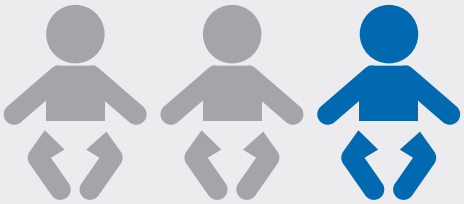
# Latest developments in **PET brain imaging**

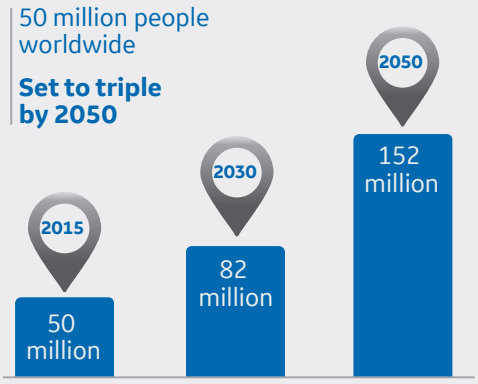
Neuroimaging is the second most frequent application in PET imaging. It represented only 5 percent of all PET procedures in 2012 and now accounts for about 10 percent. The main indications for the examination are neurodegenerative diseases as well as neuro-oncology and epilepsy[1].

## Neurodegenerative disease

Neurodegeneration includes a wide spectrum of diseases, from movement disorders to dementia. The two most common neurodegenerative diseases are Alzheimer´s disease and Parkinson´s disease. Statistics on the growing incidence of neurodegenerative diseases are staggering (see Figure 1). Dementia is now the fifth leading cause of death worldwide[2].



**One in three babies born this year in the UK** will develop dementia in their lifetime[3].




The number of people diagnosed with dementia will **triple between 2015 and 2050[4].**

***Figure 1:*** *Key facts about dementia.*

*I think an effective treatment will come out of these efforts in the near future.*

**Prof. Torsten Danfors MD, PhD,**
Section for Nuclear Medicine and PET in the Department for Surgical Services at Uppsala University, Uppsala, Sweden.

Alzheimer's disease is the most common form of dementia, accounting for 60 to 70 percent of dementia cases[5].

Treatments for dementia, and specifically for Alzheimer's disease, remain elusive. Over the last 15 years, nearly all clinical drug trials for Alzheimer's disease have failed. Still, *"There are currently more than 300 interventional trials for Alzheimer's disease (AD). 112 are drug trials and 26 of them are in phase III. Approximately 2/3 are disease-modifying therapies[6],"* Torsten Danfors, MD, PhD, Section for Nuclear Medicine and PET in the Department for Surgical Services at Uppsala University, Uppsala, Sweden, explains. *"I think an effective treatment will come out of these efforts in the near future"* (see Figure 2).

