NEUROCOGNITIVE RESEARCH AT THE UNIVERSITY OF UTAH

Poster Session
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5 – 6 pm
Clinical Neurosciences Center 1st Floor

Hosted by the Department of Neurology and Neuroscience Initiative

Poster Number, Presenter, Title:

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2. S. Weisenbach – Resting state brain network connectivity predicts cognition in healthy older adults
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31. K. Duff – Tracking functional decline in mild cognitive impairment
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33. J. Heys – Neural representations of space and time in medial entorhinal cortex
34. K. Duff – Cognitive functioning on the RBANS and APOE status
35. R. Rupper – Dementia symptom management at home
36. K. Schliep – How good are medical and death records for identifying dementia in the United States?
1. **J. Germain**

   *Resting state brain network dysfunction and cognition in late life depression*

   Objective: Older adults with depression show performance variations in multiple cognitive domains relative to their never-depressed peers (Koenig et al., 2015). Resting state (RS) brain activation studies demonstrate abnormal patterns of functional connectivity in pathways essential to higher-order cognitive functioning in a variety of neurological and psychiatric conditions (Alexopoulos et al., 2012; Gandelman et al., 2019). This study aims to examine cognitive functioning and connectivity within three major networks important to cognition in depressed and non-depressed elder adults: right and left Executive Control Network (ECN) and Default Mode Network (DMN).

2. **S. Weisenbach**

   V. Koppelmans, J. Kim, A. Arp, N. Hovatta, V. Patron, N. Grubman, J. Germain, R. Welsh, J. Zubieta, S. Langenecker

   *Resting state brain network connectivity predicts cognition in healthy older adults*

   Background: There is growing interest in coherence of functional brain networks during the resting state (RS). While evidence suggests that network coherence predicts cognitive performance in psychiatric and neurologic diseases, less is known about how within-network coherence predicts cognition in healthy aging. This study sought to elucidate relationships between DMN and CCN RS network coherence and performance on a comprehensive battery of neuropsychological tests.

3. **A. Earnest**

   L. Garrett, K. Owens, K. Nederostek, N. Allen

   *Increasing dementia training in long-term care*

   Background: Approximately 64% of residents living in long-term care (LTC) have Alzheimer’s disease or other forms of dementia. Many residents with dementia will exhibit challenging behavioral and psychological symptoms of dementia (BPSD) such as: wandering, agitation, aggression, depression, delusions, sleep or appetite changes, resistance to care, etc. Non-pharmacological management strategies are preferred first-line treatment options for BPSD. Dementia care training is essential for improving quality of life, and reducing distress and misuse of medications. Dementia training LTC is often suboptimal or lacking.

4. **R. Utz**

   *Time for living & caring (TLC): An online intervention to maximize caregivers’ use of respite*

   Respite, defined as time away from caregiving tasks and responsibilities, has been identified as the most desired and needed service to maintain caregiver wellbeing and their ability to continue the caregiving role. Our prior research found that caregivers often report dissatisfaction with how they spend their respite time; many reported “wasting” time doing lower priority activities, instead of using their respite as a reprieve from their role as vigilant caregivers to pursue activities that are personally meaningful or rewarding. Those who used respite to do what they had most desired, needed, or had planned to do had the highest satisfaction with their time-use and reported the most positive wellbeing over time. These insights led us to design a behavioral intervention that we believe will maximize positive outcomes associated with respite utilization, and will also improve our understanding of what factors—especially those related to respite time-use—have the potential to improve, or at least maintain, the wellbeing of family caregivers over time. The intervention, called Time for
Living and Caring (TLC), is based on the well-researched “Selective Optimization with Compensation” (SOC) model. It uses principles of goal setting and goal review to coach family caregivers to plan for upcoming respite time. Initial pilot work suggests high participant satisfaction and preliminary evidence of efficacy. However, TLC, as originally conceptualized, relied on trained facilitators delivering as many as 15-20 visits or phone calls to ensure fidelity. This approach has obvious challenges for sustainability and implementation. The TLC intervention is now being translated into a self-administered, web-based platform to make it more scalable for real world application. To our knowledge, this is the first intervention designed to maximize the benefit of caregivers’ respite time. We expect that the TLC online intervention will 1) have high practical utility for diverse family caregivers, 2) be a resource that formal respite providers will want to provide to their clients as a cost-efficient and effective source of support, and 3) elucidate how time-use satisfaction is a mechanism through which respite achieves the intended purpose of maintaining caregiver wellbeing.

5. R. Utz

Using participatory design & community engagement to develop online caregiver support

Background: Participatory design is the process used to develop a product in which the people destined to use it play a critical role in the design of it. We adopted a commitment to participatory design and community engagement in the development of an online intervention to support family caregivers to persons with Alzheimer’s Disease or Related Dementias (ADRD) called “Time for Living & Caring” (TLC). The TLC intervention is intended to support to ADRD family caregivers by maximizing the benefit of respite.

