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Implementation of an algorithm for differential diagnosis of patients with Parkinsonistic symptoms

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Implementation of an algorithm for differential diagnosis of patients with Parkinsonistic symptoms

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Abstract

The disorders with Parkinsonistic symptoms overlap both clinically and pathologically. Therefore differential diagnosis becomes difficult, especially early after disease onset. Studying the brain metabolism with PET FDG and the dopamine transporter system with SPECT DAT imaging several differences between the disorders can be seen.

Today neurologists at Uppsala University Hospital analyze this imaging data and combine it with the clinical data manually to make a diagnosis. This is a possible limitation and to fully use the information embedded in the data this thesis project aimed to develop a diagnostic algorithm that takes the imaging datasets and clinical data as input and propose a suitable diagnosis.

The developed algorithm has the potential to, in the future, serve as tool for combining information and generating a second opinion when making the differential diagnosis of patients with Parkinsonistic symptoms.

Keywords

classification system, differential diagnosis, Parkinson's syndrome, Parkinsonian syndromes, Parkinsonistic symptoms, DaTSCAN, PET FDG

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Populärvetenskaplig sammanfattning

Parkinsons syndrom omfattar flera neurodegenerativa sjukdomar, bland annat Parkinsons sjukdom. Dessa tillstånd överlappar varandra kliniskt så väl som patologiskt, de är därför mycket svåra att skilja åt, speciellt tidigt i sjukdomsförloppet då få symptom uppvisas. Idag finns det inga blodprov eller snabbtester för att särskilja dessa tillstånd.

När det är svårt att ställa en diagnos grundat på symptomen kan man använda sig av positronemissionstomografi (PET), för att studera aktiviteten i olika delar av hjärnan, och singelfotonemissionsdatortomografi (SPECT) kan användas för att studera aktiviteten av signalsubstansen dopamin i hjärnan. Det har visat sig att man med dessa metoder kan hitta patologiska skillnader mellan sjukdomarna. Idag får neurologen utifrån sin erfarenhet utvärdera denna bildinformation visuellt och väga samman detta med den kliniska informationen för att sedan ställa en diagnos.

I detta examensarbete implementeras en algoritm som utifrån en PET och en SPECT bild samt symptom från en patient extraherar relevant information ur bilderna utefter definierade egenskaper. Varje egenskap och symptom får rösta på de diagnoser som egenskapen tyder på. När alla egenskaper har lagt sina röster framträder en vinnande diagnos. Denna information skulle kunna hjälpa en neurolog att hitta fram till rätt diagnos tidigare.

Examensarbete 20 p
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1. Introduction

1.1 The history of Parkinson's syndrome

The symptoms like tremor (shaking), rigidity and bradykinesia (slowing of physical movement) has long been known and associated with old individuals. In 1817 James Parkinson described these as symptoms of the shaking palsy or *paralysis agitans* and claimed it to be a distinct disease.[1]

The disease was called *paralysis agitans* until the neurologist Jean-Martin Charcot started to call it "maladie de Parkinson"[2] in the 1860s when he refined the clinical description with additional detailed symptoms. Charcot studied several neurological disorders and he was determined that specific clinical signs were caused by specific anatomical lesions. Therefore Charcot added autopsy to the anatomical methods of studying these disorders. His findings contributed a lot to the understanding of spinal cord syndromes and cortical syndromes, however he did not find specific lesions causing Parkinson's disease nor did he find lesions causing several forms of epilepsy. Consequently these conditions were classified as "névroses".[3]

Charcot's work was continued by his younger colleague Édouard Brissaud and he found that the midbrain was involved in Parkinson's disease. At this time it was a new approach because general pathology studies were focused on the cortex and the spinal cord. In 1913 Frederic Lewy discovered abnormal aggregates of proteins in neurons upon autopsy of patients with Parkinson's disease. The aggregates were named Lewy bodies. [4]

As the documentation of the pathology of Parkinson's disease slowly progressed, the symptoms still were the only approach to a pre-mortem diagnosis. Early symptoms were, and still are at interest, as for all disorders, but these symptoms are subtle, often with individual differences.[5]

Jakob Billström, a physician and psychiatrist in Stockholm, began studying his own spelling mistakes and handwriting in 1915. During the following years he found that his spelling and handwriting had worsened. He recognized his small and cramped handwriting as micrographia and, as he called it, Bradygraphia and as time passed he found himself with an imbalanced posture and tendencies to fall. In 1943 he diagnosed himself as having Parkinson's syndrome and later on he published an article on early symptoms of Parkinson's syndrome.[6]

A leap forward in the exploration of the syndrome was made by Arvid Carlsson and colleges in 1957. When he gave the drug reserpine to laboratory animals, inducing Parkinsonistic symptoms by a decrease in dopamine levels, he showed that he could ease the symptoms by introducing levodopa into the animals. [7] In 2001 A. Carlsson, E. Kandel and P. Greengard was rewarded the Nobel Prize in Physiology or Medicine for their discoveries concerning "signal transduction in the nervous system".[8] Studies evaluating the effect of levodopa in patients diagnosed with Parkinson's disease were soon to follow and in 1968 a paper was published showing the improvements in patients with Parkinson's disease for the first time.[9]

1.2 Parkinson's syndrome

Parkinson's syndrome also known as Parkinsonism, atypical Parkinson's, secondary Parkinson's or Parkinson plus syndrome is a group of disorders featuring symptoms as tremor, rigidity, bradykinesia and postural instability.[28] (Sometimes the term secondary Parkinsonism refers to toxin or drug induced Parkinsonian symptoms only.)

There are some variations in which disorders are included in the group of Parkinson's syndrome. Besides the Parkinson plus disorders there are several other disorders that can show Parkinsonistic symptoms. In this study the following disorders were considered: Idiopathic Parkinson's disease (IPD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), essential tremor (ET) and dementia with Lewy bodies (DLB). All these disorders present Parkinsonistic symptoms even though ET seems not to be neurodegenerative and DLB is a kind of dementia which is pathologically closer to Alzheimer's disease. There are no cures for these diseases; all

treatments are based on alleviating the symptoms.[22,28] However, new disease modifying drugs are currently in clinical trials and improved treatment of Parkinsonism may be available in the near future. In addition, a few pilot studies with gene therapy have been published and the technique moves into clinical trials.[10,11,12]

Several brain structures are involved in the pathology of these disorders. Figure 1 - 3 show an overview of the main anatomical structures involved in Parkinson's syndrome. Figure 3 describes the terms used for positions and directions in neuroanatomy and neuroimaging.

1.2.1 Idiopathic Parkinson's disease

Idiopathic means "arising by itself"[14] and IPD refers to the "true" Parkinson's disease with degradations of the pigmented dopaminergic neurons in the substantia nigra. (Figure 1) Cytoplasmatic aggregates of proteins, named Lewy bodies, are found in these neurons. The inclusion bodies consist of proteins such as ubiquitin, synuclein and parkin. Characteristic clinical symptoms are resting tremor, bradykinesia and stiffness. A characteristic feature of IPD is the sustained response to levodopa or a dopamine agonist.[15,28]

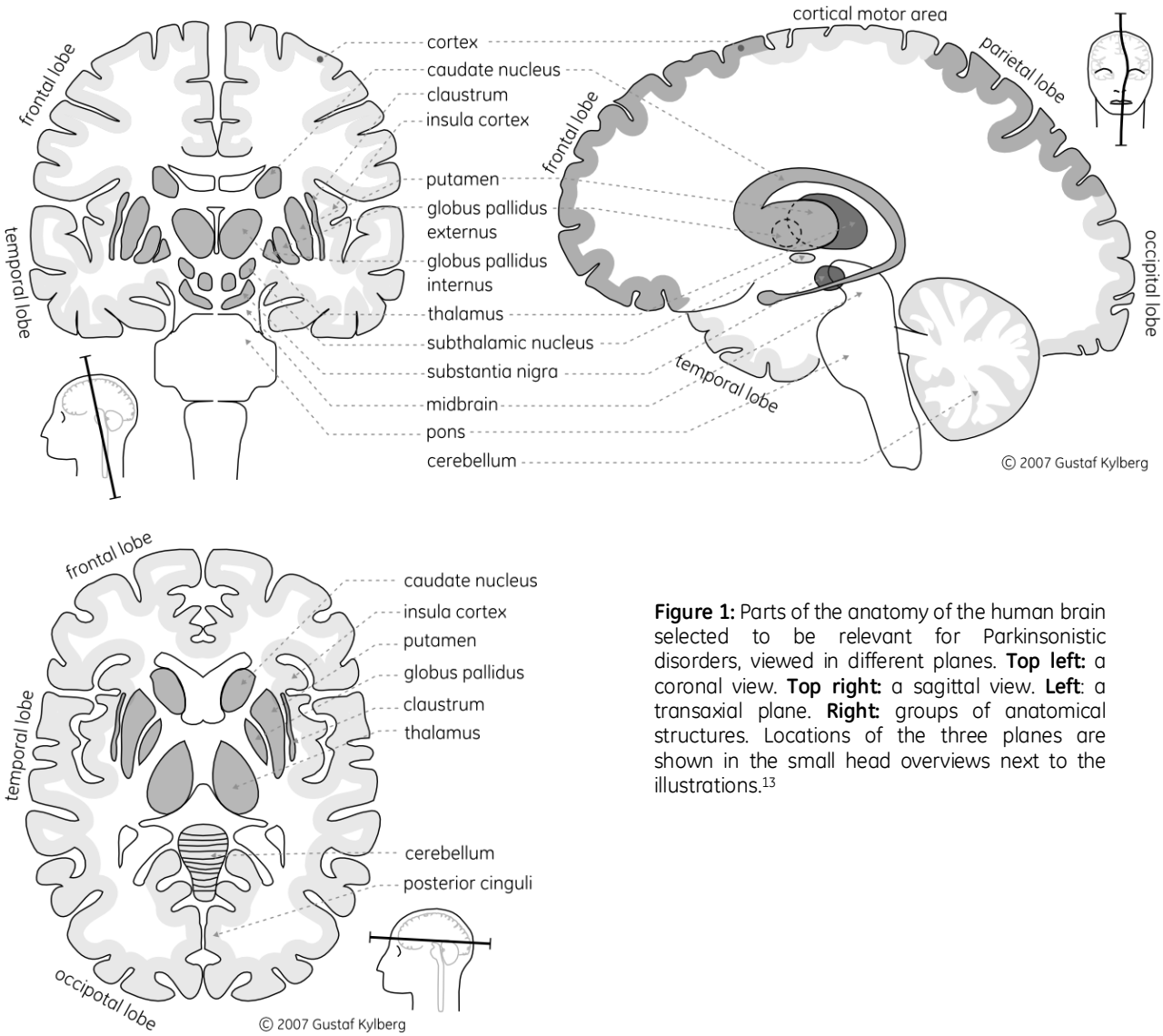

Figure 1: Parts of the anatomy of the human brain selected to be relevant for Parkinsonistic disorders, viewed in different planes. **Top left:** a coronal view. **Top right:** a sagittal view. **Left**: a transaxial plane. **Right:** groups of anatomical structures. Locations of the three planes are shown in the small head overviews next to the illustrations.[13]

There is no single cause to IPD and most patients have no family history of the disease. Still there is a genetic contribution to IPD; a number of autosomal loci with genes in which mutations that can lead to Parkinson's disease. These genes are named PARK followed by a number and more than ten of them have already been found.[16]

There is no cure and no treatment to slow down the disease progression but there are a number of symptomatic therapies: i) Levodopa, which is the main drug in IPD treatment. ii) Dopamine agonists. iii) COMT inhibitors iv) MAO-B inhibitors v) Amantadine. [2, 17] For more information about the drugs see Table 1.

There are a few surgical approaches to treat the symptoms. These can be used in cases of advanced IPD when the drug response has weakened and the side effects of the resulting high dose drug treatment becomes too severe. Severe tremor can be treated with thalamotomy, a stereotactic surgical procedure where an electric probe is inserted into the thalamus and electric current is used to burn a lesion. To reduce tremor, rigidity and dyskinesia a similar surgical treatment named pallidotomy can be performed. A less invasive, and more frequently used surgical procedure nowadays, is deep brain stimulation (DBS). Symptoms such as tremor, bradykinesia and rigidity are reduced by electrical stimulation of the thalamus, globus pallidus or subthalamic nucleus.[2, 17] For more information about surgical treatments see Table 1.

