatergic cortical inputs are essential to mediate striatal spine loss in parkinsonism.

In the context of LID two recent studies have shown benefit of anti-glutamate agents in controlling LID and MSN spine loss (Schuster et al.,2009 ; Soderstrom et al., 2010) and a correlation of LID with the severity of spine loss (Soderstrom et al., 2010).

Summary

The structural loss of the dendritic spines in the striatal MSNs compromises their filtering capacity to contain the increased cortico-striatal inputs. The reversibility of the dendritic spine loss to removal of these afferent inputs and the correlation of LID with the severity of spine loss shows the importance of the cortico-striatal inputs in LID.

1.1.5 INDUCTION OF LID AND INTERACTION OF DOPAMINE AND GLUTAMATE RECEPTORS

Induction process of LID

LID induction or priming is a process by which the brain becomes sensitized in way such that the initial administration of dopaminergic therapy modifies the response to subsequent dopamine treatment (Brotchie, 2005). Over time with repeated dopaminergic stimulation the chances of eliciting LID becomes higher. Although variable most patients go through a curve of a distinct pattern of good response to levodopa, followed by a plateau period of gradual decline and then complications of LID catapulted to a significantly high level from around the fourth to seventh year onwards. The time course of these complications may suggest a chronic induction process. However the striatum is extremely susceptible to acute doses of levodopa and hence reports of dyskinesias after a high dose of levodopa (Nadjar et al 2009; Scholz et al., 2008) are not uncommon in animal models or humans. Anecdotal reports of temporary dyskinesias have been reported in dopamine agonists when taken in high doses (Ahmed, 2007).

Following nigral cell degeneration there is failure of exogenous levodopa to keep up a constant supply of levodopa. This widely viewed concept was the basis for continuous dopaminergic stimulation (CDS). Although CDS clearly is important in dyskinesia induction and it does delay the onset of dyskinesias but eventually these complications do evolve (Nutt et al., 2007; Constantinescu et al., 2007; Hauser et al., 2007). The failure of exogenous dopamine to maintain a constant dopaminergic level is due to combination of factors including dopaminergic neuronal cell loss, abnormal pharmacokinetic profile of levodopa in terms of its short half-life and absorption characteristics and abnormal mechanisms in the storage and clearance of dopamine in the synaptic cleft. This leads to a fluctuating dopamine level in the system which leads to LID. It is important to note here that dopamine transmission involves volumetric as well as synaptic and is slower compared to glutamate which is predominantly synaptic and exhibits faster kinetics. (Rice. & Cragg et al., 2008). Therefore, exogenous administered levodopa leads to sudden boosts in dopamine levels but fails to maintain the tonic level. Both dopaminergic denervation and a pulsatile dopamine stimulation are prerequisites for LID.

The priming process of LID has now been thought to involve significant alterations of dopamine D1 and glutamate receptors which are considered essential in addition to the above. The increased sensitivity of post-synaptic dopamine receptors (predominantly D1), which are stimulated along with increased glutamatergic input, leads to changes in a number of processes which predispose to LID (Calabresi et al., 2010). These processes include changes to the dopamine and glutamate systems, downstream signalling processes etc that are detailed in the later sections. In particular striatal glutamatergic system take the centre stage, following dopamine denervation, in driving the induction process of dyskinesias (Jellinger et al., 1999; Jenner et al., 2008).

Dopamine receptors

These are of two main classes D1 like dopamine receptors (D1,D5) and D2 Like dopamine receptors (D2, D3, D4). They are all the dopamine receptors are G protein -coupled receptors (GCPR's) whose signaling is primarily mediated by interaction with and activation of GTP binding proteins. These two classes of dopamine receptors may a significantly important part in the modulation of neurones as they potentially have reciprocal functions. .

Glutamate receptors

These are of two types inotropic and metabotropic. The inotropic glutamate receptors include the alpha- amino-3 hydroxy-5-methyl-4-isoxazoleproprionic acid receptors (AMPARS), kainate and N-methyl-D-aspartate receptors (NMDARS). NMDARs are tetramers typically composed of two obligatory NR1 subunits and two NR2 subunits (NR2A-D) and, less commonly, include a NR3 (NR3 A & B) subunit. (Cull-Candy and Leszkiewicz, 2004; Liu et al., 2004; Morishita et al., 2007). NR2 subunits are key determinants of NMDAR channel properties and signaling. NR1/NR2A di-heteromers have higher peak open probability upon activation and possess shorter rise and decay times than receptors containing NR2B (Erreger et al., 2005). Conversely, NR1/NR2B di-heteromers have slower decay kinetics and exhibit a strong interaction with Ca2+/calmodulin-dependent protein kinase type II (CaMKII) (Barria and Malinow, 2005). LTP being closely linked to NMDAR-dependent Ca2+ influx and CaMKII is probably more associated with NR2B (Shepherd and Huganir, 2007).

NMDAR are the only ligand-gated ion channels which have a voltage -dependent blockade by magnesium ion. The NMDAR require two agonists, glycine and glutamate, for activation

(Paoletti et al., 2007). When this double channel activation occurs together with a significant depolarising current, the ion channel opens after the magnesium ion is expelled and permits the calcium channel into the cell (Scheggenburger ,.1993, Skeberdis et al.,2006). The calcium then functions as a second messenger to modulate synaptic strength and alters neuronal function.

NMDAR activation leads to an excitatory post synaptic potential which is slow in both its rise and decay compared to AMPAR. So glutamate neurotransmission begins with a fast response generated by AMPAR (sodium influx) followed by a membrane depolarization which changes the membrane potential to allow NMDAR channels to open and permit calcium into the neuron to elicit long-term changes. During basal excitatory synaptic transmission AMPAR's provide the excitatory postsynaptic excitatory potentials (EPSPs). NMDAR's contribute to the EPSP only when the membrane is significantly depolarised by repeated activation by AMPARs which relieves the magnesium block.

Metabotropic glutamate receptor family (mGluRs); these G protein-coupled receptors (GPCRs). mGluR's have dual role of inhibitory as well as facilitatory functions and are located both pre and post-synaptically. There are eight subtypes of mGluRs, which are divided into three groups according to their sequence homology, ligand-binding profile, and G protein-coupling specificity (Conn and Pin, 1997, Pin and Acher, 2002) . Group I mGluRs are mGluR1 and 5, which couple to Gq to activate phospholipase C, raise intracellular Ca2+ levels, and activate protein kinase C. Group II consists of mGluR2 and 3, which are coupled to Gi/o, and mediate the inhibition of adenylyl cyclase. Group III mGluRs consists of mGluR4, 6, 7, and 8. These also signal through Gi/o, are located presynaptically and function principally to inhibit neurotransmission.

AMPA receptors are ionotropic glutamate receptors comprised of 4 different subunits GluR1–4 (or GluR-A through D) that assemble to form a functional receptor channel (Nakanishi et al., 1990; Wenthold et al., 1992, 1996). These receptors are the major mediators of fast glutamatergic excitatory synaptic transmission in the central nervous system.

Changes in dopamine system

There are changes in dopamine system in an attempt to increase its availability but the underlying neurodegenerative process continues. These changes are listed below:

Presynaptic

- Increased dopamine synthesis by surviving neurones (Zigmond et al., 1990) as well as by serotonergic systems (Carlsson et al., 2009; Carta et al., 2007)
- Involvement of other neurotransmitters endocannabinoid systems, cholinergic systems (Kopin, 1993) and Adenosine (A2A)*
- Reduced transporter uptake (discussed in later sections)
- D2 inhibition

Post synaptic

- Decreased internalization of D1 receptors (Guigoni. 2007; Gainetdinov. 2004)
- Increased expression of dopamine D1 receptors (Aubert. 2005; Guigoni, 2007; Berthet et al., 2009) and glutamate receptors
- Increased sensitivity of dopaminergic receptors (Nutt et al., 1990; Aubert et al., 2005)
- Increased both canonical and non-canonical DA signaling (Cenci & Konradi et al.,2011)
- Increased NMDA stimulation * (discussed in later sections)
- Reduced expression of negative signaling modulators (Guigoni 2007 et al., Guigoni et al.,2009)
- Altered Synaptic plasticity
- Altered basal ganglia output

*both (pre& post-synaptic)

Internalization of dopamine receptors and importance in LID

Dopamine receptor inactivation includes phosphorylation by G protein coupled kinases (GRK) followed by binding to arrestin which blocks further G protein mediated signaling

and subsequently leads to receptor internalization. Following internalization these receptors can be trafficked to lysosomes, where they are ultimately degraded, or to recycling endosomes for recycling back to the cell surface in the functional process of resensitization for another round of signaling. (Stephanie et al., 2009). Increased internalization of D1 improves dyskinesias by G protein-coupled receptor kinase 6 which controls desensitization of the D1 receptor (Guigoni et al., 2009; Ahmed et al., 2010).

Inhibition of D2 receptor internalisation by RGS9-2 also helps LID (Celver et al., 2010)

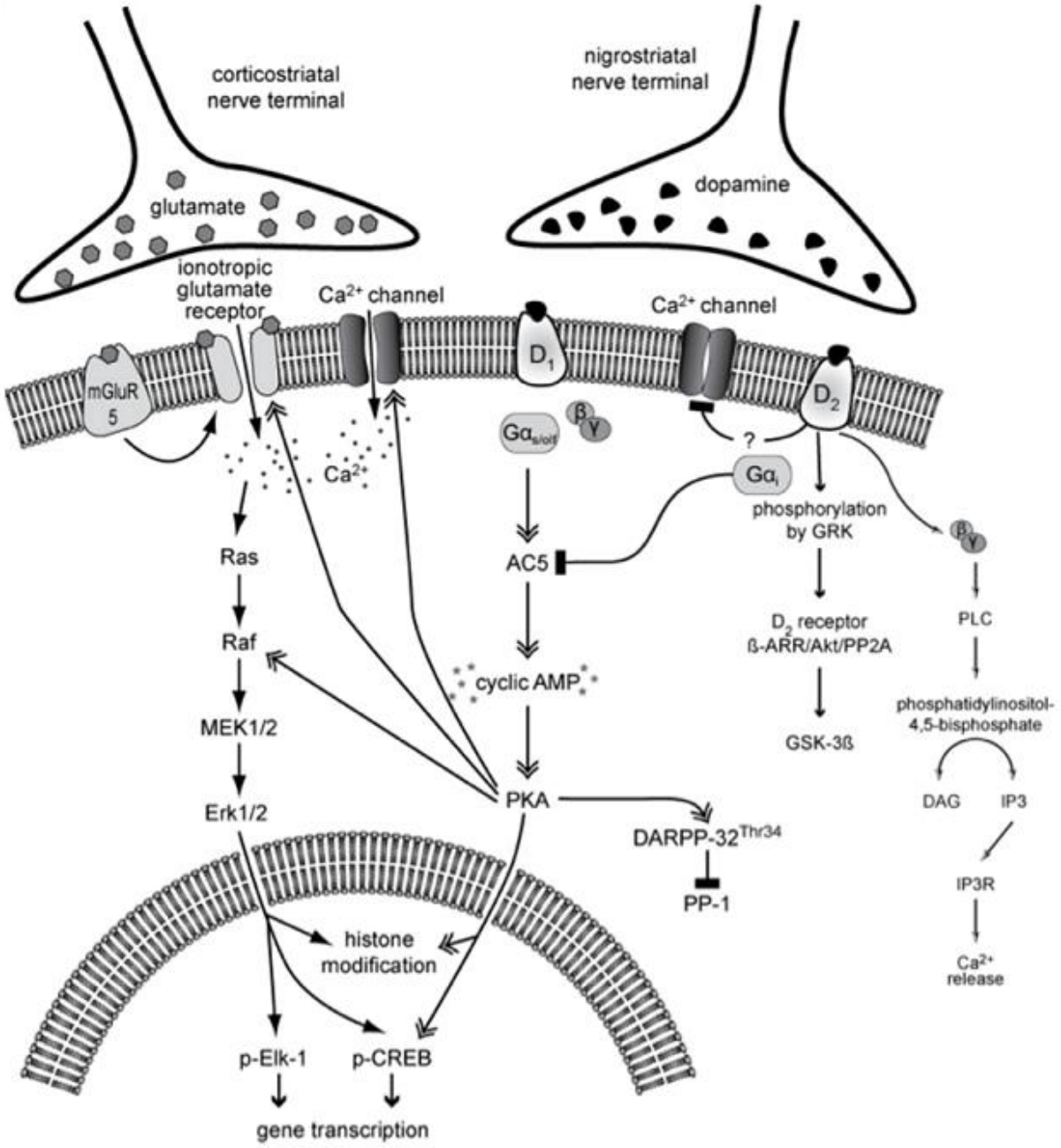
Changes in Glutamate receptors:

Inotropic glutamate receptor trafficking, targeting and recycling is extremely important in the context of LID and abnormalities of all these processes have been reported in animal studies. Changes in subunit composition, subcellular organisation and phosphorylation states in NMDA have been reported in rodent PD model, non-human primate PD model and human subjects with dyskinesias (Hallett et al., 2004; Hurley et al., 2005; Gardoni et al.,2006; Quintana, 2010). The functioning of AMPAR's need a host of proteins and enzymes to maintain LTD and LTP in the synapses (discussed in LTD and LTP section).

Perhaps the most important of all of these is NMDA stimulation and post-receptor signaling processes which would drive the processes further. It is interesting at this stage that dopamine function through D1 receptors become excessive and uncontrolled and the negative modulators are underplayed.

1.1.6 SIGNALING PATHWAYS AND LID

The signaling pathways include a canonical and a non-canonical type both of which serve an important function in the normal state. Dopamine regulates this pathway with the help of a balance between differential D1 and D2 receptor function and also by a number of modulating enzymes that keep these pathways in strict spatio-temporal control.



Picture of the signalling pathways (Cenci & Konradi et al.,2011)

cAMP---->DARRP 32 pathway or canonical pathway

D1 like receptors increase cAMP levels and activate protein kinase A (PKA) whereas D2 like receptors decrease the same (Yao et al., 2009; Corvol et al., 2001). cAMP activates PKA. This is an energy utilising step which releases PKA which in turn phosphorylates a number of proteins in signal transduction and regulation of gene expression (Huff et al.,1997). PKA phosphorylates DARPP 32 (dopamine and cyclic AMP-regulated phosphoprotein) at Thr 75. DARPP-32 is a bi-functional signaling protein that inhibits protein phosphatase1 (PP1) when phosphorylated on Thr34 thus promoting the canonical cascade but it inhibits the same pathway when dephosphoralyted at Thr 75 by Protein phosphatase 2A.

Non-canonical ERK pathway

Phosphorylated DARRP 32 (Thr 75) promotes phosphorylation of ERK via MEK (mitogen-activated protein kinase/ERK kinase) activation and is modulated by striatal-enriched phosphatase STEP at this stage (Valjent et al., 2005).

Intranuclear - genetic alterations

Phospho-ERK translocation to the nucleus results in sequential phosphorylation/activation of mitogen- and stress-activated kinase-1 (MSK1) and histone H3. This, in turn, leads to chromatin rearrangements and transcription of immediate early genes, such as c-fos (Brami-Cherrier, 2005; Santini, 2007). A recent has shown that histone phosphorylation is not exclusively done via D1-ERK-MSK1 pathway (Bertran-Gonzalez et al.,2009). CREB (cyclic AMP response element-binding protein) activation is by PKA-dependent phosphorylation of Ser133 and subsequent binding of CREB to CREB-binding protein and transcriptional activation of genes with CRE (Cole et al., 1995). D1 stimulation also increases Ser133-phosphorylated CREB via activation of ERK (Brammie-Cherier et al., 2002;Chen et al., 2006).

Phosphorylated CREB binds to CRE and AP-1 in the promoter region of many genes including c~fos and opioid precursor genes, preproenkephalin and prodynorphin (Cole et al., 1995; Konradi et al., 1994).

Relationship of these pathways with LID

Overactivity in the D1 receptor led cAMP-PKA- DARRP 32 pathway has consistently been shown following levodopa administration in animal studies both rodent and primate models. D1 receptor activates the three major products of the signaling pathways ΔFosB, DARPP-32 and ERK1 & 2 (Nicholas et al.,2008; Berton et al., 2009; Santini et al., 2007, Santini et al.,2010) through PKA. PKA inhibitor significantly reduced dyskinesias in a rat model (Lebel et al.,2010). Higher levels of Thr 34 DARPP 32 have been seen in the striatum of dyskinetic rats (Picconi et al., 2003). cAMP-DARRP32 and ERK are shown to be raised in dyskinetic non-human primate model (Santini et al., 2010). D1-mediated signaling in 'direct pathway' MSN has indeed been shown to play a major role in LID across all animal models (*mouse*, Darmopil et al., 2009 ;Santini et al., 2007; *rat*, Lindgren et al., 2010 ; Westin et al., 2007; and *macaque*, Aubert et al., 2005).

Contribution to signaling by the main players D1, D2 and Glutamate receptors:

DA concentration and the mode of release are also important. Phasic release may produce different effects from tonic release. MSNs are constantly bombarded by cortical inputs and tonic release of DA filters a sizable percentage of these glutamatergic inputs. Dopamine through different modulatory routes (D1/D2, cAMP- PKA- DARPP) gates the glutamate cortico- striatal inputs to the MSN.

D1 – NMDA interactions

D1 receptor activation primarily leads to enhancement of NMDAR responses. This is mediated by a number of signaling cascades in the striatum. The most prominent involvement is - PKA → cAMP → DARPP-32 → phosphorylation of NMDAR NR1 subunits and activation of voltage-gated Ca2+ channels, particularly L-type channels (Cepeda et al., 2009). Another important feature to note here is that D1 effect on NMDA depend on the state they are in the 'map' of the action potential curve. If the channel is in a depolarised or 'charged' state then D1 stimulation would increase NMDA activity however if it is in a hyperpolarised state then the opposite i.e. decrease in NMDA activity would happen (Cantrell et al., 1999; Lavin 2001; Durstewitz et al., 2000). D1 stimulation also enhances the trafficking of NMDA receptors and the GluR1 subunit of AMPA receptors to the membrane in neurons (Dunah et al.,2001). Also important to note that a direct interaction between the D1 receptor and the NR1a and NR2B NMDA subunits inhibits receptor function

bidirectionally (Lee et al., 2002). PKA phosphorylates the GluR1 subunit of AMPA receptors at Ser845 thus activating AMPA glutamate transmission (Banke et al.,2000). There is evidence of formation of D1R/NMDAR complexes which has further effects in causing LID and other clinical effects due to impaired trafficking of both receptors (Fiorentini, 2008; Missale et al., 2006; Pei et al.,2006 et al.,Nai et al.,2010).

D1-Electrolytes

D1 receptor activation enhances L-type Ca2+currents in medium-sized striatal neurons possibly via direct phosphorylation of the channel by PKA and inhibition of PP-1 (Surmeier, 1995), causing increased intracellular Ca2+. It also suppresses inward K+ currents.

D2 – NMDA interactions

D2 receptor activation leads to reduction of NMDA currents. In contrast to enhancing effects of D1 the default mechanism for D2 action is inhibitory (Cepeda et al., 1993). Decreased cAMP production and PKA activity are the most prominent routes. However activating the PLC–IP3–Ca2+ cascade (Hernandez-Lopez et al.,2000) and physical coupling between D2 receptors and NR2B subunits (Liu et al., 2006) also can reduce NMDA currents. D2 enhances inward K+ currents and plays a crucial protective role in order to keep the post-synaptic membrane hyperpolarised (Wilson and Kawaguchi et al., 1996). In the denervated striatum state D2 receptors also inhibits glutamate release presynaptically (Bamford et al., 2004a; Bamford et al., 2004b; Calabresi et al.,1993, Cepeda ,,2004;Yin & Lovinger et al.,2006).

Very recently it was shown that D2R's reduced glutamate release by both PKA-dependent regulation of Ca2+ entry through NMDA-type glutamate receptors as well as by produced a PKA independent reduction in Ca2+ influx through R-type voltage-gated Ca2+ channels (Higley & Sabatini et al., 2010).

Intranuclear alterations

In rat models with dyskinesia there is large expression of delta fosB and JunD transcription factors and these correlate with dyskinesias severity (Cau et al., 2010; Cenci et al.,1998; Andersson et al., 2001). There was increased level of delta-FosB proteins after chronic treatment with levodopa compared to increase of both delta FosB protiens and JunD proteins

in the acute phase signifying stability of FosB proteins over time (Valastro et al., 2007). Also there was a positive regulation of prodynorphin gene expression by FosB-related transcription factors in dyskinesias in a rat model (Andersson 2001; Pavon et al., 2006).

Calcium regulated and diacylglycerol–regulated guanine exchange factor (CalDAG-GEF)'s control ERK cascades. Levodopa was shown to atler these CalDAF-GEF proteins and interestingly the level of alteration correlated with dyskinesias (Crittenden et al., 2009). Marked deacetylation of histone 4 with phosphorylation of ERK in both rodent and non-human primate model (Nicholas et al.,2008).The upregulation of these transcription factors alter the genetic expression to maintain LID.

Persistent activation of the another protein kinase in the ERK pathway - mTOR (mammalian target of rapamycin) has been shown to be involved in dyskinesias in a mouse model. Repeated administration of L-DOPA led to a normalization of sensitized mTORC1 signaling. It appears to result from the inability of the MSNs of the direct pathway to normalize their response to L-DOPA during the course of chronic administration (Klann 2009 et al., Santini et al., 2010).

D2 receptors can trigger GSK 3 (glycogen synthase kinase 3) pathway through the formation of a signal complex of arrestin 2 ,PP2A and Akt (Beaulieu 2005 et al., 2008) and this could be relevant in LID (Morrisette et al., 2010) independent of the cAMP- DARPP pathway.

Glutamate changes

Glutamate activates multiple signaling cascades by activation of NMDA/AMPA and mGlu1/5 receptors, leading to the modulation of DARPP-32 phosphorylation and the regulation of PP-1 and PKA activities (Nishi et al., 2005). NMDA/AMPA and mGlu5 receptors in nNOS-positive interneurons stimulate the synthesis and release of NO, leading to activation of protein kinase G (PKG) and leads to DARPP 32 phosphorylation at Thr 34. The NMDA and AMPA increase Calcium in the cells and this also modulates DARRP 32. Through the mGluR5 activation it activates the DARPP 32(Thr 34) system and again opposes it through mGluR1. mGluR5 activates DARPP 32 through two pathways receptor/PLC/CK1/phospho-Ser-130 DARPP-32 as well as via ERK pathway with some

synergistic effect from A2A receptors which facilitate the ERK , increases cAMP and also increase adenosine release presynaptically. (Latini et al., 2001).

There is overwhelming evidence D1 receptors closely interact with glutamate NMDA receptors in striatal neurons. D1 receptor activation has been shown to enhance trafficking of NMDA receptor subunits, promoting clustering of NR1 and NR2 subunits with the postsynaptic density scaffolding protein PSD-95 and enhancing receptor surface expression (Hallett et al.,2006).