6. K. Ho

M. Hotchkin, J. Zhang, M. Merziakov, A. Dorfman, M. Mortenson

Gold nanocatalysis for the treatment of neurodegenerative diseases

Abstract: Drug development for neurodegenerative diseases has been challenging due to their multifaceted, complex pathophysiologic mechanisms. Clene Nanomedicine is exploring a novel therapeutic approach for the treatment of neurodegenerative diseases by developing a platform of clean-surfaced nanotherapeutics (CSNTM) that is based on the biocatalytic activity of metal-based nanocrystals. Conceptually, nanocatalysis may be understood as the application of nanocrystals to enhance cellular bioenergetic reaction rates, without requiring associated energetic investment from cells, thereby increasing cells’ net energetic capacity. In addition, because CSNTM therapeutics are made using a process that, unlike traditional methods, results in nanocrystals free of organic surface residues, the potential toxicity of these nanocrystals significantly reduced. CNM-Au8 is a concentrated suspension of 13 nm diameter, clean-surfaced, faceted gold nanocrystals that efficiently oxidize nicotinamide adenine dinucleotide hydride (NADH) to NAD+. The NAD+/NADH redox couple is essential for cellular electron exchange reactions that drive the ATP generation. In addition, NAD+ acts as a binding substrate and regulator of families of proteins that in turn serve as metabolic regulators, with far-reaching effects on DNA repair, longevity, autophagy, and other key cellular mechanisms of cell survival and axon maintenance. Here, we demonstrate the conversion of NADH to NAD+ by CNM-Au8 in a cell-free system at a rate that significantly exceeds that of other gold nanoparticles from the National Institute of Standards and Technology. CNM-Au8 treatment of primary rodent neuron-glial co-cultures elevates intracellular levels of both NAD+ and NADH, resulting in higher rates of glycolytic activity in oligodendrocytes and correspondingly higher levels of ATP production. In addition, cell-free assays demonstrate that CNM-Au8 possesses SOD-like and catalase-like activity independently of the effects on NAD+/NADH. The catalysis of reactive oxygen species (ROS)
result in lowered levels of intracellular ROS in oligodendrocytes and neurons treated with CNM-Au8 in vitro. Notably, multiple neuronal cell types are protected from glutamate-induced excitotoxic cell death by CNM-Au8. Finally, we demonstrate functional neuroprotective benefits of oral delivery of CNM-Au8 in the SODG93A mouse model of amyotrophic lateral sclerosis and the unilateral striatum lesion rat model of Parkinson’s Disease. The unique, multifaceted mechanism of action of CNM-Au8 to boost energetic capacity while simultaneously lowering oxidative stress within central nervous system cells may address the bioenergetic failure that has been described as the hallmark of many neurodegenerative diseases. CNM-Au8 thus represents a novel and promising therapeutic for treatment of neurodegenerative diseases associated with bioenergetic impairment.

7. D. Hammers
   N. Foster, J. Hoffman, T. Greene, K. Duff
   Neuropsychological, psychiatric, and functional correlates of clinical trial enrollment

Objective: Screen failure rates in Alzheimer’s disease (AD) clinical trial research are unsustainable, with participant recruitment being a top barrier to AD research progress. So far, there has been little to no emphasis on reducing screen failure rates in AD trials. The purpose of this project was to understand the neuropsychological, psychiatric, and functional features of individuals who failed screening measures for AD trials.

8. D. Scoles
   S. Paul, W. Dansithong, F. Royzen, M. Gandelman, E. Aoyama, K. Figueroa, S. Pulst
   Targeting RNA-binding proteins in neurodegenerative diseases: STAU1 ASOs in spinocerebellar ataxia type 2 (SCA2) and beyond

Increased abundance of the ATXN2 interacting protein staufen 1 (STAU1) underlies pathology of numerous neurodegenerative diseases including SCA2, ALS, and FTD. Stress granules (SGs) are dynamic membraneless organelles controlling RNA abundance, expression, and localization. We have shown that the SG protein, Staufen-1 (STAU1) is overabundant and associated with autophagy blockade and the appearance of SGs. Lowering STAU1 expression in SCA2 mice improved motor phenotype and restored expression of key cerebellar proteins, including markers of autophagy. Therefore, STAU1 appears to be a therapeutic target potentially useful for treating multiple neurodegenerative diseases.

9. N. Foster
   Implications for management of pet amyloid classification technology (IMPACT)

Background: Amyloid PET is a reliable biomarker of Alzheimer’s disease pathology. In the US, clinical amyloid PET is available to Medicare patients >65 through the IDEAS coverage with evidence development trial. Insurers need evidence amyloid PET benefits younger patients. Family reported outcomes of amyloid PET are unknown.

10. M. Kyrke-Smith, J. Shepherd
    The immediate early gene Arc in critical to the persistence of NMDAR-dependent LTD but not LTP

Activity-Regulated Cytoskeletal protein (Arc) is critical to the persistence of long-term memory. Arc regulates AMPAR endocytosis, decreasing synaptic strength. However, Arc mRNA and protein expression is increased after the induction of long-term potentiation (LTP),...
which increases synaptic strength. While some studies have found LTP to be attenuated in the absence of Arc, these results have yet to be explained in relation to synaptic weakening. To elucidate the synapse specific ways in which Arc may regulate long-term memory, we used hippocampal slices from Arc knockout animals (ArcKO) and wildtype (WT) littermates to evaluate the role of Arc in long-term depression (LTD) and LTP at CA3-CA1 synapses, in vitro. LTD was significantly attenuated in slices from ArcKO animals, compared to WT controls. There was no difference in LTP between the groups using a high frequency stimulation protocol. Surprisingly, when using a theta burst stimulation protocol that is purported to be more physiologically relevant than high frequency stimulation, LTP was significantly enhanced in the ArcKO slices. These results indicate that Arc regulates LTD persistence but not LTP, suggesting that one role in long-term memory may be the regulation of synaptic weakening. Further, paradigms used to induce LTP may stimulate expression of genes unrelated to enhancement of synaptic strength. This expression pattern may be explained by Arc’s ability to form capsid structures that package RNA for transfer between cells, potentially controlling cellular networks rather than specific synapses.

