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Magnetic Resonance Spectroscopy in Common Dementias

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1-Introduction

Aging is the primary risk factor for dementia. With increasing life expectancy and the aging populations around the world, dementia is becoming a significant public health problem of the century. The most common pathology underlying dementia in older adults is Alzheimer's disease (AD). Cerebrovascular disease and Lewy body disease pathologies are other common causes of dementia in the elderly and in many instances AD is also present in patients with dementia with Lewy bodies (DLB) and vascular dementia (VaD). A relatively less common type of dementia is frontotemporal lobar degeneration (FTLD), which tends to affect younger individuals compared to other dementia pathologies. The focus of this chapter is potential role of proton magnetic resonance spectroscopy (^{1}H MRS) in these common dementias.

2- MRS in Alzheimer's Disease

Initial magnetic resonance spectroscopy (MRS) studies in Alzheimer's disease were limited to phosphorous magnetic resonance spectroscopy (^{31}P MRS) revealing alterations in membrane phospholipid metabolism [1–4]. In 1992, Klunk et al. demonstrated the decrease in the neuronal metabolite N-acetylaspartate (NAA) on proton MRS using perchloric acid extracts from AD brains [4]. Soon after, an in *vivo* MRS study revealed elevated glial metabolite *myo*inositol to creatine (mI/Cr) levels in patients with AD along with decreased NAA/Cr [5]. Further investigations in patients with AD confirmed this finding [6–17] (Figure 1). Many of these early studies also revealed that the increase in mI/Cr and decrease in NAA/Cr in AD was not associated with a change in Cr using absolute quantification methods [10, 11, 14, 18–21]. For this reason Cr is commonly used as an internal reference in MRS studies of AD to account for individual and acquisition related variability. There have been conflicting reports on choline (Cho) levels in AD. Some studies found elevated Cho or Cho/Cr levels [8, 9, 12], while others found no changes in Cho or Cho/Cr levels in AD[10, 13, 19, 20] . Decreased glutamate plus glutamine levels have been found in a number of studies in AD [22, 23].

Regional alterations of ^{1}H MRS metabolites in patients with AD appear to be wide-spread [8, 24] involving the parietal[25, 26], medial and lateral temporal[7, 20, 27] and the frontal lobes[17, 25]. Furthermore, decreases in NAA or NAA/Cr correlate with dementia severity [6, 28],cognitive function [29, 30], behavioral and psychiatric symptoms[31, 32] indicating that NAA is a marker for AD severity on various clinical features.

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Most of the ^{1}H MRS studies in AD have utilized single voxel ^{1}H MRS. Choice of the single voxel ^{1}H MRS region for detecting and monitoring metabolite levels in AD depends both on the pathophysiology of AD and the technical considerations. The neurofibrillary pathology of AD and associated neuronal loss involves medial temporal lobes earlier and more severely than other regions of the brain. While ^{1}H MRS from the medial temporal lobe or hippocampus yields spectra of reasonable quality using long echo times (TE =130–272 ms), it may be more difficult to achieve MR spectra of consistent quality from the hippocampus using short echo times required for quantification of the mI peak (TE <35 ms) [33, 34]. At 4 Tesla using adiabatic selective refocusing for localization and TE of 46 ms it was possible to measure decreased glutamate levels from the hippocampus in AD [35]. Another region that is commonly investigated in single voxel MRS studies of AD is the posterior cingulate gyrus voxel. Posterior cingulate gyrus is severely involved with the β-amyloid (Aβ) pathology of AD [36] and ^{18}F fluorodeoxyglucose (FDG) positron emission tomography (PET) studies suggest that the synaptic activity is reduced in this region very early in the disease process such as in cognitively normal carriers of the APOE ε4 allele who are at a higher risk for AD than non-carriers [37, 38]. Recently, it was demonstrated that posterior cingulate gyrus is the hub for the resting state connectivity networks on task-free functional MRI, which are affected by AD early in the disease course [39]. It is possible to consistently get acceptable quality short-echo time MR spectra from the posterior cingulate gyrus voxel for quantification of mI levels which is critical for longitudinal evaluations and multi-site studies [34].

Human tissue studies in transgenic mouse models of AD have provided some insight into the pathologic underpinnings of decreased NAA, glutamate and increased mI levels, which closely resemble the metabolic abnormalities observed in patients with AD [40–44]. For example lower NAA and glutamate levels were associated with Aβ plaque load in mice with PS2APP mutation [44]. Magic angle spinning ^{1}H MRS in superior temporal cortex tissue from patients with AD showed a correlation between NAA concentration and neuronal density [41]. Recently, an in *vivo* ^{13}carbon (^{13}C)-MRS and ^{1}H MRS study suggested a link between increased glial or microglial activation and mI elevation in AD [45].

Our investigation of pathologic correlates of MRS metabolite changes in 54 cases with varying degree of AD pathology demonstrated that both NAA/Cr and mI/Cr levels measured antemortem are associated with the pathologic classification of AD severity [46]. Whereas mI/Cr ratio was elevated at earlier stages of pathologic involvement (i.e. intermediate likelihood AD), NAA/Cr levels were decreased only at the late stage of pathologic involvement (i.e. high likelihood AD). A combined ratio of the two metabolites as the NAA/mI , however revealed the strongest association with pathologic severity suggesting that both NAA and mI provide complementary information on AD pathology (Figure 2).

