# Alzheimer's dementia and post-traumatic stress disorder; differences and similarities in neuroimaging

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## Abstract

There are studies supporting the suggestion that a severe psychological stress in the elderly can be the risk factor of Alzheimer's dementia (AB) and other types of dementia. We have reviewed the findings of single photon emission tomography, positron emission tomography, magnetic resonance imaging and functional magnetic resonance imaging (fMRI), related to brain function and structure in AD and in post traumatic stress disorder (PTSD). There is evidence that prefrontal and orbitofrontal cortices dysfunction contributes to PTSD symptomatology. Similarities between the two different aforementioned diseases exist in the areas of (a) medial temporal lobe, (b) hippocampus and (c) cingulated cortex.

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## Introduction

Although it is known that both Alzheimer's dementia (AD) and post-traumatic stress disorder (PTSD) have certain neuroimaging findings, there is no clear correlation between them. We describe the severity and clinical characteristics of dementia, AD and PTSD and discriminate differences and similarities between the neuroimaging findings of these two pathological entities, evaluated mainly by single photon emission tomography (SPET) and positron emission tomography (PET), as well as by other imaging modalities.

## Definitions and historical events

### Dementia

Dementia is a psychosocial disorder to the growing elderly population with financial implications to our society [1]. The prevalence of dementia worldwide in 2005 was approximately 24 million people and this number is expected to nearly double every 20 years, until 2040 [2, 3].

Dementia, which means "without sense" in Latin, is a disease with progressive loss of all functions, and is most often defined by the criteria of the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) [4]. It is a syndrome with loss of function in multiple cognitive domains including memory impairment and at least one of the following: aphasia, apraxia, agnosia and disturbances in executive functioning, causing impairment in social and occupational activities.

### Alzheimer's dementia (AD)

Alzheimer's dementia is a progressive neurodegenerative disorder first affecting memory and then gradually all cognitive functions, leading to behavioural impairment and eventually causing death [5]. It is today the most common cause of dementia, accounting for 60%-70% of all dementia types [6, 7]. It is estimated that in Greece, 45.5% of the population will be over 65 years of age in the year of 2020, whereas in the European countries this percentage is estimated to be about 30%. This disease has a prevalence of 10% at the age over 65 years and much higher over 85 years [8]. Fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) PET studies contribute to an early diagnosis of 50% of AD cases. On the other hand, computed tomography (CT) and magnetic resonance imaging (MRI) have definite findings at late stages after regional brain atrophy has occurred [8].

It is today more than 100 years since Alois Alzheimer first described the disease after following a patient, during her last five years of life. Besides the symptoms he described, he and his senior colleague professor Kraepelin were the first to describe the characteristic plaques and the neurofibrillary tangles in necropsy. Additionally, they noticed that the brain had a

thin cerebral cortex [9]. It was professor Kraepelin, after Alzheimer died, that named this disease as "Alzheimer's Disease".

### Post-traumatic stress disorder

Post-traumatic stress disorder is an anxiety disorder resulting from experiencing or witnessing an extreme traumatic stressor, such as death or a serious injury. The symptoms of PTSD are characterized by persistent re-experiencing of the traumatic event, by avoidance of stimuli associated with this event, amnesia and increased arousal periods during sleep. Inappropriate irritability, difficulty in concentration, and exaggerated startle responses are also often observed in PTSD patients [10].

## The mechanisms of inducing PTSD and the memory pathways

Under normal circumstances, the fear response is the result of an important human adaptation process that prepares the body to respond to a threatening or dangerous situation. Normally, human beings can adapt to traumatic syndromes. However, when this adaptation results in an overgeneralization of danger cues, these patients perceive normal non-threatening situations as dangerous and respond with autonomic reactions and defensive behaviour [11].

Structures involved in the fear response mechanism in humans, include the lateral and central nucleus of the amygdala, the sensory cortex, the dorsal thalamus and the medium prefrontal cortex (m-PFC) including the anterior cingulate cortex (ACC) [11, 12]. The anterior cingulate cortex is part of the mPFC and will be discussed separately. Hippocampus also involved in memory function, provides contextual information about stimuli and therefore could provide a tool for studying PTSD [11]. The functional neurochemical systems that communicate between these structures are the glutamate and N-methyl-d-aspartate acid (NMDA) receptors, along with the calcium channels. The main output center for the response to fearful stimuli is the central nucleus of the amygdala, which mediates autonomic, behavioral, and endocrine response, related to fear [11]. The lateral amygdala connects directly to the central nucleus and transfers information related to fearful stimuli. NMDA receptors and calcium channel blockers may impair acquisition of fearful associations through the dorsal thalamus and the cortex [11].