There is altered trafficking of AMPA receptor subunits, increased synaptic recruitment of AMPA glutamate receptor subunits in levodopa-induced dyskinesia in the MPTP-lessoned nonhuman primate (Hallett et al., 2005 ; Hurley et al., 2005; Silverdale et al., 2010)

Several phosphorylated substrates are elevated in the dyskinetic striatum. Particularly important substrates include subunits of NMDA (Chase and Oh, 2000 and Dunah et al., 2000) and AMPA receptors (Santini et al., 2007), ERK1/2 (Pavon et al., 2006, Santini et al., 2007 and Westin et al., 2007) and the downstream targets of ERK1/2,including molecules involved in the regulation of protein translation (Santini et al., 2009) and gene transcription (Santini et al., 2009 and Westin et al., 2007).

Increased striatal glutamatergic activity is implicated in the development and maintenance of LIDs (Oh et al., 1998; Chase et al., 2000; Calon et al., 2002; Nash et al., 2002; Robelet et al., 2004).

LID in Parkinson's disease has been linked to altered dopamine and glutamate transmission within the basal ganglia. Compounds targeting specific subtypes of glutamate receptors attenuated LID and the associated activation of striatal nuclear signaling mGlur5 antagonist blocked LID and associated molecular changes (Rylander et al., 2007; Mela et al., 2007).

Very recently Cenci and Konradi have elegantly compiled data from a number of studies (Andersson et al., 2001; Cenci et al., 1999; Valastro et al., 2007; Westin et al., 2007) and have reported an increase of a multitude of phosphorylated signaling proteins (namely thr 34 DARPP 32, ERK 1 / 2, MSK 1 and phospho (Ser10) – Acetyl (Lys14) histone 3) after acute levodopa treatment in all rodents which normalised after subsequent chronic levodopa treatment in the non-dyskinetics unlike the dyskinetic group. (Cenci & Konradi,.2011).

Summary

In summary from these signaling molecular studies, there is an abnormal overactivity of the D1 and NMDA pathway with an increase in the signaling pathways and resulting in a pattern of more phosphorylation of proteins and a balance in favour of the kinases rather than the phosphatases both in the extranuclear and nuclear compartments. Chronic levodopa treatment reverts the phosphorylated products back to the original state in non-dyskinetics only and not dyskinetics. There is overwhelming evidence of increased D1 receptor signalling via striato-nigral MSN pathway leading to increased glutamate receptor system stimulation both ionotropic (NMDA, AMPA) and metabotropic (mGluR5). From the opposite angle antagonists of the glutamate system has been shown to reduce LID and the associated signaling molecules.

1.1.7 SYNAPTIC PLASTICITY AND LID

Synaptic plasticity is one of the fields that has been extensively researched in the last decade in the context of LID's and has contributed greatly to our understanding of the topic. Synaptic plasticity in simple terms is a mechanism by which neurons can modify the behaviour of the neural circuits by altering the strength and efficacy of synaptic transmission.

Synaptic transmission can either be enhanced or depressed by activity, and can be short-term as well as long-term. Indeed repeated activity in synapses and the experience guided refinements and adaptations to accommodate those activities comprise 'learning' and hence these concepts can help understand the molecular changes as well as changes to pathways in neuronal circuits.

Applying it to the basic basal ganglia circuit, the striatal medium spiny neurons are inundated with repeated excitatory glutamatergic inputs and it is interesting to know how these adapt themselves with the processes described above.

Mechanisms of LTP and LTD

There are two main forms of synaptic plasticity are long term potentiation (LTP) and long term depression (LTD). Both seem to be heavily dependent on dopamine regulation in the striatal neurons (Calabresi et al., 1992; 1996).

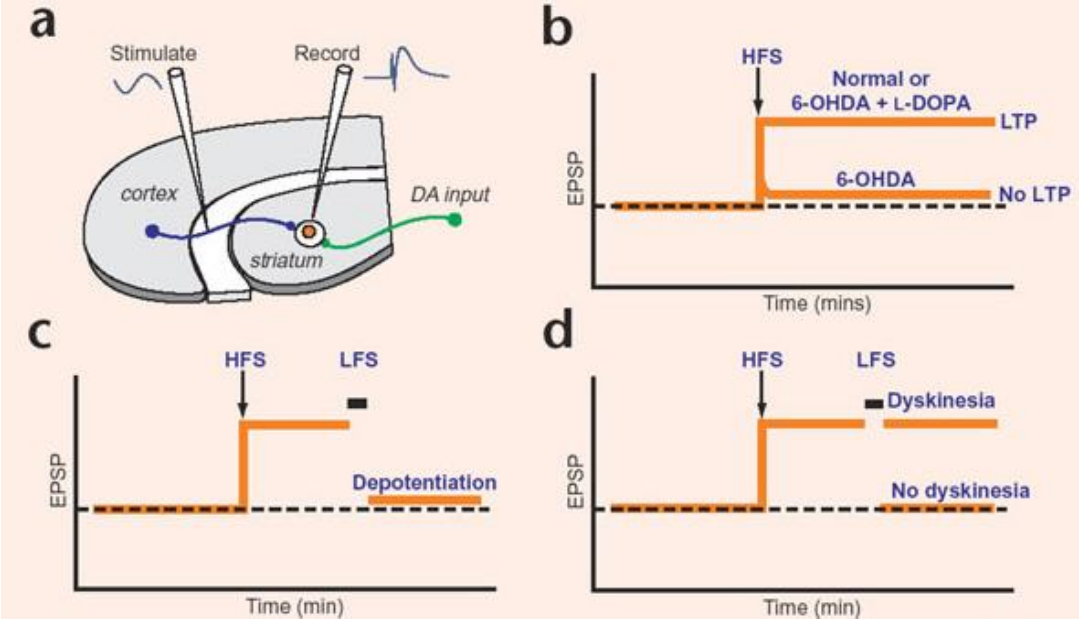


Figure 1.1.7.1 Long-term potentiation (LTP) and depotentiation in striatal slices from normal, 6-OHDA lesioned and L-DOPA treated rats. [(S Dunnett et al., Nature Neuroscience 6, 437 - 438 (2003)].

(a) Brain tissue slice cut at an oblique angle to include corticostriatal (glutamate) and nigrostriatal (dopamine, DA) inputs onto striatal neurons. (b) High-frequency stimulation (HFS) increases the amplitude of the EPSP and induces LTP at normal corticostriatal terminals. Eliminating the dopaminergic input to the striatum with 6-OHDA blocks potentiation, an effect that can be reversed with the anti-parkinsonian drug L-DOPA. (c) Low-frequency stimulation (LFS, 1−2 min) reverses potentiation to baseline levels, a phenomenon called depotentiation. (d) Whereas depotentiation is normal in rats that do not develop dyskinesia, it is blocked in those that do.

This phenomenon underlies the paradigm of long-term potentiation (LTP) in which a short burst of high frequency synaptic input (15 Hz for 15 sec or 100 Hz for 3 sec) results in strengthening of excitatory synapses for a prolonged period (hours to days). Long-term depression (LTD) is the opposite of LTP. It may be experimentally induced by prolonged low frequency (0.5 to 3 Hz) stimulation of excitatory synapses (Dudek et al., 1994). Explaining it in the context of NMDA receptor function at a molecular level, high frequency synaptic inputs may allow the excitatory postsynaptic potentials (EPSP's) generated by AMPAR

activation to accumulate and build over time. Furthermore NMDAR-dependent increase in Calcium activates protein kinases, most importantly CaMKII which leads to additional AMPARs inserted in the PSD (Citri & Malenka et al.,2008). The new synaptic AMPARs are tethered by a number of proteins (TARP-mediated interaction with PDZ).

Induction of LTD is also NMDAR-dependent and, similar to LTP induction. Mechanism of LTD is by modest increase ((submicromolar range (Lee et al., 1998)) in postsynaptic calcium concentration within dendritic spines due to modest activation of NMDARs leads to preferential activation of protein phosphatases. This leads to untethering of AMPARs from their molecular scaffolds in the PSD and their lateral movement to endocytic zones followed by endocytosis and degradation (Citri & Malenka et al.,2008). It is important to note that the direction of plasticity is controlled by the magnitude of the rise in intracellular Ca2+, with a large elevation in Ca2+ evoked by a stronger depolarization favours LTP and the opposite is true for LTD (Harney et al., 2003),

Also the mechanism for reversal of LTP i.e. de-potentiation involves the steps of inducing LTD.

WHAT DOES THESE MEAN IN PARKINSON'S DISEASE AND DYSKINESIA'S ?

In dopamine denervated experimental models of Parkinson's disease there is loss of these both neuroplasticity features of LTD and LTP. Using both toxic and genetic models of Parkinson's disease it was shown that impairment in LTD and LTP induction paralled dopamine depletion and the clinical onset of the symptoms of the disease (Calabresi et al.,1992; Goldberg et al., 2005). Interestingly, with replacement of dopamine i.e. treatment with levodopa LTP expression was restored in the 6-ODHA experimental model of Parkinson's disease (Picconi et al.,2003; Dunnett et al., 2003). When these levodopa treated animals were given low frequency stimulus the nondyskinetic group appropriately reversed the LTP. However dyskinetic group failed to reverse its previously learnt memory of LTP or in other words failed to depotentiate. Even in the face of "synaptic saturation" these receptors continued to potentiate.

This similar abnormal synaptic plasticity i.e. loss of LTP with dopamine depletion and the ability of L-dopa of restoring physiological plasticity by depotentiating processes selectively in nondyskinetic subjects have been also demonstrated in PD patients (Morgante 2006, Prescott, 2009).There are two opposing processes to LTP and LTD include de-potentiation

and de-depression respectively has been shown to be important in maintaining synaptic plasticity in striatal neurones (Picconi et al.,2003; Yasui et al.,2005, Picconi, 2011). These are physiological reversal processes and meant to delete unnecessary information and allow neurones to reset itself to respond appropriately to a given stimulus.

Striatal LTD is also influenced by several other non-dopaminergic neurotransmitters such as acetylcholine,nitric oxide and endo-cannabinoids (Wang et al., 2006; Calabresi et al.,2007; DiFilippo et al.,2009). LTD can also be induced by pre and post synaptic metabotropic glutamate receptors (Pinheiro and Mulle et al.,2008).

Newer terminologies in synaptic plasticity

Metaplasticity

Metaplasticity is a higher-order form of synaptic plasticity that regulates the expression of both LTP and LTD through processes that are initiated by cellular activity that precedes a later bout of plasticity-inducing synaptic activity. Activation by prior synaptic activity and later expression as a facilitation or inhibition of activity-dependent synaptic plasticity are fundamental properties of metaplasticity (Mockett et al., 2008)

Hypothesis for metaplasticity by altering the balance of phosphorylation and dephosphorylation of NMDARs

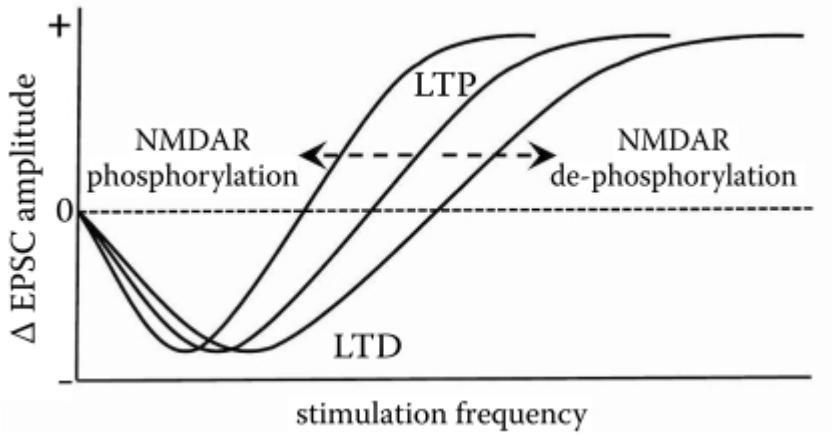


Figure 1.1.7.2 *Adapted from Biology of the NMDA Receptor. Van Dongen AM, editor.Boca Raton (FL): CRC Press; 2009 et al., Taylor & Francis Group, LLC*

While Hebbian plasticity is applicable to individual synapses (Kessels and Malinow, 2009) metaplasticity can tune and manipulate the threshold of synaptic plasticity to increase information storage capacity further and enable acquisition of stimulus-selective responses (Abraham 2008 et al.,; Mockett et al., 2008; Lee et al., 2010)

Metaplasticity is reflected by a right or left shift in the frequency–plasticity relationship. Kinase-induced enhancement of NMDAR function or number results in production of LTP at lower stimulation frequencies. Conversely, when the kinase/phosphatase balance is shifted toward dephosphorylation and suppression of NMDARs, higher stimulation frequencies may be required to elicit LTP.

Homeostatic synaptic plasticity

Homeostatic synaptic plasticity is a negative feedback mechanism neurons use to offset excessive excitation or inhibition by adjusting their synaptic strengths. With this type of plasticity saturated synapses can sense and prevent further potentiation (Pozo & Goda, 2010). A major form of this is "scaling plasticity" which is expressed by scaling up or down the synaptic transmission appropriately depending on status of network activity (Turrigiano & Nelson et al., 2004). It is slow, cumulative and dynamic in contrast to LTD or LTP which are rapidly induced, associative and input specific (Turrigiano, 2008; Pozo et al., 2010 & Goda). For optimal function both hebbian and non-hebbian types of synaptic plasticity is needed (Lee et al., 2010) and a classic example of this has recently being reported where metabotropic glutamate receptors scales down the AMPAR expression both by agonist-independent and agonist-dependent routes (Hu et al., 2010)

Homeostatic scaling is a non-Hebbian form of neural plasticity that maintains neuronal excitability and informational content of synaptic arrays in the face of changes of network activity. Homeostatic scaling is dependent on group I metabotropic glutamate receptor activation that is mediated by the immediate early gene Homer1a. Homer1a is transiently upregulated during increases in network activity and evokes agonist-independent signaling of group I mGluRs that scales down the expression of synaptic AMPA receptors. Homer1a effects are dynamic and play a role in the induction of scaling. Similar to mGluR-LTD, Homer1a-dependent scaling involves a reduction of tyrosine phosphorylation of GluA2 (GluR2), but is distinct in that it exploits a unique signaling property of group I mGluR to confer cell-wide, agonist-independent activation of the receptor. These studies reveal an

elegant interplay of mechanisms that underlie Hebbian and non-Hebbian plasticity. (Hu et al.,2010)

Potentiation (LTP) and depression (LTD) of synaptic strength, can be expressed by the synaptic insertion or removal of AMPA receptors (AMPARs), respectively (Kessels et al., 2009)

Homeostatic synaptic plasticity is a negative feedback mechanism neurons use to offset excessive excitation or inhibition by adjusting their synaptic strengths synaptic changes are associative, rapidly induced and input specific.Neurons have however developed homeostatic mechanisms that sense and prevent saturated synapses from undergoing further potentiation (Pozo et al., 2010)

Synaptic metaplasticity at a single glutamate synapse has been shown to tune plasticity threshold in response to spontaneous glutamate release presynaptically (Lee et al., 2010).

Summary

Synaptic plasticity includes a number of processes that are involved with memory and learning of neurones. The neurones adapt to repeated stimuli in the synapses by experience. In dopamine denervated state i.e. Parkinson's disease state the two main plasticity mechanisms, LTP and LTD fail. However, with chronic levodopa therapy there is recovery of these two processes. However, in the context of dyskinesias there is a barrage of increased excitatory cortico-striatal inputs to the MSNs. In the dyskinetics there is a failure of depotentiation, which is a process to revert from LTP to LTD.

1.1.8 IMPORTANCE OF PET IN PARKINSON'S DISEASE AND PARKINSON'S DISEASE DYSKINESIAS

An accuracy of 90% may be the highest that can be expected with clinical assessment using current diagnostic criteria of Parkinson's disease (Hughes. 2001). Definitive diagnosis is only by demonstration of intraneuronal Lewy body inclusions in the substantia nigra compacta . PET studies have attracted a huge recognition because of its ability to detect disease much before the onset of symptoms. Certainly Parkinson's disease is a classic example to detect preclinical changes. Important to note here are the types of tracers that have been used to make these studies possible. In PD ^{18}F-Dopa can measure terminal dopa decarboxylase activity. ^{18}F-Dopa PET shows the uptake and conversion of flourodopa to fluoro-dopamine. F-dopa crosses the blood-brain-barrier and taken up by the neurons to be converted to flouro-dopamine by the enzyme aromatic acid decarboxylase. This enzymatic conversion step may be the rate limiting factor in dopamine synthesis as well as monoaminergic neurones. F-Dopa is a measure of aromatic acid decarboxylase in these cells.

^{18}F-Dopa PET has shown clinical expression of Parkinson's disease symptoms occur when about 50% of dopamine terminal function is damaged in the posterior putamen (Morrish et al., 1995). In a typical patient with unilateral parkinsonism ^{18}F-Dopa could reveal bilaterally reduced putamen dopaminergic function, with activity being the most depressed in the putamen contra lateral to the affected limb/limbs (Brooks et al.,2010).

Although Parkinson's disease is mainly sporadic in onset, 15% of PD patients have a first-degree relative who has the disease and at least 5% of people are now known to have forms of the disease that occur due to a genetic mutations. PET can detect dopamine terminal dysfunction in the asymptomatic relatives of PD patients. ^{18}F-Dopa was used to study 32 members of unrelated familial kindreds of whom 8 showed reduced uptake in the putamen. Interestingly 3 out of those 8 of them developed clinical parkinsonism in a 5 year follow up period. (Piccini et al., 1997).

Parkin and PINK 1 gene mutations are most commonly related to early-onset parkinsonism. While homozygous mutations in recessive PD genes almost invariably cause PD, heterozygous mutations have been suggested as a susceptibility factor. Compound heterozygote gene carriers of the Parkin mutation with phenotypically mild symptoms or even those without symptoms showed significant reductions of striatal ^{18}F-Dopa uptake

(Khan et al., 2002; 2005). Similar subclinical reduction in striatal uptake has been shown in heterozygous carriers of the PINK1 gene mutation (Eggers et al.,2010).

Mutations of the LRRK2 are the most common known genetic cause for familial and sporadic PD (Healy et al.,2008). PET studies have identified abnormalities in dopamine transporter binding in asymptomatic carriers of the LRRK2 mutation (Adams et al., 2005).

Glucose metabolism studies with [^{18} F] FDG PET (discussed in detail in chapter 2)

[^{18} F] FDG PET studies can give a measure of resting glucose metabolism and hence, neuronal activity. Increased glucose metabolism have been demonstrated in the contralateral lentiform nucleus in patients with early unilateral parkinsonism (Brooks et al., 1993). Covariance analysis has shown hypermetabolism in the lentiform nucleus and thalamus with hypometabolism in the frontal ,parietal and parieto-occipital areas in PD patients (Eidelberg et al.,1994; Brooks et al.,2008).

PET studies of non-dopaminergic neurotransmission

In Parkinson's disease there is loss of serotonergic, cholinergic and non-adrenergic terminals in addition to dopaminergic terminal loss. With ^{11}C-WAY-100635 PET, a reduction in 5-HT1A receptor binding potential in the median raphe has been demonstrated (Doder et al.,2005). [^{11}C] -MP4A (N-11C-methyl-4-piperidyl acetate) PET and [^{11}C] -PMP (N-11C-methylpiperidin-4-yl propionate) PET can be used to study cholinergic function and employing both tracers a reduction of cholinergic terminals have been shown in PD (Hilker et al.,2005). [^{11}C] -RTI 32 uptake (a marker of norepinephrine [noradrenaline] and dopamine terminal function) in the thalamus and locus ceruleus of PD patients suffering from depression (Remy et al., 2005).

Microglial activation (described in detail in chapter 2)

[^{11}C] PK11195 is a marker of microglial activation. Increased binding of this tracer has been described in PD patients in the brainstem, midbrain, striatum, pallidum and frontal cortex of advanced PD patients (Gerhard et al.,2004).

PET STUDIES IN LID

Presynaptic D1 receptor imaging

^{18}F- Dopa

^{18}F-Dopa studies in PD patients with sustained response to levodopa compared to those with a fluctuating dose to the drug showed a reduction of 24 % putaminal uptake in the former compared to the latter group. However there was a considerable overlap in the uptake values in the two groups making it difficult implicate the putamen as the only site for the dopaminergic defect. (de la Fuente-Fernández et al., 2000).

[^{11}C]-d-threo-methylphenidate (MP)

The availability/ density of presynaptic dopamine transporters (DAT) can be assessed with [^{11}C]--d-threo-methylphenidate (MP) PET tracers.

[^{11}C]--dihydrotetrabenazine (DHTBZ)

The type 2 vesicular monoamine transporter (VMAT2) is the protein responsible for pumping monoamines from the cytosol into synaptic vesicles. The density of this transporter in dopaminergic terminals can be measured with [11 C]-dihydrotetrabenazine (DHTBZ) PET.

In a study by Troiano et al., 75 % of patients having both motor fluctuations and dyskinesias showed a significantly lower putaminal MP/DTBZ ratio than the rest 25 % with motor fluctuations only (Troiano et al., 2009). This study shows that there is downregulation of transporter function is an attempt to keep the synaptic dopamine level. Although this study has given support to the presynaptic theories of dyskinesias, such downregulation of transporter function is known in PD patients without any motor complications (Lee et al., 2000). These observations may only reflect disease progression (Vingerhoets et al.,2009).

Post-synaptic D1 receptor imaging

D1 [^{11}C] SCH 23390

D1 [^{11}C] SCH 23390 is a measure of D1 binding in the striatum. It's binding was normal in de novo PD but patients with on chronic treatment with levodopa show a 20% reduction in striatal D1 binding. D1 and D2 receptor availability was assessed in PD LID and PDNLID subgroups. Striatal D1 binding were normal in both groups. The caudate D2 binding was

reduced approximately 15% in both groups and the putaminal D2 binding was normal. Although this study ruled out a primary problem in dopamine receptor binding / availability in causing dyskinesias it did suggest other processes such as non-dopaminergic mechanisms may be involved (Turjanski et al.,1997).

POST SYNAPTIC D2 RECEPTOR

[^{11}C] Raclopride binding is a good measure of D2 receptor availability (Brooks,. 2008). It competes with dopamine to occupy the D2 receptors. So, in denovo PD patients the binding was increased by 20% (explaining the deficiency of dopamine) initially but then normalised with six months of dopamine replacement therapy with levodopa (Playford et al., 1992; Antonini et al., 1994). Conversely dopamine therapy usually results in a reduction of the binding of Raclopide.

In a study by Pavese et al. from our group the reduction in Raclopride binding has been shown to correlate with the clinical improvement of bradykinesia and rigidity in PD patients with levodopa treatment (Pavese et al., 2006). The reduction in Raclopride binding was found to be more in advanced PD and also in dyskinetic PD patients. In the PD LID patients, larger putaminal Raclopride binding changes correlated with the severity of dyskinesia scores during the scan. Another interesting finding in this study was that patients who had a shorter time to reach "on" state with levodopa had more reduction in Raclopride binding implying more of a presynaptic defect rather than post- synaptic sensitization (Pavese et al., 2006). Similar results were also found by de la Fuente-Fernandez et al. who found transient and sharp eight- fold rises in synaptic dopamine level in response to levodopa administration in the striatum of fluctuators as compared to two-fold rises in sustained responders which were followed by a more gradual uprise (de la Fuente-Fernandez et al.,2001). Other studies had also reported inverse correlation of Raclopride binding in advanced PD (Tedroff et al.,1996;).

These surges of dopamine levels in the synaptic cleft rather than the dopamine receptor availability would better explain the fluctuating response to levodopa (Brooks et al., 2008). This view is also strengthened by the [11 C] SCH 23390 study discussed above.

