

# Brain hypometabolism in rare genetic neurodegenerative disease: Niemann-Pick disease type C, spinocerebellar ataxia and Huntington disease assessed by FDG PET

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## ARTICLE INFO

*Article type:*  
Case Series

*Article history:*

Received: 2 Oct 2020

Revised: 16 Nov 2020

Accepted: 21 Nov 2020

*Keywords:*

<sup>18</sup>F-FDG PET

Neurodegenerative

Niemann-Pick disease type C

Spinocerebellar atrophy

Huntington disease

## ABSTRACT

Brain metabolic imaging using <sup>18</sup>F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) with contemporaneous low-dose CT may be used to assess neurodegenerative diseases. In contrast to oncology whole-body FDG PET, qualitative assessment alone in brain FDG PET is subjective and vulnerable to visual interference due to high physiologic background activity. Therefore, mild changes in brain metabolism may be visually undetectable by qualitative interpretation alone, resulting in diagnostic inaccuracy. To overcome this, some institutions may employ an objective comparison to a normal reference database. To date, there is limited literature describing brain metabolic changes in rare genetic neurodegenerative diseases such as Niemann-Pick disease Type C, spinocerebellar ataxia and Huntington disease. In this case series, we illustrate the typical FDG PET findings in the cortex and deep grey matter for these rare diseases, utilising normal database comparison including three dimensional Stereotactic Surface Projection (3D-SSP) mapping. These comparisons can generate 3D-SSP maps where metabolic changes may be expressed in standard deviations from normal (z-score) and visually depicted in a scale of colours to improve diagnostic accuracy.

► Please cite this paper as:

Kao Y H, Cheng M, Velakoulis D, Walterfang M, Sivaratnam D. Brain hypometabolism in rare genetic neurodegenerative disease: Niemann-Pick disease type C, spinocerebellar ataxia and Huntington disease assessed by FDG PET. *Asia Ocean J Nucl Med Biol.* 2021; 9(2): 167-172. doi: 10.22038/AOJNMB.2020.52511.1362

## Introduction

Positron Emission Tomography (PET) with contemporaneous low-dose CT using <sup>18</sup>F-fluorodeoxyglucose (FDG) is a common imaging modality for cancer staging of solid tumour malignancies. FDG is an intravenously injected positron emitting glucose analogue which enables non-invasive imaging assessment of tissue glucose metabolism. In recent years, brain FDG PET is increasingly used for metabolic assessment of neurodegenerative diseases. Common neurodegenerative diseases such as Alzheimer's disease and frontotemporal dementia have characteristic patterns of brain

hypometabolism which may guide clinical management.

In contrast to oncology whole-body FDG PET, qualitative assessment alone in brain FDG PET is subjective and vulnerable to visual interference due to high physiologic background activity. Therefore, mild changes in brain metabolism may be visually undetectable by qualitative interpretation alone, resulting in diagnostic inaccuracy. To overcome this, some institutions may employ an objective comparison to a normal reference database. These comparisons can generate three dimensional Stereotactic Surface Projection (3D-SSP) maps (e.g. Figure 1) where

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metabolic changes may be expressed in standard deviations from normal (z-score) and visually depicted in a scale of colours to improve diagnostic accuracy (1).

To date, there is limited literature describing brain metabolic changes in rare genetic neurodegenerative diseases such as Niemann-Pick disease Type C, spinocerebellar ataxia and Huntington disease. Our institution is a tertiary referral centre for complex neurodegenerative diseases, including such rare genetic diseases. In this pictorial review, we describe the typical brain FDG PET findings in the cortex and deep grey matter for these three rare diseases utilising normal database comparison mapping including 3D-SSP.

## Methods

All three FDG PET brain studies were performed using a standard protocol. Patients were fasted between 4 to 6 hours, then intravenously injected with 3 MBq/kg body weight of FDG, followed by a 30-minute uptake period with eyes closed in a quiet room. All studies were performed on a Siemens Biograph Horizon (Siemens, Munich, Germany) PET/CT scanner over 15 to 20 minutes with the head in the centre of the field of view. PET brain images were reconstructed using Siemens 'TrueX' time-of-flight iterative reconstruction algorithm, 8 iterations and 10 subsets, Gaussian filter, 360×360 matrix and full-width half maximum 4 mm. Low-dose CT was performed for anatomical localisation, attenuation and scatter correction, and displayed in 3 mm slice thickness.

