Published in final edited form as:

J Magn Reson Imaging. 2013 April ; 37(4): 770–777. doi:10.1002/jmri.23800.

Proton MRS in Mild Cognitive Impairment

Kejal Kantarci, M.D., M.Sc.

Department of Radiology, Mayo Clinic, Rochester, Minnesota

Abstract

Mild cognitive impairment (MCI) is a clinical syndrome operationalized for early diagnosis and treatment of Alzheimer's disease (AD). Many individuals with MCI are at the prodromal stage of AD or other dementia. Various quantitative MR techniques that measure the anatomic, biochemical, microstructural, functional, and blood-flow changes are being evaluated as possible surrogate measures for early diagnosis and disease progression in AD. The pathology underlying MCI heterogeneous, dominated by AD, cerebrovascular disease, Lewy body disease, or a mixture of these pathologies in community-based autopsy cohorts. Proton MRS metabolite markers may help identify and track etiologies that typically underlie MCI in the elderly. The role of proton MRS will especially be critical for pathophysiological processes for which a reliable biomarker does not exist such as glial and microglial activation in neurodegenerative dementia.

Keywords

Mild cognitive impairment; magnetic resonance spectroscopy; dementia; Alzheimer's disease

The incidence and prevalence of Alzheimer's disease (AD) increase significantly with aging. With improvements in healthcare and increasing life expectancy, AD has become a significant public health problem of this century (1). There are no proven treatments for AD pathology, however current efforts to arrest or slow disease progression generate the prospect for preventive interventions (2). 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 (3). Mild cognitive impairment (MCI) was established on clinical grounds in order to identify symptomatic individuals who do not meet the criteria for dementia (4). A majority of these individuals develop dementia in the future. This article reviews the proton magnetic resonance spectroscopy (^1H MRS) findings in MCI and the value of ^1H MRS for early diagnosis and disease progression in dementia. First, ^1H MRS findings in dementia syndromes that are commonly preceded by MCI will be reviewed in order to interpret the role of ^1H MRS in MCI.

^1H MRS Findings in Dementia

^1H MRS is unique among diagnostic imaging modalities, because the signals from several different metabolites that are sensitive to a different aspect of the neurodegenerative disease processes are measured within a single acquisition period. Each metabolite may be a surrogate marker to in-vivo pathologic processes at the molecular or cellular level. The potential utilities of ^1H MRS as a biomarker in MCI and dementia include early diagnosis, differential diagnosis, and monitoring of pathological progression (5).

¹H MRS metabolite markers of AD have been investigated in clinical cohorts for more than two decades and the neuronal metabolite NAA is consistently found to be lower and the glial metabolite mI is found to be higher in the ¹H MR spectra of patients with AD than cognitively normal elderly (6-15). There are conflicting reports on the membrane integrity marker choline (Cho) levels. Some studies identified elevated Cho levels (10,13,16) in people with AD, and some did not (14,17-20). Creatine (Cr) levels are typically stable in AD compared to age matched controls (14,15,18,19,21-23). For this reason, Cr peak is generally used as an internal reference to adjust for atrophy and acquisition related variability. Postmortem MRS analyses of perchloric acid extracts of AD brains show correlations between MRS metabolites and density of NFT and senile plaques in the tissues (9,24). Furthermore, ¹H MRS in studies in transgenic mouse models of AD consistently showed *in vivo* metabolite alterations with increasing age (25-27). Recently, we validated these findings in a clinical cohort by demonstrating that antemortem posterior cingulate gyrus NAA/Cr, mI/Cr and NAA/mI on MRS correlate with the likelihood of postmortem Alzheimer type pathology at autopsy (28) (Figure 1).

