Chapter 4

Functional Imaging Studies of Human Cognition Using Positron Emission Tomography

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1. Introduction

In past times behavioural neurologists have shown how discrete brain lesions provoked different types of cognitive disorders such as language, praxic, gnostic, spatial or memory domain.

They interpreted these anatomo-clinical associations conjecturing that the normal brain function (impaired by brain damage) was localized within the lesioned region (lesional hypothesis) and had been impaired from brain damage (Marshall & Fink, 2003). They also hypothesized that cognitive impairments could arise from lesions that spared the functional centers but disconnected them from other centers (disconnectional hypothesis). According this argument "basic psychological functions" are localized in a punctate fashion and complex psychological functions are constituted from many such basic functions joined together in distributed circuits. It follows that the symptoms may have arisen from a reconfiguration of the entire circuit in response to cerebral damage.

During the late 19th century, the advent of structural brain imaging, first the computed tomography (CT) and later the magnetic resonance imaging (MRI), gave the possibility to study anatomical localization of the cognitive deficits that were manifest after brain injury. Since then neuroimaging studies have helped medical doctors in clinical practice to identify cerebral damage caused by spaced-occupying lesions, strokes or degenerative processes.

During the 20th century other instrumental techniques such as single photon computed tomography (SPECT), positron emission tomography (PET), functional magnetic resonance imaging (f-MRI) or magnetoencephalography (MEG) started to be used for evaluation of cognitive activation not only in patients with cerebral lesions, but also in living normal brains and localize mental faculties in different regions of the brain. Further, functional techniques

and both can be thought as originating from imaging and functional technologies: neuroelectrical (MEG and electroencephalography), and hemodynamic (PET, SPECT, fMRI, optical).

These advances in medical technology have led to study structural brain imaging early in patients, explore relationship between structure and function or hypothesize brain cognitive functioning also in normal subjects.

For example Positron Emission Tomography has been used in healthy volunteers to study brain activation during specific goal-directed behaviours (Raichle et al., 2001) such as arithmetical computation (Dehaene et al., 1996), memory tasks, visuoconstructive abilities or specific language tasks.

Since then various neuroimaging technologies have also been applied to identify and measure a range of biological processes that occur along neurological disease associated with cognitive impairment as in neurodegenerative conditions.

In this chapter we will review some applications of PET in understanding the cognitive functions in normal subjects, in patients with cognitive deficits during normal aging or following vascular or degenerative damage.

We will also discuss how PET scanning of glucose metabolism, could be used to differentiate Alzheimer's disease from other forms of dementia such as Vascular dementia, Lewy boby dementia or Frontotemporal dementia, which helps to guide clinicians in symptomatic treatment strategies.

We will also expose how PET exam could be useful to identify potential risk of developing dementia in persons with mild cognitive impairment (MCI) resulting useful in predicting further cognitive decline.

2. Pet study of human cognitive functions

The human brain is an extremely complex organ. The energy required for this complex structure is almost exclusively covered by oxidative metabolism of glucose (Clarke and Sokoloff, 1999). Since PET is a technology based on study of glucose metabolism has great impact on research in study of human cerebral activity.

PET has been adopted in normal subject to study cognitive functions in a particular case of functional connectivity that is the so-called default mode or "**resting state connectivity**", successively extended with fMRI studies. It quantified the spatial correlation of brain activity in the absence of a specific cognitive task. Typically, this is performed by having the subject fixate a visual cue in the absence of a cognitive task (Raichle and Mintun, 2006). The baseline activity of the resting state has spatial correlations that involve the same prefrontal, medial temporal lobe and parietal lobe systems involved in some memory tasks. It could be hypothesized that memory system, especially the declarative memory system, might be activated in the resting state (Vincent et al., 2006).