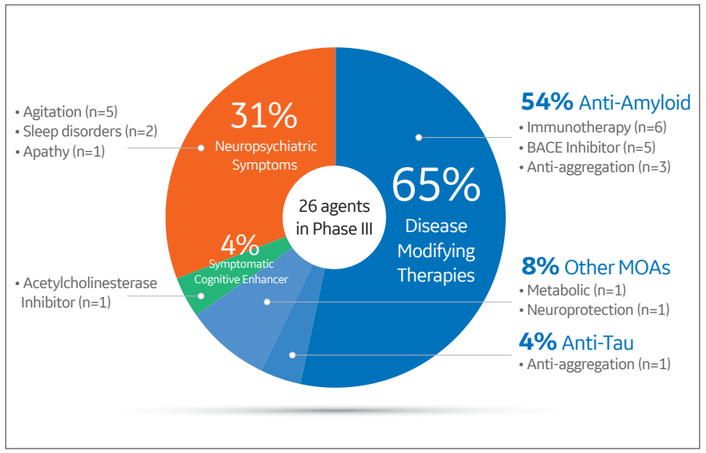



***Figure 2:*** *Mechanism of action of agents under Stage III evaluation for the treatment of Alzheimer Disease.*

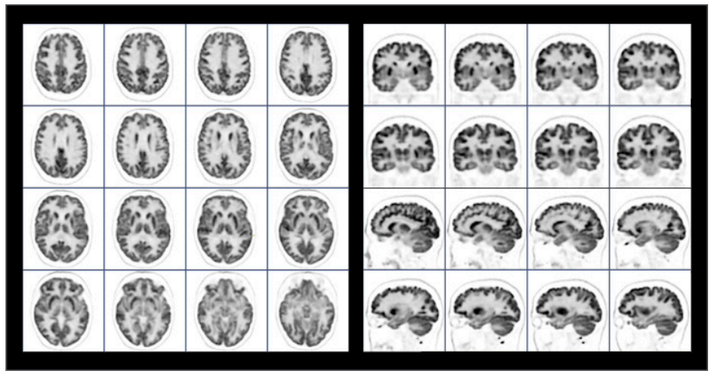
Similarly for most other neuro diseases, there are no cures or treatments that stop or slow the progression of the conditions. However, important decisions can be made to improve a patient's symptoms. Options vary depending on the underlying disease, so the importance of a correct diagnosis cannot be overestimated. For example, tremor may be treated with neurosurgery or with drugs depending on the case. In the near future there may also be disease modifying therapies[7] available that can halt progression of the disease rather than just alter the symptoms. Professor Danfors explains that these therapies may not reverse damage that has already been done to the nervous system and, therefore, to be successful, treatment must start early in the course of the disease.

## Why is it important to accurately diagnose neurodegenerative disease today?

*"There is a crucial need for precision medicine to help with diagnosis, prognosis and therapeutics in this field,"* adds Stéphane Epelbaum, MD, PhD, a neurologist at Pitié-Salpêtrière Hospital, Paris, France. *"SIGNA™ PET/MR allows us to achieve a complicated diagnosis, such as distinguishing rare dementia including corticobasal degeneration, semantic primary progressive aphasia and early onset Alzheimer's disease."*



It's also important to differentiate between neurodegenerative disease and other conditions, such as depression or the presence of a tumor that is causing memory impairment, for prognosis and patient treatment.



*Images courtesy of University Zurich Hospital, Switzerland*

***Figure 3:*** *High resolution FDG imaging acquired in Discovery MI PET/CT demonstrating normal FDG uptake.*

Even within neurodegenerative diseases, pinpointing the precise type is critical for prescribing the right medicine for treatment.

Early, precise diagnosis also impacts patient enrollment in clinical trials. In most cases, Alzheimer's disease trials are designed to include patients in the very early stages of the disease, including preclinical and mild dementia.

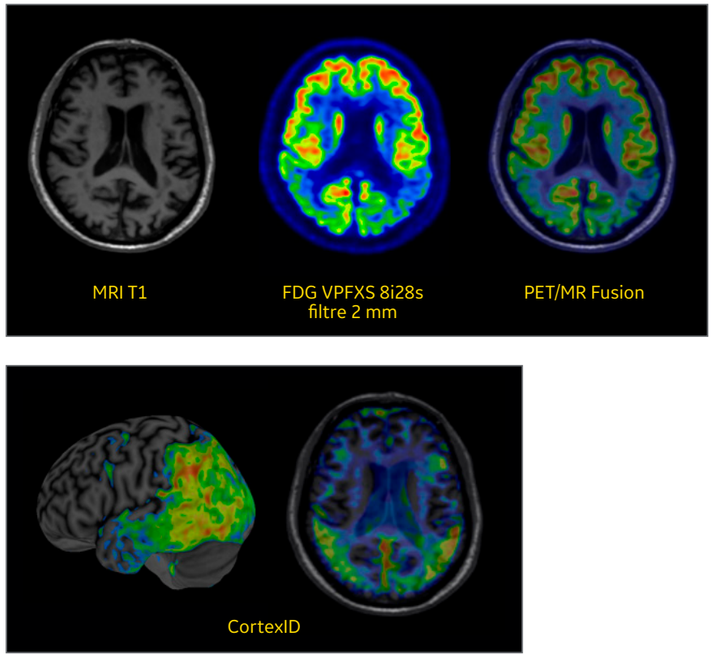



***Figure 4:*** *FDG PET imaging demonstrating lateral occipital hypometabolism. CortexID maps illustrate the severity of the hypometabolism and confirm the diagnosis of Lewy bodies dementia.*

*Molecular imaging of amyloid and tau* is, in my view, a great improvement not necessarily for clinical routine but for research.*

**Dr. Stéphane Epelbaum, MD, PhD**
Neurologist at Pitié-Salpêtrière Hospital, Paris, France.

According to Dr. Epelbaum, predicting disease progression and informing the patient and family about prognosis also requires an accurate diagnosis. For example, he explains that if a very diffused hypometabolism is detected on PET, then it is likely the patient has rapidly progressing disease. If the patient has supplementary motor cortex hypometabolism, then the diagnosis may be amyotrophic lateral sclerosis, or ALS. Dr. Epelbaum adds that patients and their families will need to prepare for the debilitating impact of these different diseases, as well as whether the disease is genetic or inherited.