Although AD is the most common etiology of MCI, Lewy body related pathology, ischemic vascular disease and infarctions are other pathophysiological processes that are common along with early AD pathology in people with MCI (29-32). ¹H MRS findings in vascular dementia is characterized by a reduction in NAA and NAA/Cr levels even in cortical regions remote from the infarction (16). White matter NAA/Cr is lower in patients with vascular dementia than in patients with AD, (33,34). NAA levels were also lower in patients with stroke who had cognitive impairment compared to those who were cognitively normal (35). Because reduction in NAA was observed in regions remote from the infarction, it is thought that the reduction in NAA/Cr is associated with neuronal dysfunction (35). Cortical mI/Cr levels on the other hand are normal in patients with vascular dementia (16,36). 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 or in a patient with MCI.

Another common dementia pathology identified in people with MCI is Lewy body pathology. Lewy body pathology by itself is less common than the mixed (AD and Lewy body) type (37). In our ¹H MRS series, patients clinically diagnosed as dementia with Lewy bodies have normal NAA/Cr levels, whereas patients with AD and vascular dementia have lower NAA/Cr levels than normal, in the posterior cingulate gyri (16). Patients with dementia with Lewy bodies have preserved neuronal numbers at autopsy (37). Likewise, normal NAA/Cr levels suggest integrity of neurons in the posterior cingulate gyri, which may be useful in distinguishing patients with dementia with Lewy bodies from AD or vascular dementia. White matter NAA/Cr however was significantly reduced in patients with DLB compared to the control group (38). It is possible that NAA/Cr is decreased in other cortical regions of people with dementia with Lewy bodies, that have not yet been studied with ¹H MRS. On the other hand, Cho/Cr ratios are elevated in patients with dementia with Lewy bodies compared to normal. Elevation of Cho in dementia with Lewy bodies and AD may be the consequence of increased membrane turnover due to dying back of the neuropil. Another explanation however is the down regulation of choline acetyltransferase activity which may be responsible for this change in both AD and dementia with Lewy bodies. Both AD and dementia with Lewy bodies are characterized by cholinergic dysfunction, although cholinergic dysfunction may be more severe in dementia with Lewy bodies than in AD (39). The finding that Cho/Cr levels decrease with cholinergic agonist treatment in AD (40), raises the possibility that Cho/Cr levels may be a useful marker of cholinergic dysfunction associated with both AD and Lewy body related pathology (Figure 2)

The Heterogeneity of Mild Cognitive Impairment

The progression of AD pathophysiological processes start decades before the clinical diagnosis of AD and the earliest cognitive impairments occur in the memory domain (41). The syndrome of amnesic MCI represents this prodromal phase in the progression of AD (4). More recently, the construct of MCI has been broadened to include individuals with impairments in non-amnesic cognitive domains such as attention/executive, language or visual-spatial processing domains (42). The clinical presentation of this broadened definition of MCI is heterogeneous. Both the amnesic and non-amnesic 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 amnesic form of MCI who progress to dementia in the future, develop AD (43-49). People with non-amnesic 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 amnesic MCI (50,51). 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 (29,30,31,32). Many of these pathologies co-exist in MCI (29) and require different therapeutic strategies.

Furthermore, all patients with MCI do not develop dementia at a similar rate (52,53). 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.

¹H MRS Findings in MCI

Early ¹H MRS studies in MCI included individuals who had impairments in memory function (i.e. amnesic MCI) (8,54-56). A majority of patients with amnesic MCI develop AD in the future, and many of these individuals have early AD pathology (46). In keeping with this, the ¹H MRS findings in amnesic MCI are similar to but milder than the findings in AD (8,55,56) (Figure 3). However there are distinct group wise differences in MRI and ¹H MRS findings between amnesic MCI and non-amnesic MCI subtypes. Patients with amnesic MCI tend to have smaller hippocampal volumes and elevated mI/Cr ratios compared to patients with non-amnesic MCI and cognitively normal controls. On the other hand, non-amnesic MCI patients have normal hippocampal volumes and normal mI/Cr ratios, but a greater proportion of these patients had cortical infarctions compared to the amnesic MCI patients (50). 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 (28,57-62). For this reason, hippocampal atrophy and elevated mI/Cr most likely represent a higher frequency of early AD pathology in patients with amnesic MCI compared to non-amnesic MCI. On the contrary, normal hippocampal volumes and mI/Cr ratios in the non-amnesic MCI subtype suggest that other pathologies in addition to AD underlie non-amnesic MCI. Higher prevalence of cortical infarctions on MRI, history of TIA and stroke in non-amnesic MCI patients suggest that cerebrovascular disease is one of the pathological contributors to non-amnesic MCI.

