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PET studies in dementia

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Measurement of local cerebral glucose metabolism (lCMRGlc) by positron emission tomography (PET) and ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) has become a standard technique during the past 20 years and is now available at many university hospitals in all highly developed countries. Many studies have documented a close relation between lCMRGlc and localized cognitive functions, such as language and visuoconstructive abilities. Alzheimer's disease (AD) is characterized by regional impairment of cerebral glucose metabolism in neocortical association areas (posterior cingulate, temporoparietal and frontal multimodal association cortex), whereas primary visual and sensorimotor cortex, basal ganglia, and cerebellum are relatively well preserved. In a multicenter study comprising 10 PET centers (Network for Efficiency and Standardisation of Dementia Diagnosis, NEST-DD) that employed an automated voxel-based analysis of FDG PET images, the distinction between controls and AD patients was 93% sensitive and 93% specific, and even in very mild dementia (at MMSE 24 or higher) sensitivity was still 84% at 93% specificity. Significantly abnormal metabolism in mild cognitive deficit (MCI) indicates a high risk to develop dementia within the next two years. Reduced neocortical glucose metabolism can probably be detected with FDG PET in AD on average one year before onset of subjective cognitive impairment. In addition to glucose metabolism, specific tracers for dopamine synthesis (^{18}F-F-DOPA) and for (^{11}C-MP4A) are of interest for differentiation among dementia subtypes. Cortical acetylcholine esterase activity (AChE) activity is significantly lower in patients with AD or with dementia with Lewy bodies (DLB) than in age-matched normal controls. In LBD there is also impairment of dopamine synthesis, similar to Parkinson disease.

Key words: PET, dementia, multicenter study, automated image analysis, Alzheimer disease, glucose metabolism, acetylcholine, dopamine

INTRODUCTION

DEMENTIA is a major burden for many countries where life expectancy is continuously growing and the proportion of aged people is rapidly growing. The devastating impairment of cognitive functions in dementia is the consequence of a severe loss of functioning synapses and neurons in the brain, in particular in limbic and neocortical association areas. Effective treatment is eagerly awaited. Some drugs that have a moderate symptomatic effect, such as the choline esterase inhibitors, are already available and some studies indicate that they are able to postpone progression by several months. Drugs inhibiting inflammation that is associated with Alzheimer plaques, and drugs targeted against specific proteins that cause or contribute to amyloid deposition in the brain are currently being developed and tested. In any case, efficient treatment needs to be installed before a large number of synapses and neurons have been damaged irreversibly, and therefore early diagnosis of dementia is of utmost importance, but currently is far from being routine practice in medicine. It is difficult clinically to distinguish between memory deficits that may still be consistent with benign aging and the very beginning of Alzheimer disease (AD) which would urgently need effective treatment to avoid irreversible brain damage. Thus techniques to diagnose AD at a very early stage, when neuroprotective treatment would still have the chance to maintain the

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essential cognitive functions, are crucial.[1] In this review, I will demonstrate that positron emission tomography (PET) is technique that, although costly, has the potential to serve this purpose.

Cerebral glucose metabolism (FDG)

The most commonly used and most widely available tracer for PET is ^{18}F-2-fluoro-2-deoxyglucose (FDG). Its uptake in the brain reflects local glucose consumption which is closely coupled to neuronal function because it provides the energy to maintain ion gradients and to synthesize neurotransmitters.[2–4] In particular, glucose metabolism is intimately linked to glutamate synthesis and its recycling via the neuroglia.[5] Thus, synaptic dysfunction and neuronal degeneration regularly lead to a decline of glucose metabolism in the affected parts of the brain. This has not only been observed in Alzheimer disease, but also in a large number of other neurodegenerative diseases. Since many neurodegenerative diseases have very distinct sites in the brain that are primarily affected, whereas other parts of the brain are spared at least at the early stages, these topographical patterns that can be imaged with FDG PET provide significant diagnostic clues (Table 1).

