...Disentangling Tau...

Tau [F18] T807 – Alzheimer’s disease dementia

Images Courtesy of Keith A. Johnson, MD
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Title: Connectomic Biomarkers of Alzheimer’s Disease Observed in Multi-Synaptic Pathways

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Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☑ NO ☐

ABSTRACT: The human brain consists of a set of complex structural and functional networks. Network-based analysis of brain white matter connections has proved promising in revealing the structural basis of cognitive dysfunction in Alzheimer’s disease (AD) and Mild Cognitive Impairment (MCI), and discovery of diagnostically and therapeutically important biomarkers. Standard approaches to computing structural connectivity often define the connection strength between two brain regions based on the tractography streamline between them. Such a direct fiber bundle is expected to be the major signal carrier between the two brain areas; however, multi-synaptic neural pathways – those relayed through other regions – also provide connectivity.

In this work, we develop and validate a novel mathematical model to account for indirect multi-synaptic neural pathways, thereby improving understanding of the brain network, and deriving more accurate connectomic AD biomarkers through augmenting the information offered by measures of direct brain connectivity. We exploit the mathematical convenience provided by Kirchhoff’s circuit laws to account for indirect pathways. We model the multiple pathways connecting two regions by analogizing individual connectivity of each fiber bundle to the electrical conductance of a resistor, making two basic cases of connectivity similar to parallel and series circuits. We then use the Kirchhoff’s circuit laws and graph Laplacian methods to compute the total connectivity of pairs of brain regions.

We validate our conductance model on a dataset of 200 subjects from the Alzheimer’s Disease Neuroimaging Initiative, and show improved classification among Normal, early MCI, and late MCI groups by using the proposed technique.
Title: Towards the Validation of Novel PET Tau Tracer T807 on Postmortem Human Brain Tissue Samples

Author(s): Marta Marquie, Marc D. Normandin, Charles R. Vanderburg, Isabel Costantino, Bradford C. Dickerson, Matthew P. Frosch, Bradley T. Hyman, Keith A. Johnson, Teresa Gomez-Isla

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Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☒ NO ☐

ABSTRACT: Introduction: The recent development of novel PHF-tau targeting PET tracers, such as T807, opens an exciting opportunity of using them as potential surrogate markers to measure tau pathology. A comprehensive approach to validate the sensitivity and specificity of T807 is critical to understand what T807 PET positivity means in terms of neuropathological substrate. Objective: To examine region and substrate specific autoradiographic and fluorescent binding patterns of T807 in human postmortem tissue representing a diverse spectrum of neurodegenerative diseases to validate the site/s of T807 binding and determine whether there is off-target binding. Methods: We studied the autoradiographic and fluorescent patterns of T807 using postmortem samples from multiple brain regions from patients with a pathological diagnosis of Alzheimer’s disease (AD), frontotemporal lobar degeneration-tau (FTLD-tau), frontotemporal lobar degeneration-TDP43 (FTLD-TDP43), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Parkinson’s disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), cerebral amyloid angiopathy (CAA) and controls. Results: Film autoradiography with [18F]T807 demonstrated that tangle containing areas in AD cases strongly bind ligand, while slides containing TDP43, LB or CAA pathology do not. Staining of adjacent sections with a fluorescent derivative of T807 and appropriate specific antibodies against PHF-1, Aβ, TDP43 and α-synuclein revealed a very strong fluorescent T807 labeling of tangles and PHF-1 containing dystrophic neurites in AD cases, Pick bodies in Pick’s disease, and neuronal and glial tau containing lesions in PSP and CBD. T807 fluorescent labeling of TDP43 inclusions and of Lewy pathology was completely absent. Studies using slides dipped in photographic nuclear
emulsion to obtain cellular resolution with [18F]T807 ligand binding are currently ongoing. **Conclusion:** Our preliminary data on the postmortem validation of T807 are very encouraging and suggest that PHF-positive neurofibrillary tangles and dystrophic neurites likely account for the majority of tau related T807 ligand binding.

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Title: An Inhibitor of the Proteasomal Deubiquitinating Enzyme USP14 Induces Elimination of Phosphorylated Tau in Cultured Neurons

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Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☐ NO ☒

ABSTRACT: The ubiquitin-proteasome system (UPS) is responsible for most selective protein degradation in eukaryotes and regulates numerous cellular processes, including cell cycle control and protein quality control. A component of this system, the deubiquitinating enzyme USP14, associates with the proteasome, where it can rescue substrates from degradation by removal of the ubiquitin tag. We previously found that a small-molecule inhibitor of USP14, known as IU1, can increase the rate of degradation of a subset of proteasome substrates. We identified a more potent USP14 inhibitor that retains specificity for USP14. The capacity of this compound, IU1-47, to enhance protein degradation in cells was tested using the microtubule-associated protein tau as a reporter. The accumulation of hyperphosphorylated tau is a hallmark of many neurodegenerative diseases, including Alzheimer’s disease, and lowering the levels of toxic tau species could be beneficial in such conditions. Using primary neuronal cultures, IU1-47 was found to accelerate the rate of degradation of wild-type tau, the pathological tau mutant P301L, the mutant P301S and the A152T tau variant. Tau pathology has been linked to its phosphorylation, and the enhancement of tau elimination by IU1-47 was preferential for phosphorylated forms of the protein. In summary, these findings provide a powerful research tool for investigating the complex biology of USP14 as well as a potential strategy for reducing the accumulation of toxic protein species.
Title: Genome-Wide Association Study of AD-Related phenotypes in Different Stages of Alzheimer Disease Progression

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Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☑ NO ☐

ABSTRACT: Previous genome-wide association (GWA) studies have considered endophenotypes such as cerebrospinal fluid (CSF) biomarkers, neuroimaging, and neuropsychological tests to understand biological processes and neurepathological mechanisms of Alzheimer’s disease (AD). However, genetic susceptibility that is distinct in different stages of AD progression has not been fully understood.

Methods: We conducted GWA studies for CSF levels of amyloid beta-42 (AB42), total tau, and phosphorylated tau, hippocampal volume (HPV), and logical memory test (LMT) in subgroups by AD stages and in the total sample from Alzheimer’s Disease Neuroimaging Initiative (ADNI) study. The ADNI sample was available with 1,076 subjects from AD (n=190), mild cognitive impairment (MCI, n=581), and clinically normal (CN, n=305) subjects as two sets of GWA data genotyped in two platforms. A total of 8,082,822 single nucleotide polymorphisms (SNPs) were tested for association in a linear regression model for the phenotypes, which were normalized after accounting for age, sex, and population substructure. We conducted association tests separately in two ADNI sets, and the results from the two sets were meta-analyzed. Top ranked SNPs (p<5x10^{-8}) in meta-analysis were examined for potential function and enriched pathways.

Results: We observed genome-wide significant (GWS, p<5x10^{-8}) association in two loci for AB42 from LOCS286114 and APOE in all subjects. In subgroups, we identified three GWS loci in CN subjects from GRIN2B, NACA2, and FAM18A5 (best SNP, rs5769666,
p-value in meta-analysis [meta-p] for AB42=3.7x10-9 from FAM18A5), two loci in MCI subjects from NRG1 and COXI8 (best SNP, rs10095844, meta-p for LMT=2.3x10-9 from NRG1), and one locus in AD subject from AKAP9 (best SNP, rs149454736, meta-p for HPV=6.8x10-9). GWS SNPs from GRIN2B, NACA2, FAM18A5, and NRG1 were significant cis-acting eSNPs (p<0.05) in hippocampus, frontal, or temporal cortex (best SNP, rs2378873, p-value in hippocampus=0.001 from NACA2). Pathway analysis demonstrated the top ranked SNPs were restricted to neuronal cells and significantly (p<6.9x10^-3) enriched in nNOS signaling, reelin signaling, and glutamate receptor signaling pathway.

**Conclusion:** We identified novel AD risk genes NACA2, FAM18A5, and COXI8, as well as known AD genes GRIN2B, NRG1, and AKAP9. Our results confirmed that different stages of AD progression are influenced by unique sets of genetic factors but enriched together in neuron-specific pathways. Genes and pathways for AD-related phenotypes in early stages of AD (CN and MCI) are potentially important for early biomarkers for AD.
Title: Associations between White Matter Lesion Microstructure and Imaging Markers of Alzheimer's Disease

Author(s): Jean-Philippe Coutu, Alison E. Goldblatt and David H. Salat

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Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☐  NO ☒

ABSTRACT: White matter lesions, or leukoaraiosis, are typically identified in vivo as white matter signal abnormalities (WMSA) on magnetic resonance imaging. WMSA are apparent in up to 95% of adults older than 60 years old and are associated with small vessel disease and several vascular risk factors. While WMSA volume has been shown to be increased in Alzheimer's disease (AD), limited evidence exists to demonstrate that the WMSA present in AD are similar in nature to those observed in non-demented older individuals. Additionally, little is known about how this typically vascular-associated tissue damage relates to more classical imaging markers of AD pathology such as cortical and hippocampal atrophy which could provide important information about the role of this tissue damage in the neurodegenerative pathology of AD. We used a large publicly-available dataset from the Alzheimer's Disease Neuroimaging Initiative which included 74 controls, 97 participants with MCI and 48 participants with AD with T1-weighted and diffusion-weighted imaging datasets. Associations were investigated between diffusion tensor imaging measures and the following imaging markers of AD: total WMSA volume, total white matter volume, ventricular volume, hippocampal volume and the average cortical thickness of regions most affected in early AD. We find that while regions like the parahippocampal white matter are indeed related to markers of neurodegeneration such as hippocampal volume and cortical thickness, WMSA tissue properties are unrelated to this phenomenon and are instead associated with mechanisms related to ventricular enlargement and total WMSA volume.
**Title:** LINCing Laminopathy and Tauopathy