MRS as a Biomarker in for Early Diagnosis of Dementia in 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 Lewy body disease (29-31). 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 (50). 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 (60,62). Both the presence of cortical infarctions (63) and hippocampal atrophy (64) are predictors of dementia risk in MCI.

There is evidence that MRS is sensitive to the pathophysiological processes associated with dementia in patients with MCI (65,66). Decreased NAA/Cr ratio in the posterior cingulate gyrus voxel is associated with an increased risk of dementia in patients with MCI (63) (Figure 4). Furthermore, posterior cingulate gyrus voxel NAA/Cr levels decline over time in patients with MCI who progress to AD diagnosis (67). 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 when cortical infarctions are present in a patient with MCI (63) (Figure 5). This is consistent with cross-sectional studies showing the added value of ^1H MRS and hippocampal volumes for discriminating cognitively impaired but non-demented individuals from cognitively normal subjects (56). Furthermore, hippocampal volumes and NAA/Cr levels are independent and complementary predictors of verbal memory on neuropsychometric testing in non-demented older adults, demonstrating that verbal memory depends on both structural and metabolic integrity of the hippocampus (68).

^1H MRS in Preclinical AD

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 (69-71). A third work group was charged to define the preclinical stage of AD in light of the evidence that the pathophysiological process of AD begins decades before the diagnosis of clinical dementia (41). The change in most well validated imaging biomarkers have been modeled for the three clinical stages of AD (i.e. preclinical AD, MCI and AD). According to this hypothetical model, the change in β -amyloid ($\text{A}\beta$) pathology imaged with PET amyloid ligands precede the change in imaging markers of neurodegeneration associated with the neurofibrillary tangle pathology of AD such as hippocampal atrophy on MRI (72). 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 pathological features of the early AD pathology such as increased $\text{A}\beta$ 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 valid biomarker does not exist. For example there is no widely accepted biomarker for glial or microglial activation. The glial metabolite mI quantified with ^1H 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 (8,54,73). We recently validated this finding in a pathology-confirmed sample of older adults with a range of AD pathology showing 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 (28) (Figure 1). Furthermore, mI/Cr levels increase in the prodementia

phase of Down's syndrome(6,74) and in presymptomatic individuals with familial dementia (75,76) even in the absence of structural MRI and NAA/Cr changes(76). The mI peak consists of glial metabolites that are responsible for osmoregulation (77,78). MI levels correlate with glial proliferation in inflammatory CNS demyelination (79). Because the dense cored amyloid deposits in AD are surrounded by clusters of microglia and astrocytes (80), it is thought that the elevation of the mI peak is related to glial proliferation and microglial activation in AD (81,82). 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 (83). It is possible that the mI/Cr levels are associated with the microglial and glial activation that surround the senile amyloid plaques. However a ^1H MRS - histology correlation study in a mouse model of spinocerebellar ataxia type 1 found elevated mI/Cr levels even in the absence of gliosis (84). Based on limited evidence, it is not 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 frontotemporal lobar degeneration even before cognitive impairment, loss of neuronal integrity and atrophy, histological confirmation is needed to better understand the biological basis of mI/Cr elevation in MCI.

Conclusions

MCI is a clinically and pathologically heterogeneous disorder. Current data indicate that a single imaging marker will be insufficient for determining the underlying pathophysiological processes that contribute to cognitive impairment in MCI. ^1H 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 ^1H MRS may be useful as a biomarker for preclinical pathological processes and potentially assessing the response to preventive interventions. 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. 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 pathological basis of ^1H MRS metabolite changes. Advances on these grounds would further increase the impact of ^1H MRS as biomarker for the early pathological involvement in neurodegenerative diseases and in turn increase the use ^1H MRS in clinical practice.