In another [11 C] Raclopride study by (Brooks et al.,1992) showed that PD patients having a fluctuating response to levodopa had a marked decrease in striatal D2 binding potential compared to untreated PD where it was normal or increased.

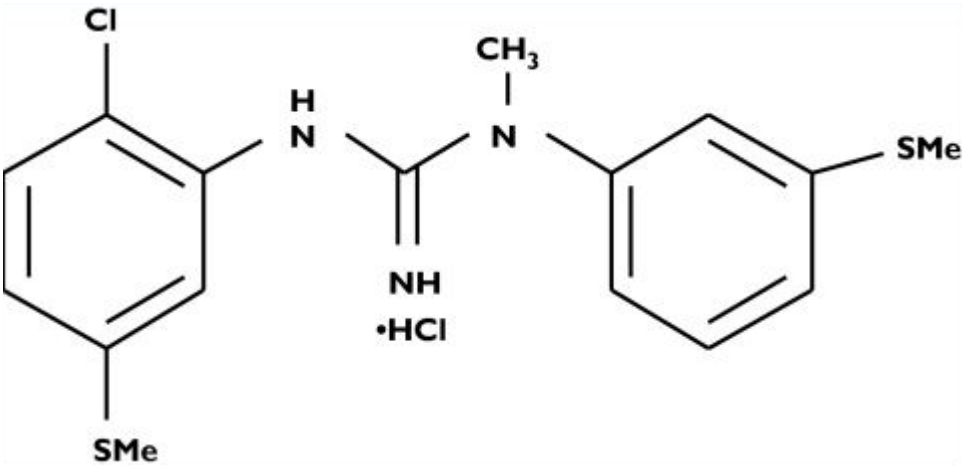
[^{11}C]- diprenorphine

^{11}C -diprenorphine PET is a non-selective marker of μ-,κ-, and δ- opioid sites, and its binding decreases with increasing levels of endogenous opioids namely dynorphin, encephalin and substance P. Dynorphin binds to κ , encephalin to δ and substance P to neurokinin 1. These opioid receptors are located both presynaptically on dopamine terminals, where they regulate dopamine release, and postsynaptically on interneurons and medium spiny projection neurons Significant reductions in ^{11}C diprenorphine binding in striatum, thalamus, and anterior cingulate have been reported in dyskinetic patients, compared with sustained responders (Piccini et al., 1997) implying higher levels of opiods in the former group.

So these imaging studies have so far shown that the dopamine levels are higher in the striatum of motor- fluctuators and dyskinetics and in fact the synaptic dopamine levels fluctuate and increase with levodopa administration. However, there is no increase in receptor availability in D1 or D2, lending support to the theory of dopaminergic neuronal damage and an abnormal pulsatile dopamine level in dyskinetics.

1.2 PET-TRACER USED FOR DYSKINESIA STUDY

[11]C CNS 5161



Chemical structure of [11C] CNS 5161 HCl (Forst et al.,2007)

Chemical name N-(2-chloro-5-methylthiophenyl)-N′-(3-methylthiophenyl)-N′-methylguanidine (CNS 5161) is a high affinity ligand

Characteristics Ki=1.87±0.25 nM . It binds to the PCP site in the NMDA receptor.

Synthesis of the ligand

The synthesis of the (PET) tracer [11C]CNS 5161 was by means of [11C] methylation of the desmethyl guanidine precursor. The compound was produced with a decay corrected radiochemical yield of 10% within 45 min after end of bombardment. The final product was prepared in a sterile saline solution suitable for clinical studies with a radiochemical purity of >96% and a specific activity of 41 GBq/mmol at time of injection (Gibbs et al., 2002 ; Robins et al., 2010).

Safety in pharmacological studies

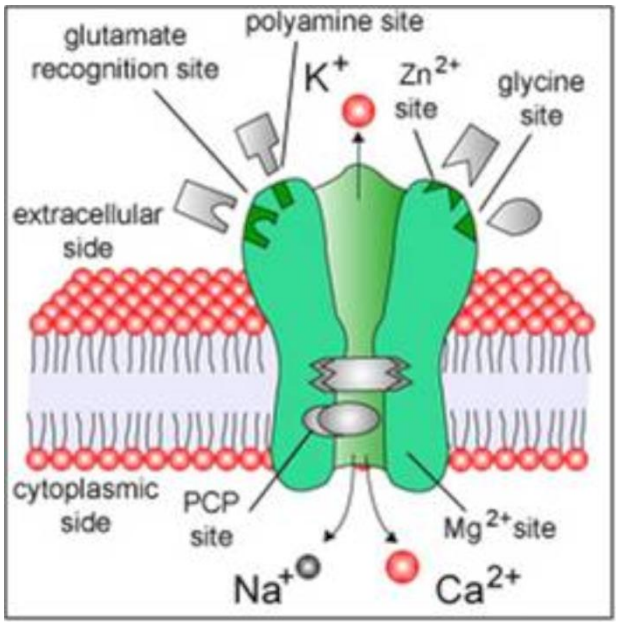
Dose escalating safety study of CNS 5161 HCl, for the treatment of neuropathic pain used successfully in neuropathic pain.CNS 5161 HCl was reasonably well tolerated up to 500

micrograms. The most common adverse events were hypertension, headache and mild visual disorders (Forst et al.,2007).

Role in CNS disorders

CNS-5161 showed increased binding affinity to activated NMDA receptors in the striatum , cortex and hippocampus of rats following stereotactic surgery to the striatum proving its property as an use dependent radiotracer (Schiffer et al., 2005). Similar reports have also been published (Beigon et al.,2007). As has been shown by these studies, CNS 5161 is a use-dependent, open channel blocker with non-competitive properties and is a highly selective blocker. It's binding will only happen when glycine and glutamate are present in excess i.e. in ''activated'' areas. Once the channel is open by the double – activation then only CNS 5161 can bind to the interior of the NMDA receptor. In simpler terms the binding of CNS 5161 will give a measure of activated NMDA receptor in areas of glutamate excess.

Picture of Glutamate receptor with its binding sites; [11C] CNS 5161 binds to the PCP site in the internal aspect of the receptor



1.3 HYPOTHESIS

Levodopa-induced dyskinesias are a major complication of therapy in Parkinson's disease. As levodopa is the gold standard therapy in this disease most patients are put on to this treatment at some point. From the clinical studies we know that about 90 % of such patients would suffer from dyskinesias after 9 years of treatment. These dyskinesias are very disabling to the patients and the treatment options are very limited. The research from animal studies have shown that administration of levodopa increases D1 receptor activity leading to increased glutamatergic stimulation and increased phosphorylation of proteins via a cascade of signaling pathways. Increased glutamate activity has been thought to be a major cause of these dyskinesias. Animal studies have also postulated that the medium spiny neurones in the striatum are subject to excessive glutamatergic cortical inputs arising secondary to an increased cortical drive from the basal ganglia and that failure to shield off these excitatory inputs may be linked to dyskinesias. Moreover experimental studies have shown that the striatal synaptic neurones in animals rendered dyskinetic by levodopa lose their plasticity to adapt to various stimuli and hence become prone to increased stimulation and dyskinesias. From the imaging studies in vivo we know that with every dose of levodopa there is a pulsatile increase in synaptic level of dopamine and the dyskinesias correlate with the level of the dopamine present in the synapses.

From treatment point of view an anti-glutamate agent Amantadine has shown some clinical benefit but the evidence is not convincing. Various studies are now able to show some benefit with the blockage of glutamate receptors and both metabotropic and ionotropic receptor antagonists seem have some effect on dyskinesias. However, because of the lack of knowledge of the precise mechanism of how the dyskinesias occur in humans, the treatment strategies are not specifically targeted. Complete blocking of an essential neurotransmitter like glutamate can jeopardise important cellular mechanisms and hence lead to serious side effects. This has been the story behind the failure of most anti-glutamate agents.

However, in spite of the huge amount research in the animal groups implicating glutamate as one of the major causative factors for Parkinson's disease dyskinesias the precise mechanism is still unclear. This has led to a paucity of treatment breakthroughs. In the last four decades

only one drug, Amantadine, has shown some practical benefit but the clinical evidence for its use is very unconvincing.

The purpose of the study is to quantify glutamate receptor function in vivo in Parkinson's disease dyskinesias using a novel PET tracer [11C] CNS 5161, a NMDA glutamate receptor antagonist. We planned to recruit PD patients both with dyskinesias and without dyskinesias, and normal age-matched volunteers. As [11C] CNS 5161 exhibits fast binding characteristics and binds to the voltage gated glutamate channel only in the open or stimulated state, we proposed to study both groups of PD patients with and withdrawn from levodopa. The study design was to compare the glutamate binding in the 'on' and 'off' state of both PD dyskinetics and non-dyskinetics. The results of the normal volunteers would also be available to compare with both the PD groups without levodopa. We hypothesised that PD patients without dyskinesias will show normal or reduced striatal NMDA binding while these will be elevated in patients with dyskinesia. We estimate the mean striatal and motor cortex NMDA binding values will have a standard deviation of 20% in both the normal subject and patient groups based on previous experience of carbon -11 tracers within the department. Based on this variance 12 subjects in each group will provide us with >80% power to detect a 25% difference in the mean [11C] CNS 5161 uptake in the above mentioned areas ($p<0.05$) between PD groups with and without dyskinesias.

1.4 MATERIALS AND METHODS

Ethics approval was obtained from the Ethics Committee of Hammersmith, Queen Charlotte's & Chelsea and Acton Hospitals Trust.

Administration of Radioactive Substances Advisory Committee (ARSAC), UK gave permission to administer the PET ligands used in the study.

SUBJECTS

Eighteen PD patients were recruited for the study from Imperial College Healthcare Trust. Eight of the PD patients had levodopa-induced dyskinesias and the rest ten were on levodopa but, were not dyskinetic. Five age-matched healthy controls were recruited by local advertisement as well as inviting spouses or relatives.

PDLID

Inclusion criteria

1. Diagnosis consistent with Idiopathic Parkinson's disease (UK Parkinson's Disease Society Brain Bank diagnostic criteria)
2. Currently on levodopa treatment and with good response to the drug
3. Presence of levodopa-induced dyskinesias
4. The ability to lie still in a PET scanner for 90 minutes.

Exclusion criteria

1. Neurological or psychiatric sequelae of PD that may interfere with the patient giving informed consent.
    - depression [Hamilton Rating Scale for Depression (Hamilton, 1960)>16 and Beck Depression Inventory (Beck et al et al., 1961)>9 or

- dementia [Mini Mental State Examination (Folstein et al., 1975) <23] or
- Any other significant neuro-psychiatric sequelae of PD, detected either before enrolment or during initial clinical assessment that may interfere with the patient giving informed consent.

2. Previous neurosurgical intervention (e.g. pallidotomy)
3. Currently treated with Glutamate antagonist
4. Significant co-morbidity (e.g. previous head injury, stroke, heart, lung, renal failure)
5. Contraindication to having a MRI brain

PD NLID

Inclusion criteria

1. Diagnosis consistent with Idiopathic Parkinson's disease (UK Parkinson's Disease Society Brain Bank diagnostic criteria)
2. Currently on levodopa treatment and with good response to the drug.
3. The ability to lie still in a PET scanner for 90 minutes.

Exclusion criteria

1. Neurological or psychiatric sequelae of PD that may interfere with the patient giving informed consent.
    - depression [Hamilton Rating Scale for Depression (Hamilton, 1960)>16 and Beck Depression Inventory (Beck et al et al., 1961) >9 or
    - dementia [Mini Mental State Examination (Folstein et al., 1975) <23] or
    - Any other significant neuro-psychiatric sequelae of PD, detected either before enrolment or during initial clinical assessment that may interfere with the patient giving informed consent.
2. Previous neurosurgical intervention (e.g. pallidotomy)
3. Currently treated with Glutamate antagonist
4. Significant co-morbidity (e.g. previous head injury, stroke, heart, lung, renal failure)

5. Contraindication to having a MRI brain
6. Presence of levodopa-induced dyskinesias

Healthy volunteers

Exclusion criteria

1. Relevant neurological, psychiatric or medical condition(psycho stimulant use/abuse)
2. Taking medication acting on CNS 5161 target
3. Involvement in other studies using ionising radiation
4. Contraindications to having a MRI scan

CLINICAL DEATILS OF SUBJECTS

These are shown in the table below

Daily levodopa equivalent units were calculated as follows:

100mg levodopa = 2mg cabergoline = 1mg pramipexole; or

1mg pergolide = 5mg ropinirole = 4mg rotigotine patch = 0:5mg rasagiline:

The conversion factors below were used for controlled release levodopa and levodopa/carbidopa/entecapone combination:

125mg controlled release levodopa = 65mg levodopa;

50mg levodopa = carbidopa = entacapone combination = 65mg levodopa

TABLE SHOWING CLINICAL DETAILS OF SUBJECTS

Subject Population								
	Gender (M/F)	Age (yrs)	Disease Duration (yrs)	H&Y stage	LEU (mg/day)	UPDRS III (Motor score) off	UPDRS III (Motor score) on	UPDRS IV (Dyskinesia Score)
PD-NLID patients N=10 Mean ± SD	8/2	66.6 ± 8.4	7.1 ± 4.1	2.4 ± 0.2	774 ± 174	36.7 ± 1.6	29.4 ± 1.5	NA
PD-LID patients N=8 Mean ± SD	3/5	66.8 ± 8.8	11.4 ± 4.3	2.6 ± 0.2	1307 ± 439**	41.8 ±2.3**	33.9 ±3.0**	6 ± 0.8
Healthy Volunteers N=5 Mean ± SD	2/3	64.7± 12.3	NA	NA	NA	NA	NA	NA

** $p<0.01$ Mann-Whitney U Test

LEU= Levodopa equivalent Units

PROCEDURE

PRE-SCAN

Consent

The study was explained to all subjects verbally and an information sheet was given to each patient which they could read at their leisure. Written consent was obtained from every subject.

Clinical assessment

PD patients were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987) Subscale 3 (Motor Examination) and 4 (Complications of Therapy) in both "off" and "on" conditions.

SCAN PROCEDURE

MRI Brain

All subjects had a1.5 Tesla MRI (GE scanner at the Robert Steiner Unit, Hammersmith Hospital). T1 volumetric MRI (3D T1 volume, pulse sequence RF-Fast, acquisition times TR 30ms, TE 3ms, flip angle 30 degrees, FOV 25 cm, matrix 156 x 256, voxel dimensions (0.98x0.98x1.6 mm) was acquired for coregistration and anatomical sampling.

T2 weighted images were acquired to rule out any structural abnormality.

PET scans

All PET scans took place at the Cyclotron Building, Hammersmith Hospital.

Each patient had two [11C] CNS 5161 PET scans – once in a practically defined "off" state following a 12-hour withdrawal of medication and the other on a separate day, in an "on" state, one hour after taking a single oral dose of Madopar (200mg levodopa and 50 mg Carbidopa).

On the day on the 'on' scan the patients were given a single dose of Madopar (200mg levodopa and 50 mg carbidopa) orally. The aim of this levodopa challenge was to scan the patients in their 'on' state. In the literature there are varied doses used for the levodopa

challenge. De la Fuente-Fernandez et al., 2004 showed that 1 h after oral administration of 250/25 mg of levodopa/carbidopa, there was a increase synaptic dopamine levels in PD subjects with and without dyskinesias. In addition to all dyskinetics achieving peak-dose dyskinesias even a stable responder has rendered dyskinetic as this dose. Other studies have successfully used a combination of 200mg levodopa and 50 mg carbidopa (Merello et al ,1994; Brusa et al., 2007). I had to be careful in choosing the Levodopa dose as giving a little extra may make the dyskinetic patients unable to stay still in the scanner for the total duration of 90 minutes to control movement artefacts and also potential problems in having arterial sampling during the total duration of the scan. For this reason a dose of 200mg levodopa and 50 mg carbidopa was chosen. All patients achieved an 'on' state with this dose immediately before the scan.

The healthy volunteers had one [11C] CNS 5161 PET scan without levodopa.

Siemens ECAT EXACT HR+ scanner was used for this study with an axial field of view of 15.5 cm. Sixty-three transaxial image planes were acquired as 2.46 mm slices with a reconstructed axial resolution of 5.4 mm and a transaxial resolution of 5.6 mm (Brix et al., 1997).

Each subject had peripheral venous cannulation as well as radial artery cannulation with a 22 G (blue) Venflon.

All subjects had a ten minute transmission scan for attenuation correction using a single rotating external photon point source of 137Cs for subsequent attenuation and scatter corrections.

Approximately 444 Mbq of [11C] CNS 5161 was administered intravenously using a ten ml syringe. All subjects underwent a ninety minute dynamic emission scan.

[11C] CNS 5161 was produced and supplied by Hammersmith Imanet, GE Healthcare.

Continuous arterial blood sampling was performed for 15 minutes with an online detector and then discrete blood samples for well counting were taken at baseline, 5, 10, 15, 20, 30, 40, 50, 60, 75, and 90 minutes. An aliquot of each discrete sample was rapidly centrifuged to obtain corresponding plasma and radioactivity concentrations that were measured in a NaI (TI) well counter for blood and plasma separately. The continuous blood counts were corrected using

the plasma/blood ratio to derive a plasma input function. The plasma was further analyzed for radiolabeled metabolites using high performance liquid chromatography (HPLC) and the plasma input function was corrected accordingly to produce a final parent radioligand input function to be used for quantification.

POST-SCAN

Data Acquisition

Dynamic scans were acquired in three-dimensional mode. PET data were corrected for attenuation, detector efficiency and scatter and reconstructed into tomographic images using filtered back projection (ramp, kernel 2.0 mm FWHM); the 3D emission data were Fourier-rebinned into 2D data sets to increase the speed of reconstruction. Reconstructed voxel sizes were 2.09 x 2.09 x 2.42

PET ANALYSIS [11C] CNS 5161

Movement correction to compensate for head movement in the scanner was done by a post hoc frame-by-frame realignment procedure. Both attenuation corrected (AC) images and non-attenuation corrected images (NAC) were subjected to movement correction. NAC images are used to reduce the influence of redistribution of radiotracer producing erroneous realignments (Dagher et al., 1998) and moreover, these images are sometimes considered to be more useful for the realignment of superficial structures (Kipper et al., 2005) e.g. scalp, compared with attenuation corrected images.

Creation of 90 minute summed image

Using Spectral analysis in Receptor Parametric Mapping software (Gunn. et al.,1997) decay corrected summed images having the total the activity of the 90 minute scan were created.

Wavelet denoising

The movement corrected images were denoised using a level 2,order 64 Battle Lemarie wavelet filter in the Matlab 6.5 (Mathworks Inc et al., Sherborn, Mass et al., USA) (Turkheimer et al., 1999).

Frame by frame realignment procedure

These frames were realigned to an single, early 'reference' frame that had a high signal-to-noise ratio, using a mutual information algorithm (Studholme et al., 1997) . The transformation parameters were then applied to the corresponding attenuation corrected dynamic images. This process was done in Analyze AVW software (Mayo Clinic,USA)

MRI

Pre-processing

Using Analyze7 AVW software each MRI was cubic resliced with windowed sinc interpolation, which gives a good representation of image characteristics during preprocessing stages. (Myers et al., 2002).

Segmentation

The T1-MRI's were segmented by Statistical Parametric Mapping (SPM) 5 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) with the following parameters (Gaussians per class - 2 2 2 4, Affine Regularisation - ICBM space template - European brains,Warping Regularisation – 1,Warp Frequency Cutoff – 25, Bias regularisation - very light regularisation (0.0001), Bias FWHM - 60mm cutoff, Sampling distance – 3).

An in-house probabilistic altas (Hammers et al., 2003) was written in each individual MRI space with the segmentation parameters in the previous step.

Creation of object map for ROI

The normalised written altas (now in MNI space) was used to create object maps for the regions of interest once the grey matter images were convolved with the probabilistic atlas and binarised at 50 % threshold in Analyze AVW. This processing necessary to change the NIFTI header in SPM5 images to match the corresponding parameters in Analyze software.

Coregistration of the MRI images to PET

The MNI T1 image was coregistered and resliced with the dynamic PET image, the summed add image and the binarized thresholded gray matter image. The process was done in SPM5 with Normal Mutual information method incorporating a six parameter rigid body transformation.

ROI analysis in Analyze AVW

The dynamic PET image was sampled with the superimposed object map and the ROI analysis was done for the following regions of interest: caudate, putamen, precentral gyrus, occipital cortex, brainstem and cerebellum. Regions of interest were defined using the object map derived from the probabilistic altas as described above.

Creating input function

The metabolite-corrected plasma input function was created in the Runclickfit software written in Matlab 6 (Mathworks, Sherborne,USA).

Kinetic Modelling

Regional tissue time activity curves were created (for one region at a time) as a function of each voxel of the regions sampled in Kinetic modelling. Spectral analysis was performed for each region of interest. I initially calculated the K1, k2, k3, k4, BP and VD for each region for all subjects. The data quantification from these traditional compartmental models was hampered by high sensitivity to noise at the voxel level, due to the slow wash-out of [C11] CNS 5161.

Rank-Shaping regularization of exponential spectral analysis (RS ESA)

The Rank-Shaping regularization of exponential spectral analysis was the method of quantification of choice in these circumstances because of two reasons, first because the skrinkage parameters are conditioned on the expected signal to noise ratio and second it allowed maximising of the exponential base range, which was otherwise constrained in Spectral analysis (Turkheimer,.2003; Hammers et al., 2007). It produces reliable estimates of volumes of distribution for both plasma and reference tissue modelling with significant levels of measurement noise (Turkheimer et al., 1994, 2007).

Statistical analysis

The left–right averaged 11C-CNS 5161 V_T values in caudate, putamen, precentral gyrus, occipital cortex and cerebellum were used for statistical analysis. Statistical analyses of clinical data were performed with InStat3 for Macintosh (University of Medicine and Dentistry,NJ, USA). Non-parametric ANOVA (Kruskal–Wallis test) was used to assess the

differences in PET measurements among groups. The non-parametric unpaired Mann–Whitney U-test was used to compare PET measurements between patients with PD NLID and PD LID in both ‘ON’ and ‘OFF’ conditions. Finally, the paired Wilcoxon test was used to assess significant changes in PET measurements following levodopa administration within each group.

1.4 RESULTS

Seven patients with Parkinson's disease-NLID had [11C] CNS 5161 PET twice - once after and once withdrawn from levodopa. The remaining three patients with Parkinson's disease-NLID only had the 'OFF' medication scan, as they withdrew their consent after the first PET session. The eight patients with Parkinson's disease-LID were scanned twice, once with and once without levodopa, and they all developed involuntary movements following levodopa administration on the day of the 'ON' condition PET scan. In six of these patients the dyskinesia severity was mild and did not interfere with the scanning procedure. The remaining two patients had moderate dyskinesias with significant head movement. The same two patients also had significant head movement during the 'OFF' condition scan. None of the images of these two patients could be analysed.

Regional mean [11C] CNS 5161 V_T values in all subjects (controls, patients with PD-NLID and PD-LID) are shown in Table 1.4.1 and Fig. 1.4.1.

Table 1.4.2 shows regional mean [11C] CNS 5161 V_T values in the seven patients with PD-NLID and six patients with PD-LID in both 'ON' and 'OFF' states.