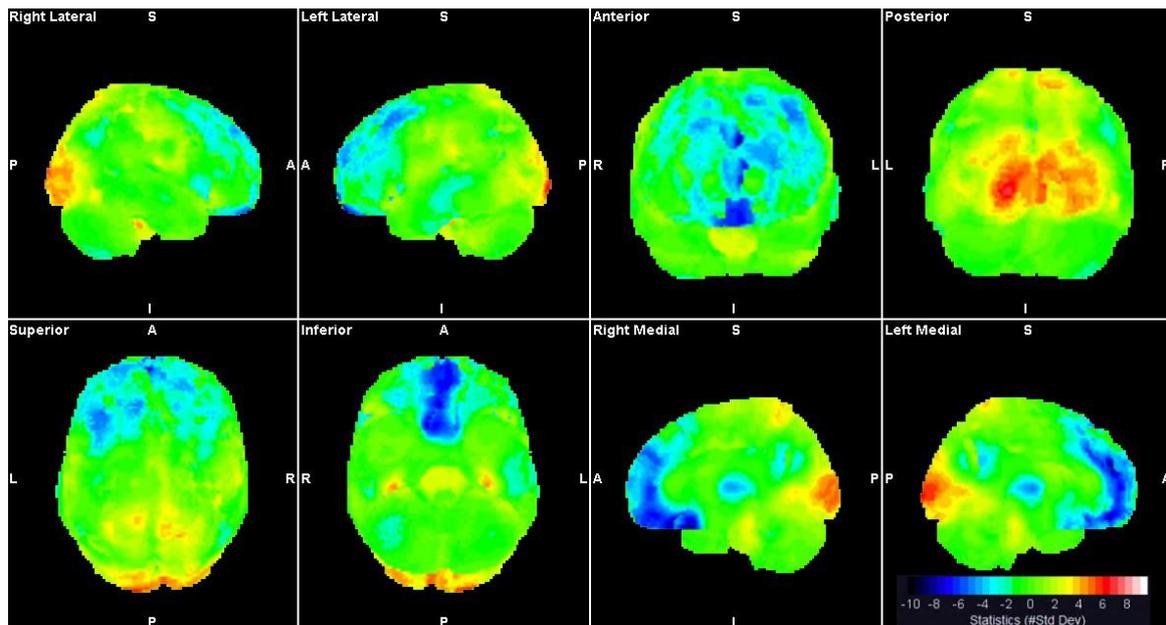
Diagnostic reporting was performed using Siemens proprietary software SyngoVia. Apart from visual assessment, FDG PET data were also compared to a normal reference database using Siemens proprietary software 'Scenium'. Scenium displays brain metabolic changes as

colour-coded visual map of standard deviations (SD; z-score) in 12 mm voxels which may be scrolled through in axial, coronal and sagittal planes like any sectional imaging (e.g. Figure 2). Scenium further displays the data in eight common 3D-SSP views, i.e. six standard orientations and two mesial orientations. These 3D-SSP maps are colour coded according to z-scores derived from normal database comparison. Results are visually displayed in a rainbow colour scale (e.g. Figure 2C; colour bar) where normal is green (zero SD), white is intense hypermetabolism (+10 SD) and black is very severe hypometabolism (-10 SD).