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"**Functional effective connectivity**" consists in the measure of correlation of connectivity among brain regions or better the influence of brain nodes on each other. PET studies have been applied to quantify causal interactions between brain regions (McIntosh et al., 1994; Horwitz et al., 2005). This measure estimates the strength of connectivity between cerebral areas and statistically infers a causal effect of connectivity. For example a PET study of human working memory for faces has suggested that the network for underlying activity changes as the task requirements change (McIntosh et al., 1996). Models of connectivity have been explored with PET in the study dynamic neural networks underlying **language processing** using specific tasks such as word generation (Warburton et al., 1996) or reading (Price and Friston, 1997). PET studies have also been applied to demonstrate **hemispheric dominance of language**. The laterality of language is usually achieved by activating language areas and comparing the relative strength of activation between the right and the left hemispheres (Stippich et al., 2003; Lohmann et al., 2004). Studies on multiple groups have reported a strong correlation with PET or fMRI compared with intraoperative mapping techniques and the results of classical Wada test (Roux et al., 2003; Woermann et al., 2003; Atlas et al., 1996).

PET or task-activated fMRI can locate, with a high spatial resolution, both receptive and productive language areas. One practical application of PET for language localization consists in the presurgical evaluation of epileptic or brain tumor patients. This PET neurosurgical application makes possible a precise **localization of essential language** areas in individual patient rather then participating areas. Essential language areas are ones that when removed result in a language deficit; while participating areas are ones that are activated during language paradigms, but do not result in a post-operative language deficit after surgical resection, because these are areas of redundant processing or because other areas learn to take over the same function. Currently, there is no way to distinguish essential from participating areas with non-invasive imaging and improving the detection of essential areas is a major goal of clinical functional imaging. Language areas found to be lateralized in left hemisphere with a variety of language tasks are essentials four: prefrontal cortex (inferior frontal gyrus, superior frontal gyrus and the anterior cingulate), angular gyrus (excluding the supramarginal gyrus), ventrolateral temporal lobe (superior temporal, middle temporal, inferior temporal and fusiform gyri) and retrosplenial cortex. This means that studies on patients with lesion of anterior lateral prefrontal cortex (known as Broca's area) overemphasize the role of these cerebral areas in onset of language disorder (Broca's aphasia) as confirmed by patients with isolated lesions of "Broca's areas" having only apraxis deficits of articulation rather then aphasia. On the other hands a real and permanent Broca's aphasia requires more extensive cerebral lesions involving anterior frontal gyrus, middle frontal gyrus and peri-central gyri. These functional studies suggest that a wide area of left frontal lobe participate in language processing outside the classical confines of Broca's area, as confirmed by clinical cases of people with large frontal stroke and receptive aphasia which later may evolve into a so-called expressive aphasia. Task activated fMRI provide evidence of cortical reorganization of language areas, do to tumoral lesions or after a surgical resection.

PET, fMRI, MEG and EEG have been used in numerous studies to **investigate the cerebral sites of declarative memory** (for a review see Gazzaniga, 2004) that consists in explicit memory

for facts and events. Declarative memory has often been studied using the so-called "subsequent memory effect" that is brain activity during encoding of items that are subsequently forgotten. On the other way the retrieval of declarative memory has been studied with the "old/new effect" that consists is the comparison of brain activity recorded during correctly recognized old items versus correctly identified new items. Memory for events involves processing in the medial temporal lobes (Milner et al., 1998) and in the prefrontal cortex. Frontal lobe activity is related to both encoding and retrieval of memory events for both long-term and short-term memory.

Functional memory localization has been applied in presurgical evaluation of epileptic (Detre, 2004) or brain tumor patients and predicts post-surgical memory deficits following temporal lobectomy (Rabin et al., 2004).

Episodic (conscious memory of events) and semantic memory (memory concerned with ideas, meanings, and concepts which are not related to personal experiences) might recruit different brain areas (Tulving and Markowitsch, 1998). In fact, amnesic patients with specific episodic memory impairment (intact priming, category learning, learning of artificial grammars) have temporal lobe damage, while patients with semantic deficits show dysfunction in prefrontal cortex. In particular left prefrontal cortex increases activity during semantic encoding while right prefrontal cortex increases activity during retrieval task. Recent neuroimaging studies implicate also the parietal lobe in episodic memory (Wagner et al., 2005).

