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# BRAIN IMAGING: A MIRROR FOR MILD COGNITIVE IMPAIRMENT IDENTIFICATION

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**ABSTRACT:** Imaging has played a variety of roles in the study of Mild Cognitive Impairment (MCI) over the last decades. In the beginning, computed tomography (CT) and then magnetic resonance imaging (MRI) were used diagnostically rule out other causes of dementia. Currently, a variety of imaging techniques including structural and functional MRI and positron emission tomography (PET) studies of cerebral metabolism with fluoro-deoxy-D-glucose (FDG) and amyloid tracers such as Pittsburgh Compound-B (PiB) showed characteristic changes in the brains of patients with MCI. None, of the imaging modality, can serve all purposes as each has unique strengths and weaknesses. The present modalities and their respective application are discussed in this article. The challenge for the future will be to combine imaging biomarkers for efficiently facilitating the diagnosis, disease staging and most importantly the development of effective disease-modifying therapies.

**KEYWORDS:** Mild Cognitive impairment, Cognition, Neuroimaging, Magnetic resonance imaging.

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## 1.INTRODUCTION

Neuroimaging is paving paths of transformation in mild cognitive impairment (MCI) research and practice in the last decades. Diagnostically, neuroimaging has moved from a minor exclusionary role to a central position. In research, neuroimaging is helping to address many of the scientific questions which is outlined in the work of Selkow et al. (2011) [1] providing insights into the effects

of MCI and its temporal and spatial evolution. Moreover, imaging is an established tool in drug discovery, as a safety marker specifically required in therapeutic trials as a part of inclusion criteria and as an outcome measure [2]. Simultaneously, the potential of neuroimaging has expanded rapidly with new techniques and novel approaches of acquiring images and of analyzing them. This article cannot be comprehensive. Instead, it addresses broad categories of structural, functional and molecular imaging in MCI. The specific modalities included are magnetic resonance imaging (MRI; both structural and functional), Diffusion tensor imaging (DTI) and positron emission tomography (PET; for assessment of both cerebral metabolism and amyloid). These modalities have different limitations, strengths and as a result, have different and often complementary roles and scope.

**Imaging in the diagnosis and prognosis of MCI**

There is uncertainty inherent in a clinical diagnosis of MCI, which impels to search for diagnostic imaging markers. A definitive diagnosis still needs histopathological confirmation and the inaccessibility of the brain means imaging has a key role as a "window on the brain [3]." Earlier imaging first computed tomography (CT) and then MRI was applied for the exclusion of potential surgically treatable causes of cognitive decline. However, currently, imaging in diagnosis also includes providing positive support for a clinical diagnosis of MCI in symptomatic individuals by identifying characteristic patterns (signatures) of structural and functional cerebral alterations [4]. Even though, visualization of the specific molecular (amyloid deposits) pathology of the MCI is possible with amyloid imaging. On the contrary, this increasing specificity for MCI, imaging also contributes to differential diagnosis in practice by identifying alternative and/or contributory pathologies. Neuroimaging is central to identifying vascular and non-Alzheimer's disease (AD) degenerative pathologies and helps in the recognition of the prevalence of mixed pathology in dementia. In 2004, Petersen et al. [5] elaborated, that identification of MCI underlying pathology has immediate prognostic importance [6-7]. Mitchell and Shiri-Feshki [9] in his meta-analysis concluded that a small fraction of patients with MCI progress to clinical AD over 5–10 years.

**A. Structural neuroimaging**

Structural imaging deals with the structure of the nervous system and the diagnosis of gross (large-scale) intracranial disease (such as a tumor) and injury [10].Usually MRI and DTI is carried out for the structural imaging of the brain.