**Author(s):** Bess Frost, Farah Bardai, and Mel Feany

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**Mass. ADRC/BU ADC SPONSORED PROJECT:** NO

**ABSTRACT:** Dysfunction of the nuclear lamina has been strongly implicated in the cellular mechanisms underlying aging, because mutations in lamin cause the accelerated aging syndrome progeria. The segmental nature of progeria has been a longstanding mystery in aging research: certain aspects of aging appear to be recapitulated in the syndrome, while others, particularly neurodegeneration, are not. Preliminary data suggests that acquired lamin misregulation though aberrant cytoskeletal-nucleoskeletal coupling mediates neuronal death in a Drosophila model of tauopathies. In addition, we observe robust alterations in the nuclear lamina in neurons from patients with Alzheimer's disease, the most common tauopathy. To demonstrate that lamin dysfunction can promote brain aging, we deplete lamin function genetically in the Drosophila nervous system and observe markedly decreased lifespan accompanied by age-dependent neurodegeneration. These findings provide strong evidence for conserved cellular aging mechanisms among neurons and other somatic tissues, and identify a new pathway mediating neuronal death in currently untreatable human neurodegenerative disorders, including Alzheimer’s disease.
Title: Identification of Novel Calcineurin/NFAT Transcriptional Targets Mediating Alzheimer’s Disease Synaptic Dysfunction

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Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☒ NO □

ABSTRACT: Previous studies in Alzheimer’s disease (AD) patients and in AD transgenic animals have suggested that the presence of soluble amyloid β peptides and/or tau potentially leads to chronic activation of the neuronal calcium dependent phosphatase calcineurin (CaN, also termed protein phosphatase 2B). Upon activation, CaN is responsible for at least two broad types of effects biologically relevant to AD pathophysiology. First, CaN leads to a rapid post-translational modulation of postsynaptic proteins such as coflin and AKAP79, a process associated with long-term depression. Second, CaN dephosphorylates the nuclear factor of activated T cells (NFAT), which leads to its translocation to the nucleus and to the expression of target genes implicated in neuronal survival. Importantly, our previous work has shown that targeted inhibition of CaN/NFAT alleviates Aβ-mediated neurotoxic events, suggesting that the transcriptional impact of this particular cascade may be of relevance in the disease.

In order to characterize the expression profile changes dependent upon CaN/NFAT-activation in neurons, intrahippocampal injections of adeno-associated vectors coding for wild-type CaN (wtCaN), constitutively activated CaN (CACaN) and GFP (control vector) were performed in wild-type mice. After laser capture microdissection of the transduced neuronal cells, a whole genome micro-array assay identified 6 genes differentially modulated by CACaN (as compared with wtCaN and GFP): Neuronatin (NNAT), Nurr1 (Nr4a2), VGF
nerve growth factor (VGF), Hippocalcin (HPCA), Heat shock protein 5 (Hspa5) and corticotropin-releasing hormone (CRH). Further validation by qRT-PCR in human hippocampal tissue confirmed the significant increased expression of VGF and CRH in AD compared with aged-matched controls.

By using in vivo gene transfer, we demonstrate that CaN activation impacts the expression level of a set of genes in neurons. In particular, our findings highlight for the first time a possible link between a chronic induction of calcineurin and CRH, a peptide hormone and neurotransmitter potentially involved in the stress response in Alzheimer’s disease. Further studies will decipher if interfering with the CRH cascade, may alleviate amyloid induced, CaN-dependent, neurotoxic effects.
Title: Death-Associated Protein Kinase 1 Regulates Amyloid Precursor Protein Processing

Author(s): Byeong Mo Kim¹, Mi-Hyeon You¹, Matthew P. Frosch²,³, and Tae Ho Lee¹

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Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☒ NO ☐

ABSTRACT: Extracellular deposition of the neurocytotoxic amyloid β (Aβ) peptide from sequential amyloid precursor protein (APP) processing as well as intracellular accumulation of tau protein is a critical step in the development of Alzheimer’s disease (AD). Therefore, the ability to define regulatory mechanisms controlling APP processing and tau function will be critical for elucidating the pathogenesis and for designing strategies for preventing and/or treating neurodegenerative diseases. We have previously shown that death-associated protein kinase 1 (DAPK1) induces abnormal tau protein accumulation and phosphorylation thereby interfering with tau function. Originally identified as an important positive mediator of apoptosis, DAPK1 kinase activity-deficient mice are more efficient learners and have better spatial memory than wild type mice and DAPK1 is also genetically linked to late onset AD. These results suggest that aberrant DAPK1 activation might contribute to age-dependent neurodegeneration. However, the possible role of DAPK1 in APP processing and Aβ generation still remains ill-defined. In this study, therefore, we aimed to elucidate the mechanisms of DAPK1 action APP processing and Aβ secretion using various cell lines and mouse model. We demonstrated here that inhibition of DAPK1, but not kinase-deficient mutant K42A, promoted Aβ secretion in neuronal cells. Moreover, DAPK1 using gene knockout, knockdown or pharmacological inhibitors were found to significantly reduce secretion of Aβ40 and Aβ42 peptides. We also showed that DAPK1 could interact with APP and that DAPK1, but not K42A, remarkably triggered Thr668 phosphorylation of APP, which may initiate and facilitate the amyloidogenic APP processing leading to the generation of
Aβ. Furthermore, DAPK1 knockout mice showed significantly reduced levels of Aβ and dramatically decreased insoluble Aβ40 and Aβ42 levels compared with DAPK1-WT littermates in APP-Tg2576 mice. These results indicate that DAPK1 has effects on amyloidogenic processing of APP by triggering APP phosphorylation at 1hr668 and that DAPK1 might be a potential therapeutic target to inhibit amyloidogenic APP processing and to lower Aβ secretion.
Title: Multiscale Neural Decoding in Brain-Machine Interfaces for People with Tetraplegia

Author(s): Wasim Q. Malik, Emery N. Brown, Leigh R. Hochberg

Institution: Massachusetts General Hospital

Mass. ADRC/BU ADC SPONSORED PROJECT: ✔

ABSTRACT: We are investigating the BrainGate brain-machine interface for rehabilitation and motor function restoration in individuals with tetraplegia due to ALS, stroke and spinal cord injury. Our approach consists of recording movement-related motor cortical signals using chronically implanted 96-channel microelectrode arrays, and decoding these signals to achieve real-time assistive device control. Conventional brain-machine interfaces use single-unit action potentials (SUA) for neural decoding. Although information-rich, SUA signals suffer from substantial temporal variability, causing system instability and requiring frequent manual decoder recalibration. We recently investigated an alternative neural signal source, namely multiunit activity (MUA), for the first time in humans. MUA represents the summed activity of an ensemble of single-units, and is therefore inherently more stable. We conducted offline “open-loop” analysis of data recorded under motor imagery, i.e. the participant observed a computer-controlled cursor moving on screen in a center-out task and imagined controlling its movement. Specialized computational algorithms were used to reconstruct the imagined trajectory by decoding neural signals. Using data from 5 research sessions with 1 participant, we found that MUA decoding performance, measured in terms of trajectory correlation, was significantly higher than that of SUA. We then evaluated real-time “closed-loop” neural control of a computer cursor in 10 sessions with 2 participants. The behavioral task consisted of reach-and-grasp movements of the cursor using neural signals to acquire targets on the computer screen. We found that MUA consistently and significantly outperformed SUA, as indicated by its higher successful target acquisition rate and less jittery trajectories. Thus our results show that MUA not only boosts system stability and robustness compared to SUA but also provides improved decoding performance. MUA may therefore be used as a complementary signal source to SUA in multiscale brain-
machine interfaces, increasing the clinical feasibility of this approach for rehabilitation of severe motor disability caused by neurodegenerative diseases and neurotrauma.
Title: Rejuvenating the Dentate Gyrus with an Expansion of the Adult-Born Neuron Population to Enhance Memory Precision in Adulthood and Aging


Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☐ NO ☒

ABSTRACT: Neural stem cells in the dentate gyrus (DG) generate dentate granule neurons throughout life, a process exquisitely sensitive to the environment. Adult-born dentate granule neurons contribute to encoding functions important for minimizing interference during storage of episodic memories such as pattern separation. These observations suggest that adult hippocampal neurogenesis represents an adaptive mechanism of encoding by which generation and integration of new neurons is governed by environmental demands on hippocampal circuitry to maintain memory precision. However, the underlying mechanisms by which mature dentate granule neurons sense and transduce changes in activity to dictate lineage homeostasis are poorly understood. Here, we interrogated the impact of decreasing synaptic inputs onto mature dentate granule neurons on their competition for perforant path inputs with adult-born dentate granule neurons and also on neural stem cell activation. Using a novel genetic system by which we reversibly eliminate a subset of dendritic spines on mature dentate granule neurons, we found that adult-born dentate granule neuronal integration and activation of neural stem cells are bidirectionally sensitive to these alterations. We have harnessed this strategy to determine how rejuvenening the DG with expanded cohorts of adult-born
dentate granule neurons at distinct stages of maturation impacts encoding and memory precision in adulthood and in aging. Our studies indicate that multiple feedback loops within the adult neurogenic lineage mediate nuanced adaptation to changes in activity of mature dentate granule neurons. Importantly, targeting adult hippocampal neurogenesis is sufficient to reverse impairments in pattern separation and memory precision in aging.
Title: Novel Repressors of α-Synuclein Gene Identified in Gene-Expression High Throughput Screen-A Potential Therapeutics for Parkinson’s Disease

