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Mood, cognition and *in vivo* protein imaging: the emerging nexus in clinical neuroscience

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SUMMARY

Introduction—Disorders of mood and cognition overlap in the elderly and there is an emerging consensus that both groups of disorders share neurobiological substrates.

Methods—Salient peer reviewed articles focusing on late-life depression, structural neuroimaging and recent developments in positron emission tomography based *in vivo* protein imaging.

Results—Epidemiological and clinical evidence indicates that mood and cognition in the elderly are clinically inter-related and common neurobiological mechanisms may underlie both groups of disorders. Degenerative, vascular and related mechanisms like genetically programmed abnormal protein deposition may provide the underlying neurobiological links between these disorders.

Conclusions—Modern neuroimaging approaches such as positron emission tomography (PET) based *in vivo* protein binding may help further elucidate common pathophysiological mechanisms and assist in the early identification of patients at risk for developing dementia over time. These developments have important mechanistic and public health significance in the elderly.

Keywords

protein imaging; cognition; late-life depression; dementia prodrome

Historically, disorders of mood and cognition have been conceptualized and managed clinically as distinct entities. Their genetic underpinnings, pathophysiological mechanisms and clinical outcomes have been treated as very distinct with little overlap between these entities. There is, however, a growing evidence base, largely based on epidemiological and clinical observations, that suggest that mood disorders, especially in late-life and cognitive disorders overlap from both phenomenological and pathophysiological perspectives. These findings have important implications for both the diagnosis and long-term management of patients diagnosed with these disorders.

In this review, we will begin by presenting the epidemiological and clinical findings that establish a link between depression and the dementias. This will be followed by a discussion of plausible pathophysiological links between mood and cognitive disorders and of modern

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neuroimaging techniques aimed at identifying and estimating the protein load using *in vivo* approaches. We will conclude by discussing the implications of this line of enquiry for the neurobiology and the long-term management of these disorders including the concept of dementia prophylaxis.

RELATIONSHIP OF MDD TO AD

Major depressive disorder (MDD) and other clinically significant forms of 'minor depression' are among the most common mental disorders in the elderly (Blazer *et al.*, 1987; Alexopoulos *et al.*, 1988; Ruegg *et al.*, 1988; Parmelee *et al.*, 1989; Koenig and Blazer, 1992; Parmelee *et al.*, 1992; Blazer, 1994). MDD has been identified both as a risk factor and a prodrome of Alzheimer's disease (AD) in clinical and community samples (Reding *et al.*, 1985; Kral and Emery, 1989; Kokmen *et al.*, 1991; Jorm *et al.*, 1991; Alexopoulos *et al.*, 1993b; Speck *et al.*, 1995; Devanand *et al.*, 1996; Henderson *et al.*, 1997; Steffens *et al.*, 1997; Bassuk *et al.*, 1998; Chen *et al.*, 1999; Yaffe *et al.*, 1999; Geerlings *et al.*, 2000; Jorm, 2000; Lockwood *et al.*, 2000; Visser *et al.*, 2000; Jorm, 2001; Lockwood *et al.*, 2002; Wilson *et al.*, 2002; Green *et al.*, 2003; Sweet *et al.*, 2004; Cannon-Spoor *et al.*, 2005; Gatz *et al.*, 2006; Rapp *et al.*, 2006; Steffens *et al.*, 2006). Community based studies have identified clinical depression, including depressive symptoms as a risk factor for the subsequent development of dementia. Devanand *et al.* using a population based sample from northern Manhattan (NY, NY) found that after controlling for age, gender, education and initial level of cognition, depressed mood at baseline was associated with the development of AD with an odds ratio (OR) of 2.5 (Devanand *et al.*, 1996). In the religious order study, > 600 elderly individuals were examined annually for as long as seven years (Wilson *et al.*, 2002). Depressive symptoms at baseline predicted the subsequent development of AD in this sample and notably, with each additional symptom, the risk of AD increased by 20%. Depressive symptoms were associated with more rapid decline in episodic memory and visuospatial ability but not in semantic or working memory in this sample. The Multi Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study examined the relationship between depressive symptoms and AD (Green *et al.*, 2003). Analyzing data from a large sample of 4,046 individuals, the investigators concluded that depressive symptoms are associated with the development of AD, and that this association was stronger when depressive symptoms occurred in the year immediately prior to the onset of AD symptoms. In a study of older, educated individuals in the Netherlands, with an average follow up of 3.2 years, those with depressed mood on enrollment were more likely to develop AD, though the association was not significant among lower educated persons in the study (Geerlings *et al.*, 2000). Not all studies found the same relationship between depression and the subsequent development of AD. A community based study in Australia found no association between baseline depression and the development of dementia 3–6 years later (Henderson *et al.*, 1997). In a rural Pennsylvania based study, subjects with depression at the start of the study were were found to be at slightly higher risk for developing dementia (relative risk 1.27) on follow up, though the risk was not statistically significant (Chen *et al.*, 1999). Another study of 2,812 elderly residents of New Haven, Connecticut observed that elevated levels of depression at baseline were associated with an increased risk of cognitive decline in those who were placed in the 'medium', as opposed to the 'high' category of cognitive functioning at baseline (Bassuk *et al.*, 1998).