11. K. Supiano
   M. Luptak, T. Andersen, C. Beynon, Y. Jung, E. Iacob, B. Wong
   Assessing preparedness for death and grief in bereaved and soon-to-be bereaved dementia family caregivers

   Background: While most people navigate the death of a family member to dementia with coping skills, social supports and time, 10-20% of grievers experience a state of prolonged, ineffective mourning known as complicated grief (CG).

12. B. Allred
   The incremental validity of short-term practice effects in determining amyloid positivity

   Background: Alzheimer’s disease research has shifted from focusing on cures to prevention and early intervention. Simpler and more economical methods are needed to identify those who have AD pathology but may not yet be showing symptoms. Practice effects (PE) are improvements on cognitive tests due to repeated exposure to the testing material. While PE are often viewed as error in repeat testing, some have used them to identify older adults at greater risk for cognitive decline, including those with more Alzheimer’s pathology. The current study compared both 1) baseline cognitive performances and 2) short-term PE to amyloid burden in 27 non-demented, community-dwelling older adults.

13. K. Morton, J. Hoffman
   J. Yap
   Lipopolysaccharide endotoxemia induces amyloid-b and p-tau formation in the rat brain

   Amyloid beta (Ab) plaques are not specific to Alzheimer’s disease and occur with aging and other neurodegenerative disorders. Soluble brain Ab may be neuroprotective and increases as an acute phase reactant in response to neuroinflammation. Sepsis is associated with both short and long-term neurocognitive compromise by poorly understood mechanisms. The objective of this project was to determine, in a rat endotoxemia model of sepsis, whether neuroinflammation and soluble Ab production are associated with Ab plaque and hyperphosphorylated tau deposition in the brain.
14. **V. Koppelmans**  
R. Welsh  
*Differences in regional cerebellar volume between adults with ALS and healthy older adults*

Introduction: Amyotrophic Lateral Sclerosis (ALS) is characterized by progressive paralysis that is caused by degeneration of motor neurons of the central nervous system.\(^1\) The extent of degeneration in the motor homunculus correlates with the magnitude of functional disability in ALS.\(^2\) Though cerebellum plays a crucial part in motor control and coordination via projections to the motor cortex, it is understudied in ALS. There are some indications that the cerebellum is affected in ALS,\(^3,4\) but these results are based on very few and small studies, which used MRI processing methods that were not tailored to detect effects in the cerebellum. Here, we apply a processing pipeline designed to acquire precise measures of cerebellar volumes. We test for differences in cerebellar volumes between ALS subjects and healthy aged-matched individuals. We hypothesize that cerebellar volumes of motor regions are smaller in ALS subjects than in controls. For reference, we also report on volume of cerebral motor regions that are known to be affected in ALS (i.e., the premotor and primary motor cortices).

15. **D. Hammers**  
K. Duff, A. Wang, K. Smith, N. Foster  
*Bad air, bad cognition: The effects of wintertime inversions on executive functioning among elderly residents*

Background: Cognitive declines have been observed in response to exposure to reduced air quality across ages and geographic locations, though these studies have focused on areas of chronic air pollution. Less is known about the impact of acute and periodic air pollution on cognition that occurs during Utah wintertime ‘inversions’, which arise due to a unique geographic \times climate interaction and provide ‘optimal’ conditions for the acute accumulation of pollution as cooler winter air is trapped on the valley floor. Nineteen days in the winter of 2013-2014 were categorized as unhealthy for older adults and other sensitive groups in the Salt Lake Valley.

16. **N. Allen**  
M. Litchman, J. Murray, C. Brunker, C. Berg  
*RT-CGM data sharing between older adults with and without cognitive decline and their care partners: A feasibility study protocol*

Background: People with type 1 diabetes (T1D) are aging. Older adults with T1D are more prone to hypoglycemia and hypoglycemia unawareness. Older adults with or without cognitive impairment and diabetes may benefit from real-time continuous glucose monitoring (RT-CGM) technology. RT-CGM data sharing via mobile device with a care partner may enhance safety in older adults. The purpose of this study is to
- Adapt RT-CGM with data sharing training for patients and care partners
- Evaluate the feasibility, acceptability, adherence and clinical data related to RT-CGM use and data sharing.
- Evaluate hypoglycemia confidence, quality of life and data sharing experience.
17. K. Morton, J. Hoffman
   R. Kirk, R. Kesner
   Experimental lipopolysaccharide-induced experimental sepsis in rats results in hippocampal abnormalities

Purpose: The hippocampal stratum lacunosum moleculare (SLM) contains perforant fibers connecting the entorhinal cortex to the dentate gyrus (DG) and other hippocampal subregions and shows early neurodegeneration in Alzheimer’s dementia (AD). Many patients with sepsis display acute and chronic neurocognitive impairment. We have reported that neuroinflammation, blood brain barrier (BBB) disruption (by contrast enhanced MRI [CEMR]) and deposition of amyloid beta (Ab) plaques (by immunohistochemistry and [18F] flutametamol PET) occur in the cortex of rats with lipopolysaccharide (LPS)-induced experimental sepsis. Here, we examine the effect of LPS on the hippocampus, including BBB integrity, Ab plaque deposition and specific neurocognitive function.

