Brad Dickerson - selected publications

1 Dickerson, B. C. & Wolk, D. A. (2013). Biomarker-based prediction of progression in MCI: Comparison of AD signature and hippocampal volume with spinal fluid amyloid-beta and tau. *Frontiers in Aging Neuroscience, 5,* 55.
Notes: Objective: New diagnostic criteria for mild cognitive impairment (MCI) due to Alzheimer's disease (AD) have been developed using biomarkers aiming to establish whether the clinical syndrome is likely due to underlying AD. We investigated the utility of magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) biomarkers in predicting progression from amnesic MCI to dementia, testing the hypotheses that (1) markers of amyloid and neurodegeneration provide distinct and complementary prognostic information over different time intervals, and that (2) evidence of neurodegeneration in amyloid-negative MCI individuals would be useful prognostically. Methods: Data were obtained from the ADNI-1 (Alzheimer's Disease Neuroimaging Initiative Phase 1) database on all individuals with a baseline diagnosis of MCI, baseline MRI and CSF data, and at least one follow-up visit. MRI data were processed using a published set of a priori regions of interest to derive a measure known as the ``AD signature,'' as well as hippocampal volume. The CSF biomarkers amyloid-beta, total tau, and phospho tau were also examined. We performed logistic regression analyses to identify the best baseline biomarker predictors of progression to dementia over 1 or 3 years, and Cox regression models to test the utility of these markers for predicting time-to-dementia. Results: For prediction of dementia in MCI, the AD signature cortical thickness biomarker performed better than hippocampal volume. Although CSF tau measures were better than CSF amyloid-beta at predicting dementia within 1 year, the AD signature was better than all CSF measures at prediction over this relatively short-term interval. CSF amyloid-beta was superior to tau and AD signature at predicting dementia over 3 years. When CSF amyloid-beta was dichotomized using previously published cutoff values and treated as a categorical variable, a multivariate stepwise Cox regression model indicated that both the AD signature MRI marker and the categorical CSF amyloid-beta marker were useful in predicting time-to-event diagnosis of AD dementia. Conclusion: In amnesic MCI, short-term (1 year) prognosis of progression to dementia relates strongly to baseline markers of neurodegeneration, with the AD signature MRI biomarker of cortical thickness performing the best among MRI and CSF markers studied here. Longer-term (3 year) prognosis in these individuals was better predicted by a marker indicative of brain amyloid. Prediction of time-to-event in a survival model was predicted by the combination of these biomarkers. These results provide further support for emerging models of the temporal relationship of pathophysiologic events in AD and demonstrate the utility of these biomarkers at the prodromal stage of the illness
Frontotemporal Dementia Unit, Massachusetts General Hospital and Harvard Medical School Boston, MA, USA ; Department of Neurology,

2 Bakkour, A., Morris, J. C., Wolk, D. A., & Dickerson, B. C. (2013). The effects of aging and Alzheimer's disease on cerebral cortical anatomy: specificity and differential relationships with cognition. *NeuroImage, 76,* 332-344.
Notes: Although both normal aging and Alzheimer's disease (AD) are associated with regional cortical atrophy, few studies have directly compared the spatial patterns and magnitude of effects of these two processes. The extant literature has not addressed two important questions: 1) Is the pattern of age-related cortical atrophy different if cognitively intact elderly individuals with silent AD pathology are excluded? and 2) Does the age- or AD-related atrophy relate to cognitive function? Here we studied 142 young controls, 87 older controls, and 28 mild AD patients. In addition, we studied 35 older controls with neuroimaging data indicating the absence of brain amyloid. Whole-cortex analyses identified regions of interest (ROIs) of cortical atrophy in aging and in AD. Results showed that some regions are predominantly affected by age with relatively little additional atrophy in patients with AD, e.g., calcarine cortex; other regions are predominantly affected by AD with much less of an effect of age, e.g., medial temporal cortex. Finally, other regions are affected by both aging and AD, e.g., dorsolateral prefrontal cortex and inferior parietal lobule. Thus, the processes of aging