Using data from a clinical sample, Alexopoulos *et al.* observed that patients diagnosed with MDD who concurrently presented with executive function impairment were more likely to develop clinical dementia on follow up (Alexopoulos *et al.*, 1993a). Reporting on a sample of 57 elderly patients diagnosed with MDD, they demonstrated that 43% of patients with MDD and cognitive impairment progressed to clinical dementia over time. This occurred even when the mood and cognitive symptoms improved with antidepressant treatment. Kral and coworkers reporting on a sample of elderly patients diagnosed with MDD also observed that a large

proportion of patients evolved clinically into dementia over a span of 8 years (Kral and Emery, 1989).

DEPRESSION AND COGNITION

Cognitive performance of depressed late-life patients has been well described in studies over the past 15 years. Deficits have been reported in domains of attention, language, episodic recall, semantic recall, nonverbal recall, visuospatial/visuoconstruction, working memory, and executive function (Abas *et al.*, 1990; King *et al.*, 1991; Boone *et al.*, 1994; Boone *et al.*, 1995; Lesser *et al.*, 1996; Palmer *et al.*, 1996; Kramer-Ginsberg *et al.*, 1999; Lyness *et al.*, 1999; Yaffe *et al.*, 1999; Nebes *et al.*, 2000; Palsson *et al.*, 2000; Nebes *et al.*, 2001b; Swainson *et al.*, 2001; Elderkin-Thompson *et al.*, 2003; Elderkin-Thompson *et al.*, 2004b). Specifically, they have reduced language fluency (Wolfe *et al.*, 1987; King *et al.*, 1991; Boone *et al.*, 1994; Brown *et al.*, 1994; Palmer *et al.*, 1996), poor processing speed and attentional ability (Boone *et al.*, 1995; Yaffe *et al.*, 1999; Nebes *et al.*, 2000; Palsson *et al.*, 2000; Nebes *et al.*, 2001a), poor inhibition of conflicting information (Palmer *et al.*, 1996), and impaired visuospatial skills (Boone *et al.*, 1994; Boone *et al.*, 1995; Lesser *et al.*, 1996). Patients have deficits in complex tests such as the Wisconsin Card Sort (Boone *et al.*, 1994; Brown *et al.*, 1994; Boone *et al.*, 1995; Lesser *et al.*, 1996), which assesses abstract problem solving and flexibility when using environmental feedback. Recall is compromised when recalling unstructured word lists or semantically organized verbal stories (King *et al.*, 1991; Palmer *et al.*, 1996; Kramer-Ginsberg *et al.*, 1999; Palsson *et al.*, 2000; Swainson *et al.*, 2001). The deficit appears also in recall of nonverbal designs (Lesser *et al.*, 1996; Palmer *et al.*, 1996; Elderkin-Thompson *et al.*, 2004b). Researchers using the full scale Weschsler Adult Intelligence Scale III (WAIS III) and the verbal IQ and Performance IQ subscales of the WAIS III have also observed deficits (Boone *et al.*, 1995; Palmer *et al.*, 1996).