Longitudinal MRS studies in patients with AD demonstrate gradually decreasing NAA, NAA/Cr and NAA/mI levels compared to controls [47, 48, 49]. The change in NAA and NAA/Cr also correlate with the cognitive decline [48, 50]. Although the data is limited, no study has yet reported a longitudinal increase in mI or mI/Cr levels in patients with AD. The reasons may be twofold: 1) Lower reliability of mI quantification compared to NAA [48, 51, 52]; 2) Stage of the AD pathologic process. If the elevation of mI is an early event in the pathologic progression of AD, it is possible that a plateau is reached in the mI elevation towards the later stages of the pathologic process, which remains to be investigated.

The applications of MRS as a biomarker for treatment response in clinical trials have been limited to single-site studies. The change in NAA/Cr correlated with the change in Alzheimer's Disease Assessment Scale, cognitive part (ADAS-cog) scores during a cholinesterase inhibitor treatment trial [53]. Short-term or temporary increases in NAA/Cr and

Glu/C in cholinesterase inhibitor treated patients versus placebo [54–56], and one trial found no effect on NAA/Cr ratio but found a decrease in Cho/Cr and mI/Cr ratio in the hippocampus albeit in the absence of cognitive response [57]. Overall, MRS appears to be a feasible biomarker in single-site clinical trials in AD. Efforts to extend these applications to multi-site clinical trials are underway [33, 51]. Larger sample sizes may be needed for MRS compared to structural MRI measurements (e.g. hippocampal volumes) to detect a similar effect size [49]. However, effect sizes of a single treatment may differ among imaging markers of different pathophysiological processes. For example a treatment that improves neuronal function may dramatically improve NAA levels but not significantly alter atrophy rates. Therefore effects of the intervention should be considered when comparing imaging markers of different biological sensitivity on sample size and power.

3- MRS in Dementia with Lewy Bodies (DLB)

Presence of Lewy bodies in substantia nigra is the pathological feature of Parkinson's disease. Although cortical Lewy bodies can occasionally be detected in Parkinson's disease, cortical Lewy bodies presenting with dementia is recognized as DLB; a distinct neurodegenerative disease with established clinical and pathologic criteria [58]. DLB is frequently accompanied by AD in patients with dementia [59]. Lewy body pathology by itself is less common than the mixed (AD and DLB) type[60]. In our ^{1}H MRS series, patients clinically diagnosed as probable DLB have normal NAA /Cr levels, whereas patients with AD, vascular dementia and frontotemporal dementia have lower NAA /Cr levels than normal, in the posterior cingulate gyri [61]. Normal NAA /Cr levels in the posterior cingulate gyri in patients with DLB suggest integrity of neurons in this region which is in keeping with the preserved neuronal numbers found in the in the neocortex of DLB patients at autopsy [60]. Normal neocortical NAA or NAA /Cr levels may be useful in distinguishing patients with dementia with Lewy bodies from other dementia syndromes. Reduced NAA/Cr have been detected in the hippocampi of patients with DLB [62], however it is important to note that many patients with DLB may have hippocampal atrophy due to the presence of concomitant neurofibrillary tangle pathology of AD [63] making it hard to determine whether the low NAA/Cr levels in DLB is associated with the co-existent AD pathology. One study found reduced white matter NAA/Cr in patients with DLB compared to the control group suggesting white matter involvement in DLB[64]. The white matter involvement in DLB was later confirmed by diffusion tensor imaging studies [65, 66].

We found elevated Cho /Cr in the posterior cingulate gyri of patients with DLB (Figure 1). Elevation of Cho in DLB and AD may be the consequence of increased membrane turnover due to dying back of the neuropil. Another explanation however is down regulation of choline acetyltransferase activity which may be responsible for this change in both AD and DLB. Activity of choline acetyltransferase, the enzyme responsible for acetylcholine synthesis from free choline, is reduced earlier and more severely in the disease course of DLB than AD [67]. Furthermore, patients with DLB who were treated with cholinesterase inhibitors have shown substantial cognitive improvement [68], revealing the functional significance of acetylcholine deficiency in DLB. The finding that Cho /Cr levels decrease with cholinergic agonist treatment in AD [69] raises the possibility that Cho /Cr levels may be a bio-marker of therapeutic efficacy both in AD and dementia with Lewy bodies drug trials.