Meanwhile approximately 20 years have passed since the first descriptions of the typical AD findings in FDG PET.[6] It has been noted from the beginning that the temporo-parietal association cortex is most affected, with the angular gyrus usually being located the center of the metabolic impairment, and frontolateral association cortex is also involved frequently.[7] These changes are different from those of normal aging, which leads to predominantly mesial frontal metabolic decline and may cause some apparent dorsal parietal (rather than temporo-parietal) and fronto-temporal (perisylvian) metabolic reduction due to partial volume effects caused by atrophy.[8,9] There may be a distinct hemispheric asymmetry, which usually corresponds to the predominant cognitive deficits (language impairment in the dominant, and visuospatial disorientation in the sub-dominant hemisphere). Voxel-based comparisons with normal reference samples clearly showed that the posterior cingulate gyrus and the precuneus are also impaired early on.[10] This is usually not directly obvious by mere inspection of FDG PET scans because metabolism in that area is above the cortical average in normal brain,[11] and with beginning impairment it returns to the level of surrounding cortex but does not stick out as a hypometabolic lesion. Thus, this important diagnostic sign is easily missed by standard visual interpretation of FDG PET brain scans. On the background of sufficient numbers of FDG PET scans in normal controls it is more and more becoming standard to base the interpretation of patient studies not merely on visual interpretation of the tracer distribution, but on quantitative mapping with reference to an appropriate normal sample.[12–15] These technical advances also overcome the ambiguities of qualitative image interpretation and reduce the variance that is introduced by variable individual experience and expertise of the physician.

Within a collaboration of nine institutions across Europe and one in Japan (Table 2), named "Network for efficiency and standardisation of dementia diagnosis

Table 1 Characteristic FDG PET findings in neurodegenerative diseases

Disease	Brain regions with reduced FDG uptake	References
Alzheimer disease (AD)	temporoparietal association cortex posterior cingulate cortex and precuneus variably also frontolateral association cortex	Reviews: (7, 10, 85)
Dementia with Lewy bodies (LBD)	as in AD, plus primary visual cortex	(58, 86, 87)
Frontotemporal dementia (FTD)	predominantly frontomesial, also frontolateral and temporal	(88–91)
Parkinson disease	cortical impairment similar to LBD possible (high uptake preserved in striatum)	(92–98)
Multiple system atrophy*	putamen, brainstem, cerebellum, often also cerebral cortex	(99–103)
Progressive supranuclear palsy	frontal, basal ganglia and midbrain	(35, 37, 104, 105)
Corticobasal degeneration	mainly parietal and central cortex, striatum and thalamus possibly also frontal cortex often very asymmetric	(35, 106–108)
Spinocerebellar degeneration	variable, depending on subtype, may be similar to MSA	(38, 109, 110)
Chorea Huntington	caudate nuclei, putamen, with progression also thalamus and cortex	(111–115)

*: including sporadic olivopontocerebellar atrophy and striatonigral degeneration

(NEST-DD)," we performed a retrospective study in 639 FDG PET scans, including 109 normal controls, 396 patients with probable AD (according to NINCDS-ADRDA criteria), and various other dementing diseases and related disorders. The PET scans were processed in a uniform manner by Gaussian filtering and spatial normalization, as provided by the SPM'99 software package (Welcome Institute, London), and were entered into a common database. From this data base we developed an algorithm to discriminate AD patients from controls that includes adjustments to handle data stemming from scanners with different spatial resolutions, and a correction for age effects by linear regression. With this procedure, discrimination between AD and controls was achieved with 93% sensitivity and 93% specificity. Even when limiting the analysis to very mild AD which could not be diagnosed by the Mini Mental Status Examination (MMSE) alone because these patients had scores of 24 (out of 30) or higher but required extensive additional neuropsychological testing, sensitivity was still 83%, maintaining 93% specificity.[8] The procedure provides a map of statistically abnormal brain areas in each patient (Fig. 1) that can also be used in other diseases. It is available for scientific evaluation by submission of FDG PET scans (that were obtained under resting conditions with eyes closed and ears unplugged 20–60 min after tracer injection) to the consortium's internet server (via WWW.NEST-DD.ORG).