In the 'OFF' state

In the 'OFF' medication state, patients with PD-NLID and PD-LID had similar [11C] CNS 5161 V_T values in all the examined regions. Kruskal–Wallis one-way analysis of variance showed no statistically significant effect of group (controls, PD-NLID and patients with PD-LID in the 'OFF' medication state) on [11C] CNS 5161 V_T for all regions sampled in the study (caudate, putamen, precentral gyrus, occipital cortex, brainstem and cerebellum).

In the 'ON' state

Following levodopa, there was a divergent response in the two patient groups. The patients with PD-NLID showed a significant decrease in V_T values in caudate ($p = 0.02$), putamen ($p = 0.02$) and precentral gyrus ($p = 0.03$), whereas patients with PD-LID showed a significant increase in V_T values compared to baseline in putamen ($p = 0.03$) and precentral gyrus ($p =$

0.03). However, there were no significant changes in V_T in the occipital cortex, brainstem and cerebellum of both groups of patients when given levodopa (Table 1.4.2).

When comparing the 'ON' state between groups (Mann–Whitney U-test) (Table 1.4.1 and Fig. 1.4.1), patients with PD-LID had significantly higher mean [11C] CNS 5161 V_T for caudate, putamen and precentral gyrus relative to PD-NLID. [11C] CNS 5161 V_T values for occipital cortex, brainstem and cerebellum in the 'ON' state were not different between patients with Parkinson's disease-NLID and Parkinson's disease-LID.

Figure 1.4.2 shows individual plots of putaminal [11C] CNS 5161 uptake in controls and in the two groups of patients with Parkinson's disease in both 'OFF' and 'ON'conditions.

No correlation was found between striatal [11C] CNS 5161 V_T values and disease severity both 'OFF' and 'ON' medication, as measured by the UPDRS ('OFF' medication, caudate: p = 0.2, r = 0.31 and putamen: p = 0.6, r = 0.14; 'ON' medication, caudate: p = 0.1, r = 0.53 and putamen: P = 0.1, r = 0.52). Similarly, we found no correlation between striatal [11C] CNS 5161 V_T values both 'OFF' and 'ON' medication and levodopa equivalent units ('OFF' medication, caudate: P = 0.2, r = 0.31 and putamen: P = 0.2, r = 0.31; 'ON' medication, caudate: P = 0.2, r = 0.39 and putamen: P = 0.3, r = 0.33). Parkinson's disease-NLID. [11C] CNS 5161 V_T values for occipital cortex, brainstem and cerebellum in the 'ON' state were not different between patients with Parkinson's disease-NLID and Parkinson's disease-LID.

Table 1.4.1. ^{11}C-CNS 5161 Volume of distribution (V_T)

Region	Healthy Volunteers	PD-NLID patients		PD-LID patients		Mann-Whitney U Test	
		off L-dopa N=10	on L-dopa N=7	off L-dopa N=6	on L-dopa N=6	off L-dopa PD-NLID vs PD-LID	on L-dopa PD-NLID vs PD-LID
Caudate Mean ± SD	4.82 ±1.10	4.21 ± 0.55	3.06 ± 0.77	4.1 ± 0.94	4.44 ± 1.13	ns	p = 0.022
Putamen Mean ± SD	5.62 ± 0.60	5.05 ± 0.67	3.49 ± 1.26	4.98 ± 1.1	5.49 ± 1.0	ns	p = 0.022
Pre-central cortex Mean ± SD	4.57 ± 0.51	4.60 ± 0.71	3.19 ± 1.05	4.80 ± 0.8	5.37 ± 0.84	ns	p = 0.005
Occipital cortex Mean ± SD	5.22 ± 0.74	4.27 ± 1.0	3.32 ± 1.56	4.98 ± 1.02	4.96 ± 0.82	ns	ns
Brainstem Mean ± SD	3.32 ± 1.29	3.24 ± 0.71	3.37 ± 1.63	3.87 ± 0.73	3.91 ± 0.64	ns	ns
Cerebellum Mean ± SD	4.85 ± 0.67	4.37 ± 1.89	3.62 ± 1.89	5.80 ± 1.60	5.20 ± 1.03	ns	ns

Table 1.4.2 [11C] CNS 5161 Volume of distribution (V_T): Results of within group comparison between off and on conditions, Wilcox on matched-pairs signed-ranks test. * p < 0.05

Region	PD-NLID patients		PD-LID patients	
	off L-dopa	on L-dopa	off L-dopa	on L-dopa
	N=7	N=7	N=6	N=6
Caudate Mean ± SD	4.07 ± 0.50	3.06 ± 0.77*	4.1 ± 0.94	4.44 ± 1.13
Putamen Mean ± SD	5.0 ± 0.73	3.49 ± 1.26*	4.98 ± 1.1	5.49 ± 1.0*
Pre-central cortex Mean ± SD	4.3 ± 0.71	3.19 ± 1.05*	4.80 ± 0.8	5.37 ± 0.84*
Occipital cortex Mean ± SD	4.22 ± 1.0	3.32 ± 1.56	4.98 ± 1.02	4.96 ± 0.82
Brainstem Mean ± SD	3.17 ± 0.77	3.37 ± 1.63	3.87 ± 0.73	3.91 ± 0.64
Cerebellum Mean ± SD	4.09 ± 0.7	3.62 ± 1.89	5.80 ± 1.60	5.20 ± 1.03

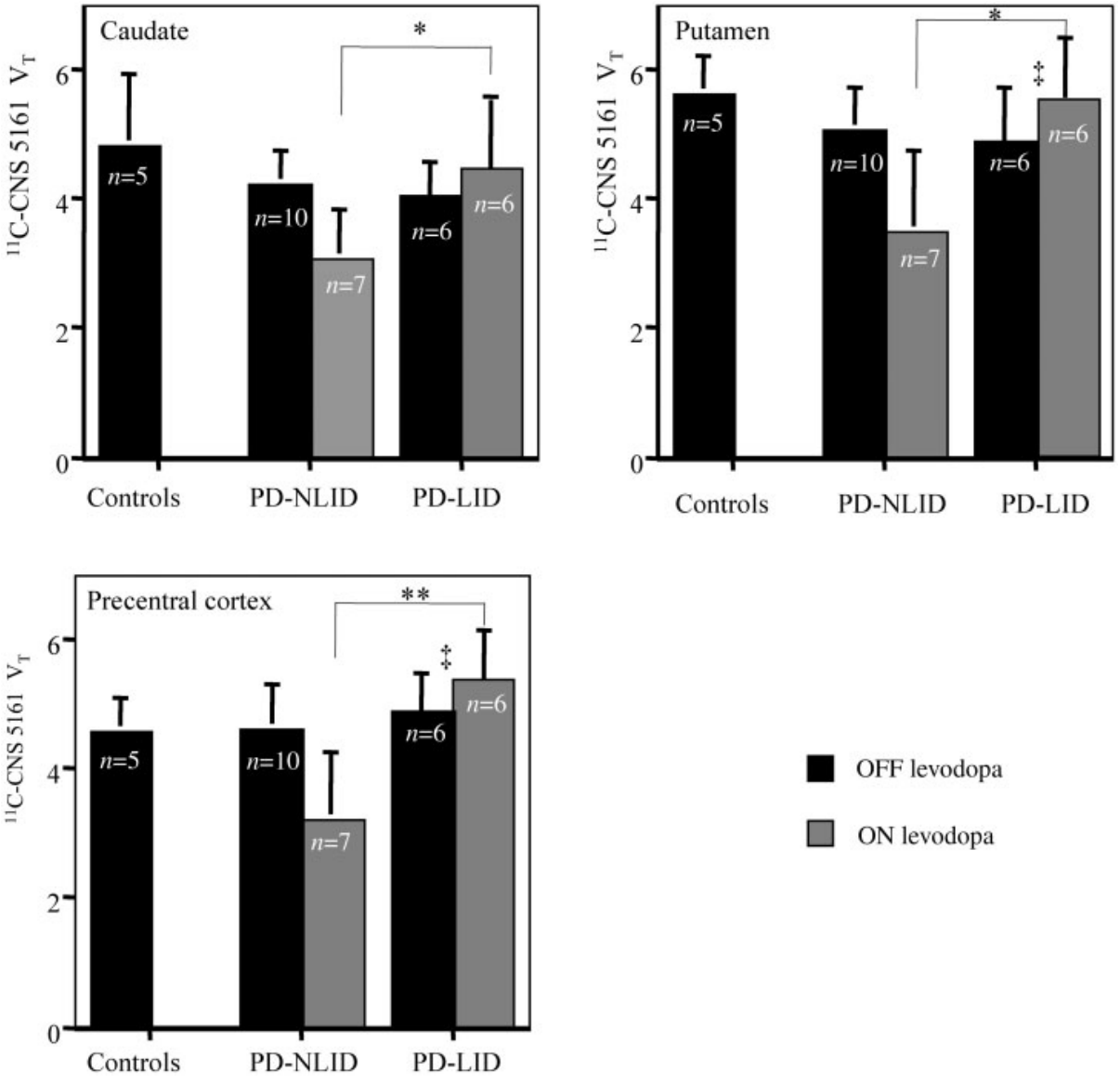


Figure 1.4.1 Regional [11C] CNS 5161 volume of distribution (V_T) values (mean SD) 'OFF' and 'ON' levodopa in controls, patients with Parkinson's disease without dyskinesias (PD-NLID) and patients with Parkinson's disease with dyskinesias (PD-LID). n = the number of subjects in each group. **p < 0.01; *p< 0.05; Mann–Whitney U-test; ‡ p < 0.05 paired Wilcoxon test

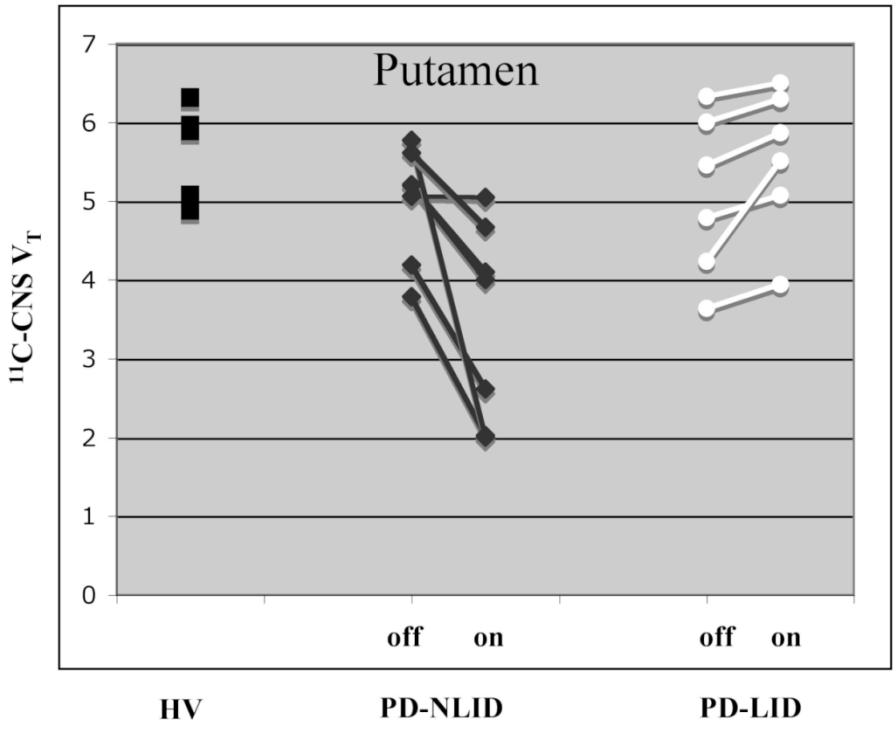


Figure 1.4.2 Individual plots of putaminal [11C] CNS 5161 volume of distribution (V_T) values in healthy volunteers (HV) and in the two groups of Parkinson's disease patients in both 'OFF' and 'ON'conditions. PD-NLID = patients with Parkinson's disease without dyskinesias; PD-LID = patients with Parkinson's disease with dyskinesias.

1.5 DISCUSSION

This is the first in vivo study to demonstrate glutamatergic activity in patients with Parkinson's disease with and without LIDs. The main findings are:

1. When comparing the 'on' state between groups (Mann–Whitney U-test) (Table 1.4.1 and Fig. 1.4.1), patients with Parkinson's disease-LID had significantly higher mean 11C-CNS 5161 V_T for caudate, putamen and precentral gyrus relative to patients with Parkinson's disease-NLID. 11C-CNS 5161 V_T values for occipital cortex, brainstem and cerebellum in the 'on' state were not different between patients with Parkinson's disease-NLID and Parkinson's disease-LID.
2. The PD dyskinetics and PD non-dyskinetics had no significant differences of [11C] CNS 5161 V_T in the 'off' state and had similar values as the controls. But in the 'on' state i.e. when given levodopa the two patient groups had a divergent response. While the dyskinetic group had significantly higher receptor activation compared to their 'off' state , the non-dyskinetics had the opposite response i.e. decrease in receptor activation.

Since our LID-patients with Parkinson's disease had more severe UPDRS scores than NLID-patients with Parkinson's disease, it could be argued that our findings could simply reflect differences in Parkinson's disease severity. However, the two groups were at a similar Hoehn and Yahr stage. In the 'OFF' medication state, they had similar 11C-CNS 5161 V_T values in all the examined regions and they were not different from healthy volunteers. Additionally, no correlation was found between UPDRS scores and striatal [11C] CNS 5161 uptake. It is therefore, unlikely that the difference in non-medicated UPDRS scores is the sole explanation for the differences in [11C] CNS 5161 V_T values seen after administration of levodopa to the dyskinetic and non-dyskinetic Parkinson's disease groups.

Anti-parkinsonian drugs particularly those directly acting on the glutamate system could affect the PET results by blocking glutamate receptors. All patients who were on anti-glutamate drugs such as Amantadine were excluded from the study.

Dopaminergic drugs as well as dopamine agonists can also interfere with the PET results by different mechanisms either by stimulating receptors directly or by influencing the basal

ganglia circuitry. Differing doses of anti-parkinsonian medications can also affect PET results. For this reason we withdrew all dopaminergic drugs as well as dopamine agonists overnight to give the patients a drug free interval of at least 12 hours before the scan. This protocol has been used in several PET studies reported in the literature (van Eimeren et al., 2010 , Pavese et al 2006 , Morishita et al., 2011; De la Fuente-Fernandez et al., 2004).

Again the study design to have two different scans did take off some off some of the above compounding issues. Each patient had two different scans on two separate days – the only difference being a single challenge dose of Madopar (Levodopa/Carbidopa 200/50mg) and this dose was same for all as all these patients. The amount of stimulation of the dopamine receptors could be different amongst these patients but the attempt was made to study the effect of this levodopa challenge in the two groups of patients i.e. dyskinetic and non-dyskinetic.

Lastly, Levodopa could also potentially increase regional cerebral blood flow in the brain. To circumvent this issue I had looked at the difference in not only the motor areas but a non-motor area – occipital cortex. If the results were simply due to blood flow effect then it would be the same in all areas and not selective.

[11C] CNS 5161 uptake was measured in our study. [11] CNS 5161 is a use-dependent, open channel NMDA receptor blocker which means it binds to the receptor only in conditions where glutamate is present in excess. The [11C] CNS 5161 selectively binds to the PCP (Phencyclidine) binding site which is present in the internal aspect of the receptor and can only be accessed when the channel is activated or opened (De Souza et al., 1993) . The opening of the channel happens by a double activation step, first glutamate and glycine binds to the exterior or the extracellular aspect of the receptor which leads to an influx in calcium. This relieves the magnesium block that otherwise keeps the channel closed in resting states (Nowak et al.,1984; Mayer et al., 1984). It is only after this step that [11C] CNS 5161 gets access to the PCP site. This is the only gate of entry to the PCP site of NMDA receptor for Phencyclidine (MacDonald et al., 1991; Lerma et al.,1991), MK-801 (Memantine) (Huettner and Bean, 1988; MacDonald et al., 1991; Jahr et al., 1992; Dzubay and Jahr, 1996) or for any ligand binding specifically to that site within a timespan of couple of hours (De Souza et al., 1993;. Zukin and Javitt, 1993). The PCP site can be accessed even with the channel being

closed but, through a much slower process of diffusion across the lipid bilayer and has a t1/2 of over three hours (Zukin and Javitt et al.,1993) which is far beyond our scan time. It is also known that the presence of glutamate significantly increases the likelihood of channel opening with MK-801 and PCP (De Souza et al., 1993) and this has been very recently shown for [11C] CNS 5161(Biegon et al.,2007). In addition , Schiffer et al. have shown in a recent in-vivo rat study that [11C] CNS-5161 exhibited increased binding affinity for activated NMDA receptors in the ipsilateral striatum and cortex but not cerebellum following stereotactic striatal surgery performed within minutes of [11C] CNS 5161 injection (Schiffer et al., 2005). It is therefore likely that [11C] CNS 5161 in the context of our study, shows similar selectivity to bind to activated glutamate receptors in a 'use-dependent'pattern and its uptake should provide a adequate measure of glutamate channel activation.

From the animal studies, both in the rodent and primate PD models, increased glutamatergic activity has been seen in the dyskinetics. Higher glutamate receptor activation implies an excessive presence of glutamate in the synapses and this was seen in our dyskinetic group compared to the non-dyskinetic group in the 'on' state.

Interestingly the non-dyskinetics showed a decrease in the receptor activation in response to levodopa. Looking at it in a different way, if this group were to show no increase in the receptor activation following levodopa the explanation of a relatively low glutamate level compared to dyskinetics would have sufficed. But the fact that the non-dyskinetics showed a significant decrease may imply the presence of an active process to counteract excess glutamate.

Moreover, there was a selective pattern of receptor activation in both groups. The significant changes that I found in the 'on' state in both groups were in the striatum and motor cortex in PD NLID and the putamen and motor cortex in PD LID , with no significant changes in the brainstem, cerebellum or occipital cortex (non-motor area). As discussed in section 1.1.5 of this thesis the likely anatomical substrates for LID are possibly the MSN's in the striatum where there is an excess of corticostriatal inputs secondary to an increased stimulation arising from the basal ganglia circuit. The exogenously given levodopa increases D1 activity through the direct pathway MSNs. This then leads to increased signaling via D1 – NMDA pathway which results in increased phosphorylation of substrates in both canonical and non-canonical pathways and an excessive activation of glutamate. Chronic levodopa treatment leads to alterations in the synaptic plasticity of these MSN neurones. Animal studies have shown that

the non-dyskinetics counteract the overactive signaling drive and excess glutamatergic stimulation when given levodopa. There neurones still have the adaptability and plasticity to downscale the process. This is not the case in dyskinetics.

Reason for reduced glutamate activation in the 'on' state of non-dyskinetics

The reason for the non-dyskinetics having a reduction in glutamate receptor activation is because of D2 – NMDA interactions both in the striatum and motor cotex. Striatal presynaptic D2 stimulation inhibits the release of glutamate (Calabresi et al., 1993; Bamford, 2004a; Bamford et al., 2004b; Picconi et al., 2004; Dani & Zhou et al., 2004; Yin & Lovinger et al., 2006; Surmeier et al., 2007; Higley & Sabatini 2010). These are in response to the presence a relatively high glutamate in the striatal synapse which resulted from exogenous levodopa →D1-NMDA→excess glutamate. D2 – NMDA leading to suppressed glutamate has also been described in cortical neurones (Wang, 2002; Kotecha et al., 2002; Tseng and O'Donnell 2004; Beazley et al., 2006; Zheng 1999; Trantham-Davidson et al., 2004).

Explanation for increased glutamate activation in the 'on' state of dyskinetics

The dyskinetic PD group when given levodopa activates the striatal D1 receptors MSNs in the striato-nigral pathway followed by D1 – NMDA interactions leading to increased glutamate receptor activation as described above. Increased cortical D1- NMDA interaction leading to glutamate enhancement has been reported in a number of studies (Cepeda et al., 1992; Cepeda et al., 2009; Wang & O'Donnell, 2001; Grace & Lavin et al., 2001; Kruse et al., 2009).

D2 mediated glutamate release and the processes just discussed would try and keep the synaptic membrane in a down-state to shield off further bombardment from the cortico-striatal inputs (Calabresi et al.,1987). With increasing numbers of asynchronous volleys of cortico-striatal inputs, D1 activity takes over with increased membrane depolarisation, increased intracellular calcium, increased cAMP- signaling pathways finally leading to an increased glutamate activation (Stern et al., 1997; Cepeda et al.,2001; Dani and Zhou et al.,2005; Mahon et al.,2006; Westphal et al.,1999). It seems therefore , in the dyskinetics there is a failure of the descaling mechanisms paralleling our patients' inability to control the excessive movements.

Recently an experimental study showed levodopa administration in the striatum but neither GP nor SnR triggered dyskinesias in a rodent PD model that was already rendered dyskinetic following chronic levodopa treatment (Buck et al., 2010). Also MSN spine loss in LID (Schuster. 2009; Soderstrom et al., 2010) and a correlation of LID with the severity of spine loss (Soderstrom et al., 2010) all point towards the corticostriatal afferents and the striatum to be the primary area of damage.

Our study is in concordance with animal studies which have shown increased glutamate neurotransmission with levodopa in dyskinetics. Our findings also support experimental studies implicating the striatum to be the main structure and the failure to contain the overwhelming volleys of corticostriatal afferents to the striatal MSNs may be the main mechanism involved in the generation of LID.

1.6 CONCLUSION

Our study shows is the first in vivo study in human subjects to demonstrate the NMDA glutamate system overactivity with levodopa administration in dyskinetics. This study is in line with the animal studies which have shown glutamate overactivity taking the centrestage in causing the dyskinesias due to levodopa. Our findings lend support to the use of glutamate antagonists in dyskinesias due to levodopa. We have also shown that the glutamate activity in the non-dyskinetic PD patients are suppressed when they are given levodopa. This suggests the presence of an active descaling mechanism in the non-dyskinetic PD patients which is absent in the dyskinetics, implying a failure to contain the excess glutamate in the latter. Therefore from a therapeutic perspective anti-glutamate agents could have a beneficial effect in controlling LIDs.

It is well known the spillover of glutamate into the extracellular space can activate presynaptic ionotropic and metabotropic glutamate receptors. Although our study is limited to the NMDA subunits of the inotropic glutamate system it does reflect the picture of increased glutamate activation in both the inotropic and metabotropic receptors. It therefore explains why the non-NMDA glutamate antagonists i.e. AMPA and metabotropic, have been successful in attentuating dyskinesias in animal studies. Topiramate, an AMPA glutamate antagonist, significantly reduced levodopa-induced dyskinesias in the MPTP-lesioned marmoset model of PD (Silverdale et al.,2005). Combined AMPA and NMDA receptor blockade at low doses have been found to be effective in reducing LID in animal models (Bibbiani et al., 2005).

The failure of anti-NMDA agents in LIDs have been due to side-effects or lack of efficacy. Remacemide and riluzole in a larger trials and was found to be safe and well tolerated but did not show any demonstrable anti-dyskinetic benefit. Dextromethorphan failure in clinical trials were due to a narrow therapeutic window. NR2B-selective antagonist traxoprodil reduces LIDs in levodopa-treated PD patients but met with side effects of dissociation and amnesias. Glutamate is an excitatory neurotransmitter which is essential for normal synaptic activity and the failure of the anti-NMDA drugs is mostly because of the non-selectivity in receptor blockade. Novel NMDA antagonists drugs which spare normal physiologic activity whilst blocking the receptors which are pathologically overstimulated and ‘opened’ by the presence

of excessive glutamate i.e. open-channel blocker may be more effective in circumventing the side-effects. Also NMDA antagonists having less affinity which have a lesser dwell time in the receptor (faster off-rate) may be better tolerated as seen in the case of memantine a which is widely used in dementia.