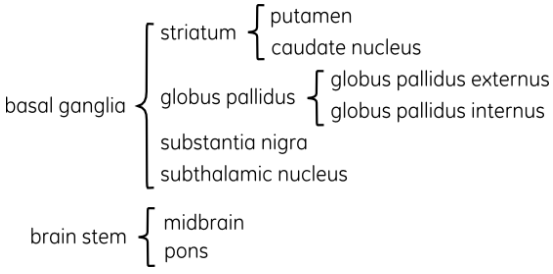

Figure 2: The hierarchy of a few anatomical structures involved in the Parkinsonistic syndromes.[18]

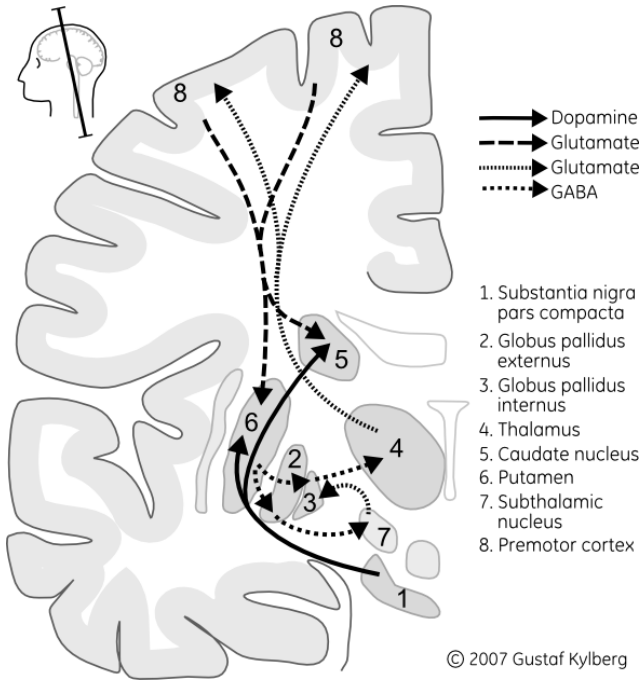

Figure 3: Schematic view of the normal basal-ganglia function. These pathways are essential for voluntary movement. As can be seen several structures and neurotransmitters are involved. If only one of them is affected the voluntary movement is too.[2,18]

1.2.2 Progressive supranuclear palsy

Patients with PSP often have a symmetric onset of Parkinsonistic symptoms. Features such as vertical gaze palsy (difficulty looking up- and downwards) and falls are predominant among the early symptoms. PSP patients tend to lean backwards in posture and gait contrary to IPD and MSA patients; retropulsion contra propulsion.[16] Behavioural changes may also appear as early signs and are often observed by someone in the patient's immediate surroundings. About 20% of the patients respond to levodopa; however patients may only benefit from the treatment initially.[19]

Pathologically PSP results in atrophy in frontoparietal cortex and the midbrain. The atrophy in the midbrain can be seen with CT or MRI. Consequently late stages PSP can be differentiated from the other Parkinsonian disorders by measuring the anterioposterior diameter of the midbrain in a sagital plane of an MRI scan.[28]

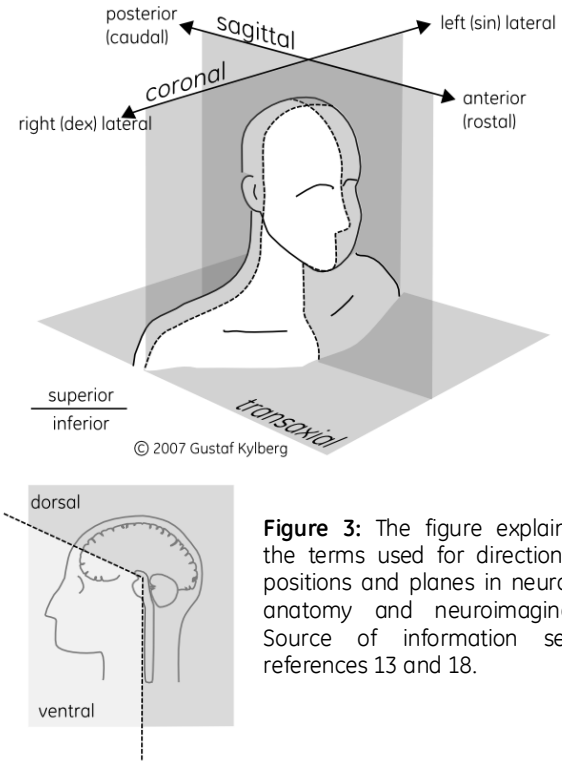

Figure 3: The figure explains the terms used for directions, positions and planes in neuro-anatomy and neuroimaging. Source of information see references 13 and 18.

Levodopa and amantadine treatment may be tested while carefully considering the side-effects. Moreover, it is important that information about the high risk of falling and sleep disruptions is given to the patient.[22, 28] For more information about the drugs see Table 1.

1.2.3 Multiple system atrophy

MSA is divided into three subtypes, MSA-c, MSA-a and MSA-p. The letter 'c' stands for cerebellar dysfunction, 'a' for autonomic dysfunction and 'p' for Parkinsonian subtype. The subtypes have a significant overlap both clinically and pathologically. MSA progresses faster than IPD and the patients have a mean survival of 6 years from disease onset.[28]

Patients with MSA may respond poorly to levodopa treatment although 30% of the patients obtain a good response initially.[28] Still levodopa and dopamine agonists are the main drugs in MSA treatment. The antiviral drug amantadine can be used and often a drug to treat the hypotension is co-administrated.[22]

For more information about the drugs see Table 1.

1.2.4 Corticobasal degeneration

CBD can mimic the characteristic symptoms of IPD such as rigidity, asymmetric bradykinesia and postural instability. One of the symptoms is quite rare, the alien limb phenomenon. The patient experiences no control whatsoever of the affected limb; it has its own life, so to speak. An affected arm may move and grasp objects involuntarily to the patient.[28]

There is no cure and patients seldom respond to levodopa. Still a low dose treatment with levodopa and dopamine agonist may show some effect. For some patients treatment with amantadine has shown positive effect.[22,28] For more information about the drugs see Table 1.

1.2.5 Essential tremor

ET is the most common movement disorder. In contrast to many other Parkinsonian disorders, ET can begin at almost any time during life. The mean age at disease onset is 45 years but the variance is high. Tremor of hands and arms are common symptoms even though tremor symptoms can affect any voluntary muscle. The tremor present in ET is usually action tremor while IPD patient's tremor, normally is resting tremor. Tremor often worsens with stress.[22]

About half of the cases of ET are caused by mutations in the genes ETM1 or ETM2 and the rest is due to causes unknown today.[20]

The surgical treatment deep brain stimulation, mentioned as a treatment of IPD in section 1.2.1, can often be effectively used to treat the tremor symptoms of ET.[21] Drug treatments of ET involve beta-blockers and gabapentin.[22] For more information about the drugs see Table 1.

1.2.6 Dementia with Lewy Bodies

Clinical symptoms of DLB overlap with IPD as well as with Alzheimer's disease. DLB is the second most frequent cause of dementia.[23]

Besides signs of dementia, symptoms include fluctuation in alertness and attention is as well as hallucinations that the patient can describe in detail.[22]

The pathology of DLB has similarities with IPD. For instance the cytoplasmatic inclusion bodies, the Lewy bodies, which are present in DLB, are similar to those in IPD. Another feature these two disorders have in common is the dopaminergic neuron loss of substantia nigra.[28]

Patients with symptoms of dementia are referred to the department of geriatrics while those with Parkinsonistic symptoms are referred to the department of movement disorders. The symptoms of DLB overlap the area of dementia and Parkinsonism and due to the division of departments this group of patients may not get the optimal treatment.[15]

Treatment with levodopa and low dose of a dopamine agonist can help and so can treatment with memantine and cholinesterase inhibitors. DLB patients are highly sensitive to antipsychotics which may cause life threatening side-effects.[22] For more information about the drugs see Table 1.

1.3 Other causes of Parkinsonistic symptoms

As many as 50 different diseases can, in some stages, show Parkinsonistic symptoms. Diseases include Alzheimer's disease (AD), Frontotemporal dementia (FTD), Dopa-responsive dystonia, Pick's disease, Huntington's disease and Creutzfeldt-Jakob disease.

Exposure to toxins including manganese, carbon monoxide, cyanide, methanol and carbon disulfide can result in Parkinsonistic symptoms, even chronical and progressing symptoms. Drugs like antipsychotics, calcium channel blockers, antidepressants, chemotherapeutics and estrogens can induce these symptoms as well. Drug or toxin induced Parkinsonism differs from the Parkinsonian disorders, symptom onset is often abrupt and has a rapid progression.[22]

Structural lesions due to tumours, basal ganglia calcification and multiple infarcts may also cause Parkinsonistic symptoms.[24]

1.4 Normal ageing

To some degree Parkinsonistic symptoms may be a part of the natural ageing process. The normal process of ageing has some resemblances to Parkinson's disease; loss of

Table 1: List of treatments used in the field of the Parkinsonistic disorders. Source of information: 2,17,21 and 22

Drug treatments
Amantadine – an antiviral drug that stimulates the release of dopamine by being an antagonism of the NMDA receptor. Used for IPD, PSP, MSA and CBD.
Cholinesterase inhibitors – inhibits the cholinesterase enzyme which catalyzes the hydrolysis of the neurotransmitter acetylcholine resulting in symptoms as tremor and nausea. Used for DLB.
COMT-inhibitors – a Catechol-o-methyl-transferase inhibitor prevents the breakdown of levodopa and dopamine. Used for IPD.
Dopamine agonists – activates the dopamine receptors. Some studies indicate that dopamine agonists may slow down the progression of IPD. Used for IPD, MSA, CBD and DLB.
Gabapentin – developed for treatment of epilepsy. It is used for pain relief. Used for ET.
Levodopa – an intermediate in the biosyntheses of dopamine and can unlike dopamine cross the blood-brain barrier. Levodopa is usually co-administrated with a dopa-decarboxylase inhibitor. Used for IPD, PSP, MSA, CBD and DLB.
MAO-B inhibitors – act by inhibit the monamine oxidase-B and in this way reducing the breakdown of dopamine. Used for IPD.
Memantine – is a NMDA receptor agonist that activates the NMDA receptor which is involved in the memory process. Developed for Alzheimer's disease. Used for DLB.
Surgical treatments
DBS – deep brain stimulation. Electrodes are implanted with stereotactic surgery into brain structures as the thalamus, globus pallidus interna or subthalamic nucleus. The electrodes are connected to a pulse generator; thereby the areas surrounding the electrodes are electrically stimulated resulting in reduced tremor, rigidity and bradykinesia of the patient. Used as the main surgical treatment from mid 1990s and forward. Used for IPD and ET.
Pallidotomy – an invasive procedure where an electrical probe is inserted in the globus pallidus, using stereotactic surgery, that burn a lesion with and electric current. Used in the past for IPD.
Thalamotomy – an invasive procedure where a part of the thalamus is destroyed by insertion of an electric probe, using stereotactic surgery, that burn a lesion with an electric current. Used in the past for IPD.

dopaminergic neurons in substantia nigra and a slightly lower metabolism globally in the brain is to some degree present during normal aging. However there are differences in the amount and pattern of the neuron loss as well as in the response to levodopa.[16]

1.5 Differential diagnosis

Diagnosis of patients with Parkinsonistic symptoms is mainly done by studying the set of symptoms, order of appearance and medical history of the patient; in other words a strict clinical approach is used as a first step. The main clinical features of the different disorders are to a high degree overlapping each other. This results in a frequent dilemma for doctors trying to make a differential diagnosis. The fact that more or less all of the Parkinsonistic disorders have some response to levodopa adds to the complexity. In early stages of IPD the misdiagnosis rate can be as high as 20 to 30%.[25] Even for movement disorder specialists, a misdiagnosis rate of 10% for IPD is not exceptional.[37] Making a differential diagnosis in this area is to a high extent based on finding supporting features for one diagnosis and excluding features for the other diagnoses. If there are atypical findings, or too few separating symptoms, functional brain imaging can be used to further assist diagnosis.[5,24,25]

Still the only way to a definite diagnosis is by studying lesion in the brain at an autopsy, however this is done post mortem, due to natural reasons, and the findings will not benefit the current patient.

1.5.1 Clinical approach

The diagnosis of IPD can be relatively straight forward using the Unified Parkinson's Disease Rating Scale (UPDRS)[26] for evaluation of the present symptoms and if a positive and durable effect is obtained when administrating levodopa. The rating scale considers forty-two items corresponding to different symptoms. Most items can have a score from zero to four depending on the severity of the symptom while a few features have the score zero or one (no/yes).[5] It is important to study the medical history of the patient to eliminate toxin and drug induced Parkinsonism as well as other conditions presenting the symptoms.[5,15]

There are specific rating scales for the other Parkinsonian disorder. For an example there is the PSPRS, UMSARS[27] and WHIGET to rate symptoms of PSP, MSA and ET. The mini mental test (MMT) may be used to determine whether or not a patient has dementia.

Diagnostic problems arise when: i) symptoms are few, as in early stages of the disease; ii) symptoms overlap between the disorders; iii) treatment with levodopa has poor or no effect and iv) there are atypical findings in symptoms or medical history.[28]

Often patients with an uncertain diagnosis are followed up with additional clinical investigations to monitor the progression of the disease and hopefully a more robust diagnosis can be made. This monitoring procedure can persist for many years and there are cases of re-diagnosis after as long as 10 years from disease onset.[22,23]

1.5.2 Functional brain imaging approach

Functional imaging has been proven to offer a great insight into the pathology of Parkinson's syndrome.[24] For individual patients this may result in a more robust diagnosis, which may lead to improved treatment and earlier after disease onset.[5, 29]

1.5.2.1 SPECT imaging

The main imaging method used in clinical practice for evaluating Parkinsonistic conditions is Single Photon Emission Computed Tomography (SPECT).

