Functional and Structural Neuroimaging in Frontotemporal Degeneration

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The evolution of human brain mapping depended on much diverse expertise from physics and biology through mathematics and statistics, to neurology, neuropsychiatry, and neuropsychology. The realization of this dependence on the expertise of many individuals from many disciplines represents the basis of an enterprise focussed on the understanding the functional (and structural) architecture of the human brain and the methodological developments that have supported their achievement.

Structural MRI provides an in-depth evaluation of the central nervous system anatomy. The enhanced anatomical detail allowed by recent MRI scanners has outlined patterns relatively specific of different neurological diseases. A number of tools of varying technological complexity have been developed to rate the structural changes taking place in the brains of patients with cognitive impairment, ranging from simple subjective rating scales to sophisticated computerized algorithms. On the other hand, functional magnetic resonance (fMRI) is a tool that by exploiting the principles of traditional MRI, allows mapping and studying the function of brain, i.e. “looking at the brain while it works”. It is a non-invasive technique, based on the measurement of MRI signal changes associated with alterations in local blood oxygenation levels (for a critical discussion, see Logothetis and Pfeuffer, 2004).

The functional imaging methods of positron emission tomography (PET), single photon emission tomography (SPECT) allow the in vivo measurement of several parameters of brain function. These include oxygenation levels, perfusion, metabolism, and also neurotransmission. Noteworthy, radiolabelled tracers for receptor occupancy or enzymatic activities represent a unique tool for the in vivo measurement of specific neurotransmission systems. Direct measures of therapeutic targets by PET may provide unique information on drug action in vivo, allowing studies of the effects in selected patient populations (Halldin et al., 2001). The instrumentations and reconstruction algorithms are different for PET and SPECT because of the properties of positron and gamma emissions. The availability of positron emitting radioisotopes, such as carbon, oxygen and fluorine, which can fit into biological relevant molecules without altering their biological properties, gives PET substantial advantages. Such tracers or radiopharmaceuticals closely share the properties of normally occurring brain substances. On the other hand SPECT, with gamma emitting elements like iodine or technetium, is more widely available. These methods are sensitive to modifications taking place at the cellular level, which are not necessarily reflected in morphological abnormalities. They are thus providing a different type of information, in comparison with structural imaging such as MRI.

PET and SPECT functional data have been extensively applied in neurological research. These methods offer the opportunity to improve diagnosis by providing regional functional measurements, which can be used to substantiate a clinical judgement. Technical aspects, in particular high-resolution scanners and advanced methods of data analysis, are crucial factors to take into account in the evaluation of dysfunctional brain.
The most widely used tracer for brain studies with PET is F-2-fluoro-2-deoxy-D-glucose\(^{(18)}\) (F-FDG\(^{(18)}\)) (Reivich et al., 1985). PET can provide steady-state measurements of brain functional parameters, such as oxygen consumption by inhaling O\(_2\)\(^{(15)}\) or glucose metabolism and blood flow by i.v. injection of F-FDG\(^{(18)}\) and radioactive labelled water (H\(_2\)O\(^{(15)}\)), respectively. H\(_2\)O\(^{(15)}\) with PET is also used in functional activation studies to evaluate regional cerebral blood flow changes associated with cognitive performances, either in normal subjects or in patients.

In addition, PET radiolabelled tracers for receptor occupancy or enzymatic activities represent a unique tool for measurements of specific neurotransmission systems. Research for receptors alterations, in particular dopaminergic and serotonergic ones, as well as for enzymatic activity and receptors occupancy by drugs (i.e. neuroleptics) have been carried out. The general aim was to find a suitable tracer for assessing, in vivo, the pre- and post-synaptic components of a specific neurotransmitter system and for evaluating the effects of therapy. Imaging of amyloid in Alzheimer's disease and other dementias has been recently reported (Nordberg A [2004] PET Lancet Neurol 3:519-27).

Quantitative measurements of cerebral blood flow, oxygen consumption, glucose metabolism, semiquantitative assessment based on ratios of different regions of interest (ROIs) (Herholz et al., 1999), together with different statistical approaches and neural network classification have been proposed for an improvement in the diagnostic accuracy of functional neuroimaging in neurodegenerative and dementia conditions (Azari et al., 1993; Kippenhan et al., 1992; Minoshima et al., 1995; Herholz et al. 2002; Zuendorf et al., 2003). Statistical Parametric Mapping (SPM) has been largely applied to PET and SPECT steady-state resting studies with the aim to provide automated voxel-based measurements of brain functional parameter changes in disease conditions. In particular, SPM comparisons with samples of matched normal subjects have significantly improved the study of patient groups and single cases (Signorini et al., 1999; Mosconi et al., 2005). The resulting SPM foci in PET and SPECT perfusion or metabolism studies are characterized in terms of spatial extent and peak height according to a Gaussian distribution and usually refer to significant brain regional hypometabolism or hypoperfusion.