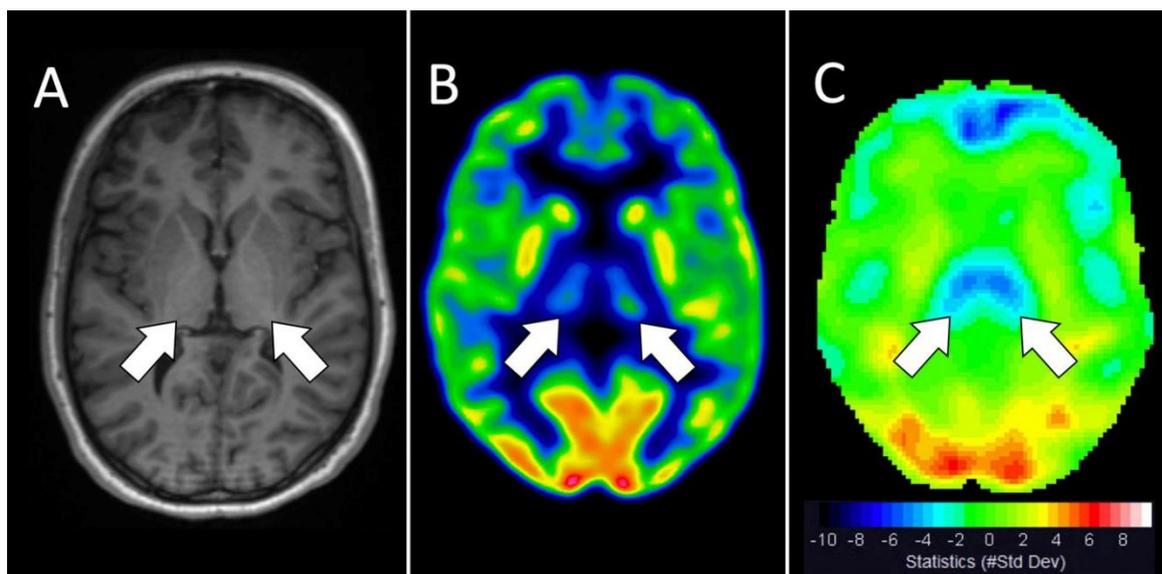
### *Niemann pick disease type C*

Niemann Pick disease type C is due to autosomal recessive gene mutations in the NPC1 (95%) or NPC2 (5%) gene, affecting around 1 in 90,000 live births. These gene mutations cause defective transport of low-density lipoprotein resulting in organ accumulation of free cholesterol and glycosphingolipids. Niemann-Pick disease type C is clinically heterogeneous ranging from a neonatal progressive fatal disorder to an adult onset neurodegenerative disease (2, 3). Neurological features include vertical supranuclear gaze palsy, cerebellar ataxia, dysarthria, dysphagia and dementia. Imaging studies have described atrophy of the cerebral cortex (especially frontal lobe), deep grey matter and hippocampus (4, 5).

Figures 1 and 2 depict frontal lobe and thalamic hypometabolic changes in a 16 year old female patient. She presented with learning difficulties, poor balance and speech impairment. Physical examination revealed ataxia, dystonia, vertical supranuclear gaze palsy and splenomegaly. Her genetic studies found her to be a compound heterozygote for two pathogenic variants in NPC1. She does not have a family history of a similar disorder.



**Figure 1.** Niemann-Pick disease type C. 3D-SSP map shows severe bilateral hypometabolic changes (dark blue; -6 to -8 SD) in the frontal lobes (best seen in anterior view) and thalamus (mesial views). There is also mild hypometabolism of the posterior cingulate gyri (mesial views; light blue; -4 SD). The rainbow colour bar at the bottom left represents the colour coded z-scores derived from normal database comparison, where normal is green (zero SD), white is intense hypermetabolism (+10 SD) and black is very severe hypometabolism (-10 SD)



**Figure 2.** Niemann-Pick disease type C. Trans-axial views of MRI (A), FDG PET (B) and normal database comparison map (C) depicting severe bilateral thalamic hypometabolism (arrows; dark blue; -6 SD). MRI was unable to detect any significant structural abnormality with the thalami, highlighting the additional benefit of FDG PET

### ***Spinocerebellar ataxia***

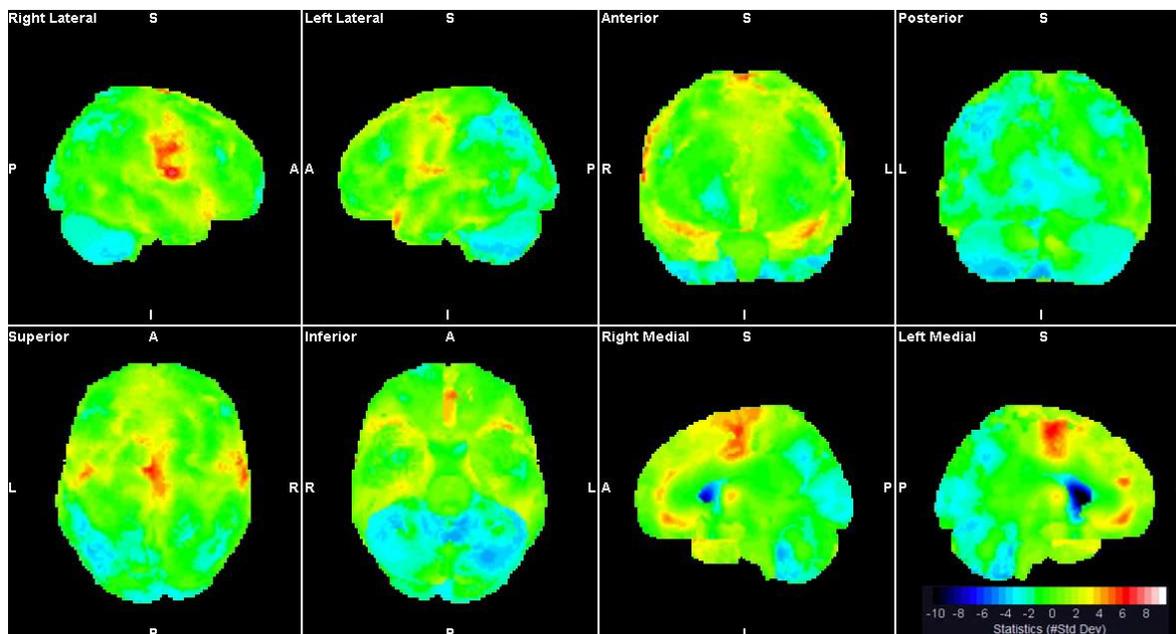
Spinocerebellar ataxias (SCAs) are a large group of autosomal dominant disorders causing spinal cord and cerebellar degeneration. The underlying genetic abnormalities vary widely reflecting the numerous SCA subtypes with an overall prevalence of 2.7 per 100,000, with SCA3 being the most common (6). Cerebellar ataxia is a common feature across all types of SCA, while other clinical features vary across the subtypes which may include neuropathy, tremors, pyramidal and extra-pyramidal signs, ocular signs,