Acknowledgments

The author thanks Denise A. Reyes for helping with the manuscript preparation.

Grant Support: Dr. Kantarci's research program is supported by the R01 AG40042, P50 AG16574/Project1 and R21 NS066147.

References

1. Rocca WA, Petersen RC, Knopman DS, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimers Dement*. 2011; 7(1):80–93. [PubMed: 21255746]
2. Sperling RA, Jack CR Jr. Aisen PS. Testing the right target and right drug at the right stage. *Sci Transl Med*. 2011; 3(111):111cm133.
3. Thal LJ, Kantarci K, Reiman EM, et al. The role of biomarkers in clinical trials for Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2006; 20(1):6–15. [PubMed: 16493230]
4. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Archives of Neurology*. 2001; 58(12):1985–1992. [PubMed: 11735772]

5. Kantarci K. 1H magnetic resonance spectroscopy in dementia. *Br J Radiol.* 2007; 80(Spec No 2):S146–152. [PubMed: 18445744]
6. Huang W, Alexander GE, Daly EM, et al. High brain myo-inositol levels in the predementia phase of Alzheimer's disease in adults with Down's syndrome: a 1H MRS study. *American Journal of Psychiatry.* 1999; 156(12):1879–1886. [PubMed: 10588400]
7. Jessen F, Block W, Traber F, et al. Proton MR spectroscopy detects a relative decrease of N-acetylaspartate in the medial temporal lobe of patients with AD. *Neurology.* 2000; 55(5):684–688. [PubMed: 10980734]
8. Kantarci K, Jack CR Jr, Xu YC, et al. Regional metabolic patterns in mild cognitive impairment and Alzheimer's disease: A 1H MRS study. *Neurology.* 2000; 55(2):210–217. [PubMed: 10908893]
9. Klunk WE, Panchalingam K, Moosy J, McClure RJ, Pettegrew JW. N-acetyl-L-aspartate and other amino acid metabolites in Alzheimer's disease brain: a preliminary proton nuclear magnetic resonance study. *Neurology.* 1992; 42(8):1578–1585. [PubMed: 1353623]
10. Meyerhoff DJ, MacKay S, Constans JM, et al. Axonal injury and membrane alterations in Alzheimer's disease suggested by in vivo proton magnetic resonance spectroscopic imaging. *Annals of Neurology.* 1994; 36(1):40–47. [PubMed: 8024260]
11. Miller BL, Moats RA, Shonk T, Ernst T, Woolley S, Ross BD. Alzheimer disease: depiction of increased cerebral myo-inositol with proton MR spectroscopy. *Radiology.* 1993; 187(2):433–437. [PubMed: 8475286]
12. Parnetti L, Lowenthal DT, Presciutti O, et al. 1H-MRS, MRI-based hippocampal volumetry, and 99mTc-HMPAO-SPECT in normal aging, age-associated memory impairment, and probable Alzheimer's disease. *Journal of the American Geriatrics Society.* 1996; 44(2):133–138. see comment. [PubMed: 8576501]
13. Pfefferbaum A, Adalsteinsson E, Spielman D, Sullivan EV, Lim KO. In vivo spectroscopic quantification of the N-acetyl moiety, creatine, and choline from large volumes of brain gray and white matter: effects of normal aging. *Magnetic Resonance in Medicine.* 1999; 41(2):276–284. [PubMed: 10080274]
14. Schuff N, Amend D, Ezekiel F, et al. Changes of hippocampal N-acetyl aspartate and volume in Alzheimer's disease. A proton MR spectroscopic imaging and MRI study. *Neurology.* 1997; 49(6):1513–1521. [PubMed: 9409338]
15. Shonk TK, Moats RA, Gifford P, et al. Probable Alzheimer disease: diagnosis with proton MR spectroscopy. *Radiology.* 1995; 195(1):65–72. see comment. [PubMed: 7892497]
16. Kantarci K, Petersen RC, Boeve BF, et al. 1H MR spectroscopy in common dementias. *Neurology.* 2004; 63(8):1393–1398. [PubMed: 15505154]
17. Krishnan KR, Charles HC, Doraiswamy PM, et al. Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. *American Journal of Psychiatry.* 2003; 160(11):2003–2011. [PubMed: 14594748]
18. Moats RA, Ernst T, Shonk TK, Ross BD. Abnormal cerebral metabolite concentrations in patients with probable Alzheimer disease. *Magnetic Resonance in Medicine.* 1994; 32(1):110–115. [PubMed: 8084225]
19. Parnetti L, Tarducci R, Presciutti O, et al. Proton magnetic resonance spectroscopy can differentiate Alzheimer's disease from normal aging. *Mechanisms of Ageing & Development.* 1997; 97(1):9–14. [PubMed: 9223122]
20. Rose SE, de Zubicaray GI, Wang D, et al. A 1H MRS study of probable Alzheimer's disease and normal aging: implications for longitudinal monitoring of dementia progression. *Magnetic Resonance Imaging.* 1999; 17(2):291–299. [PubMed: 10215485]
21. Ernst T, Chang L, Melchor R, Mehninger CM. Frontotemporal dementia and early Alzheimer disease: differentiation with frontal lobe H-1 MR spectroscopy. *Radiology.* 1997; 203(3):829–836. [PubMed: 9169712]
22. Mohanakrishnan P, Fowler AH, Vonsattel JP, et al. Regional metabolic alterations in Alzheimer's disease: an in vitro 1H NMR study of the hippocampus and cerebellum. *Journals of Gerontology Series A-Biological Sciences & Medical Sciences.* 1997; 52(2):B111–117.
23. Schuff N, Capizzano AA, Du AT, et al. Selective reduction of N-acetylaspartate in medial temporal and parietal lobes in AD. *Neurology.* 2002; 58(6):928–935. [PubMed: 11914410]

