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Functional Neuroimaging in Evaluating Dementia

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Functional neuroimaging using PET and SPECT has been extensively applied to the study of neurodegenerative diseases. The cerebral functions studied in these pathologies are mainly glucose metabolism and blood flow, but studies of specific targets such as dopaminergic, cholinergic, serotoninergic neurons, reactive glial cells and amyloidal deposits have been also applied.

These techniques are indeed unique in the evaluation of the multiple neurotransmitter/neuroreceptor systems of the human brain. In particular, neurotransmission and neuropharmachological studies by tomographic imaging techniques allow to measure the distribution and regional function of various molecular components that is at the basis of the neuronal communication like receptors, membrane carriers, neurotransmitters and enzymes. PET methods represent a unique tool for the study of the neurochemistry of the brain in normal and in neurology.

The diseases most frequently studied with PET include dementia and movement disorders, that are also representing the accepted clinical routine application for PET and SPECT in neurology.

Dementia and Alzheimer disease(AD) Bilateral hypometabolism in the parietal and temporal cortices detected by PET and [18F]FDG is typically seen in patients with AD and not in patients with other forms of dementia or in age-matched control subjects. This pattern is generally bilateral but it can be asymmetric, particularly in the early phase of disease. Extent and location of the hypometabolic areas correlate with clinical and neuropsychological symptoms. As metabolism and perfusion in AD are matched, such patterns are similar to those observed in perfusion studies by SPECT. However, PET shows higher sensitivity than SPECT and it is positive also in more than 80% of patients with very mild AD. In clinical practice, PET is used to differentiate AD from fronto-temporal dementia, vascular dementia, dementia with Lewi bodies and depression, particularly using perfusion, metabolism and dopamine transportes studies. Moreover, due to the very high sensitivity, PET can be used to predict the cognitive decline in patients without a clear-cut clinical diagnosis such as in Mild Cognitive Deficit (MCI). In the near future, the use of PET in dementia is expected to increase. This is due to various factors, such as the higher accuracy of PET reading through automatic analysis (i.e. SPM) and availability of large data-bases of both normal subjects and AD patients. In addition, although [18F]FDG plays a major role for this diagnosis, other tracers are becoming available, that could predict the disease in patients at risk (i.e. [11C]PK11195 and tracers for amyloidal deposits, AchE tracers).

Here, I will provide examples from the current literature and personal data on the role of functional neuroimaging in degenerative dementia and in the early diagnosis.

Alzheimer's disease

The diagnosis of dementia is based on the clinical evaluation, supplemented by neuropsychological findings (Corey-Bloom et al., 1995). However, functional imaging methods such as PET and SPECT are playing an increasing role in the investigation of Alzheimer's disease and other degenerative conditions (Messa et al 1994; Herholz et al., 2002). The most common form of dementia, Alzheimer's disease (AD) is characterised by several well known neuropathological features, which result in a loss of synaptic activity. This dysfunction is readily reflected in regional decreases of cerebral metabolic activity and blood flow that are not simply a consequence of tissue loss (Ibanez et al., 1998). The reduction of metabolism shows a characteristic topographic distribution, involving the associative cortex in the temporo-parietal areas of both hemispheres, with the angular gyrus usually being the center of the metabolic impairment (Herholz et al., 2002). Frontolateral association cortex is also frequently involved to a variable degree whereas, primary motor, somatosensory and visual cortical areas are relatively spared. This pattern corresponds in general to the clinical symptoms, with impairment of memory and associative thinking, including higher-order sensory processing and planning of action. Longitudinal studies have shown that the severity and extent of metabolic impairment in temporal and parietal cortex increases as dementia progresses, and frontal involvement becomes more prominent (Mielke et al., 1994). The decline of metabolism is in the order of 16 to 19% over 3 years in association cortices, which contrasts with an absence of significant decline in normal control subjects

The hypometabolism appears to be related to amyloid deposition, at least in areas which are still metabolically viable (Mega et al., 1999). The histochemical correlate of reduced glucose metabolism is a pronounced decline in cytochrome oxidase activity in AD relative to controls, whereas adjacent motor cortex does not show such differences (Valla et al., 2001).

A prospective study of FDG PET addressed the issue of progression rate of AD, which can vary considerably and is particularly difficult to predict in patients with mild cognitive impairment (Herholz et al., 1999). The cohort study included patients with possible or probable AD, 40% with possible, 60% with probable AD, most with presenile onset. Follow-up data were obtained from 73% of patients. In cross-sectional analysis at entry, impairment of glucose metabolism in temporo-parietal or frontal association areas measured with FDG PET was associated significantly with dementia severity, clinical classification, as possible vs. probable AD, presence of multiple cognitive deficits, and disease progression.