18. C. Pernici, P. West
   Saturated dentate gyrus long-term potentiation and associated memory deficits in a mouse model of temporal lobe epilepsy

Rationale: Cognitive and psychiatric dysfunction significantly impacts the quality of life of patients with epilepsy. Furthermore, these debilitating comorbidities may arise from the underlying neurobiology of epilepsy (primary), as a consequence of seizures (secondary), and/or as a side-effect of antiseizure drugs (iatrogenic). In all of these cases, pathophysiology is poorly understood and no effective treatments exist. Accordingly, rodent models of epilepsy with cognitive and/or psychiatric comorbidities are needed. Our previous work has demonstrated that electrically-induced acute seizure models have impaired dentate gyrus (DG) mediated spatial learning and memory and attenuated DG synaptic plasticity (Remigio et al. Neurobiol Dis. 2017; 105:221-234). However, an understanding of cognitive dysfunction in models that experience genuine spontaneous recurrent seizures (SRSs) is needed. Therefore, the aim of these experiments was to evaluate the effects of SRSs on DG-mediated cognitive function and synaptic plasticity in the intra-amygdala kainate (IAK) mouse model of temporal lobe epilepsy.

19. K. Duff
   R. Frost, Y. He, D. Hammers, J. Sonnen, J. Hoffman, N. Foster
   Clinical FDG-PET and autopsy findings in patients scanned to distinguish Alzheimer’s disease from frontotemporal degeneration

Background: Alzheimer’s disease (AD) and frontotemporal degeneration (FTD) often cause similar symptoms, which can impede accurate clinical diagnosis and appropriate management. Atypical presentations of dementing diseases are particularly difficult to distinguish and could benefit from advanced neuroimaging. Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) in a research cohort has high positive predictive value in differentiating clinically prototypical, pathologically confirmed AD and FTD; however, the accuracy of diagnostic classification in a clinical sample is less well studied. There is little information about the accuracy of diagnostic classification in clinical samples consisting of patients with atypical or complex illness resulting in an uncertain clinical diagnosis.
Staufen blocks autophagy in neurodegeneration

Response to cellular stress represents a highly conserved pathway in evolution. Cells respond to stress with modified synthesis of new proteins by the formation of stress granules (SGs), inhibition of translation initiation and by increased recycling of cellular components through autophagy. One of the master regulators of this response is the mechanistic target of rapamycin (mTOR) kinase. We recently reported that Staufen1 (STAU1), a stress granule protein, was overabundant in the rare neurodegenerative disorder SCA2 and provided a link between SG formation and autophagy (Paul et al, 2018). In cells harboring mutant ATXN2, STAU1 could also be increased by bafilomycin A consistent with impaired autophagosome lysosome fusion (Paul et al, 2018). Here we now examine this association and show the molecular mechanism leading to autophagic block in cells with microtubule associated protein tau (MAPT), presenilin 1 (PSEN1), huntingtin (HTT), TAR DNA-binding protein-43 gene (TARDBP) or C9orf72-SMC8 complex subunit (C9orf72) mutations underlying a great number of neurodegenerative diseases. We found that STAU1 overabundance was present in all cell lines and animal models tested, that it was post-translational, and that it was associated with an increase in phosphorylated mTOR (P-mTOR) and autophagic block. Exogenous expression of STAU1 in wild-type cells was sufficient to reduce autophagic flux by itself. Mechanistically, STAU1 directly interacted with the mTOR-5'UTR and enhanced mTOR translation. As STAU1 itself is degraded by autophagy, this interaction and the resulting autophagic block results in a maladaptive amplifying response to chronic stress. Targeting STAU1 by RNAi decreased mTOR hyperactivity and normalized mTOR downstream targets in dividing cells, post-mitotic neurons and animal models of SCA2 and ALS-TDP-43 or C9orf72 associated neurodegeneration. In summary, STAU1 is necessary and sufficient to mediate a maladaptive cellular stress response and is a novel target for RNAi-mediated treatment of neurodegenerative diseases.

Basal ganglia calcification in Down Syndrome young adults is associated with deficits in executive function on the IED: Calcification in the DS Ts65Dn mouse increases with age