**1. Magnetic resonance imaging**

Nuclear magnetic resonance is the scientific principle behind MRI, which was initially investigated by Isidor Rabi [11], later on, Felix Bloch and Edward Purcell in then 1940s [12-13] further investigated the NMR phenomenon in liquids and solids. Paul Lauterbur and Sir Peter Mansfield [14-15] formulate the basis for MRI. All the above five of scientists are Nobel laureates- in 1944 in Physics Rabi awarded the Nobel Prize, followed by Bloch and Purcell in 1952 in Physics received the Nobel Prize for nuclear magnetic resonance. Later on, Lauterbur and Mansfield shared the Nobel

Physiology or Medicine in 2003 for developments in MRI. In 1977 the first human MRI images were obtained and since 1980s MRI scanners have become increasingly popular in medical [16]. Tomography and CT were two of the most important radiological methods before the development of MRI. Tomography was invented in the 1930s by radiologist Alessandro Vallebona and is based on moving the X-ray tube and the film synchronously in opposite directions. The development of computers in the 1970s led to the emergence of CT [17]. In the present scenario, CT is still mostly used as it is rather inexpensive, has a short imaging time and technical developments enabled its usage e.g. in angiography. The disadvantages of CT compared to MRI are the moderate to high doses of ionizing radiation and inferior spatial resolution. Medical MRI based on the imaging of protons of hydrogen nuclei, as hydrogen is present in water, which is abundant in human tissues. Various analysis methods are currently available the structure of in vivo. MRI is based on the magnetic properties of atomic nuclei. A strong, uniform, an external magnetic field applied for alignment of protons, which are generally oriented random fashion within the water nuclei of the tissue examined. This magnetization or alignment disrupted by the introduction of an external Radio Frequency (RF) energy. The atomic nuclei back to their resting alignment via various relaxation processes and by doing so it emit RF energy. After a few periods of interval followed by the initial RF, the emitted signals are measured [18]. The frequency information contained in the signal from each location in the imaged plane converted to corresponding intensity levels, which then displayed as shades of gray in a matrix arrangement of pixels via Fourier transformation [19, 20]. Different types of images created with the variation of the sequence of RF pulses applied & collected. Echo (TE) known as the time between the delivery of the RF pulse and the receipt of the echo signal as Time. The amount of time between successive pulse sequences applied to the same slice known as Repetition Time (TR) [21]. Target tissue characterized by two different relaxation times – T1 and T2. T1 or longitudinal relaxation time is the time constant that determines the rate at which excited protons return to equilibrium. Longitudinal relaxation time measures time taken for spinning protons to realign with the external magnetic field [22]. T2 or transverse relaxation time is the time constant, which determines the rate at which excited protons reach equilibrium or go out of phase with each other. Transverse relaxation time measures time taken for spinning protons to lose phase coherence among the nuclei spinning perpendicular to the main field [23].

**1.1 MRI imaging sequences**

T1-weighted and T2-weighted scans are the most common MRI sequences. Of these two, scan T1-weighted images generated by using short TE and TR times. T2-weighted images are generated by using longer TE and TR times and the contrast and brightness predominately determined by the T2 properties of tissue [24]. T1- and T2-weighted images differentiated by looking at the CSF. On T1-weighted imaging, CSF appears dark and on T2-weighted imaging, it appears bright. Apart from them, the third commonly used sequence is the Fluid Attenuated Inversion Recovery (Flair). Flair

sequence and T2-weighted image are quite similar except that the TE and TR times are very long. In Flair, abnormalities remain bright but normal CSF fluid attenuated and made dark. Flair sequence is quite sensitive to pathology and makes the differentiation between CSF and an abnormality much easier [24].

**1.2 MRI in the Study of MCI**

A characteristic structural finding in MCI is atrophy of cortex and hippocampus [25]. Neuropathological studies demonstrated the presence of neuropathological changes in the MTL in MCI [26]. Moreover, MTL atrophy studies have whole-brain widespread cortical GM decline in areas including the anterior and posterior cingulate, lateral temporal and parietal cortices, insula and thalamus [27]. The heterogeneity of MCI is also reflected by atrophy patterns and indicates different brain structures were affected according to MCI subtype [28]. According to that study, amnestic single and multiple domain MCI was characterized by Grey matter (GM) loss the medial and inferior temporal lobes, multiple domain groups also had atrophy in posterior temporal lobe, parietal association cortex and posterior cingulate [28]. In contrast, the non-amnestic single atrophy in the left anterior inferior temporal lobe and single domain MCI subjects with attention deficits suffered from atrophy in the basal forebrain and hypothalamus [28]. As previous studies showed that MCI subjects will remain stable and some will progress to dementia, great interest focused on attempts to identify the features predicting future conversion. A recent longitudinal 15-year follow-up study, of ventricular enlargement, concentrating on healthy aging and MCI revealed that the rate of annual ventricular volume change was greater in subjects with MCI compared to healthy controls. The rate of ventricular volume expansion accelerated further 2.3 years prior to MCI diagnosis [29]. The cortical areas observed to lose GM in relation to the conversion from MCI to AD inferior and middle temporal gyrus, posterior cingulum precuneus inferior frontal and supramarginal gyrus.