Author(s): Shuchi Mittal, Barbara J. Caldarone, Dennis J. Selkoe, Marcie A. Glicksman, and Clemens R. Scherzer

Institution: Brigham and Women’s Hospital, Harvard Medical School

Mass. ADRC/BU ADC SPONSORED PROJECT:  YES ☐  NO ☒

ABSTRACT: It is known that simply increasing dosage of wild-type alpha-synuclein (SNCA) is sufficient to cause dopaminergic neurodegeneration and Parkinson’s disease (PD) in rare kindreds carrying a duplication or triplication of the locus and it is widely believed that SNCA over expression may play a similar role in the common, sporadic disease. Brains of most patients with Parkinson’s are littered with intracellular accumulations of α-synuclein, a small 140 amino-acid protein. To rid brains of Parkinson’s patients of α-synuclein toxicity one can attempt to break down or clear the protein from the brain, block its transformation into toxic species, or ameliorate the consequences of α-synuclein toxicity. We hypothesize, that the most direct and acute solution should address the problem at its origin and simply turn off excessive SNCA transcription. An innovative high-throughput gene expression assay was developed and performed to screen 1,126 FDA-approved drugs and a diverse set of natural products and health supplements. A small subset of hits has been identified and confirmed which consistently lowered the expression of endogenous SNCA mRNA as well as protein abundance in neuronal cells. As these drugs are FDA-approved they have a suitable toxicity profile and some of them are known to penetrate the blood-brain barrier. These hits are target-specific and lack neuronal toxicity. Excitingly, one of the hits also lowered endogenous SNCA mRNA expression in the PD vulnerable substantia nigra region of wild-type mice brain. This study has also delineated the regulatory pathway underlying the drug effect – there by elucidating a novel, druggable pathway as a target for alpha-synuclein modulating drugs. Moreover, if confirmed in clinical trials, the alpha-synuclein-lowering drugs so identified may yield the first disease-modifying medications for patients with Parkinson’s.
Title: Beta-Amyloid in Chronic Traumatic Encephalopathy, Alzheimer’s Disease, and Normal Aging: Evidence for Non-Overlapping Etiologies

Author(s): Philip H. Montenigro, Victor Alvarez, Robert A. Stern, Ann C. McKee, Thor D. Stein

Institution: Boston University School of Medicine, Boston VA Medical Center

Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☒ NO ☐

ABSTRACT: OBJECTIVE: To determine whether amyloid beta (Aβ) pathology in chronic traumatic encephalopathy (CTE) differs from Alzheimer’s disease (AD) and normal aging.

BACKGROUND: CTE is a neurodegenerative disease associated with repetitive traumatic brain injury (RTBI). It is characterized by a distinct pattern of tau accumulation that was recently categorized into four CTE stages (I-IV) based on the extent of tauopathy. Deposition of Aβ is also associated with trauma and CTE. However, the relation between Aβ, tau, and normal aging in CTE is unknown.

DESIGN/METHODS: 114 autopsy cases with both a history of RTBI and a neuropathological diagnosis of CTE (McKee et al 2013) were compared to 319 cases of neuropathologically diagnosed AD and to a large non-selected cohort of 2,332 normal aging cases (Braak 2011).

RESULTS: Aβ deposition occurred in 43% of CTE cases. Compared to the normal aging cohort, Aβ appeared at an earlier age and at an accelerated rate in CTE. The odds of developing neuritic Aβ were 11.1 times higher in the CTE cohort ($\chi^2=0.97$, $p=0.025$), and a weighted two-sample chi-square test demonstrated that the distribution of Aβ plaques by age in CTE was distinct from the distribution in normal aging ($\chi^2=21.4$, $p = 0.0015$). Age-adjusted multiple linear regression analysis demonstrated that the presence diffuse Aβ pathology predicted significantly greater CTE tau-pathological stage at the time of
death ($\beta=0.53$, $p=0.003$) whereas the contribution of age on stage was negligible ($\beta=0.026$, $p<0.001$). Moreover, we hypothesized that more A$\beta$ pathology would accumulate in the cortical sulcus, where RTBI shear strains are highest, compared to the gyral crests. A significantly greater A$\beta$1-40 plaque burden was, in fact, found in the sulcus of CTE cases ($t=2.21$, $p=0.029$).

CONCLUSION: Overall, these findings suggest that tau and A$\beta$ pathologies in CTE are found in a distribution and progression pattern that is distinct from normal aging and AD.
Title: Impairment in the Hippocampal Representation of Space in a Mouse Model of Alzheimer’s Disease

Author(s): Kevin Neville, PhD; Daniel Graziano; Stephen Gomperts, MD, PhD

Institution: Massachusetts General Hospital

Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☒ NO □

ABSTRACT: Background: Progressive impairment of hippocampal-dependent memory is the sine qua non of Alzheimer’s disease (AD), but the systems level manifestations of beta-amyloid (Aβ) on hippocampal function in AD remain poorly understood. Aβ has been associated with aberrant neuronal excitability in mouse models of AD, but such excitability has not yet been related to systems measures of hippocampal function. To evaluate the impact of Aβ on hippocampal function, we performed multiple single unit recordings in awake, behaving APPswe/PS1deltaE9 (APP/PS1) mice. Methods: 6 APP/PS1 and 5 littermate control mice (mean age 1.4 years) underwent awake hippocampal tetrode recordings acquired during repeated experience on two distinct linear environments. Results: Hippocampal neurons of APP/PS1 mice were more likely to have place fields than those of littermate controls. However, compared to the place cells of control mice, APP/PS1 place cells showed impaired representation of space. In addition, place cells of APP/PS1 mice but not control mice failed to distinguish between distinct environments. Finally, participation of hippocampal neurons in task-related sharp-wave ripples was greater in APP/PS1 mice than controls. Conclusions: These systems level deficits in the APP/PS1 model of AD provide a novel link between Aβ and the memory impairments that arise in AD, and hold promise as new biomarkers for AD therapeutics development.
**Title**: Conserved Epigenomic Signatures between Mouse and Human Elucidate Immune Basis of Alzheimer's Disease

**Author(s)**: Andreas R. Pfennig, Elizabeta Gjoneska, Hansruedi Mathys, Gerald Quon, Anshul Kundaje, Manolis Kellis, Li-Huei Tsai

**Institution**: Massachusetts Institute of Technology

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**ABSTRACT**: Alzheimer's disease (AD) is a severe age-related neurodegenerative disorder characterized by accumulation of beta-amyloid (Aβ) plaques and neurofibrillary tangles, synaptic and neuronal loss, and cognitive decline. Several genes have been implicated in AD, but chromatin state alterations during neurodegeneration remain uncharacterized. Here, we profile transcriptional and chromatin state dynamics across early and late pathology in the hippocampus of an inducible mouse model of AD-like neurodegeneration. We find a coordinated downregulation of synaptic plasticity genes and regulatory regions, and upregulation of immune response genes and regulatory regions, which are targeted by factors that belong to the ETS family of transcriptional regulators, including PU.1. Human regions orthologous to increasing-level enhancers show immune cell-specific enhancer signatures as well as immune cell expression quantitative trait loci (eQTL), while decreasing-level enhancer orthologs show fetal brain specific enhancer activity. Surprisingly, AD-associated genetic variants are specifically enriched in increasing-level enhancer orthologs implicating immune processes in AD predisposition. Indeed, increasing enhancers overlap known AD loci lacking protein-altering variants and implicate additional loci that do not reach genome-wide significance. Our results reveal new insights into the mechanisms of neurodegeneration and establish the mouse as a useful model for functional studies of AD regulatory regions.
Title: Understanding the Function of hsa-miR-92a and has-miR-92a-1* in Multiple Sclerosis

Author(s): Radhika Raheja¹, Roopali Gandhi¹

Institution: ¹Ann Romney Center for Neurologic Diseases, Brigham and Women’s Hospital, Boston, USA

Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☐ NO ☑

ABSTRACT: MicroRNA (miRNAs) are single stranded, small non-coding RNA molecules that regulate gene expression and protein synthesis and are involved in fundamental biological processes such as cell proliferation, differentiation and survival. Dysregulated expression of miRNAs is associated with several diseases including cancer, viral infections, and immune related disorders. Thus microRNAs provide a new avenue to understand disease pathogenesis and progression. The role of miRNAs in autoimmune diseases such as multiple sclerosis (MS) has not been completely elucidated. Recent miRNA profiling studies in brain lesions, CSF and immune cell populations provide compelling evidence that miRNA expression differs significantly in MS patients compared to healthy controls. The biological relevance of these differences and how they might contribute to disease pathogenesis is still not clear.