Functional studies on **working memory** (memory that makes possible the temporary retention of information) suggest an overlapping of brain mechanism with attention (Jha, 2002) and associative learning in prefrontal cortex (Fuster et al., 2000). This association has also been demonstrated on behavioural studies (Sheth and Shimojo, 2003). Many of the changes in cerebral activation studied with PET during working memory tests are task specific. PET studies executed during Wisconsin Card sorting Test, which depends heavily on working memory, has demonstrated reduction of activation with age in the dorsolateral prefrontal cortex. On the other hand PET executed during Raven's Progressive Matrices, which also has a working memory component, but depends more on visuospatial processing, has demonstrated reduction of activation with age in in portions of the inferolateral temporal cortex more involved in visuo-spatial processing (Esposito ed al., 1999).

Recent PET studies of brain activation during tasks of **visuospatial processing** have reported that age-related cognitive changes are accompanied by altered cerebral activation in temporo-occipital and extrastriate regions (Grady et al., 1994). Increased prefrontal activation was found both during face and location processing (Grady et al., 1994) and during memory recall (Cabeza et al., 1997a), while reduced prefrontal activation was reported during memory encoding (Grady et al., 1995; Cabeza et al., 1997b).

Temporal resolution of hemodynamic techniques such as PET or fMRI can be improved combining the activation maps from these imaging modalities with high-temporal resolution information obtained by other sources such as EEG/MEG or information on tissue oxygenation obtained from diffusion optical tomography. Recent methods of statistical combination of

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these techniques may provide benefits especially to neurosurgeon (Fischl et al., 2001; Dale et al., 2000).

3. Pet study of cognitive functions in cerebrovascular disease

Cerebrovascular disease affects prominently elderly persons through alterations in brain structure and metabolism that produce cognitive decline. Cognitive deficit revealed in cerebrovascular disease regards especially the domains of executive functions (Starkstein et al., 1996), attention, language (Powell et al., 1998) and less prominent memory deficits (Villardita, 1993; Tierney et al., 2001). Vascular cognitive disorders may be caused by multiple neuropathological substrates, including multi-infarct encephalopathy, single infarcts in strategic areas, lacunas and lacunar states, Biswanger's leukoencephalopathy and leukoarariosis, hippocampal sclerosis, watershed infarcts and neuronal loss/atrophy due to diffuse hypoperfusion (Ferrer, 2010). These substrates can be a consequence of different vascular diseases including atherosclerosis, small vessel disease, hypertensive angiopathy, inflammatory disease of blood vessels, inherited vascular disorders such as amyloid angiopathy and CADASIL (central autonomic dominant arteriopathy with subcortical infarcts and leukoencephalopathy) or the consequence of single or multiple cerebral hemorrhages.

Despite the considerable degree of accuracy in diagnosing Alzheimer's disease (AD), the clinical differentiation with Vascular cognitive impairment (cognitive impairment in absence of dementia) and mixed dementia (Alzheimer's disease plus cerebrovascular disease) remains a matter of controversial opinions and one of the most challenging diagnostic issues (Misciagna et al., 2005). Dementia in older adults is frequently caused by the combined conditions of Alzheimer disease and cerebrovascular disease (mixed disease) since frequently occur together in overlap presentations (such as vascular lesions in Alzheimer Disease or cerebral atrophic condition in Cerebrovascular Disease). Nevertheless, there is evidence that they contribute separately to the development of cognitive impairment and dementia (Snowdon et al., 1997; Bennett, 2001).

The differential diagnosis between Alzheimer disease and dementia in cerebrovascular disease known as Vascular Dementia (VaD) is based on presence of vascular risk factors (such as hypertension, atrial fibrillation, obstructive arteriopathy, previous strokes or transitory ischemic attacks), clinical features (such as acute onset, stepwise progression, emotional lability) (Hachinski et al., 1974) and is supported by results of neuropsychological tests and neuroimaging. Whereas computed tomography or magnetic resonance are able to detect morphological lesions related to vascular disease, these modalities cannot determine functional impairment. PET allows imaging of the localized and/or diffuse metabolic disturbances responsible for cognitive impairment and dementia and is effective in differentiating vascular from degenerative dementia (Heiss and Zimmermann-Meinzingen, 2012). In particular PET can differentiate areas of focal cortical and subcortical hypometabolism that differ from the typical metabolic pattern seen in AD characterized by marked hypometabolism in association

areas (Benson et al., 1983). In patients with severe Vascular Dementia, PET reveals a significative reduction of metabolism in widespread cerebral regions as middle frontal cortex, temporoparietal cortex, basal ganglia, cerebellum and brainstem (Mielke et al., 1992). Hypometabolism is more marked than AD in subcortical areas and primary sensorimotor cortex, while it is less affected in the association areas.