As, hydrogen atoms are naturally abundant in people and other biological organisms, particularly in water and fat. Some nuclei of the atom are able to absorb and emit radio frequency energy when placed in an external magnetic field. In clinical and research MRI, hydrogen atoms most often used to generate a detectable radio frequency signal that received by antennas in close proximity to the anatomy examined [30]. MRI scans specifically map the location of water and fat in the body. Radio waves pulse excite the nuclear spin energy transition, and magnetic field gradients localize the signal in space. By varying the parameters of the pulse sequence, different contrasts generated between tissues based on the relaxation properties of the hydrogen atoms therein. Proton molecule alignment under the magnetic field used in the identification of MCI and AD as compared to healthy control [18].

**2. Diffusion tensor imaging**

Diffusion MR imaging of the brain was first applied for use in clinical neuroradiology during early 1990 [31]. Since that time, enormous improvement makes forward the technology of diffusion

imaging, this makes greatly improved image quality and enabled many new clinical applications. Moreover, the advancement DTI and fiber tractography has opened an entirely new noninvasive window on the white matter connectivity of the human brain [32]. DTI and fiber tractography has advanced the scientific understanding of many neurologic and psychiatric disorders and usually applied clinically for the pre-surgical mapping of eloquent white matter tracts before intracranial mass resections [33]. DTI is a quantitative MRI technique that measures the movement of water within the tissue microstructure [34]. It is an extended form of diffusion-weighted imaging, which measures water diffusion in three gradient directions to allow an estimation of the trace of the diffusion tensor. DTI employs rigorous repetitions of scanning and application of magnetic diffusion gradient in more directions (at least six) to acquire a diffusion tensor [34]. From the tensor, the two commonly derived quantitative measures that inform us about cellular microstructure are fractional anisotropy and mean diffusivity. Fractional anisotropy is a measure of anisotropic water diffusion, and reflects the degree of directionality of cellular structures within the fiber tracts and therefore their structural integrity. It obtained from the magnitude of diffusion tensor due to anisotropy. In a purely isotropic media, fractional anisotropy would be zero, and with increasing anisotropy, the value tends to one [35]. Mean diffusivity is a measure of diffusion in the non-colinear direction or free diffusion. It represents a loss of anisotropy, which results in an increase in free water diffusion and consequentially increased mean diffusivity [36]. Loss of anisotropic diffusion related back to abnormalities within the cellular microstructure to provide information about their structural integrity.

**2.1 Diffusion tensor imaging as Applied to MCI**

DTI studies in MCI have further investigated the posterior circuitry hippocampus, parahippocampal white matter, temporal white matter, and posterior cingulum, affected in Alzheimer's disease [37]. There was reduced anisotropy in the posterior cingulum, especially on the left, when MCI subjects compared to control [38]. The microstructural abnormality in the posterior cingulum correlated with performance on a delayed verbal recall test, which demonstrates episodic memory ability – a function of the posterior cingulum [38]. White matter regions connecting the posterior cingulum and other limbic structures affected in MCI. Both temporal white matter and parietal white matter found to have reduced anisotropy in MCI subjects compared to controls [39]. The parahippocampal white matter, i.e. fibers projecting from the hippocampus and entorhinal cortex affected in MCI. Thus far, all comparative cross-sectional DTI studies involving MCI and control subjects have shown consistent findings of white matter microstructural changes in the parahippocampal white matter, splenium of the posterior cingulum, temporal white matter, parietal white matter, and corpus callosum. They have also demonstrated a greater posterior than anterior involvement. Only one study found a reduction in anisotropy in the frontal matter [40]. The internal capsule has generally reported to spared; however, the centrumsemiovale, which made up of association fiber bundles