Developing drugs that target specific subtypes of glutamate receptors in use-dependent sites may be the way forward in treating levodopa-induced dyskinesias.

CHAPTER 2

PARKINSON'S DISEASE DEMENTIA (PDD)

2.1.1 INTRODUCTION

Parkinson's disease is the second most common degenerative disease. Although motor symptoms predominate during the initial presentation of the disease, non-motor symptoms gradually build up over time. It is now increasingly recognised that the impact of the non-motor symptoms have a huge bearing on the patients, carers and the society as a whole. Parkinson's disease dementia forms a substantial part of the non-motor symptoms. The incidence rate is about four to six-fold compared to the normal population and a third to one half of the Parkinson's disease patients would suffer from dementia. The risk of dementia in a Parkinson's patient seems inevitable if they live longer than twenty years with the disease. With the increasing life expectancy, dementia in Parkinson's disease is expected to be more of a problem in future.

The problem is huge but the treatment options are little. The cause of dementia in Parkinson's dementia is still unclear and therefore therapeutic targets are less. Around a third of the dementia sufferers in Parkinson's disease have concomitant Alzheimer's type pathology. It is now possible to image amyloid with [11C] PIB and several groups have found increased amyloid load in Alzheimer's disease. It is important to look into amyloid pathology in PDD to gain further insight into the cause of the disease as it might open up potential therapeutic targets.

2.1.2 EXTENT OF THE PROBLEM

PDD accounts for 3 - 4 % of all dementia patients in the general population. The estimated prevalence of PD-D in the general population aged 65 and over was found to be 0.2 to 0.5% (Aarsland et al.,2005)

The incidence rate of dementia is increased 4- 6 times in PD patients as compared to controls (Breteler et al., 1995; Rajput et al., 1987; Aarsland et al., 2010). Incidence rates of 95 – 112 % in 1,000 patient-years have been published indicating that ~10% of a PD population will develop dementia per year (Aarsland et al., 2001; Marder et al., 1995 ; Hobson et al., 2005). Incidence estimates of dementia in PD correlate with the patient's age and increase with age from 2.7% per year at ages 55 to 64 to 13.7% per year at ages 70 to 79 (Mayeux et al., 1990; Biggins et al., 1992; Aarsland et al., 2001) and can reach upto 90 % by age 90 years (Buter. 2008).

Point Prevalence rate

Point prevalence of PDD is approximately 30% (Aarsland et al., 2005). In other studies, prevalence rates of dementia in PD patients have been reported between 20 – 48 % (Brown et al., 1984; Hobson et al., 2004; Athey et al., 2005; de Lau et al., 2005; Cummings et al., 1988). In newly diagnosed PD patients about a third may have cognitive decline (Reid et al., 1989; Foltynie et al., 2004)

Period (Cumulative) Prevalence

As PDD patients have a significantly higher mortality compared to non-demented PD counterparts, estimating the prevalence at discrete time points will not reflect the true extent of the disease (Buter et al., 2008; Emre et al., 2007). Period prevalence may be a more accurate measure in these circumstances. The period or cumulative prevalence is reported to be very high and at least 75% of PD patients who survive for more than 10 years would develop dementia (Aarsland et al., 2010a). Various other studies have shown period prevalences ranging from 48 % to ~ 80% (Reid et al., 1996; Aarsland et al., 2003; Portin et al., 1986; Healy et al., 2005; Buter et al., 2008; Healy et al., 2008)

Morbidity and Quality of life

PDD has a profound influence on the quality of life of the patients as well as the carers. It contributes specifically to the carers' burden over and above the motor disabilities associated with the disease (Aarsland et al.,1999 et al.,2007; Schrag et al.,2000; Martínez-Martín et al.,2005).

PDD patients are more likely to require higher levels of institutional compared to non-demented PD patients matched for the same level of physical disabilities (Tison et al., 1995; Aarsland et al., 2000; Parashos et al., 2002). Management of these patients has a direct bearing on the health care burden to the society (Spottke et al., 2005).

Mortality

More importantly there seems to be a significantly higher mortality in PD patients with dementia compared to the ones without (Louis et al., 1997,: Rippon et al., 2005, Buter et al., 2008; Levy et al., 2002). Recently in a long-term prospective study, Forsaa et al have reported a two- fold higher hazard ratio in demented patients compared to the non-demented PD ones, after adjusting for motor disabilities (Forsaa et al., 2010).

Mean time from onset of dementia and course

The mean time from onset of PD to dementia is approximately 10 years although it can vary widely in different patients (Hughes et al., 2000; Aarsland et al., 2003). Very recently Aarsland et al have shown that the rate of global cognitive decline in PDD patients is non-linear. The authors report that after a relatively stable period there is an inflection point in the trajectory of cognitive decline at approximately 13 years following which there is a rapid downhill course (Aarsland et al., 2010b). Interestingly an inflection point has also been noted in AD patients as well (Johnson et al., 2009). In one prospective study, the mean annual decline on the MMSE during 4 years was 1point in non-demented and 2.3 points in the PD-D group, the latter figure being similar to the decline observed in patients with AD (Aarsland et al., 2004).

Risk factors

Although several factors like age, disease duration, lower education, male gender, visual hallucinations etc have been reported as possible risk factors for dementia (Levy et al., 2000; Galvin et al.,2006), only few were found to be more consistently associated in longitudinal

studies. These were older age, axial extrapyramidal system involvement and mild cognitive impairment at baseline (Emre et al., 2007). Non- tremor dominant PD alone was the strongest predictor of high mean cortical Lewy body score. This subgroup of PD also demonstrated to have a higher cortical amyloid plaque load and cerebral angiopathy than early disease onset and tremor dominant groups (Selikhova et al., 2009).

Age

Young onset PD patients have a lesser chance of suffering from dementia. Regardless of the disease duration young patients tend not to get this complication. After median disease duration of 18 years, only 19% of young onset PD patients (13% of those younger than 60 years and 43% of those 60 years or older) had cognitive impairment only (Schrag et al., 1998). In a recent clinic-pathological study it was shown that the earlier disease onset PD patients had the longest delay to the onset of cognitive decline (Selikhova et al., 2009).

2.1.3. Terms and abbreviations for the Lewy body disorders

Before going in to the clinical diagnosis and expression of the disease, it will be helpful to clear few terms and abbreviations used confusingly in the literature.

Term	Abbreviation
Dementia with Lewy bodies	**DLB**
Parkinson disease	**PD**
Parkinson disease with dementia	**PDD**
Lewy body dementias (PDD and DLB)	**LB dementias**
Lewy body disease (PD, PDD, and DLB)	**LBD**

(Lippa et al., 2007)

2.1.4 DIAGNOSIS OF PARKINSON'S DISEASE DEMENTIA

Clinical distinction between PDD and DLB, at least in the research setting, is by the temporal requirement that Parkinsonism precedes dementia by more than 12 months (McKeith et al., 2005). These criteria however do not otherwise indicate differences between PDD and DLB.

Emre et al., published a detailed criteria for the diagnosis of PDD based on the studies using the one year rule, as the primary source (Emre et al., 2007). However, on a simple and a practical basis a diagnosis of PDD is applicable when dementia develops within the context of established PD, whereas a diagnosis of DLB is appropriate when the diagnosis of dementia precedes or coincides within 1 year of the development of motor symptoms (Lippa et al., 2007; Emre et al., 2007).

The detailed diagnostic criteria are given below.

2.1.4.1 Features of dementia associated with Parkinson's disease

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:

- Impairment in more than one cognitive domain
- Representing a decline from premorbid level
- Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:

• Attention: Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day

• Executive functions: Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)

• Visuo-spatial functions: Impairment in tasks requiring visual-spatial orientation, perception, or construction

• Memory: Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall

• Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present

2. Behavioral features:

• Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior

• Changes in personality and mood including depressive features and anxiety

• Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects

• Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions

• Excessive daytime sleepiness

III. <u>Features which do not exclude PD-D, but make the diagnosis uncertain</u>

• Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging

• Time interval between the development of motor and cognitive symptoms not known

IV. <u>Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D</u>

• Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:

Acute confusion due to

a. Systemic diseases or abnormalities

b. Drug intoxication

Major Depression according to DSM IV

• Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Criteria for the diagnosis of probable and possible PD-D

Probable PD-D

A. Core features: Both must be present

B. Associated clinical features:

• Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)

• The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis

C. None of the group III features present

D. None of the group IV features present

Possible PD-D

A. Core features: Both must be present

B. Associated clinical features:

• Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention

• Behavioral symptoms may or may not be present

OR

C. One or more of the group III features present

D. None of the group IV features present

2.1.5 CLINICAL EXPRESSION OF THE DISEASE

The salient clinical features of PDD are an insidious onset and slowly progressive course of cognitive impairments in attention, executive and visuospatial functions as well as memory, with relatively preserved core language functions. Executive functioning seems to be predominantly affected (Canavan et al., 1989; Lewis et al., 2005). Some of these features need to be discussed in a little more detail to understand the profile of these patients as compared to DLB and AD.

Assessment of Global Efficiency

The test proposed for assessing global effeiciency in PDD is the Mattis Dementia Rating Scale (DRS). It looks at five areas, most of which are particularly sensitive to the changes that characterize subcortical-frontal dementias (attention; initiation and perseveration; conceptualization; memory)

Attention

Deficits in attention are one of the consistent features in PDD. Several studies have convincingly shown the impairment of attention in these patients but, most do not clearly distinguish PDD from AD or DLB (Aarsland et al., 2003). One study which looked at fluctuating attention in addition to other parameters showed that PDD and DLB patients differed significantly in the tasks of reaction time and vigilance in comparison to those with AD or PD (Ballard et al.,2002). This study emphasized the deficit of fluctuating attention in the Lewy body dementias. Varnese et al have very recently demonstrated that fluctuating cognition is a vital parameter to distinguish between PDD and DLB. Different subsets of cognition are impaired in PDD and fluctuating cognition is the clinical variable associated with a DLB pattern of impairment in PDD. PDD with cognitive fluctuations has the same clinical phenotype of DLB unlike PD non-fluctuators (Varnese et al., 2010)

Memory

Memory impairment as a presenting complaint is seen in 67 % with PDD, 94% with DLB and 100 % with AD (Noe et al., 2004). Memory impairment is often the earliest feature of both AD and DLB, but with time, cognitive deficits become widespread (Salmon et al.,

2009). This lower percentage could be explained by the insidious onset and the presence of other motor deficits in PDD patients. Differences were noted on the Memory subscale of the DRS between PDD-DLB compared to AD but only in the milder severity group (Aarsland ,2003; Litvan et al.,1991; Paolo et al., 1995)

Amongst the short-term memory group digit span assessment showed a difference between PDD and AD (Starkstein et al., 1996). Verbal memory tests of list learning and story recall were impaired to the same extent in PDD and AD patients (Noe et al., 2004; Starkstein et al., 1996; Pillon et al., 2003; Kuzis et al.,1999). Verbal and visual memories are affected in PDD and AD but, less severely in the former group (Pillon et al., 1993; Noe et al., 2004). Cued recall seems to be particularly more impaired in PDD (Pillon et al., 1993; Higginson et al., 2005).

Executive function

Verbal fluency accounts for the major part of the Initiation and Perseveration Scale of the DRS. PDD patients may be more selectively impaired in tests of verbal fluency compared to the AD group. Initiation, perseveration and construction skills may be more severely deranged compared to AD (Aarsland et al., 2003). In a recent study, DLB and PDD with fluctuations had predominant deficits in attention and initiation/perseveration domains compared to the PDD without fluctuations (Varnese et al., 2010). Concept formation has been tested using the "Conceptualization subscale" of the DRS and various other tests (Aarsland et al., 2003; Litvan et al., 1991; Paolo et al.,1995; Noe et al., 2004). Trail Making Test is quite useful in testing conceptualization ability and it is a process of complex visual scanning with a motor component that mainly assesses shifting aptitude (Reitan et al., 1955). DLB patients have more deficits in the conceptualisation scores compared to PDD (Aarsland et al., 2003). Overall, significant executive functioning deficits are present in PDD patients, probably more compared to AD (Emre et al., 2007).

Construction, Praxis and Instrumental Functions

Although PDD has been reported to be mainly a "dysexecutive " dementia, instrumental functions may also be impaired, reflecting possible cortical involvement (Cummings et al.,1988). These functions can be elicited by testing complex visual functions including visioconstructional tasks (Clock drawing test), Visio-spatial tasks (the Benton line orientation test) and Visio-perceptional tasks (Benton face recognition test), and language (Boston

naming test). The Clock-Drawing Test and design copying tests showed impairment in all groups but more so in the Lewy body dementia group (Paolo et al.,1995; Cormack et al., 2004). The general pattern of greater visuoperceptual, visuospatial, and visuoconstructional deficits, attention, and executive function impairment is more prevalent in Lewy body dementia than AD (Guidi et al.,2006; Stravitski et al.,2006; Salmon et al.,2009) , but it is much more conspicuous in cases of DLB (Hamilton et al., 2008; Mosimann et al., 2004). The AD group had significant problems with speech content and anomia whereas PDD patients had smaller phrase length, impaired speech melody and dysarthria, implying more serious deficits in core language functions in AD (Pillon et al., 1993; Cummings et al., 1988).

Subcortical and cortical dementia

The main characteristics of subcortical dementia syndrome are a slowing down of cognitive processes (bradyphrenia), a preferential disturbance of the fundamental processes (memory, motivation, attention, etc.) and a relative preservation of specific functions (speech, praxis, gnosis) (Habib et al.,1989).

In subcortical dementias the major deficits are in working (immediate) memory and retrieval of information from longer term memory stores, reflecting dysfunction of frontostriatal systems (Perry et al., 1996). Janvin et al. showed that Lewy body dementia group were twice more likely to have a subcortical dementia profile than having a cortical-type deficit while the opposite was true for the AD group. Also Lewy body dementias dominated the subcortical profile by a ratio of 1.5 as compared to AD (Janvin et al., 2006). Pagonabarraga et al. have shown an abrupt decrease in the cortical functions in PDD which differentiated them from MCI-PD (mild cognitive impairment inPD), and nondemented PD patients. (Pagonabarraga et al., 2008).

Conclusions on the Profile of Cognitive Impairment

PDD patients have impaired attention, memory, executive and instrumental functions. There are some phenomenological differences between PDD and AD, particularly in executive functions, so that a “subcortical” or “dysexecutive” pattern predominates in PD-D, although having ‘grey’ areas. These patterns may be easier to see in the earlier phases of the disease but, the picture is much more blurred in the advanced stages of the disease making clinical differentiation very difficult.

2.1.6 PATHOLOGICAL STUDIES IN PARKINSON'S DISEASE DEMENTIA

Molecular classification of parkinsonian disorders

The essential neuropathology of PD neuronal loss in the SNc associated with Lewy pathology (Gelb et al.,1999). However, neuronal loss in the SNc is found in a wide range of Parkinsonian disorders as listed below in Table 2.1.6.1 and dementia can be a feature in several of these disorders. These disorders are broadly classified as those with and without α-synuclein pathology.

α-synucleinopathies
•Parkinson's disease
•Dementia with Lewy bodies
•Multiple system atrophy
•Neurodegeneration with brain iron accumulation
Non-α-synucleinopathies
Tauopathies
•Progressive supranuclear palsy
•Corticobasal degeneration
•FTDP-17
•Guam Parkinson-dementia complex
•Dementia pugilistica
TDP-43 proteinopathies
•FTLD-TDP
•Perry syndrome*
Nonspecific degeneration in the SNc
•Autosomal recessive juvenile parkinsonism
•Some cases of parkinsonism due to mutations in LRRK2

Table 2.1.6.1 Molecular classification of parkinsonian disorders FTLD-TDP=frontotemporal lobar degeneration with TDP-43 inclusions. FTD-17=frontotemporal dementia with parkinsonism linked to chromosome 17. *Parkinsonism with pallidonigral TDP-43 proteinopathy.

α-synuclein and Lewy pathology

Aggregations of α-synuclein neuronal inclusions, collectively referred to as Lewy pathology, are characterised by Lewy bodies (LB), which are globular eosinophilic inclusions in neuronal perikarya (Spillantini et al., 1997). Inclusions can also develop in neuronal cell processes which take a spindle– or thread-like Lewy neurites. (Figure 2.1.6.1). These aggregations can be of different types – those having haloes and well-defined appearances are

described as classical Lewy bodies and those having less compact appearances without haloes are referred to as cortical-type Lewy bodies.

While Lewy pathology is usually found in the SNc, this pathology is also found in many selectively vulnerable neurons throughout the CNS in end-stage PD, PDD, and DLB, including the spinal cord, medulla, pons, midbrain, diencephalon, basal forebrain, amygdala, olfactory bulb, limbic cortex, and higher order association cortices (See table below)

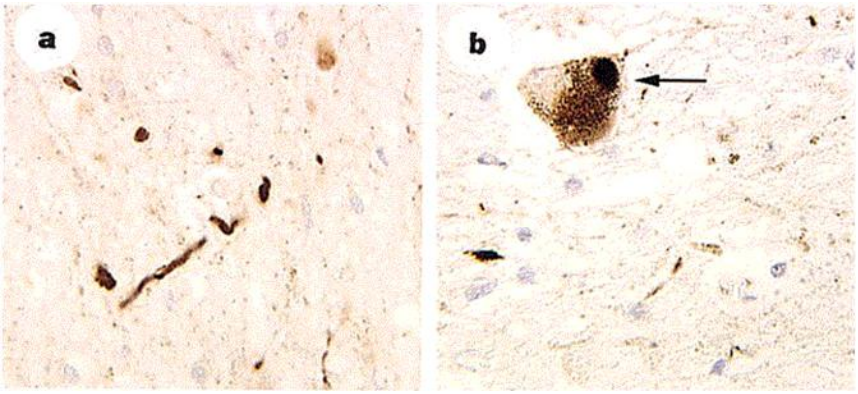


Figure 2.1.6.1 Showing a,-Synuclein-positive Lewy neurites in the substantia nigra. b, - α -Synuclein-positive Lewy body (arrow) in pigmented nerve cell of the substantia nigra (Picture source-Spillantini et al et al.,Nature 388, 839-840 1997)

2.1.6.3. Braak staging

Braak et al. have proposed a staging system for Lewy pathology in PD, possibly progressing from enteric and autonomic nervous system to the brainstem and then to cortical areas (Braak et al., 2003) (Table 2.16.2). The stages correspond roughly to the classification of Lewy body disorders proposed by Osaka et al. (1988) which was used in the consensus criteria for the diagnosis of DLB (McKeith et al.,1996;2005).

According to Kosaka *	According to Braak
	• Enteric nervous system • Peripheral autonomic system • Spinal Cord
Brainstem Lewy body disease	Braak PD stages 1-2 • Vagal dorsal motor nucleus • Lower raphe nuclei • Locus coeruleus
Transitional Lewy body disease	Braak stages 3 – 4 • Substantia nigra pars compacta • Amygdala, basal nucleus of Meynert • Intralaminar thalamic nuclei • Hippocampal CA sector
Diffuse Lewy body disease	Braak stages 5 -6 • Cingulate cortex • Temporal cortex • Frontal cortex • Parietal cortex

*The same affected areas are assumed for the Kosaka criteria as listed for the Braak criteria.

Table 2.1.6.2 : Anatomical regions susceptible to Lewy pathology, according to two major classification schemes

Pathogenesis of PDD

Pathological studies of PDD can be broadly classified into three main groups: coexisting AD pathology, nigral and brainstem pathology with increased LBs and the third, limbic and cortical LB-type degeneration (Emre et al., 2007). On the basis of the recent studies using α –synuclein immunohistochemistry, and assessing several potential pathological correlates simultaneously, the third group seems to play a major role in PDD. But, whether there is a spread of LB pathology from the brainstem to the cortex, implying PD and DLB are part of a continuum, or whether LB pathology in cortical and subcortical areas occurs concurrently is a matter of debate.

Although DLB and PD are thought to be part of the same clinical spectrum, neuropathological studies differ widely as regards to the aetiological processes. While some reports have suggested significant differences between DLB and PDD, others have found few neuropathological differences but none significantly robust enough to enable their differentiation (Aho et al.,2008; Beach et al.,2008; Hely et al.,2008; Lashley et al.,2008 et al., Oinas et al.,2009; Parkkinen et al., 2001; Aarsland et al.,2005; Sabbagh et al.,2009; Aarsland et al.,2004; Guo et al.,2005; Tsuboi et al.,2005; Jellinger et al.,2006a).

Neurotransmitter defects – cholinergic, noradrenergic and dopaminergic defects have also been reported as a cause for dementia in PD (Nakano et al., 1984; Emre et al., 2003).

Role of α-synuclein, amyloid- β and tau proteins

Abnormal deposition of α-synuclein, amyloid- β and hyperphosphorylated tau proteins have all been thought to cause the dementia in Parkinson's disease.

Amyloid- β and Alzheimer's type changes (with amyloid plaques and neurofibrillary tangles) are the most common co-occurring pathology that accompanies Lewy pathology i.e. PDD and DLB (Dickson et al., 2009). Recent clinic pathological studies have reported Alzheimer's type changes in about a third to half of the PDD cases (Galvin et al., 2006; Sabbagh et al.,2010). Although some studies (Jellinger et al., 2006b; Ballard et al., 2006) agree that the difference in the pathology between PDD and DLB could related to the amount of concomitant Alzheimer's disease-type pathology , others clearly differ in their views (Aarsland et al.,2005; Tsuboi et al.,2007). Between 10% and 55% of patients with Alzheimer's disease have coexistent Lewy bodies (Hansen et al., 1990; Jellinger et al., 1990). When AD type changes are seen in PDD there are usually other concomitant neuropathological changes, including limbic and cortical Lewy bodies and degeneration of subcortical monoaminergic and cholinergic pathways (Burack et al., 2010). It is also interesting to note that there is no correlation between the clinical stages of dementia and neuropathological findings in PDD, PDD with LB, and PDD with AD (Galvin et al., 2006).

Jellinger had reported that DLB brains showed a significantly higher burden of (diffuse) amyloid plaques in the striatum and slightly more severe tau pathology than PDD brains despite similar neuritic Braak stages. In DLB the striatal load of Amyloid-β had an inconsistent correlation with the Braak neuritic stages but in PDD there was no correlation at all. He also reported an excess of α-synuclein pathology (both Lewy neurites and Lewy bodies) in DLB compared to PDD (Jellinger et al., 2006a).

2.1.6.5. Conclusion

Dickson et al. have concluded that from a pathological point of view PDD and DLB cannot be differentiated (Dickson et al., 2009) and have formulated a probability statement (Table below) which indicates only the likelihood that the pathology would contribute significantly to the Lewy-related cognitive disorder (DLB or PDD).

Very recently several neuropathological reports have implied a combined and possibly, synergistic mechanism of neurodegeneration and fibrillary protein aggregation to explain the concurrent presence of α-synuclein, amyloid- β and tau proteins which are markers for both AD and PD and their role in the causation of dementia in PD. (Parkkinen et al.,2008; Kalaitzakis et al.,2009; Jellinger et al.,2010).