Functional neuroimaging studies
Functional neuroimaging has radically influenced neuroscience research in the last decade. In the case of neuropsychology and cognitive neuroscience, it has provided important insights into the brain organization of cognitive functions, such as memory and language, and in the in vivo assessment of the functional modifications associated to normal aging and dementia. New insights and conceptual breakthroughs have led to improved detection and evaluation of dementia, and there are many more new approaches now in development. There is every reason to expect these advances will continue and be translated into clinical practice. While the contribution of CT and structural MRI to clinical diagnosis remains "ancillary" in the case of the most common cognitive disorders, functional imaging with PET, SPECT and fMRI are now considered important clinical and research tools in neurology.

Both PET and SPECT providing images and data that represent the distribution in the brain of a specific biochemical process can detect modifications that occur at the cellular level and do not reflect gross focal structural changes. For example, in Alzheimer's disease, several well known neuropathological features result in a loss of synaptic activity. This dysfunction is readily reflected in regional decreases of cerebral metabolic activity and blood flow. The metabolic reductions measured with both oxygen and glucose
consumption, which is coupled to a reduction in regional perfusion, is not simply a consequence of tissue loss (Ibanez et al., 1998).

The diagnosis of dementia is based on the clinical evaluation, supplemented by neuropsychological findings (Corey-Bloom et al., 1995). However, PET and SPET are playing an increasing role in the investigation of dementia.

In the Report of the Quality Standards Subcommitee of the American Academy of Neurology: Practice parameter: Diagnosis of dementia (an evidence-based review (Knopman et al. 2001), the authors state that, “Biomarkers for AD and other dementias are critically needed, and the validation of these markers will require cross-sectional studies and longitudinal, population-based studies with diagnosis confirmation at autopsy. If a goal of therapy for patients with dementia is to intervene before the disease has diminished cognitive function, imaging techniques or biomarkers must be capable of detecting AD pathology in asymptomatic individuals. The same consideration applies to Lewy Body Dementia and Frontotemporal Degeneration pathology”. “FDG-PET appears superior to MRI measures of hippocampal atrophy because changes in cerebral glucose metabolism antedate the onset of memory decline whereas the MRI hippocampal changes do not”. “SPECT and PET may be helpful in distinguishing FTD from AD. Many patients with FTD show hypoperfusion of anterior cerebral cortex with relative sparing of posterior cortex with SPECT and PET”. However we must consider that: “In these Class II studies, the highly selected participant pool makes it difficult to generalize on the reported specificities and sensitivities”.

In AD, the reduction of metabolism has a characteristic topographic distribution, involving the associative cortex in the temporo-parietal areas of both hemispheres, with the angular gyrus usually being the centre of the metabolic impairment (Herholz et al., 2002) (see Figure 1, A). Frontolateral association cortex is also frequently involved to a variable degree. Primary motor, somatosensory and visual cortical areas are relatively spared. This pattern corresponds in general to the clinical symptoms, with impairment of memory and high-order cognition, including complex perceptual processing and planning of action, but with relative preservation of primary motor and sensory function. These changes differ from those of normal aging, which leads to predominantly medial frontal metabolic decline and may cause some apparent dorsal parietal and frontotemporal (perisylvian) metabolic reduction due to partial volume effects caused by atrophy (Zuendorf et al., 2003).^(8)

Medial temporal hypometabolism is often seen in AD patients with severe memory impairment (Perani et al., 1993), but also in MCI and other amnestic disorders (Nestor et al., 2003). Depending on subject selection, it may also have prognostic impact. Data are accumulating that the presence of the AD metabolic pattern in MCI predicts conversion to clinical dementia of Alzheimer type, and therefore indicates “incipient AD”. Non-demented patients with mild cognitive impairment may indeed show metabolic impairment of association cortices, which is characteristic of AD. MCI patient groups when compared to normal controls typically show significantly impaired metabolism (Minoshima et al., 1997). Anchisi et al. (2005) have demonstrated that neuropsychological testing alone 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 FDG PET adds significant information by separating those who will progress within the next twelve months from those who will remain stable (see Figure 2).
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. According to widely accepted diagnostic criteria, three different clinical syndromes are delineated (Neary et al. 1998): the frontal variant of FTD 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” is associated with prevalent semantic/cognitive impairment and “progressive aphasia” is characterized by early non-fluent aphasia.