A major challenge for biomedicine is differentiating the mechanisms of aging in normal, accelerated and Alzheimer’s disease (AD). Down syndrome (DS) is a major cause of genetic imbalance causing brain disease throughout the lifespan: intellectual disabilities due to developmental perturbations in the young through premature aging and AD in the old, and therefore provides an important genetic model to study aging and AD. Previous reports found basal ganglia, especially globus pallidus calcification (GPCa) in DS from birth and more severe with increased age. However, the genetic and neural basis, the cognitive effects of GPCa, and whether it is associated with aging or AD are still elusive. To fill the gap, we first measured MRI in a young aged DS cohort (n=27; 16-28 years old) and age, sex-matched control cohort (n=18, 18-28 years old), and found GPCa in 18.5% of DS subjects while in none of controls, suggesting an early onset and higher prevalence of GPCa in DS, which is consistent with previous reports. Second, by integrating GPCa and the cognitive deficits in this DS cohort, we showed significant correlation between GPCa and the Cambridge Neuropsychological Test Automated Battery (CANTAB) Intra-Extra Dimensional Set Shift test (IED), but not the other two major DS cognitive deficits, IQ or CANTAB Paired Associates Learning (PAL) tests, suggesting a possible specific cognitive consequence of
GPCa in DS. Third, significant correlation of GPCa and white matter integrity in DS was found in bilateral posterior thalamic radiation (PTR), which is also one of the most age-sensitive measures in general population. Interestingly, CANTAB-IED and diffusivity of PTR are significantly correlated in the study cohort. Forth, by comparing the rare individuals with partial trisomy 21 to the ones with full trisomy 21, we determined a subset of critical genes on chromosome 21 (HSA21), involved in the pathogenesis of GPCa in DS. Importantly, this subset of critical genes is almost identical to the ones in Ts65Dn mouse, the major mouse model for DS. One possible gene candidate in this critical region is CLDN14, a regulator of renal calcium transport, also expressed in oligodendrocyte lineage cells. Fifth, we measured MRI and CT on aged (13-27 months) Ts65Dn mice. Our results showed, for the first time, severe thalamic lesions in 69% of Ts65Dn mice, while minor thalamic lesions in 31% of paired wild type siblings. Further histological calcium staining using Von Kossa method revealed calcium deposits in the Ts65Dn thalamic lesions. Finally, we asked whether GPCa is associated with apolipoprotein E (ApoE), the strongest genetic risk factor for AD outside HSA21, and showed no significant correlation between GPCa and the ApoE polymorphism. Taken together, our results suggest critical HSA21 genes causing GPCa, a possible pathogenetic mechanism that associate with frontostriatal circuits (involving globus pallidus, thalamus and cortex) and specific cognitive deficits (CANTAB IED) in DS. The study in both young adults with DS and the aged Ts65Dn mouse model implicated a genetic system that associated with both development and accelerated aging. However, no evidence in this study implicates direct association of GPCa and AD in DS. The study results also provide unique example of how a common mechanism (blood perfusion) can be associated to early aging through a subtle imbalance of expression of specific gene(s).

22. N. Foster
N. Allen, K. Garrett, A. Wang, M. Briley, K. Duff, J. Ying, R. Holbrook
Patient-centered outcomes in primary and interdisciplinary cognitive specialty care management of cognitive impairment

Background & Objective: The role of interdisciplinary cognitive specialty clinics is controversial. Cognitive clinics are widely available. Early referral is the standard of care in Europe. In the US, lacking practice standards, most cognitive problems are managed in primary care. Referrals to specialty teams are inconsistent and often delayed after dementia has progressed. Medicare advantage plans are not required to include cognitive specialty teams in their provider panel; evidence could change this. Knowing cognitive status is particularly important for patients expected to the self-manage their diabetes. We identified patient-centered outcomes drawing from a patient and care partner advisory panel to compare community-based primary care clinics and in a interdisciplinary cognitive specialty clinic.

23. D. Morgan
N. Allen
A nurse practitioner dementia co-management model in primary care

Background: 33,000 Utahns currently living with dementia; projected to increase by 28% by 2025. Majority of dementia patients are managed in Primary Care settings. Care-partners report dissatisfaction in several areas of care provided by PCPs. PCPs report feeling ill-equipped to manage this population without additional support. Opportunities exist to redefine the current standard of care.
24. S. Paul  
W. Dansithong, K. Figueroa, D. Scoles, S. Pulst  
PAS kinase, nutrient sensor regulates autophagy in spinocerebellar ataxia type 2 (SCA2)

The cellular nutrient and energy sensors — AMP-regulated kinase (AMPK), mechanistic target of rapamycin (mTOR) kinase and PAS kinase (PASK) — play critical roles in maintaining cellular homeostasis including autophagy pathway and that misregulated sensors could contribute to neurodegenerative disease pathogenesis. Neurodegenerative disease, spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant ataxia affecting cerebellar Purkinje cells and other neurons in the cerebellum, brainstem, cerebrum and spinal cord caused by CAG repeat (polyglutamine) expansion in the ATXN2 gene. Demonstrating that Staufen1 (STAU1), RNA-binding and stress granule protein, overabundance is associated with misregulated RNA and autophagy malfunction in SCA2 (Paul et al. 2018). However, the role of ATXN2 and its link to nutritional sensor regulation is poorly understood. Here, we show that PASK levels and mTOR activities are increased along with autophagy pathway proteins in CRISPR/Cas9-mediated ATXN2-Q58 KI HEK-293 cells. We also demonstrate that mTOR expression is regulated by STAU1, suggesting STAU1-induced autophagy malfunction through mTOR activation. Changes in mTOR activity are predicted to modify autophagy pathway. Targeting PASK ex-vivo by RNAi restored STAU1 levels to normal and restored abnormally active mTOR signaling in ATXN2-Q58 KI cells. Reduction of Pask in vivo normalized Stau1 levels in SCA2 (ATXN2Q127) mouse model. These results put PASK in a novel stress response pathway that affects autophagy and targeting PASK may present a novel therapeutic target for some forms of neurodegeneration.