Diagnostic algorithms for FDG PET analysis have now been developed further to also include discrimination of AD from other types of dementia (publication in preparation). Diagnostic procedures will be cross-validated using data from a prospective study conducted by the same consortium, which closed patient recruitment in October 2002 and also comprises a large set of clinical and neuropsychological data, including CT or MRI, and molecular tests.

Table 2 Institutes and principal investigators participating in the European Network for Efficiency and Standardisation of Dementia Diagnosis (NEST-DD)

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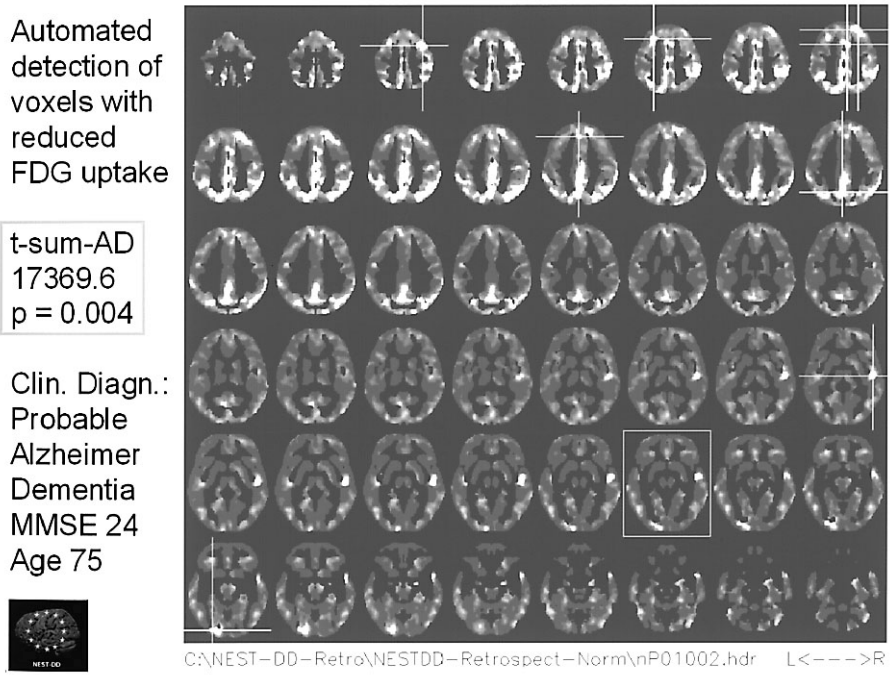

Fig. 1 Age-adjusted t-map of a patient with mild AD, as described by Herholz et al.[8] Significant voxels ($p < 0.05$) are marked white, and maxima of connected clusters are marked by crosshairs. The t-sum-AD is the sum of the t-values in all significant voxels within those brain regions that are typically affected in AD. Its value of 17,639 in this patient clearly exceeds the normal range of t-sum-AD (95% confidence limit 10,953) as determined in 109 normal controls, indicating that this scan is abnormal at an error probability of 0.4%.

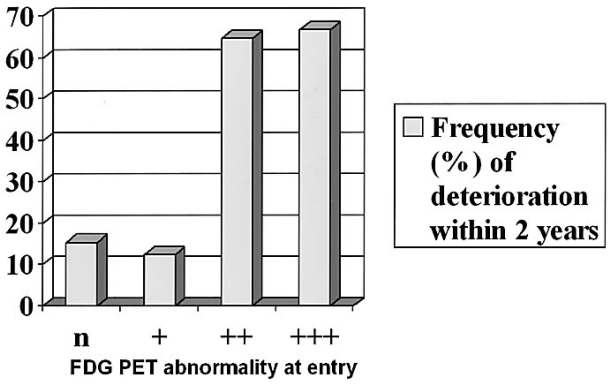

Fig. 2 Frequency of clinical deterioration in patients with cognitive deficits and suspected AD, but not yet fulfilling the NINCDS-ADRDA criteria for probable AD with MMSE 24 or higher. Frequency is low in patients with normal (n) or mildly abnormal (+) FDG PET at entry, but is high with moderately (++) and severely abnormal (+++) FDG PET as defined by a metabolic ratio of 0.8 or less (modified from Herholz et al.[29]).