and AD have both differential and partially overlapping effects on specific regions of the cerebral cortex. In particular, some frontoparietal regions are affected by both processes, most temporal lobe regions are affected much more prominently by AD than aging, while sensorimotor and some prefrontal regions are affected specifically by aging and minimally more by AD. Within normal older adults, atrophy in aging-specific cortical regions relates to cognitive performance, while in AD patients atrophy in AD-specific regions relates to cognitive performance. Further work is warranted to investigate the behavioral and clinical relevance of these findings in additional detail, as well as their histological basis; ROIs generated from the present study could be used strategically in such investigations.
Frontotemporal Dementia Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

3 Dickerson, B. C. & Wolk, D. A. (2012). MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults. *Neurology, 78,* 84-90.
Notes: OBJECTIVE: New preclinical Alzheimer disease (AD) diagnostic criteria have been developed using biomarkers in cognitively normal (CN) adults. We implemented these criteria using an MRI biomarker previously associated with AD dementia, testing the hypothesis that individuals at high risk for preclinical AD would be at elevated risk for cognitive decline. METHODS: The Alzheimer's Disease Neuroimaging Initiative database was interrogated for CN individuals. MRI data were processed using a published set of a priori regions of interest to derive a single measure known as the AD signature (ADsig). Each individual was classified as ADsig-low (>/= 1 SD below the mean: high risk for preclinical AD), ADsig-average (within 1 SD of mean), or ADsig-high (>/= 1 SD above mean). A 3-year cognitive decline outcome was defined a priori using change in Clinical Dementia Rating sum of boxes and selected neuropsychological measures. RESULTS: Individuals at high risk for preclinical AD were more likely to experience cognitive decline, which developed in 21% compared with 7% of ADsig-average and 0% of ADsig-high groups ($p = 0.03$). Logistic regression demonstrated that every 1 SD of cortical thinning was associated with a nearly tripled risk of cognitive decline ($p = 0.02$). Of those for whom baseline CSF data were available, 60% of the high risk for preclinical AD group had CSF characteristics consistent with AD while 36% of the ADsig-average and 19% of the ADsig-high groups had such CSF characteristics ($p = 0.1$). CONCLUSIONS: This approach to the detection of individuals at high risk for preclinical AD-identified in single CN individuals using this quantitative ADsig MRI biomarker-may provide investigators with a population enriched for AD pathobiology and with a relatively high likelihood of imminent cognitive decline consistent with prodromal AD.
Frontotemporal Dementia Unit, Department of Neurology, Massachusetts Alzheimer's Disease Research Center, and Athinoula A Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Boston, USA.bradd@nmr.mgh.harvard.edu

4 Wolk, D. A. & Dickerson, B. C. (2011). Fractionating verbal episodic memory in Alzheimer's disease. *NeuroImage, 54,* 1530-1539.
Notes: The aim of this study was to determine the neural correlates of different stages of episodic memory function and their modulation by Alzheimer's disease (AD). Several decades of work has supported the role of the medial temporal lobes (MTL) in episodic memory function. However, a more recent work, derived in part from functional neuroimaging studies, has suggested that other brain structures make up a large-scale network that appears to support successful encoding and retrieval of episodic memories. Furthermore, controversy exists as to whether dissociable MTL regions support qualitatively different aspects of memory (hippocampus: contextual memory or 'recollection'; perirhinal/lateral entorhinal cortex: item memory or 'familiarity'). There is limited neuropsychological support for these models and most work in AD only has examined free recall memory measures. We studied the relationship between performance on different stages of the Rey Auditory Verbal Learning Test (AVLT), a 15-item word list learning task, and structural MRI measures in mild AD patients. Structural measures included hippocampal volume and cortical thickness of several ROIs known to undergo atrophy in AD. Correlation and multiple regression analyses,