The magnitude of cognitive dysfunction in patients with MDD appears to be spread somewhat equally across all domains, including executive functions and memory, when compared with patients with AD where memory impairments are more striking than impairments in executive function. A meta analysis of late-life depression studies that weighted studies according to size and divided patients into hospitalized and nonhospitalized groups found that a generally uniform effect size deficit existed across all domains (Elderkin-Thompson *et al.*, 2004a). No domain appeared selectively impaired relative to the other domains. From a neuroanatomical perspective, while the association between activation of the temporal region and recall has been well substantiated, the frontal region is also implicated in recall and attentional tasks as well as executive functions (Cabeza and Nyberg, 2000; Kramer *et al.*, 2005; Alessio *et al.*, 2006). Alexopoulos has suggested the use of the ‘depression-executive dysfunction syndrome’ of late-life to reflect the dysfunction of the dorsolateral neural circuits and its association with reduced physical and cognitive functioning of the patient, (Alexopoulos *et al.*, 2002) poor response to treatment and high rates of relapse (Kalayam and Alexopoulos, 1999). Functional imaging studies of overlapping neural network functionality are consistent with the neuropsychological findings that multiple cognitive domains can become compromised at an early stage of a disease process even though the disease itself may be considered localized.

DEPRESSION AND MCI

The attentional, recall and executive deficits observed among depressed patients are also closely associated with early AD (Robbins *et al.*, 1996), and depression is considered a major risk factor for the development of dementia (van Reekum *et al.*, 1999; Geda *et al.*, 2006; Lopez *et al.*, 2006). Among patients with mild cognitive impairment (MCI) of the amnestic type, the memory deficit is an isolated deficit (Winblad *et al.*, 2004). MCI patients who are impaired in multiple domains usually have a memory impairment, but it is of less magnitude than that

observed in patients classified as amnestic MCI (Lopez *et al.*, 2006). The multiple-domain form of MCI is the most prevalent form of MCI (Lopez *et al.*, 2006) and is a better indicator of mild AD than memory impairment alone (Masur *et al.*, 1994; Jacobs *et al.*, 1995; Kluger *et al.*, 1999; Petersen *et al.*, 2001; Winblad *et al.*, 2004). The neuropsychological profile of a multiple-domain MCI person appears similar to the profile of late-life depressed persons observed in the meta-analysis (Elderkin-Thompson *et al.*, 2004a).

MECHANISMS LINKING DEPRESSION AND DEMENTIA

While the weight of the evidence indicates a significant relationship between a history of depression and the development of dementia, especially AD, the precise mechanisms that link these two disorders is not well understood. There are several plausible mechanisms. These include neuronal atrophy (degeneration), vascular pathophysiology, genetic susceptibility and amyloid deposition.

ATROPHY

MRI has been extensively applied to the study of brain structure in psychiatric diseases (Coffey *et al.*, 1988; Krishnan *et al.*, 1988; Morris and Rapoport, 1990; Zubenko *et al.*, 1990; Rabins *et al.*, 1991; Coffey *et al.*, 1993; Fujikawa *et al.*, 1993; Sheline *et al.*, 1996; Alexopoulos *et al.*, 1997; Krishnan *et al.*, 1997; Kumar *et al.*, 1997a, 1997b; Kumar *et al.*, 1998; Lai *et al.*, 2000; Kumar *et al.*, 2002b; Steffens *et al.*, 2002). Volumetric reductions occur in patients diagnosed with late-life depression predominantly in the prefrontal regions and hippocampus when compared with controls (Steffens *et al.*, 2002; Ballmaier *et al.*, 2004). A reduction in the volume of the orbitofrontal cortex has been reported in patients with late-life depression (Lai *et al.*, 2000). Additionally, smaller volumes of the caudate nucleus and the cerebellar vermis have been reported in patients with depression when compared with controls (Krishnan, 1993). These findings formed the basis of speculation that abnormalities in the subcortical-frontal pathways may underlie the depression in some instances. Our findings indicate that smaller frontal lobe volumes in patients with MDD are circumscribed and occur in the anterior cingulate, gyrus rectus and the orbitofrontal regions (Ballmaier *et al.*, 2004). Recently, our group (Ballmaier *et al.*, 2007) demonstrated smaller hippocampal volumes, largely restricted to the CA1 and subiculum subfields in patients with late-life depression when compared with controls. The differences were more striking in the group with late onset depression (operationally defined as onset of the first episode occurring after age 60). Smaller hippocampal volumes were also associated with poorer performance on specific cognitive tasks in this study.