Table 2.1.6.3 : Probability of Lewy-related cognitive disorder (Dickson et al.,2009)

Kosaka criteria	NFT stage 0–2/ CERAD possible	NFT stage 3–4/ CERAD probable	NFT stage 5–6/ CERAD definite
Brainstem	Low	Low	Low
Transitional	High	Intermediate	Low
Diffuse	High	High	Intermediate

Data based on NIA–Reagan criteria (Hyman, 1997) for Alzheimer's disease-type pathology. The probability matrix is shown as proposed by the third Consortium of Dementia with Lewy Bodies, (McKeith et al.,2005) in which Lewy pathology and Alzheimer's disease-type pathology determines the likelihood of a Lewy-related cognitive disorder (DLB or PDD). Distribution of Lewy bodies and Alzheimer's disease-type pathology are the two major axes in the matrix. CERAD=Consortium to Establish a Registry for Alzheimer's Disease. NFT=neurofibrillary tangles.

2.1.7. PET STUDIES IN PARKINSON'S DISEASE DEMENTIA

The broad approaches to the understanding of dementia in Parkinson's disease are

a) Co-occurring Alzheimer's type pathology in the cortex ,
b) Neurotransmitter defects due to loss of ascending projection neurones from the ventral tegmentum (mainly subcortical with loss of mesolimbic and mesocortical projections)
c) The spread of Lewy body pathology (α synuclein) from brainstem to the cortex, which may suggest PD and DLB is a part of the same continuum.

PET imaging has been used to understand a number of these processes. In particular finding of a PET ligand [11C] PIB which binds to fibrillar amyloid has made a great contribution in Alzheimer's disease. In addition, metabolic imaging of the glucose metabolism with [18F] FDG has also been useful to know the changes in neuronal activity. In a number of neurodegenerative diseases including PD microglial activation also have been thought to be a major contributor to the disease and imaging with [11C] PK11195 can be useful in this scenario. I will briefly discuss about these approaches before moving on to the rationale of using PET in our study.

Co-occurring Alzheimer's type pathology is found in about a third of the cases. Using [11C] PIB, two fold increases in amyloid has been detected in Alzheimer's disease (Klunk et al.,2004 Archer et al., 2006; Engler et al., 2006; Fagan et al., 2006; Edison et al.,2007; Rabinovici et al.,2007; Jack et al., 2008;). [18F] FDG is a marker of neuronal activity and gives a measure of the regional resting glucose metabolism in the brain. It has provided a good deal of knowledge about the pattern of several neurodegenerative diseases including Parkinson's disease, Parkinson's plus syndromes, Alzheimer's disease. [18F]FDG-PET studies show that rCMRGlc is decreased by 10 to 20% in temporoparietal, occipital cortical regions and posterior cingulate gyri in subjects with AD (Hoffman et al.,1989; Minoshima et al.,1997; Hoffmann et al., 2007; Edison et al., 2007). Many studies have shown the retention of [C11] PIB in cortical AD brain regions to be inversely related to the cerebral glucose metabolism as measured by [18F] FDG (Klunk et al., 2004; Edison et al.,2007). [18F] FDG scans shows a similar distribution of hypometabolism in Parkinson's disease dementia with predominant reduction of glucose metabolism in the posterior cingulate, posterior parietal and temporal association areas, frontal association areas being affected to a lesser degree, and

primary cortical regions, basal ganglia and cerebellum being spared (Bohnen2003). This striking similarity in the pattern of glucose metabolism and neuronal dysfunction suggests an association between Lewy body and Alzheimer pathology (Brooks et al., 2008).

Microglia are the resident macrophages of the cental nervous system and form a part of the innate immune sysytem. These cells are quiescent in the normal physiological state. However, in response to pathophysiological brain insults such as injury or disease,they are activated. These cells then, express a translocator protein (18 kDa) (TSPO) in addition to several proinflammatory markers. . TPSO is a five transmembrane domain protein that is localized primarily in the outer mitochondrial membrane. It abundant in peripheral organs, particularly in adrenal glands, kidney, heart and lungs as well as haematogenous cells, but present in low levels in the intact central nervous system. It is localized at these contact sites when formed (Culty et al., 1999). With increased mitochondrial activity such as during inflammation TPSO tends to form homopolymers (Delavoie, F. et al., 2003*)*. [11C] PK11195 is a specific ligand for TSPO (Shah et al., 1994) and can reflect the alterations of microglial activation and hence, inflammation. Microglial activation has been demonstrated in a number of neurodegenative conditions by the use of [11C] PK11195 PET. Gerhard et al., showed that the the[11C] PK11195 binding was raised in the brainstem, basal ganglia and fronto-temporal cortical regions of Parkinson's disease patients. Increased binding of this radiotracer has been demonstrated in Parkinson's disease (Gerhard et al., 2007) , Huntington's disease (Tai et al.,2007) and also Alzheimer's disease (Edison et al., 2007).

Neurotransmitter dysfunction includes loss of cortical cholinergic activity and dopaminergic dysfunction. Using a PET ligand , N 11C Methyl-4-piperydyl acetate (MP4A) which a substrate of acetylcholinesterase, severe loss of cortical cholinergic activity has been shown in PDD patients (Kuhl,1996; Nakano 1984; Emre et al.,2003). Performance on attention and working memory function were found to correlate with loss of cortical cholinesterase activity in PDD (Bohnen, 2003; Bohnen et al., 2006). One study used [18F] Fdopa and MP4A in PD and PDD. They found non-demented PD and PDD having moderate and severe cholinergic dysfunction respectively. Frontal and temporoparietal FDOPA and MP4A binding covaried in PDD suggesting a role for both cholinergic and dopaminergic functions (Hilker et al., 2005).

Dopaminergic dysfunction in PDD has also been noted by other PET researchers (Ito et al., 2002). Interestingly, Rinne et al. found a correlation to the reduction of [18F] Dopa uptake to performance of executive tasks (Rinne et al., 2000).

In conclusion , the pathology dementia in Parkinson's disease is likely to be multifactorial incorporating the different processes discussed above and section 2.1.6. However, β amyloid imaging may be the most important as it carries a huge therapeutic potential. In addition imaging glucose metabolism and microglial activation may give us further insight into the pathogenesis of the disease.

2.1.8 RATIONALE OF THE STUDY

Dementia is a major disabling complication of Parkinson's disease. The incidence of the disease is rising with improving the life expectancy of the population. From the pathological studies we have seen a four- to sixfold higher risk of dementia in PD patients compared to the normal population. Clinically it is difficult to distinguish between different forms of dementia and neuropathologically there is no clear explanation for the cause of dementia in PD (Sections 2.1.5 and 2.1.6). One third to one half of the Parkinson's disease with dementia (PDD) patients do have Alzheimer's type amyloid pathology in the brain. It is now possible to image amyloid in Alzheimer's dementia with [11C] PIB. It is important to look into amyloid pathology in PDD and DLB to gain further insight into the cause of the disease as it might develop potential therapeutic targets. In Alzheimer's diease abnormal glucose metabolism and inflammation have been shown along with β amyloid deposition. Both abnormal brain glucose metabolism and microglial activation has been seen in the Parkinson's disease patients do not have dementia as studied with [18F] FDG and [11C] PK11195 respectively. Using [11C] PIB, [18F] FDG and [11C] PK11195 we planned to study the processes mentioned above to get further insight into pathogenesis of dementia in Parkinson's disease. We planned to conduct this study by recruiting PDD patients locally from our hospital. We proposed to recruit PD patients and age matched healthy controls to compare with PDD patients.

In addition, we planned to pool our [11C] PIB data in a multicentre study (Austin Health, Melbourne, University of Melbourne, Australia; Turku PET Centre, University of Turku, Finland and our centre) to compare amyloid load in PDD, DLB, PD and healthy controls.

2.1.9 OBJECTIVES OF THE STUDY OF DEMENTIA IN PARKINSON'S DISEASE

The objectives of this study were to assess in vivo using PET -

1. The regional cerebral amyloid load in PDD and DLB patients and to compare this with PD patients who do not have dementia and age matched healthy controls

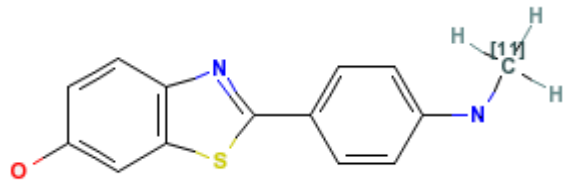
2. The difference in brain metabolism in PDD compared to PD and healthy controls

3. The extent of inflammation in the PDD patients compared to PD

4. Correlation of inflammation, glucose metabolism and amyloid load in PDD and PD.

2.2 PET TRACERS I HAVE USED IN THE STUDY OF PARKINSON'S DISEASE DEMENTIA

2.2.1. [11C] PIB



2.2.1.1 Chemical structure of [11C] PIB shown in diagram above

2.2.1.2

N-Methyl-[11C]-2-(4′-methylaminophenyl)-6-hydroxybenzothiazole

2.2.1.3 Synthesis

[11C]PIB was readily synthesized by standard [11C]-methylation of 2-(4′-aminophenyl)-6-methoxymethoxybenzothiazole with [11C] methyl iodide, followed by hydrolysis (Mathis et al., 2003). The average radiochemical yield was 12.1% at the end of synthesis based on [11C] methyl iodide, and the average specific activity was 185 GBq/μmol (2.3 Ci/μmol) at the end of synthesis. Radiochemical and chemical purities were >95% as determined by high-performance liquid chromatography (HPLC).

2.2.1.4 Characteristics

[11C]PIB, Pittsburgh compound B, is a neutral derivative of thioflavin-T. It has a binding affinity (Ki) of 4.5 nm for aggregated β-amyloidal (1-40) fibrils in the AD brain (Mathis et al., 2003). Amyloid fibrils present in AD plaques, is formed from Aβ protofibrils which itself is a end- product of the breakdown Amyloid precursor protein (APP) by secretases. In comparison to the amyloid fibrils,the binding of [11C]PIB to neurofibrillary tangles was low.

Saturation binding studies with [11C] PIB to homogenates of frontal cortex from postmortem advanced AD brain showed a Kd of 1.4 nm and a Bmax of 1900 pmol per g of tissue. There was no specific binding of [11C]PIB to homogenates of frontal cortex from age-matched

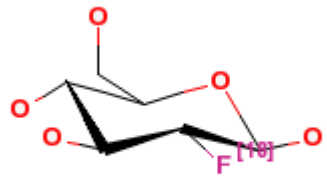
control brain as well as to homogenates of cerebellum from AD brain or control brain (Klunk et al.,2003).

2.2.1.5 Utility In-vivo studies

The first in vivo human study with [11C] PIB was reported by Klunk et al., with 16 patients with mild AD and nine healthy people (Klunk et al.,2004). [11C]PIB showed a rapid uptake in the brain tissue and substantial (upto two- fold) retention in the frontal, parietal, temporal and occipital cortices but low entry into the cerebellum and subcortical white matter of the patients, unlike healthy controls who showed a rapid entry and clearance of [11C] PIB in cortical and subcortical grey matter, including the cerebellar cortex.

Since then it has been widely accepted as a marker of fibrillar amyloid binding in human in-vivo studies (Klunk et al.,2004; Archer et al., 2006 et al., Engler et al., 2006; Fagan et al., 2006; Rabinovici et al.,2007; Jack et al., 2008;). Our group Edison et al., have shown two-fold rises in cortices of AD brains (Edison et al.,2007).

2.2.2. [18F] FDG



2.2.2.1 Chemical Structure shown in diagram above

2.2.2.2 Chemical name

[18F]Fluoro-2-deoxy-2-D-glucose

2.2.2.3 Synthesis

18F] FDG was synthesized by a direct electrophilic fluorination of 3, 4, 6-tri-O-acetyl-d-glucal with [18F]F2 gas with a radiochemical yield of 8%. [18F]FDG was also prepared by reacting 18F-labeled acetyl hypofluorite, prepared by reaction of 18F-labeled molecular fluorine with sodium acetate in glacial acetic acid, and tri-acetyl-d-glucal at room temperature. Overall radiochemical yield was about 24% with a radiochemical purity of 98%. The specific activity of [18F]FDG was about 25 GBq/mmol (685 mCi/mmol). With further advancement of technology various methods have then been used to give a yield of 12- 17 % with 96 – 99 % radiochemical purity (Nishijma et al.,2002; Brodack et al., 1988; Yu et al.,2006).

2.2.2.4 Rationale of use

The phosphorylation of glucose, an initial and important step in cellular metabolism, is catalyzed by hexokinases. [18F] FDG PET measures the cerebral glucose metabolism. Hexokinases by converting glucose to glucose-6-phosphate, help to maintain the downhill gradient that results in the transport of glucose into cells through the facilitative glucose transporters (GLUT1-13). 2-Deoxy-d-glucose (2DG) was first developed to inhibit glucose utilization by cancer cells as phosphorylation of this compound would inhibit the phosphorylation of glucose (Laszlo et al.,1960)

2-[18F] Fluoro-2-deoxy-d-glucose ([18F] FDG) was later developed for molecular imaging studies (Fowler et al., 2002). FDG is moved into cells by glucose transporters and is then phosphorylated by Hexokinase to FDG-6- phosphate. FDG-6- phosphate cannot be metabolised further in the glycolytic pathway and is trapped intracellularly. However, it is important to note because FDG and glucose, are transported and phosphorylated by the same process, the rate of tissue accumulation of the end-product, FDG-6-phosphate, is proportional to the rate of glucose utilisation. Altered rates of glycolysis and glucose transport in cells can be reflected by the uptake of [18] FDG relative to other normal cells. As a PET tracer [18F] FDG can therefore be used to assess alternations in glucose metabolism in brain.

2.2.2.5 Lumped Constant in FDG studies

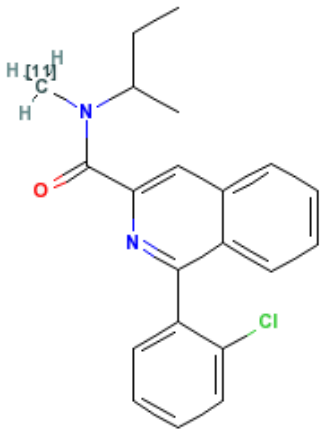
Although FDG and glucose go through the same metabolic processes they differ in their rates of transport and phosphorylation, and respective volumes of distribution (VDs) in the brain

tissue. Therefore, rigorous calculation of the glucose metabolic rate (MRGlc) in units of mmol/100 g/min of FDG requires a proportionality constant, known as the lumped constant (LCFDG). The LCFDG represents the ratio of the metabolic rate of FDG (MRFDG) to the metabolic rate of glucose (MRGlc).

2.2.2.6 Utility in vivo studies

[18F]FDG measures the regional cerebral glucose metabolism (rCMRGlc) and synaptic activity. [18F]FDG-PET studies show that rCMRGlc is decreased by 10 to 20% in temporoparietal, occipital cortical regions and posterior cingulate gyri in subjects with AD (Hoffman et al.,1989; Minoshima et al.,1997; Edison et al., 2007). Many studies have shown the retention of [C11] PIB in cortical AD brain regions to be inversely related to the cerebral glucose metabolism as measured by [18F] FDG (Klunk et al., 2004; Edison et al.,2007).

2.2.3 [11C] R PK11195



2.2.3.1 Chemical Stucture – shown in the diagram above

2.2.3.2 Chemical name

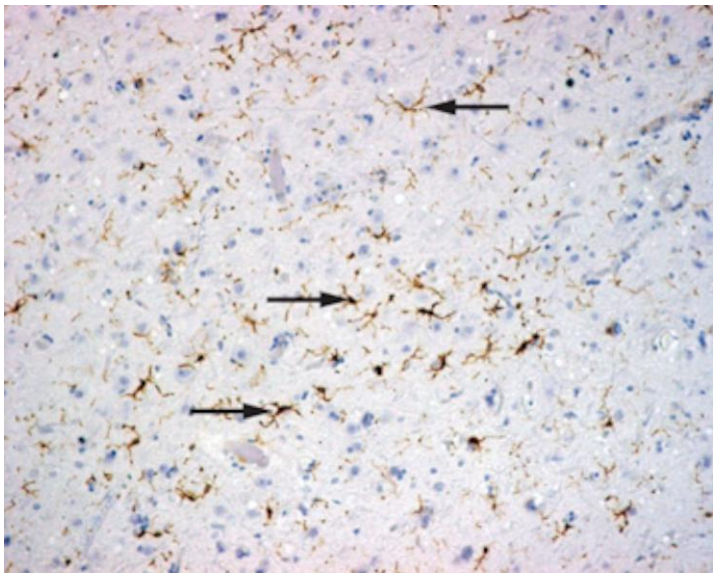
1-(2-Chlorophenyl)-N-[11C]methyl-N-(1-methylpropyl)-3-isoquinoline carboxamide

2.2.3.3 Synthesis

[11C]R-PK11195 is synthesized from R-desmethyl-PK11195 with [11C]methyl iodide. The 11C-labeled enantiomers were prepared with a reproducible radiochemical yield of 80% (decay-corrected) based on [11C]methyl iodide. Total synthesis time was 45 min. Radiochemical purity was >99% with specific activities varying between 20 and 96 GBq/μmol (0.54 and 2.6 Ci/μmol) at the end of synthesis.

2.2.3.4 Rationale for use

Microglia are the resident macrophages of the cental nervous system and form a part of the innate immune sysytem. These cells are quiescent in the normal physiological state. However ,they are exquisitely sensitive to brain injury and disease, and in response to pathophysiological brain insults can alter their morphology and phenotype to adopt a ‘ activated state’. In the activated state, these cells express a number proinflammatory cytokines and in particular, the mitochondria of these cells express a translocator protein (18 kDa) (TSPO) [11C]R PK11195 specifically binds to TPSO (Rupprecht et al., 2006) and can reflect the alterations of microglial activation and hence, inflammation.



Picture showing the altered ,’ swelled’ state of activated microglia (arrows) in the brain.

2.2.3.5 Utility in in-vivo studies

[11C] PK 11195 has been shown to have increased binding in a number of inflammotory CNS disorders. Our department has shown increased binding of this radiotracer in Parkinson's disease (Gerhard et al., 2007) , Huntington's disease (Tai et al.,2007) and also Alzheimer's disease (Edison et al., 2007).

Gerhard et al., showed that the the [11C] PK11195 binding was raised in the brainstem, basal ganglia and fronto- temporal cortical regions of Parkinson's disease patients.

2.3 MATERIALS AND METHODS

2.3.1 Ethics committee permission was obtained from the Ethics Committee of the Hammersmith Hospitals Trust to be able to conduct this research

2.3.2 Permission to administer radiotracers was obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC) UK.

2.3.3. SUBJECTS AND PROCEDURES

2.3.3.1.SUBJECTS

The inclusion criteria for PDD subjects:

- age 50-79 yrs,
- diagnosed with PDD based on the consensus clinical diagnostic criteria before their enrolment into the study
- ability to give informed consent
- a reliable history from the patient's care giver
- adequate visual and auditory acuity to complete the psychological testing

The exclusion criteria were:

- extensive white matter disease on MRI which, in the opinion of a consultant radiologist, was over and above the few lacunes associated with normal aging,
- major depression based on DSM-1V criteria,

- a current or recent history of drug or alcohol abuse/dependence,
- any significant disease or unstable medical condition that could influence neuropsychological testing,
- pregnancy,
- participants in whom MRI was contraindicated,
- history of schizophrenia, schizoaffective disorder, bipolar disorder or any
- history of ECT and

- history of cancer within the past 5 years except localised skin and prostate cancer

.

PD subjects without dementia were age- matched and satisfied the brain bank criteria for the diagnosis

11 PDD subjects, 8 PD subjects without dementia and 35 control subjects were recruited from the movement disorder clinics at the Imperial College NHS trust. Due to restrictions in performing scans in healthy controls different control groups were studied – 17 for [11C] PIB, 8 for [18F] FDG and 10 for [11C] PK11195. Part of the data from six PDD and six PD patients from our centre which were available at that time, were pooled together with data from two other centres Austin Health, University of Melbourne, Australia, and the University Hospital of Turku, Finland. This multicentre study had 13 DLB, 12 PDD, 10 PD and 41 control subjects. The demographic details are given in Tables 2.4.1.1 and 2.4.1.4.

The study was both verbally explained to the patients as well as an information sheet was provided for them to read at their own leisure. Written consent was obtained from every patient. All patients had an MRI Brain, and three PET scans on three separate days. On the day of the MRI they also had a detailed neuropsychometry test along with a clinical assessment.

2.3.3.2 Clinical examination and Neuropsychiatry tests

Dementia was excluded in control subjects and PD subjects without dementia by detailed clinical examination and neuropsychological testing while significant cerebral atrophy was excluded by T1-weighted and structural damage by T2-weighted MRIs.

All patients and controls had the following tests as has been used previously in Alzheimer's dementia studies in our department (Edison et al., 2007; Edison et al., 2008)

1. Mini-Mental State Examination (MMSE),
2. Warrington short recognition memory tests (WRTM) for words and faces,
3. AD Assessment Scale Word List Learning test and 30 minute delayed recall, (Rosen et al.,1984)
4. Immediate and delayed recall of modified complex figure, (Becker et al.,1987)
5. Digit Span forwards, (Wechsler et al.,1997).

6. Clock drawing, (Sunderland et al.,1989)
7. 30-item Boston Naming Test,(Saxton ,2000; Borod et al.,1980; Kaplan et al., 1983)
8. Letter fluency (FAS),(Benton et al.,1968)
9. Category fluency (animals, birds, and dogs)

2.3.3.3 MRI Brain:

MRIs were obtained with a 1.5 Tesla GE scanner.

T1 volumetric MRI (3D T1 volume, pulse sequence RF-Fast, acquisition times TR 30ms, TE 3ms, flip angle 30 degrees, FOV 25 cm, matrix 156 x 256, voxel dimensions (0.98x0.98x1.6 mm) was acquired for co-registration and assessment of atrophy

T2 weighted images were acquired to rule out any structural abnormality and control subjects.

2.3.3.4 [11C]PIB-PET Scan:

[11C] PIB was manufactured and supplied by Hammersmith Imanet plc at the Cyclotron Building, Hammersmith Hospital. All patients and controls were scanned using a Siemens ECAT EXACT HR+ 962 scanner (Brix et al.,1997). Head position was checked using a short two minute transmission scan using an external rotating 68Ge source. A 10 minute transmission scan was also performed to measure tissue attenuation. Dynamic emission scans were acquired in three-dimensional mode. All subjects had an intravenous bolus injection of [11C] PIB - mean injected dose 370 (SD±20) MBq. PET emission scans were acquired over 90 minutes. All data processing and image reconstruction was performed using standard Siemens software which included scatter correction. Reconstruction of emission data was carried out using filtered backprojection method (ramp, kernel 2.0 mm FWHM); the 3D emission data were Fourier-rebinned into 2D data sets to increase the speed of reconstruction.

