

## PET studies in inherited neurodegenerative disorders

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In this talk, Dr. David Brooks emphasized the three main roles that Positron Emission Tomography (PET) has in the study of neurogenetic disorders. On one hand, PET is able to identify distinct pathological patterns between genetic and sporadic cases. On the other hand, PET can help investigators to distinguish subclinical dysfunction in at-risk individuals; and third, PET may act as a biomarker to test putative neuroprotective and restorative agents. For this purpose, he presented PET data obtained in some of the most prevalent neurodegenerative diseases, both in their sporadic and in their familial-monogenic presentations. The first evidence he showed was on to how PET may overcome the limitations of other techniques such as structural MRI for detecting early changes in the progression of Alzheimer's disease (AD). An invaluable contribution of PET for the study of AD is the seminal work on the effects that the  $\epsilon 4$  genotype has on regional changes in cortical glucose metabolism, even in young non-symptomatic carriers of the two alleles of the gene. Although there is not a distinguishable pattern of brain metabolism changes between familial and sporadic AD, PET has demonstrated changes in subclinical at-risk carriers of the APP717 mutation, one of the most common presentation of the preselinin mutation responsible for a hereditary form of AD. Dr. Brooks also mentioned the recently developed amyloid plaque tracers, which allow PET to visualize not only synaptic dysfunction, but to monitor putative anti-amyloid formation treatments. Then, he talked about the importance of PET in the evaluation of Parkinson's disease (PD). PET is able to quantify striatal dopamine (DA) terminal function in vivo by measuring DA storage and transporter binding. It has been shown that idiopathic PD is characterized by rather unilateral compromise of posterior dorsal putamen DA terminals, with later involvement of the anterior putamen and head of caudate. Conversely, DA function in pallidal, amygdala, and cingulate areas is upregulated at earlier stages, only being affected later in the disease. This pattern of changes detected by PET is typical and can distinguish IPD subjects from sufferers of recessive parkinsonism, such as *parkin* carriers, as well as detect at-risk individuals presenting LRRK2 mutations, the most common gene kindred known to be associated with dominant genetic parkinsonism. Severe loss of striatal glucose metabolism and dopamine D1 and D2 binding are very sensitive markers of Huntington's disease (HD) and is also a practical window to detect active disease as well as gene and preclinical gene carriers. PET has also proven useful to monitor the functional effects of focal dopamine replacement via implantation of fetal cells or the infusion of glia-derived neurotrophic factor (GDNF) into the putamen. Other entities on which PET can discriminate genetic from sporadic presentations are the motor neuron diseases, such as Amyotrophic Lateral Sclerosis (ALS) – distinguishing *D90A SOD1* ALS from sporadic ALS- and the genetic dystonias as well.