Using SPECT, a tracer which is a biological molecule, radiolabeled with a short lived γ-emitter like ^{99m}Tc (half-life 6.01 h) or ^{123}I (half-life 13.13 h), is injected[31]. A SPECT camera is principally a gamma camera that rotates around the patient and creates multiple 2D images by detecting the γ-rays emitted by the tracer, these 2D projections are then reconstructed to a 3D image.[31]

SPECT scans used in this study were acquired using the radiotracer DaTSCAN® from GE Healthcare. The molecule used, ^{123}I-

iofupane, binds to the dopamine transporter protein. The dopamine transporter protein (DAT) is located on the presynaptic membrane of dopaminergic neurons. It is involved in the reuptake of dopamine and thereby affects the amount of synaptic dopamine.[30]

1.5.2.2 PET imaging

When using Positron Emission Tomography (PET) a tracer which is a biological compound radiolabeled with a short lived positron emitting isotope like ^{18}F (half-life 109.77 min) or ^{11}C (half-life 20.38 min) is injected. An emitted positron will immediately collide with its antiparticle, the electron, in a annihilation event and two photons with 511 keV are emitted in almost opposite direction to each other. The PET scanner uses circular arrays of detectors and when two photons are detected at the same time (i.e., within a very short time window) it is known that an annihilation event has occurred along the straight line connecting the two detectors. These events called coincidences form projections and from this data a 3D image can be reconstructed.[31]

The PET scans used in this study were all acquired with the tracer ^{18}F-FDG. FDG is the glucose analogue fluorodeoxyglucose and when labelled with ^{18}F it is used to reveal metabolic information. The main clinical applications for PET FDG scans are in oncology but FDG is also used for differential diagnosis of Alzheimer's disease (AD) and Frontotemporal dementia (FTD). However, the metabolic pattern can provide information also for differential diagnosis of Parkinsonistic disorders.

In research F-dopa tracers are used to get information about the dopamine system using PET cameras.[30]

1.6 Aim

Differential diagnosis in Parkinsonism is difficult, especially at early stages. Dopamine transporter (DAT) imaging (e.g. using DaTSCAN) is widely used to help distinguish between ET and Parkinsonian syndromes but further refinement of the diagnosis is difficult without additional information. However, if the DAT image is combined with a scan showing perfusion or metabolic information the combined information may aid to the differential diagnosis of Parkinsonian disorders.[29] This has been recognised at Uppsala University Hospital and patients referred for a DaTSCAN normally has a PET FDG scan performed as well. Today the DaTSCAN and FDG scans are analysed separately and it is up to the physician to visually or quantitatively extract relevant information and combine it with clinical data to make the differential diagnosis. This is a difficult and subjective process and hence limits the full use of the available data.

The purpose of the work described in this thesis was to overcome these difficulties by proposing a method for integrating all available information. We describe a system for making a combined analysis of DaTSCAN, PET FDG and clinical data and presenting highlighted diagnostic information that will assist the physician in making the final diagnosis.

The disorders to be considered initially were: IPD, PSP, MSA, CBD, DLB and ET. AD and FTD were added later on.

2. Material and methods

2.1 Material

This study contains data from forty-nine patients with Parkinsonistic symptoms. Due to the atypical findings and the troubles of making a diagnosis based on clinical data these patients have been referred to DaTSCAN imaging. Twenty-one of them have been referred to an additional PET FDG scan. The scans were performed at Uppsala University Hospital between 2005 and 2007.

To allow for detection of abnormal metabolism and DAT function in the patient data, a normal material consisting of imaging data from healthy control subjects were constructed. The DaTSCAN normal material consisted of 10 healthy controls and the PET FDG normal material consisted of 20 healthy controls.

The clinical records of the patients were accessed and processed by a neurologist

(Torsten Danfors). Symptomatic features established in section 2.1.3.1 were sorted out for each subject. The available properties for a clinical feature were set to yes, no or unknown.

The imaging and clinical data were made anonymous to guarantee an objective analysis and for patient integrity. A sequence number was assigned to each subject for identification.

2.1.3 Symptomatic profiles

Dr. Danfors provided a list of characteristic symptoms for each of the six disorders. These symptoms were used as clinical features. Minor modifications were made on the basis of the literature.[19,22,28] Table 2 shows the symptomatic profiles composed of these features.

2.1.4 Imaging profiles

In the resent years several studies have been published in the field of neuroimaging exploring differences in the pathology of the disorders within Parkinsonism. Literature studies were performed to find papers where the metabolism or the dopamine transporter function in the brain of subjects with Parkinsonistic symptoms has been investigated with PET and SPECT imaging. [5, 13, 20-23, 25, 32-39] The addition of AD and FTD to the considered diagnoses, in line with the paragraph 1.6, was based on following endnotes: 32, 33 and 39. The search has been done mainly through the search engine PubMed.[34]

Metabolic PET FDG studies show similar results as perfusion SPECT studies in IPD, PSP, MSA and CBD, consequently both articles with metabolic and perfusion studies were considered.[40]

Two sets of profiles were created, one set describing glucose/perfusion patterns and one set describing dopamine transporter function. Table 3 shows the two sets of imaging profiles.

2.2 Methods

2.2.1 Processing DaTSCAN data

All DaTSCAN datasets have been reconstructed, corrected for attenuation and smoothed with the software Hermes, except for the scans in the normal material.

Each dataset was processed according to the following. First the scan was spatial normalized to fit a normal template in MNI space using a fully automated method.[41] In this space, a set of volumes of interests (VOIs) corresponding to the anterior and posterior putamen and caudate nucleus were defined. In addition, a VOI located in the occipital and temporal lobe was defined. This region is free from specific binding of the tracer and is hence suitable for use as a reference region.[23] After applying the VOIs to the data, Striatal

	mean age at onset	asymmetric onset	alien limb phenominon	early falls	resting tremor	posture tremor	hypokinesis	rigidity	propulsion	retropulsion	dementia (MMT)	depression	hallucinations	dysautonomia	l-dopa responsive	sensitiv to neuroleptics	gaze palsy	gait disturbance	swallowing difficulties	dysarthria
IPD	59	y	n	n	y	-	y	y	y	-	y/n	y/n	-	y	y	-	n	y/n	-	-
PSP	63	n	n	y	n	-	y	y	-	y	y/n	-	-	-	-	-	y	y	y	y
MSA	54	y/n	n	y/n	y	-	y/n	y	y/n	y/n	-	-	-	y	-	-	n	-	-	y/n
CBD	63	-	y/n	-	-	-	y	y	-	-	y/n	y/n	-	-	-	-	-	y	-	-
DLB	45	y/n	n	y/n	-	-	-	y	-	-	y	-	y	-	-	y	y/n	-	-	-
ET	76	-	n	-	-	y	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 2: Symptomatic profiles for six disorders presenting Parkinsonistic symptoms. y = yes, n = no, y/n = yes or no, the symptom is a supporting feature. Symptoms arise along the progression of these disorders; a patient may show only a few of the symptoms, especially in early stages of the disease. This data is based on a table with characteristic symptoms provided by Danfors and on additional information from the literature, see endnote 19, 22 and 28.

Binding Ratios (SBRs) were computed by subtracting the reference VOI value from each of the Striatal VOIs and then dividing the new value with the value of the reference VOI. The SBRs were exported to tab-separated text files for further processing.

2.2.2 Processing PET FDG data

Each PET FDG dataset were provided in the ecat7 file format and were dynamic datasets with seven frames. The last three frames, spanning from 30 to 45 minutes after injection, were aligned to each other and summed into one sum image. This summarized image was then spatially normalized to fit a standard template brain defined in MNI space using a fully automated method.[41] The scans were intensity normalized to image mean. The features defined in the section 2.1.3.2 were drawn as regions of interest (ROIs) on transaxial slices of the template in MNI space. The ROIs were combined into VOIs. An MRI template in MNI space, the spatial normalization template and the book *Pocket Atlas of Sectional Anatomy* by Moller et al.[13] were used as guidance while drawing the VOIs. Two sets of VOIs were tested.

The VOIs were used to calculate the mean VOI values for each patient scan and were exported to tab-separated text files for further processing.

2.3 Algorithm design

2.3.1 Preferred characteristics

To design a suitable algorithm for differential diagnosis, a number of preferred properties were identified. The method should: i) be able to propose a diagnosis based on features extracted from PET FDG and DaTSCAN data; ii) be robust to missing features in the input data; iii) be able to be trained on a small test dataset; iv) be flexible and allow addition

DaTSCAN						PET FDG													
putamen	caudate nucleus	putamen-caudate ratio	striatum asymmetry			putemen	caudate nuclues	thalamus	globus pallidus	cerebellum	brain stem	frontal cortex	temporal cortex	parietal cortex	cortical motor area	occipatal cortex	cortical asymmetry	posterior cinguli
-	o/-	-	+	IPD		-/o/+	-/o	+/o	+/o	+/o	o	o	-/o	-/o	+/o	-/o	o	o
-	-	-	o	PSP		-	-/o	*	o	o	-	-	o	+/o	-/o	o	o	o
-	-	-	o	MSA		-	-/o	+/o	o	-	-/o	*	o	+/o	o	o	o	o
-	o/-	o	+	CBD		-	-	-	o	-	-/o	-/o	o	-	o	o	+	o
o	o	o	o	ET		+	+	o	o	o	o	o	-	o	o	o	o	o
-	-	o	o	DLB		o	o	o	o	o	o	-/o	-	-	o	-	o	o
o	o	o	o	AD		o	o	o	o	o	o	-/o	-	-	o	o	o	-
-	-	o	o	FTD		-/o	o	o	o	o	o	-	-/o	o	o	o	o	o

- = decreased, 0 = normal, + = increased, / indicates supporting feature otherwise defining, * conflicting data

Table 3: Summary of the imaging profiles for IPD, PSP, MSA, CBD, ET, DLB, AD and FTD regarding the modalities of FDG PET and DaTSCAN. The literature is to a high degree unanimous, even though two features has conflicting data, these are market with * in the table.

Left part: DaTSCAN features and its properties for the different Parkinsonian disorders. The signs – and + indicates respectively lower and higher uptake than observed in healthy controls. When the / sign is used the feature may show both the alternatives, the feature is regarded as a supporting but not defining feature.

Right part: PET FDG features and its properties for the different Parkinsonian disorders. The signs – and + indicates lower respectively higher metabolism than observed in healthy controls. When the / sign is used the feature may show both the alternatives, the feature is regarded as a supporting but not defining feature.

The information is gathered from the following papers: 5, 16, 23-27, 29 and 33-36. A few properties are from perfusion SPECT studies but perfusion SPECT and FDG PET show highly similar results for these conditions.[40]

of clinical data as input; v) show how strong a proposed diagnosis is; vi) provide insight into why the algorithm proposes a certain diagnosis and vii) allow for further training if new training data becomes available.

Güvenir et al. proposed an algorithm named Voting Feature Intervals (VFI5) to learn differential diagnosis of erytemato-squamous skin diseases.[42] These skin diseases overlap clinically and it is difficult to differentiate between them. Each symptom was called a feature. The features were measured in a decimal number. In each feature dimension, intervals corresponding to symptoms of the diseases were defined from a training dataset with known diagnosis.

When the VFI5 classifies symptoms of a patient, each feature value falls into an interval that will, in turn, vote for a corresponding diagnosis. The votes are summarized and the diagnosis with the maximum amount of votes is declared as the suitable (most probable) diagnosis.[42]

This algorithm has several criteria that are desired in this project. It can easily handle missing features; the system will simply not receive any votes from this feature. It is possible to adjust the weights and intervals and adding a feature is relatively easy. Moreover, the algorithm makes diagnosis based on a voting process that can be viewed; there are no black boxes.[42]

When using intervals to define the votes of a feature value, it results in, more or less, sharp edges between the different diseases. We hypothesized that a smooth distribution, without sharp edges, would better mimic the nature of the features where a feature can be a supporting feature or a defining feature. In addition, a smooth distribution of votes allows a more extreme feature value to generate a higher vote than a near to normal value. By using overlapping distributions of normal and disease values a feature value can show, for instance, hypometabolism to a degree of 0.71 and normal metabolism to a degree of 0.29 at the same time. This can be seen as fuzzy sets used in fuzzy logics where the elements has degrees of membership contrary to classical set theory.

In the weighted version of VFI each feature has a weight attached to it. These weights are

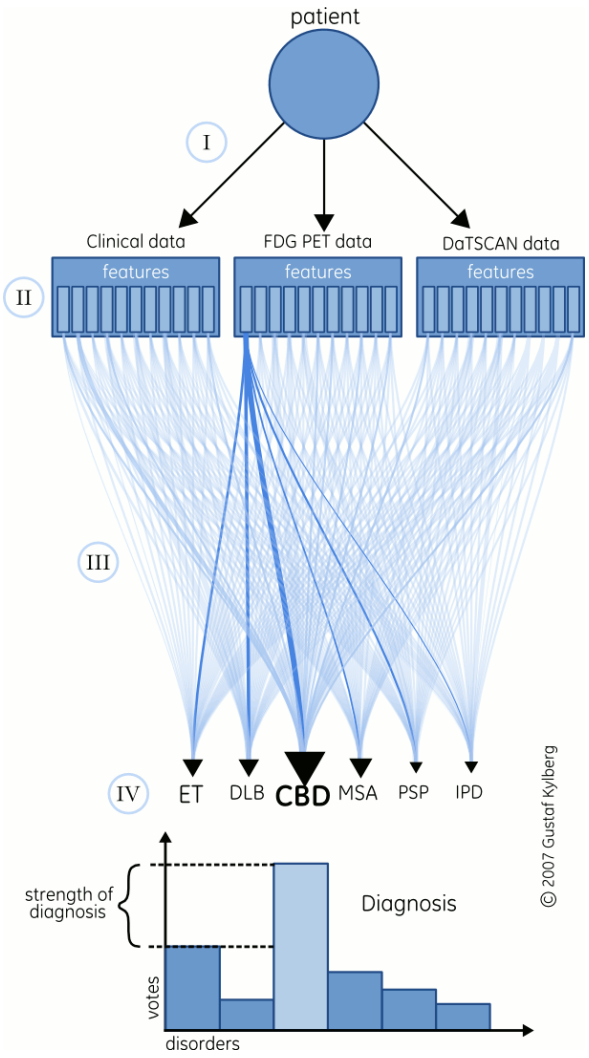

Figure 4: Schematic view of the principles behind the voting system. The chronological order is top to bottom. In the **first step** you collect as much data as possible. The ideal situation is when FDG PET, DaTSCAN and clinical data are all available. In the **second step** features are extracted from the data. Image data are processed with VOI analysis and compared to a normal material. The clinical data are sorted into clinical features. During the **third step**, the election, each feature will vote for each of the diagnosis. The votes depend on the difference between the feature's value and the normal material as well as feature and diagnosis specific weights. In the last, **fourth, step** the disorder with the highest amount of votes is proposed as the diagnosis.

optimized to differentiate between the disorders. In our work each feature will have weights for each diagnosis due to the fact that features have different importance in different disorders. A feature can be a defining feature for one disorder while it is just a supporting feature for another disorder, see section 2.1.3.2 and Table 3.