25. M. Euler  
K. Duff  
Task-related EEG activation as a biomarker for early Alzheimer’s disease

Despite recent progress in developing biomarkers for Alzheimer’s disease (AD), the existing suite of measures faces limitations related to invasiveness, cost, high technological demands, and low accessibility. To help address these challenges, this project will investigate EEG mid-frontal theta power (MFT), as a potentially inexpensive, non-invasive, and easily-implemented alternative. It is proposed that because AD involves the loss of cognitive and neural reserve, individuals in early stages should require increased mental exertion to achieve a given level of task performance. In turn, EEG MFT has been strongly linked to mental exertion, and as such may be over-activated in early Alzheimer’s stages.

This project, recently funded by the National Institute on Aging, will recruit three groups of older adults (n = 40 each; 65 years-old or older; 50% female) who are either cognitively-intact, or meet diagnostic criteria for amnestic Mild Cognitive Impairment or mild AD. Participants will be drawn from a larger, ongoing study of established AD biomarkers (APOE status, PET amyloid burden, hippocampal volume). MFT will be measured in a separate EEG session, using a simple task that is well-established to elicit MFT and related signals in these groups. Analyses will examine (1) whether individuals with Mild Cognitive Impairment and mild AD exhibit greater MFT when performing at the same level as intact individuals, and (2) whether MFT correlates with established biomarkers in the full study sample. Thus, the present study aims to assess both the potential mechanisms by which MFT may be elevated in early AD (vis-à-vis its relation to systemic, diffuse, or focal markers—APOE status, global amyloid burden, or hippocampal volumes), as well as its translational potential, relative to more costly and invasive markers.
26. K. Morton, J. Hoffman

BACE1 regulation in a rat sepsis model

Purpose: Survivors of sepsis experience both short- and long-term neurocognitive impairment. We have shown that experimental lipopolysaccharide (LPS) induced sepsis in a rat results in secondary neuroinflammation and the deposition of cortical and hippocampal Aβ plaque. BACE1 constitutes the first step in the formation of Aβ plaques in the brain. BACE1 is increased in late-onset Alzheimer’s disease but not in the familial form. By RNAseq analysis, neither BACE1 nor γ-secretase transcription was increased in the brains of rats following LPS administration. However, BACE1 translation is inhibited by microRNA9 (miR9). Therefore, increased BACE1 levels could occur in the face of decreased miR9. The purpose of this study was to determine whether systemic administration of a single high dose of LPS results in alterations in miR9 and BACE1 expression.

27. K. Duff
A. Dixon, K. Suhrrie, S. Porter, D. Hammers

Reliable change in cognition over one week in community-dwelling older adults: A validation study

Reliable change methods can aid neuropsychologists in understanding if performance differences over time represent clinically meaningful change or reflect benefit from practice. The current study sought to externally validate the previously published standardized regression-based (SRB) prediction equations developed by Duff for commonly administered cognitive measures: the Hopkins Verbal Learning Test – Revised, the Brief Visual Memory Test – Revised, Symbol Digit Modality Test, and the Trail Making Test Parts A and B. This study applied Duff’s SRB prediction equations to an independent sample of community-dwelling participants with amnestic Mild Cognitive Impairment (MCI) assessed twice over a one-week period. Using pairwise t-tests, large and statistically significant improvements were observed on most measures across one week. However, the observed follow-up scores were consistently below expectation compared to predictions based on Duff’s SRB algorithms. In individual analyses, a greater percentage of MCI participants showed smaller-than-expected improvement/practice effects based on normal distributions. These findings help to further support the validity of Duff’s one-week SRB prediction equations in MCI samples. Additionally, these findings are consistent with several other studies in the literature reporting an absence or a reduction of practice effects in MCI across a number of cognitive measures and retest intervals. As such, they further support the ability of these SRB prediction equations applied over one week to potentially possess diagnostic and prognostic value, and inform treatment recommendations.

28. M. Gandelman
S. Paul, W. Dansithong, K. Figueroa, D. Scoles, S. Pulst

STAU1 as a new target to modulate neuronal function and survival during ER stress

The endoplasmic reticulum (ER) has a central role integrating signals that regulate synaptic plasticity and gene expression, affecting learning, memory, behavior and survival. On activation, the ER stress sensor PERK phosphorylates the α-subunit of eukaryotic translation initiation factor-2 (eIF2α), which controls global protein synthesis rates by inhibiting translation at the level of initiation. In the healthy nervous system, PERK/p-eif2a represent a key regulation element for controlling rates of protein synthesis essential for learning and memory formation, however during pathology ER stress can lead to sustained overactivation of PERK/p-eif2a and downstream activation of CHOP, a pro-apoptotic factor. This causes
chronic translational attenuation, leading to synapse loss and neuronal death in multiple neurological diseases, including FTD, prion disease, traumatic brain injury, Parkinson’s disease and Alzheimer’s disease. In agreement, pharmacological interventions that reduce p-eif2a and restore translation have been found to boost learning and memory.

