Functional brain imaging applications to differential diagnosis in the dementias

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Purpose of review
The diagnosis of dementia rests on an improved knowledge and a better detection of early impairments, to which functional imaging can certainly contribute.

Recent findings
Progress has been observed at different levels. First, the understanding of different dementias has benefited from explorations of the neural substrate of dementia symptoms and from research into new markers. Second, diverse variables (clinical, anatomical, biochemical) have been related to impaired cerebral activity in Alzheimer's disease and other dementias, and progress in image analysis and in multimodal data acquisition has allowed a better understanding of the significance of brain activity disturbances. Third, functional imaging has been applied in well-designed clinical studies, and has provided important arguments for the diagnosis of characteristic clinical syndromes in the dementias.

Summary
The functioning of neural networks responsible for clinical symptoms in dementia remains an important research topic for functional imaging. The development of new tracers and new techniques for image processing should also improve the usefulness of brain imaging as a diagnostic tool.

Keywords
dementia, imaging

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Abbreviations

AchE	acetylcholine esterase
AD	Alzheimer's disease
CBF	cerebral blood flow
DLB	dementia with Lewy bodies
FDG	2-[(18)F]fluoro-2-deoxy-D-glucose
FTD	frontotemporal dementia
MCI	mild cognitive impairment without dementia
MRI	magnetic resonance imaging
MTR	magnetization transfer ratio
PET	positron emission tomography

Introduction

Functional imaging is an essential tool to study the neural substrate and the physiopathology of clinical syndromes in different dementias. That research will constitute the main purpose of this article. When functional disturbances are sufficiently characteristic, functional imaging may be used for the differential diagnosis of dementias. Assessing the relative sensitivity and specificity, and eventually the advantage of different techniques for reaching a specific diagnosis remains difficult because neuropathological confirmation is rare and a between-study comparison of percentages is not fair, whereas a within-study comparison of different functional imaging techniques is infrequent. In practice, there is a trade-off in functional imaging between, for example, ongoing refinements in image analysis, the availability of the techniques and the feasibility of studies in clinical versus research settings.

Diagnostic value of functional imaging in Alzheimer's disease

Different variables need to be considered when evaluating the diagnostic value of functional imaging, such as the size of the population, the probability of the diagnoses, the technique and the method for image analysis (for example, the pattern considered to be characteristic of Alzheimer's disease; AD). When compared with a clinical diagnosis, the visual analysis of single-photon emission computed tomography images has been shown to increase the likelihood of a neuropathological diagnosis of AD [1•]. In a large population of 138 cases with different neuropathologically confirmed diagnoses, the visual analysis of positron emission tomography (PET) images identified patients with AD and patients with any neurodegenerative disease, with a sensitivity of 94% and specificities of 73% and 78%, respectively [2•]. Those results were confirmed for questionable or mild AD. In that study, a 'non-characteristic' PET image predicted that subsequent progression to definite dementia occurred in only 30% of the cases. Other methods for image analysis will be reviewed in the following paragraphs. They might improve both the sensitivity and specificity of functional imaging for the diagnosis of dementia, but implementation in the clinical environment would require more resources.

The meaning of the regional brain distribution of functional activity in Alzheimer's disease

AD has been characterized for a long time by a metabolic decrease predominant in the posterior associative cortices. Before concentrating on AD, it is important to underline that the distribution of cerebral activity observed with functional imaging is not unique to AD pathology, as demonstrated by values of specificity in diagnostic studies and by data on non-Alzheimer dementias discussed in subsequent paragraphs. For example, a reversible 'AD compatible' decrease of perfusion in the posterior associative cortices was observed in hyperthyroid dementia, emphasizing the essential relationship between the clinical syndrome and functional imaging [3].

Evolution of cerebral functional activity in Alzheimer's disease

In the early stages of AD, some authors have suggested that hypoperfusion would start in the medial temporal regions, where lowered cerebral blood flow (CBF) might subsequently reach a plateau [4]. Activity in the lateral temporoparietal (and medial posterior) associative cortices would progressively decrease with the severity of dementia, and would become more important than impaired activity in the hippocampal areas, producing the typical pattern reported in most studies, whereas functional impairment would occur later in the prefrontal regions [5]. However, the magnitude and the sequence of longitudinal CBF changes may vary between different AD populations or according to different analysis procedures [6]. In keeping with the heterogeneity of AD, the selective impairment of episodic and semantic memory in a subgroup of patients was associated with hypoperfusion in the bilateral mesial temporal regions of interest, whereas the posterior associative cortices were predominantly involved in AD patients with more widespread cognitive impairment [7•].