2.3.3.5 [18F]FDG PET

[18F] FDG was manufactured and supplied by Hammersmith Imanet plc at the Cyclotron Building, Hammersmith Hospital.All PD and PDD subjects and healthy controls were scanned using a Siemens ECAT EXACT HR+ 962 scanner. Subjects were asked to fast for four hours before the scan. An intravenous bolus injection of 185 (±8) MBq of [18F]FDG was administered. A 60 minute dynamic emission scan was acquired using predefined protocol with time frames 1x15s, 1x5s, 4x10s, 4x30s, 4x60s, 4x120s and 9x300s. Studies were performed in a minimally illuminated room with minimal auditory stimulation and at the same time avoiding sedation because these factors may alter neural firing and neural activity in several areas of the cortex resulting in erroneous results. All subjects had radial artery cannulation to allow for blood monitoring. Continuous online sampling was performed for 15 minutes and then discrete blood samples were taken at baseline, 5, 10, 15, 20, 30, 40, 50 and 60 minutes. A haematocrit was estimated from the baseline blood sample and plasma glucose levels were measured on selected samples**.** Data acquisition was similar to that of [11C] PIB.

2.3.3.6 [11C](R)PK11195-PET:

All patients and controls had [11C](R)PK11195-PET scans using an ECAT EXACT HR++ (CTI/Siemens 966) camera. Data were acquired in three-dimensional mode at the Cyclotron Building, Hammersmith Hospital. The scanner has an axial field of view of 23.4 cm and provides 95 transaxial planes with a spatial resolution of 4.8 mm FWHM (transaxial, 1 cm off axis) and 5.6 mm (axial, on axis) after image reconstruction (Spinks et al.,2000). This high-resolution, high-sensitivity tomograph permits interrogation of small volume structures. A transmission scan, used to correct for attenuation of emitted radiation by skull and soft tissues, was acquired using a single rotating photon point source of 150 MBq of ^{137}Cs. Thirty seconds after the start of the emission scan, a mean dose of 296 (SD± 18) MBq [11C] (R) PK11195 in 5 ml normal saline was injected intravenously over 10 seconds. [11C](R)PK11195 was manufactured and supplied by Hammersmith Immanent plc. Emission data were then acquired over 60 minutes in list-mode and rebinned into 18 time frames post acquisition.

2.3.4 ANALYSIS OF SCANS

2.3.4.1 [11C] PIB

MRI images

The following pre-processing steps were done with each MRI using SPM (Statistical Parametric Mapping 99, Wellcome Department of Imaging Neuroscience, UCL, London, UK) .

First the transaxial planes were oriented parallel to the AC-PC line. Then, a grey matter image was produced by segmenting each MRI. This image was thresholded at 50 % probability.

PET images

PET images were obtained in 32 frames over 90 minutes. Two PET images were created in Matlab (Mathworks Inc et al., Sherborn, Mass et al., USA) –

- 10 – 90 minute add image incorporating the 15th - 32nd frame and
- 60 – 90 minute add image summing the activity in 27th - 32nd frames.

The PET images were coregisterd to each individual's MRI and then normalised to standard stereotactic space (Montreal Neurological Institute, Quebec, Canada) using SPM.

ROI (Regions of interest) analysis (Using Analyze AVW software)

A standard template of ROI was created by convolving the grey matter MRI image with an in house probabilistic brain atlas (Hammers 2003). This individualized template or 'object map' was used to sample grey matter regions.

Ratio image generation

I used the cerebellum as a reference region because it is relatively free of fibrillar plaques (Joachim et al.,1989) and the [11C] PIB uptake is extremely low (Klunke et al.,2004; Nordberg et al., 2004). I first calculated the cerebellar uptake value by sampling the 60-90 minute PET image with the superimposed object map. The 60-90

minute image was then divided by the cerebellar uptake value giving a Ratio image, by using the image calculator in the same software. Target to cerebellar [11C] PIB uptake ratios at 60 to 90 minutes provide a blood flow independent measure of 11C-PIB retention (Price et al., 2004, Lopresti 2005, Kemppainen et al., 2006,. Aalto et al.,2009).

In simple terms the cerebellum uptake value was first calculated and then the brain regions were divided with it to get the target: cerebellum ratio which is unitless and it gives us the measure of the target region PIB uptake relative to the cerebellum. Regions sampled were anterior and posterior cingulate cortex, thalamus, striatum, frontal, temporal, parietal and occipital cortical regions were studied. In addition we examined the rCMRGlc in the hippocampus, amygdale, parahippocampal gyrus and medial temporal lobe as well.

2.3.4.2 [18F]FDG-PET

A dynamic 3D series was acquired over the whole brain volume. Voxel-by-voxel parametric images of regional cerebral metabolic rate for glucose (rCMRGlc) were produced from brain uptake and plasma input functions using spectral analysis (Cunningham and Jones, 1993). A lumped constant (Krohn et al., 2007) of 0.48 was used.

For ROI analysis of [18F]FDG scans, the PET images were coregistered to the corresponding MRI and then spatially normalised to MNI space. Gray and white matter were combined when creating the object map and the regions were sampled in the similar way as for [11C]PIB.

Functions of the anterior and posterior cingulate cortex, thalamus, striatum, frontal, temporal, parietal and occipital cortical regions were studied. In addition we examined the rCMRGlc in the hippocampus, amygdala, parahippocampal gyrus and medial temporal lobe as well.

2.3.4.3 [11C](R)PK11195-PET

PET IMAGES

- Parametric binding potential maps were created by the simplified reference tissue model (SRTM), using Receptor Parametric mapping software (RPM) written in Matlab 5 (Lammertsma and Hume et al.,1996; Gunn et al.,1997; http://www.bic.mni.mcgill.ca/users/jaston/rpm_statistics.html).
- 60 minute summed activity image were also created using the same software.

Cluster analysis for calculating reference input function

Because of the widespread pattern of activation of microglia in Parkinson's disease, an a priori unaffected region is not possible to be defined as a reference area (Larner et al., 1997). Cluster analysis was, therefore, used to provide a reference tissue input function for non-specifc uptake. This was done by identifying and extracting a cluster of voxels in each subject that matched the characteristics of 'normal' grey matter. The data for 'normal' grey matter was derived from previous studies with the same tracer in healthy controls and patients and it incorporates the kinetics of six pre-defined tissues (normal gray and normal white matter, skull, muscle, gray matter with reactive microglia, vasculature that is rich in the receptor in endothelial cells and smooth muscles). This form of supervised clustering algorithm thus helps to cluster into areas of specific binding and at the same time takes out unwanted nuisance signals arising from areas of the brain known to have a rich density of PBBS receptors such as the meninges (Turkheimer et al., 2007). The clustering code is implemented in the software package SUPERPK (Imperial Innovations, Imperial College London) written in Matlab (The Mathworks Inc et al., Natick MA). Further work from our unit has validated the SRTM using cluster analysis to define the reference input function as the most reproducible and sensitive technique for generating BP maps.

Both PET images, parametric and summation, were coregistered to the respective MRI scans using mutual information algorithm in SPM software. The summation

images had high blood flow dependent signal in the large vessels and served as a good anatomical substrate for the coregistration process.

Spatial normalization into standard stereotaxic space and the rest of the ROI analysis were the same as for PIB analysis.

2.3.4.4 Statistical Parametric mapping (SPM) analysis:

The PET data was smoothed with 6mm x 6mm x 6mm kernel filter prior to SPM analysis. Patients and control subjects were interrogated for microglial activation, amyloid load and glucose metabolism using a voxel threshold of $p<0.005$ and extent threshold of 50 voxels. The statistical threshold that was utilized defined a $p<0.005$ level for the individual voxels and a minimum of 50 voxels for each set of connected voxels, and a corrected $p<0.05$ threshold at the cluster level was accepted as significant. If there was no significant cluster at the above defined threshold, voxel threshold was dropped to $p<0.05$ and extent threshold of 50 voxels.

Microglial activation and glucose metabolism between PDD and PD was interrogated using a voxel threshold of $p<0.05$ and extent threshold of 50 voxels. Statistical maps were corrected for multiple comparisons using cluster level inference derived from random field theory as implemented in SPM. In assessing cerebral glucose metabolism, individual rCMRGlc image was normalized to the corresponding pons, and ANCOVA was applied to remove the confounding effects of global on regional uptake variance.

2.3.4.5 Statistical analysis:

Statistical interrogations of ROI data were performed using SPSS for Windows version 14 (SPSS, Chicago, Illinois, USA).

2.4 RESULTS

2.4.1 [11C] PIB

Results from [11C] PIB has been divided into two subdivisions as part of the data from six PDD and six PD patients from our centre which were available at that time, were pooled together with data from two other centres Austin Health, University of Melbourne, Australia, and the University Hospital of Turku, Finland. This study named 'Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography' was published in a peer review journal and the manuscript is attached at the end of the thesis. This subdivision is referred to Part A.

Part B refers to the results of all PDD patients from our centre.

Part A Results

Table 2.4.1.1 shows the demographic characteristics of the subjects and table 2.4.1.2 outlines the mean [11C]PIB uptake in the DLB,PDD, PD and control groups.

Individually, 11 of the 13 patients with DLB had significantly increased amyloid load in one or more cortical regions as opposed to 2 out of 13 PDD patients. Nine of the 13 subjects with DLB had [11C]PIB levels in the AD range (an [11C]PIB uptake RATIO.1.5) in at least one cortical area.

Ten of the 12 patients with PDD had normal [11C]PIB uptake while two patients with PDD showed a similar pattern of increased amyloid load to the majority of the patients with DLB. In these two subjects with PDD, striatal uptake of [11C]PIB was also increased.

The two subjects with PDD who had high [11C]PIB uptake did not differ clinically from other subjects with PDD. None of the 10 non-demented PD patients showed any significant increase in [11C]PIB uptake compared with controls.

None of the non- demented PD or controls had a significant cortical amyloid load.

The tables 2.4.1.1; 2.4.1.2; 2.4.1.3, and figure 2.4.1.1. relate to Part A

Table **2.4.1.1 Demographic and clinical details of the subjects in Part A**

	DLB	PDD	PD	Controls
Number of subjects	13*	12‡	10ᵠ	41#
Age(mean (SD) (range))	72.2 (5.2) (62–80)	69.3 (6.9) (56–80)	68.2 (6.3) (58–75)	67.8 (7.8) (55–82)
Sex (male)	10/13	10/12	7/10	24/41
MMSE {mean (SD) (range)}	20.3 (7.4) (10–28)	21.8 (2.8) (17–26)	28.8 (1.5) (26–30)	29.9 (0.3) (29–30)
Duration of diagnosis of dementia (yrs)	4.2 (2.6)	3.52 (1.5)	-	-
Duration of PD symptoms (yrs)	3.4 (1.8)	10.6 (4.8)	9.2 (3.9)	-
UPDRS	16.3 (13.8)	38.2 (12.9)	30.5 (6.9)	-

Values are mean (SD) unless otherwise indicated.

*10 DLB from Melbourne and three from Turku.

‡ Six PDD from London and six from Turku.

ᵠ Seven PD from London and three from Turku.

#17 HC from London, 12 HC from Turku and 12 from Melbourne.

"Mean age from London was 64.8 (6.2) years, mean age from Turku was 65.1 (7.6) years and mean age from Melbourne was 72.3 (5.1) years.

DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; PDD, Parkinson's disease dementia; UPDRS, Unified Parkinson's Disease Rating Scale

Table **2.4.1.2 [11C] PIB uptake in DLB,PDD, PD and control groups - Part A (Results)**

	Anterior cingulate gyrus	Posterior cingulate gyrus	Thalamus	Striatum	Frontal cortex	Temporal cortex	Parietal cortex	Occipital cortex	Whole cortex
DLB									
Mean	1.72	1.74	1.22	1.46	1.52	1.36	1.45	1.34	1.46
SD	0.31	0.41	0.14	0.27	0.26	0.26	0.32	0.27	0.26
Median	1.75	1.78	1.21	1.43	1.57	1.31	1.46	1.32	1.51
% increase	43***	56***	12***	34***	35***	26***	36***	21***	32***
PDD									
Mean	1.26	1.28	1.06	1.1.19	1.18	1.13	1.15	1.16	1.18
SD	0.34	0.35	0.20	0.21	0.26	0.20	0.26	0.16	0.24
Median	1.15	1.16	1.02	1.15	1.11	1.07	1.02	1.11	1.09
% increase	14	13	4	7	9	6	6	4	8
PD									
Mean	1.10	1.17	1.07	1.15	1.08	1.07	1.11	1.12	1.10
SD	0.07	0.12	0.06	0.07	0.06	0.06	0.09	0.07	0.06
Median	1.10	1.14	1.08	1.12	1.08	1.07	1.11	1.12	1.10
% increase	1	4	4	4	0	1	3	1	2
HC									
Mean	1.16	1.19	1.06	1.12	1.11	1.09	1.09	1.14	1.11
SD	0.11	0.12	0.08	0.05	0.07	0.06	0.07	0.07	0.06
Median	1.14	1.19	1.09	1.11	1.11	1.09	1.09	1.13	1.11

$p < 0.001$

Table 2.4.1.3 [11C]PIB uptake RATIO in control subjects from three centres - Part A Results

	Anterior cingulate gyrus	Posterior cingulate gyrus	Thalamus	Striatum	Frontal cortex	Temporal cortex	Parietal cortex	Occipital cortex	Whole cortex
London									
Mean	1.097	1.098	1.001	1.097	1.083	1.062	1.073	1.111	1.081
SD	0.088	0.081	0.075	0.052	0.057	0.037	0.047	0.045	0.039
Melbourne									
Mean	1.258	1.246	1.102	1.112	1.173	1.117	1.107	1.16	1.145
SD	0.107	0.076	0.051	0.042	0.069	0.049	0.073	0.091	0.059
Turku									
Mean	1.155	1.289	1.116	1.165	1.106	1.122	1.13	1.174	1.135
SD	0.076	0.102	0.053	0.039	0.046	0.068	0.079	0.076	0.057

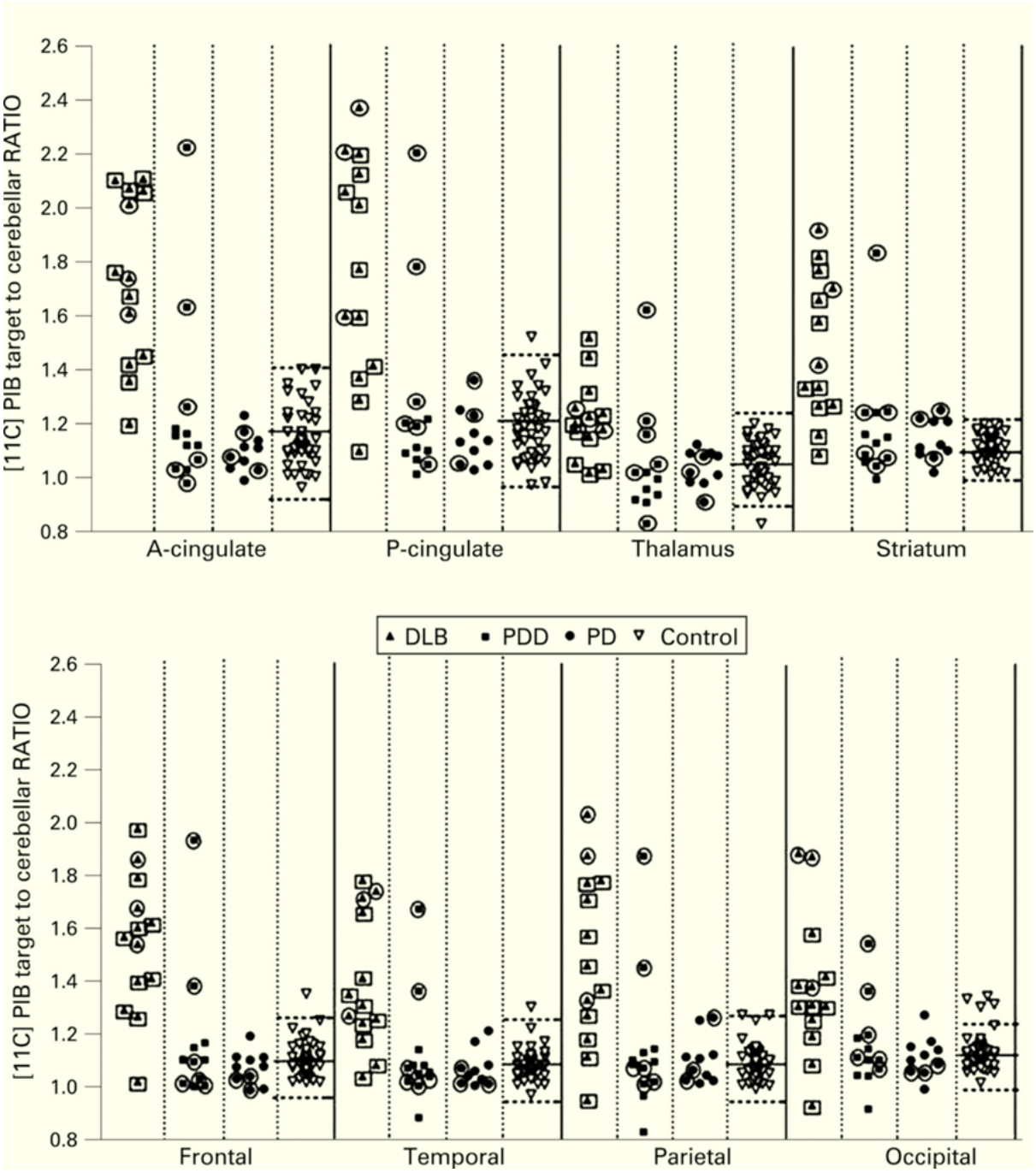


Figure 2.4.1.1 [11C]PIB uptake RATIO in the cingulate cortices (anterior (A) and posterior (P)), thalamus, striatum, and frontal, temporal, parietal and occipital cortex in individual subjects with DLB,PDD and PD from Melbourne (symbols with square border), Turku (symbols with circular border) and London (symbols with no border). Control subjects are from all three sites. Individually, 11 of 13 subjects with DLB showed significant [11C] PIB uptake RATIO, while two subjects with PDD showed a significant uptake RATIO. None of the patients with PD showed significant [11C] PIB uptake.DLB, dementia with Lewy bodies; PD, Parkinson's disease; PDD, Parkinson's disease dementia.

Table 2.4.1.4 Demographic data of Part B

	PDD	**PD**	**Controls**
Number of subjects	11	8	35
Mean Age (SD)	69.3 (6.9)	68.2 (6.3)	67.8 (7.8)
Age Range	56-80	58-75	55- 82
Sex (male)	7/11	5/8	24/35
MMSE (SD)	21.8 (2.8)	28.8 (1.5)	29.9 (0.3)
MMSE range	17-26	26-30	29-30
Duration of diagnosis of dementia at the time of scan (SD)	3.52 (1.5) yrs	-	-
Duration of PD symptoms (SD)	10.6 (4.8) yrs	9.2 (3.9)	
UPDRS (SD)	38.2 (12.9)	30.5 (6.9)	-

Table 2.4.1.5 Details of neuropsychometric tests in PDD, PD and Controls

		MMSE *(/30)*	Immediate Word Recall *(/10)*	Delayed Word Recall *(/10)*	Forward Digit Span *(/14)*	Clock Drawing *(/5)*	Boston Naming Tests *(/30)*	FAS	Semantic	Short Words *(/25)*	Short Faces *(/25)*
PDD	Mean	21.8	4.3	3.2	6.6	2.3	23	29.2	18	15.6	18.2
	SD	2.8	2.4	1.6	2.6	1.9	3.1	5.5	4.8	2.8	3.5
PD	Mean	28.8	7.7	6.9	12.2	4.8	28.2	44.7	42.4	22.3	22.8
	SD	1.5	1.2	1.6	1.1	0.6	2.5	4.8	4.8	2.3	1.6
Controls	Mean	29.4	8.2	7.8	13.4	4.9	28.2	46.8	47.4	24.1	24
	SD	1.2	0.9	1.4	0.5	0.6	1.5	2.2	2.8	0.9	0.8

2.4.1.6 [11C] PIB RESULTS FROM PDD SERIES – PART B

Table 2.4.1.6 showing [11C]PIB uptake in PDD, PD subjects and healthy controls (HC)

		Ant Cingulate	Post Cingulate	Thalamus	Striatum	Frontal Lobe	Temporal lobe	Parietal lobe	Occipital lobe
PDD	Mean	1.15	1.17	0.97	1.15	1.14	1.11	1.11	1.17
	SD	0.14	0.09	0.13	0.11	0.12	0.09	0.10	0.14
	P value	0.14	0.03	0.21	0.10	0.11	0.06	0.15	0.12
	% Increase	4.83	6.30	-3.51	4.44	4.85	4.67	3.16	4.91
PD	Mean	1.15	1.19	1.08	1.15	1.16	1.11	1.17	1.19
	SD	0.13	0.18	0.10	0.10	0.11	0.09	0.12	0.10
	P value	0.16	0.10	0.04	0.11	0.04	0.08	0.03	0.03
	% Increase	4.76	8.29	7.60	4.51	7.21	4.80	9.38	7.48
HC	Mean	1.10	1.10	1.00	1.10	1.08	1.06	1.07	1.11
	SD	0.09	0.08	0.07	0.05	0.06	0.04	0.05	0.05

As a group there was no increase in [11C]PIB uptake in PD or PDD subjects. In the PD group all the subjects had an [11C]PIB uptake Ratio of less than 1.4 in all cortical regions except in one PD subject where the [11C]PIB uptake was increased in posterior cingulate, but the glucose metabolism was not reduced in any other cortical region. All PDD subjects had an [11C]PIB uptake RATIO of less than 1.4 in cortical regions except for one subject who showed an uptake ratio of 1.5 in the occipital cortical region. Interestingly this PDD patient showed a reduction in glucose metabolism (rCMRGlc=0.16, where mean-2SD was 0.186) in the anterior temporal lobe. SPM did not detect any significant increase in the [11C]PIB uptake between PD and controls nor PDD and controls. SPM analysis did not show any significant increase in the [11C] PIB uptake between PD and controls nor PDD and controls.

2.4.2 [11C] PK 11195 Results

PDD compared to controls

The PDD patients showed a statistically significant 35 – 65% increase of [11C]PK11195 BP in anterior and posterior cingulate, striatum, frontal, temporal, parietal and occipital cortical regions. Individually, six PDD subjects showed significant increases (more than mean control BP +2SD) in these regions.

Figure 2.4.2.1B shows the SPM comparing [11C]PK11195 BP increases in the 11 PDD subjects compared with 10 control subjects. SPM shows significant increases in microglial activity in frontal, temporoparietal and occipital cortical regions at a voxel threshold of $p<0.005$ and extent threshold of 50 voxels.

PD compared to controls

[11C] PK11195 results show an increase of 25 – 30% in microglial activation in temporal and occipital regions in PD patients. Increases were present in the frontal and parietal areas but it was just below the statistical cut off (frontal $p < 0.064$, parietal $p< 0.06$). Individually 3 PD patients showed a significant increase in anterior and posterior cingulate and frontal, temporal, parietal and occipital areas.

Figure 2.4.2.1A shows the statistical parametric maps (SPM) localising the significant increases in [11C]PK11195 BP for eight PD subjects compared to ten control subjects. The SPM shows significant microglial activity in temporoparietal and occipital cortical regions at voxel threshold of $p<0.005$ and an extent threshold of 50 voxels.

PDD compared to PD patients

On testing between the two groups (non-demented PD and PDD) there were no significant differences noted in the ROI analysis. SPM analysis showed a minimally increased microglial activity in PDD compared to PD at voxel threshold of $p<0.05$ and extent threshold of 50 voxels (Figure 2.4.2.2).