We have identified the RNA-binding protein STAU1 as a novel modulator of ER stress; required for apoptosis induced by the PERK/p-eif2a/CHOP pathway. STAU1 levels increased in response to multiple pharmacological ER stressors. Overexpression of STAU1 was sufficient to activate PERK/p-eif2a/CHOP, leading to apoptosis. Cortical neurons and skin fibroblasts derived from Stau1 knockout mice showed attenuated UPR and were resistant to apoptosis caused by ER stress. In fibroblast samples obtained from patients with Spinocerebellar Ataxia type 2, Amyotrophic lateral sclerosis or Frontotemporal dementia STAU1 levels were highly increased and the PERK/p-eif2a/CHOP pathway was basally active. In all these models STAU1 knockdown reduced PERK/p-eif2a/CHOP activation and restored cell survival. Taken together, these results suggest STAU1 makes cells vulnerable to ER stress and precipitates apoptosis. STAU1 is a novel target to prevent overactivation of the PERK/p-eif2a/CHOP axis and restore neuronal survival and plasticity in multiple neurological conditions.

29. G. Liu
P. Men, G. Kenner
Animal studies of novel iron chelating agents as potential multi-targeting therapeutics for Alzheimer’s disease

Background: According to the Alzheimer’s Association, every sixty-five seconds someone in the United States develops Alzheimer’s disease (AD). Unfortunately, there is no way to prevent or cure AD, and the current medicines on the market are only able to provide moderate symptomatic delay. It is also very frustrating that the mechanisms underlying AD’s evolution remain largely unknown and the pace of developing disease-modifying drugs (DMDs) is extremely slow. Obviously, there is an urgent and unmet need for rapidly developing new therapeutics for AD.

In recent years, growing evidence indicates that iron accumulation as well as its associated oxidative damage in the brain plays an important role in AD onset and progression. Therefore, iron-chelating agents have been suggested as new potential DMDs for the neuronal deterioration of AD. However, some obstacles concerning iron chelators’ toxic side effects and bioavailability, such as brain targeting and blood–brain barrier (BBB) penetration, have hindered further investigation both in the understanding of the pathophysiological role of iron in AD and in the evaluation of the efficacy and safety of chelation therapy. To overcome these obstacles, new iron chelating agents with lowered toxicity and improved bioavailability have been developed in our laboratory, and evaluated for their therapeutic effectiveness in AD animals.

30. N. Foster
ProActive dementia care improves patient-centered outcomes: Mobile software implementation with MemoryCarePartner

Background: Early identification and cognitive evaluation of Alzheimer’s disease are major goals of the United States National Plan to Address Alzheimer’s Disease. Achieving these goals is expected to improve care and minimize disease complications. In the US, where most
cognitive problems are managed solely in primary care, the role of specialty clinics is controversial and referrals are inconsistent and often delayed. Providers without a dementia focus may offer little or no family education and support. Mobile software applications can provide an engaging experience and can be tailored to individualized needs based upon user input. One of the primary benefits is providing family education and support early and helping them plan and know what to expect from medical visits.

31. K. Duff  
  S. Porter, K. Suhrie, A. Dixon, D. Hammers  
Tracking functional decline in mild cognitive impairment

Diagnostically, significant functional decline is needed to indicate that a patient has progressed from Mild Cognitive Impairment (MCI) to dementia. Typically, the report of functional changes is a subjective report of the patient or a family member, which may be difficult to track over time. The current study sought to objectively evaluate functional abilities in individuals with MCI and track them over approximately one and a half years. Eighty-one older adults (age M=75.5 years, education M=16.5 years, 56% male) with amnestic MCI (single- or multi-domain) were assessed at baseline and one and a half years follow-up visits with three subscales of an objective measure of daily functioning, the Independent Living Scales (ILS: Managing Money, Managing Home and Transportation, and Health and Safety), and an objective measure of cognition, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Dependent t-tests compared the baseline and follow-up scores on the ILS and RBANS. Despite no change on the RBANS across one and a half years (e.g., Total Scale score: t[80]=−0.69, p=0.50), 2 of the 3 ILS subscales showed a statistically significant decline across this same period: Managing Home and Transportation, t[80]=2.75, p=0.007, and Health and Safety, t[79]=2.10, p=0.04, with the third scale showing a trend towards decline (Managing Money, t[80]=1.68, p=0.09). Although the declines on the ILS tended to be relatively small (e.g., approximately 2 T-score points), this objective measure of daily functioning does appear sensitive enough to track these changes in this mildly impaired cohort that is at risk for progressing to dementia.

32. K. Dassel  
  L. Edelman, J. Butler, J. Telonidis  
Utah geriatric education consortium (UGEC): Evaluation of Alzheimer’s disease and related dementia online training modules

The Utah Geriatrics Education Consortium (UGEC) focuses on integrating geriatric training into 20 long-term care centers across the state of Utah. A supplemental arm on the UGEC is focuses specifically on providing ADRD education to family caregivers, direct-care workers, providers, and health professions students. To accomplish this goal, expert faculty and clinicians at the University of Utah created an online asynchronous dementia training program that includes video-recorded presentations, a threaded case study, and supplemental information. Modular topics include: 1) Overview of dementia, 2) Understanding behaviors and how to approach them, 3) Team communication strategies within nursing homes, and 4) Communication and responding to behaviors. Prior to enrolling in the course, participants completed a demographic survey and a modified 15-item version of the Alzheimer’s Disease Knowledge Scale (ADKS; Carpenter et al., 2008). After completing the modules, participants complete a satisfaction survey and the ADKS. A total of 75 participants completed both the pre and post surveys. Participants were primarily female (81.3%), well educated (65% had a bachelor’s degree or higher), non-Hispanic White (92%), and were comprised of health care professionals (e.g., RN, CNA, OT etc.: 48%), informal
caregivers (14.7%) or “Other” (e.g., students; 37.3%). Satisfaction evaluation data showed that the majority of participants reported that the information presented was very clear (75%), was useful for their work (86%), and would improve the care that they provide to their geriatric patients (92%). Open-ended responses provided positive feedback and areas for improvement. Positive comments included an appreciation of the threaded case study, the use of video-lectures, and the convenience of an online, self-paced program. Areas for improvement included shortening the videos into smaller segments, increasing interaction in terms of audio/visual demonstrations, and reducing repetitive content. Out of 15 possible points on the ADKS, the mean pre-course scores of 13.31 (S.D.=1.47) and a mean post-score of 13.72 (S.D.=1.32), which was a statistically significant increase (t=-2.464, p=.02). In conclusion, participants who completed the UGEC ADRD online educational modules demonstrated increased knowledge of ADRD and reported that the training was clear, useful for their work, and convenient.