connecting the internal capsule and corpus callosum, found to have a significantly increased mean diffusivity in MCI subjects as compared to controls [38]. Subcortical grey matter structures, which might be highly susceptible to vascular pathologies such as lacunar infarcts or neurodegeneration, may also lead to the clinical syndrome of MCI [41]. These deep gray matter structures, such as the thalamus and lentiform nucleus, receive afferent projections from the substantial innominata in the nucleus basalis of Meynert, which consists of fibers rich in acetylcholine and choline acetyltransferase [42]. In one study, a reduction in fractional anisotropy found in the right thalamus in amnestic MCI subjects as compared to controls [43]. This finding lends support to the fact that there may be vascular contributors to the pathology of MCI and Alzheimer's disease, or that degeneration of the cholinergic fibers arise as part of the cholinergic theory of Alzheimer's disease leading to secondary neurodegeneration into areas in which they project [44]. Structural MRI studies have shown that when a demonstrable amount of volume loss has occurred in the hippocampus, a known pathological process in Alzheimer's disease, there are associated memory deficits. So far, only one study has reported significant increases in mean diffusivity in bilateral hippocampi in MCI [45]. However, another study that looked at the hippocampus failed to detect any significant changes in DTI measures. This indicates that changes in anisotropy in the hippocampus may not be readily detectable by DTI during MCI due to atrophy occurring in different regions of the hippocampus. When the regions where changes found were compared between Alzheimer's disease and MCI subjects, they showed distinctive similarities. The only reported difference was in the posterior cingulate and splenium of the corpus callosum [46]. Therefore, DTI considered having potential utility in clinical practice in early detection of MCI and monitoring its progression. This achieved by analyzing regions such as the posterior cingulate, which have been demonstrated to be affected in MCI and proven to be affected in the AD, correlating microstructural abnormalities with subjective symptomatology or objective neuropsychological testing. A summary of findings from all the reviewed DTI studies of MCI presented. There are a number of limitations to the studies currently available in the literature. Most of the studies have small sample sizes, are convenience samples recruited from memory/dementia clinics, diagnostic criteria for MCI were not uniform and longitudinal follow-up is generally lacking. Hence, diffusion of the water molecule in the brain, used for identification of degenerated neurons, neuronal fiber tract, and specific brain region. This diffusion mechanism help in identification of MCI and AD as compared to healthy control individual.

**B. Functional neuroimaging**

Functional neuroimaging is used to measure the aspect of brain function, generally for the better understanding of the relationship between specific brain areas and mental function by using advent neuroimaging technology. Functional magnetic resonance imaging (fMRI), Arterial spin labeling

(ASL), Fluorodeoxyglucose (FDG) PET, Amyloid PET, Magnetic resonance spectroscopy (MRS) is used for functional analysis of the brain.

**1.Functional magnetic resonance imaging**

Most of the fMRI method based on the blood-oxygen-level-dependent (BOLD) contrast, which relies on neurovascular coupling. In 1890, Sherrington found that the vascular the brain varied functional activity [47]. Later on it was found that the blood flow is regulated by a mechanism – either neuronal or biochemical – that is dependent on neuronal firing, but independent of the cerebral metabolic rate [48] and more recently, it has been speculated that the hemodynamic responses might be regulated by neurotransmitter-related signaling [49, 50]. Venous blood in the active brain area is more oxygenated hemoglobin, and relatively less deoxygenated. Oxyhaemoglobin is diamagnetic in nature, thus having little effect surroundings whereas deoxyhemoglobin is paramagnetic, introducing magnetic inhomogeneity and distortions to its environment [51]. Hence, the in the amount hemoglobin leads to enhancement in MRI in the active brain areas and the BOLD contrast thus represents hemodynamic changes. The Ogawa et al. [66] showed that paramagnetic used as a naturally occurring contrast agent in fMRI. Belliveau et al., 1991 performed the fMRI experiment thereafter, in the primary visual task [52]. Although, in their study, the contrast agent. Logothetis et al. [53] showed that BOLD responses in fMRI studies correlate with neuronal local field potentials as demonstrated by simultaneous fMRI and intracortical recordings in monkey visual cortex, and thus the BOLD neuronal input and activated area. In general, the localization of activation in fMRI studies is the time when the BOLD response is at its peak. Frahm et al. [54] showed that undershoot reflects the time when the perfusion and oxygen consumption gravitate to a new equilibrium state to compensate for the initial nonoxidative glucose consumption. Logothetis et al. [53] partly, can also indicate shown that neural inhibition precedes the undershoot. A linear relationship between able to interpret actual brain activity. There is some ambiguity on the relations of hemodynamic and neural responses as one study reported that the coupling was linear [53] however, other studies have demonstrated that there are also nonlinear effects that may complicate the interpretation of fMRI results [54-56]. D'Esposito et al., [57] when fMRI is used in elderly individuals, the interpretation of the BOLD signal is further exacerbated by alterations in the cerebrovascular system that may affect neurovascular coupling. D'Esposito et al. and Bangen et al. [57-58] showed that these changes that may occur even in clinically asymptomatic elderly subjects include altered cerebrovascular ultrastructure, reduced elasticity of vessels, increased atherosclerosis, reduced cerebral blood flow in the resting state, decreased resting-state cerebral oxygen consumption metabolic rate and reduced vascular reactivity to chemical modulators. However, despite these limitations, BOLD fMRI has produced important information on brain function, will likely improve our understanding of the neurovascular coupling.

