1.

Mild Cognitive Impairment in an Urban Primary Care Environment

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Introduction: The aim of the current study is to determine the causes and clinical characteristics of mild cognitive impairment (MCI) in older adults attending an urban primary care clinic.

Method: 1867 primary care patients age 65 and older were approached, 428 completed a clinical assessment and were diagnosed (237 normal cognition and 191 MCI). Participants underwent cognitive testing, physical and neurological exam, and informant interview for cognitive symptoms, daily function, and behavioral adjustment. Subtypes of MCI were identified as follows: Prodromal AD, stroke, medical illness, psychiatric disorder, and other (substance abuse, DD).

Results: The rate of MCI in the primary care clinic was 43%. Objective memory test scores were lowest in the prodromal AD subtype while psychomotor speed was lowest in the CVD subgroup. In terms of health, the groups had comparable rates of hypertension (85%) and diabetes (45%). Compared to NC, MCI patients had higher rates of heart attack (19% vs. 11%), COPD (18% vs. 8%), congestive heart failure (20% vs 12%), hyperlipidemia (70% vs. 61%), and stroke (12% vs. 7%).

Discussion: Informants reported higher rates of memory, language, and behavioral symptoms in MCI patients. Moreover, MCI patients self-identify more problems with memory and depression than NC patients. The MCI due to stroke subgroup had the slowest sequential tracking and the prodromal AD group had the worst verbal memory. Future approaches to diagnosis and treatment of MCI in primary care environments must recognize the high prevalence of non-AD causes and presence of significant medical comorbidity in this population.

2.

Behavioral and neural correlates of word retrieval treatment for aphasia and dementia

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Word retrieval deficits are pervasive in acquired neurogenic disorders, and particularly problematic in aphasia and dementia, which collectively affect more than 6 million Americans (Alzheimer's Association, 2012; Roger et al., 2011). Whereas word retrieval in individuals with aphasia or dementia may be improved or at least maintained, respectively, via behavioral treatment (e.g., Jokel & Anderson, 2012), questions remain regarding: (a) identifying efficient treatments that evoke immediate gains as well as long-term maintenance of those gains, (b) discerning which parts of speech (e.g., nouns vs. verbs) respond to behavioral treatment, (c) determining the neural and behavioral mechanisms that support treatment-induced linguistic recovery, and (d) distinguishing prognostic variables that can guide clinicians in their prescription of the type and amount of behavioral treatment needed to achieve functional change. Accordingly, this study utilized a multiple baseline, single-subject across subjects and behaviors design to examine both immediate and long-term effects of an anomia treatment on the language skills of participants with acquired neurogenic disorders (i.e., aphasia, dementia), as well as identify neural changes (using MRI) that accompany these behavioral treatment effects. The project also explores whether pre-treatment activation and/or structural connectivity may serve as prognostic indicators by examining correlations between these imaging measures and post-treatment behavioral outcomes. Finally, by collecting pilot data from individuals with either aphasia or dementia, we are exploring whether neural correlates of language learning (i.e., treatment effects) differ in individuals with static versus progressive forms of brain damage, respectively.

3.

Presenilin 1 (A79V) Mutation: Neuropathologic Phenotype

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Studies of the phenotype of familial Alzheimer Disease (FAD) associated with the Presenilin 1 (PSEN1) A79V mutation are limited. Neuropathologic studies in three individuals from two families are presented. From family A, subjects A1 and A2 presented with memory deficits at age 46 and 58, and died at 61 and 71, respectively. The proband of family B (B1), a male, had mood changes, memory impairment and confusion at age 57. He died at age 67. For neuropathologic studies of these subjects, histological and immunohistochemical techniques as well as molecular genetic analyses were carried out. DNA extracted from brain tissue. Severe atrophy of frontal, parietal and temporal lobes was noted. The caudate nucleus and putamen were moderately atrophic. There was enlargement of the lateral ventricles. Neuronal loss and gliosis as well as microvacuolar changes in the neuropil were observed in neocortex, hippocampus and subcortical nuclei. Neuritic and diffuse plaques, neurofibrillary tangles and neuropil threads were observed in neocortex and hippocampus. Diffuse plaques were also observed in caudate nucleus and occasionally in subcortical white matter. In the cerebellar molecular layer, numerous diffuse plaques were present. Amyloid angiopathy was observed in all cases. In one case (B1), Lewy bodies were observed in the amygdala; Lewy neurites were observed in the amygdala and substantia nigra. Genetic analysis determined the presence of the A79V PSEN1 mutation in all subjects and each subject carried the APOE e3/e4 genotype. This study describes the main neuropathologic characteristics associated with the PSEN1 A79V mutation.