controlling for age, education, and gender, were performed in 146 mild AD patients (MMSE 23.3+/-2.0). To evaluate the robustness of these relationships, similar analyses were performed with additional standardized verbal memory measures. Early immediate recall trials (e.g. Trial 1 of the AVLT) were not associated with the size of MTL regions, but correlated most strongly with inferior parietal, middle frontal gyrus, and temporal pole ROIs. After repeated exposure (e.g. Trial 5 of the AVLT), immediate recall was correlated with both MTL and a similar distribution of isocortical structures, but most strongly the temporal pole. For delayed recall, only the hippocampus correlated with performance. In contrast, for delayed recognition discrimination, the perirhinal/entorhinal cortex correlated more strongly than the hippocampus; no other isocortical regions were strongly associated with performance. Convergent results were found for immediate and delayed trials of other memory tests. The current results suggest that a richer understanding of the memory deficits in AD can be gained by examining multiple measures, which tap different aspects of memory function. Furthermore, the present findings are consistent with models hypothesizing different stages of verbal list learning map onto dissociable brain regions. These data have implications for understanding the anatomic basis of processes underlying episodic memory, particularly related to a division of labor within the medial temporal lobes and within the large-scale MTL-cortical memory network
Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA.
david.wolk@uphs.upenn.edu

5 Dickerson, B. C. (2011). Quantitating severity and progression in primary progressive aphasia. *Journal of Molecular Neuroscience, 45,* 618-628.
Notes: Primary progressive aphasia (PPA) is an insidiously progressive clinical syndrome that includes at its core an impairment in language. From a clinical perspective, there are a variety of diagnostic challenges; international consensus has only recently been reached on the nomenclature for specific clinical subtypes. There are at present no established treatments, and efforts to develop treatments have been hampered by the lack of standardized methods to monitor progression of the illness. This is further complicated by the multiplicity of underlying neuropathologies. Although measures developed from work with stroke aphasia and from work with disorders such as Alzheimer's disease and frontotemporal dementia have provided a valuable foundation for monitoring progression, PPA presents unique challenges to clinicians aiming to quantify impairments for the purposes of full characterization and monitoring, and ultimately with the goal of designing clinical trials of interventions to make a meaningful difference in patients' lives. In this review, I will summarize the main points made in my presentation at the 2010 International Conference on Frontotemporal Dementia, expand from there to summarize our current approach to monitoring progression of PPA, and finally will outline some ideas about goals for the development of better tools for this purpose

6 Dickerson, B. C., Stoub, T. R., Shah, R. C., Sperling, R. A., Killiany, R. J., Albert, M. S. et al. (2011). Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. *Neurology, 76,* 1395-1402.
Notes: OBJECTIVE: Since Alzheimer disease (AD) neuropathology is thought to develop years before dementia, it may be possible to detect subtle AD-related atrophy in preclinical AD. Here we hypothesized that the "disease signature" of AD-related cortical thinning, previously identified in patients with mild AD dementia, would be useful as a biomarker to detect anatomic abnormalities consistent with AD in cognitively normal (CN) adults who develop AD dementia after longitudinal follow-up. METHODS: We studied 2 independent samples of adults who were CN when scanned. In sample 1, 8 individuals developing AD dementia (CN-AD converters) after an average of 11.1 years were compared to 25 individuals who remained CN (CN-stable). In sample 2, 7 CN-AD converters (average follow-up 7.1 years) were compared to 25 CN-stable individuals. RESULTS: AD-signature cortical thinning in CN-AD converters in both samples was remarkably similar, about 0.2 mm ($p < 0.05$). Despite this small absolute difference, Cohen d effect sizes for these differences were very large (> 1). Of the 11 CN individuals with baseline low AD-signature thickness (>/=