The metabolic ratio, which reflects the pattern of metabolic pathology in AD, is generally higher in VaD than in AD. Both in VaD and AD there is a parallel decline of the metabolic ratio with increasing dementia severity suggesting equal ability to discriminate VaD and AD in early and advanced stages of the disease. The volume of functional loss detected with PET is also important since it includes the effects of incompletely infarcted tissue and morphologically intact but deafferented cortex. Diagnostic accuracy for classification of patients in VaD versus AD is clearly superior for FDG PET even in patients with mild cognitive impairment (Mielke et al., 1994).

In a study on 153 subjects PET differentiated VaD from AD demonstrating lower metabolism in deep gray nucley, cerebellum, primary cortices, middle temporal gyrus and anterior cingulate cortex in VaD, whereas in AD showed lower metabolism in hippocampal region, orbitofrontal, posterior cingulate and posterior parietal cortices (Kerrouche et al., 2006).

PET can also detect vascular inflammatory changes (Mehta et al., 2012) and their interaction with amyloid depositions for development of mixed dementias after stroke (Heiss & Zimmermann-Meinzingen, 2012). Microglia activation that occurs in patients with mild cognitive deficits is not proven to be correlated with amyloid deposition as imaged by 11C-PIB (Okello et al., 2009). However, in animal models, the inflammation due to an infarct is exacerbated in the presence of amyloid; compared to animals without amyloid deposition the infarcts induced in presence of amyloid grew over time (Whitehead et al., 2007). The interaction of inflammatory reaction and amyloid deposition can be relevant for development of dementia in cerebrovascular disease as studied by multitracer PET with PK 11195 and PIB (Mok et al., 2010).

Episodic memory decline and hippocampal cerebral volume (typically associated with Alzhemier disease) are related to temporo-parietal hypometabolism (Desgranges, Chételat and Eustache, 2004) while executive dysfunction and white matters hyperintensities (typical of cerebrovascular disease) correlate with frontal lobe hypometabolism (Tullberg et al 2004). On the bases of this hypothesis a fluorodeoxyglucose-PET longitudinal study on 38 subjects ranging from normal condition to dementia in a follow up of 2 years have demonstrated a different pattern of metabolic decline in condition of dementia in Alzheimer disease or in cerebrovascular disease. In fact low baseline hippocampal volume can predict development of medial temporal hypometabolism; on the other hand white matter hyperintensities can predict hypometabolism over time in the fronto-parietal regions (Kuczynski et al., 2008). These studies suggest that pattern of cognitive decline studied with neuropsychological test batteries, anatomic changes and study of cerebral metabolism are useful in defining etiology of dementia in cerebrovascular disease and understand future evolution of cognitive deficits.

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4. Pet study of cognitive functions in normal ageing, mild cognitive impairment and degenerative dementias