In a study of carriers of the PS-1 mutation [8•], regional cerebral perfusion abnormalities were detected in the hippocampal complex and in the posterior associative cortices before the development of the clinical symptoms of AD. A metabolic pattern similar to that observed in AD was previously reported in cognitively normal carriers of the apolipoprotein E epsilon4 allele with a familial history of AD [9]. Those patients were followed over an interval of approximately 2 years, and they suffered a significant decline in glucose metabolism in the vicinity of the parahippocampal gyrus, temporal, posterior cingulate and the prefrontal cortices, basal forebrain and thalamus [10•]. The authors emphasized the availability of PET to test the efficacy of treatments for attenuating this functional decline.

Changes in brain activation in Alzheimer's disease

An impaired odour discrimination is reported in AD, and a decrease in right piriform and anterior ventral temporal activation was observed during olfactory stimulation when patients were compared with elderly controls [11]. Brain activation was studied for forced choice face recognition, and the authors demonstrated that different functional networks are activated for similar tasks in AD and in elderly controls [12•]. AD patients presented increases or decreases of activation compared with control subjects. Cerebral activation in AD remains to be explained in terms of performance and strategy during cognitive tasks. Moreover, the relationship between brain activation and atrophy is a complex one, for increased activation has been related to the loss of cortical gray matter, suggesting a possible compensation in some (but not all) brain regions in AD [13].

Relationships between brain activity and clinical variables

The degree of hypoperfusion in the temporoparietal areas of demented patients at the first visit has been shown to predict the achievement of endpoints such as loss of activity in daily living, incontinence and death as a result of end-stage AD [14•]. This was in keeping with a previous study [15], which showed that temporal metabolism in questionable AD predicted the evolution to a probable diagnosis of this dementia. Several questions are not yet settled, such as the influence of demographic variables (premorbid intelligence, for example) on the level of metabolism observed at a given stage of dementia [16].

AD, with its clinical heterogeneity, remains a particularly interesting condition to study clinical and metabolic relationships. Retrieval in verbal episodic memory has been related to left entorhinal activity in AD [17], whereas verbal semantic memory tests in AD patients have been correlated to glucose metabolism in the left inferior temporal gyrus [18]. AD patients with apathy were shown to have anterior cingulate hypoperfusion compared with patients without apathy [19•]. Clinical–metabolic correlations have essentially been studied in transversal studies, using either a-priori hypothesized regions of interest or (more convincingly) voxel-based statistical analysis, which takes the entire brain volume of activity into account. However, reports on the sensitivity of functional imaging show that few demented patients may have normal activity distribution, whereas abnormal metabolism was observed in asymptomatic at-risk subjects. More sensitive methods for image analyses and longitudinal studies are required to explore further the multifactorial clinical–metabolic relationships.

Relationship between functional and anatomical data in Alzheimer's disease

The characteristic functional involvement of the temporoparietal and posterior cingulate cortices in presymptomatic and clinically demented AD patients has been reproduced by both longitudinal and cross-sectional voxel-based morphometry studies using magnetic resonance imaging (MRI), which have also demonstrated medial temporal atrophy [20,21•]. Possible artefacts introduced by stereotactic anatomical standardization of atrophied brains have been discussed when voxel-based statistical mapping methods are used to analyse brain imaging in patients [22], but automated techniques are capable of facilitating the serial measurement of medial temporal volumetric changes in AD [23•]. New computational approaches distinguishing variations in gray matter distribution from variations in gyral patterns have shown that the greatest deficits in gray matter loss were mapped in the temporoparietal cortices [24•]. Degeneration within the prefrontal cortex appeared to be most prominent in the inferior gyrus in patients with AD [25].

Studies that combined functional and anatomical imaging have shown that between-group comparisons of regional metabolic values are diagnostically superior to volume measurements [26•], and that atrophy is not sufficient to explain the reduction of brain activity in AD [27,28]. However, conflicting results exist for the medial temporal region, which might depend on differential pathophysiology, sensitivity or susceptibility to artefacts of functional and volumetric measurements [29]. Regional perfusion and brain metabolism are correlated in AD, but there remain many anatomical variables that might account for reduced cerebral activity in the disease. A decrease in metabolic activity was suggested to be related to reduced synaptic activity more than to neuronal loss [30]. A decrement of cytochrome oxidase histochemistry, used as an intracellular measure of oxidative energy metabolic capacity, has been shown in the posterior cingulate cortex of AD patients, and might contribute to the metabolic impairment observed in functional imaging [31].