24. Klunk WE, Panchalingam K, McClure RJ, Stanley JA, Pettegrew JW. Metabolic alterations in postmortem Alzheimer's disease brain are exaggerated by Apo-E4. *Neurobiology of Aging*. 1998; 19(6):511–515. [PubMed: 10192209]
25. Marjanska M, Curran GL, Wengenack TM, et al. Monitoring disease progression in transgenic mouse models of Alzheimer's disease with proton magnetic resonance spectroscopy. *Proc Natl Acad Sci U S A*. 2005; 102(33):11906–11910. [PubMed: 16091461]
26. Oberg J, Spenger C, Wang FH, et al. Age related changes in brain metabolites observed by 1H MRS in APP/PS1 mice. *Neurobiol Aging*. 2008; 29(9):1423–1433. [PubMed: 17434239]
27. Chen SQ, Wang PJ, Ten GJ, Zhan W, Li MH, Zang FC. Role of myo-inositol by magnetic resonance spectroscopy in early diagnosis of Alzheimer's disease in APP/PS1 transgenic mice. *Dement Geriatr Cogn Disord*. 2009; 28(6):558–566. [PubMed: 20093832]
28. Kantarci K, Knopman DS, Dickson DW, et al. Alzheimer disease: postmortem neuropathologic correlates of antemortem 1H MR spectroscopy metabolite measurements. *Radiology*. 2008; 248(1):210–220. [PubMed: 18566174]
29. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol*. 2009; 66(2):200–208. [PubMed: 19743450]
30. Molano J, Boeve B, Ferman T, et al. Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study. *Brain*. 2010; 133(Pt 2):540–556. [PubMed: 19889717]
31. Petersen RC, Parisi JE, Dickson DW, et al. Neuropathologic features of amnesic mild cognitive impairment. *Arch Neurol*. 2006; 63(5):665–672. [PubMed: 16682536]
32. Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology*. 2005; 64(5):834–841. [PubMed: 15753419]
33. Kattapong VJ, Brooks WM, Wesley MH, Kodituwakku PW, Rosenberg GA. Proton magnetic resonance spectroscopy of vascular- and Alzheimer-type dementia. *Archives of Neurology*. 1996; 53(7):678–680. [PubMed: 8929176]
34. MacKay S, Ezekiel F, Di Sclafani V, et al. Alzheimer disease and subcortical ischemic vascular dementia: evaluation by combining MR imaging segmentation and H-1 MR spectroscopic imaging. *Radiology*. 1996; 198(2):537–545. [PubMed: 8596863]
35. Ross AJ, Sachdev PS, Wen W, Valenzuela MJ, Brodaty H. 1H MRS in stroke patients with and without cognitive impairment. *Neurobiol Aging*. 2005; 26(6):873–882. [PubMed: 15718046]
36. Waldman AD, Rai GS, McConnell JR, Chaudry M, Grant D. Clinical brain proton magnetic resonance spectroscopy for management of Alzheimer's and sub-cortical ischemic vascular dementia in older people. *Arch Gerontol Geriatr*. 2002; 35(2):137–142. [PubMed: 14764351]
37. Gomez-Isla T, Growdon WB, McNamara M, et al. Clinicopathologic correlates in temporal cortex in dementia with Lewy bodies. *Neurology*. 1999; 53(9):2003–2009. [PubMed: 10599772]
38. Molina JA, Garcia-Segura JM, Benito-Leon J, et al. Proton magnetic resonance spectroscopy in dementia with Lewy bodies. *European Neurology*. 2002; 48(3):158–163. [PubMed: 12373033]
39. Tiraboschi P, Hansen LA, Alford M, et al. Early and widespread cholinergic losses differentiate dementia with Lewy bodies from Alzheimer disease. *Archives of General Psychiatry*. 2002; 59(10):946–951. [PubMed: 12365882]
40. Satlin A, Bodick N, Offen WW, Renshaw PF. Brain proton magnetic resonance spectroscopy (1H-MRS) in Alzheimer's disease: changes after treatment with xanomeline, an M1 selective cholinergic agonist. *American Journal of Psychiatry*. 1997; 154(10):1459–1461. [PubMed: 9326834]
41. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7(3):280–292. [PubMed: 21514248]
42. Petersen RC. Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*. 2004; 256(3):183–194. [PubMed: 15324362]

43. Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. *Neurology*. 2002; 59(2):198–205. [PubMed: 12136057]
44. Bowen J, Teri L, Kukull W, McCormick W, McCurry SM, Larson EB. Progression to dementia in patients with isolated memory loss. *Lancet*. 1997; 349(9054):763–765. [PubMed: 9074575]
45. Flicker C, Ferris SH, Reisberg B. Mild cognitive impairment in the elderly: predictors of dementia. *Neurology*. 1991; 41(7):1006–1009. [PubMed: 2067629]
46. Jicha GA, Parisi JE, Dickson DW, et al. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Arch Neurol*. 2006; 63(5):674–681. [PubMed: 16682537]
47. Meyer JS, Xu G, Thornby J, Chowdhury MH, Quach M. Is mild cognitive impairment prodromal for vascular dementia like Alzheimer's disease? *Stroke*. 2002; 33(8):1981–1985. [PubMed: 12154249]
48. Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer disease. *Archives of Neurology*. 2001; 58(3):397–405. see comment. [PubMed: 11255443]
49. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology*. 1999; 56(3):303–308. erratum appears in *Arch Neurol* 1999 Jun;56(6):760. [PubMed: 10190820]
50. Kantarci K, Petersen RC, Przybelski SA, et al. Hippocampal volumes, proton magnetic resonance spectroscopy metabolites, and cerebrovascular disease in mild cognitive impairment subtypes. *Arch Neurol*. 2008; 65(12):1621–1628. [PubMed: 19064749]
51. Mariani E, Monastero R, Ercolani S, et al. Vascular Risk Factors in Mild Cognitive Impairment Subtypes. Findings from the ReGAI Project. *Dement Geriatr Cogn Disord*. 2007; 24(6):448–456. [PubMed: 17975314]
52. Busse A, Hensel A, Guhne U, Angermeyer MC, Riedel-Heller SG. Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology*. 2006; 67(12):2176–2185. [PubMed: 17190940]
53. Fischer P, Jungwirth S, Zehetmayer S, et al. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology*. 2007; 68(4):288–291. [PubMed: 17242334]
54. Catani M, Cherubini A, Howard R, et al. (1)H-MR spectroscopy differentiates mild cognitive impairment from normal brain aging. *Neuroreport*. 2001; 12(11):2315–2317. [PubMed: 11496102]
55. Chantal S, Braun CM, Bouchard RW, Labelle M, Boulanger Y. Similar 1H magnetic resonance spectroscopic metabolic pattern in the medial temporal lobes of patients with mild cognitive impairment and Alzheimer disease. *Brain Research*. 2004; 1003(1-2):26–35. [PubMed: 15019560]
56. Chao LL, Schuff N, Kramer JH, et al. Reduced medial temporal lobe N-acetylaspartate in cognitively impaired but nondemented patients. *Neurology*. 2005; 64(2):282–289. [PubMed: 15668426]
57. Barkhof F, Polvikoski TM, van Straaten EC, et al. The significance of medial temporal lobe atrophy: a postmortem MRI study in the very old. *Neurology*. 2007; 69(15):1521–1527. [PubMed: 17923614]
58. Bobinski M, Wegiel J, Tarnawski M, et al. Relationships between regional neuronal loss and neurofibrillary changes in the hippocampal formation and duration and severity of Alzheimer disease. *Journal of Neuropathology & Experimental Neurology*. 1997; 56(4):414–420. [PubMed: 9100672]
59. Gosche KM, Mortimer JA, Smith CD, Markesbery WR, Snowdon DA. Hippocampal volume as an index of Alzheimer neuropathology: findings from the Nun Study. *Neurology*. 2002; 58(10):1476–1482. [PubMed: 12034782]
60. Jack CR Jr, Dickson DW, Parisi JE, et al. Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. *Neurology*. 2002; 58(5):750–757. [PubMed: 11889239]
61. Zarow C, Vinters HV, Ellis WG, et al. Correlates of hippocampal neuron number in Alzheimer's disease and ischemic vascular dementia. *Ann Neurol*. 2005; 57(6):896–903. [PubMed: 15929035]
62. Jagust WJ, Zheng L, Harvey DJ, et al. Neuropathological basis of magnetic resonance images in aging and dementia. *Ann Neurol*. 2008; 63(1):72–80. [PubMed: 18157909]