1 SD below cohort mean), 55% developed AD dementia over nearly the next decade, while none of the 9 high AD-signature thickness individuals (>/= 1 SD above mean) developed dementia. This marker predicted time to diagnosis of dementia (hazard ratio = 3.4, p < 0.0005); 1 SD of thinning increased dementia risk by 3.4. CONCLUSIONS: By focusing on cortical regions known to be affected in AD dementia, subtle but reliable atrophy is identifiable in asymptomatic individuals nearly a decade before dementia, making this measure a potentially important imaging biomarker of early neurodegeneration
Department of Neurology, Massachusetts Alzheimer's Disease Research Center, Massachusetts General Hospital, MA, USA. bradd@nmr.mgh.harvard.edu

7 Dickerson, B. C. & Wolk, D. A. (2011). Dysexecutive versus amnesic phenotypes of very mild Alzheimer's disease are associated with distinct clinical, genetic and cortical thinning characteristics. *Journal of Neurology, Neurosurgery and Psychiatry, 82,* 45-51.
Notes: OBJECTIVE: To investigate whether some patients with very mild Alzheimer's disease (AD) demonstrate disproportionate executive dysfunction relative to amnesia and how this relates to functional impairment in daily life, future clinical decline, APOE genotype and regional cortical thickness measured from MRI scan data. METHODS: The Alzheimer's Disease Neuroimaging Initiative dataset was interrogated for a primary sample of patients with very mild AD dementia (n=100) and a secondary confirmatory sample of patients with mild cognitive impairment (n=396). An executive predominant subgroup was defined as having executive performance >/=2 SDs worse than memory performance and a memory predominant subgroup was defined conversely. A priori regions of interest from a previous study of an AD patient sample were used to obtain cortical thickness measures. RESULTS: Despite equivalent global measures of impairment (Mini-Mental State Examination, Clinical Dementia Rating (CDR) Sum of Boxes), executive predominant patients (n=88) were more impaired on other executive measures and in the CDR Judgement and Problem Solving box (p<0.005) while memory predominant patients (n=56) were more impaired on other memory measures (p<0.05). The APOE-epsilon4 allele was much more frequent in the memory predominant subgroup (p<0.0001). Frontoparietal cortical regions were thinner in the executive predominant group than in the memory predominant group (p<0.05). CONCLUSIONS: A dysexecutive clinical phenotype of very mild AD is not rare and is associated with more problem solving difficulties and possibly more rapid progression compared with patients with a predominant amnesic phenotype. Executive predominant AD may reflect an alternative underlying pathophysiology related to genetic status, reflected in more prominent pathological alterations in frontoparietal regions subserving executive function. These findings, which deserve further investigation, may have implications for diagnosis, prognostication, monitoring and related issues involved in clinical research and care
MGH Frontotemporal Dementia Unit, Boston, Massachusetts, USA. bradd@nmr.mgh.harvard.edu

8 Sperling, R. A., Dickerson, B. C., Pihlajamaki, M., Vannini, P., LaViolette, P. S., Vitolo, O. V. et al. (2010). Functional alterations in memory networks in early Alzheimer's disease. *Neuromolecular.Med., 12,* 27-43.
Notes: The hallmark clinical symptom of early Alzheimer's disease (AD) is episodic memory impairment. Recent functional imaging studies suggest that memory function is subserved by a set of distributed networks, which include both the medial temporal lobe (MTL) system and the set of cortical regions collectively referred to as the default network. Specific regions of the default network, in particular, the posteromedial cortices, including the precuneus and posterior cingulate, are selectively vulnerable to early amyloid deposition in AD. These regions are also thought to play a key role in both memory encoding and retrieval, and are strongly functionally connected to the MTL. Multiple functional magnetic resonance imaging (fMRI) studies during memory tasks have revealed alterations in these networks in patients with clinical AD. Similar functional abnormalities have been detected in subjects at-risk for AD, including those with genetic risk and older individuals with mild cognitive impairment. Recently, we and other groups have found evidence of functional alterations in these memory