With normal aging neocortical neurons are lost in specific regions (Morrison, 1997), dendridic trees undergo progressive regression and axons degenerate leading to an age-related axonal loss. This process leads to a decrease of myelinated nerve fibers of 45% from the age of 20 to 80 years (Marner et al., 2003) and a reduction of the number of synapses by 15 to 50% (Pannese, 2011). The cerebral morphological changes that occur during normal ageing develop cognitive changes in particular about memory that could be considered age-related and a physiological process. These cognitive changes are related to physiological age-related brain atrophy with concomitant ventricular enlargement (Rusinek et al., 2003) and to a diffuse and frontally accentuated degrease of glucose metabolism as revealed with PET (Pawlik et al., 1989). The condition of "age associated memory impairment" is characterized by self perception of memory loss and standardised memory test score that shows low performances in memory tasks compared with younger adults. By contrast, "mild cognitive impairment" (MCI) is considered a transitional state between normal ageing and dementia (Petersen, 2004). Subjects with MCI are indipendent in activity daily living even if suffer with cognitive deficits in particular in the area of memory (in the amnestic form of MCI) typically in delayed recall, althought non-memory cognitive domains might also be impaired (in non-amnestic form of MCI). Patients with the amnestic subtype of MCI frequently progress to Alzheimer disease (AD) (Petersen et al., 2006) so that MCI is associated with an increased risk of developing dementia. When cognitive impairment concerns not only memory, but also other cognitive domains (such as abstract reasoning, judgment capabilities, language, praxic, gnostic or spatial function) dementia is often diagnosed (American Psychiatric Association, 2000). Alzheimer Disease is the most common cause of progressive form dementia in which cognitive decline interferes significantly with activities of daily living. Other causes of common degenerative dementia include dementia with Lewy bodies (characterized by fluctuating consciousness, parkinsonian symptoms and progressive decline in visuospatial, visuoperceptual, literacy and praxic skills, including visual allucinations) and Frontotemporal dementia (characterized by executive dysfunction, changes in personality and behaviour, semantic deficits and progressive aphasia). Secondary forms of dementia include depression (pseudo-depressive dementia), drug toxic effects or other medical conditions.

Many of brain changes that occur in neurodegenerative disease can be evidenced by neuroimaging technologies designed to identify alterations of cerebral biological processes. The main brain change consists in focal or diffuse cerebral atrophy induced from neuronal synaptic degeneration and loss of neurons. Some forms of dementia have a particular pattern of athophy (Josephs et al., 2007). For example, widespread atrophy or medial temporal atrophy points toward a pathologic diagnosis of Alzheimer Disease, fronto-temporal loss suggest a diagnosis of Frontotemporal Dementia (Neary et al., 2005), more focal atrophy predominantly involving the premotor and supplemental motor area suggests Corticobasal Degeneration (CBD) or Progressive Supranuclear Palsy (PSP) (Whitwell et al., 2010); on the contrary Lewy bodies disease is characterised by posterior cortical atrophy (Crutch et al., 2012). Other cerebral

anomalies observed in auptoptical studies conducted in middle-aged adults (Price & Morris, 1999), patients with MCI (Petersen et al., 2006) or Alzheimer Disease (Braak & Braak, 1991) consist in presence of plaques of amyloid ß and neurofibrillary tangles of tau protein.

Neurofibrillary tangles have been observed in the hippocampus and temporal regions in MCI, in neocortical areas (frontal and parietal cortex) as MCI progress to AD. Patients with autoptical diagnosis of Alzheimer disease have a hight number of both amyloid plaques and neurofibrillary tangles (McKhann et al., 1984).

Cerebrospinal fluids (CSF) studies conducted on patients with AD (Sidoryk-Wegrzynowicz et al., 2011) or post-mortem (Reinikainen et al., 1990) have documented alterations in cholinergic, serotonergic, dopaminergic, somatostatinergic, noradrenergic and glutamatergic neurotransmitters. These and other pathogenetic mechanism as insulin resistance (Craft, 2006) contribute to compromise cerebral regional glucose metabolism studied in PET techniques.

Studies conducted on patients with AD often use the radiolabelled glucose analogue FDG (**[18]FDG-PET**) to measure cerebral glucose metabolism, which indicates the levels of neurosynaptic activity. PET studies have demonstrated that Alzheimer's disease is characterized by regional impairment of cerebral glucose metabolism in neocortical association areas (posterior cingulate, temporoparietal and frontal multimodal association cortex), whereas the primary visual and sensorimotor cortex, basal ganglia, and cerebellum are relatively well preserved (for a review see Herholz, 2003).

An automated voxel-based analysis of FDG-PET images can distinct AD from controls with 93% sensitivity and 93% specificity as dimonstrated in a multicentre study comprising 10 PET centers (Herholz et al., 2002).