VASCULAR

MRI determined high intensity lesions are more frequently observed in patients with late-life MDD when compared with controls. The putative link between high intensity lesions and MRI lesions has been interpreted as support for a vascular basis to depression in late-life (Krishnan *et al.*, 1997; Kumar *et al.*, 2002a). The high intensity lesions may account for some, though not all of the cognitive deficits observed in patients with late-life MDD (Lesser *et al.*, 1996; Salloway *et al.*, 1996; O'Brien *et al.*, 1998; Kramer-Ginsberg *et al.*, 1999; Nebes *et al.*, 2001b). It is important to remember that while AD is not typically conceptualized as a vascular dementia, mixed vascular-degenerative dementias are increasingly recognized both clinically and neuropathologically. Vascular mechanisms clearly contribute to late-life depression and preliminary work in our laboratory indicates that smaller frontal lobe volumes (degeneration) and high intensity lesions (putatively linked to vascular disease) detected using MRI are complementary, albeit autonomous pathways to MDD (Kumar *et al.*, 2000, 2002a). These pathways are comparable to mechanisms and pathways that have been implicated in AD and mixed dementia and suggest that neurodegeneration and vascular compromise may represent pathophysiological mechanisms that transcend traditional diagnostic boundaries.

THE ROLE OF AMYLOID AND TAU

In a preliminary, but important, report on the neuropathological correlates of cognitive changes in patients initially diagnosed as having late-life MDD, Sweet *et al.* examined post mortem brain tissue in nine patients diagnosed as having late-onset major depression and one patient diagnosed with bipolar disorder (Sweet *et al.*, 2004). This sample of patients had MDD without clinical evidence of dementia during the initial assessment and participated in research protocols for patients with late-life major depression. The follow-up period varied from 7 to 87 months. Eight patients evolved clinically into dementia over time and the remaining two did not develop dementia. Post mortem examination of brain tissue showed neuropathological hallmarks of AD in six subjects. Diffuse Lewy body pathology was found in one subject and rare diffuse amyloid plaques restricted to the middle frontal gyrus in another subject. Three patients with AD pathology also displayed evidence of vascular disease and the other three demonstrated Lewy body pathology (dementia with Lewy bodies being the secondary diagnosis). In another recent neuropathological study, increased numbers of plaques and tangles in the hippocampal region were identified in post mortem tissue in AD patients with prior episodes of major depression (Rapp *et al.*, 2006). The density of plaques and tangles were even greater in patients in whom there was concurrent depression and dementia at the time of the initial AD diagnosis (Rapp *et al.*, 2006).

NEURODEGENERATIVE CHANGES IN AGING AND AD

Neuropathological, neuroimaging, and clinical research support the idea that the dementing process leading to AD begins years before a clinical diagnosis of probable AD can be confirmed (McKhann *et al.*, 1984). Post-mortem studies of non-demented older people (Price and Morris, 1999) indicate that tangle density in healthy aging correlates with age, but that some cases demonstrate widely distributed neuritic and diffuse plaques throughout neocortex and limbic structures. This preclinical AD group also shows increased tangles. Braak and Braak have shown that neurofibrillary tangle density increases in some individuals, presumably those who will eventually develop AD, very early in adult life, perhaps even by the fourth decade (Braak and Braak, 1991). The diffuse amyloid deposits in middle-aged non-demented subjects are consistent with an early stage of AD pathology and suggest that the pathological process progresses gradually, taking 20 to 30 years for the clinical manifestation of dementia (Arai *et al.*, 1999). Our studies (Small *et al.*, 1995, 2000), confirmed by others (Reiman *et al.*, 1996, 2001), indicate lower regional brain metabolism in middle-aged and older persons with a genetic risk (APOE-4), lending further support for a prolonged presymptomatic AD stage.