Many of the main symptoms of PTSD e.g. nightmares, flashbacks, amnesia for the traumatic event, dissociative episodes or exaggerated startle response, represent at least in part, disturbances in neurocognitive processing [13].

The anterior cingulate gyrus is responsible for the maintenance of social mores, fear-related behavior, and selective attentional processing, as evidenced by the Stroop task: a test which examines executive functions. Anterior cingulate dysfunction may also play a role in the re-experiencing phenomena of sexual abuse and combat reported in PTSD, as indicated by PET studies [14-16].

The orbitofrontal cortex is also important for the process of extinction and hyperarousal symptoms. Working or explicit memory and the motor cortex are thus likely to play a role in the pathophysiology of re-experiencing in PTSD patients [15].

In an ongoing study of ours we have studied 1270 PTSD patients. The majority of these patients (77.9%) reported a stressful event just before the onset of dementia, while the rest of this group (22.1%) reported an insidious onset of a stressful event. This study started after the consultation of professor P. Grammaticos (Tsolaki M. and Grammaticos P. personal communication).

Functional neural processes have been widely studied by using techniques such as functional MRI, PET, and SPET as we shall mention below.

## Functional imaging

*In early AD and mild cognitive impairment (MCI),* functional imaging with PET or SPET has high sensitivity and can detect subtle pathophysiologic changes in the brain before structural changes actually occur [17, 18]. The regional cerebral blood flow (rCBF) measurements in dementia patients were first studied by European researchers in the late 1960s before the emergence of cross-sectional imaging devices [19, 20]. In the late 1970s and early 1980s, $^{18}$F-FDG and oxygen-15 ($^{15}$O) were used in PET to study rCBF [21-23]. PET camera has a spatial resolution of 5-6 mm, which theoretically may decrease to approximately 2.5 mm, which is the range of the $\beta^+$ particles into the tissues. Spatial resolution of SPET and MRI cameras are 8mm and 3mm, respectively. A PET examination may lead to 10 times lower radiation burden to the patient, in comparison to SPET, as the radionuclides in use for PET studies usually have a shorter half life [8]. SPET, cross-sectional rCBF imaging techniques developed in the late 1960s were soon established as a valuable clinical examination for the diagnosis of dementia disorders [24-27].

Most clinical SPET brain studies utilize a lipophilic substance called hexamethyl-propylene-amine oxime (HMPAO) labelled with technetium-99m ($^{99m}$Tc). Favorable characteristics of this agent include high first-pass extraction across the intact blood brain barrier (BBB) and close correlation with rCBF. Once across the BBB, the radiopharmaceutical enters the neuron and becomes a polar hydrophilic molecule remaining trapped inside the cell. Although up to 15% of the dose washes out in the first 2 min, there is little loss over the next 24 h. SPET image acquisition can be done anywhere from 15 min to 2 h after the injection of 555-740 MBq. The patient remains at a comfortable, quiet, dimly lit room, with open eyes and an intravenous butterfly already inserted, 10 min before and 5 min after the administration of the radiopharmaceutical [28].

Furthermore, there are other radiopharmaceuticals which can be used for rCBF brain studies in AD patients. These include isopropylamphetamine ($^{123}$I-IMP), trimethyl-hydroxymethyl-iodinebenzyl-propanediamine ($^{123}$I-HIPMD), dimethyl-sulphocarbamate labelled with thallium-201 ($^{201}$Tl), ethyl cysteinate dimer ($^{99m}$Tc-ECD) and xenon-133 ($^{133}$Xe).

Since 1985, it is possible to image metasynaptic muscarinic receptors by using either a muscarinic antagonist called quinuclidyl-benzylate ($^{123}$I-QNB), or iodine labelled lomerazine. Patients at an advanced stage of AD show a significant decrease of radiotracer uptake at the metasynaptic muscarinic receptor imaging [29]. It is also feasible to differentiate AD from dementia with Lewy bodies (DLB) by using radiolabelled cocaine analogues which are dopamine transporter radiopharmaceuticals [30] or even by assessing the cardiac uptake of metaiodobenzyloguanidine ($^{123}$I-MIBG), which is severely reduced in DLB, but remains normal in AD [31]. Theoretically, an NMDA receptor imaging agent, such as $^{123}$I- MK801, could be also used for SPET studies [32].