networks even among cognitively intact older individuals with occult amyloid pathology, detected by PET amyloid imaging. Taken together, these findings suggest that the pathophysiological process of AD exerts specific deleterious effects on these distributed memory circuits, even prior to clinical manifestations of significant memory impairment. Interestingly, some of the functional alterations seen in prodromal AD subjects have taken the form of increases in activity relative to baseline, rather than a loss of activity. It remains unclear whether these increases in fMRI activity may be compensatory to maintain memory performance in the setting of early AD pathology or instead, represent evidence of excitotoxicity and impending neuronal failure. Recent studies have also revealed disruption of the intrinsic connectivity of these networks observable even during the resting state in early AD and asymptomatic individuals with high amyloid burden. Research is ongoing to determine if these early network alterations will serve as sensitive predictors of clinical decline, and eventually, as markers of pharmacological response to potential disease-modifying treatments for AD
Department of Neurology, Center for Alzheimer's Research and Treatment, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115, USA. reisa@rics.bwh.harvard.edu

9 Dickerson, B. C. & Eichenbaum, H. (2010). The episodic memory system: neurocircuitry and disorders. *Neuropsychopharmacology, 35,* 86-104.
Notes: The ability to encode and retrieve our daily personal experiences, called episodic memory, is supported by the circuitry of the medial temporal lobe (MTL), including the hippocampus, which interacts extensively with a number of specific distributed cortical and subcortical structures. In both animals and humans, evidence from anatomical, neuropsychological, and physiological studies indicates that cortical components of this system have key functions in several aspects of perception and cognition, whereas the MTL structures mediate the organization and persistence of the network of memories whose details are stored in those cortical areas. Structures within the MTL, and particularly the hippocampus, have distinct functions in combining information from multiple cortical streams, supporting our ability to encode and retrieve details of events that compose episodic memories. Conversely, selective damage in the hippocampus, MTL, and other structures of the large-scale memory system, or deterioration of these areas in several diseases and disorders, compromises episodic memory. A growing body of evidence is converging on a functional organization of the cortical, subcortical, and MTL structures that support the fundamental features of episodic memory in humans and animals
Department of Neurology, Massachusetts Alzheimer's Disease Research Center, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02129, USA. bradd@nmr.mgh.harvard.edu

10 Dickerson, B. C., Bakkour, A., Salat, D. H., Feczko, E., Pacheco, J., Greve, D. N. et al. (2009). The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cerebral Cortex, 19,* 497-510.
Notes: Alzheimer's disease (AD) is associated with neurodegeneration in vulnerable limbic and heteromodal regions of the cerebral cortex, detectable in vivo using magnetic resonance imaging. It is not clear whether abnormalities of cortical anatomy in AD can be reliably measured across different subject samples, how closely they track symptoms, and whether they are detectable prior to symptoms. An exploratory map of cortical thinning in mild AD was used to define regions of interest that were applied in a hypothesis-driven fashion to other subject samples. Results demonstrate a reliably quantifiable in vivo signature of abnormal cortical anatomy in AD, which parallels known regional vulnerability to AD neuropathology. Thinning in vulnerable cortical regions relates to symptom severity even in the earliest stages of clinical symptoms. Furthermore, subtle thinning is present in asymptomatic older controls with brain amyloid binding as detected with amyloid imaging. The reliability and clinical validity of AD-related cortical thinning suggests potential utility as an imaging biomarker. This "disease signature" approach to cortical morphometry, in which disease effects are mapped

across the cortical mantle and then used to define ROIs for hypothesis-driven analyses, may provide a powerful methodological framework for studies of neuropsychiatric diseases Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02129, USA. bradd@nmr.mgh.harvard.edu