In principle, FTD is identified easily on FDG PET scans by a distinct frontal or frontotemporal metabolic impairment (Grimmer et al. 2004). Apparently, mesial frontal metabolic impairment is most common and can be found in nearly every case of FTD (Salmon et al. 2003). Very frequently, there is also prominent focal atrophy of the frontal and temporal lobe in one hemisphere, corresponding to a metabolic deficit that might be also very asymmetric, or centered in the anterior pole of the temporal lobe and extending to other association areas. Some patients with FTD can also manifest sociopathic behaviour. Sociopathy in FTD results from a combination of diminished emotional concern for the consequences of their acts and disinhibition, which might follows right frontotemporal dysfunction, as shown by neuroimaging (Mendez et al 2005).

In patients with the frontal variant of frontotemporal degeneration, behavioral abnormalities may vary from apathy with motor slowness, to disinhibition with agitation. Apathetic and disinhibited Behavioral syndromes are associated with different functional metabolic patterns (Franceschi et al., 2005). This study showed that apathetic and disinhibited Behavioural syndromes are 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 (see Figure 3). The in vivo measurements of 5-HT2A receptor density revealed a significant reduction in orbito-frontal, frontal medial and cingulate cortex, thus suggesting that the serotonergic system, tightly bound to the function of prefrontal cortex, is important for behavioral modulation. 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 (Stuss and Benson DS, 1986).

Semantic dementia is usually regarded as a variant of FTD with similar histopathological features and tau protein deposition (Kertesz and Munoz 1998). Its main clinical symptoms are the progressive inability to comprehend common concepts, often associated with fluent aphasia, but there are less emotional disturbance and repetitive, compulsive behaviours than in FTD (Hodges et al. 1992). Metabolic impairment is similar to FTD (Ibach et al. 2004), but appears to be more focused on the left temporal rather than the frontal lobes (Diehl et al. 2004).

Primary progressive (non-fluent) aphasia is another related syndrome associated with left frontal and temporal hypometabolism (Kempler et al. 1990; Cappa et al. 1996; Nagy et al. 1999) that may also affect additional brain areas to a lesser degree, suggesting that it is not a strictly focal impairment. A similar condition also seems to exist for the right hemisphere, clinically consisting of progressive prosopagnosia (Tyrrell et al. 1990).
FTD can be differentiated from corticobasal degeneration with predominant parietal metabolic reduction (Hosaka et al. 2002). Frontal metabolic impairment is also part of many other diseases and conditions, including progressive supranuclear palsy (in combination with midbrain impairment) (Karbe et al. 1992), and cocaine abuse (Volkow et al. 1992). Moderate frontal dysfunction and hypometabolism is also observed in many psychiatric disorders.

Automatic methods have been explored for distinction between FTD 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 FDG PET may be more accurate than clinical judgment in predicting histopathological diagnosis (Foster et al. 2004). This discrimination is of primary interest in dementia patients with presenile onset, whereas there may be substantial overlap of the FTD pattern with frontotemporal impairment and the AD pattern with predominant temporoparietal impairment especially in senile dementia patients (Herholz et al. 2004).

Activation studies

Neurodegenerative disorders affect the normal activation pattern in a number of ways. As predictable, functional activation in dementia patients is decreased in the areas most affected by the pathology. Some studies of verb processing, verbal and non-verbal learning, and working memory in AD have found a reduced activation of the areas which are activated by healthy persons to carry out the same task (Grossman et al., 2003). Interestingly, medial temporal activation patterns during a memory task have been found to be as much reduced in MCI patients as in AD patients, possibly suggesting a very early functional damage in the medial temporal lobe (Machulda et al., 2003). There is evidence that reduced activation of normally active areas is accompanied by cortical reorganization in AD and frontotemporal dementia (Rombouts et al., 2003). On the other hand, the recruitment of wider networks can also be evident in dementia. Activations larger than in normal controls have been found in the medial temporal lobe and other cortical areas during verbal and non-verbal learning, working memory, semantic, and visuospatial tasks (Sperling et al., 2003; Kato et al., 2001; Prvulovic et al., 2002). It is conceivable that compensatory mechanisms may be functional in the relatively early stages of the disease, while in later stages activation decreases (Dickerson et al., 2004).