4- MRS in Vascular Dementia

Cerebrovascular disease is another common pathology observed in patients with dementia in autopsy series. In most cases however, vascular pathology co-exist with the pathology of AD, and pure vascular pathology is relatively uncommon [70]. Vascular lesions are more common in patients with dementia than normal elderly [71]. In a patient with the clinical

diagnosis of AD and cerebrovascular disease, the challenge is to identify how much if any of the two pathologies are contributing to dementia, so that appropriate therapies can be planned. MRS studies indicate that NAA and NAA /Cr levels are reduced in patients with vascular dementia. White matter NAA /Cr is lower in patients with vascular dementia than in patients with AD, reflecting the white matter ischemic damage in vascular dementia with respect to the cortical degenerative pathology in AD [72, 73]. NAA levels are further decreased in patients with stroke who have cognitive impairment compared to those who are cognitively normal even in regions remote from the infarction, suggesting NAA /Cr is a marker for neuronal dysfunction which may extend beyond the region of infarction [74]. Cortical mI /Cr levels on the other hand are normal in patients with vascular dementia[61, 75, 76] (Figure 1). Because mI /Cr is elevated in patients with AD, mI /Cr may help identify the presence of AD in a demented patient with cerebrovascular disease. Studies that include histopathological confirmation are necessary in order to clarify the role of mI /Cr in differential diagnosis of vascular dementia, mixed dementia (vascular dementia and AD), and AD.

5- MRS in Frontotemporal Lobar Degeneration

MRS metabolite changes in frontotemporal dementia are similar to the changes encountered in AD: lower NAA /Cr and higher mI /Cr than normal [21, 77, 78] (Figure 1). NAA /Cr is lower and mI /Cr is higher levels in the frontal cortex of patients with frontotemporal dementia than patients with early AD, suggesting that regional ^{1}H MRS measurements may help differentiate neurodegenerative disorders that display regionally specific involvement[18, 79]. It should be noted however that while regional differences may be prominent during early stages of the pathological process in neurodegenerative diseases, these differences may be lost as neurodegenerative pathology involves majority of the cerebral cortex in later stages [61, 77].

Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) is an autosomal dominant tauopathy that is linked to mutations in the gene encoding for the microtubule-associated protein tau (*MAPT*) on chromosome 17 [80–83]. Mutations in *MAPT* result in filamentous accumulation of hyperphosphorylated tau in neurons and glia leading to neurodegeneration and atrophy [84–86]. Progressive accumulation of filamentous tau and subsequent neuronal death is central to the pathogenesis of many neurodegenerative diseases including Alzheimer's disease (AD), and may begin years before the onset of clinical symptoms. We recently demonstrated ^{1}H MRS metabolite abnormalities in presymptomatic carriers of mutations in the gene encoding for *MAPT* on chromosome 17. The severity of ^{1}H MRS and MRI abnormalities was associated with the proximity to the estimated age of symptom onset. NAA/mI ratio was fully outside of the control range in presymptomatic *MAPT* mutation carriers who had five years to reach or who were past the estimated age of symptom onset, indicating presence of ^{1}H MRS metabolite abnormalities related to neurodegeneration, years before the onset of symptoms and atrophy in *MAPT* mutation carriers (Figure 3).

6- MRS in Mild Cognitive Impairment and other Alzheimer's Disease Risk Groups

There are no proven treatments for AD pathology, however current efforts to arrest or slow disease progression generate the prospect for preventive interventions [87]. There is considerable interest in early diagnosis by identifying individuals with cognitive difficulties who eventually progress to dementia, from those who are aging with normal cognitive function [88]. Mild cognitive impairment (MCI) was established on clinical grounds in order

to identify symptomatic individuals who do not meet the criteria for dementia [89]. A majority of people with MCI develops dementia in the future.

The progression of AD pathophysiological processes start decades before the clinical diagnosis of AD and the earliest cognitive impairments occur in the memory domain [90]. The syndrome of amnestic MCI represents this prodromal phase in the progression of AD [89]. More recently, the construct of MCI has been broadened to include individuals with impairments in non-amnestic cognitive domains such as attention/executive, language or visual-spatial processing domains [91]. The clinical presentation of this broadened definition of MCI is heterogeneous. Both the amnestic and non-amnestic subtypes of MCI may present with involvement of a single cognitive domain or multiple cognitive domains. It is clear from several independent studies that most people with the amnestic form of MCI who progress to dementia in the future, develop AD[92–98]. People with non-amnestic MCI on average have more vascular comorbidity and infarctions as well as a higher prevalence of extra pyramidal features, mood disorders, and behavioral symptoms than people with amnestic MCI [99, 100]. The etiology of MCI is also heterogeneous. A variety of early stage dementia-associated pathophysiological processes such as AD, cerebrovascular disease and Lewy body pathology have been identified in patients with MCI at autopsy [101, 102], [103, 104]. Many of these pathologies co-exist in MCI [103] and require different therapeutic strategies. Furthermore, all patients with MCI do not develop dementia at a similar rate [105, 106]. The heterogeneity of MCI warrants development of non-invasive biomarkers that can predict the rate of future progression to different dementias, for early diagnosis and treatment with potential disease-specific preventive interventions.