**1.1 Functional MRI and MCI**

lesions in AD appear in the MTL, the focus of imaging studies in MCI [59]. However, the findings on MTL function in MCI have been controversial. Machulda et al. [60] activation in MCI controls was detected while they were asked to encode pictures of people engaged in activities of daily living. Dickerson et al. [61] In contrast, increased hippocampal activity in MCI compared was present during face-name pairs. The discrepancy between these findings related to differences in the definition of MCI or in the severity of cognitive decline. Dickerson et al. [61] In support of the latter possibility, it has been shown that MCI subjects with greater impairment, as evaluated by the CDR Sum of Boxes scale, recruit the para-hippocampal gyrus to a larger extent during visual encoding and thus the increased activation may reflect a compensatory mechanism for the progressive neuro-pathological burden in the MTL. Miller et al. [62] Accordingly, it has been shown recently in a follow-up hippocampal activity in MCI subjects predicted a greater degree and cognitive decline, even when accounting baseline cognitive status, age, education, gender, hippocampal volume, and APOE status. It has also been demonstrated that the hippocampal activity in the MCI subjects does not show dynamic attenuation associated with healthy controls, the learning difficulties in MCI. The brain structure that is reported to exhibit functional changes related to MCI in fMRI studies is the. When MCI subjects undertook a task activation in posterior cingulate cortex older subjects. Heun et al. 2007 [63] activity in MCI correct recognition processing, been detected in MCI subjects who later progressed to dementia. The integrity of the default mode network, or resting state activity, investigated in MCI [64]. Anterior frontal was observed in MCI compared to controls, with frontal cortex [65]. The more impaired MCI displayed a loss parietal regions during memory tasks, however, the less impaired MCI subjects still had the capability of these structures. also correlated with hippocampal function, suggesting that the MTL have an impact on cortical function. between control and MCI thus been detected as discussed above [66]. Since the functional changes in the brain probably precede the structural alterations, suggested that fMRI might detect subjects0 with cognitive impairment in an earlier phase than structural imaging. Functional MRI (fMRI) increasingly used to probe the functional integrity of brain networks supporting memory and other cognitive domains in aging and early AD. Ogawa et al. 1990 [67-68] fMRI is a noninvasive imaging technique which provides an indirect measure of neuronal activity, inferred from measuring changes in blood oxygen level–dependent (BOLD) MR signal. Whereas fluoro-deoxy-D-glucose (FDG)-PET thought to be primarily a measure of synaptic activity, BOLD fMRI is considered to reflect the integrated synaptic activity of neurons via MRI signal changes because of changes in blood flow, blood volume, and the blood oxyhemoglobin/ deoxyhemoglobin ratio [53]. FMRI can be acquired during cognitive tasks, typically comparing one condition (e.g., encoding new information) to a control condition (e.g., viewing familiar information or visual fixation on a crosshair), or during the resting state to investigate the functional connectivity (FC-MRI) within specific brain networks. Fc-

MRI techniques examine the correlation between the intrinsic oscillations or time course of the BOLD signal between brain regions [69] and have clearly documented the organization of the brain into multiple large-scale brain networks [70]. Both task-related and resting fMRI techniques have the potential to detect early brain dysfunction related to AD, and to monitor therapeutic response over relatively short time periods; however, the use of fMRI in aging, MCI, and AD populations thus far has been limited to a relatively small number of research groups. Decreased or increased brain blood oxygen signifies brain metabolic state. Brain oxygenated and deoxygenated applied for the identification of MCI and AD as compared to the healthy control.