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4.

Olfaction in Older Adults At-Risk for Alzheimer's Disease: Association with Cognitive Performance and Imaging

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Introduction: Olfactory deficits are present in patients with Alzheimer's disease (AD) and in prodromal stages, such as mild cognitive impairment (MCI) [1,2]. However, the extent of olfactory deficits in pre-MCI stages, as well as across the spectrum of MCI (early (EMCI) and late (LMCI)) has not been evaluated to date. The goal of this pilot study was to assess olfaction in older adults with subjective cognitive decline in the absence of clinically-relevant cognitive deficits (SCD), EMCI and LMCI patients, as well as healthy controls (HC). In addition, we evaluated the relationship between olfactory function and cognition, as well as brain atrophy.

Methods: 14 participants (7 HC, 3 SCD, 2 EMCI, 2 LMCI) underwent olfactory testing with the University of Pennsylvania Smell Identification Test (UPSIT), along with comprehensive clinical and neuropsychological examination and structural magnetic resonance imaging (MRI). Structural MRI scans were processed using Freesurfer version 5.1 and voxel-based morphometry in SPM8. UPSIT raw and percentile scores were evaluated for differences across groups using an ANOVA model. Associations between UPSIT percentile scores and selected neuropsychological test performance measures, as well as atrophy in selected brain regions of interest (ROI), were assessed using Pearson correlation. Finally, voxel-wise associations between whole-brain grey matter (GM) density and UPSIT raw and percentile scores were analyzed in SPM8 using standard, previously described techniques [3].

Results: UPSIT scores were significantly different across diagnostic groups ($p<0.05$), with the LMCI group showing the most marked deficits. Average memory performance was positively associated with the UPSIT percentile score across all participants (Figure 1A) and within only the HC and SCD participants (Figure 1B). ROI analyses showed that atrophy in the temporal lobe and superior orbitofrontal lobe were associated with lower UPSIT scores across the full sample and within HC and SCD participants only. Voxel-wise analyses demonstrated a positive association between poorer UPSIT performance and reduced GM density in the bilateral orbitofrontal and temporal lobes (voxel-wise $p<0.01$ (uncorrected), $k=200$ voxels; Figure 1C).

Conclusions: Reduced olfactory function is associated with worse cognition and brain atrophy in regions involved in olfactory processing, even in the absence of clinically-relevant cognitive decline. Future plans include replication and extension of this pilot study in larger samples.

5.

Cerebral hypometabolism in carriers of the intron 10 +3 *MAPT* mutation

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Introduction: Multiple systems tauopathy with presenile dementia (MSTD), a form of frontotemporal dementia with parkinsonism-17 (FTDP-17), is a neurodegenerative disorder caused by an (a) to (g) transition at position +3 of intron 10 of the microtubule associated protein tau (*MAPT*) gene. While altered glucose metabolism has been reported in subjects with sporadic bvFTD, it has yet to be reported in an MSTD sample of this size carrying the *MAPT* intron 10 +3 mutation.

Methods: Eleven mutation carriers and eight non-carriers were imaged using FDG PET with standard techniques. Images were then assessed on a voxel-wise basis for the effect of mutation carrier status, covaried for age at scan and gender. Results were displayed at a voxel-wise threshold of $p<0.01$ (uncorrected) and minimum cluster size (k) = 50 voxels. SPM8 was used for all pre-processing and voxel-wise statistical analyses.