The European multicenter study for early dementia diagnosis, NEST-DD project, within the Vth European Program, 2000-2004, provided the largest known data base with more than 1.000 subjects with dementia and cognitive disturbances included (AD, FTD, LBD, CVD,MCI) and normal controls. A new diagnostic indicator of FDG PET scan abnormality, based on age-adjusted t statistics and an automated voxel-based procedure was validated in a large data set comprising 110 normal controls and 395 patients with probable Alzheimer's disease (AD) that were studied in eight participating centers (Herholz et al., 2002). In patients with probable AD the decline of FDG uptake in posterior cingulate, temporoparietal, and prefrontal association cortex was related to dementia severity. These effects were clearly distinct from age effects in controls, which leads to predominantly medial frontal metabolic decline suggesting that the disease process of AD is not related to normal aging. The method provided 93% sensitivity and specificity for distinction of mild to moderate probable AD from normals, and 84% sensitivity at 93% specificity for detection of very mild probable AD (defined by Mini MentalScore 24 or better).

Patients with late-onset AD may show less difference between typically affected and non-affected brain regions than usually seen in early-onset AD, which could potentially lead to reduced diagnostic accuracy with FDG PET (Mosconi et al., 2005). This could reflect the fact that at older age multifactor damage to the brain is likely to accumulate and, actually, also in neuropathological studies the proportion of unclassifiable dementia is highest in the oldest old. Thus, in very old multi-morbid patients, FDG PET is probably of little diagnostic use, which is in accord with general clinical wisdom.

Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) is an operational diagnostic entity used to describe a progressive cognitive disorder not yet evolved in dementia (Petersen et al., 2001). Clinically, mild cognitive impairment (MCI) is defined as impairment in one or more cognitive domains (typically memory, such as in amnesic MCI), or an overall mild decline across cognitive abilities that is greater than would be expected for an individual's age or education, but that is insufficient to interfere with social and occupational functioning, as is required for a dementia syndrome. According to the criteria used, MCI can imply a pre- Alzheimer disease (AD) state, or a more general predementia state. The outcome in any case of MCI is uncertain, however, and many subjects with MCI remain stable or even revert to a normal cognitive state (Luis et al., 2003). The current main issue for diagnosis of AD with PET is early diagnosis when patients present with a mild cognitive deficit (MCI), but before clinical dementia arises. Among community-dwelling elderly MCI has a prevalence highly related to diagnostic criteria, ranging from 2.8% to 23%. Several clinical studies reported the annual conversion rate to AD, which widely ranges from 15 to 40%. The identification of pre-clinical AD among MCI patients is thought to be mandatory for diagnosis and prognosis, and for possible timely treatment with drugs which might be effective.

Neuroimaging and genetic testing have aided in the identification of individuals at increased risk for dementia. The measurement of change in cognitive and functional status in MCI remains challenging, because it requires instruments that are more sensitive and specific than those considered adequate for research in dementia.

A [18F]FDG-PET study in a large multicenter sample of MCI subjects was aimed to verify whether specific glucose metabolic patterns characterize the diagnostic category of amnesic MCI and to evaluate whether this brain functional parameter may be useful in identifying preclinical AD cases (Eu NEST-DD project, Anchisi et al, 2005). At clinical follow-up, the MCI subjects who converted to AD were those that showed at the [18F]FDG-PET baseline study a significant bilateral hypometabolism in the inferior parietal, posterior cingulate, and hippocampal regions. In MCI non-converters, the dorsolateral frontal cortex was significantly hypometabolic when compared to controls. These data suggest that in subjects with MCI, prodromal AD can already be identified before appearance of the fully developed clinical dementia syndrome by [18F]FDG-PET study. In addition, they demonstrated that by neuropsychological testing alone one can identify subjects who are likely not to progress to dementia because their memory deficit is relatively mild, thus providing a high negative predictive value with regard to progression. However, prediction based on neuropsychological testing is less reliable for MCI patients with more severe memory impairment. In these patients [18F]FDG PET adds significant information by separating those who will progress within the next few months from those who will remain stable.