IN VIVO SP AND NFT MEASURES

Previous feasibility analysis demonstrated the possibility of brain receptor imaging with PET (Small *et al.*, 2006a). Using receptor-binding concepts, the feasibility of imaging Aβ (and tau) aggregates (SPs and NFTs, respectively) in the living brain of AD patients can be established by analogous analysis. This assumes that the molecular imaging probe binds to the aggregate site(s) in a saturable and specific manner, similar to neuroreceptor binding.

A feature of the pathogenesis of AD is the pathological aggregation of the β-amyloid peptide into fibrillary SPs and the hyperphosphorylation of the tau protein into NFTs. The prospect of *in vivo* visualization of these neuropathological lesions has driven several groups [e.g. Pittsburgh (Klunk *et al.*, 2003b, 2004), UCLA (Shoghi-Jadid *et al.*, 2002), University of Pennsylvania (Kung *et al.*, 2003)] to search for imaging biomarkers of these pathologies. The ideal AD imaging biomarker should be specific for the intended molecular targets (e.g. amyloid and tau aggregates or both), clear well from non-specific binding areas (i.e. have low general lipid binding, like white matter), and yield a reliable signal to noise ratio for amyloid/tau to non-specific sites. All this assumes that the probe binds to the aggregate site(s) in a saturable

and specific manner, similar to neuroreceptor binding, although it is now apparent that amyloid and tau aggregates are complex conglomerates that contain multiple binding sites with different affinities for probes (e.g. [18F]FDDNP binds at sites different from thioflavin probes in general). Similar to receptor binding, binding of Aβ (and tau) aggregates should be displaceable in vivo (Kepe *et al.*, 2006).

Two ligands emerged as primary candidates for imaging protein aggregates in the living brain. These are 1,1-dicyano-2-[6-(dimethylamino)-2-naphthalenyl]-propene ([18F]FDDNP) and N-methyl-[11C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole (Pittsburgh compound B or PIB). PET studies using both ligands are able to discriminate between AD patients and controls, potentially track conversion from mild cognitive impairment to dementia (see Figure 1) and discriminate patients diagnosed with AD from Prion dementia (Small *et al.*, 2006b;Mintun *et al.*, 2006;Boxer *et al.*, 2007;Rabinovici *et al.*, 2007).

Results in living patients with [18F]FDDNP confirm the *in vitro* analysis of feasibility about *in vivo* detection of brain pathologies in dementia patients. Analysis of binding data in all neocortical areas of AD patients offers an understanding of the progressive nature of the disease in agreement with the Braak model of brain neuropathological changes (Braskie *et al.*, unpublished observation). Excellent correlations with glucose metabolic rates (FDG-PET) in the same subjects are also observed. Initial neuropathological processes occur in the medial temporal lobe, expanding later to the rest of the temporal lobe, the parietal lobe and finally engulfing the whole neocortex. Brain pathology accumulation in the medial/lateral temporal lobe, and not the average Logan standard uptake volume (SUV) throughout the cortex, is emerging as a key tool to identify early brain pathology in agreement with earlier reports (Shoghi-Jadid *et al.*, 2002). The sensitivity of [18F]FDDNP to both NFTs and SPs offers an opportunity to follow the neuropathological evolution of the disease, initiated by intraneuronal NFT formation in the transentorhinal cortex, entorhinal cortex and hippocampus. [18F]FDDNP also has permitted the visualization of tauopathies in living patients. Frontal lobe dementia patients present prominent frontal and temporal signals compared with controls, suggesting [18F]FDDNP utility in differentiating FTD from AD (Small *et al.*, 2002; Boxer *et al.*, 2007).

PIB retention also differentiates AD patients from controls (Klunk *et al.*, 2003a, 2004). Healthy control subjects show little PIB retention in cortical areas, while patients diagnosed with AD show PIB retention in frontal, temporal and parietal regions. In the cerebellum and the white matter, areas without known amyloid distribution, retention in controls and AD patients were comparable with PIB. However, the pattern is somewhat distinct from the pattern of distribution of protein aggregates in the brain that typically begins in the entorhinal areas and progress to involve the other limbic and neocortical areas.