**2. Arterial spin labeling**

ASL is another type functional MR imaging technique. ASL measures cerebral blood flow (CBF) using arterial water as an endogenous contrast agent [71-72]. In ASL, a region is applied for saturation of towards the brain, a signal is derived by observing the effects of the spin inversions locally in the brain [73]. ASL is a direct measure the blood flow, and not depend on many physiological effects in the same way as BOLD [74]. In addition, ASL localizes the brain activation areas more precisely as compared to BOLD since it reflects changes in the arterial side of the vasculature however the BOLD the venous side [75].

**2.1 ASL and MCI**

MCI patients have hypoperfusion in bilateral parietal lobes [76], posterior cingulate cortex (PCC) [77] and precuneus [78], left (L) occipital lobe, and bilateral frontal and temporal lobes [79], compared to healthy controls (HC). A study also showed an increase in perfusion in the L hippocampus, [80] right (R) amygdala and basal ganglia [including a rostral head of the R caudate nucleus, ventral putamen, and globus pallidus] [81]. Considering patients with fully developed AD, hypoperfusion areas are also present in the PCC and precuneus, bilateral parietal and temporal lobes, [82] and bilateral superior and middle frontal gyri [83]. Additionally, temporo-occipital and parieto-occipital association cortices, L limbic lobe, and L orbitofrontal cortex also depicted hypoperfusion in certain studies. On comparison task at baseline or at risk of AD [due to their APOE4 genotype and family history showed reduced activation in the para-hippocampal gyrus [29] and hippocampus compared to controls. It is relevant that amnestic MCI patients at risk of AD presented elevated perfusion in the hippocampus at baseline, which might suggest that individuals with MCI or AD may lack the dynamic capability to modulate regional CBF in response to task demands [80]. From these studies, concluded that MCI and AD depict similar regions of perfusion changes, in particular, more or less restricted areas of hypoperfusion in the PCC, precuneus, and other parietal regions, along with areas of hyperperfusion in the middle temporal lobe in some studies [81]. Specifically, the identification of hypoperfusion in the PCC and precuneus had a sensitivity/specificity of 91%/ 80percentage, however using a combination of different regions in subjects with amnestic and dysexecutive MCI the accuracy was 60–70% [85]. The increased and decreased CBF implies that

central nervous metabolism is highly variable during the transition from normal cognition to AD through MCI. Supports the hypothesis that there is an early compensatory cellular mechanism coupled to the vascular mechanism associated with the AD pathological process that appears to more pronounced in MCI state.

**3. Fluorodeoxyglucose PET**

Brain FDG PET primarily indicates synaptic activity [86]. Because the brain relies almost exclusively on glucose as its source of energy, the glucose analog FDG is a suitable indicator of brain metabolism and, when labeled with Fluorine-18 [half-life 110 min] is conveniently detected with PET [87]. The brain's energy budget is overwhelmingly devoted to the maintenance of intrinsic, resting [task-independent] activity, which in cortex largely maintained by glutamatergic synaptic signaling [88]. FDG uptake strongly correlates at autopsy with levels of the synaptic vesicle protein synaptophysin [89]. Hence, FDG PET is widely accepted to be a valid biomarker of overall brain metabolism too which ionic gradient maintenance for synaptic activity is the principal contributor [90-91].