## The role of PET imaging

*"The identification of pathophysiology and progression markers has really moved forward in the multi-modality work-up of neurodegenerative diseases, both structurally and functionally thanks to MRI and PET,"* adds Dr. Epelbaum.

MRI provides structural imaging and although it is useful, it may not provide a definitive diagnosis on the specific type of neuro degenerative disease. However, by fusing PET with 3D MRI, it can detect both structural abnormalities such as atrophy as well as hypometabolism resulting from the atrophy. A morpho-metabolic pattern is typical of AD.

Fusing PET and MRI images can be achieved by acquiring data at the same time in a PET/MR imaging system or by registering images acquired in different imaging systems, typically a PET/CT and MRI.

*"Molecular imaging of amyloid and tau* is, in my view, a great improvement not necessarily for clinical routine but for research,"* Dr. Epelbaum explains. *"FDG PET is very helpful for enabling a positive diagnosis of Alzheimer's disease but also for differential diagnosis when you look for other diseases such as frontotemporal dementia."*

*"In early onset Alzheimer's, structural MRI is sometimes inconclusive because there is only mild hippocampal atrophy. With the high-quality imaging from digital PET, we can identify diffuse hypometabolism or rule it out to provide a definitive diagnosis,"* Dr. Epelbaum says. *"Digital PET imaging allows for a finer interpretation of brain metabolic changes. In my opinion, the images are the highest quality that I've seen. And, it is clear to me that today PET/MR is the best clinical tool—a one-stop-shop for the patient with neurodegenerative disease"* (see Figure 5).

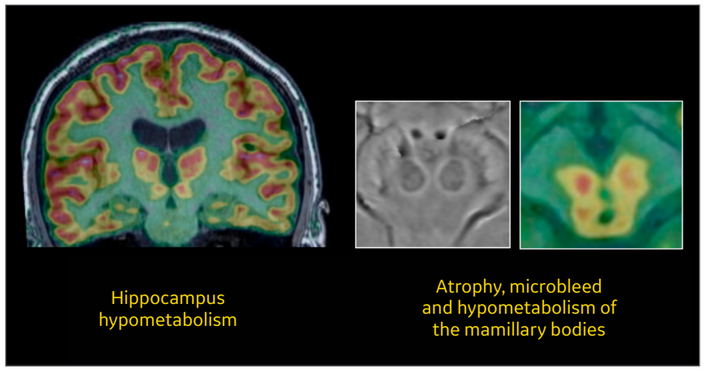



***Figure 5:*** *PET images acquired with a GE digital detector available in both SIGNA™ PET/MR and Discovery™ MI PET/CT systems.*

In one patient with severe amnesia with numerous intrusions, disorientation and dysexecutive syndrome, the MRI of the hippocampus appeared normal. The PET showed slight hypometabolism in the hippocampus; upon further examination, hypometabolism was found in the mamillary bodies, which is indicative of Korsakoff syndrome[8].

*"I think this is the first time someone has diagnosed Korsakoff syndrome on PET,"* Dr. Epelbaum says[8].

A retrospective review of the MRI imaging data for this patient showed a very important atrophy and hypointensity of the mamillary bodies in the SWAN MRI image.

Professor Danfors also combines DaTscan SPECT or dopamine imaging with 11C-PE2I* PET/CT together with FDG PET/CT to help confidently diagnose the type of neurodegenerative disease. The use of MRI is a plus, he says, yet it is possible to assess important differential diagnoses such as normal pressure hydrocephalus, tumors, cerebrovascular disorders and atrophy with CT.

## Neuro-oncology

Although CT and MR are often used in the initial diagnosis of brain tumors, the addition of PET can help differentiate the diagnosis when either test is inconclusive or not specific. Amino acid PET* is emerging as an invaluable imaging test for defining tumor response to radiation treatment and chemotherapy. Contrast-enhanced MR can be influenced by edema, necrosis, vascular alteration and inflammation, which can lead to pseudoprogression and pseudoresponse assessments[9].

There are four indications for the use of amino acid PET in neuro-oncology[9]. In the initial diagnosis, amino acid PET can differentiate neoplastic versus non-neoplastic tissue, delineate tumor extent for resection planning, localize the tumor for biopsy planning and assist with prognostication[10].

After initial debulking surgery, amino acid PET is used for assessing the resection extent, to assist with radiotherapy planning or to monitor chemoradiation therapy, and prognostication[10].

In patients undergoing chemoradiotherapy, amino acid PET can detect treatment-induced changes, such as pseudoprogression, as well as monitor treatment response. It can also provide a baseline for adjuvant therapy monitoring[10].

When used for patient follow-up post-treatment, amino acid PET can identify radionecrosis or relapse, monitor adjuvant therapy and delineate the tumor extent for resection planning[11].