Early ^{1}H MRS studies in MCI included individuals who had impairments in memory function (i.e. amnestic MCI) [8, 29, 107, 108]. A majority of patients with amnestic MCI develop AD in the future, and many of these individuals have early AD pathology [95]. In keeping with this, the ^{1}H MRS findings in amnestic MCI are similar to but milder than the findings in AD [8, 29, 108]. However there are distinct group wise differences in MRI and ^{1}H MRS findings between amnestic MCI and non-amnestic MCI subtypes. Patients with amnestic MCI tend to have smaller hippocampal volumes and elevated mI/Cr ratios compared to patients with non-amnestic MCI and cognitively normal controls. On the other hand, non-amnestic MCI patients have normal hippocampal volumes and normal mI/Cr ratios, but a greater proportion of these patients have cortical infarctions compared to the amnestic MCI patients [99]. Both hippocampal atrophy and elevated mI/Cr are sensitive markers of early AD pathology, and the severity of these abnormalities correlate with the pathologic severity of AD [46, 109–114]. For this reason, hippocampal atrophy and elevated mI/Cr most likely represent a higher frequency of early AD pathology in patients with amnestic MCI compared to non-amnestic MCI. On the contrary, normal hippocampal volumes and mI/Cr ratios in the non-amnestic MCI subtype suggest that other pathologies in addition to AD underlie non-amnestic MCI. Higher prevalence of cortical infarctions on MRI, history of TIA and stroke in non-amnestic MCI patients suggest that cerebrovascular disease is one of the pathological contributors to nonamnestic MCI.

The pathologic and clinical heterogeneity of MCI require multimodality imaging markers that are sensitive to the various dementia related pathophysiological processes for early diagnosis in patients with MCI. The most common dementia-related pathologies observed in MCI include AD, cerebrovascular disease and DLB [102–104]. Lesions that are associated with cerebrovascular disease on MRI include infarctions and white matter hyperintensities on T2 weighted images. These cerebrovascular lesions are more common in patients with MCI compared to cognitively normal older adults [99]. An MR marker that is highly sensitive to the pathophysiological processes of AD specifically the neurofibrillary tangle pathology-associated neurodegeneration early in the disease course is hippocampal atrophy [112, 114].

Both the presence of cortical infarctions [115] and hippocampal atrophy [116] are predictors of dementia risk in MCI.

There is evidence that ^{1}H MRS is sensitive to the pathophysiological processes associated with the risk of dementia in patients with MCI [117, 118]. Decreased NAA/Cr ratio in the posterior cingulate gyrus voxel is associated with an increased risk of dementia in patients with MCI [115]. Furthermore, posterior cingulate gyrus voxel NAA/Cr levels decline over time in patients with MCI who progress to AD diagnosis [48]. ^{1}H MRS is complementary in predicting future progression to dementia in MCI when considered with other strong predictors of dementia risk in MCI such as hippocampal volumes and cortical infarctions. Decreased posterior cingulate gyrus NAA/Cr increases the risk of progression to dementia in MCI patients with hippocampal atrophy and the risk of dementia increases even further if cortical infarctions are present in a patient with MCI [115] (Figure 4). The complementary role of multimodality imaging markers in predicting the risk of dementia in MCI is consistent with cross-sectional studies showing the added value of ^{1}H MRS and hippocampal volumes for discriminating cognitively impaired but non-demented individuals from cognitively normal subjects [108] and distinguishing AD patients from cognitively normal[119]. Furthermore, hippocampal volumes and NAA/Cr levels are independent and complementary predictors of verbal memory on neuropsychometric testing in nondemented older adults, demonstrating that verbal memory depends on both structural and metabolic integrity of the hippocampus [120].

Recently, the diagnostic criteria for AD and MCI were revised by two separate workgroups charged by the National Institute on Aging and Alzheimer's Association [121–123]. A third work group was charged to define the preclinical stage of AD in light of the evidence that the pathophysiological process of AD begin decades before the diagnosis of clinical dementia [90]. The change in most well validated imaging biomarkers have been hypothetically modeled for the three clinical stages of AD (i.e. preclinical AD, MCI and AD). According to this hypothetical model, the accumulation of β-amyloid (Aβ) pathology imaged with PET amyloid ligands or measured with cerebrospinal fluid (CSF) Aβ-42 levels precede the change in imaging markers of neurodegeneration associated with the neurofibrillary tangle pathology of AD such as hippocampal atrophy on MRI [124]. The model that emerged from evidence on well validated imaging biomarkers will be critical for tracking disease progression and for assessment of primary and secondary preventive interventions in individuals at the preclinical and MCI stage of AD.

Several well validated imaging biomarkers exist for various pathologic features of the early AD pathology such as increased Aβ load on PET, atrophy on structural MRI or glucose metabolic reductions on PET. However there are other features of AD pathology for which a well-validated biomarker does not exist. For example there is no widely accepted biomarker for glial or microglial activation. The glial metabolite mI quantified with ^{1}H MRS may potentially be useful as a biomarker for glial activation in neurodegenerative diseases including AD.