These studies have shown that cortical brain alterations begin in the posterior cingulate regions and spread to the temporal and prefrontal cortices. This pattern of brain metabolism is useful to differentiate patients with AD from other forms of dementia and from cognetively health people (Silverman et al., 2001).

Regional cortical hypometabolism also correlates with greater cognitive losses so that [18]FDG-PET can differentiate patients with MCI from others with AD or normal subjects (Small et al., 2006).

When [18]FDG-PET is added to standard clinical assessment, diagnostic accuracy for dementia of Alzheimer type increases sensitivity and specificity (Jagust et al., 2007). [18]FDG-PET is important in helping differential diagnosis between AD and Frontotemporal Dementia since the latter dementia do not seem to respond well to currently available symptomatic treatments.

Longitudinal studies of patients with MCI have found that if baseline assessment with [18]FDG-PET scan suggests an AD-like pattern, the probability of conversion in AD within several years is extremely hight (Drzezga et al., 2005; Chételat et al., 2003). Therefore in these MCI patients pharmacological treatment with specific anti-dementia drugs could be achieved, so that might be modified the trend of the desease and reduce social costs of illness.

[18]FDG-PET assists the diagnosis of AD when combined with specific genetic assessment. In fact hypomethabolism in posterior cingulate, parietal, prefrontal, entorhinal and temporal

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regions have been found to predict future cognitive decline in older APOE ε4 carriers than non-carriers (Small et al., 2000). Moreover several [18]FDG-PET studies have shown that patients with MCI and AD-like metabolic pattern are hightly predictive of conversion to AD within several years, in particular in patiens that are APOE ε4 carriers (Mosconi et al., 2004).

[18]FDG-PET scans, when combined with Magnetic Resonance imaging and other biomarkers, are likely to improve diagnostic accuracy (Mueller et al., 2005) and might be used to monitor treatment that affect cerebral blood flow, metabolism, or neuronal dysfunction.

Characteristic patterns of regional hypometabolism are also seen in other degenerative dementia (Bohnen et al., 2012). Frontotemporal dementia is identified by distinct frontal or frontotemporal metabolic impairment that are typically quite asymmetrically centered in the frontolateral cortex and the anterior pole of temporal lobe. Dementia with Lewy bodies shows reduction of glucose metabolism in primary visual cortex in addition to that in posterior association areas. Other degenerative disorders show typical hypomethabolism in the specifically affected brain structures: the putamen and cortex in corticobasal degeneration, the caudate nucleus in Huntington's chorea, the frontal cortex and midbrain in progressive supranuclear palsy, pons and cerebellum in olivopontocerebellar atrophy.

In recent years different small molecule probes have been developed for use with PET to measure deposits of amyloid- ß plaques and tau tangles in vivo (Klunk et al., 2004; Kudo et al., 2007). The most studied amyloid-binding radiotracer is **[^{11}C]PIB** ([^{11}C]-labelled Pittsburg Compound B) which is a derivative of thioflavin-T amyloid dye that binds specifically amyloid-ß plaques but not neurofibrillary tangles. Studies using [^{11}C]PIB-PET have demonstrated cortical retention in patients with AD compared with normal subjects (Klunk et al., 2004). Studies of MCI patients have showed that [^{11}C]PIB uptake is increased in approximately 50% of them (Kemppainen et al., 2007). [^{11}C]PIB-PET could potentially be used to diagnose cerebral amyloid angiopathy since it also detects cerebrovascular amyloid (Johnson et al., 2007). PET studies with [^{11}C]PIB is useful in differential diagnosis of degenerative type of dementia, since patients with Lewy bodies dementia show lower binding than in AD, while patients affected with Fronto-temporal dementia show no cortical binding (Rowe et al., 2007).

Recently several ^{18}F labelled amyloid tracers are commercially available permitting large scale clinical use (Rowe and Villemagne, 2011).

[^{18}F]-BAY94-9172-PET, based on amyloid legand florine-18, could be used to discriminate patients with AD from frontotemporal dementia and healthy controls (Rowe et al., 2008).

Tau deposition in neurofibrillary tangles together with amyloid can be specifically detect by the tracer **[^{18}F]-FDDNP**, providing additional insight in AD pathology (Small et al., 2008).