Another interesting finding obtained with fMRI and PET in the study of dementia disturbances concerns the involvement of the default networks (Lustig et al., 2003). This is a specific set of regions, which consistently shows deactivation during a wide range of tasks with different stimulus modalities in normal individuals (Gusnard et al., 2001; Celone et al. 2006). These commonly deactivated regions include large sections of the lateral parietal cortex, the medial parietal cortex (including posterior cingulate and precuneus), and the medial frontal cortex. The function of this default network has been attributed to monitoring the environment, the subject’s internal state and emotions, and various forms of undirected thought. The demonstrated impairment in the function of this default network in AD and other dementias may explain disorders of insight and awareness of own cognitive deficits and of the surrounding environment, and may contribute to the development of agitation following minor environmental stimulation, and to the context-dependent performance in activities of daily living.

Structural imaging studies
A number of tools of varying technological intensity have been developed to rate the structural changes taking place in the brains of patients with cognitive impairment, ranging from simple subjective rating scales to sophisticated computerized algorithms. Structural changes provide markers to track the biological progression of disease.

Assessment of Regional atrophy using visual rating scales. MR can directly visualise the hippocampus and other critical medial temporal structure (MTL) in substantial cytoarchitectonic detail. Scheltens and colleagues (1992) have developed a subjective visual rating scale to assess MTL atrophy on plain MR films (the subjective MTL atrophy score). The score is assigned based on visual rating of the width of the choroid fissure, width of the temporal horn, and height of the hippocampal formation.

Volumetric measures of Regional atrophy. A T1-weighted 3D-technique is employed for MR image acquisition (MP-RAGE or SPGR). Recent developments in computer science may help detect early sensitive and specific disease signatures. They are referred to as computational neuroanatomy (Ashburner et al. 2003). These approaches are automated, avoiding error-prone and labour-intensive manual measurements. Such algorithms can offer unprecedented precision as some can detect brain volume differences of 0.5% between images from the same subject (Fox et al 1997).

The individual algorithms can be categorized into two broad classes: algorithms devised to detect group differences at one point in time and algorithms devised to detect prospective changes over time. The first category may be useful to define disease-specific signatures. The second can be applied to one or more individuals to track natural disease progression or as modified by treatment. Voxel-based morphometry (Ashburner & Friston's method, 2000) requires that registered grey matter images are smoothed with an 8-12 mm filter. This leads to normally distributed data and allows the use of statistical parametric tools. The statistical approach of the A&F method (SPM) is based on the general linear model, and identifies regions of tissue with increased or decreased density or concentration that are significantly related to the effects under study. Ideally, the threshold for significance should be set at p<0.05 corrected for multiple comparisons, but when there is a prior hypothesis of the expected effect a more liberal threshold of p<0.001 uncorrected can be used. However, like every statistical test, the larger the effect size and group size, the higher the sensitivity of the method for identifying differences. A protocol to carry out voxel-based morphometry based on SPM in patients with neurodegenerative disorders has been developed (“optimized VBM”) requiring to register images onto a “customized template”, i.e. an average image of the cases under study (Good et al 2001).

With voxel-based morphometry, hippocampal atrophy has been visualized in Alzheimer's disease as well as volume in the posterior cingulate gyrus and adjacent precuneus, and the temporoparietal association cortex (Frisoni et al. 2002).

In FTD several structural MRI studies have been published, including the frontal variant, progressive aphasia, and semantic dementia. Visual assessment of traditional structural imaging allows to appreciate mild to moderate enlargement of cortical sulci in the anterior frontal and temporal regions. This can be substantiated with a digital analysis of frontal lobar grey matter volumes, showing marked tissue loss on both sides, more marked to the
left. Recently Miller and coworkers have suggested a different pattern of brain atrophy to distinguish the frontotemporal lobar degeneration variants (frontal dementia, progressive aphasia and semantic dementia) based on voxel-based morphometry analysis. Frontal and semantic dementias seemed to be mainly characterized by common regions of atrophy located in the ventromedial frontal cortex, the posterior orbital frontal regions bilaterally, the insula, and the left anterior cingulate cortex. Specific regions of atrophy in frontal but not semantic dementia affected the right dorsolateral frontal cortex and the left premotor cortex, while semantic dementia patients showed atrophy in the anterior temporal cortex and the amygdala/anterior hippocampal region bilaterally (Rosen et al 2002). In the progressive aphasia group voxel-based morphometry showed a predominance of frontal atrophy, and reduced gray matter in the left superior temporal and inferior parietal regions (Rosen et al. 2002).