seizures and dementia. Cerebellar atrophy is a consistent imaging feature across all subtypes, although other imaging features may differ. Basal ganglia abnormalities have been described for SCAs 2, 3 and 17, while SCAs 2 and 7 may show atrophy of the pons (7-9). Hypometabolism affects the cerebellum and, depending on subtype, may also affect the caudate, putamen, thalamus, brainstem or parietal lobe (10).

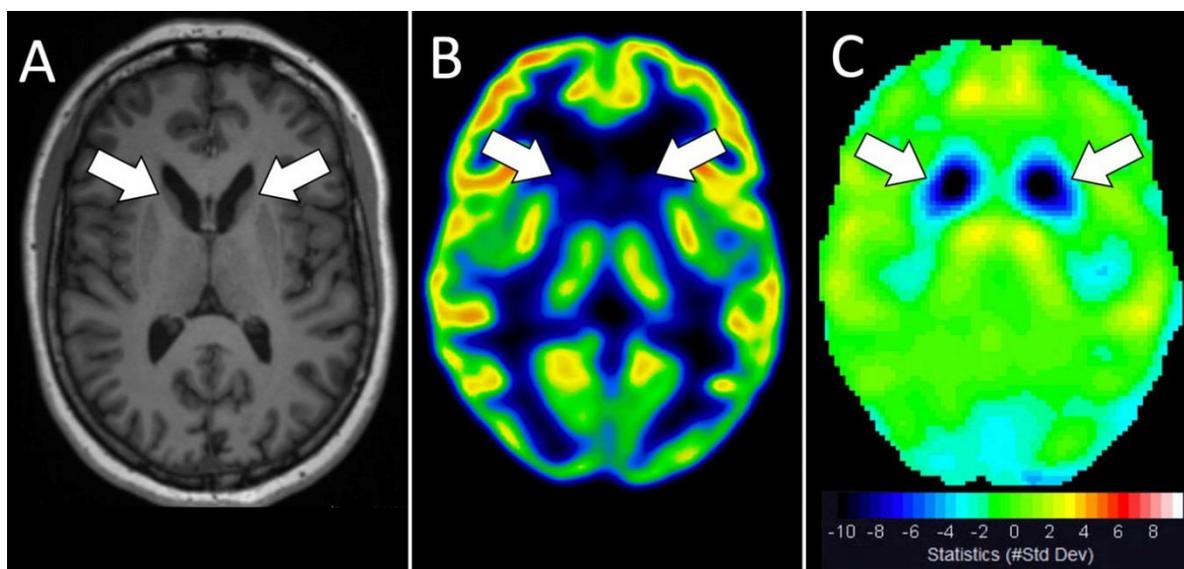
Figures 3 and 4 depict cerebellar and caudate hypometabolism in a 24 year old female patient. She has a history of gait disturbance, frequent

falls and cognitive impairment. She has a strong family history of ataxia and dementia involving multiple maternal relatives. Physical examination showed cerebellar signs (ataxia, dysarthria) and moderate cognitive impairment. On the basis of her clinical and imaging findings,

her working diagnosis is that of an autosomal dominant triplet repeat expansion with anticipation. Her preliminary genetic studies were so far negative for SCAs 1, 2, 3 and 6; further genetic testing (e.g. SCA 17) has been planned.