**3.1 Utility of FDG PET in the Study of MCI**

In patients with MCI compared with HC, voxel-wise ANOVA demonstrated a pattern of reduced FDG uptake in the bilateral inferior parietal cortex, superior temporal cortex, precuneus, posterior cingulate cortex, mesial temporal cortex, and right dorsolateral prefrontal cortex [92-95]. aMCI subjects with exclusive or prevalent long-term memory deficits and a slow cognitive progression did not show the FDG-PET hypometabolism pattern typical of AD. They had reduced glucose metabolism in the medial temporal lobe structures with no amyloid load visualized by PET imaging in these structures [96]. In addition to the consistent pattern of reduced metabolism in the hippocampal structures, hypometabolism in the frontomedial cortex, insula and anterior superior temporal cortex was present in some subjects [97-98]. A few subjects showed the reduction of glucose metabolism in the posterior cingulate cortex [99], which can be interpreted as a functional disconnection effect due to the severe involvement of the hippocampal structures. As reported in the literature, even in the absence of grey matter loss or amyloid toxicity in the posterior cingulate cortex [99] grey matter loss in the medial temporal lobe structures is sufficient to cause remote metabolic effects in connected regions [100]. The use of FDG-PET in the diagnosis of prodromal AD, FTLD, and DLB in MCI subjects mainly relied on the patterns of hypometabolism. In particular, the pattern of hypometabolism in the posterior cingulate and posterior temporoparietal areas that characterize MCI converting to AD considered helpful in the diagnosis of AD in MCI subjects [101]. In the diagnosis of MCI possibly due to DLB, again the primary role of FDG-PET may be the identification of non-neurodegenerative conditions, based on the negative predictive value of a normal scan [102].

## 4. Amyloid PET

On April 6, 1992, the food and drug administration (FDA) approved the clinical use of amyloid beta imaging probe Amyvid (Florbetapir-F-18) injection for the evaluation of AD [103]. Amyloid imaging provides an in vivo quantitative estimate of Aβ amyloid pathology that may serve this role. The PET ligand N-methyl (11C) 2-[4'-methylaminophenyl]-6-hydroxybenzothiazole, or Pittsburgh Compound-B [PiB], has been the most widely studied and promising agent to date. PiB is a thioflavin-T derivative that binds to fibrillar amyloid. PiB retained in patients with AD in a pattern consistent with pathological descriptions of amyloid plaque distribution. The 11C-Pittsburgh compound B (11C-PiB) radiotracer used to measure regional 11C-PiB binding retention rates, thus allowing for the visual and quantitative measurement of Aβ deposition. 11C-PiB is a fluorescent derivative of thioflavin T that preferentially targets and binds to fibrillar Aβ forms found in dense core plaques with high affinity and specificity [104]. Thioflavin binds specifically with Aβ40 and Aβ42 fibrils and insoluble plaques containing the aforementioned Aß peptides. PiB binds low affinity to soluble or nonfibrillar Aß plaques until plaques have reached a crucial magnitude, which has yet to be determined. Price et al. [105] first reported PiB based categorization of MCI in their research work. Sperling et al. [106] in there in vivo amyloid imaging that high level of amyloid deposition is associated with aberrant default network functional magnetic resonance imaging [fMRI] activity in asymptomatic older individuals. Amyloid-PET has positive and negative imaging based on the uptake of the isotopes at grey and white matter [107]. Amyloid radiopharmaceutical binds with the amyloid beta plaques within the neurons. Negative scan shows spores to neuritic plaques and is consistent with a neuropathological diagnosis of AD at the time of image acquisition. A negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive scan is used for visualization of moderate to frequent amyloid neuritic plaques. The neuropathological examination had shown that this amount of amyloid neuritic plaque is present with AD [107]. Binding of chemical compound with the amyloid beta and the intensity the fluorescence can help in identification of MCI and AD from healthy control individuals.

### 4.1 Amyloid PET in MCI

Amyloid imaging will be an important tool in the diagnosis and prognosis of patients with MCI. Both amnestic and non-amnestic subtypes of MCI are heterogeneous populations with prodromal AD represented in both groups [108]. Understanding the role of the distribution of amyloid deposition in the different phenotypic expressions of AD will be valuable in enhancing our understanding of the pathophysiologic process of the disease [109]. While our current cohort is modest in number, limiting statistical inference, elevated uptake is associated strongly with predictors of conversion to AD and eventual clinical progression. Nonetheless, further longitudinal study needed to confirm that the presence of amyloid in this and similar cohorts signify early clinical AD [110]. If effective anti-amyloid therapy becomes available for the treatment of MCI, it will be

critical to distinguish those patients likely to benefit from those who would bear the cost and adverse events with no prospect of improvement. Amyloid imaging with PiB may be one way to make this important distinction [111]. Amyloid-positive a-MCI patients with poor memory and greater medial temporal lobe atrophy than the amyloid-negative patients. In temporal, parietal, posterior cingulate, and frontal regions FDDNP-PET binding found decreased in control as compared to healthy control [109].