Data are accumulating that presence of the AD metabolic pattern in MCI predicts conversion to clinical dementia of Alzheimer type, and therefore indicates "incipient AD". The predictive power of posterior cingulate metabolic impairment was documented by Minoshima et al. already in 1997 (Minoshima et al. 1997). Other groups find a similar reduction of posterior cingulate and hippocampal lCMRglc in MCI and mild AD (Nestor et al. 2003). There are subjects with a high premorbid cognitive level, who can experience a substantial decline of cognitive function before reaching the lower normal limit of standard neuropsychological tests. A longitudinal study of cognitively normal subjects indicated that cognitive decline to MCI within 3-years follow-up is related to metabolic reductions in entorhinal cortex at entry, independent of Â4 status (Mosconi et al., in press). Progression to dementia usually is associated with additional metabolic impairment in temporoparietal and posterior cingulate cortex. Even at an asymptomatic stage, impairment of cortical glucose metabolism has been observed in preclinical stage in subjects at high risk for AD due to family history of AD and ApoE Â4 homozygosity [Reiman et al., 2004; Small et al., 2000). In middle-aged and elderly asymptomatic ApoE Â4-positive subjects, temporoparietal and posterior cingulate lCMRglc declines by about 2% per year.

Few studies so far also compared [18F]FDG PET with other biomarkers (Mosconi et al., 2004). PET prediction accuracy was best (94%) within the Â4+ group. In another report, MCI subjects were followed over 16 months, the positive and negative predictive values of [18F]FDG PET for progression to AD were 85% and 94%, respectively, whereas corresponding values for the ApoE4 genotype were 53% and 77% only (Drzezga et al., in press). By combination of the two indicators, predictive values increased to 100% in subgroups of patients with concurrent genetic and metabolic findings. When comparing phosphorylated tau protein in CSF with [18F]FDG PET in MCI, Fellgiebl and colleagues found similar findings with both tests (Fellgiebel et al., 2004).

Regional perfusion studies with SPECT in MCI provided comparable results. For example, Borroni and colleagues (2006) evaluated the potential role of 99mTc-ECD-SPECT and memory scores in predicting conversion to AD in MCI subjects. Thirty-one MCI subjects underwent a clinical and neuropsychological examination, and a regional cerebral blood flow SPECT scan at baseline. Subjects had been followed periodically through 2 years in order to monitor the progression of cognitive symptoms. Canonical variate analysis of principal components was able to separate all subjects who converted to AD from those who remained stable, the former being characterized by a specific hypometabolic pattern, involving the parietal and temporal lobes, precuneus, and posterior cingulate cortex. Canonical correlation analysis of combined baseline memory deficits and SPECT images identified pre-clinical AD with a sensitivity and specificity of 77.8%. The pattern of hypoperfusion with 99mTc-ECD SPECT and the severity of memory deficits thus predict the risk of progression to probable AD dementia in MCI subjects. Another study indicated that combining targeted neuropsychology testing, platelet amyloid precursor protein ratio with SPECT may reach a prediction accuracy even close to 90% (Borroni et al., 2005).

All these very promising results, however, still have to be confirmed in larger studies and current practice guidelines that rely on clinical judgement, neuropsychological testinand neuroimaging should be revised substantially. Greater consensus is needed to standardize definitions and research methodology for MCI, so as to make future studies more comparable and more useful for designing effective treatment strategies.

Frontotemporal Lobe Degeneration

According to widely accepted diagnostic criteria, three different clinical syndromes are delineated within Frontotemporal Lobe Degeneration (FTLD). The frontal variant of FTLD (fvFTLD) is characterized by prevalent behavioral symptoms, with early change in personality and difficulty in modulating behavior, often resulting in inappropriate responses and activities; "semantic dementia", associated with prevalent semantic/cognitive impairment and "progressive aphasia", characterized by early non-fluent aphasia (Neary et al., 1998).

FTLD is readily identified on FDG PET scans by a distinct frontal or frontotemporal metabolic impairment that typically is quite asymmetrically centered in frontolateral cortex and the anterior pole of the temporal lobe from where it may extend to other association areas (Grimmer et al., 2004). Apparently, medial frontal metabolic impairment can be found in nearly every case of fvFTLD (Salmon et al., 2003). In patients with the fvFTLD, behavioral abnormalities may vary from apathy with motor slowness, to disinhibition with agitation. Franceschi et al. (2005) showed that apathetic and disinhibited behavioral syndromes were associated with different functional metabolic patterns, the former showing a prevalent dorsolateral and frontal medial hypometabolism, the latter a selective hypometabolism in interconnected limbic structures, such as the cingulate cortex, hippocampus/amygdala, and nucleus accumbens. The selective lateral prefrontal and frontal medial involvement in the apathetic syndrome and the prevalent hypometabolism in limbic structures in the disinhibited patients correspond to the dorso-lateral and the orbito-frontal syndrome, classically described in experimental and clinical series of focal lesions. In addition, the in vivo measurements of 5-HT2A receptor density by PET and 11C MDL revealed a significant reduction in orbito-frontal, frontal medial and cingulate cortex, thus suggesting that the serotoninergic system is important for behavioral modulation, being tightly bound to the function of prefrontal cortex. The evidence that behavioral disorders in fv-FTLD are associated with serotoninergic system dysfunction provides information usefull for therapeutic approaches with SSRIs.