63. Kantarci K, Weigand SD, Przybelski SA, et al. Risk of dementia in MCI: combined effect of cerebrovascular disease, volumetric MRI, and 1H MRS. *Neurology*. 2009; 72(17):1519–1525. [PubMed: 19398707]
64. Jack CR Jr, Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*. 1999; 52(7):1397–1403. [PubMed: 10227624]
65. Martinez-Bisbal MC, Arana E, Marti-Bonmati L, Molla E, Celda B. Cognitive impairment: classification by 1H magnetic resonance spectroscopy. *Eur J Neurol*. 2004; 11(3):187–193. [PubMed: 15009164]
66. Metastasio A, Rinaldi P, Tarducci R, et al. Conversion of MCI to dementia: Role of proton magnetic resonance spectroscopy. *Neurobiol Aging*. 2006; 27(7):926–932. [PubMed: 15936850]
67. Kantarci K, Weigand SD, Petersen RC, et al. Longitudinal 1H MRS changes in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging*. 2007; 28(9):1330–1339. [PubMed: 16860440]
68. Zimmerman ME, Pan JW, Hetherington HP, et al. Hippocampal neurochemistry, neuromorphometry, and verbal memory in nondemented older adults. *Neurology*. 2008; 70(18):1594–1600. [PubMed: 18367703]
69. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7(3):270–279. [PubMed: 21514249]
70. Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7(3):257–262. [PubMed: 21514247]
71. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7(3):263–269. [PubMed: 21514250]
72. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010; 9(1):119–128. [PubMed: 20083042]
73. Huang W, Alexander GE, Chang L, et al. Brain metabolite concentration and dementia severity in Alzheimer's disease: a (1)H MRS study. *Neurology*. 2001; 57(4):626–632. [PubMed: 11524470]
74. Shonk T, Ross BD. Role of increased cerebral myo-inositol in the dementia of Down syndrome. *Magnetic Resonance in Medicine*. 1995; 33(6):858–861. [PubMed: 7651126]
75. Godbolt AK, Waldman AD, MacManus DG, et al. MRS shows abnormalities before symptoms in familial Alzheimer disease. *Neurology*. 2006; 66(5):718–722. [PubMed: 16534109]
76. Kantarci K, Boeve BF, Wszolek ZK, et al. MRS in presymptomatic MAPT mutation carriers: a potential biomarker for tau-mediated pathology. *Neurology*. 2010; 75(9):771–778. [PubMed: 20805522]
77. Brand A, Richter-Landsberg C, Leibfritz D. Multinuclear NMR studies on the energy metabolism of glial and neuronal cells. *Developmental Neuroscience*. 1993; 15(3-5):289–298. [PubMed: 7805581]
78. Urenjak J, Williams SR, Gadian DG, Noble M. Proton nuclear magnetic resonance spectroscopy unambiguously identifies different neural cell types. *Journal of Neuroscience*. 1993; 13(3):981–989. [PubMed: 8441018]
79. Bitsch A, Bruhn H, Vougioukas V, et al. Inflammatory CNS demyelination: histopathologic correlation with in vivo quantitative proton MR spectroscopy. *American Journal of Neuroradiology*. 1999; 20(9):1619–1627. [PubMed: 10543631]
80. Dickson DW. The pathogenesis of senile plaques. *J Neuropathol Exp Neurol*. 1997; 56(4):321–339. [PubMed: 9100663]
81. Ross BD, Bluml S, Cowan R, Danielsen E, Farrow N, Tan J. In vivo MR spectroscopy of human dementia. *Neuroimaging Clinics of North America*. 1998; 8(4):809–822. [PubMed: 9769343]
82. Sailasuta N, Harris K, Tran T, Ross B. Minimally invasive biomarker confirms glial activation present in Alzheimer's disease: a preliminary study. *Neuropsychiatr Dis Treat*. 2011; 7:495–499. [PubMed: 21931491]