**Figure 3.** Spinocerebellar ataxia. 3D-SSP map shows significant hypometabolism of bilateral cerebellum (best seen in inferior view; blue; -4 to -5 SD) and caudate heads (mesial views; black; -10SD). There is also mild to moderate parietal lobe hypometabolism (light blue; -3 to -4 SD)



**Figure 4.** Spinocerebellar ataxia. Trans-axial views of MRI (A), FDG PET (B) and normal database comparison map (C) depicting severe bilateral caudate atrophy and hypometabolism (arrows; -10 SD)

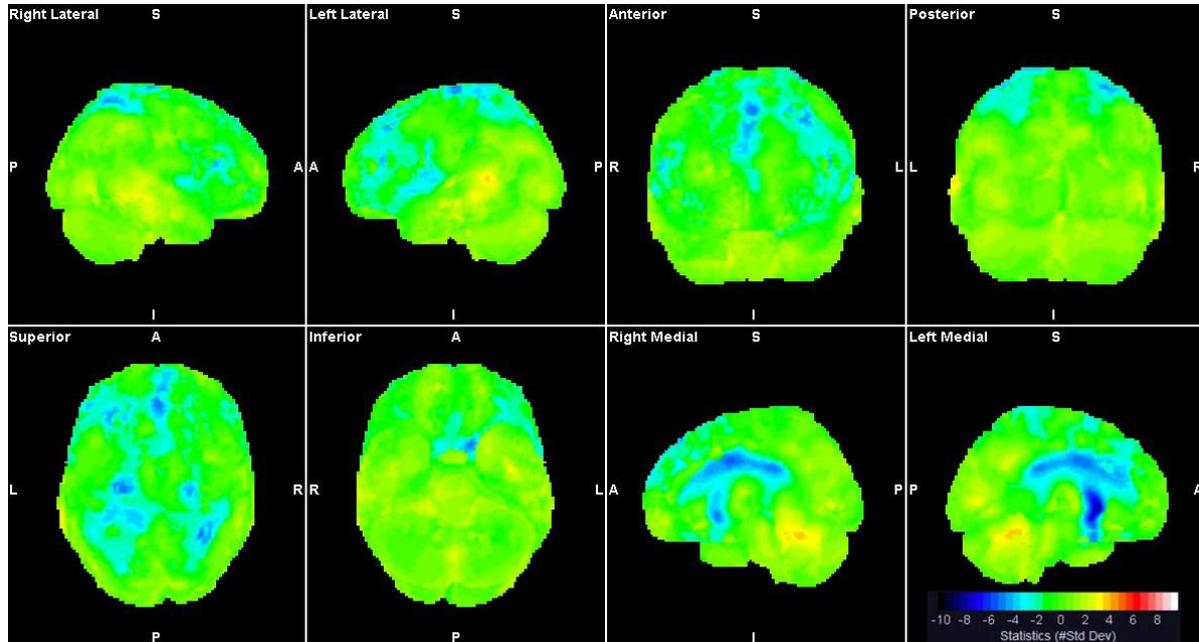
### Huntington disease

Huntington disease is an autosomal dominant neurodegenerative disorder clinically characterised by choreiform movements, psychiatric and cognitive dysfunction. It is caused by cytosine-adenine-guanine (CAG) trinucleotide repeats in the huntingtin gene with a prevalence of 2.7 per 100,000 (11). A consistent