Semantic dementia, as a variant of FTD with similar histopathological features and tau protein deposition, is characterized by the progressive inability to comprehend common concepts, often associated with fluent aphasia, but there are less emotional disturbances and repetitive, compulsive behaviors than in the frontal variant (Hodges et al., 1992). Metabolic impairment appears to be more focused on the left temporal cortex, rather than the frontal lobes (Diehl et al., 2004).

Primary progressive (non-fluent) aphasia is associated with left frontal and temporal hypometabolism (Cappa et al., 1996) that may also affect additional brain areas to a lesser degree, suggesting that it is not a strictly focal impairment.

Automatic methods have been explored in order to distinguish between FTLD and AD. An analysis using multivariate methods such as principal components analysis (PCA) and partial least squares (PLS) regression achieved over 90% accuracy in a sample of 48 patients (Higdon et al., 2004). Preliminary results of a prospective study indicated that [18F]FDG PET may be more accurate than clinical judgment in predicting histopathological diagnosis (Foster et al., 2004).

Dementia with Lewy Bodies (DLB)

Clinical presentation in DLB is with progressive cognitive decline with particular deficits of visuospatial ability as well as frontal executive function accompanied by usually only mildly to moderately severe parkinsonism. Further accompanying features include spontaneous recurrent visual hallucinations and conspicuous fluctuations in alertness and cognitive performance (Verghese et al., 1999). The main differential diagnoses are with Alzheimer's disease (AD) and Parkinson's disease dementia (PDD). Ancillary investigations, particularly neuroimaging, can aid in differential diagnosis (Geser et al., 2005). Reduced [18F]FDG PET uptake is found to be very similar to AD, but also in primary and associative visual cortex, which are usually spared in AD. The impairment of glucose metabolism in visual cortex may well be the correlate of the impairment of visual processing and visual hallucinations (Imamura et al., 1999).

Another characteristic finding in DLB that is related to the parkinsonism, are the changes of dopaminergic activity and reduced dopamine transporters at presynaptic level (Lucignani et al., 2002).

Prion diseases

The typical regional pattern of metabolic impairment differs between major neurodegenerative diseases that may cause dementia. Thus, [18F]FDG PET also has the potential to improve early and differential diagnosis, and it may be used to monitor disease progression and treatment effects. Creutzfeldt-Jakob disease is clinically characterized by rapidly progressive dementia, often accompanied by insomnia, myoclonus and other extrapyramidal disorders. In all cases reported so far, cerebral glucose metabolism was severely reduced and in a multifocal pattern (Engler et al., 2003). The PET results were in accordance with histological findings and the patient's clinical condition.

Fatal Familial Insomnia (FFI) is an autosomal dominant prion disease clinically characterized by alterations of the sleep-wake cycle, dysautonomia and motor signs (Lugaresi et al., 1986). The histopathological hallmark of FFI is severe neuronal loss especially in the anterior-ventral and medial-dorsal nuclei of the thalamus associated with a variable involvement of the inferior olive, striatum and cerebellum, in addition, a mild to moderate spongiform degeneration is present in the cerebral cortex of subjects with the longest disease duration. The thalamic hypometabolism demonstrated by [18F] FDG PET is an early marker of FFI and suggests a relationship between the thalamic dysfunction and the associated long term memory and attention impairment (Perani et al., 1993).

Knowing how and when the degenerative process starts is important in neurodegenerative diseases. [18F] FDG and PET demonstrated glucose hypometabolism limited to the thalamus and cingulate cortex of homozygous patients in the early phase of the disease, while the involvement of other brain regions depends on disease duration (Cortelli et al., 1997) Comparison between neuropathological and [18F] FDG PET findings showed that although hypometabolic areas and areas with neuronal loss co-distributed extensively, the hypometabolism was actually more widespread than neuronal loss and significantly correlated with the presence of protease resistant prion protein.

A study of pre-symptomatic subjects, carriers of the FFI mutation, showed the cerebral metabolism, clinical, neuropsychological examinations and polysomnography within the normal ranges before disease onset. Selective hypometabolism was detected in the thalamus while spectral-EEG analysis disclosed an impaired thalamic sleep spindle formation in one case that was evaluated very close to the start of the disease (a year before) (Cortelli et al. 2005). All these data indicate that the neurodegenerative process associated with FFI begins in the thalamus and spreads very rapidly.