Cross-sectional studies indicate that mI/Cr is elevated in MCI and mild AD even in the absence of a decrease in NAA/Cr [6, 8, 107]. Our data in a pathology-confirmed sample of older adults with a range of AD pathology further showed that the mI/Cr elevation is associated with intermediate likelihood (i.e. an earlier stage) AD pathology whereas the decrease in NAA/Cr is associated with higher likelihood (i.e. a later stage) AD pathology [46] (Figure 2). Furthermore, mI/ Cr levels increase in the pre-dementia phase of Down's syndrome[15, 125] and in pre-symptomatic individuals with familial dementia [126, 127] even in the absence of structural MRI and NAA/Cr changes[127]. The mI peak consists of glial metabolites that are responsible for osmoregulation [128, 129]. MI levels correlate with glial

proliferation in inflammatory CNS demyelination [130]. Because the dense cored amyloid deposits in AD are surrounded by clusters of microglia and astrocytes [131], it is thought that the elevation of the mI peak is related to glial proliferation and microglial activation in AD [45, 132]. A significant correlation between mI/Cr levels and amyloid load measured with Pittsburgh Compound-B PET imaging was found in a population-based sample of 311 cognitively normal older adults [133] (Figure 5). It is possible that the mI/Cr levels are associated with the microglial and glial activation that surround the senile amyloid plaques. However, a ^{1}H MRS - histology correlation study in a mouse model of spinocerebellar ataxia type 1 found elevated mI/Cr levels even in the absence of gliosis [134]. Based on limited evidence, it is not be possible to attribute elevation in mI solely to glial activation in neurodegenerative diseases. Although there is evidence that mI/Cr elevation is an early marker in sporadic AD, familial AD and FTLD even before cognitive impairment, loss of neuronal integrity and atrophy, histological confirmation is needed to better understand the pathologic basis of mI/Cr elevation in MCI.

MCI is a clinically and pathologically heterogeneous disorder. MRS may potentially provide information on the underlying pathologies in patients with MCI that is not available from other imaging biomarkers. Data from cognitively normal older adults and cognitively normal adults at risk for familial dementia suggest that MRS may be useful as a biomarker for preclinical pathological processes and potentially assessing the response to preventive interventions.

7- Future Perspectives

Although significant progress has been made on improving the acquisition and analysis techniques in ^{1}H MRS, translation of these technical developments to clinical practice have not been effective. The main reasons for ineffective translation of technology to clinical practice or patient-oriented research are two fold: 1) Lack of standardization for multi-site applications and normative data 2) Insufficient understanding the pathologic basis of ^{1}H MRS metabolite changes. Advances on these grounds would further increase the impact of ^{1}H MRS as biomarker for the early pathological involvement in neurodegenerative diseases and in turn increase the use ^{1}H MRS in clinical practice.

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Key points

- Neurodegenerative dementias are characterized by elevated myoinositol and decreased N-acetylaspartate levels
- The increase in myoinositol appear to precede decreasing N-acetylaspartate levels in neurodegenerative diseases
- N-acetyl aspartate to myoinositol ratio in the posterior cingulate gyri decrease with increasing burden of Alzheimer's disease pathology
- 1H MRS is sensitive to the pathophysiological processes associated with the risk of dementia in patients with mild cognitive impairment
- Although significant progress has been made on improving the acquisition and analysis techniques in 1H MRS, translation of these technical developments to clinical practice have not been effective due to lack of standardization for multisite applications and normative data as well as insufficient understanding the pathologic basis of 1H MRS metabolite changes.

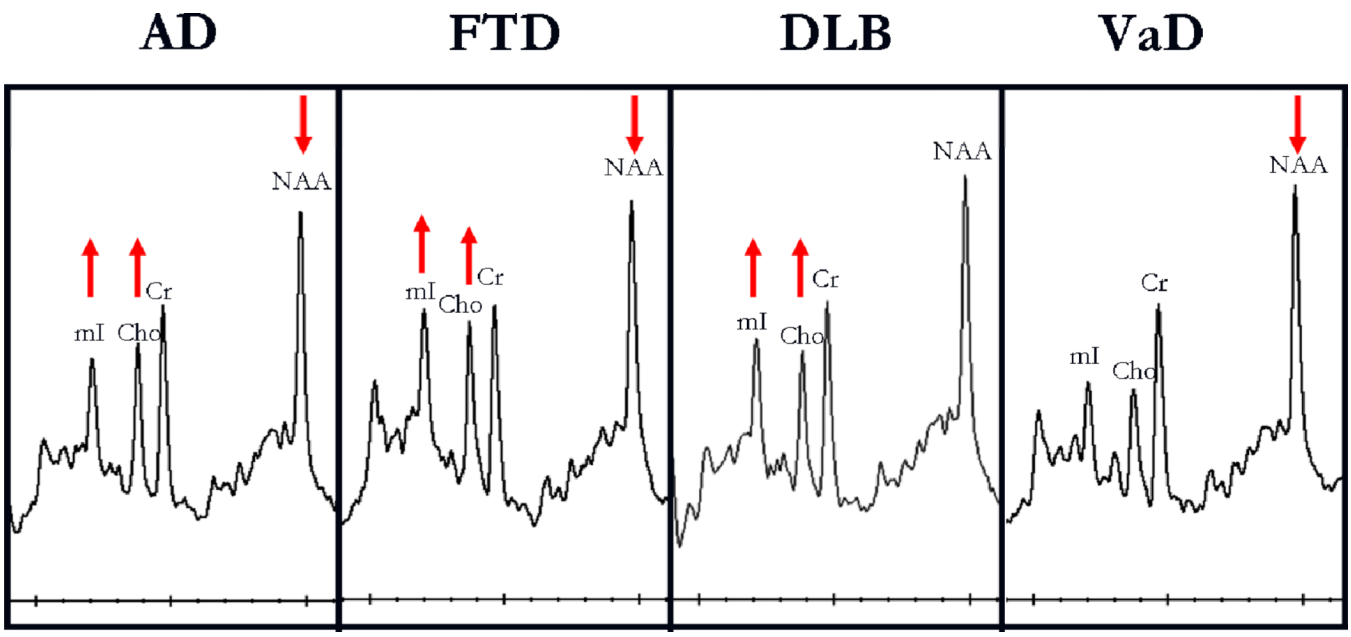

Figure 1. Posterior cingulate gyrus voxel ^{1}H MRS findings in common dementia syndromes
Alzheimer's disease (AD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), vascular dementia (VaD). Cho = choline; Cr = creatine NAA = N-acetylaspartate, Ml=