We have studied miRNA expression in immune cells and plasma from MS patients and have focused on hsa-miR92a and hsa-miR92a-1* miRNAs for further analysis. miR-92a and miR-92a-1* belong to the miR17/92 cluster that is known to play a role in regulating hematopoietic lineages and immune cell function. In a mouse model of MS, deficiency of the 17-92 cluster alleviated MS disease progression. Interestingly, we have shown that hsa-miR-92a-1* is significantly increased in plasma from relapsing remitting MS patients (RRMS) compared to secondary progressive MS patients (SPMS) and healthy controls (HC). Further, monocytes purified from peripheral blood cells collected from a small discovery set group (8 untreated RRMS and 8 HCs) showed a significant increase in expression of hsa-miR-92a in RRMS patients compared to HC. In-silico analysis using miRNA target predicting algorithms such as DIANA-MICROT, micornaorg and Tarbase, was carried out to determine putative targets of miR-92a and miR-92a-1*. Some
of the targets of these miRNAs include IL10, ICAM1, ITGAV, CDC42, MYD88, CXCL9, CCL5 that are linked to MS. Based upon these in-silico results, we generated gene interaction networks to cluster the predicted targets into pathways that could contribute to MS progression such as T cell differentiation, proliferation, apoptosis, inflammation and adhesion. We are currently working to validate these findings in in vitro monocytes and activated T cells derived from MS patients and HC. We believe that understanding the physiological role of these miRNAs will provide a better understanding of the disease and unravel novel therapeutic agents or drug targets that can help combat disease.
Title: Longitudinal Shape and Morphometry Analysis in Neurodegenerative Disease

Author(s): Martin Reuter

Institution: A.A. Martinos Center for Biomedical Imaging, MGH

Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☒ NO □

ABSTRACT: Large amounts of longitudinal neuroimaging data are collected to study neurodegenerative diseases such as Alzheimer’s (AD) and Huntington’s disease (HD), and disease modifying therapies. Analysis and discovery/extraction of imaging biomarkers from this increasingly large amount of data requires automated methods to register, segment and process images. In longitudinal studies, the knowledge that sequential images belong to the same person can be incorporated into the analysis to significantly increase reliability and sensitivity, and thus the ability to detect very small changes as required in drug trials. Here we develop a longitudinal image-processing pipeline that significantly increases reliability of reported morphometric estimates, reducing required sample size by approximately 50%. Furthermore, we introduce novel imaging biomarkers based on spectral shape analysis with increased power to distinguish groups. Finally we demonstrate that atrophy patterns are not linear, but follow a sigmoidal pattern (slow changes early, increased atrophy rates around conversion), indicating that non-linear models will yield increased statistical power compared to conventional analysis methods that do not account for this non-linear behavior.
Title: Accelerated Decline in White Matter Integrity in Clinically Normal Individuals at Risk for Alzheimer's Disease

Author(s): Anna Rieckmann, Trey Hedden, Koene RA Van Dijk, Reisa A Sperling, Keith A Johnson, Randy L Buckner

Institution: MGH

Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☒ NO ☐

ABSTRACT: Human imaging studies have identified white matter abnormalities in Alzheimer's disease (AD; e.g. Scheltens et al. 1992; Salat et al. 2009). Yet, cross-sectional imaging studies in clinically normal older individuals show little evidence for an association between markers of AD risk, such as APOE4 genotype and amyloid burden, and white matter integrity (e.g. Hedden et al. 2012; Nyberg & Salami, 2014). This could suggest that accelerated loss of white matter integrity occurs downstream of early preclinical markers of AD, and might only become apparent in longitudinal designs that follow clinically normal older adults at risk for AD over time. Here, 102 older adults (mean age: 73.85, range 66-87) with assessments of APOE4 genotype and amyloid burden underwent MRI scans for measuring white matter integrity at two time points, approximately 2.61 years apart (range 2.25 -3.25). White matter integrity was assessed as fractional anisotropy (FA) in 12 major white matter tracts. Linear mixed effects models with markers of AD risk as predictors of FA decline showed that amyloid burden at baseline was associated with steeper decline in FA in the parahippocampal cingulum bundle ($p < 0.05$, bonferroni-corrected). Further exploration of confounding variables including head motion, registration inaccuracies and grey matter atrophy showed that these had no significant effect on the association between amyloid and decline of white matter integrity. The parahippocampal cingulum bundle connects the hippocampus to the cingulate cortex and previous work has identified this fiber tract as a possible pathway by which the hippocampus is “disconnected” from cortical areas in AD (Salat et al. 2010). The current study extends these findings and shows that amyloid burden modifies the integrity of this pathway already in the preclinical stages of AD.
Title: Relationship between Longitudinal Amyloid Accumulation and T807-TAU

Author(s): Aaron Schultz, Jasmeer Chhatwal, Elizabeth Mormino, Molly LaPoint, Alex Dagley, Reisa Sperling, and Keith Johnson

Institution: MGH / Martinos Center

Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☑  NO ☐

ABSTRACT: Background: \(^{18}\)F-T807 is a new radioligand for in vivo imaging of tau pathology. We previously observed significant cross-sectional relationships between amyloid burden and T807 signal in inferior temporal regions; we now investigate the relationship between longitudinal rate of amyloid accumulation and inferior temporal T807 binding.

Methods: We examined 75 cognitively normal elderly with retrospective longitudinal PiB-PET imaging relative to cross-sectional T807-PET imaging from the Harvard Aging Brain Study (HABS – P01AG036694; Age=76.1±6.1; Baseline CDR=0; e4+/e4- 19/56). Longitudinal PiB measurements were made over a period of 3.2±1.2 years with 2.5±.7 PiB-PET visits per subject. Amyloid measurements were made as DVRs across a distributed cortical region using a cerebellar grey reference region. Tau measurements were made with T807-PET computed as SUVRs with a cerebellar grey reference. Both PiB and T807 utilized structural ROIs as defined by Freesurfer.

Results: The results show a significant relationship between baseline amyloid burden and inferior temporal T807 (t(70) = 4.38; p<0.001), and a significant relationship with rate of accumulation (t(70) = 2.36; p=0.021). When both baseline amyloid burden and rate of accumulation were included in the model, baseline amyloid burden remained significant (p<0.001) whereas rate of accumulation did not (p=0.94). All models included age at T807 scan, sex, and the time between the latest PiB scan and T807-PET imaging.

Conclusion: We observed a significant association between baseline amyloid burden and inferior temporal T807 binding, as well as an association between with T807-binding and
the rate of amyloid accumulation, though the rate effect did not survive when controlling for baseline amyloid. As the inferior temporal cortex is among the earliest sites of neocortical tau pathology, these results are consistent with the hypothesis that amyloid pathology influences the spread of tau pathology into neocortex. Further follow-up and a larger sample size is needed to verify these preliminary results.
Massachusetts Alzheimer's Disease Research Center
Boston University Alzheimer's Disease Center
Harvard NeuroDiscovery Center
Twenty-Eighth Annual Scientific Poster Symposium
Friday February 27th, 2015
9am-12noon
Thier Building, 55 Fruit St, Boston, MA 02114
MGH

Title: Tau and Amyloid Deposits Relate to Distinctive Cortical Atrophy Patterns in Cognitively Normal Elderly

Author(s): Jorge Sepulcre1,2, Aaron P. Schultz2, Alex Becker1, Reisa Sperling2,3,4, Keith A. Johnson1,3,4

Institution: 1Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; 2Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA; 3Centre for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, 4Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.

Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☒ NO ☐

ABSTRACT: Background: Alzheimer’s disease (AD) neuropathological processes are thought to affect brain function before cognitive manifestations appear. AD neurodegeneration is a complex phenomenon where misfolded amyloid-β (Aβ) and Tau proteins accumulates in the human brain. The introduction of molecular imaging techniques such as Positron Emission Tomography (PET) has facilitated early detection and visualization of brain pathology in elderly subjects, such as Aβ deposits and, more recently, Tau deposits. In this study, we aim to evaluate the brain spatial distribution of a novel PET Tau tracer –known as 18F-T807- and identify its association with Aβ deposition and grey matter (GM) volume loss in a sample of cognitively normal participants in the Harvard Aging Brain Study to gain insight about their spatial relationships in elderly individuals.

Methods: Eighty-eight subjects (mean age (SD): 76.2 (6.2), M/F: 39/49) underwent two PET imaging acquisitions and MRI. PET Procedures: 1) 11C-PiB that binds fibrillar Aβ plaques; and 2) 18F-T807 that binds Tau neurofibrillary tangles and neurites were used in the study. PiB PET data was expressed as DVR and T807 as SUVR (cerebellar grey reference). We used a voxel-based morphometry strategy to obtain the segmented GM
volume maps of each individual. All PET data were spatially normalized to a MNI template (SPM software). The average time elapsed between the two PET scan sessions was 5.3 months, with a range of 0 to 20 months. Spatial Distribution Covariations and Hubs: we used voxel-by-voxel regressions and degree of spatial co-variations to investigate in-situ and off-situ spatial correspondences between maps of 18F-T807, 11C-PiB and GM volume. Degree of spatial co-variations were obtained by quantifying the amount of significant correlations between brain voxels. In-situ and off-situ correlations between voxels of different imaging modalities are two analytical approaches that complement each other. In-situ correlations analyze how Tau or Aβ relates to GM atrophy in the same spatial coordinates or co-registered voxels. In contrast, off-situ correlations investigate how Tau or Aβ intensities in a given voxel relate to GM intensities in the rest of the voxels of the brain. As result, the off-situ approach obtain the hub-regions of Tau-GM or A-GM interactions.

Results:
- Tau and Aβ deposits are predominantly located in different regions of the cortical mantle. Aβ locates intensively in lateral and midline frontal and parietal areas, while Tau predominates in temporal lobe area, particularly in ventral and lateral temporal inferior regions.
- Tau deposits spatially correlate with in-situ atrophy in anterior medial and inferior temporal lobe areas. Aβ deposits and in-situ GM atrophy are spatially associated in a more widespread manner. We found negative spatial correlations between deposits of Aβ and local GM volume in lateral temporal, parietal and frontal regions, as well as medial and inferior temporal areas.
- We have also investigated the off-situ relationships between Tau, Aβ and GM atrophy. Tau deposits in the medial and inferior temporal, and orbitofrontal areas accumulate a disproportionate number of negative correlations with GM volume at distributed locations of the human cortex. On the other hand, Aβ intensities in traditional locations for this pathological marker congregate high amount of negative correlations with GM volume of voxels of the brain. Thus, these areas serve as hub-regions for Tau- and Aβ-GM atrophy interactions.
- Finally, Tau and Aβ deposits display direct in-situ associations -positive correlations- in heteromodal areas of frontal, parietal and temporal lobes, most highly in inferior-lateral temporal cortex. Inferior-lateral temporal cortex is indeed critical to understand the off-situ relationships between Tau and Aβ pathology. These findings support the network nature of the AD-related pathology at in-vivo level.