**5. Magnetic resonance spectroscopy**

MRS or in other words nuclear magnetic resonance (NMR) spectroscopy is a non-invasive, ionizing-radiation-free analytical technique. It used to study metabolic changes in brain disorders [112]. MRS is an analytical technique used to complement the more common MRI for the characterization of tissue [113]. Both MRS and MRI techniques typically acquire the signal from hydrogen protons (other endogenous nuclei such as those of Carbon, Nitrogen, and Phosphorus are also used). Although, MRI acquires a signal from primarily from protons, which reside within water and fat, which are approximately a thousand times more abundant than the molecules detected with MRS [114]. Due to which, MRI mostly uses the larger available signal very clean 2D images formation, although MRS very frequently only acquires a signal from a single localized region, referred to as a "voxel". MRS used to determine the relative concentrations and physical properties of a variety of bio-chemicals frequently referred to as "metabolites" due to their role in metabolism [112]. MR spectroscopy conducted on the same machine as conventional MRI. MRI scan implies a powerful magnet, radio waves, and a computer for creation of the detailed images. MR spectroscopy is applied for molecules such as hydrogen ions or protons. The frequency of these metabolites (chemical shift) is measured in units called parts per million (ppm) and plotted on a graph as peaks of varying height. With the measurement of each metabolite's chemical shift (ppm) and comparing it to normal brain tissue, the neuroradiologist can determine the type of tissue present. MRS assesses brain metabolite levels and its parameters expressed as concentration or ratios to standardized values. On examination of region-specific changes in AD, lower N-acetyl aspartate (NAA), NAA/Creatine (Cr), higher myo-Inositol (mI), and mI/Cr ratios found in parietal regions [114]. Parietal NAA/mI ratios deemed a valid discriminator of AD. In MCI, NAA/mI ratios lowered and Choline (Cho)/Cr ratios increased in the posterior cingulate gyrus, however, mI/Cr ratios increased in the hippocampus. Clinically, a reduce NAA markers are predictive of phenol conversion to dementia and cognitive dysfunction [115-116]. NAA/Cr and NAA/mI ratios discriminate AD from VaD and glutamate/Cr ratios differentiate DLB from AD. Metabolic ratios are substantially lower in AD patients compared to VaD, but higher in widespread brain regions relative to DLB [117]. Although, MRS is able to study molecular processes in the brain non-invasively without exposure to ionizing radiation, this technique limited by its low sensitivity. Resultant attenuated signal strength makes it difficult to recommend its use by clinicians for diagnostic purposes in AD and MCI [117]. MRS is

able to predict the occurrence of MCI or AD because of metabolic alteration in the brain. These altered metabolites identified based on their varying chemical shift [ppm] in diseased and healthy control brain of individuals.

## 2. CONCLUSION

The search for therapies that can modify the course of AD to slow, delay, or prevent it is clearly the most important challenge. Academia and industry have a major aim to find biomarkers that could identify disease-slowing effects earlier and/or with significantly fewer subjects exposed to the treatment. Imaging is being increasingly incorporated into trial designs to measure the effects of therapy on fibrillary amyloid [with amyloid imaging] on atrophy (with MRI) and on metabolism (PET and fMRI). As increasingly, biologically active therapies studied, so to have side effects increased. Imaging appears as a means of detecting potential adverse effects, which can initially be clinically silent or go unrecognized because of a patient's level of cognitive impairment and confusion. Particularly with more biologically active therapies, regular monitoring, or safety scans, are now a prerequisite in such trials. It may be necessary to intervene at a very early stage to affect disease modification has led to an interest in "prevention" studies. Preclinical intervention studies, almost by definition, are difficult to power on clinical outcomes. Imaging and other biomarkers are likely to needed to select subjects for these studies and to provide outcome measures that can assess whether therapies are having a disease-modifying effect which could effectively translate into a delay in clinical onset of MCI.

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## CONFLICT OF INTEREST

None

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