11 Dickerson, B. C. & Sperling, R. A. (2009). Large-scale functional brain network abnormalities in Alzheimer's disease: insights from functional neuroimaging. *Behavioural Neurology, 21,* 63-75.
Notes: Functional MRI (fMRI) studies of mild cognitive impairment (MCI) and Alzheimer's disease (AD) have begun to reveal abnormalities in large-scale memory and cognitive brain networks. Since the medial temporal lobe (MTL) memory system is a site of very early pathology in AD, a number of studies have focused on this region of the brain. Yet it is clear that other regions of the large-scale episodic memory network are affected early in the disease as well, and fMRI has begun to illuminate functional abnormalities in frontal, temporal, and parietal cortices as well in MCI and AD. Besides predictable hypoactivation of brain regions as they accrue pathology and undergo atrophy, there are also areas of hyperactivation in brain memory and cognitive circuits, possibly representing attempted compensatory activity. Recent fMRI data in MCI and AD are beginning to reveal relationships between abnormalities of functional activity in the MTL memory system and in functionally connected brain regions, such as the precuneus. Additional work with "resting state" fMRI data is illuminating functional-anatomic brain circuits and their disruption by disease. As this work continues to mature, it will likely contribute to our understanding of fundamental memory processes in the human brain and how these are perturbed in memory disorders. We hope these insights will translate into the incorporation of measures of task-related brain function into diagnostic assessment or therapeutic monitoring, which will hopefully one day be useful for demonstrating beneficial effects of treatments being tested in clinical trials
Department of Neurology, Harvard Medical School, Boston, MA, USA.
bradd@nmr.mgh.harvard.edu

12 Bakkour, A., Morris, J. C., & Dickerson, B. C. (2009). The cortical signature of prodromal AD: regional thinning predicts mild AD dementia. *Neurology, 72,* 1048-1055.
Notes: OBJECTIVE: We previously used exploratory analyses across the entire cortex to determine that mild Alzheimer disease (AD) is reliably associated with a cortical signature of thinning in specific limbic and association regions. Here we investigated whether the cortical signature of AD-related thinning is present in individuals with questionable AD dementia (QAD) and whether a greater degree of regional cortical thinning predicts mild AD dementia. METHODS: Participants included 49 older adults with mild impairment consistent with mild cognitive impairment (Clinical Dementia Rating [CDR] = 0.5) at the time of structural MRI scanning. Cortical thickness was measured in nine regions of interest (ROIs) identified previously from a comparison of patients with mild AD and controls. RESULTS: Longitudinal clinical follow-up revealed that 20 participants converted to mild AD dementia (progressors) while 29 remained stable (nonprogressors) approximately 2.5 years after scanning. At baseline, QAD participants showed a milder degree of cortical thinning than typically seen in mild AD, and CDR Sum-of-Boxes correlated with thickness in temporal and parietal ROIs. Compared to nonprogressors, progressors showed temporal and parietal thinning. Using receiver operating characteristic curves, the thickness of an aggregate measure of these regions predicted progression to mild AD with 83% sensitivity and 65% specificity. CONCLUSIONS: Thinning in specific cortical areas known to be affected by Alzheimer disease (AD) is detectable in individuals with questionable AD dementia (QAD) and predicts conversion to mild AD dementia. This method could be useful for identifying individuals at relatively high risk for imminent progression from QAD to mild AD dementia, which may be of value in clinical trials

13 Dickerson, B. C., Sperling, R. A., Hyman, B. T., Albert, M. S., & Blacker, D. (2007). Clinical prediction of Alzheimer disease dementia across the spectrum of mild cognitive impairment. *Archives of General Psychiatry, 64,* 1443-1450.