83. Kantarci K, Lowe V, Przybelski SA, et al. Magnetic resonance spectroscopy, beta-amyloid load, and cognition in a population-based sample of cognitively normal older adults. *Neurology*. 2011; 77(10):951–958. [PubMed: 21865577]
84. Oz G, Nelson CD, Koski DM, et al. Noninvasive detection of presymptomatic and progressive neurodegeneration in a mouse model of spinocerebellar ataxia type 1. *J Neurosci*. 2010; 30(10): 3831–3838. [PubMed: 20220018]

Figure 1. Posterior cingulate gyrus voxel ^1H MRS findings by pathological diagnosis of AD
 The pathological diagnosis of AD is classified as low, intermediate and low 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/ml ratio ($R_N^2=0.40$) (28). With permission from *Radiology*.

Figure 2. Posterior cingulate gyrus voxel ^1H MRS findings in common dementia syndromes Alzheimer's disease (AD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), vascular dementia (VaD).

Figure 3. Posterior cingulate gyrus voxel ^1H MRS findings in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) compared to a cognitively normal subject
 An 8 cm^3 ($2 \times 2 \times 2\text{ cm}$) voxel includes the right and left posterior cingulate gyri and inferior precuneate gyri. The anterior border of splenium, the superior border of corpus callosum and the cingulate sulcus are used as the anatomical landmarks for voxel placement.

Figure 4. Lower NAA/Cr increases the risk of dementia in MCI

Estimates of the probability of remaining free of dementia over time based on age, gender, and education -adjusted Cox models with NAA/Cr as the predictor. Estimates assume a 76 year old patient with 14.6 years of education and represent a weighted average of the curves for men and women where the weights are the proportion of men and women in our sample (63). With permission from *Neurology*.

Figure 5. 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 (63). With permission from *Neurology*.