2.3.2 The emerging classification algorithm

I have designed a voting system inspired by the VFI algorithm described in the previous section. This system too divides the information into features. The imaging and clinical data are processed and feature-values are extracted. Instead of applying vote generating intervals for each feature, distribution functions and weights that are feature and diagnosis specific are applied. The generated votes from all the features are summarized and a diagnosis is proposed. A schematic view of the principles behind the voting system is shown in Figure 4.

It is of interest to have a measure of the strength of the proposed diagnosis. If the voting results is examined a strength measure can be defined through the relative margin of victory i.e.

$$\text{strength} = \frac{v_{1:st} - v_{2:nd}}{v_{1:st} + v_{2:nd}} \qquad (1)$$

where v = votes. This means that if a diagnosis has won with a great margin the strength is great too. On the contrary if there are no given winner the strength will be weak.

The structure of the system, with a large and variable number of features with similar properties, made an object-oriented language suitable and the system was implemented in JAVA.

2.3.3 Stepping through the algorithm

Below follows a step by step description of how the voting system works. First the available imaging and clinical data are collected. Then the image processing and VOI analysis is performed according to paragraph 2.2.1 and 2.2.2.

The voting system uses methods for reading the output files from the pre-processing and methods for loading the clinical data as well as loading a file containing all the weights and feature properties.

A subject's VOI values are collected in a case object and the normal values, weights and feature properties are collected in feature

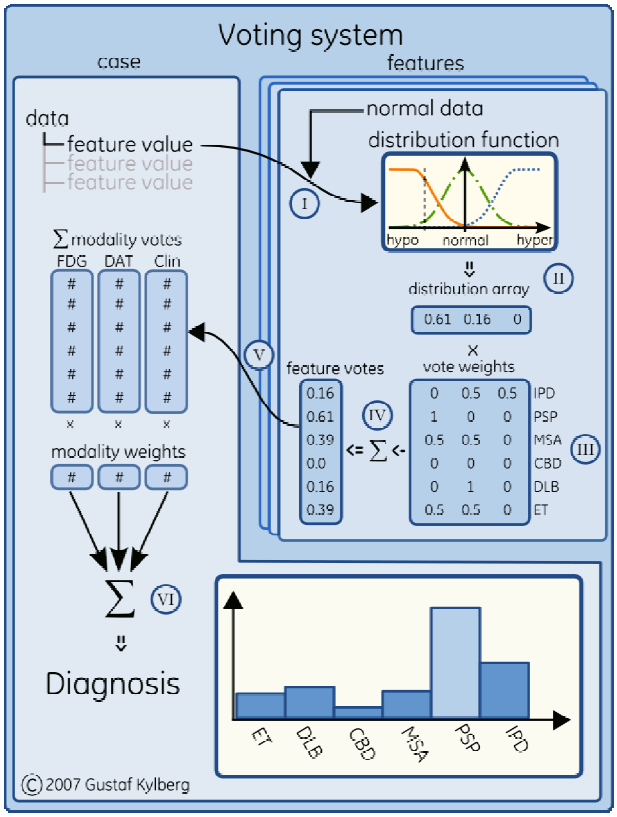

Figure 5: An architectural overview of the voting system. The system consists of three classes; *Voting system*, *case* and *feature*. The *case* class stores all the feature values and votes for a subject. The *Voting system* harbours the cases and features and holds the election. During the election a *case* object communicates with the *feature* objects. **Step I:** a feature value is sent to the corresponding feature and the *z*-score is calculated with the normal data. **Step II:** the distribution function receives the *z*-score and creates a distribution (three values with the degree of memberships). **Step III:** the distribution is multiplied by the weight table that are feature specific. **Step IV:** The values are summarized for each disorder resulting in a set of votes. **Step V:** the *case* object receives the votes and adds them to the right modality. **Step VI:** modality weights are put on and the votes are summarized. This is the election turnout. The winning diagnosis is the proposed diagnosis of the subject. A bar chart containing the votes and the strength of the diagnosis is exported.

objects. After loading the VOI values additional features like asymmetries and ratios are calculated by the system. When this is completed the election takes place. All the patient's feature values are sent to the corresponding feature object which converts the VOI-value to a set of votes via the multiplication of a z-score, a distribution function and corresponding weight factors. The z-score is the dimensionless quantity defined by

$$\text{z-score} = \frac{x - \bar{x}}{s} \qquad (2)$$

where x = value, $\bar{x}$ = mean and s = standard deviation. Mean and standard deviation is calculated from VOI-values of the normal material. The patient object receives these votes from the feature object and summarizes the votes for each modality and a modality specific weight is put on. The diagnosis is made and the diagnosis strength is calculated. For a schematic view of the class structure and their interactions see Figure 5.

The result of the voting is presented in a bar chart showing the election turnout and the diagnosis strength, see Figure 6. This is done by a plotting class in the voting system that is powered by the free JAVA library JFreeChart.[43]

The system can load multiple patients with varying information content and saves all the details of the election process in a text file, see appendix 3 for a sample output.

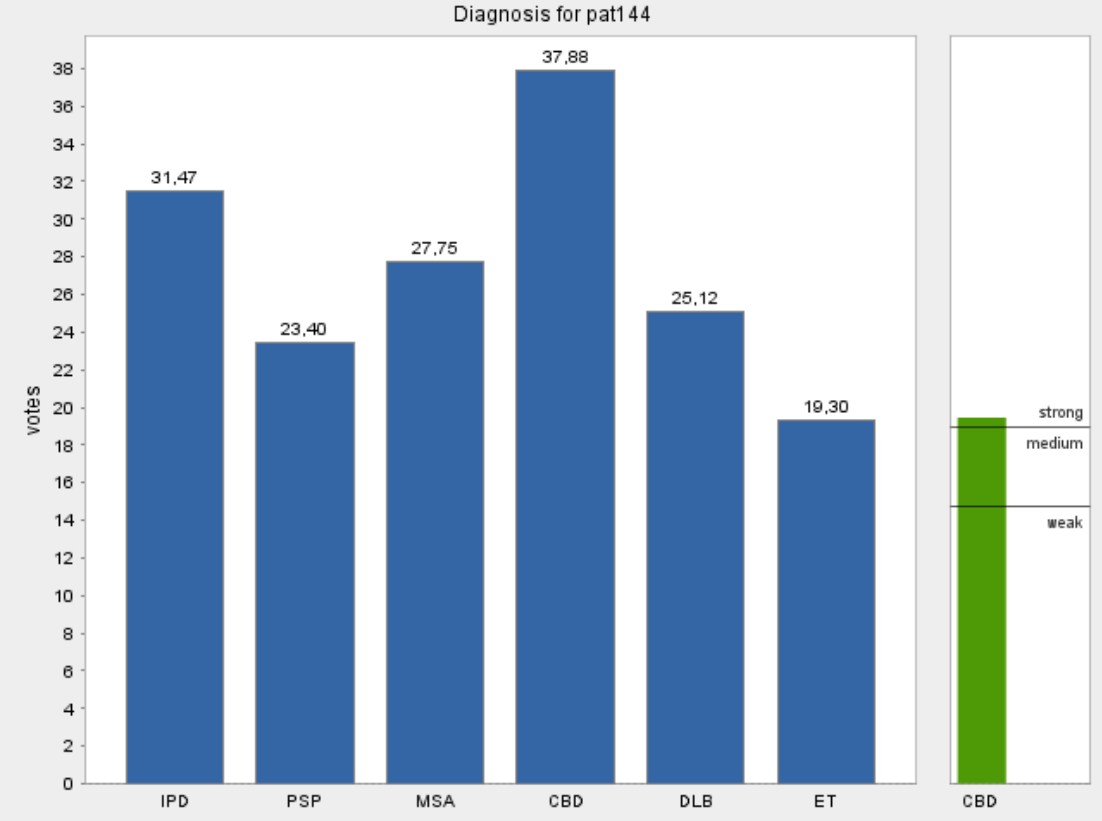

Figure 6: This is an example of the bar charts exported by the voting system. The **left subplot** has the number of votes at the *y*-axis and the different conditions at the *x*-axis. The **right subplot** shows the diagnosis strength with lines showing levels for a weak, moderate or strong diagnosis. To allow a fast and intuitive judgment of the diagnosis the bar showing strength is coloured according to its degree of strength; green for strong, yellow for moderate and read for weak.

2.3.4 Stages of the implementation

In the first stage the voting system was implemented to handle DaTSCAN data and differentiate between IPD, PSP, MSA, CBD, DLB and ET. Then the system was extended to handle PET FDG data was well. In the next stage, clinical information was added and methods were implemented for saving the election details as well as for diagnosis visualization. In a third stage, the system was further extended to also handle dementia cases (AD and FTD). The purpose was to test the system's ability to differentiate between a broader collection of neurodegenerative disorders.

The three stages involved only small structural differences in the code but the functionality was expanded step by step.

3. Experiments and results

3.1 Initial testing of the algorithm

As an initial test, six phantom datasets were created from the pathological and symptomatic profiles defined in section 2.1.3 to mimic the six different disorders. The phantoms were created as a text file with feature values in z-scores. The phantoms were diagnosed through the voting system and after a few adjustments of the weights (without conflicting with the profiles), these phantoms were correctly diagnosed. This confirmed that the imaging and symptomatic profiles were correctly used by the system.

The phantoms were also used to test the noise sensitivity of the system. This was done by adding noise to the feature values. Low levels of noise did not do very much but with higher levels of noise the performance was degraded. At this stage the values were randomly changed in the interval [-4, 4] standard deviations.

3.2 Calculating normal VOI values

By processing the normal material, according to section 2.2.3, VOI values were obtained. The mean and standard deviation were calculated for each feature. This information was written into the feature properties file.

3.3 Evaluation of the diagnosis strength measure

The diagnosis strength measure defined in equation 1, section 2.3.2, was evaluated to establish suitable levels for weak, moderate and strong diagnosis.

The lower limit of the diagnosis strength measure was estimated by diagnosing healthy controls from the normal material; strengths of these diagnoses were considered to be too weak (the diagnosis strengths of ET among healthy controls based on DaTSCAN were excluded because of pathological similarities between ET and normal). The diagnosis strengths for the phantoms were, as expected, at a higher level. When diagnosing the highly noisy phantoms the diagnosis strengths obtained were considered as weak.

This reasoning led to a definition of a moderate to strong limit of roughly 0.9 and a weak to moderate limit of roughly 0.7.

3.4 Testing and refining of the algorithm

Using the first set of VOIs resulted in a relatively wide range of VOI-values in the normal material. This led us to refine the VOIs, focusing on the shape of cortical VOIs as Figure 7 shows.

The largest area to be refined is the feature properties with the diagnosis specific weights. Each feature has three weights for every disorder. These weights were initially set using the disorder profiles defined in 2.1.3 where the weight for a supporting relation between feature and disorder was set to 0.5 and a defining relation was set to 1 as a weight.

The initial weights had to be slightly tweaked in the initial testing, see section 3.1.

During tests with PET FDG data from healthy controls, the fitting of VOIs in regions of the basal ganglia was not robust. Therefore the putamen and caudate nucleus features were temporally excluded from the FDG features.

3.5 Diagnostic performance

When assessing diagnostic performance, a gold standard dataset with confirmed diagnosis is essential. Such a dataset was

constructed by selecting a subset of the subjects. These were cases where the clinical diagnosis was supported by the imaging data when analyzed by the neurologists. The subset contained six patients, of which four were diagnosed with IPD, one with PSP and one with CBD.

This subset of data was diagnosed with the voting system. The exported bar-charts are found in appendix 1. Four bar charts per case are presented in the appendix to show the three modality's influence on the final diagnosis. To visualize the election procedure the details of the election for subject pat108 is shown in appendix 3.

The results show that the diagnosis proposed by the system varies in strength but they are consistent with the diagnosis made by the neurologists. The four subjects with IPD (according to the standard of truth used) show different patterns in DaTSCAN, PET FDG and clinical information. For subject pat108, the FDG data contributes the most and the clinical information is very weak. In contrast pat123 has clinical information that presents a relative strong suggestion while the DAT and FDG data is weak.