Notes: Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, USA. bradd@nmr.mgh.harvard.edu
OBJECTIVE: To determine whether clinical assessment methods that grade the severity of impairments within the spectrum of mild cognitive impairment (MCI) can predict clinical course, particularly among very mildly impaired individuals who do not meet formal MCI criteria as implemented in clinical trials. DESIGN: Cohort. SETTING: Community volunteers. PARTICIPANTS: From a longitudinal study of normal (Clinical Dementia Rating [CDR] = 0; n = 77) and mildly impaired (CDR = 0.5; n = 167) participants with 5 or more annual clinical assessments, baseline level of cognitive impairment in daily life was graded using CDR sum of boxes (CDR-SB) and level of cognitive performance impairment was graded using neuropsychological test scores. MAIN OUTCOME MEASURES: Five-year outcome measures included (1) probable Alzheimer disease (AD) diagnosis and (2) clinical "decline" (CDR-SB increase > or = 1.0). Logistic regression models were used to assess the ability of baseline measures to predict outcomes in the full sample and separately in the subjects who did not meet formal MCI criteria as implemented in a multicenter clinical trial (n = 125; "very mild cognitive impairment" [vMCI]). RESULTS: The presence of both higher CDR-SB and lower verbal memory and executive function at baseline predicted greater likelihood of probable AD and decline. Five-year rates of probable AD and decline in vMCI (20%, AD; 49%, decline) were intermediate between normal participants (0%, AD; 28%, decline) and participants with MCI (41%, AD; 62%, decline). Within vMCI, likelihood of probable AD was predicted by higher CDR-SB and lower executive function. CONCLUSIONS: Even in very mildly impaired individuals who do not meet strict MCI criteria as implemented in clinical trials, the degree of cognitive impairment in daily life and performance on neuropsychological testing predict likelihood of an AD diagnosis within 5 years. The clinical determination of relative severity of impairment along the spectrum of MCI may be valuable for trials of putative disease-modifying compounds, particularly as target populations are broadened to include less impaired individuals

14 Dickerson, B. C., Salat, D. H., Bates, J. F., Atiya, M., Killiany, R. J., Greve, D. N. et al. (2004). Medial temporal lobe function and structure in mild cognitive impairment. *Annals of Neurology, 56,* 27-35.
Notes: Department of Neurology, Gerontology Research Unit, Massachusetts General Hospital, MGH-East (149-2691), 149 13th Street, Charlestown, MA 02129, USA. bradd@nmr.mgh.harvard.edu
Functional magnetic resonance imaging (fMRI) was used to study memory-associated activation of medial temporal lobe (MTL) regions in 32 nondemented elderly individuals with mild cognitive impairment (MCI). Subjects performed a visual encoding task during fMRI scanning and were tested for recognition of stimuli afterward. MTL regions of interest were identified from each individual's structural MRI, and activation was quantified within each region. Greater extent of activation within the hippocampal formation and parahippocampal gyrus (PHG) was correlated with better memory performance. There was, however, a paradoxical relationship between extent of activation and clinical status at both baseline and follow-up evaluations. Subjects with greater clinical impairment, based on the Clinical Dementia Rating Sum of Boxes, recruited a larger extent of the right PHG during encoding, even after accounting for atrophy. Moreover, those who subsequently declined over the 2.5 years of clinical follow-up (44% of the subjects) activated a significantly greater extent of the right PHG during encoding, despite equivalent memory performance. We hypothesize that increased activation in MTL regions reflects a compensatory response to accumulating AD pathology and may serve as a marker for impending clinical decline

15 Dickerson, B. C., Goncharova, I., Sullivan, M. P., Forchetti, C., Wilson, R. S., Bennett, D. A. et al. (2001). MRI-derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. *Neurobiology of Aging, 22,* 747-754.
Notes: Department of Neurological Sciences, Rush University, Chicago, IL 60612, USA
With high resolution, quantitative magnetic resonance imaging (MRI) techniques, it is now possible to examine alterations in brain anatomy in vivo and to identify regions affected in the

earliest stages of Alzheimer's disease (AD). In this study, we compared MRI-derived entorhinal and hippocampal volume in healthy elderly controls, patients who presented at the clinic with cognitive complaints, but did not meet criteria for dementia (non-demented), and patients with very mild AD. The two patient groups differed significantly from controls in entorhinal volume, but not from each other; in contrast, they differed from each other, as well as from controls, in hippocampal volume, with the mild AD cases showing the greatest atrophy. Follow-up clinical evaluations available on 23/28 non-demented patients indicated that 12/23 had converted to AD within 12-77 months from the baseline MRI examination. Converters could be best differentiated from non-converters on the basis of entorhinal, but not hippocampal volume. These data suggest that although both the EC and hippocampal formation degenerate before the onset of overt dementia, EC volume is a better predictor of conversion