Results: Eight of the mutation carriers showed mild cognitive impairment at the time of the PET scan (MMSE = 25.3 +/- 2.4), while three carriers were not impaired at the time of scan (MMSE = 28.0 +/- 0.0). Non-carriers had no cognitive impairment at the time of PET scan (MMSE = 27.1 +/- 1.6). Overall, *MAPT* mutation carriers showed lower FDG uptake bilaterally in the hippocampus, parahippocampal gyrus, amygdala, superior parietal lobule, and in the prefrontal cortex compared to non-carriers.

Conclusions: The present findings suggest individuals with the *MAPT* mutation at position +3 of intron 10 show symmetrical glucose hypometabolism relative to non-carriers in the medial temporal lobe, parietal cortex, and frontal cortex. These metabolic changes overlap previously described patterns of neurodegeneration in MSTD patients and are consistent with the characteristics of their cognitive dysfunction.

6.

Brain activation during working memory performance in Mild Cognitive Impairment

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Working memory (WM) ability declines with aging and in neurocognitive disorders and contributes to the characteristic long-term memory impairment observed in Alzheimer's disease. We assessed WM performance with a sequential letter n-back task in 31 older adults with MCI and 17 with Age Associated Memory Impairment (AAMI) during functional magnetic resonance imaging data acquisition. Task accuracy decreased across 0 -, 1 - , and 2 – back conditions for MCI participants and from 1 – to 2- back conditions for AAMI participants. Response latency increased from 0 – to 2 – back for those with MCI and 0 -, 1 - , and 2 – back for those with AAMI, suggesting that the task generated expected incremental resource demands. Task-specific regions of increased activation with increasing WM load included bilateral precuneus and middle frontal gyri. We found increased activation for MCI participants in left precentral gyrus, superior temporal gyrus, left cerebellar tonsil, and right anterior cingulate, and increased activation for AAMI in the thalamus, right cuneus, left middle frontal gyrus, and superior frontal regions. Region of interest analyses revealed greater medial temporal lobe deactivation during WM performance and thalamic deactivation during attention task performance in AAMI participants. These data indicate that, overall, this n-back WM task elicited expectable regional activation. In addition, we observed group-specific, regionally distinct activation patterns implicating deficiencies in neural resource allocation in MCI.

7.

Tau phosphorylation and truncation at D421 precedes Danish amyloid deposition in mice expressing mutant *BRI2* and TauP301S.

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Familial Danish dementia (FDD) is an autosomal dominant neurodegenerative disease caused by a mutation in the *BRI2* gene. FDD is characterized by vascular and parenchymal Danish amyloid (ADan) deposition, and by neurofibrillary tangles (NFTs) that appear to be biochemically identical to those found in patients with Alzheimer disease. A transgenic animal model of FDD (Tg-FDD) shows ADan deposition and neuroinflammation, but fails to produce NFTs. To determine the relationship between ADan and tau in vivo, Tg-FDD mice were crossed with mice expressing the FTDP-17 TauP301S (0N4R) (Tg-Tau). At neuropathologic examination, Tg-Tau x Tg-FDD mice showed ADan deposition similar to that of Tg-FDD mice. Tg-Tau x Tg-FDD mice showed a statistically significant difference in the number of AT8-positive (4-fold increase) and Tau-C3 (D421)-positive (10-fold increase) neuronal perikarya compared to Tg-Tau mice at 6 months of age, before ADan deposition was observed. Biochemical analysis showed an increase in the amount of AT8 and AT100 sarkosyl-insoluble tau. No statistically significant difference in the expression of the TauP301S transgene between Tg-Tau and Tg-Tau x Tg-FDD mice was observed. Expression of the Danish mutant form of the amyloid precursor protein *BRI2* with the FTDP-17 TauP301S results in a significant increase in phosphorylated and C-terminally cleaved neuronal tau. Since changes in tau in Tg-Tau x Tg-FDD mice are detected before ADan deposits are observed, we postulate that soluble forms of ADan or abnormal function of mutant BRI2 may play a role in mediating NFT formation in this animal model.