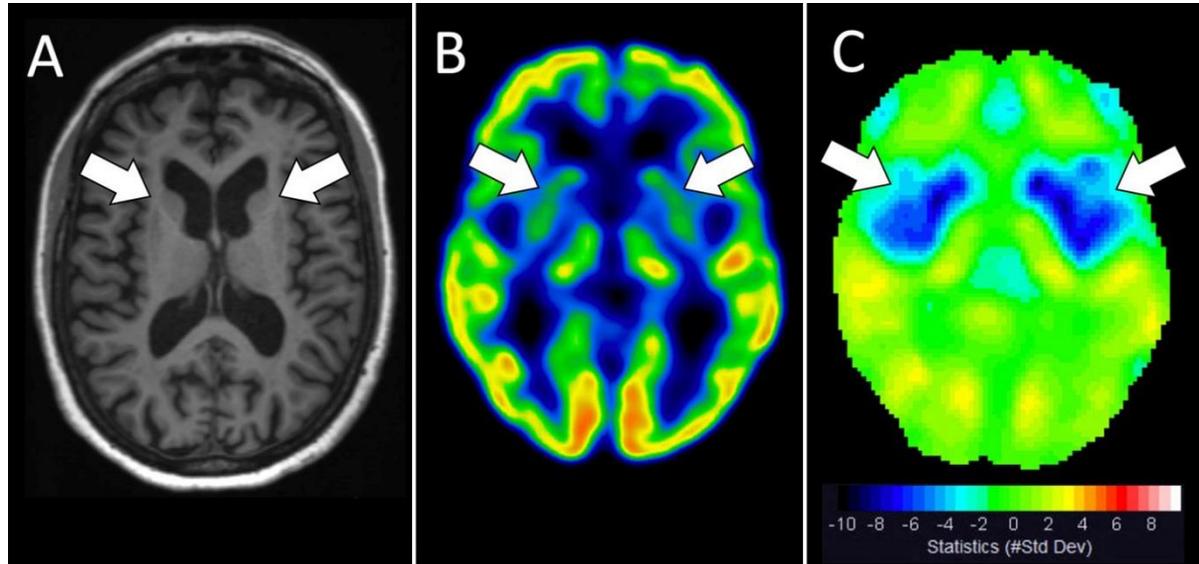
MRI imaging finding is progressive atrophy of the caudate and putamen (12). There is also cortical atrophy, typically starting from the posterior cortex then progressing to the anterior cortex as the disease progresses with time (13). On FDG PET, bilateral caudate and putamen hypometabolism has been described, as well as frontotemporal and parietal hypometabolism (13).

Figures 5 and 6 depict severe hypometabolism of bilateral caudate heads and lentiform nuclei in a 58 year old female patient. She was investigated for progressive cognitive dysfunction, unsteady gait and involuntary choreic movements. Her

family history was complex but her father was suspected to have a similar disorder. Her genetic studies was positive for 43 trinucleotide repeats on one allele, confirming the diagnosis of Huntington disease.



**Figure 5.** Huntington disease. 3D-SSP map shows severe hypometabolism of bilateral caudate heads (mesial views; dark blue; -8 SD). There is also hypometabolism of bilateral anterior cingulate gyri (mesial views; blue; -6 to -7SD), frontal lobes and parietal lobes (best seen in superior view; blue; -4 to -6 SD)



**Figure 6.** Huntington disease. Trans-axial views of MRI (A), FDG PET (B) and normal database comparison map (C) depicting severe atrophy and hypometabolism of bilateral caudate heads and lentiform nuclei (arrows; dark blue; -8 to -9 SD)

## Discussion

Our case examples illustrate the typical brain hypometabolic changes in the cortex and deep grey matter for Niemann-Pick disease Type C, spinocerebellar ataxia and Huntington disease depicted using normal database comparison mapping including 3D-SSP. The hypometabolic pattern of these rare genetic neurodegenerative

disorders are distinctly different from common dementias such as Alzheimer disease or frontotemporal dementia. A key difference is the significant hypometabolism of subcortical deep grey matter (e.g. thalamus, basal ganglia) which are usually uninvolved in common dementias.

The normal brain's physiologic environment is highly metabolically active. This makes visual

interpretation of brain FDG PET very challenging and subjective, even if semi-quantitative metrics such as Standardized Uptake Values (SUV) are employed. Normal database comparison maps such as 3D-SSP objectively accentuate any brain metabolic changes to improve pattern recognition and diagnostic confidence over qualitative assessment alone (1). The use of z-scores to express metabolic changes is also an objective method of measuring disease severity and for monitoring disease progression in follow-up scans. In addition, FDG PET complements structural imaging such as MRI to detect functional brain abnormalities that may not be apparent on MRI (e.g. Figure 2).

## Conclusion

This case series illustrates the typical brain FDG PET findings in the cortex and deep grey matter for Niemann-Pick disease Type C, spinocerebellar ataxia and Huntington disease, utilising normal database comparison including 3D-SSP mapping.

## Conflicts of interest

All authors, Yung Hsiang Kao, Melissa Cheng, Dennis Velakoulis, Mark Walterfang and Dinesh Sivaratnam, declare no conflicts of interest. There is no source of funding .

## Ethical approval

This research was approved by institutional research and ethics committee HREC 2005.198.

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