Neuropathological studies indicate that neurodegeneration begins many years before the onset of clinical AD.[16] Memory impairment is the first clinical sign of impending AD, but it is difficult to distinguish from more benign forms of memory deficits, including the normal decline of most memory functions with age. In recent years, the concept of "mild cognitive deficit" (MCI) has been developed by Petersen et al.,[17] which in its core refers to a type of memory deficit similar to AD, but without the other criteria of AD (in particular, absence of cognitive impairment in another cognitive domain). Thus, it has been demonstrated that MCI often precedes AD, with a conversion rate from MCI to AD of approximately 10–15% per year.[17] With this low conversion rate and the lack of clear differentiation from benign and reversible forms of memory impairment, the diagnosis is of limited clinical use.

Data are accumulating that FDG PET can provide a much better prediction of rapid conversion from MCI to clinical dementia of Alzheimer type than the clinical criteria. In a longitudinal study, we studied patients with mild cognitive deficits, mostly limited to the memory domain, with MMSE scores of 24 or higher and not yet fulfilling the criteria of probable AD.[18] They were therefore diagnosed as "possible AD," and most of these patients would have fulfilled the criteria of MCI (which were not yet used by us at that time). We found that 60–70% of those patients who already had moderate or severe metabolic impairment of association cortices in FDG PET declined on MMSE by 3 points or more within 2 years (mostly leading to clinical dementia), whereas only 10–20% of patients without such metabolic impairment had that decline[19] (Fig. 2). More recently, the predictive value of PET for imminent conversion to AD has been confirmed in MCI.[20,21] These observations also correspond to group studies that have shown abnormal metabolism in association cortices in elderly asymptomatic patients at high genetic risk for AD.[22–24] These studies also suggest that mesial temporal (entorhinal) metabolism is reduced very early in apolipoprotein E4 positive individuals, but that has not generally been confirmed. In our experience, mesial temporal lobe metabolism is not preferentially reduced in most cases of AD. It rather seems that the well-known mesial temporal lobe atrophy in AD that is best detected on MRI is correlated with remote metabolic deficits in temporo-parietal and frontal association cortex and in the posterior cingulate cortex.[25] Back-extrapolation of the progression of the metabolic impairment from a sample of 47 own AD patients indicated that the typical reduction of FDG uptake in association cortex can be detected on average one year before onset of clinical symptoms as noted by the patient (unpublished data). Thus, FDG PET is useful for early diagnosis of AD.

Depression is the most important clinical condition that can lead to memory impairment without dementia. Therefore, depression in old age may be difficult to differentiate from beginning AD, and it has even been reported that depression in old age is a risk factor for dementia.[26] Since treatment of depression and AD is essentially different, and many antidepressants have anticholinergic side effects that are particularly unwelcome in AD with its intrinsic cholinergic deficit, better tools for diagnostic differentiation are needed. With FDG PET, depression is associated with global reduction of cerebral glucose metabolism, with some accentuation in the frontal lobe.[27,28] Present data indicate that the metabolic alterations in depression are distinct from those in AD.[29,30] Yet, data are still preliminary at this stage, and it remains to be seen whether we can identify a subgroup of patients with clinical depression who have a high risk for conversion to AD.

Frontotemporal dementia (FTD) is characterized clinically by leading changes in personality and behavior, such as apathy or disinhibition, whereas memory impairment may be absent or less prominent.[31] There are no unique histopathological characteristics of FTD, which is the main manifestation of so-called Pick complex[32] that includes also primary progressive aphasia and semantic dementia. Clinical differentiation from AD is usually not very difficult, but FTD is usually not diagnosed at an early stage because mild symptoms are difficult to verify objectively. FTD often is associated with severe impairment of language production, and there are even variants such as semantic dementia and primary progressive aphasia, where the language disorder is the leading symptom and dementia may be missing (at least at the beginning).[33] Familial FTD may be associated with parkinsonism and with mutations in the tau gene on chromosome 17.[34] In principle, FTD is identified easily on FDG PET scans by a distinct frontal or fronto-temporal metabolic impairment. It seems, that FTD can also be differentiated from

corticobasal degeneration with predominant parietal metabolic reduction,[35] although histopathological features may overlap.[36] Yet, frontal metabolic impairment is also part of many other diseases and conditions, including progressive supranuclear palsy (in combination with midbrain impairment),[37] spino-cerebellar atrophy,[38] and cocaine abuse.[39] There are also cases with combinations of frontal and temporo-parietal metabolic impairment which could represent either AD or FTD, and there are not yet sufficient studies to provide reliable numbers on the accuracy of differentiation.