Table 2.4.2.1: [11C]PK11195 uptake in PD and PDD subjects compared to controls.

		Anterior cingulate gyrus	Posterior cingulate gyrus	Thalamus	Striatum	Frontal cortex	Temporal cortex	Parietal cortex	Occipital cortex	Whole cortex
PDD	Mean	0.50	0.58	0.52	0.50	0.49	0.46	0.47	0.52	0.49
	SD	0.20	0.21	0.22	0.18	0.18	0.14	0.16	0.14	0.16
	p value	0.04	0.02	0.28	0.00	0.01	0.02	0.01	0.01	0.01
	% Increase	35.32	38.48	9.97	65.06	52.12	31.84	48.28	37.38	41.32
PD	Mean	0.43	0.51	0.51	0.38	0.42	0.44	0.42	0.49	0.44
	SD	0.18	0.17	0.17	0.14	0.15	0.10	0.15	0.12	0.13
	p value	0.19	0.11	0.30	0.10	0.06	0.03	0.06	0.02	0.05
	% Increase	17.74	20.72	8.62	25.17	30.13	25.36	32.87	30.13	27.75
HC	Mean	0.37	0.42	0.47	0.30	0.32	0.35	0.32	0.38	0.35
	SD	0.10	0.10	0.14	0.08	0.08	0.08	0.10	0.08	0.09

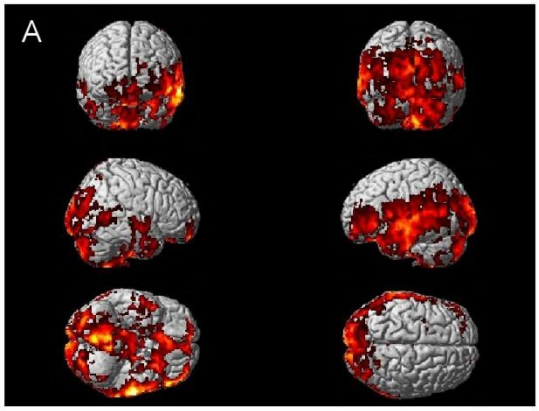


Figure 2.4.2 .1A shows [11C]PK11195 uptake in eight PD subjects compared with 10 control subjects showing significant increase in microglial activity in temporoparietal and occipital cortical regions at a $p<0.005$ and extent threshold of 50 voxels.

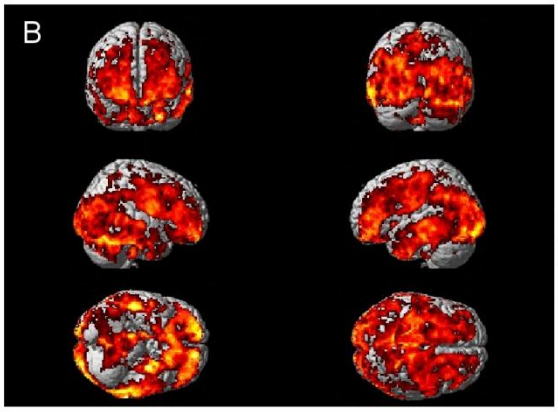


Figure 2.4.2.1 B shows [11C]PK11195 uptake in 11 PDD subjects compared with 10 control subjects showing significant increase in microglial activity in frontal, temporoparietal and occipital cortical regions at a $p<0.005$ and extent threshold of 50 voxels.

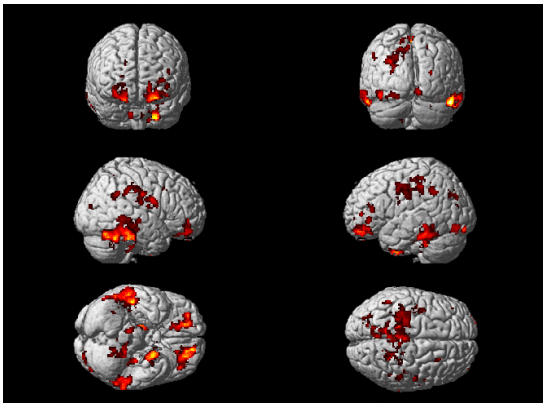


Figure 2.4.2.2: [11C]PK11195 Binding Potential between PDD and PD subjects shows minimally increased microglial activity in 11 PDD subjects compared to 8 PD subjects at voxel threshold of $p<0.05$ and extent threshold of 50 voxels.

Table 2.4.2.2 : Significant areas of elevated [11C] PK11195 BP in PDD subjects compared to controls localised by SPM (voxel threshold of $p<0.005$ and extent threshold of 50 voxels)

Region	Coordinates			Z- Score	Corrected	Cluster size
	x	y	z		p value	
Left posterior temporal gyrus	-68	-38	-10	4.23	<0.0001	777
Left precentral gyrus	-30	-28	56	4.18	<0.0001	6020
Right lateral gyrus (Occipital lobe)	40	-90	-14	4.10	<0.0001	725
Left lateral occipito temporal gyrus	-30	-6	-44	3.99	<0.0001	2402
Left parahippocampal gyrus	-30	-2	-30	3.97	<0.0001	2402
Left lateral gyrus (Occipital lobe)	-26	-98	-10	3.94	<0.0001	711
Brainstem	12	-26	-14	3.71	<0.0001	1315
Left middle and inferior temporal gyrus	-60	-34	-26	3.61	<0.0001	777
Right orbitofrontal gyrus	22	54	-14	3.56	<0.0001	749
Right precentral gyrus	50	2	24	3.47	0.001	640
Right middle frontal gyrus	20	42	-2	3.37	<0.0001	749

The coordinates are in Montreal Neurological Institute (MNI) space

Table 2.4.2.3: Significant areas of elevated [11C] PK11195 BP in PD subjects compared to controls as localised by SPM ($p<0.005$ extent threshold 50 voxels)

Region	Coordinates			Z- Score	Corrected p value	Cluster size
	x	y	z			
Left middle and inferior temporal gyrus	-64	-18	-10	4.64	<0.0001	1483
Left inferior frontal gyrus	-52	32	-8	4.36	0.024	318
Left superior temporal gyrus	-66	-26	-2	4.19	<0.0001	1483
Left orbitofrontal gyrus	-34	58	-14	3.50	<0.0001	318
Left cuneate gyrus	0	-92	20	3.46	0.024	789

The coordinates are in Montreal Neurological Institute (MNI) space

2.4.3. [18F] FDG RESULTS

PDD compared to controls

PDD subjects showed significant reduction in glucose metabolism compared to the control subjects in the posterior cingulate gyrus and temporal, parietal and occipital cortices (Table 2.4.3.1). Interestingly parieto-occipital areas showed larger reductions in metabolism compared to temporal regions. Individually nine out of the eleven PDD patients showed a significant reduction in glucose metabolism in the parieto-occipital or posterior cingulate. SPM analysis also showed a significant reduction in glucose metabolism in PDD subjects compared to the control subjects in frontal, temporal, parietal and occipital regions at a voxel threshold of $p<0.005$ as demonstrated in figure 2.4.3.1A

PD compared to controls

ROI analysis did not reveal any significant reduction in glucose metabolism in the cortical regions. SPM analysis did not reveal any significant reduction in glucose metabolism at a voxel threshold of $p<0.005$, and extent threshold of 50 voxels. However, reducing the voxel threshold for significance to $p<0.05$ showed a reduction in glucose metabolism in PD subjects in frontal, temporal, parietal, and also occipital cortices (shown in figure 2.4.3.1B).

PDD compared to PD subjects

An SPM comparison between PDD and PD subjects with a threshold of $p<0.05$ and extent threshold of 50 voxel showed there was a significant reduction in frontal, temporal, parietal and occipital cortical rCMRglc in PDD compared to PD (figure 2.4.3.2).

Table 2.4.3.1: Shows rCMRglc in PDD, PD and HC (healthy controls)

		Ant cing gyrus	Post cing gyrus	Thalamus	Striatum	Frontal cortex	Temporal cortex	Parietal cortex	Occipital cortex	Med temp cortex	Whole cortex
PDD	Mean	0.27	0.30	0.21	0.30	0.26	0.21	0.24	0.23	0.19	0.24
	SD	0.04	0.04	0.04	0.04	0.04	0.03	0.04	0.05	0.03	0.04
	p value	0.0819	0.0139	0.0012	0.1954	0.0717	0.0003	0.0064	0.0002	0.0020	0.0038
	% decrease	9.15	13.32	36.65	5.57	8.72	23.45	16.95	30.79	17.33	16.60
PD	Mean	0.31	0.34	0.25	0.31	0.26	0.30	0.29	0.29	0.211	0.28
	SD	0.43	0.05	0.02	0.05	0.03	0.02	0.04	0.05	0.01	0.03
	p value	0.18	0.35	0.04	0.32	0.10	0.30	0.27	0.29	0.18	0.34
	% decrease	-6.10	-2.59	14	3.9	-6.3	2.5	-3.8	-4.25	3.5	-2.17
HC	Mean	0.29	0.34	0.29	0.32	0.29	0.26	0.28	0.30	0.22	0.28
	SD	0.03	0.03	0.05	0.04	0.02	0.02	0.02	0.02	0.02	0.02

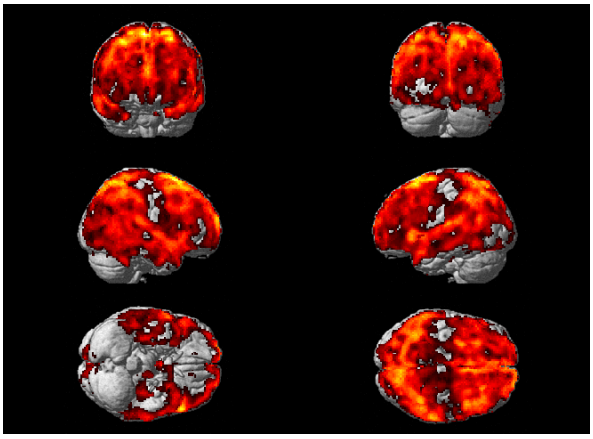


Figure 2.4.3.1A shows reduction in rCMRGlc in 11 PDD subjects compared with 8 control subjects showing significant reduction in frontal, temporoparietal and occipital region at voxel threshold of $p<0.005$ and extent threshold of 50 voxels

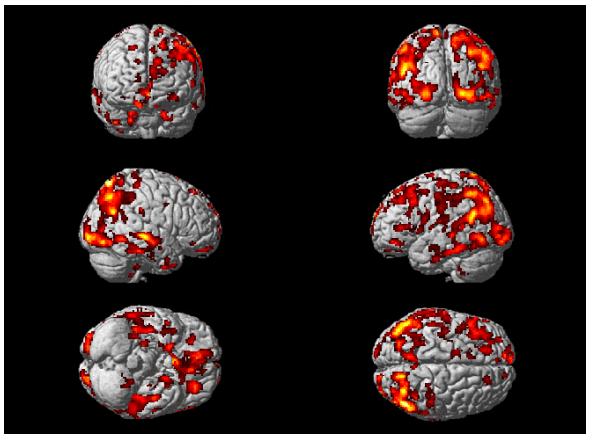


Figure 2.4.3.1B shows reduction in rCMRGlc in eight PD subjects compared with eight control subjects showing significant reduction in frontal, temporoparietal and occipital region at voxel threshold of $p<0.05$ and extent threshold of 50 voxels

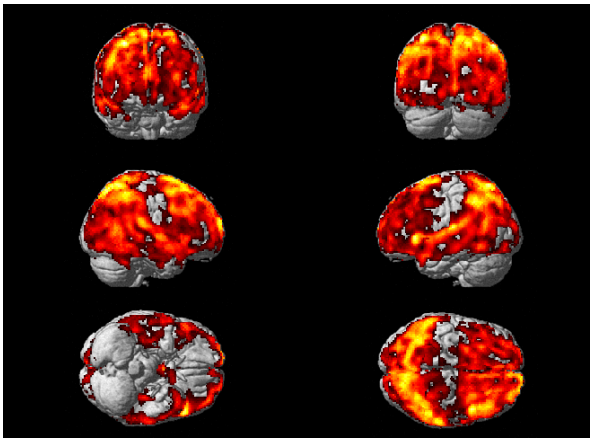


Figure 2.4.3.2 Shows significantly reduced glucose metabolism using [18F]FDG in 11PDD subjects compared to eight PD subjects at voxel threshold of $p<0.05$ and extent threshold of 50 voxels

Table 2.4.3.2 Significant areas of reduced FDG localised by SPM in PD vs controls. (voxel threshold of $p<0.05$ and extent threshold of 50 voxels)

Region	Coordinates			Z- Score	Corrected p value	Cluster size
	x	y	z			
Right parietal superior gyrus	20	-58	26	4.22	<0.0001	7815
Right parietal lobe	38	-68	48	4.17	<0.0001	7815
Right lateral gyrus (Occipital lobe)	24	-96	-4	3.72	<0.0001	7815
Right nucleus accumbens	6	12	-6	3.68	0.013	2875
Right orbitofrontal gyrus	32	38	-10	3.54	0.013	2875
Left superior frontal gyrus	-8	42	-12	3.07	0.013	2875
Left parietal superior gyrus	-26	-46	74	3.66	<0.0001	8793
Left posterior temporal gyrus	-60	-54	14	3.40	<0.0001	8793
Left parietal lobe	-48	-58	22	3.32	<0.0001	8793

The coordinates are in Montreal Neurological Institute (MNI) space

Correlation between Neuropsychometric testing and [11C] PIB uptake, [11C] PK 11195 binding and [18F] FDG uptake

Non-parametric tests did not show any correlation with memory test scores and the amyloid binding, microglial acivation or glucose uptake in this study.

2.5 DISCUSSION

2.5.1 DISCUSSION [11C] PIB

In the Part A multicenter study, only a minority (2 out of the 13) PDD patients showed a significantly raised amyloid load in at least one cortical area as compared to 11 out of 13 DLB patients. Similar incidence is also seen in our Part B PDD study where as groups both demented and non-demented PD patients did not show any significant cortical amyloid load compared to age-matched controls. Individually there was only one PDD patient showing an amyloid rise of 1.5 in the occipital lobe only. One out of the ten non-demented PD patients also showed raised amyloid level (1.4) in only the posterior cingulate gyrus.

These studies show that B amyloid deposition does not have a significant role in the pathogenesis of PDD which are in agreement with neuropathological studies (Aarsland et al.,2005) . Recently published [11C] PIB studies (Gomperts et al.,2008; Maetzler et al.,2008; Maetzler et al.,2009; Foster et al., 2010) have also reported low amyloid load in PDD patients and the brief findings are as follows. Significant cortical [11C] PIB positivity in PDD was reported in 4 of 12 patients (25 %) (Maetzler et al., 2009) ; 2 out of 10 patients (20 %) (Maetzler et al., 2008), none out of seven patients (Gomperts et al., 2008) and 4 out of 15 patients (Foster et al., 2010). Autopsy results were available in 2 of the 4 PIB-positive PDD patients and in 1 of the 11 PIB-negative cases in Foster's study. The PIB-positive PDD showed diffuse Lewy body pathology with amyloid plaques and the PIB-negative showed no amyloid but, only diffuse Lewy body pathology. Overall the numbers of patients in these studies were similar to our group and none of them support amyloid as a major contributor to the pathogenesis of dementia in PD.

The above results in PDD are in sharp contrast to our DLB patients who show a raised amyloid uptake in more than 80 % of the cases. These results are in agreement with other neuroimaging studies (Gomperts et al., 2008; Rowe et al.,2008). The DLB and PDD patients differed only in the time of the onset of the dementia. This implies that the co-occurence of amyloid may have accelerated the onset of dementia. These patients have significant amyloid load and may benefit from treatment with anti-amyloid drugs.

There was no correlation between amyloid load and MMSE ratings in these patients which is similar to the findings of other studies – neuropathological and neuroimaging (Foster et al.,

2010; Galvin et al.,2006; Sabbagh et al.,2010). These findings were also reflected in our group's AD study, where there was no correlation between cortical amyloid load and MMSE was seen if [11C]PIB negative cases were excluded from the analysis (Edison et al., 2007). Non-parametric tests showed no correlation between the neuropsychometric tests and amyloid uptake.

2.4.2 DISCUSSION [11C] PK 11195

In this study we have demonstrated increased cortical microglial activation in both PDD and PD subjects compared to healthy control subjects, the spatial extent of the activation being greater in PDD.

Gerhard et al. from our group had shown increased [11C] PK11195 binding in the brainstem, striatum, pallidum, temporal and frontal cortex of 18 PD patients compared to 11 controls. Interestingly when eight of the 18 patients were examined longitudinally after two years the [11C] PK11195 binding remained unaltered in spite of clinical deterioration (Gerhard et al., 2006). These findings together with our data suggest there is widespread microglial activation in the early stages of PD involving the brainstem and cortex. The presence of widespread cortical microglial activity in the non-demented PD group may imply that the disease has spread even before the cognitive decline starts. In PDD there is further inflammation. The sequence of events seem to follow the Braak staging (Braak et al., 2003) of Lewy body pathology in PD (Brooks et al.,2010). Microglial activation therefore seems to mirror the Lewy body spread. Microglial activation alongside Lewy body disease has been reported in pathological studies in the substantia nigra ,striatum and cerebral cortex (Mogi et al., 1994; Mogi et al.,1996; Sawada et al., 2006 et al., Nagatsu et al., 2007; Hirsch et al., 2009) and the aggregated α-synuclein in Lewy bodies could switch the neurones to a vulnerable state to be attacked by activated microglia leading to neuronal death and disease progression (Schwab and Schluesener et al., 2004; Zhang et al., 2005). Our findings could explain why all patients of PD inevitably develop dementia if they survive long enough (Hely et al.,2008) and it may be only a matter of time for sufficient damage to occur before dementia sets in.

In our study, although as groups there was increased microglial activity in the cortical association regions in both PD and PDD subjects, more extensive in the latter. Individual

analyses showed considerable inter-subject variability . It could simply reflect variable cortical levels of Lewy body involvement or it could be that in some subjects the microglial activation 'switches off' or 'engulfment-promoted' cell death could be avoided in some if the neurone evades contact with the microglia (Schwab and Schluesener et al., 2004). Ongoing microglial activation causes neuronal damage by releasing cytokines and other toxic chemicals. However, the damage might continue even if the microglial activation subsides as apoptotic cascades may have already being triggered. The latter theory might explain why all patients may not show [11C] PK11195 activity although there may be clinical worsening.

2.5.3 DISCUSSION [18F] FDG

Summarising the results of [18F] FDG, there is significant reduction in the glucose metabolism in the posterior cinglulate, frontal , temporal , parietal and occipital areas in PDD patients compared to controls. Interestingly it was possible to detect temporo-parietal hypometabolism in the non-demented PD patients using SPM analysis.

Widespread cortical hypometabolism with particularly severe involvement of the temporoparietal areas have been reported in earlier studies in PDD (Peppard et al., 1992; Vander Borght et al., 1997, Klein et al.,2010). Studies have also noted cortical involvement particularly temporo-parietal areas in non-demented PD patients but to a lesser degree compared to PDD (Peppard et al.,1992; Hu 2000). A very recent in vivo study with [18F] FDG and [11C] PIB by Jokinen et al. have also reported hypometabolism in all cortical areas in PDD patients with but quite distinct occipital involvement and not surprisingly all of their 11 PD patients failed to show any PIB uptake (Jokinen et al., 2010) . Occipital lobe involvement in PD has also been reported before (Bohnen et al.,1999; Vander Borght et al., 1997). These neuroimaging studies are similar to our study both in the distribution of the abnormal resting glucose state and also the differences in the groups of PDD, PD and controls.

But, is there any pathological basis to explain our findings?

Lewy bodies are predominantly formed of abnormal alpha-synuclein which is a misfolded aggregated form of the 'normal' protein. These proteins usually found in the synaptic boutons and axons and they accumulate in vulnerable neurones (Braak and Tedrici et al.,2005). [18F] FDG is a marker of neuronal activity and an intraneuronal pathology like Lewy bodies in the perikarya or lewy neurites in the cell processes could potentially disrupt glucose metabolism.

As per Braak classification of Lewy body disease, spread to the cortex happens at a very late stage of the disease (Braak et al., 2003) and identical to microglial activation cortical hypometabolism in non demented PD patients may imply that these patients have reached the Braak's stage 5 or 6 before the appearance of cognitive symptoms (Brooks et al.,2010).

However, it is important to note that glucose metabolism as a marker of disease progression in PD has limitations, as they can fluctuate with surgical and medical treatment (Feigin et al.,2001, Su et al., 2001; reviewed Brooks et al., 2010). Moreover, we acknowledge that our study in not longitudinal and hence, disease progression may be difficult to comment on.

In this study reductions in glucose metabolism correlated with increases in microglial activation across the combined PD and PDD cohorts. Combining the findings from above mentioned studies, the pattern of involvement hints towards a predominantly alpha-synuclein, Lewy body pathology.

Moreover ,decreased glucose metabolism and increased microglial activation in PDD compared to PD may suggest ongoing disease process and the absence of PIB uptake in these patients may suggest a pathology other than amyloid in causing the dementia.

2.6 CONCLUSION

In conclusion, this study has demonstrated that cortical microglial activation and glucose hypometabolism starts much earlier than the clinical manifestations of cognitive impairment in PDD. Although DLB and PDD are often considered parts of the same disease spectrum DLB patients have a significant amyloid load unlike PDD. In PDD patients amyloid deposition does not play a significant role in the pathogenesis of dementia. Anti-amyloid treatment in such patients may not be effective. Suppressing or halting microglial activation could prove to be potential neuroprotective targets in PDD if started prior to the cognitive symptoms appearing.

Manuscripts arising from this research that have been published in peer reviewed journals.

1. Glutamate NMDA receptor dysregulation in Parkinson's disease with dyskinesias

Imtiaz Ahmed,[1],* Subrata K. Bose, [1],* Nicola Pavese, [1] Anil Ramlackhansingh, [1] Federico Turkheimer, [1] Gary Hotton, [1] Alexander Hammers[1,2] and David J. Brooks[1]

[1] Centre for Neuroscience, Imperial College, London, UK

[2] Fondation Neurodis, Hoˆ pital Neurologique Pierre Wertheimer, Lyon, France

Brain. 2011 Mar 2

2. Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography

P Edison, [1] C C Rowe,[2] J O Rinne,[3] S Ng,[2] **I Ahmed**,[1] N Kemppainen,[3] V L Villemagne,[2]
G O'Keefe,[2] K Na°gren,[3] K R Chaudhury,[4] C L Masters,[2] D J Brooks[1],[5]

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[3] Turku PET Centre, University of Turku, Finland;
[4] Kings College London, UK;
[5] Hammersmith Imanet, GE Healthcare, London, UK
J Neurol Neurosurg Psychiatry. 2008 Dec; 79(12):1331-8.

Manuscripts arising from this research that has been submitted in peer reviewed journals.

The relationship between microglial activation, amyloid deposition and glucose metabolism in Parkinson's disease (PD) and Parkinson's disease dementia (PDD) – Submitted to Neurobiology of Ageing (Apr 2012).

Edison P *, Ahmed I *, Gelosa G, Turkheimer FE, Chaudhuri R, Walker Z, Brooks DJ

(*Contributed equally to this work)

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