Conclusions:
At preclinical stages of Alzheimer’s disease, Tau and Aβ deposits show strong spatial interdigitations in heteromodal and associative areas of the cortical mantle, particularly in lateral temporal and frontal lobes. However, Tau and Aβ deposits associate with distinctive spatial patterns of brain atrophy.
Title: A Therapeutic miRNA for Brain Disorders

Author(s): Kai C. Sonntag, Woori Kim, Yenarae Lee, Donna L. McPhie, Kwang-Soo Kim, Bruce M. Cohen

Institution: Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, MA 02478

Mass. ADRC/BU ADC SPONSORED PROJECT: ☑️

ABSTRACT: One of the main hurdles in developing novel therapeutics for age-related disorders is the still limited understanding of both the biology of normal aging and the mechanisms of disease pathology. Aging and age-related disorders are characterized by slow progressive deterioration or death of neurons, and are influenced by age- and disease-specific factors, including genetic predisposition, dysfunctional proteins, and compensatory mechanisms and molecules that are important in cell survival. If the cellular defense mechanisms are compromised, the penetrance of disease-specific mechanisms becomes higher and cell survival less likely. Among the regulatory factors that govern gene and protein networks and, consequently, influence neuronal health and function are small molecules such as miRNAs. It is increasingly appreciated that even small disturbances of these regulatory factors can have profound effects on cell survival in response to stress.

We have identified a novel mechanism in neurons, mediated by miR-126, which regulates the effects of numerous neurotrophic and neuroprotective growth factors (GF). Specifically, we found that elevated levels of this miRNA are neurotoxic and increase the vulnerability of neurons to a variety of non-specific and disease-specific toxic factors, including Staurosporine (STS), Alzheimer's disease (AD)-associated amyloid beta 1-42 oligomers (Aβ1-42), and 6-OHDA which induces oxidative stress in dopamine (DA) neurons mimicking Parkinson's disease (PD) pathology. Mechanistically, miR-126 targets a series of factors in PI3K/AKT/GSK-3β and MAPK/ERK signaling pathways and small increases of this miRNA cause a downregulation of these signaling cascades, impairing the effects of neurotrophic and neuroprotective GF, such as IGF-1, NGF, BDNF, and soluble amyloid precursor protein α (sAPPα). In turn, inhibiting miR-126 enhances the actions of GF without disturbing normal neuronal cell function.
Our data indicate that miR-126 may play a profound role in neuronal cell survival, at least in part by regulating GF/PI3K/AKT and MAPK/ERK signaling. While its elevation is neurotoxic, its inhibition is neuroprotective, suggesting that targeting this miRNA may have therapeutic potential for neurological and age-related disorders.
Title: Neuron-to-Neuron Propagation of Phosphorylated High-Molecular-Weight Tau Species Derived from Tau-Transgenic Mouse and Human Alzheimer's Disease Brain

Author(s): Shuko Takeda, Susanne Wegmann, Hansang Cho, Sarah Devos, Allyson D. Roe, Samantha B. Nicholls, Caitlin Commins, Chloe Nobuhara, Isabel Costantino, Matthew P. Frosch, Daniel Irimia, and Bradley T. Hyman

Institution:

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Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☑ NO ☐

ABSTRACT: The cognitive deficit in Alzheimer’s disease (AD) is most closely linked with progression of tau pathology in a hierarchical pattern that spreads throughout the brain during disease progression. Better understanding of the molecular basis of tau propagation is key to preventing disease progression. Accumulating evidence suggests a trans-synaptic mechanism of tau transfer between neurons; however, the tau species involved in propagation remains unclear. To identify specific tau species responsible for propagation, we used a novel 3-chamber microfluidic device to examine neuronal tau uptake, axonal transport, and synaptic transmission. We examined uptake and propagation properties of different tau species derived from cortical extracts from the tau transgenic mice as well as human AD postmortem cortices. We found that PBS-soluble phosphorylated high-molecular-weight (HMW) tau, though very low in abundance, are taken up, axonally transported, and passed-on to synaptically connected neurons. Furthermore, a unique large-pore probe in vivo microdialysis technique was employed to investigate the presence of HMW tau in brain interstitial fluid (ISF). We demonstrated that HMW tau with similar biochemical characteristics can be identified in the brain ISF of tau mice obtained while they were awake and behaving, raising the possibility that it is a normal product in the brain; this ISF can also donate tau that can be taken up by neurons in culture. Taken together, our findings suggest that rare species of soluble...
phosphorylated HMW tau is the endogenous form of tau involved in propagation and could be a target for therapeutic intervention and biomarker development.
Title: Removing Endogenous Tau is Neuroprotective and does not Prevent Tau Spreading


Institution: Massachusetts General Hospital

ABSTRACT: Tau protein aggregation into neurofibrillary tangles (NFTs) is a key feature of several neurodegenerative disorders, including Alzheimer’s disease (AD) and frontotemporal dementia, and correlates strongly with cognitive decline. Progressive tangle appearance in AD follows a highly consistent pattern: starting in the entorhinal cortex, NFT pathology then "spreads" to synaptically connected regions. In mice, restriction of human mutant P301L tau expression to the EC revealed trans-synaptic travel of misfolded tau5-7. A "prion-like" progression of tau misfolding, in which aberrantly folded tau recruits naïve endogenous mouse tau in downstream cells and templates toxic aggregation, is widely viewed as a possible mechanism for the spread of tau pathology8-10. Consistent with this idea, endogenous mouse tau can co-aggregate with human tau. Neurons expressing mutant tau ultimately die, presumably of intracellular tau aggregate accumulation. Here we directly tested the hypothesis that tau spreading and toxicity rely on prion-like mechanisms of corrupting endogenous tau by misfolded "seeds".

In contrast to expectations based on prion analogy, we show that synaptic tau transmission occurs independently of endogenous tau in postsynaptic cells. Comparing 18-month old mice expressing human P301L tau in the EC in the presence (ECrTgTau) or absence (ECrTgTau-Mapt0/0) of endogenous tau, we found similar extend of tau propagation. Tau propagation in absence of mouse tau was confirmed using AAV-mediated human tau expression in Mapt0/0. Neuron-to-neuron transmission of transgenic tau thus can occur independently of endogenous tau and, in that, differs from prion-like templated misfolding. Surprisingly, ECrTgTau-Mapt0/0 mice had significantly less tau...
hyperphosphorylation, lacked pathological misfolding, and showed less gliosis than ECrTgTau mice. Furthermore, mice with P301L tau expression throughout the cortex developed tangles both in the presence (rTg4510) and absence (rTg4510-Mapt0/0) of endogenous tau, but the pronounced transgenic tau induced brain atrophy and neuronal loss were rescued on the Mapt0/0 background. Our data show that the lack of endogenous tau protects neurons against toxicity associated with mutant tau expression and aggregation, therefore dissociating tau spreading, aggregation, and toxicity in vivo.
Title: Synaptic Plasticity Deficits in Mouse Models of Down Syndrome and Alzheimer’s Disease

Author(s): Christopher M. William, Lubna Saqran, Matthew A. Stern, Matthew P. Frosch, Bradley T. Hyman

Institution: Massachusetts General Hospital

Mass. ADRC/BU ADC SPONSORED PROJECT: ☑️ NO ☐️

ABSTRACT: Investigations using intact neural circuits in mouse models of Down syndrome (DS) may provide an approach to identifying the physiological basis for neurodevelopmental delay in the disease. Synaptic plasticity plays a critical role in the refinement and function of neural circuits and may be impaired in DS. To test this hypothesis, we have assayed visual system plasticity in a partial duplication mouse model of DS, the Ts65Dn line.

Ocular dominance plasticity (ODP) is the process by which loss of vision in one eye, monocular deprivation (MD), during a postnatal critical period, results in an increase in the area of primary visual cortex responsive to the non-deprived eye, in strengthening of responses to stimulation of the non-deprived eye and in weakening of responses to stimulation of the deprived eye. Using expression of the immediate early gene Arc to define the areal domain responsive to non-deprived eye stimulation following a 4-6 day period of MD, we find that trisomic mice do not demonstrate the expansion in the coronal width of the responsive domain that occurs in similarly-treated, non-trisomic littermates (trisomic width, 944 ± 77.89 microns, n=5; non-trisomic width, 1087 ± 87.44 microns, n=13; p=0.0028, T-test). Optical imaging of intrinsic signals in awake mice was used to measure the magnitude of responses to stimulation of each eye before and after MD. Non-trisomic mice demonstrate strengthening of responses to non-deprived eye stimulation (pre-MD dF/F, 0.4%, n=5; post-MD, 0.57%, n=6; p=0.01), however, trisomic mice do not (pre-MD, 0.55%, n=9; post-MD, 0.46%, n=5; p=0.13). These data suggest that DS model mice exhibit defects in early postnatal developmental plasticity.
Amyloid-beta accumulation secondary to amyloid precursor protein (APP) overexpression has been implicated in early-onset Alzheimer disease in DS, however, whether elevations in amyloid-beta can impair synaptic function earlier in life is less clear. We previously found that overexpression of mutant APP can block critical period ocular dominance plasticity (William et al., 2012, J Neurosci 32(23):8004-8011). We find that transgenic mice that neuronally-express and secrete amyloid-beta in the absence of APP (BRI-Abeta40 and BRI-Abeta42 strains), also demonstrate critical period ODP deficits following MD by Arc assay and by optical imaging, suggesting that elevated expression of amyloid-beta alone can contribute to critical period ODP deficits.