Functional magnetic imaging techniques in Alzheimer's disease

When we consider the number of biochemical, anatomical, demographic or clinical variables that may be related to brain functional activity in AD, it remains important to explore new functional parameters to improve our understanding of the physiopathology of the disease. MRI of the regional cerebral blood volume has shown decreased values in the cortical and hippocampal regions of AD patients, even when atrophy was used as a covariate [32]. An apparent coefficient of water diffusion was not statistically different between AD and controls in that study. However, it was found to be relatively increased in the temporal stem

and posterior cingulate, the occipital, and parietal white matter in another population of AD patients compared with control subjects [33]. Another study [34] demonstrated a reduced magnetization transfer ratio (MTR) and increased mean diffusivity in the cortical gray matter of AD patients compared with control subjects. A decrease in the MTR has been found in the hippocampus of AD patients with very mild dementia [35]. A low MTR ratio indicates a reduced capacity of the macromolecules in tissue membranes of the brain to exchange magnetization with the surrounding water molecules, reflecting damage to these membranes. Increased water diffusivity reflects a disintegration of brain tissue compartments. Further studies are required to correct the values for brain atrophy and to specify their meaning. The measurements with ^{1}H-magnetic resonance spectroscopy of absolute metabolite concentrations in the associative neocortex showed abnormal results in AD. Abnormalities of N-acetyl aspartate were disputed in mild AD, but they were positively correlated to the severity of dementia [36,37]. This probably reflects decreased neuronal viability in AD. A weak, but significant positive correlation was observed between regional cerebral glucose metabolism measured using 2-[(18)F]fluoro-2-deoxy-D-glucose (FDG)–PET and N-acetyl aspartate relative signal intensity in AD patients [38•]. Diffusion tensor imaging showed a highly significant reduction in the integrity of the association white matter fibre tracts in the splenium of the corpus callosum, superior longitudinal fasciculus, and cingulum in patients with probable AD compared with normal controls [39].

Assessment of physiopathological hypotheses in Alzheimer's disease using functional imaging

The clinical benefit observed in AD with acetylcholine esterase (AchE) inhibitor therapy has been associated with an increase of metabolism and perfusion in the medial temporal and cortical associative cortices [40–42]. Radiolabelled substrates allow the measurement of cerebral AchE activity with PET [43•], and cortical activity is reduced in AD patients compared with controls [44•]. AchE activity was proved to be reduced *in vivo* in AD patients taking AchE inhibitor treatment [45].

Activated microglia have been detected *in vivo* in the entorhinal, temporoparietal and cingulate cortex of AD patients using a specific ligand of the peripheral benzodiazepine binding sites, illustrating the brain's immune response to neuronal degeneration [46•]. Detection of amyloid plaque burden *in vivo* in the brain of patients with AD is also an aim of functional imaging.

Mild cognitive impairment

MRI volume sampling with co-registered and atrophy corrected FDG–PET scans were used to demonstrate that entorhinal cortex glucose metabolism and hippocampal

volume were the most accurate variables to distinguish mild cognitive impairment without dementia (MCI) from controls [26•]. Both imaging modalities identified the temporal neocortex as best separating MCI and AD. Widespread changes accurately classified AD and controls. In most between-group comparisons, regional metabolic values were diagnostically superior to volume measurements. In keeping with those results, a measure of temporoparietal cerebral metabolism was shown to predict the evolution of patients with MCI to AD [47]. A regional decrease in perfusion in the hippocampal–amygdaloid complex, the posterior cingulate, the anterior thalamus, and the anterior cingulate had already been shown to be most prominent among MCI patients who subsequently converted to AD [48]. MRI has been used to show that the hippocampal-apparent diffusion coefficient was higher in MCI and AD patients than in control subjects [33].

The predictive value of FDG–PET was further demonstrated in a longitudinal study of initially normal elderly control subjects [49••]. Subjects declining at follow-up and non-declining controls were matched for demographic variables. Glucose metabolism in the entorhinal cortex was shown to predict cognitive decline to MCI or even to AD. Among those who declined, the baseline entorhinal cortex metabolism predicted longitudinal memory and temporal neocortex metabolic impairments.