When looking at the result for pat118 no modality can present other than a weak diagnosis alone, but together they present a moderate strong diagnosis.

DaTSCAN alone points towards wrong diagnosis for pat144 but when adding the remaining information the system finds the right diagnosis and if one look closely the right diagnosis is on a close 2nd place when only DaTSCAN data is used.

The DaTSCAN data seldom contributes with a suggestion of great strength although it can divide the disorders into groups, more or less likely diagnoses.

3.6 Addition of diagnoses

In agreement with section 1.6 we extended the system to handle AD and FTD. The field of dementia is overlapping with the field of Parkinsonism. For instance DLB is often included in Parkinsonism while being a form of dementia. Hence an addition of AD and FTD were a natural step.

A literature study of review articles discussing PET FDG and DaTSCAN in dementia was done to complement the pathological profiles and the file containing feature properties was complemented with weights of AD and FTD.

When running the 20 AD patients' PET FDG images through the voting system four of them were correctly diagnosed with a high strength while four were correctly diagnosed

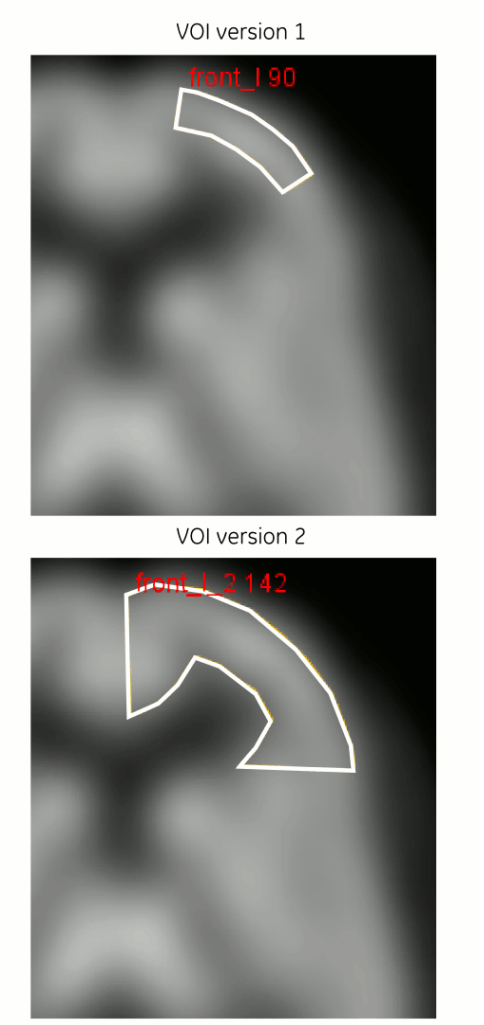

Figure 7: These are two screenshots that shows two versions of the frontal cortex VOI in a transaxial slice. The normal template brain is in the background. In version 2 the strategy has been to fully enclose the gray matter and it stretches over more slices. The 2nd version showed a more robust result.

with a moderate strength. The twelve weak diagnoses contain AD, IPD and PSP although AD stands for seven of them, see appendix 4. The feature properties and weights used in this test were only rough estimations based on the pathological profiles.

We did not access the clinical data regarding these subjects and the standard of truth in the AD diagnoses was based on clinical follow-ups.

4. Discussion

4.1 The use of the voting system

The developed algorithm is a way of systematically evaluate each feature's contribution to the different diagnosis. It has the potential to, in the future, serve as an objective tool for generating a second opinion when making the differential diagnosis of patients with Parkinsonistic symptoms.

The algorithm is flexible and can be altered and trained to improve the performance. It provides diagnostic information based on a combination of the available information and the system offers an insight in to the decision making procedure; there are no black boxes.

The voting system is constructed to categorize a patient into one of the defined diagnoses based on imaging and clinical data. Thus, diagnosing a healthy subject based on DaTSCAN data the system will propose ET as the diagnosis and with a great strength.

The diagnosis strength measure defined in section 2.3.2 and evaluated in section 3.3 has roughly estimated thresholds for weak, moderate and strong diagnosis. This measure has to be further explored to serve as a reliable measure of the diagnosis quality.

4.2 Weights and feature properties

At several times temporary malfunction of the classification system could be derived to the feature- and diagnosis-specific weights. Without any automatic training with a training dataset the adjustments of the 1134 weights (1512 after the addition of AD and FTD) are an impossible task. The use of an initially weight setup based on the disorder profiles with values of 0, 0.5 or 1 probably works against the diagnostic performance of the voting system.

The basal ganglia VOIs defined for the FDG data were poorly fitted after spatial normalization of the subjects imaging data. This could be improved by redrawing these VOIs or adjust the parameters for the spatial normalization.

4.3 The material

At a first glance 49 subjects seems fine for a thesis project like this one. However this group contained only 21 subjects with both FDG and DAT information and only 6 of these had a reliable diagnosis to be used as a truth.

A common dilemma and weakness in neuroimaging studies is the lack of a rigorous standard of truth for diagnosis. The gold standard of truth is obtained through investigation of lesions in the brain at an autopsy. Studies using the gold standard have to span over up to ten years or more. A common compromise is to use a standard of truth based on clinical follow-ups. By monitoring the disease progression for several years after the first clinical investigation a quite robust diagnosis can be obtained.

In my thesis project the material lacked even this information due to the fact that the scans were performed during the last three years. This led us to use the small subset of patients for whom the clinical diagnosis was coherent with the diagnosis made by the neurologists when accessing the imaging data.

The limited material did not cover all the disorders which would be preferable, only three of six were covered.

The subjects in this project were patients referred for imaging due to the difficulties of making a clinical diagnosis. Accordingly, these patients were difficult cases and did not show clear and typical signs of one distinct disorder.

4.4 Disorder profiles

In the literature several different methods of defining features and describing abnormalities in imaging data are used and all may not be fully comparable. There were a few contradicting findings when summarizing the

pathological profiles. When only small differences were present newer studies with more subjects and with better standard of truth were selected. In two cases the feature for the specific disorder were disabled by setting the current weights to zero.

4.5 Addition of diagnoses

When the system was to diagnose subjects with AD based on PET FDG data only the results were mixed. Some cases were correctly diagnosed with a high strength while others had a weak diagnosis. One noticeable detail is that no incorrect diagnoses were proposed with a moderate or high strength.

To be able to draw any conclusions on the diagnostic performance the weights and feature properties have to be optimized.

The addition of AD and FTD did not alter the diagnostic performance of the Parkinsonistic disorders, i.e. the system did not lose its earlier skills of differentiating the original disorders.

5. Further development

Expanding the disorder space

The set of disorders considered by the classification system should be expanded to cover a wider range of disorders managing not only Parkinsonistic but all neurodegenerative disorders.

This is a natural step and has several advantages. For instance solving the problem for patients that show atypical symptoms of both Parkinsonism and dementia; besides the diagnostic confusion these symptoms are traditionally divided between the departments of geriatrics and movement disorders.

The addition of AD and FTD is rather straight forward as seen in section 3.6, even though the clinical profiles were left out. Moving towards covering all major neurodegenerative disorders follows the same principle.

Refining the VOI analysis

The cortical VOIs for PET FDG analysis can be changed to surface projections of the cortical areas. This strategy could improve the robustness of the image analysis.

The use of a normal material can be refined by using age compensation when comparing subjects' VOI-values to the normal material. Age compensation in VOI analysis of DaTSCAN data has yield good results.

System training

To be able to develop the voting system into a fully operational application it has to be trained, i.e. automatically tuning of all the weights and vote distribution properties to optimize the differentiating power between the disorders.

At first a measure of the overall fitness of the system has to be defined. This measure should consider how well the system diagnoses subjects with each disorder. Then a genetic algorithm can be used to optimize the weights by evolving a population of weight tables.

It would be preferable, after an initial training, to be able to further train the system when new training data is available without compromising the previous ability to differentiate between certain disorders.

When the feature properties have been tuned and thereby the classification system's performance has been improved the strength measure has to be adjusted as well.

Diagnosis result visualization

There is much to do on the visualization of the diagnosis result. It can for instance be interesting to sort and show the features in supporting and non supporting groups. Perhaps in the next generation of the voting system this information can be highlighted in the actual image data showing features that point to different diagnoses with an amount of votes.

Addition of modalities

If other modalities or tracers come into ordinary clinical use, these can be added to the system. For instance diffusion tensor imaging (DTI) has shown interesting contribution to the Parkinsonistic disorders.[44]

6. Acknowledgements

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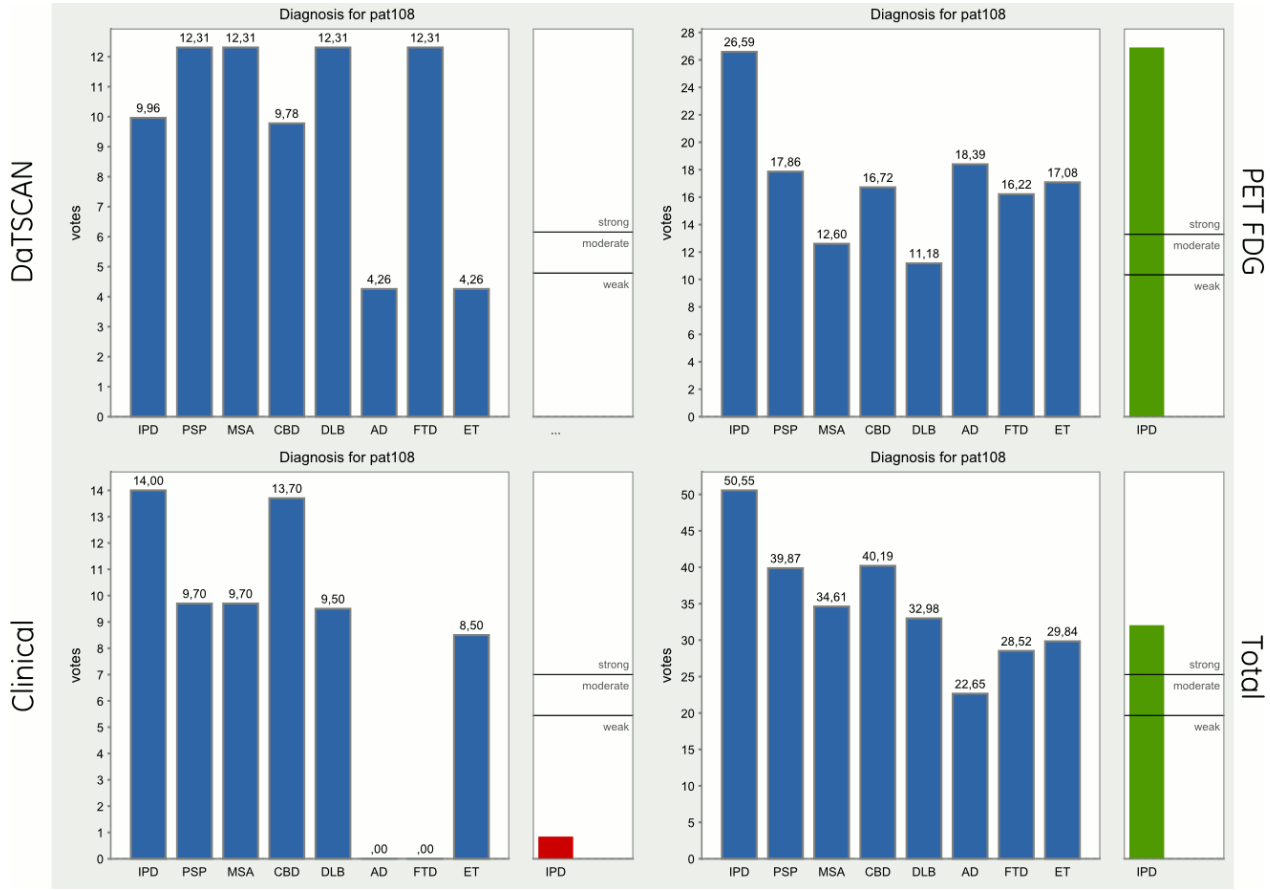
pat108, (IPD)