These studies suggest that synaptic plasticity defects may impair neural system function in DS and lay the foundation for future studies in model mice exploring the roles of duplicated genes, including APP, in causing synaptic dysfunction.
Title: Characterization of Novel Gamma-Secretase Modulators in Processing of the Amyloid-Beta Precursor Protein and in the Therapeutics of Alzheimer's Disease

Author(s): Martin Zhang, Joe Ward, Frank Raven, Steve Wagner, and Rudolph E. Tanzi

Institution: Massachusetts General Hospital

Mass. ADRC/BU ADC SPONSORED PROJECT: NO

ABSTRACT: Alzheimer's disease (AD) is a devastating neurodegenerative disease with no cure. Considerable genetic, biochemical and molecular biological evidence support the "amyloid-hypothesis" in the pathogenesis of AD, stating that the excessive accumulation of a small peptide, amyloid-β (Aβ), is the primary pathological event leading to AD. Aβ is generated through a sequential proteolytic cleavage from the amyloid-β precursor protein (APP) via β- and γ-secretase. One class of promising drugs for AD is known as γ-secretase modulators (GSMs), a group of small molecules that modulate the cleavage activity of γ-secretase in the processing of APP and specifically lowering Aβ levels without altering cleavage of other substrates, e.g. Notch. These GSMs bind directly to γ-secretase complex, decreasing the levels of longer Aβ species (e.g. Aβ42 and Aβ40) and increasing the levels of shorter Aβ species (e.g. Aβ38 and Aβ37). Here we have developed a novel series of GSMs and characterized those with desirable safety-profile and high aqueous solubility. We showed these GSMs significantly modulated γ-secretase processing of APP and lowered both Aβ42 and Aβ40 levels. Importantly, these GSMs did not affect the processing of Notch, an essential protein involved in development. These data provide further in-depth support of the "amyloid-hypothesis" in the pathogenesis of AD and provide the mechanism-of-actions utilizing these novel GSMs to lower Aβ levels in the therapeutics of AD. Our results warrant follow-up characterization of these GSMs in animal-based neurobehavioral studies and further strongly support them as excellent candidates in clinical development.
**Massachusetts Alzheimer's Disease Research Center**  
**Boston University Alzheimer's Disease Center**  
**Harvard NeuroDiscovery Center**  
**Twenty-Eighth Annual Scientific Poster Symposium**  
**Friday February 27th, 2015**  
**9am-12noon**  
**Thier Building, 55 Fruit St, Boston, MA 02114**  
**MGH**

**Title:** An Evolutionarily Conserved Stress Response Protects Neurons in the Aging Brain

**Author(s):** Joseph M. Zullo, Tao Lu, Liviu Aron, Hyun-Min Kim, Takamune Saito, Monica P. Colaiávovo & Bruce A. Yankner

**Institution:** Department of Genetics, Harvard Medical School

**Mass. ADRC/BU ADC SPONSORED PROJECT:**  
YES ☐  NO ☒

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**ABSTRACT:** Neurons are long lived cells with high energetic, secretory, and electrophysiological burdens. Maintaining neuronal function over the life of the organism in the face of the stress generated by these activities requires integrating multiple damage signaling pathways to maintain the viability and functional competence of irreplaceable post-mitotic cells. We have shown that the transcription factor NRSF/REST has a key role in this process through repression of apoptotic genes, as well as potentiating stress responses during normal aging. However, in Alzheimer's disease, REST is lost from the nucleus along with its protective function, potentially contributing to the pathological neuronal loss characteristic of the disease. We further demonstrated that many of these protective effects are conserved in the functionally orthologous C. elegans SPR-4 transcription factor, as well as the apparent organization of the REST epigenetic repressive complex. Here, we extend these findings to characterize the role of the spr genes in regulating stress responses and longevity in the worm. We find that members of the complex are required for normal protein homeostasis and stress responses, and contribute to the efficacy of multiple longevity extending treatments.
Title: Differential Declines in Letter vs. Category Fluency over 4 years in Biomarker-Defined Preclinical Alzheimer’s Disease

Author(s): Kathryn V. Papp, Elizabeth Mormino, Rebecca E. Amoriglio, Keith A. Johnson, Reisa A. Sperling, Dorene M. Rentz

Institution: BWH, MGH

Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☑️ NO ☐

ABSTRACT:

Background: AD and its precursor MCI are often characterized by declines in episodic memory but decrements in semantic memory (i.e., memory for meaning, general knowledge and factual information) are also observed. In addition, growing evidence indicates that subtle alterations in cognition may emerge even earlier than the MCI stage, i.e., in clinically normal (CN) older adults with biomarker evidence of preclinical AD. Our objective was to investigate semantic knowledge by contrasting category vs. letter fluency in relation to baseline beta-amyloid (Aβ) deposition in clinically normal older adults over the course of 4 years.

Methods: A total of 132 CN older adults (Aβ+ =40, Aβ- =92) from the Harvard Aging Brain Study completed neuropsychological batteries including measures of Letter Fluency (generation of words to the letters F-A-S) and Category Fluency (generation of words in the categories of animals, vegetables, and fruits) annually over a total of 4 time points (mean age=73.43 +/-5.98). Subjects were deemed clinically normal at baseline by CDR=0 and performance above education-corrected cut-offs on the Delayed Recall of Logical Memory and the MMSE (mean=29.14 +/-0.89)Verbal fluency was examined longitudinally in relation to Aβ+ status while controlling for age, sex, years of education, and APOE-ɛ4 status.

Results: At baseline, there were no differences in performance between groups on number of words produced for either letter or category fluency. However, Aβ+’s exhibited declines in category fluency longitudinally while Aβ-’s performed consistently
over time [F(3, 124)=3.759, p=0.013]. In contrast, there were no differences between groups in phonemic fluency longitudinally [F(3, 124)=1.057, p=0.370].

Conclusions: These findings provide biomarker validation for the specificity of declines in category fluency to underlying AD pathology. Our results also suggest that changes in semantic processing occur earlier in the AD trajectory than previously hypothesized, that is, at the preclinical stage. Measures of semantic knowledge may be useful cognitive outcome measures in secondary prevention trials.
Title: Couples’ Experiences of Alzheimer’s Disease: A Narrative Perspective

Author(s): Ryan T. Daley, Maureen K. O’Connor, and Renee L. Beard

Institution: Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA
Boston University Alzheimer’s Disease Center, Boston, MA
College of the Holy Cross, Worcester, MA

Mass. ADRC/BU ADC SPONSORED PROJECT: ☒ NO ☐

ABSTRACT: Alzheimer’s disease (AD) research pertaining to both spousal caregivers and individuals diagnosed with AD has primarily used quantitative methods to identify lifestyle factors associated with the disease process. Such methods treat spousal caregivers and individuals diagnosed with AD as detached entities. This study seeks to understand the interpersonal effects of AD processes on 12 dyadic couples (N=24), where one is diagnosed with early stage AD and the other is a spousal caregiver. In this mixed-methods study, several quantitative tools are used to collect cognitive and caregiver data alongside extensive dyadic interviews. Grounded theory methods are used to code and analyze data collected from these interviews. Major themes identified through the grounded theory process include a “we” versus “I” approach to daily life, passive versus active approaches to the diagnosis, present versus future orientations, and optimistic versus pessimistic outlooks. These findings help to dispel the commonly held understanding that couples dealing with AD are always negatively affected by the progression of the disease process. Spousal bonds provide couples dealing with AD the opportunity to manage their daily lives both as a couple and individual entities. These findings could have implications for future research in the areas of mental mindset as well as couples therapy, for couples dealing with AD.
Title: Modeling and Elucidating the Pathobiology of Impact-Induced Traumatic Brain Injury in the Mouse

Author(s): Chad Tagge¹, Andrew Fisher¹, Olga Minaeva¹, Mark Wojnarowicz¹, Amanda Gaudreau¹, Juliet Moncaster¹, Noel Casey¹, Sudad Saman², Christopher Nowinski¹, Robert Cantu¹, Thor Stein¹,³, Rudolph Tanzi⁴, Neil Kowall¹,³, William Moss⁵, Garth Hall⁵, Patric K Stanton⁶, Ann McKee¹,³, Lee Goldstein¹

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Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☒  NO ☐

ABSTRACT: Traumatic brain injury (TBI) ranks among the leading causes of traumatic death and is a leading cause of serious long-term disability. Our research team is uncovering evidence linking repetitive impact-induce TBI and concussions with the later development of chronic traumatic encephalopathy (CTE). We developed and characterized a new impact-induced TBI model to replicate the physical injury seen in impact-induced TBI. Our model consists of using non-anesthetized, analgesic injected mice to understand the physical response and assess neurological impairments immediately following impact-induced TBI. From these studies, we are able to recapitulate key clinical features observed in individuals following concussion. We demonstrated through the use of high-speed videography that head acceleration during impact is similar to the head acceleration found in our blast-induced TBI model (Goldstein, 2012). A finding which points to traumatic head acceleration as a major pathogenic contributor to both impact and blast-related TBI. Our model links the kinematics of head motion to the acute physical and neurological deficits following concussion, and additionally, can provide insights to the biological response following
conussion and the mechanistic linking to the later development of CTE-linked neuropathology and neurobehavioral deficits.
Title: Monitoring Molecular Aging of Lens Proteins using Quasi-Elastic Light Scattering