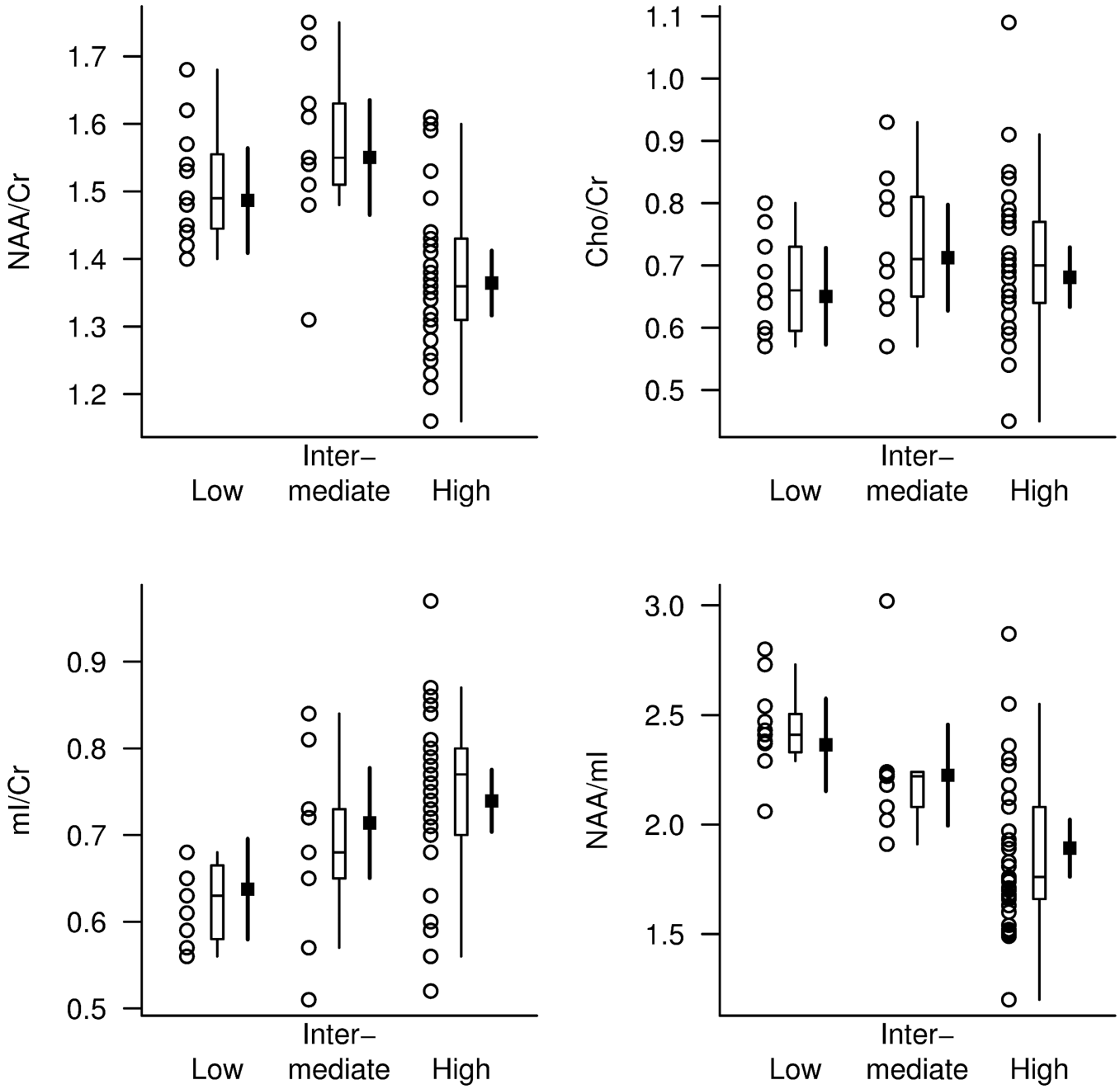

Figure 2. Posterior cingulate gyrus voxel ^{1}H MRS findings by pathological diagnosis of AD

The pathological diagnosis of AD is classified as low, intermediate and high likelihood of AD. For each pathological diagnosis, the plot shows individual values, a box plot of the distribution, and the estimated mean and 95% CI for the mean. The strongest association was observed with the NAA/mI ratio (RN ^{2}=0.40) [46]. Cho = choline; Cr = creatine NAA = N-acetylaspartate, Ml=