8.
Alzheimer's Disease Multiple Intervention Trial (ADMIT)

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Background: Given the lack of disease-modifying therapies, it is important to explore new models of longitudinal care for older adults with dementia. In a previous clinical trial, we demonstrated that collaborative care for Alzheimer's disease reduces patients' neuropsychiatric symptoms as well as caregiver stress. However, these improvements in quality of life were not associated with delays in subjects' functional decline.

Objective: To conduct a randomized trial to determine whether best practices primary care plus home-based occupational therapy delays functional decline among patients with Alzheimer's disease compared to subjects treated in the control group.
Participants: A total of 180 adults aged ≥45 years who are diagnosed with possible or probable Alzheimer's disease; subjects must also have a caregiver willing to participate in the study. Subjects and their caregivers are enrolled from clinical practices in an urban public health system serving Indianapolis, Indiana, USA.

Interventions: All patients receive best practices primary care, which represents the local adaptation and implementation of our prior collaborative care intervention. Intervention patients also receive in-home occupational therapy delivered in twenty-four sessions over two years in addition to best practices primary care. The focus of the occupational therapy intervention is delaying functional decline. The in-home sessions are tailored to the specific needs of each patient-caregiver dyad.

Outcomes: The primary outcome is the Alzheimer's Disease Cooperative Studies Group Activities of Daily Living Scale; secondary outcome measures are two performance-based measures including the Short Physical Performance Battery and Short Portable Sarcopenia Measure.

9.

Analysis of the Inverse Association between Cancer and Alzheimer's disease: Results from the Alzheimer's Disease Neuroimaging Initiative Cohort

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Although a number of studies support a reciprocal inverse association between diagnoses of cancer and Alzheimer's disease (AD), to date there has not been any systemic investigation of the neurobiological impact of or genetic risk factors underlying this effect. To facilitate this goal, this study aimed to replicate the inverse association of cancer and AD using data from the NIA Alzheimer's Disease Neuroimaging Initiative, which includes age-matched cases and controls with information on cancer history, AD progression, neuroimaging, and genomic data. Subjects included individuals with AD (n=234), mild cognitive impairment (MCI, n=542), and healthy controls (HC, n=293). After controlling for sex, education, race/ethnicity, smoking, and apolipoprotein E (*APOE*) e2/3/4 allele groups, cancer history was protective against baseline AD diagnosis (p=0.042), and was associated with later age of AD onset (p=0.001). Cancer history appears to result in a cumulative protective effect; individuals with more than one cancer had a later age of AD onset compared to those with only one cancer (p=0.001). Finally, a protective effect of AD was also observed in individuals who developed incident cancer after enrolling (post-baseline visit); 20 individuals with MCI and 9 HC developed cancer, while no AD patients had subsequent cancer diagnoses (p=0.013). This supports previous research on the inverse association of cancer and AD, and importantly provides novel evidence that this effect appears to be independent of *APOE*, the major known genetic risk factor for AD. Future analyses will investigate the neurobiological and genetic basis of this effect.

10.

The Modified Memory Impairment Screen by Telephone identifies Mild Cognitive Impairment

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Alzheimer's disease (AD) pathology can begin years before symptoms emerge and early identification is critical for preventive intervention. Telephone screening for clinical and research applications would be useful to identify risk during the preclinical period. Ideally, this screening assessment would distinguish Age Associated Memory Impairment (AAMI) from Mild Cognitive Impairment (MCI), a condition characterized by greater than expected memory impairment for age and substantially increased risk for AD. We modified the Memory Impairment Screen by Telephone (MIS-T; Lipton et al., 2003) to increase sensitivity to milder memory impairment by increasing the number of items from four to eight. We administered the modified instrument by telephone to 133 older adults with subjective memory complaints. Participants were classified as AAMI or MCI using the Montreal Cognitive Assessment and the Clinical Dementia Rating. A t-test showed that participants with MCI performed worse on the modified MIS-T than did participants with AAMI ($t=-7.74$, $p <01$). Linear regression analyses showed that performance on the modified MIS-T predicted performance on the California Verbal Learning Test-2 ($B=.59$, $p<.01$) and the Verbal Paired Associate Test ($B=.88$, $p<.01$). Further, logistic regression showed the modified MIST-T effectively differentiated AAMI and MCI (LL=90.68, modified MIS-T OR=2.16, $p < .01$). Results suggest that the modified MIS-T is a valid and sensitive memory measure that can be administered by telephone to differentiate AAMI from MCI. This instrument might be applied in clinical and research settings to determine whether further evaluation of memory decline is indicated.