Author(s): S. Sarangi\textsuperscript{1,2}, O. Minaeva\textsuperscript{1,2}, J.A. Moncaster\textsuperscript{2}, F. Weng\textsuperscript{3}, C. Rook\textsuperscript{3}, D. Ledoux\textsuperscript{3}, J.I. Clark\textsuperscript{4}, D.G. Hunter\textsuperscript{3}, L.E. Goldstein\textsuperscript{1,2}

Institution: \textsuperscript{1}Dept. of Biomedical Engineering, Boston University, Boston, MA 02215 \textsuperscript{2}Boston University School of Medicine, Boston MA 02118 \textsuperscript{3}Boston Children’s Hospital, Boston, MA 02115 \textsuperscript{4}University of Washington School of Medicine, Seattle, WA 98195

Mass. ADRC/BU ADC SPONSORED PROJECT: \hspace{1cm} YES ☐ NO ☒

\textbf{ABSTRACT:} The lens in the eye is a complex integrated structure, characterized by high protein density, and optimized for transparency. Water-soluble crystallin proteins make up the major component of the lens. As the lens ages, the crystallins undergo various post-translational modifications. These perturbations tend to disrupt the normal functioning of the proteins, facilitating aggregation and consequently insolubilization. The oligomeric aggregates formed with aging increase light scattering from the lens which ultimately manifest as cataracts. Aggregate formation and can be measured \textit{in vitro} and \textit{in vivo} using the technique of quasi-elastic light scattering (QLS), also known as dynamic light scattering (DLS). QLS measures temporal correlations of intensity fluctuations of light in a scattering medium, and the generated auto-correlation function (ACF) can be utilized to extract diffusion coefficients and particle size distributions.

We have investigated molecular aging of human lens proteins \textit{in vitro} as well as \textit{in vivo}. For \textit{in vitro} experiments, posthumous human lenses are homogenized and the soluble portion is examined. Results show an increase in light scattering intensity for homogenized soluble human lens proteins as well as in correlation function decay time \( \tau \) (which is directly related to diffusion coefficient). We have performed a clinical study at Boston Children’s Hospital to detect molecular aging effects in lenses of healthy control subjects \textit{in vivo}. In the data acquired from the nuclear region of the lens, we see an increase in light scattering intensity with age. Similar to the \textit{in vitro} results, there is an increase in average decay time (tau) with age. QLS has proven to be a useful tool in evaluating changes in the lens proteins \textit{in vitro} and \textit{in vivo}. We are further working on
interpreting scattering data in conjunction with techniques like gel electrophoresis and electron microscopy to understand molecular mechanisms that occur during aging.
Title: Novel Synaptotagmin 1-Presenilin 1 Interactions and their Implications in Alzheimer’s Disease Pathogenesis

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Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☐ NO ☒

ABSTRACT: Synaptic loss is the strongest correlate of memory deterioration in Alzheimer’s disease (AD). Synaptic dysfunction is caused by local accumulation of amyloid β (Aβ), and in particular neurotoxic Aβ42. Aβ is a proteolytic product of a subsequent processing of the amyloid precursor protein by two enzymes - β-secretase and presenilin 1 (PS1)/γ-secretase. Continuous, default or experimentally induced neuronal activity causes an increase in Aβ production, which is strongly related to intracellular calcium flux and synaptic vesicle exocytosis. To gain further insight into Ca2+-dependent regulation of the Aβ production, we performed a mass spectrometry screen and found synaptotagmin 1 (Syt1) as a novel PS1 interactor that binds directly to PS1 in high Ca2+. Syt1 is a calcium sensor in neurotransmitter release and is involved in trafficking of synaptic vesicles at the active zone of the synapse. The interaction was confirmed in vitro and in vivo by co-immunoprecipitation and Förster resonance energy transfer (FRET) experiments. The role of Syt1 in Aβ40 and Aβ42 production, and in the stability and trafficking of β- and γ-secretases was investigated using Syt1 knock-down and overexpression approaches. Our experiments demonstrate that PS1 interacts with Syt1 in a Ca2+-dependent manner, and that Syt1 overexpression and knock-down result in increased and decreased levels of secreted Aβ, respectively. Hence, they bring together important players in the AD pathogenesis: synapse, Ca2+, PS1 and Aβ production. The discovery that Syt1 (via its Ca2+-induced interaction with PS1) affects Aβ at the synapse opens new avenues for therapeutic interventions focusing at the synapse.
Title: Optogenetic Rescue of Disrupted Slow Oscillations in an Animal Model of Alzheimer's Disease

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ABSTRACT: Slow oscillations are important for consolidation of memory during sleep, and Alzheimer's Disease (AD) patients experience both sleep and memory disturbances. Thus, we examined slow oscillation activity in an animal model of AD, APP/PS1 mice, using voltage sensitive dye Rh 1691 through cranial windows. APP/PS1 mice exhibit aberrant slow oscillation activity prior to plaque deposition, with a cohort of mice lacking slow oscillations altogether. Aberrant excitatory activity within the cortical circuit was responsible for slow oscillation dysfunction, since topical application of GABA restored slow oscillations in APP/PS1 mice. In addition, month-long treatment with light activation of Channelrhodopsin-2 (ChR2) expressed in excitatory cortical neurons restored slow oscillations by synchronizing neuronal activity and facilitating state transitions. Driving slow oscillation activity at the normal frequency with ChR2 halted amyloid plaque deposition and prevented calcium overload associated with this pathology. Thus, targeting slow oscillatory activity in AD patients might prevent neurodegenerative phenotypes and slow disease progression.
Title: Characterization of White Matter Degeneration due to Alzheimer’s Disease through a Novel Computational Diffusion Image Analysis Framework

Author(s): Ender Konukoglu, Jean-Philippe Coutu, Bruce Fischl and David Salat

Institution: Massachusetts General Hospital / Harvard Medical School

ABSTRACT: Beyond its impact on the cortical gray matter, Alzheimer’s Disease (AD) also has a substantial impact on the white matter. Degradation of myelin and axonal integrity start happening at the very early stages of the disease and progress throughout the later stages. Characterization of AD related tissue degeneration in the white matter might provide important insights into the initiation and progression mechanisms of the disease as well as yield novel biomarkers for early stage diagnosis. Diffusion weighted magnetic resonance imaging (dMRI) provides non-invasive in-vivo observations on the tissue microstructure that allow us to do such characterizations. dMRI data can be modeled in a range of ways to produce voxel-wise maps of several different properties of the tissue microenvironment, which are sensitive measures for identifying tissue degradation. Prior works have already shown that AD related changes could be detected in dMRI-derived maps even at the very early stages of the disease. However, to date statistical analyses of dMRI data have only focused on analyzing each measure independently despite the fact that different measures quantify different aspects of the same underlying microenvironment and are likely to be complementary. We believe a multivariate approach that jointly analyzes all the measures taking into account their correlations can characterize the tissue degeneration more accurately and may provide information not available through the examination of each parameter in isolation. For example, it is possible that different forms of histopathology, or different disease stages, will have different signatures on the dMRI-based measures. In this project we develop tools for multivariate statistical analysis of dMRI data and apply these procedures to characterize patterns of white matter degeneration associated with Alzheimer’s disease and mild cognitive impairment. Our results demonstrate spatial variation of degeneration patterns associated with Alzheimer’s disease. Furthermore, degeneration due to mild cognitive impairment and Alzheimer’s differ in patterns as well as in magnitude.
Title: White Matter Integrity Changes Preceding Alzheimer’s Disease in Mild Cognitive Impairment

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Mass. ADRC/BU ADC SPONSORED PROJECT:  YES ☐  NO ☒

Abstract: Introduction: White matter (WM) damage is a common occurrence in older adults, and its presence is elevated in Alzheimer’s disease (AD). Vascular dysfunction is the primary mechanism of WM lesions, and this damage likely contributes to cognitive impairment and dementia [1,2]. Little is known about the developmental trajectory of these lesions, and there is conflicting evidence about whether differences in lesions exist between individuals with mild cognitive impairment (MCI) who will eventually convert to AD (MCI-C) and those who will not (MCI-NC) [3,4]. Furthermore, it has been suggested that more information regarding these lesions can be extracted beyond simply quantifying total volume [5]. The goal of this study was to assess quantitative and qualitative aspects of the longitudinal changes in WM damage in individuals with MCI-C and MCI-NC, and to determine whether they contain information that may be useful in enhancing our knowledge of AD conversion.

Methods: Four groups of individuals taken from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) were used in a cross-sectional analysis (healthy controls, n=104; MCI-NC, n=115; MCI-C, n=116;...
AD, n=124) and the MCI-NC and MCI-C were then used in a follow-up longitudinal analysis. In the longitudinal analysis, MCI-C individuals were aligned in time to the point of AD conversion along a single timeline. Each was then age-matched to an MCI-NC individual. Data were processed using FreeSurfer’s Longitudinal Processing Stream [6]. White matter signal abnormalities (WMSAs) were automatically segmented using a novel procedure that combines T1, T2, and PD-weighted images in concert with a multivariate Gaussian classifier and a region-growing heuristic based on individual’s intensity profiles. The mean Mahalanobis distance (MD) of each individual’s WMSAs from their baseline normal appearing white matter (NAWM) was calculated for each time point as a “lesion quality score,” and total volumes of WMSA and NAWM were extracted. Additionally, hippocampal volume was extracted for the longitudinal analyses as this is a known structural indicator of AD [7].