These methods are now used both for verification of the diagnosis of dementia as well as for the discrimination of different types of dementia. The diagnostic accuracy of PET and SPET studies to distinguish patients with AD from healthy elderly subjects was found in an evidence-based review to be comparable to the accuracy of a pathology diagnosis [33]. Concerning the discrimination between different types of dementia i.e. AD, Lewy body dementia and frontotemporal dementia, both PET and SPET studies have higher diagnostic sensitivity than clinical evaluation [33, 34].

## In MCI and AD patients

In MCI and AD patients rCBF findings are typical for AD and increase the probability of accurate diagnosis from 84% to 92% in case of "probable AD" and from 67% to 84% in patients with "possible AD" [35]. Reduction of rCBF in the temporoparietal regions is the most consistent change in mild to moderate AD [36, 37].

A recent three years follow up of MCI patients after a rCBF-SPET study, found reduced rCBF in the inferior parietal lobule, the angular gyrus or the precunei. This study had a high predictive value and discriminative ability to detect MCI subjects that finally became AD patients [38]. The $^{99m}$Tc-HMPAO-SPET studies also contribute to the differential diagnosis of AD and of Parkinson's disease. These two different pathological entities share a clinical pattern of subcortical dementia, characterized by rCBF reduction at the temporoparietal cortex. Cognitive impairment in AD is characterized by a decrease of the rCBF concerning the posterior parietal and the temporal brain cortex [29], as shown in Figure 1. In Parkinson's disease there is a reduction of rCBF at the occipital cortex, whereas in the long-lasting dementia of AD this reduction is found in the superior frontal cortex [29]. By using a rectangular shaped region of interest (ROI) during processing, an underestimation of rCBF differences in the AD patients was detected. It seems that, a ROI shaped according to the anatomical brain structures is preferable [29]. There are indications that the asymmetry of brain lesions in AD concerns mainly the left hemisphere, which shows greater decrease of the rCBF. On the contrary, the occipital visual cortex, somatosensory and motor cortex, basal ganglia, thalamus and cerebellum have a normal rCBF [28]. There seems to be a difference in the affected brain regions between early and late onset of AD. Elderly AD patients show involvement of the medial temporal lobes (MTL) associated with a marked memory loss whereas rela-