The early success with the use of [18F]FDDNP (Shoghi-Jadid *et al.*, 2002) and PIB (Klunk *et al.*, 2004) offers an unprecedented opportunity to follow the neuropathological evolution of AD in living subjects. These *in vivo* probes can also be applied to examine the biology of related disorders such as depression where there is considerable overlap in neurobiological substrates. Post mortem studies in patients with late-life depression are limited and point to focal pathological changes that may contribute to the pathophysiology of the disorder (Rajkowska, 2000). Post mortem tissue from well characterized samples will help better elucidate the pathways to depression, especially if the post mortem data can be integrated with antemortem neuroimaging findings.

NEUROSCIENTIFIC IMPLICATIONS

Depression in the elderly is characterized by multiple cognitive aberrations perhaps most striking in the domains of executive functions, attention and memory. Executive function impairment is associated with poorer clinical response to antidepressants and a more chronic

course of illness. Long-term response to antidepressants may be modest in patients where the mood disturbance is a prodrome of dementia. Specific cognitive profiles may help identify depressed patients at risk for developing dementia over time. Vascular, degenerative, genetically mediated abnormal protein deposition and other biological processes may serve as common neurobiological processes to both depression and dementia in the elderly. Neuroimaging provides a critical link between the phenotype and its underlying neurobiological underpinnings. Protein imaging in vivo may help in ascertaining the protein load in critical brain regions in patients diagnosed with late-life depression without clinical evidence of dementia at baseline. Comparable to patients currently diagnosed with MCI, higher protein binding at baseline may predict the subsequent conversion to AD over time. The relationship of regional binding of both FDDNP and PIB to specific cognitive domains such as language, memory and executive functioning in patients with MDD will provide insights into brain-protein-behavior relationships in this patient group. If higher protein binding is associated conversion to AD, this finding will have profound implications for pharmachotherapy in patients with MDD. Patients diagnosed with MDD are treated with a combination of antidepressants and psychosocial approaches. Currently, there is no evidence base to recommend the prophylactic use of cognitive enhancers in patients diagnosed with late-life MDD. However, if PET imaging helps in identifying a subgroup of patients ‘at risk’ for developing dementia over time, it will help us reconceptualize management approaches to patients diagnosed with MDD. The approaches have broad implications and include more precise psychosocial approaches such as family education on the dementia spectrum, disease progression and recommendations about driving and conservatorship. As more effective compounds become available over time, the early identification of patients at risk for developing specific neurodegenerative disorders will become critical and widespread. A combination of judicious clinical assessment combined with precise neuroimaging measures is likely to have major clinical and public health impact.

KEY POINTS

- Mood and cognition in the elderly are interrelated
- Depression in late-life is both a risk factor and a prodrome of dementia
- Plaques and tangles may be imaged in vivo using positron emission tomography (PET)

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CONFLICT OF INTEREST

The University of California, Los Angeles (UCLA), owns a U.S. patent, Methods for Labeling β-Amyloid Plaques and Neurofibrillary Tangles (6,274,119), that uses the approach outlined in this article and has been licensed to Siemens. The FDDNP synthesis was performed at the UCLA Cyclotron Laboratory under Dr Satyamurthy’s direction. Drs Small, Huang, Cole, Satyamurthy, and Barrio, who are among the inventors, report receiving royalties and will receive royalties on future sales. Dr Small reports receiving consulting fees, lecture fees, or both from Abbott, Brainstorming, Dakim, Eisai, Forest, the Memory Fitness Institute, Myriad Genetics, Novartis, Ortho-McNeil, Pfizer, Radica, and Siemens, stock options from Dakim, and a grant from GlaxoSmithKline; Dr Kepe, consulting fees from Siemens; Dr Huang, lecture fees from GlaxoSmithKline; Dr Satyamurthy, consulting fees from PETNet Pharmaceuticals and Siemens; Dr Barrio, consulting fees and lecture fees from Nihon Medi-Physics, Bristol-Myers Squibb, PETNet Pharmaceuticals, and Siemens; and Dr Kumar, one-time consultant to Bristol-Myers Squibb.