33. J. Heys  
D. Dombeck  
Neural representations of space and time in medial entorhinal cortex

The hippocampus and entorhinal cortex are thought to be necessary for encoding episodic memories (i.e. memories of specific personal experiences that occur in a spatial-temporal context). In support of this idea, neurons in the hippocampus and medial entorhinal cortex (MEC) fire selectively as function of animal position within an environment (O’keefe and Dostrovsky 1971; Hafting et al. 2005), and are thought to encode spatial aspects of episodic memories. While the vast majority of studies in MEC have focused on neural representations of space, it is unclear if or how MEC supports temporal aspects of episodic memory. To answer this question, we developed a “Door-Stop” (DS) task for head-fixed mice in virtual reality that combines both a locomotion dependent, spatial navigation phase, and an immobile timing phase. We then performed cellular resolution functional imaging in MEC during the DS task. During the timing phase of the task, we found many individual neurons that fired at regular, fixed delay times from the moment that the animal stopped to wait at the door (Heys and Dombeck, 2018). Across the population of these simultaneously recorded temporal coding neurons in MEC, we found that different cells fire selectively at all phases spanning the temporal interval, and therefore provide a neural representation that could be used to encode the entire wait time interval. We also found that optogenetic inactivation of the MEC caused a disruption in the animal’s ability to perform the timing task, demonstrating a causal link between MEC activity and timing function. Furthermore, we found that temporal encoding cells and spatial encoding cells exhibit a predisposition for encoding either time or space, respectively, when animals were switched between different environments. Finally, we found that the temporal coding neurons exhibit fully formed temporal representations from the first moments of exploration in a novel environment, suggesting that the MEC elapsed time-encoding sub-network does not require learning to form temporal representations. Our findings provide new insight into the functional domains of MEC and demonstrates the likely existence of different sub-circuits that encode either time or space during animal locomotion.

34. K. Duff  
Cognitive functioning on the RBANS and APOE status

Although the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a widely-used brief battery for the evaluation of cognitive changes in later life, no studies have examined performance on the RBANS in older adults based on APOE genotype status,
for which the e4 allele is a risk factor for Alzheimer’s disease. Thirty-nine older adults with varying levels of cognitive functioning were divided into two groups based on their APOE genotype status: no copies of the e4 allele (n=14) or one or more copies of the e4 allele (n=25). They were all administered the RBANS as part of a baseline assessment for a study of biomarkers of Alzheimer’s disease. Results indicated that although the two groups were comparable in terms of age, education, sex, an estimate of premorbid intellect, and current depressive symptoms, they showed statistically significant differences on: Immediate Memory Index (t[37]=2.8, p=0.008, d=0.09), Delayed Memory Index (t[37]=4.5, p<0.001, d=1.5), and Total Scale score (t[37]=3.2, p=0.003, d=1.0). For each of these Indexes, those with no copies of the e4 allele had better cognitive scores than those with one or more copies of the e4 allele (1.2 – 2.1 standard deviation units). No differences were observed on the Visuospatial Constructional, Language, or Attention Indexes. Although the RBANS is widely used in clinical and research settings, including in individuals with suspected Alzheimer’s disease, this is the first study to show how genetic factors, such as APOE, negatively affect performance on this brief battery.

35. R. Rupper
   A. Brody, T. Shuman, J. Doyle
   Dementia symptom management at home

Background: Alzheimer’s Disease and Related Disorders (dementia) poses a significant challenge to our public health. While many persons with dementia are cared for by friends and family in the community with the assistance of home healthcare, most home healthcare clinicians and agencies are ill prepared to care for this population and therefore have difficulty assisting patients and caregivers in maintaining quality of life leading to adverse patient outcomes, increased caregiver stress and burnout, and healthcare utilization. This study will therefore utilize a cluster randomized controlled design at 3 study sites to examine the ability of a multi-component evidence-based practice primary palliative care quality improvement program for home healthcare registered nurses, occupational therapists and physical therapists to improve the quality of life and reduce healthcare utilization for persons with dementia and their informal caregiver.

36. K. Schliep
   S. Ju, N. Foster, M. Varner, J. VanderSlice, T. Ostbye, J. Tchanz, K. Smith
   How good are medical and death records for identifying dementia in the United States?

Introduction: Retrospective studies using electronic health records (EHR) in large cohorts may be a feasible way to assess effects of early life conditions on dementia risk, but diagnostic accuracy should be determined.