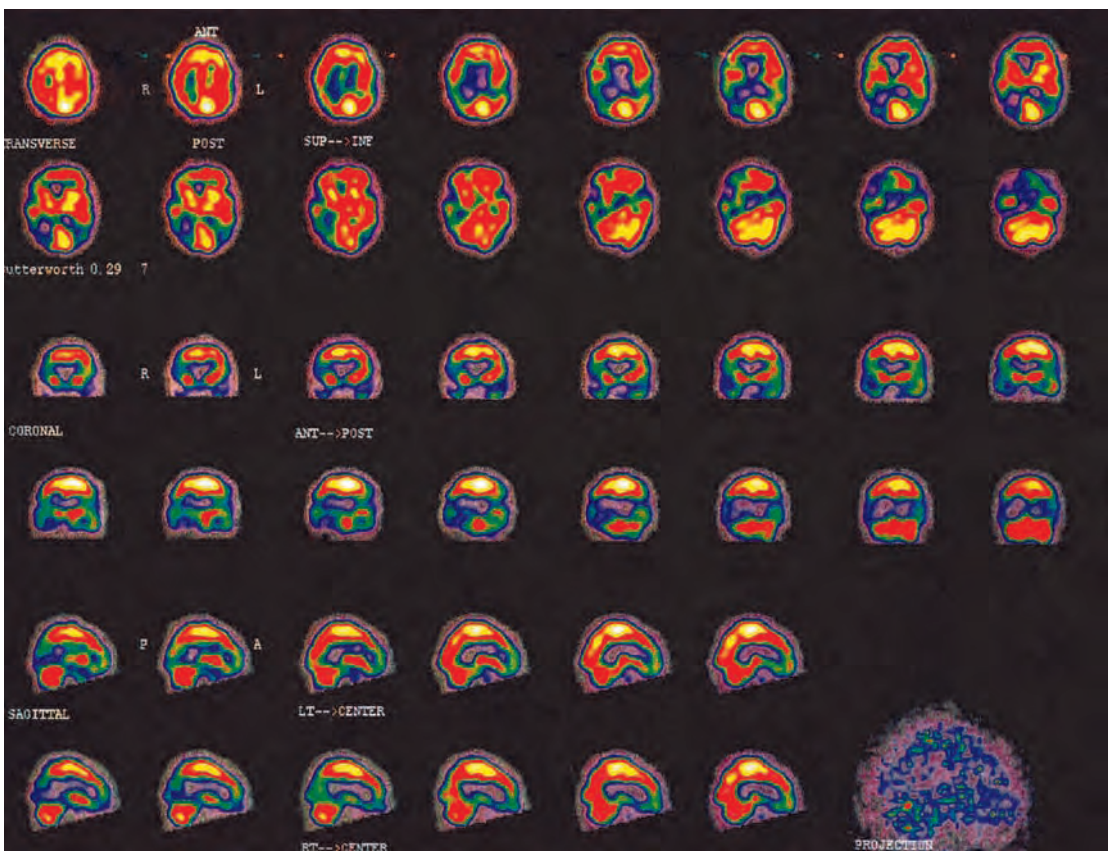


**Figure 1.** A SPET study in a patient with memory function impairment lasting 3 years, indicating AD, confirmed by mapping and semiquantitative analysis, showing bilateral reduction of rCBF in the temporal and parietal cortices.

tively younger patients with early onset of the disease predominantly have decreased rCBF in the posterior cortical regions [39].

What seems to be important in PET studies is the relationship between cerebral oxygen metabolic rate and cerebral perfusion, which is mostly affected at the advanced stages of dementia and has no correlation with age [29]. One of the major findings from the initial cross-sectional imaging PET studies was the regional and selective vulnerability of cerebral cortices, such as temporal and parietal cortices in AD. Reductions in global CBF and incerebrial metabolism were also found [22, 23]. Advanced brain mapping techniques revealed a preclinical reduction of metabolism in the posterior cingulate and cinguloparietal transitional cortices [40-42], while autopsy in end-stage AD patients revealed severe brain degeneration in the above areas [43].

The different imaging findings of AD related to age, have also been shown in voxel based morphometric studies with MRI [44] and should be considered in clinical practice. In patients with MCI and probable AD, fMRI revealed increased activity in the right superior frontal gyrus, bilateral middle temporal, middle frontal, anterior cingulate, and in the fusiform gyri [45]. Activity in other regions such as the right parahippocampal gyrus, left inferior frontal gyrus, bilateral cingulate and lingual gyri, right lentiform nucleus, right fusiform gyrus, and left supramarginal gyrus in AD, was decreased [45]. Relating these findings to those of SPET and PET imaging, it is obvious that in AD there is a predominant at the left brain hemisphere reduction of rCBF-SPET in the posterior parietal and temporal cortices with a frontal cortex involvement at severe cases, whereas the reduction of PET metabolism may also concern the posterior cingulate and cingulo-parietal transitional cortices, sparing the basal ganglia [22-23, 29, 40-42].

## In post-traumatic stress disorder

In post-traumatic stress disorder neuropsychological testing, sensory evoked potentials, electroencephalography, polysomnography, and various modalities for functional brain imaging, including SPET, PET and fMRI have been used to investigate neurocognitive processing [13]. Neuroimaging studies using MRI, PET, and SPET have provided valuable information on the pathophysiology of PTSD [46, 47]. Structural abnormalities in PTSD found with MRI include reduced hippocampal volume [48, 49] and nonspecific white matter lesions [50]. These abnormalities might reflect pretrauma vulnerability to developing PTSD or they may be a consequence of traumatic exposure in PTSD [51]. Disturbances in sensory processing are believed to play a prominent role in the hyperarousal symptoms of PTSD, such as the exaggerated startle response. Evoked potentials (also known as event-related potentials) have provided the most important tool to date in the study of sensory processing in PTSD [52, 53].

Although one recent MRI study detected no difference in hippocampal volume in PTSD abused children [54], another MRI study in adults with PTSD having explicit memory deficits, detected right-sided hippocampal atrophy [48]. One $^{15}O$-$H_2O$ PET study reported decreased blood flow of the right hippocampus in PTSD women whose traumatic experience was childhood abuse in contrast to sexually abused women with no PTSD [14]. In a SPET study comparing Vietnam combat veterans with PTSD to combat veterans without PTSD and to noncombatant controls, only the PTSD group exhibited left amygdala activation in response to exposure to combat sounds [55].