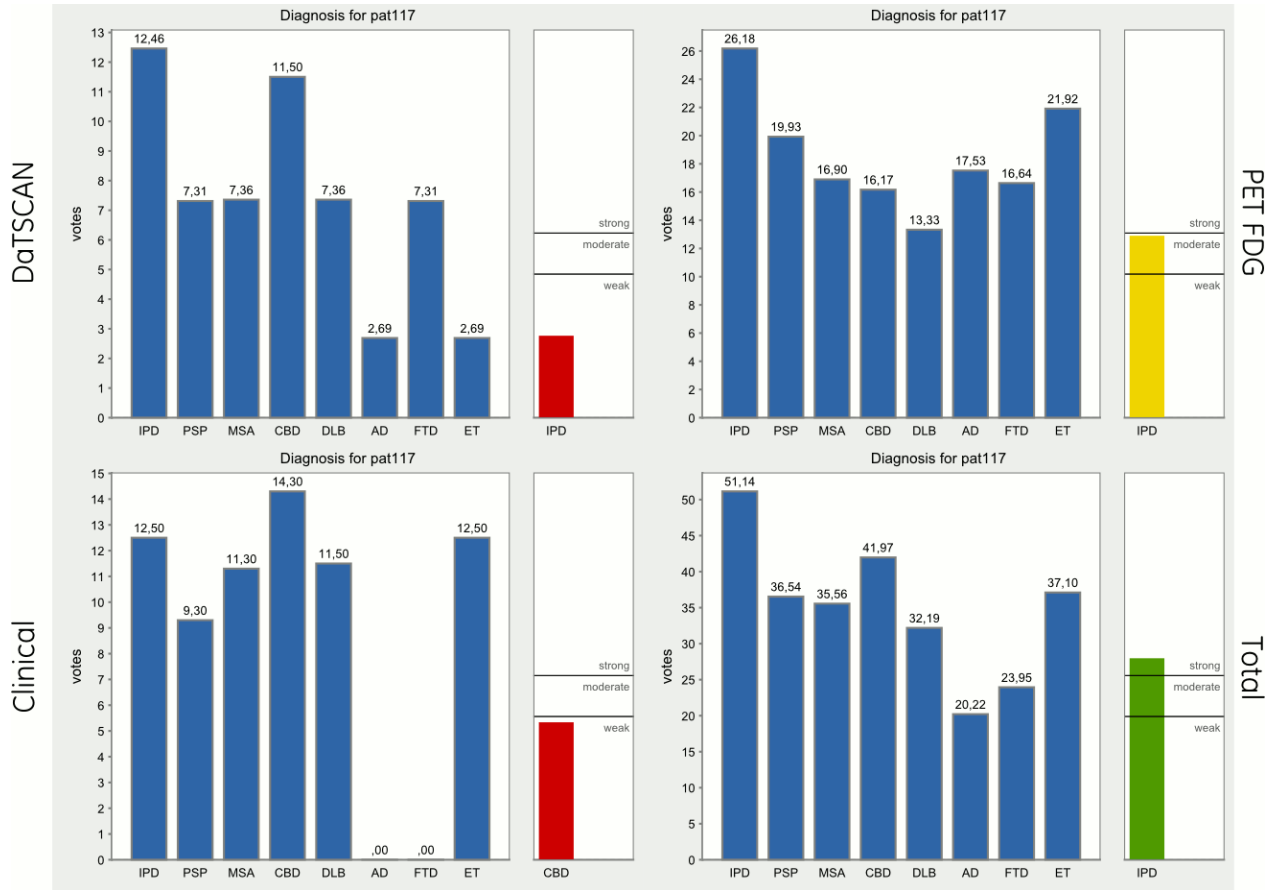


These are four bar-charts created by the voting system while diagnosing the subject pat108. *Top left:* Diagnosis based on DaTSCAN data only. *Top right:* Diagnosis based on PET FDG data only. *Bottom left:* Diagnosis based on clinical data only. *Bottom right:* The final diagnosis where the three modalities are weighted and summarized.

Diagnosis in brackets is made by the neurologists, see paragraph 3.5 for standard of truth.

Appendix 1 - Diagnosing a subset of the subjects

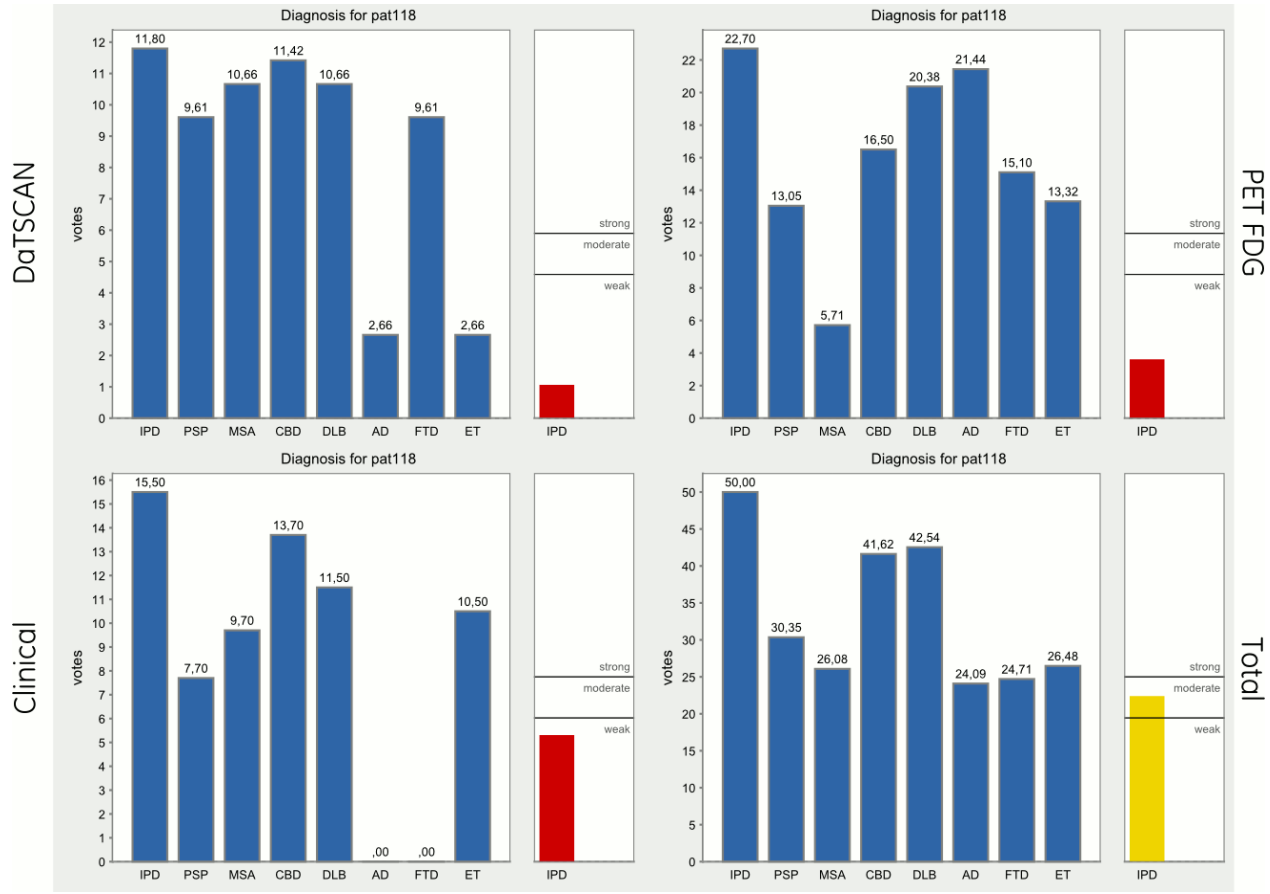
pat117, (IPD)



These are four bar-charts created by the voting system while diagnosing the subject pat117. *Top left:* Diagnosis based on DaTSCAN data only. *Top right:* Diagnosis based on PET FDG data only. *Bottom left:* Diagnosis based on clinical data only. *Bottom right:* The final diagnosis where the three modalities are weighted and summarized.

Diagnosis in brackets is made by the neurologists, see paragraph 3.5 for standard of truth.

pat118, (IPD)

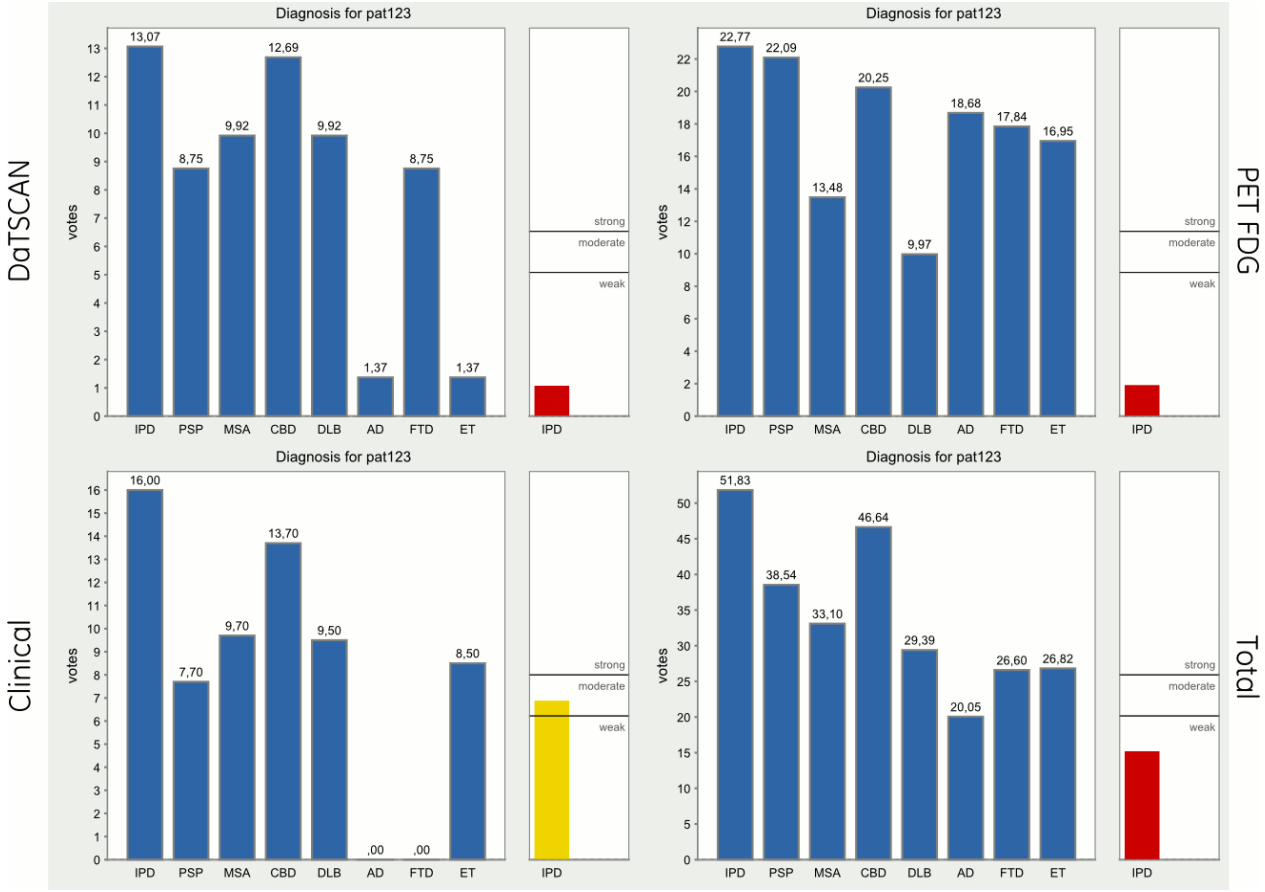


These are four bar-charts created by the voting system while diagnosing the subject pat118. *Top left:* Diagnosis based on DaTSCAN data only. *Top right:* Diagnosis based on PET FDG data only. *Bottom left:* Diagnosis based on clinical data only. *Bottom right:* The final diagnosis where the three modalities are weighted and summarized.

Diagnosis in brackets is made by the neurologists, see paragraph 3.5 for standard of truth.

Appendix 1 - Diagnosing a subset of the subjects

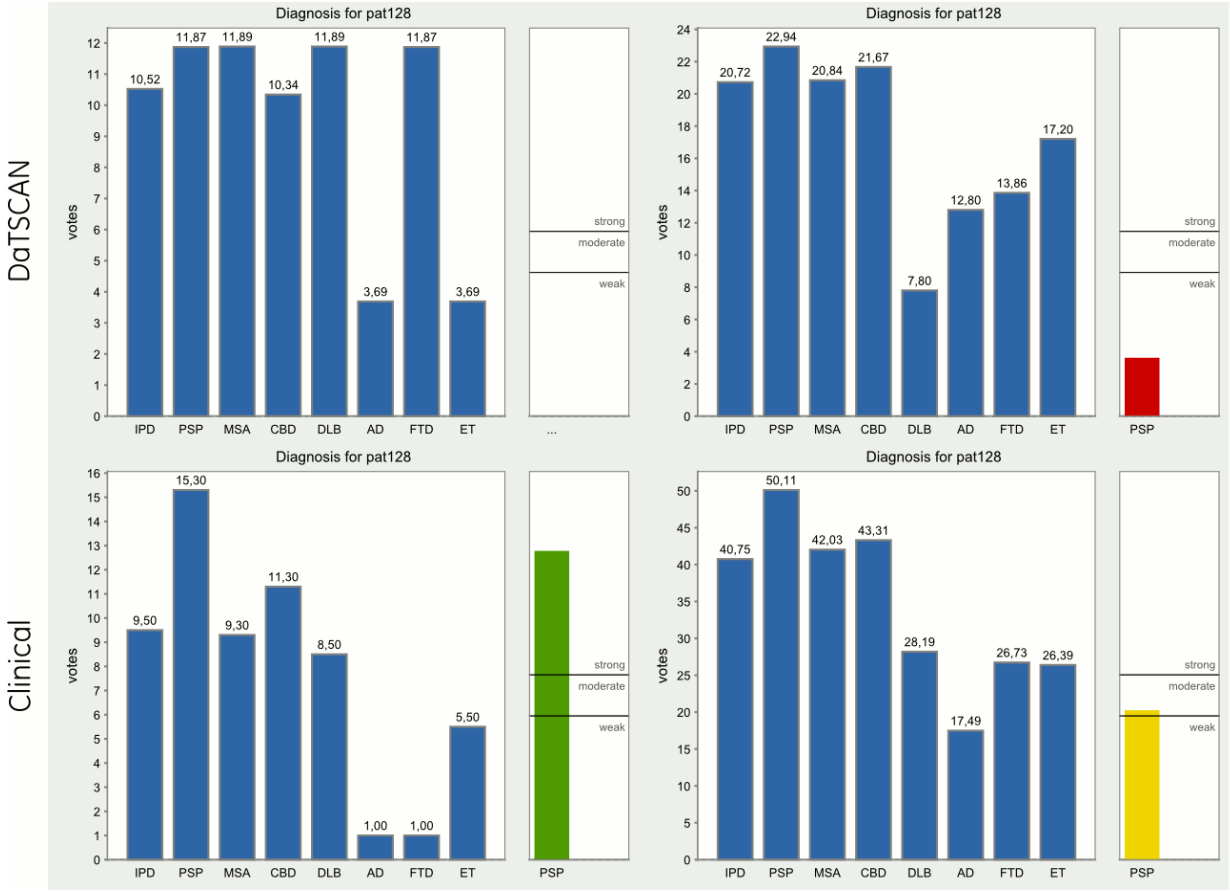
pat123, (IPD)



These are four bar-charts created by the voting system while diagnosing the subject pat123. *Top left:* Diagnosis based on DaTSCAN data only. *Top right:* Diagnosis based on PET FDG data only. *Bottom left:* Diagnosis based on clinical data only. *Bottom right:* The final diagnosis where the three modalities are weighted and summarized.