Diagnosis of vascular dementia (VD) is a difficult issue because there is not yet a consensus about clinical criteria, and correspondence between existing criteria (e.g., ICD-10, DSM-IV, NINDS-AIREN, CAMDEX) is poor.[40,41] The frequency of pure vascular dementia is low in most European and American autopsy series,[42] but seems to be considerably higher in Japan.[43] Because cerebral arteriosclerosis is frequently present also in elderly subjects with AD (but also in elderly subjects without dementia), and cerebrovascular lesions are detected with high sensitivity on MRI (on T2-weighted images, with or without fluid signal suppression), whereas structural imaging provides no specific signs of AD, there may be a clinical tendency to diagnose VD based on the MRI findings too frequently when the correct diagnosis would rather have been mixed dementia, as seen by neuropathologists in 20–40% of dementia cases, at least in Europe and the U.S.[42] There seem to be no distinctive features of VD in FDG PET (apart from those patients who have multiple cortical ischemic infarcts that are seen as corresponding lesions on MRI/CT and PET). Several studies suggested that a diffuse global reduction of cerebral glucose metabolism is a typical finding in VD, and that the degree of that reduction in association cortex is similar to that seen AD.[44,45] Thus, the contrast between metabolic impairment in association areas and preserved metabolism in primary areas, basal ganglia and cerebellum, that is typical for AD but not for VD, seems to provide the best distinction with FDG PET between these two types of dementia.[44]

Local cerebral blood flow (CBF) is usually also reduced in areas with impaired neuronal function and reduced glucose metabolism. Thus, the typical impairment of association areas seen with FDG PET has also been described for CBF images obtained with PET and SPECT.[46,47] Similar findings have been reported also with PET measurements of oxygen metabolism.[48] It has been suggested that glucose metabolism is more impaired in AD than oxygen metabolism,[49] and that vascular reactivity is preserved in AD but impaired in VD,[50] but it is not yet whether these findings can be used for clinical differential diagnosis. FDG PET images are superior to the other techniques with respect to signal to noise and are easily obtained under clinical conditions, since blood sampling and calculation of metabolic rates of glucose are not required for identification of the typical pattern.[8] FDG PET has been validated in autopsy-confirmed series,[51] whereas ^{15}O-water-PET was not proven to be clinically useful.[47] In the few direct comparisons of FDG PET with SPECT that have been performed,[52–54] FDG PET was always shown to be more accurate. Since the highest benefit of function imaging for diagnosis of dementia probably will be obtained in cases that do not yet present with the typical symptoms of AD but may have more subtle symptoms that would be classified clinically as MCI,[20,55–57] high accuracy is certainly needed. Whether PET could be cost effective compared with SPECT in that situation in spite of its higher price has not yet been studied.

In summary, differentiation of AD from most other types of dementia is possible with FDG PET, because most other diseases that may lead to dementia types have different patterns with respect to affected brain areas (Table 1). Besides differentiation from vascular dementia, probably the most difficult issue is differentiation from Lewy body diseases (Parkinson disease and dementia with Lewy bodies) which involve the same areas as in AD, and primary visual cortex in addition.[58,59] Yet, the diagnostic value of the latter finding is not yet entirely clear. The largest sample of dementia patients studied with FDG PET and confirmation of diagnosis by autopsy was collected from multiple centers by Silverman et al.[51] It confirmed that the sensitivity to detect AD is higher than 90% (as suggested by other studies without confirmation by autopsy), and found that specificity for discrimination from other dementia types is only in the order of 70%. It remains to be seen whether that latter figure can be improved my better standardization with automatic procedures for detection of abnormal metabolism and disease-associated patterns. Another possibility for improvement certainly is the use of tracers that are specific for particular transmitter systems that are impaired to a different degree in different dementia diseases, as reviewed in the next paragraphs.