11.
Enhanced cerebral bioenergetics with dietary ketosis in Mild Cognitive Impairment

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BACKGROUND: Metabolic disturbance is a promoter of neurodegeneration, and cerebral glucose hypometabolism is prominent in Alzheimer's disease (AD). Ketone metabolism compensates for glucose hypometabolism and confers other benefits pertinent to neurodegeneration, suggesting its potential as a preventive or therapeutic intervention for AD. In a prior controlled trial, we showed that six weeks' carbohydrate restriction induced ketogenesis and produced improvements in metabolic parameters and memory performance in older adults with Mild Cognitive Impairment (MCI). Those benefits were attributed to the correction of hyperinsulinemia but also to the presumed enhancement of cerebral bioenergetic function associated with ketone metabolism.

OBJECTIVE: To assess the effect of dietary ketosis on cerebral metabolites in older adults with MCI.

METHODS: We enrolled a sample of five MCI participants in a six-week, ketogenic dietary regimen and performed pre- and post-intervention proton magnetic resonance spectroscopy to investigate changes in neurochemical metabolites. We also assessed cognitive function and metabolic and anthropometric factors.

RESULTS: We observed a significant increase in myo-inositol (mI; $p = 0.02$) and trends for increases in N-acetyl-aspartate (NAA; $p = 0.09$) and creatine + phosphocreatine (Cr; $p = 0.11$). Working memory ($p = 0.01$) and long-term memory ($p = 0.07$) performances also improved and were associated with the changes in Cr.

CONCLUSIONS: This study offers novel, preliminary evidence of cerebral bioenergetic enhancement with dietary ketosis in aging humans. Further investigation is warranted to assess the preventive and treatment implications of this intervention for age-related memory decline and dementia.

12.

Altered Default Mode Network Connectivity in Older Adults with Cognitive Complaints, Early and Late Amnestic Mild Cognitive Impairment

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Resting State functional Magnetic Resonance Imaging (RS-fMRI) is a technique that can be used to measure changes in connectivity between spatially distinct brain areas. One such network, the Default Mode Network (DMN), has consistently been reported to show altered connectivity in AD. The DMN consists of the precuneus and posterior cingulate cortex. This network is thought to play a role in internal tasks such as, daydreaming, imagining, and, more relevantly, retrieving memories. Therefore, investigating the DMN may unveil early clues as to abnormal connectivity patterns in populations susceptible to AD. Our RS-fMRI data was collected from subjects of an ongoing cohort study on a Siemens 3T scanner that also received extensive neurocognitive testing and assessments outside of the scan. A DMN connectivity map was derived from RS-fMRI data using the independent component analysis (ICA). Group comparisons were then carried out between older adults with self-assessed and informant-verified cognitive complaints (SCD) but normal neuropsychological performance (n=19), individuals in the early and late stages of mild cognitive impairment (EMCI, n=13, and LMCI, n=13, respectively), and healthy controls (HC, n=15). Particular focus on connectivity was made in DMN memory areas such as the hippocampus and dorsal thalamic nuclei. F-contrasts were used to measure the effect of diagnostic group, with age and gender as covariates. Grey matter atrophy as the potential confounding factor was controlled for using the Biological Parametric Mapping (BPM) toolbox. Our results found that our HC group showed an increase in connectivity compared to prodromal groups SCD and EMCI in brain areas that serve memory. Therefore, indicating altered DMN connectivity could be important in assessing prodromal neurodegenerative associated with AD.