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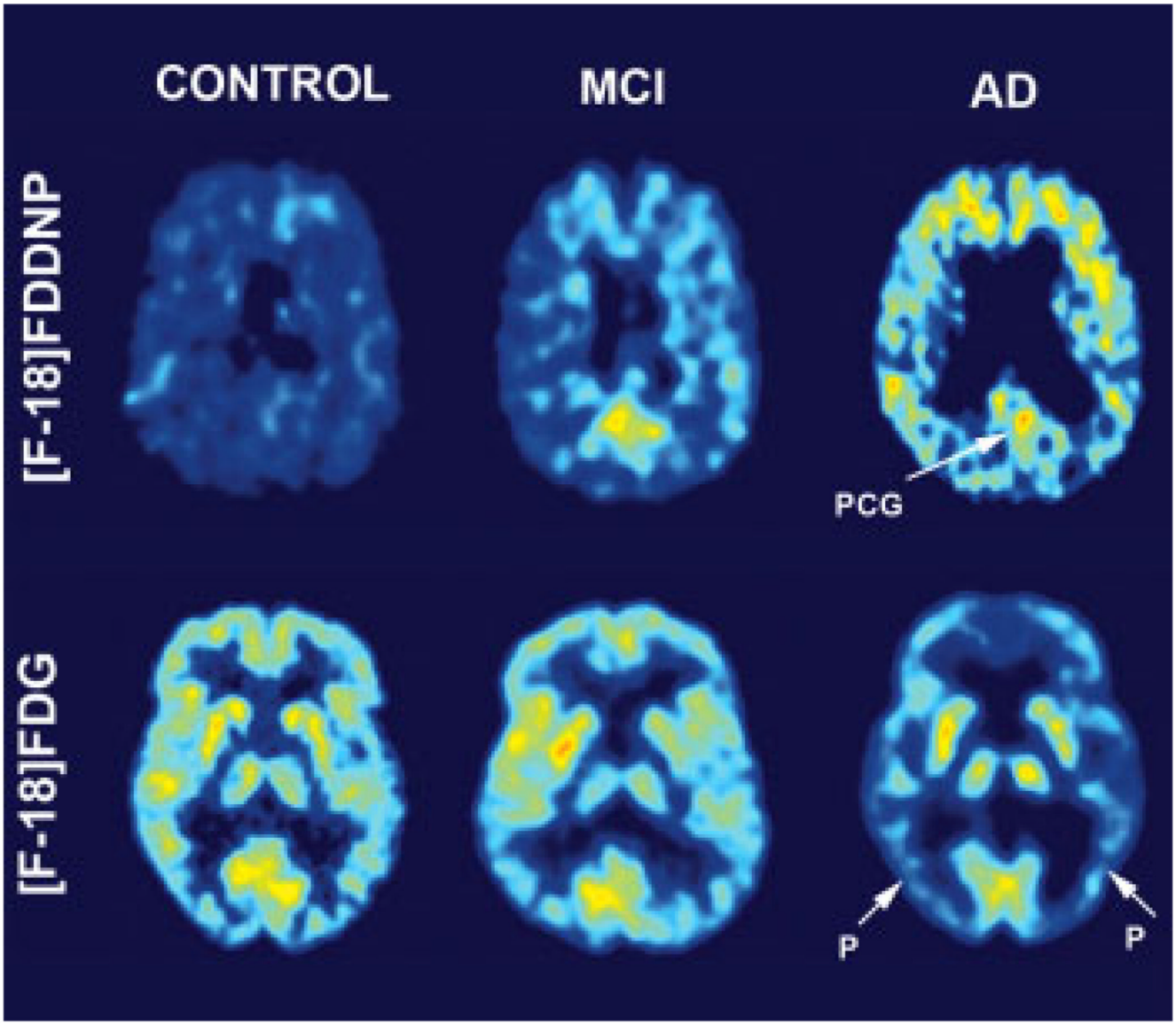

Figure 1.
Provides representative examples of PET images (FDDNP) binding and glucose metabolism in subjects diagnosed with MCI (mild cognitive impairment), AD (Alzheimer disease), and Healthy Control. Bright areas show increased glucose utilization and FDDNP binding. Note decrease in glucose metabolism and increase in FDDNP binding from MCI to AD. P, Parietotemporal Cortex; PCG, Posterior Cingulate Cortex.