Specific neurotransmitters: Dopamine

Although FDG PET is a very powerful diagnostic tool because it gives a comprehensive image of synaptic function, it lacks specificity with regard to individual transmitter systems. There are neurodegenerative diseases involving specific neurotransmitters that do not have a distinct appearance on FDG PET scans, probably because the cells synthesizing and releasing these transmitters are too few or too widely dispersed to have a local impact on energy consumption. The most evident example is Parkinson disease, where the substantia nigra pars compacta with its profound degeneration of dopaminergic neurons is too small and metabolically too similar to the rest of the midbrain to be easily recognized in FDG PET scans. The lack of dopamine in the striatum also does not induce a major change of glucose consumption there,

possibly because of the primarily inhibitory effect of dopamine and the complicated subsequent neuronal net of mostly inhibitory transmission downstream seen together causes a slight increase of glucose consumption that is too small to be of major diagnostic use.[60] In these instances, we need tracers that image specifically that particular neurotransmitter system.

We used ^{18}F-fluorodopa (F-DOPA) to study the dopaminergic system. The tracer is a substrate to DOPA decarboxylase which is expressed in abundance by dopaminergic neurons. The product, ^{18}F-fluorodopamine, accumulates in proportion to decarboxylase activity which in turn reflects the amount of viable dopaminergic cells. The typical finding in Parkinson disease is a severe reduction of tracer accumulation, predominantly in the posterior part of the putamen, indicating loss of more than 50% of dopaminergic neurons projecting to this part of the striatum (see review by Brooks[61]).

The pathological hallmark of Parkinson disease are intracellular deposits consisting mainly of alpha-synuclein and ubiquitin, which are called Lewy bodies and are located in the midbrain, in particular in the substantia nigra. Yet, in dementia with Lewy bodies (DLB) these pathological deposits may also occur in the cortex, even without prominent occurrence in the brainstem. Patients with DLB often clinically have fluctuating levels of attention and consciousness, optical hallucinations, and may develop the motor features of Parkinson disease.[62,63] On the other hand, up to 30% of patients with Parkinson disease develop dementia and often also intermittent hallucinations in particular under treatment with dopaminergic drugs. It is conceivable that Parkinson disease and DLB represent the main manifestations of the spectrum of Lewy body disorder with the possibility of intermediate manifestations, and progression of primary midbrain lesions to involve cortical areas and vice versa. The nosological classification of DLB is even more complicated by the fact that cortical Lewy bodies may also occur to a variable extent in Alzheimer disease.[64]

Even in Parkinson disease without dementia and normal FDG PET scans, a correlation between F-DOPA accumulation in the basal ganglia and memory tests scores has been described,[65] suggesting that the dopaminergic degeneration by itself can affect cognitive functions. It has also been demonstrated that there is a reduction of cortical F-DOPA accumulation in Parkinson disease.[66] On the other hand, a reduction of F-DOPA accumulation in the basal ganglia has also been noted in DLB, even in patients without motor signs of Parkinsonism,[67] whereas F-DOPA uptake in the basal ganglia is completely normal in AD. Thus, F-DOPA PET may be currently the best tool to detect all types of Lewy body disease *in-vivo*. It remains to be determined whether ligands for biogenic amine transporter sites, such as ^{18}F-beta-CFT[68] and ^{11}C-dihydrotetrabenazine,[69] and ligands for D2 and D1 receptors will provide additional insight into the pathophysiology of Lewy body diseases and may further refine clinical diagnosis.

Specific neurotransmitters: Acetylcholine

Impairment of cholinergic neurotransmission in the central nervous system leads to severe cognitive impairment.[70] Anticholinergic drugs can induce memory impairment even in normals. Cholinergic innervation of the cerebral cortex has its origin mostly in some basal nuclei, of which the nucleus basalis magnocellularis (of Meynert) is most important. Degeneration of cholinergic neurons has been observed in several neurodegenerative diseases, most notably in Alzheimer and Parkinson disease,[71,72] whereas it may be mostly intact in vascular dementia.[73] Thus, *in-vivo* diagnosis of cholinergic degeneration could contribute to diagnosis of and differentiation between dementing diseases.