Diagnosis in brackets is made by the neurologists, see paragraph 3.5 for standard of truth.

pat128, (PSP)

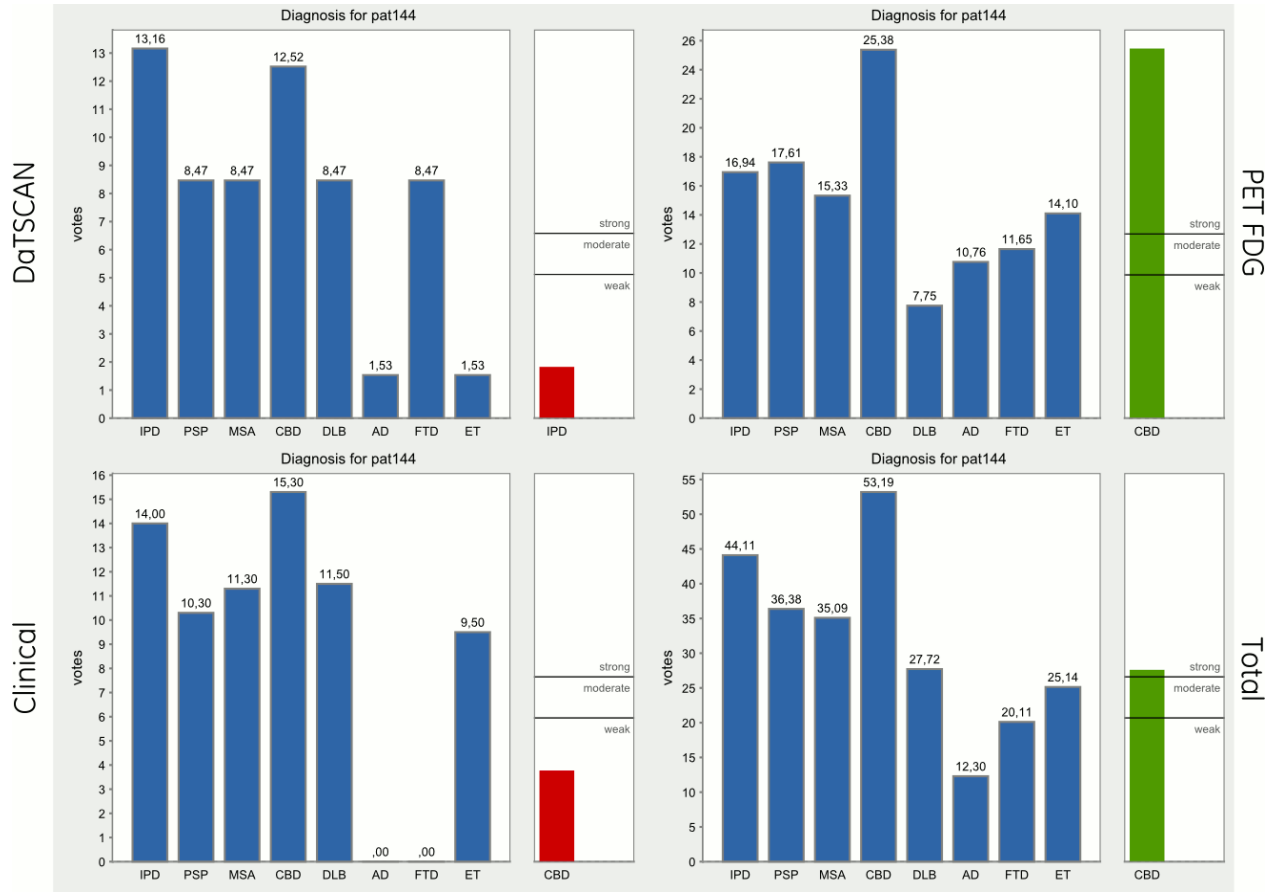


These are four bar-charts created by the voting system while diagnosing the subject pat128. *Top left:* Diagnosis based on DaTSCAN data only. *Top right:* Diagnosis based on PET FDG data only. *Bottom left:* Diagnosis based on clinical data only. *Bottom right:* The final diagnosis where the three modalities are weighted and summarized.

Diagnosis in brackets is made by the neurologists, see paragraph 3.5 for standard of truth.

Appendix 1 - Diagnosing a subset of the subjects

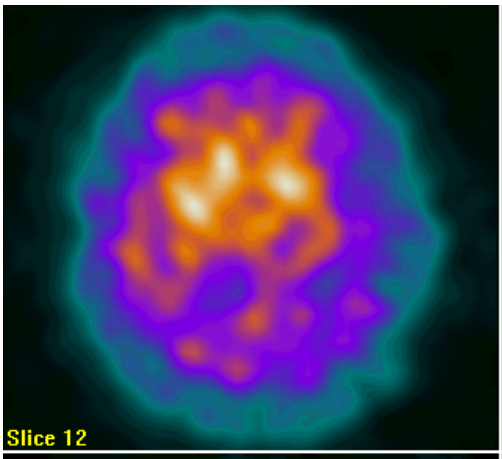
pat144, (CBD)

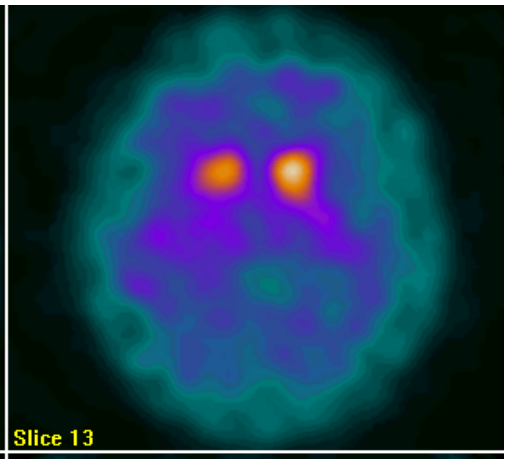


These are four bar-charts created by the voting system while diagnosing the subject pat144. *Top left:* Diagnosis based on DaTSCAN data only. *Top right:* Diagnosis based on PET FDG data only. *Bottom left:* Diagnosis based on clinical data only. *Bottom right:* The final diagnosis where the three modalities are weighted and summarized.

Diagnosis in brackets is made by the neurologists, see paragraph 3.5 for standard of truth.

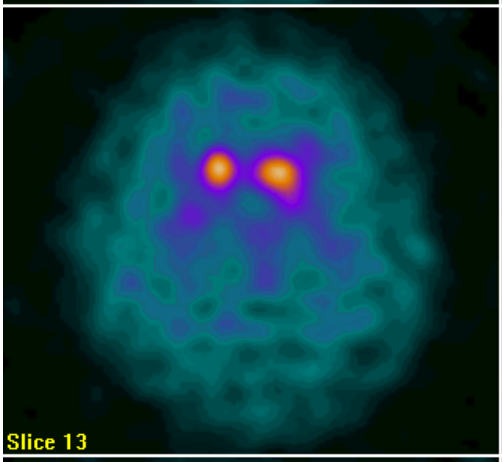
pat108 (IPD)

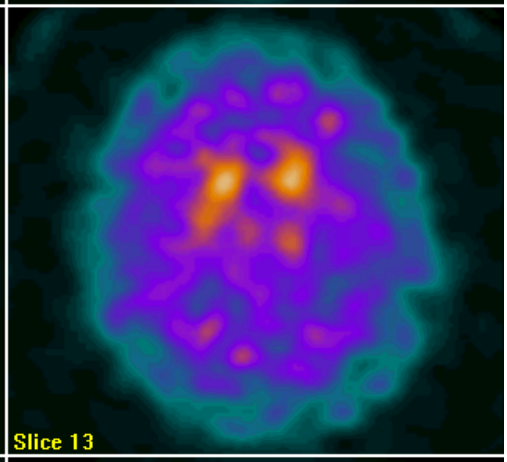




pat123 (IPD)

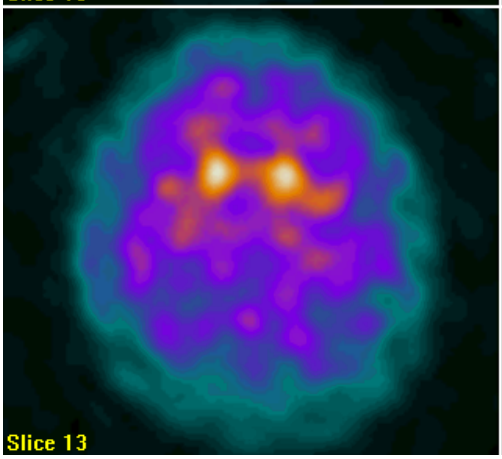
pat117 (IPD)

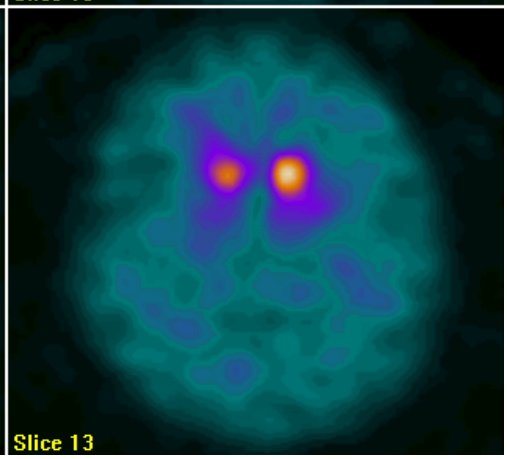




pat128 (PSP)

pat118 (IPD)





pat144 (CBD)

These are one-slice screenshots of the DaTSCAN data for the six subjects in the subset discussed in section 3.5. The slices shown are in the transaxial plane and the subjects are seen from the feet with the head facing upwards. The diagnosis made by the neurologist based on clinical and imaging data are written in brackets. For a quick guide in neuro-anatomy, see Figure 1: transaxial view.

Appendix 2 –Imaging data for the subset of subjects

pat108 (IPD)

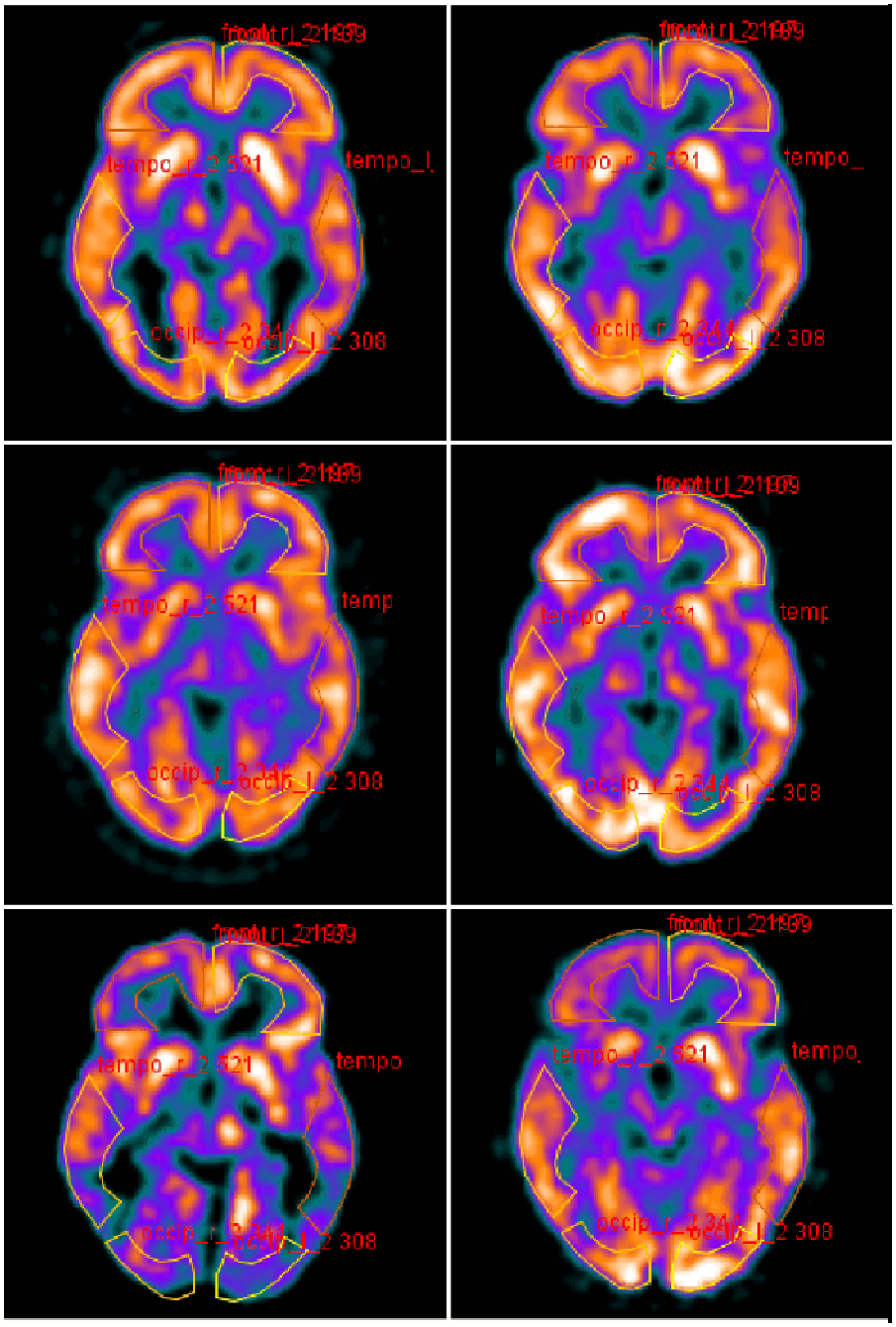
pat123 (IPD)

pat117 (IPD)

pat128 (PSP)

pat118 (IPD)

pat144 (CBD)