Vascular dementia
Global cognitive impairment has been related to both whole cortical and frontal hypoperfusion in vascular dementia. Frontal lobe perfusion was associated with subcortical hyperintensity volume measured on MRI, but not with performances on executive functions [50]. This is in keeping with the idea that executive and attentional functions would depend on distributed (but specific) cerebral networks.

Dementia with Lewy bodies
A study of autopsy-confirmed AD and patients with dementia with Lewy bodies (DLB) [51•] has shown a significant metabolic reduction involving the parietal, temporal, posterior cingulate and frontal association cortices, in both conditions compared with control subjects. Only DLB patients showed metabolic impairment in the occipital cortex. Clinically diagnosed probable AD patients showed a significantly higher frequency of primary visual metabolic reduction among those who later fulfilled clinical criteria for DLB. Therefore, a decrease in occipital activity was proposed as a potential antemortem marker to distinguish DLB from AD [52•]. However, occipital hypometabolism is not universal in DLB [53].

Occipital glucose metabolism was observed in DLB with and without parkinsonism, compared with AD patients [54].

Defects in nigrostriatal dopamine pathways in DLB have been demonstrated with functional neuroimaging using ligands probing pre- and post-synaptic dopaminergic systems [55–57]. On the other hand, DLB patients appeared to have less frequent medial temporal functional impairment than an AD group [58]. Accordingly, hippocampal and parahippocampal volumes have been shown to be significantly larger in individuals with DLB compared with AD patients [59]. Caution is mandatory when FDG–PET is used for the differential diagnosis of parkinsonian syndromes with dementia, for hypometabolism in associative cortices and in the caudate has been reported in advanced non-demented patients with Parkinson's disease [60].

Frontotemporal dementia
A decrease of activity in the frontal and temporal lobes has been confirmed in different cases of frontotemporal dementia (FTD) [61]. Frontotemporal hypoperfusion has been reported in patients with bulbar onset motor neuron disease when they present with cognitive impairment [62]. In keeping with the heterogeneity of the syndrome, dementia in schizophrenic patients has been characterized by memory and executive dysfunction and by lowered frontotemporal CBF [63]. Hypoperfusion in the frontal, anterior cingulate and temporal cortex and in the caudate nucleus has been shown on mean single-photon emission computed tomography images of patients with FTD standardized in a common stereotactical space [64•], as already reported for PET data [65]. The neural substratum of the heterogeneity of FTD has not been much explored by functional imaging [66]. In the domain of behavioural neurology, dramatic changes of self, defined by essential changes in previous social values, have been related to prevalent non-dominant frontal hypoperfusion in FTD patients [67]. The density of degenerating astrocytes was inversely correlated to CBF in FTD, but relationships with other lesions were not reported [68].

Miscellaneous dementias
Although there is no consistent pattern of CBF changes that characterize Creutzfeldt–Jakob disease, a case study of the Heidenhain variant has illustrated the pathophysiological interest of functional imaging. MRI appeared normal in the patient, but his profound visual impairment was accompanied by a marked decrease of perfusion in the primary and associative visual cortices [69].

A study in a population of patients with the clinical phenotype of classical corticobasal degeneration confirmed a characteristic pattern of asymmetrical metabolic impairment in the perirolandic cortical areas and in the central grey nuclei [70•]. Not all patients were impaired when performing gestures on verbal command or to imitation. Those who performed more poorly than elderly volunteers had a significant decrease of metabo-

lism in the anterior cingulate cortex, suggesting that a global attentional factor was involved. When apraxia was defined as an inability to correct in a second trial erroneous gesture performance, only 38% of patients with corticobasal degeneration were shown to have a visuo-imitative upper limb apraxia related to metabolic impairment in a superior parietal-frontal network.

Conclusion

Functional imaging certainly provides useful information in the differential diagnosis of dementia. However, the sensitivity of current studies is not maximal and specificity is relatively poor. Technical progress in image analysis, such as whole-brain voxel-based analyses, multi-modal co-registration in brain atlases, or anatomically driven metabolic measurements, can provide more precise information. But refined pathophysiological research is of the greatest importance to explore further the influence of multiple clinical and biological variables on brain activity measurements. There is also an ongoing search for imaging *in vivo* more specific brain markers in different diseases.

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