Recent functional imaging techniques in PTSD patients with $^{18}F$-FDG PET [56, 57] and functional MRI neuroimaging studies [58] during provocation of symptoms and cognitive activation have also showed increased activity in the amygdala and the anterior paralimbic structures, which are known to regulate negative emotions, like fear. In addition, these studies showed failure of activation of the cingulate cortex, which might play an inhibitory role in response to trauma-related stimuli [59] and also found reduced activity in Broca's area (motor speech) and other nonlimbic cortical regions [56]. These studies suggest that limbic regions and the prefrontal and temporal cortices are also involved in the pathogenesis of PTSD.

Patients with PTSD studied under resting conditions, by $^{99m}Tc$-HMPAO-SPET, showed increased CBF in the cingulate, the temporal and parietal regions, the caudate/putamen and the orbital and hippocampal regions [61]. Also SPET imaging of PTSD patients showed increased uptake of the radiotracer

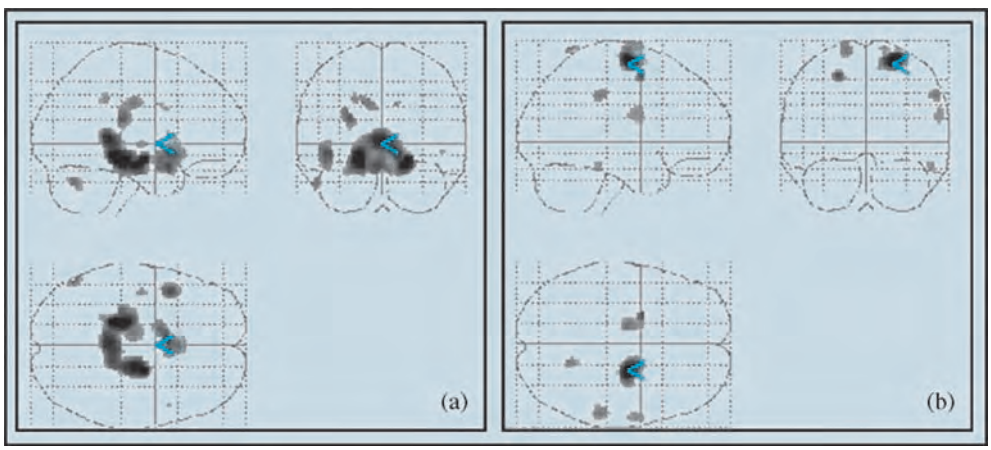


**Figure 2.** Maximum intensity projection images of (a) increased rCBF and (b) decreased rCBF levels in PTSD patients [60].

in limbic regions, i.e. hippocampus, parahippocampal gyrus, anterior cingulate gyrus, isthmic portion of the cingulate gyrus, and a portion of rhinencephalon [60] and decreased uptake of the radiotracer in the left parietal angular gyrus, left frontal precentral gyrus, left inferior temporal gyrus, and right occipital sub-gyral white matter [60], as demonstrated in Figure 2. The above findings [60-62] along with findings from SPET and PET studies using symptom provocation paradigms [55, 56] support the hypothesis of the involvement of the limbic regions, which are thought to regulate emotion and memory, in the pathophysiology of PTSD. Others in a preliminary analysis of rCBF patterns among PTSD patients and control groups during script-driven imagery found differential activation patterns in limbic and cortical regions [63]. PTSD patients did not activate the amygdala as did normal controls after activation process but activated bilateral insular/opercular regions more robustly than normal controls [64].

*In conclusion*, the present review describes pathophysiological characteristics and anatomical and functional imaging findings in AD and PTSD. Similarities between AD and PTSD exist in the areas of (a) medial temporal lobe, (b) hippocampus and (c) cingulate. Perhaps a severe psychological stress in elderly would be the beginning of neurodegeneration.

The main functional and structural imaging findings in AD are regional and selective vulnerability of temporal and parietal cortices, as well as metabolic reduction in other areas of the limbic system, along with a marked reduction in hippocampal volume and atrophy of the medial temporal lobe.

In PTSD, findings are more heterogeneous as there is anterior cingulate dysfunction, hippocampal atrophy and amygdala activation. Prefrontal and orbitofrontal cortices dysfunction, also contributes to PTSD. Stress, neurodegeneration dementia and PTSD seem to be correlated.

What seems consistent among various studies is that brain regions involved in the processing of memory, emotion/fear, and visuospatial orientation, when examined with nuclear medicine techniques demonstrate functional aberrations.

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