These are one-slice screenshots of the PET FDG data for the six subjects in the subset discussed in section 3.5. The slices shown are in the transaxial plane and the subjects are seen from the feet with the head facing upwards. Some of the VOIs that were used are overlaid in the pictures. The diagnosis made by the neurologist based on clinical and imaging data are written in brackets. For a quick guide in neuro-anatomy, see Figure 1: transaxial view.

The following table is an example of the output data from the voting system when diagnosing the subject "pat108". It contains all the features with corresponding feature value in z-score and the resulting votes for each disorder (the numbers below is rounded off to two decimals). The table is saved by the voting system in a tab-separated text file. Below the table the votes are summarized in the same way as the system does it to show the last step in the making of the diagnosis. The votes in bold letters at the very bottom are the weighted and summarized votes that are presented in the bar charts, see Appendix 1 page 1 for subject pat108's bar chart. At this time the basal ganglia features from PET FDG were disabled.

caseID	mode	feature	z-score		IPD	PSP	MSA	CBD	DLB	AD	FTD	ET
pat108	DAT	nuc_caudatus_l	-3.30	votes:	1.00	0.88	0.88	0.88	0.88	0.12	0.88	0.12
pat108	DAT	nuc_caudatus_r	-3.76	votes:	1.00	0.94	0.94	0.94	0.94	0.06	0.94	0.06
pat108	DAT	put/caud_l	0.92	votes:	0.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00
pat108	DAT	put/caud_r	0.97	votes:	0.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00
pat108	DAT	putamen_l	-3.85	votes:	0.94	0.94	0.94	0.94	0.94	0.06	0.94	0.06
pat108	DAT	putamen_l_ant	-4.50	votes:	1.00	0.98	0.98	1.00	0.98	0.02	0.98	0.02
pat108	DAT	putamen_l_post	-2.49	votes:	0.70	0.70	0.70	0.70	0.70	0.30	0.70	0.30
pat108	DAT	putamen_r	-4.19	votes:	0.97	0.97	0.97	0.97	0.97	0.03	0.97	0.03
pat108	DAT	putamen_r_ant	-4.65	votes:	1.00	0.99	0.99	1.00	0.99	0.01	0.99	0.01
pat108	DAT	putamen_r_post	-2.52	votes:	0.71	0.71	0.71	0.71	0.71	0.29	0.71	0.29
pat108	DAT	striatum_asym	0.04	votes:	0.72	1.28	1.28	0.72	1.28	1.28	1.28	1.28
pat108	DAT	striatum_l	-3.90	votes:	0.95	0.95	0.95	0.95	0.95	0.05	0.95	0.05
pat108	DAT	striatum_r	-4.22	votes:	0.97	0.97	0.97	0.97	0.97	0.03	0.97	0.03
pat108	FDG	brainstem	2.07	votes:	0.43	0.00	0.22	0.43	0.43	0.43	0.43	0.43
pat108	FDG	caud_l	-0.85	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	FDG	caud_r	-1.28	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	FDG	cerebell_l	-0.29	votes:	0.98	1.00	0.02	0.02	0.98	0.98	0.98	0.98
pat108	FDG	cerebell_r	0.16	votes:	1.00	0.99	0.00	0.00	0.99	0.99	0.99	0.99
pat108	FDG	cortical_asym	0.01	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	FDG	front_l	0.53	votes:	0.95	0.00	0.00	0.47	0.47	0.47	0.00	0.95
pat108	FDG	front_r	0.48	votes:	0.96	0.00	0.00	0.48	0.48	0.48	0.00	0.96
pat108	FDG	motor_l	1.39	votes:	1.00	0.69	0.69	0.69	0.69	0.69	0.69	0.69
pat108	FDG	motor_r	2.57	votes:	1.00	0.27	0.27	0.27	0.27	0.27	0.27	0.27
pat108	FDG	occip_l	-0.84	votes:	1.00	0.87	0.87	0.87	0.13	0.87	0.87	0.87
pat108	FDG	occip_r	-1.18	votes:	1.00	0.76	0.76	0.76	0.24	0.76	0.76	0.76
pat108	FDG	parie_l	-0.83	votes:	1.00	0.87	0.87	0.13	0.13	0.13	0.87	0.87
pat108	FDG	parie_r	-1.90	votes:	1.00	0.50	0.50	0.50	0.50	0.50	0.50	0.50
pat108	FDG	post_cinguli_l	-2.58	votes:	0.00	0.00	0.00	0.00	0.00	0.77	0.00	0.00
pat108	FDG	post_cinguli_r	-2.87	votes:	0.00	0.00	0.00	0.00	0.00	0.84	0.00	0.00
pat108	FDG	put_ant_l	0.50	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	FDG	put_ant_r	-0.55	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	FDG	put_post_l	-0.16	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	FDG	put_post_r	-2.51	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	FDG	putamen_asym	0.04	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	FDG	putamen_l	0.24	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	FDG	putamen_r	-1.78	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	FDG	tempo_l	0.21	votes:	0.99	0.99	0.99	1.00	0.00	0.00	0.00	0.00

Appendix 3 - Sample election printout

pat108	FDG	tempo_r	0.29	votes:	0.98	0.98	0.98	1.00	0.00	0.00	0.00	0.00
pat108	FDG	thalamus_asym	0.04	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	FDG	thalamus_l	-2.98	votes:	0.50	0.50	0.09	0.82	0.18	0.50	0.82	0.18
pat108	FDG	thalamus_r	-3.53	votes:	0.50	0.50	0.04	0.91	0.09	0.50	0.91	0.09
pat108	CLIN	dysautonomia	0.00	votes:	0.00	1.00	0.00	1.00	1.00	0.00	0.00	1.00
pat108	CLIN	rigidity	1.00	votes:	1.00	1.00	0.50	1.00	1.00	0.00	0.00	0.00
pat108	CLIN	depression	0.00	votes:	1.00	1.00	1.00	1.00	1.00	0.00	0.00	1.00
pat108	CLIN	propulsion	1.00	votes:	1.00	0.00	0.50	0.00	0.00	0.00	0.00	0.00
pat108	CLIN	postural_tremor	0.00	votes:	1.00	1.00	1.00	1.00	1.00	0.00	0.00	0.00
pat108	CLIN	hallucination	0.00	votes:	1.00	1.00	1.00	1.00	0.00	0.00	0.00	1.00
pat108	CLIN	alien_limb	0.00	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	CLIN	hypokinesis	1.00	votes:	1.00	1.00	0.50	1.00	0.00	0.00	0.00	0.00
pat108	CLIN	gait_disturb	1.00	votes:	1.00	1.00	0.00	1.00	0.00	0.00	0.00	0.00
pat108	CLIN	retropulsion	0.00	votes:	1.00	0.00	0.50	1.00	1.00	0.00	0.00	1.00
pat108	CLIN	dementia	0.00	votes:	0.50	0.50	1.00	0.50	0.00	0.00	0.00	1.00
pat108	CLIN	dysarthria	0.00	votes:	1.00	0.00	0.50	1.00	1.00	0.00	0.00	1.00
pat108	CLIN	swallow_diffi	0.00	votes:	1.00	0.00	1.00	1.00	1.00	0.00	0.00	1.00
pat108	CLIN	early_falls	1.00	votes:	0.00	1.00	0.50	1.00	0.50	0.00	0.00	0.00
pat108	CLIN	gaze_palsy	0.00	votes:	1.00	0.00	1.00	1.00	1.00	0.00	0.00	0.50
pat108	CLIN	hyperkinesis	0.00	votes:	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pat108	CLIN	resting_tremor	0.00	votes:	0.50	1.00	0.50	1.00	1.00	0.00	0.00	1.00
pat108	CLIN	l-dopa_respons	1.00	votes:	2.00	0.20	0.20	0.20	0.00	0.00	0.00	0.00

	IPD	PSP	MSA	CBD	DLB	AD	FTD	ET
Sum of the DaTSCAN votes:	9.9	12.3	12.3	9.7	12.3	4.2	12.3	4.2
Sum of the PET FDG votes:	13.3	8.9	6.3	8.4	5.6	9.2	8.1	8.5
Sum of the Clinical votes:	14.0	9.7	9.7	13.7	9.5	0.0	0.0	8.5
The total weighted* sum of votes	**50.5**	**39.9**	**34.6**	**40.2**	**33.0**	**22.7**	**28.5**	**29.8**

* In this case the weights are 1 for DaTSCAN, 1 for Clinical votes and 2 for PET FDG votes.

The system was expanded to consider Alzheimer's disease (AD) and Frontotemporal dementia (FTD) among the available diagnoses. To briefly test the diagnostic performance of AD twenty PET FDG scans of AD patients were loaded and diagnosed with the voting system. The resulting diagnoses with corresponding strengths are shown in the figure below.

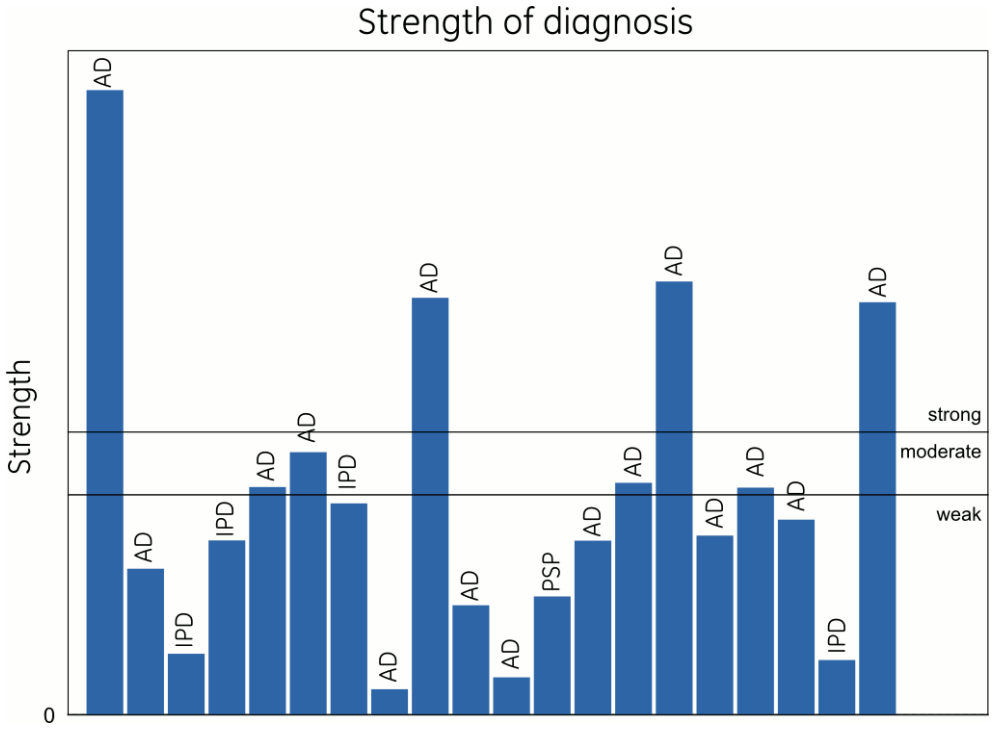


Figure: This is a plot of diagnosis and strength made by the voting system for the twenty subjects with Alzheimer's disease based on PET FDG data only. Four out of twenty were diagnosed correctly with a high strength while another four were diagnosed correctly with a moderate strength. Among the subjects with weak diagnosis one can find AD as well as IPD and PSP, however seven of the twelve weak diagnoses are correct. The feature properties and weights used in this test were based on the extended pathological profiles.