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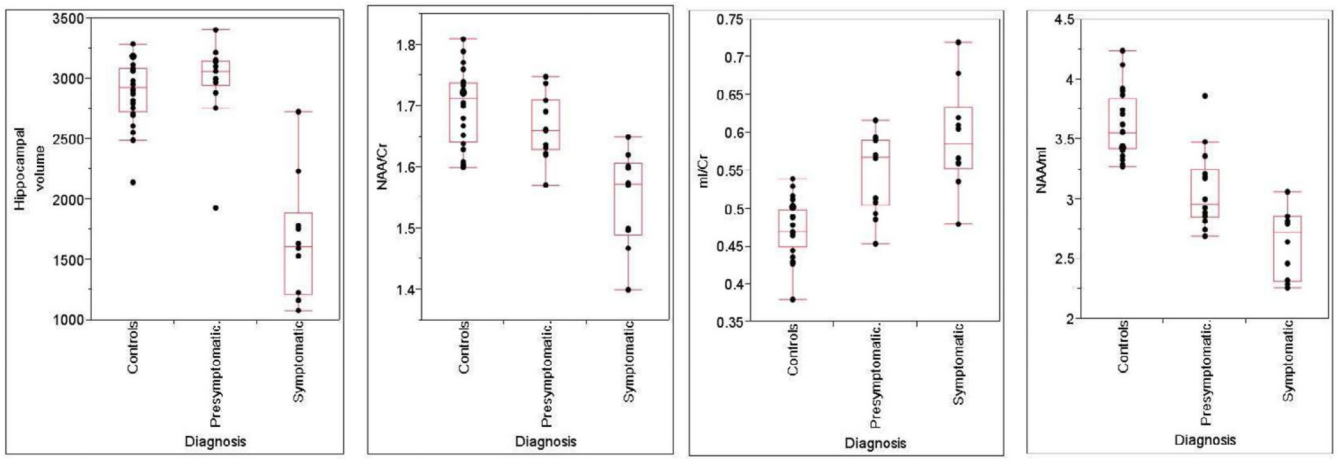

Figure 3. Box plots show the hippocampal volumes (corrected for the total intracranial volume) and ^{1}H MRS metabolite ratios

Controls (n=24), presymptomatic (n=14) and symptomatic (n=10) *MAPT* mutation carriers[127]. Cr = creatine NAA = N-acetylaspartate, Ml=

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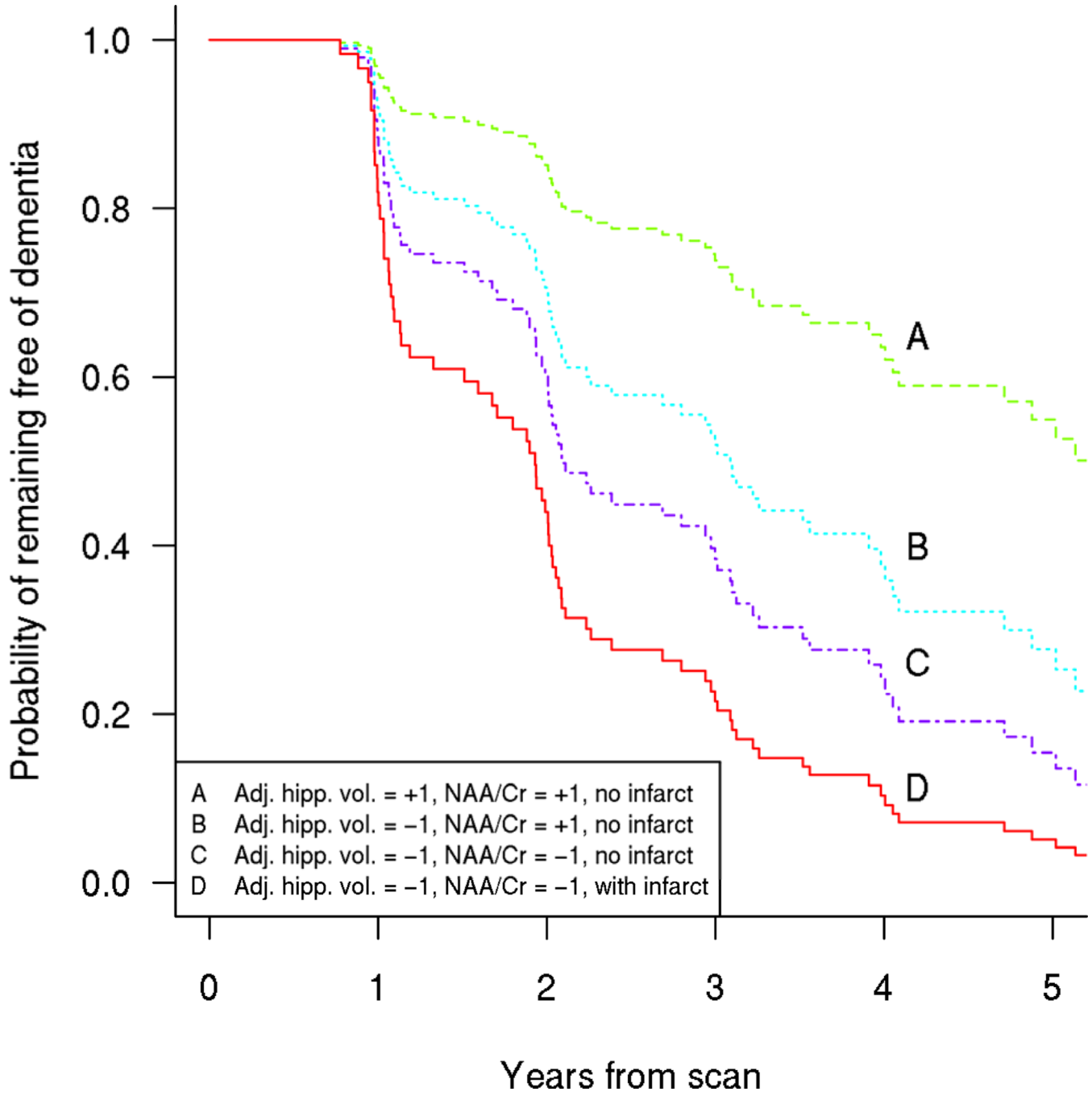