The uptake of amino acid PET in tumors is high due to tumor cells having an increased need for amino acids due to their rapid rate of proliferation[12]. Carbon-11 and fluorine-18 labeled amino acids are commonly used for PET imaging in neuro-oncology as they target protein synthesis or amino acid transport.

According to Professor Danfors, amino acid PET complements the use of MRI and can help in the staging and re-staging of brain tumors.

A woman with a partially resected high-grade glioma of the right frontal lobe was treated with radiotherapy (RT). The baseline tumor activity was measured with amino acid PET after RT and then followed over time to monitor the effect

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of therapy. The patient was then successfully treated with temozolomide with a decreased uptake of AA. Treatment had to stop due to side effects. Follow-up T1 MRI scans showed increased contrast enhancement which could be an effect of radiation therapy or a tumor recurrence. In this case, the combination of amino acid PET and MRI demonstrated a recurring tumor (see Figure 6).

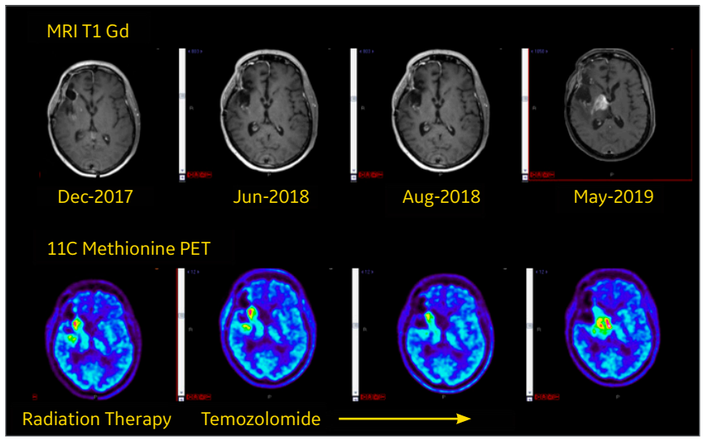


***Figure 6:*** *In this patient, amino-acid PET demonstrated a recurrent high-grade tumor after surgery and radiotherapy, a positive effect of chemotherapy and later tumor recurrence.*

## Epilepsy

Even though epilepsy only affects approximately 0.5 percent of the general population, it is a debilitating disease for the 25 to 30 percent of patients who continue to experience seizures despite anti-epileptic treatment and are therefore candidates for surgery[13]. An electroencephalogram (EEG) is used in the diagnosis of epilepsy to help understand where a seizure starts and where the epileptic activity travels.

*"EEG and MRI are the cornerstones of the investigation and often complemented FDG PET,"* says Professor Danfors.

For example, a 26-year-old man with therapy resistant epilepsy had a normal EEG and a normal 3T MRI. In this case, FDG PET helped localize a small lesion in the insula where the epileptic seizure started (see Figure 7). Today, Professor Danfors estimates that half of the epilepsy patients seen in his department receive FDG PET.

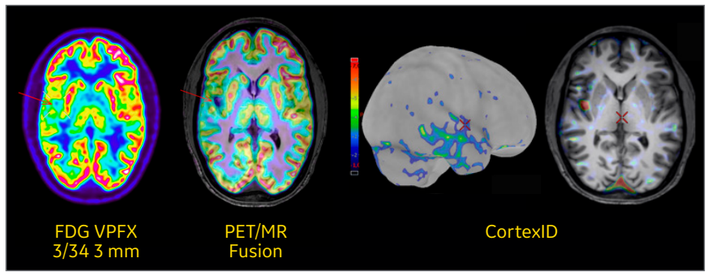


***Figure 7:*** *Patient with therapy-resistant epilepsy and no lesion on MRI where FDG PET imaging was used to plan the surgical procedure.*



*"The digital PET has really improved my diagnosis because the resolution is much better,"* he explains. *"FDG shows the functional status of the patient. It does not only show the seizure onset zone but the functional deficit zone. Cortex ID is a fantastic program that surgeons find useful as well. It provides statistical images projected on slices or on the 3D-surface of the brain. FDG shows the functional status of the patient, including the seizure onset zone and the functional deficit zone."*

As the incidence of neurodegenerative diseases increases, there is a greater need for precise diagnosis and prognosis to help appropriately manage patients. PET imaging is growing in use due to its ability to help clinicians differentiate the type of dementia and disease. Additionally, PET continues to be an important tool in the workup on neuro-oncology and epilepsy patients. Thus it is an ideal complement to MR imaging.

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* PET Radiopharmaceutical may not be approved by ministers of health in all regions.

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