In recent years, a few tracers have been developed for *in-vivo* imaging of cerebral AChE with positron emission tomography (PET).[74,75] We used a piperidine analogue of acetylcholine, ^{11}C-labeled *N*-methyl-4-piperidyl-acetate (MP4A), and developed a non-invasive method to obtain quantitative measurements of cortical AChE activity in normal subjects and AD.[76,77] The tracer is freely diffusible in brain and thus initially is distributed in proportion to local blood flow. As a substrate of AChE, it is hydrolyzed by this enzyme and accumulates depending on enzyme activity because the hydrolyzed product is trapped in brain. AChE in human cortex is mainly expressed in the cholinergic axons, and to a lesser extent also in some cholinoceptive neurons. With impaired function and neurodegeneration of these cholinergic axons, the amount of cortical AChE is reduced which can be detected by reduced accumulation of MP4A.

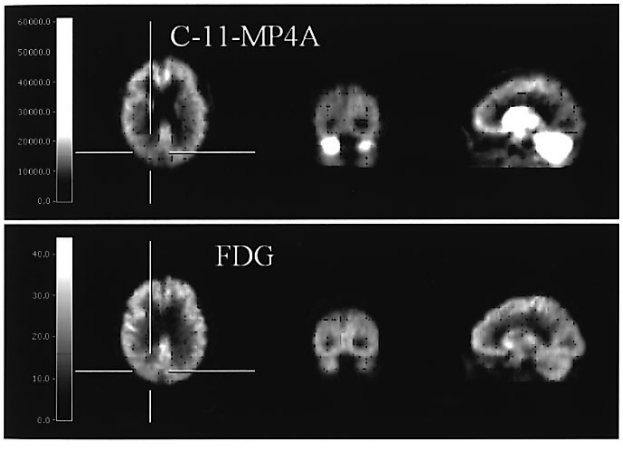

Fig. 3 Severe impairment of cortical AChE activity (less than 50% of normal reference values), in particular in occipital cortex (marked by crosshairs in orthogonal cuts), as measured by ^{11}C-MP4A PET (*top row*), in a patient with probable Lewy body dementia. Occipital glucose metabolism is also impaired, but to a lesser degree (*bottom row*).

Reduced AChE activity in AD has now been observed in several studies with MP4A.[78,79] It is reduced in all cortical areas, most severely in occipital and temporal cortex. When compared to Parkinson disease in which AChE may be reduced without dementia, the reduction in AD is more severe, in particular in parieto-temporo-occipital association cortex. Of course, additional AChE inhibition due to the action of choline esterase inhibitors which are used therapeutically in AD to enhance synaptic acetylcholine levels by inhibition of hydrolysis can also be measured by MP4A.

The few histochemical studies in DLB that have been performed so far indicated a particularly severe degeneration of cholinergic neurons.[80] It is of considerable clinical interest, whether this severe deficit may contribute to fluctuations of consciousness and the hallucinations that are characteristic for DLB. This is the topic of an ongoing scientific study. Preliminary results indicate that there is in fact a severe reduction of cortical AChE activity in DLB. The potential of the cholinergic deficit to cause hallucinations was illustrated by the case of an 83-year old woman, who had probable DLB with moderately severe dementia (mini mental status examination [MMSE] score 18 of 30), fluctuating consciousness, and recurrent visual and auditory hallucinations. FDG PET was only mildly abnormal, but AChE activity was severely reduced in occipital cortex (Fig. 3).

Thus, the assessment of specific neurotransmitter systems with PET is likely to contribute substantially to clinical distinction between different neurodegenerative diseases that may lead to dementia. Besides the two tracers reported here, receptor ligands for the cholinergic, dopaminergic, and serotonergic system and newly developed tracers that label amyloid plaques are likely to play an important role.[81–84] The full clinical relevance of these developments probably will turn up when more specific and also course-modifying drugs for dementia treatment become available.

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