Figure 4. Multiple MR markers of underlying dementia pathologies improve the ability to identify patients with prodromal dementia over a single MR marker

Estimates of the probability of remaining free of dementia for four patient groups with increasingly negative prognoses. Group A has adjusted hippocampal volume and NAA/Cr 1 SD above MCI average and no cortical infarctions. Group B has adjusted hippocampal volume 1 SD below MCI average with NAA/Cr 1 SD above MCI average and no cortical infarctions. Group C has adjusted hippocampal volume and NAA/Cr both 1 SD below MCI average and no cortical infarctions. Group D has adjusted hippocampal volume and NAA/Cr both 1 SD below MCI average and cortical infarctions [115]. Cr = creatine NAA = N-acetylaspartate

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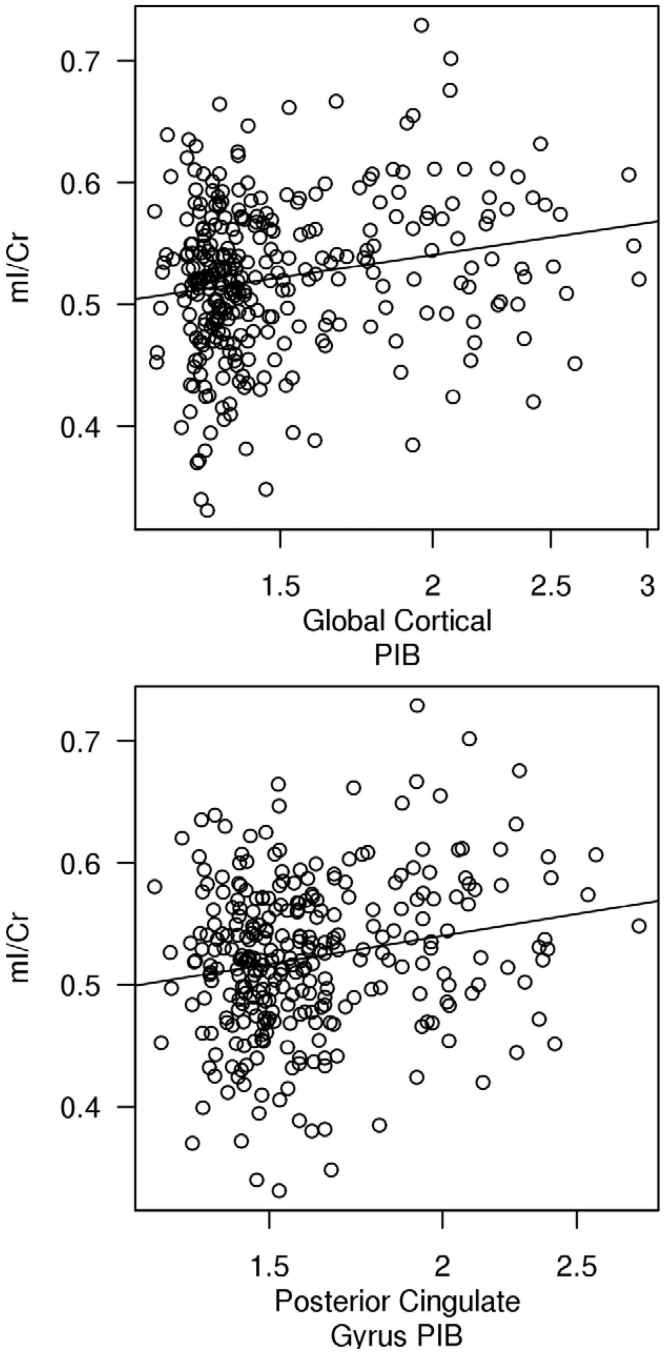

Figure 5. Association between posterior cingulate mI/Cr and PiB retention

Scatter plots demonstrate the association between log transformed global cortical PIB retention ratio and mI/Cr (upper panel); between log transformed posterior cingulated cortical PIB retention ratio and mI/Cr (lower panel)[133]. Cho = choline; Cr = creatine NAA = N-acetylaspartate, MI=, PIB =

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