Other PET legands have been used in research to measure functionality of many neurotransmitter systems such as serotoninergic, cholinerdic and dopaminergic. The neurotrasmitters systems are impaired in various types of dementia and may help in differential diagnosis and in the definition of pathophysiological process. **MPPF** (4-[^{18}F]-fluoro-N-piperazynil-N-2-methoxy-phenyl-pyridinil benzamide) is a molecular imaging probe for 5-HT$_{1A}$ receptors which density correlates with the number of pyramidal neurons of the hippocampus (Kepe et

al., 2006). Patients with AD show diminished hippocampal signal, while patients with MCI show binding values intermediate between controls and Alzheimer's disease patients (Kepe et al., 2006). Since MPPF binding correlates with neuronal losses in the hippocampus, therefore it can be used as an early diagnostic measure in the continuum between MCI and dementia conversion, before onset of symptoms of dementia. PET radioligands used to visualize cholinergic nicotinic receptors correlate with cognitive measure of attention in Alzheimer's disease (Kadir et al., 2006). PET measures of cholinergic system with **^{11}C-nicotine** can be used to assess nicotine binding sites in the brain before and after treatment with anti-cholinesterase drugs (Kadir et al., 2007).

[^{11}C]ß-CFT ([^{11}C]2ß-carbomethoxy-3ß-4fluorophenyl tropane) is a molecular dopamine reuptake ligand used to study the cerebral dopaminergic system. Striatal uptake of [^{11}C]ß-CFT is reduced in patients with AD (Rinne et al., 1998). The ligand **[^{11}C]-PK11195** has been used in other PET research to measure microglial activation as response to neuronal degeneration in patients with Alzheimer Disease (Cagnin et al., 2001). Microglial activation seems to be an inflammatory reaction to amyloid deposition that might increase the formation of pathological protein deposits.

5. Conclusions

An enormous progress has been made in the science of human cognition using neuroimaging and integration with neuropsychological assessment, multimodal structural and functional imaging technologies based on study of cerebral glucose metabolism as in Positron Emission Tomography. PET exam has led to a revolution in understanding of the basic neuroscience principles involved in where and how the brain processes information both in normal subjects and in patients with cerebral lesions.

Different PET methodologies in combination with traditional neuroimaging techniques are more and more used to accurately localize and characterize cognition not invasively.

The current clinical applications of using PET or other functional neuroimaging to mapping cognitive function include lateralization and presurgical mapping of language and memory mapping (Stufflebeam and Rosen, 2007). The development of advanced techniques and the combination of imaging technologies is further expanding the understanding of cognitive processing and is extending the clinical applications of functional neuroimaging into new areas.

With recent advances in neuroimaging technology novel PET applications are developing to measure various biological processes or to study cognitive alterations in patients with diseases that affect central nervous system. Combining PET procedures with other neuroimaging studies, genetic risk measures and other biomarkers measures from other tissues it might increase diagnostic sensitivity and specificity in particular in differential diagnosis of dementia, in the early stages of vascular or degenerative dementia, since presence of different PET pattern (neocortical association areas in AD, frontolateral cortex and anterior pole of temporal lobe in FTD, posterior association areas in LBD).

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PET investigations will increase understanding and monitor pathophysiological process of many neurological diseases, track the biological effects of treatments in clinical trials and assist in identifying responders to specific treatments (Reiman et al., 2001). Several of the neuroimaging technologies in development promise in proving measurement of potential biomarkers but further research is necessary to validate their use. In fact many of these methods are still used in research settings and require further studies to better understand their clinical usefulness. Another limitation to the adoption of PET techniques is the relatively high cost and lack of wide availability, but when compared costs to the high diagnostic accuracy of PET, these benefits incurred high costs (McMahon et al., 2003). In future, with more extensive use of these new PET technology, costs will also decline and improvement of diagnostic accuracy will lead to cost saving. For example healthy adults with risk factors for cognitive decline (e.g. age, previous head trauma, familiar history) might undergo a PET check scan for measures of cognitive decline risk and physicians will use medications or other interventions to prevent or delay onset of disease or avoid future cognitive losses.

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