In dementias, the detection of gray matter loss has allowed to better understand the biological basis of the clinical signs and symptoms, monitor disease progression, and assess the effect of the disease modifying drugs presently under study. However, gray matter loss on T1-weighted images has limited ability to capture the whole range of morphostructural changes associated with the neurodegeneration. First, tissue shrinkage on T1-weighted images cannot discriminate neuronal from glial and axonal loss as well as neuronal loss from age-associated shrinkage of healthy neurons. Second, on T1-weighted images cannot appreciate the white matter damage that might arise in AD from neurofilament tau pathology.

Techniques to probe into the finer structure of the brain have recently been developed such as diffusion tensor and magnetization transfer imaging that and are providing increasingly precious information to elucidate the pathophysiology of dementia conditions.

Diffusion imaging is based on the physical properties of moving water protons. Motion is higher where protons have no constraints (i.g. in the CSF) and lower where protons are confined within organized tissues such as the intracellular matrix or the axonal cytoplasm. MR imaging can detect and quantify such motion through the apparent diffusion coefficient (ADC). In the white matter, not only the ADC is lower than in the CSF, but proton motion is highly oriented in the direction of the axonal fibre (i.e. anisotropic), and the direction of the motion can be quantified through the fractional anisotropy index (FA). Axonal loss and demyelination due to Wallerian degeneration are picked up as increased ADC and decreased FA. Gliosis of the white matter, by disrupting the normal axonal structure, also gives rise to decreased FA, but the ADC is normal or decreased due to the boundaries to proton motion represented by glial cell membranes. There is ground to believe that microstructural pathology exceeding the macrostructural changes that can be appreciated through T1-weighted images is present in dementia conditions and should be correlated with cognitive performance.

Recently Borroni and coworkers (2006) reported a diffusion tensor imaging study in frontal and temporal variants of frontotemporal dementia, showing that fvFTD and tvFTD syndromes are not only associated with separate patterns of grey matter atrophy, as already described, but also with an extensive and different patterns of white matter reduction. Noteworthy, these findings that were evident in the early phase of disease, contribute to the different clinical syndromes in FTD and could be responsible of the further
progression of atrophy in temporal regions and in frontal regions in the later disease stages.

In another diffusion tensor imaging and voxel-based morphometry study in early progressive supranuclear palsy (PSP), Padovani and coworkers (2006) reported a comprehensive characterisation of grey and white matter changes. In PSP patients compared to controls, VBM analysis showed significant clusters of reduced grey matter in premotor cortex, frontal operculum, anterior insula, hippocampus and parahippocampal gyrus, bilaterally. With regard to subcortical brain regions, the pulvinar, dorsomedial and anterior nuclei of the thalamus, and superior and inferior culliculum were affected, bilaterally. White matter was also damaged since the authors found a bilateral decrease in fractional anisotropy in several fiber tracts such as the superior longitudinal fasciculus, anterior part of corpus callosum, arcuate fascicolus, posterior thalamic radiations, and internal capsule, likely involving corticobulbar tracts. These data provide evidence for both grey and white matter degeneration in PSP, since the early disease stage. The specific structural changes suggest that atrophy of cortical and subcortical structures and neurodegeneration of specific fiber tracts contribute to neurological deficits in PSP.

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Figure 1. The figure shows the metabolism pattern found in a probable Alzheimer’s Disease (AD) patient. Below the corresponding statistical parametric maps, demonstrating the significant temporoparietal and posterior cingulate cortex involvement.
Figure 2. SPM maps showing the pattern of reduced FDG uptake in subjects with amnesic mild cognitive impairment (aMCI), superimposed on a standardized magnetic resonance imaging brain template. The aMCI subjects subsequently converted to AD, (see text for details). (Modified from Anchisi et al., 2005)
Figure 3. Hypometabolism in two FTD patient groups compared with normal controls. Significant hypometabolic areas are shown in SPM maps in blue. Bilateral hypometabolism in the frontal medial and dorsolateral frontal cortex in apathetic patients (A), and bilateral hypometabolism in the medial temporal cortex (hippocampus/amygdala structures), thalamus, and ventral striatum in disinhibited patients (B), see text for details. (Modified from Franceschi et al., 2005).