RESULTS: WMSA volume as a raw score and as a ratio of total WM was significantly different in AD individuals in the cross-sectional analysis, but not between any other pairs of groups. No time points during the longitudinal analysis showed a significant difference in WMSA total volume or WMSA to total WM ratio between MCI-C and age-matched MCI-NC. The MD of WMSAs from baseline NAWM was significantly different between MCI-C and MCI-NC for all time points after MCI-C conversion to AD (p<0.05). Repeated measures ANOVAs conducted for every 1-year time period along the study timeline demonstrated a significant interaction in the rate of WMSA MD change between MCI-C and MCI-NC beginning 18 months prior to MCI-C conversion to AD and ending 6 months after conversion (Figure 1). Hippocampal volume was significantly different between MCI-C and MCI-NC 24 months prior to MCI-C conversion to AD and for all time points thereafter. A significant interaction in rate of hippocampal volume change was seen starting 6 months prior to MCI-C conversion and ending 6 months after MCI-C conversion.

CONCLUSIONS: Qualitative changes in the appearance of WMSAs predate quantitative changes in WMSA volume during the progression from MCI to AD. Tissue property changes within WMSAs, as measured by their MD from NAWM, begin 18 months prior to AD conversion, and are timed similarly to changes in hippocampal volume that occur during AD progression. Volumetric changes in WMSA occur gradually after AD onset, and are less robust for differentiating between MCI-C and MCI-NC. This suggests that WMSA are important to the AD conversion process, and may be an important component of the disease pathology. Furthermore, they may indicate a biological process involving the cerebrovasculature that is critical to our understanding of AD. Future work will include the investigation of the spatial distribution of these lesions.

Title: New Tests of Language Help Differentiate Mild Cognitive Impairment from Healthy Aging


Institution: Massachusetts General Hospital, Cornell University, Massachusetts Institute of Technology, Harvard-MIT Division of Health Science and Technology

ABSTRACT: Clinical assessments of suspected cognitive decline generally limit their evaluation of language to lexical changes, e.g. confrontation naming and verbal fluency. Few assess language syntax or the complex interactions required between syntax and semantics for language use and comprehension. In this collaborative inter-institutional pilot project (Mass General Hospital, MIT and Cornell) we developed a more sensitive measure of language and provide first results of its effectiveness in differentiating a population diagnosed as Mild Cognitive Impairment, amnestic type (68-82 years old) from a matched population of Healthy Aging (65-80 years old) and a young control group (20-29 years old). A standardized elicited imitation task with complex sentences reveals a significantly poorer performance in the MCI population. Experimental design of sentences begins to reveal the linguistic source of the deficit at the level of syntax-semantics interaction. A working memory test (Brown-Peterson) and a general cognitive assessment (Addenbrooke’s Cognitive Estimation-R and MMSE) are shown to differentiate MCI and HA groups but they do not correlate with the linguistic results, suggesting that more general cognitive deficits do not explain the language decrement in MCI. Our results have implications for expansion of clinical tools for assessment in prodromal Alzheimer’s disease at the same time that they advance our understanding of the nature of the language decline involved.
Title: Deciphering the Mechanisms by which Inhibiting APP Dimerization Reduces Abeta Production

Author(s): C.D. Chen, P.C. Mullen, E. Zeldich, L. E. Brown, J.A. Porco, Jr., and C.R. Abraham

Institution: Boston University School of Medicine

Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☐ NO ☒

ABSTRACT: Objectives: Increased amyloid precursor protein (APP) dimerization has been shown to enhance Abeta peptide formation. Our goal was to identify small molecules that inhibit APP dimerization and lower Abeta levels.

Methods: We conducted a high throughput screen (HTS) for small molecule modulators of APP dimerization using APP-Firefly luciferase enzyme complementation to detect APP dimerization. Selected modulators identified from a library of 77,440 compounds were tested for their effects on Abeta and other APP fragments using ELISA and western blotting, respectively. To define the mechanism by which APP dimerization affects the production of Abeta, APP phosphorylation was examined by IP-western blotting using anti Abeta/APP antibody for IP, and anti-phospho-tyrosine for western blot.

Results: One APP dimerization inhibitor significantly lowered Abeta and sAPPbeta levels without affecting sAPPalpha or gamma-CTF levels, suggesting that blocking the dimerization is preventing the cleavage by beta-secretase in the amyloidogenic processing pathway of APP. Interestingly, this inhibitor and its analog increased APP phosphorylation on tyrosine.

Conclusions: Inhibition of APP dimerization has previously been suggested as a therapeutic target for AD. To our knowledge, this is the first HTS effort to identify small molecule modulators of APP dimerization. The findings reported here further support the notion that modulation of APP dimerization could be a viable means of reducing the production of Abeta. The precise mechanism of action of the identified inhibitors is currently being investigated.
Title: Klotho Protects Hippocampal Neurons from Glutamate and Oligomeric Aβ-Induced Toxicity

Author(s): E. Zeldich, C.D. Chen and C.R. Abraham

Institution: Boston University School of Medicine

Mass. ADRC/BU ADC SPONSORED PROJECT: NO

ABSTRACT: Objectives: Neurodegenerative diseases such as Alzheimer’s disease, Parkinson disease and amyotrophic lateral sclerosis are mediated partially through the accumulation of reactive oxygen species (ROS) that leads to oxidative stress and subsequent neuronal cell death. Our study explored the role the anti-aging protein Klotho and Klotho-enhancing compounds plays in the viability of hippocampal neurons that are considered to be among the most vulnerable to oxidative conditions.

Methods: Primary hippocampal neurons and mouse hippocampal neuronal cell line HT22 were subjected to glutamate and oligomeric Aβ (oAβ)-induced cytotoxicity. To test the effect of exogenously added Klotho, cells were pretreated with recombinant mouse Klotho or small molecule Klotho-enhancing compounds that were identified through a high throughput screen. The effect of endogenously increased Klotho was tested by comparing the cytotoxic effect of glutamate and oAβ on primary hippocampal neurons from Klotho overexpressing mouse embryos and neurons from wild type littermates. Cell death was assessed by the extent of ATP, release of LDH to the media, and the accumulation of ROS. The activation of anti-oxidative pathways was performed using western blot analysis, qRT-PCR and an anti-oxidative stress array.

Results: Pretreatment with recombinant Klotho protected rat primary hippocampal neurons and HT22 neurons from glutamate and oAβ-induced cytotoxicity. In addition, primary hippocampal neurons obtained from Klotho overexpressing mouse embryos were more resistant to both cytotoxic insults compared to neurons from wild type littermates. Furthermore, our results show that this neuroprotective effect of Klotho is mediated through the enhanced expression of two antioxidant enzymes of the redox system: peroxiredoxin-2 (Prx-2), and thioredoxin reductase-1 (Trxrd-1). Klotho induced phosphorylation of PI3K/Akt pro-survival pathways that was associated with sustained
Inhibitory phosphorylation of the transcription factor forkhead box O3a (FoxO3a), which contributed to the induction of Prx-2. In addition, two optimized Klotho-enhancing compounds were demonstrated to be neuroprotective in the glutamate-induced cell death assay in the HT22 cell line and mimicked the effect of the Klotho protein.

Conclusions: Klotho is a new therapeutic target aimed to foster neuronal survival and overcome neuronal damage associated with neurodegeneration.
Title: Pittsburgh Compound-B (PiB): Radiologic-Pathologic Correlations in a series of 18 Autopsied Cases

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Mass. ADRC/BU ADC SPONSORED PROJECT: YES ☒ NO ☐

ABSTRACT: Introduction: The development of amyloid imaging has made it possible to identify amyloid deposition \textit{in vivo}, and recent studies suggested that Pittsburgh Compound-B (PiB) binds to fibrillar Aβ in the form of amyloid plaques and cerebral amyloid angiopathy (CAA). Objective: To carefully study the correlations of \textit{in vivo} [C-11] PiB PET uptake and postmortem pathological and biochemical measured of β-amyloid in a series of 18 brains from individuals who were imaged while alive and came to autopsy. Methods: Pathological diagnoses were as follows: 5 Alzheimer’s disease (AD), 6 dementia with Lewy bodies (DLB), 3 mixed AD/DLB, 1 progressive supranuclear palsy and 2 controls. Relations between [C-11] PiB PET uptake measured as SUVR (standardized uptake value ratio in the region relative to cerebellar gray matter), multiple postmortem measures of amyloid deposition (PiB, Thioflavin-S and 10D5 plaque burdens, and NAB61 oligomeric Aβ burden) and ELISA detection of soluble Aβ species (Aβ40, Aβ 42 and oligomeric Aβ) were studied in four regions of interest (ROI) (middle frontal, superior temporal sulcus, inferior parietal and occipital cortices). Results: \textit{In vivo} [C-11] PiB PET retention values very significantly correlated with all postmortem measures of amyloid deposition in the ROI. [C-11] PiB PET uptake also correlated with postmortem brain levels of Aβ42 and oligomeric Aβ but not with measures of cognition. Most cases with SUVR values higher than the cut-off of 1.50 had intermediate of frequent CERAD neuritic plaque score at postmortem, except for three cases, all of whom were DLB with a high load of non-neuritic plaques and one of them
also had CAA. **Conclusion:** Our study supports an excellent correlation between antemortem PiB PET retention and postmortem brain Aβ amyloid accrual. In addition to neuritic plaques, non-neuritic plaques and CAA accounted for *in vivo* PiB binding in this autopsy series.

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Tau [F18] T807 – Progressive Nonfluent Aphasia

Images Courtesy of Keith A. Johnson, MD