POSTER PRESENTATIONS 2
2C: NEUROPATHOLOGY

Presenter's Name: Cosma, Delaney

Additional Authors: Khan A, Hammond R

Abstract Title: Cortical dysplasia: teaching pathology to a machine

Many patients with epilepsy do not achieve adequate pharmacologic control of their seizures and must consider surgical options. Many such patients undergo temporal lobectomy and experience a marked reduction in the frequency and severity of their seizures. However, many are less fortunate. One suspected factor for the latter group is the limited ability of clinical imaging to delineate subtle epileptogenic abnormalities, leading to subtotal resection of lesional tissue.

A long-range goal in this field is to increase the sensitivity and specificity of detecting such abnormalities by "training" MRI with pathology, feature analysis and machine learning. A key component of this is the ability to segment histopathology to facilitate its mapping to co-registered MRI.

Reliable automated segmentations were developed to extract a number of features including neuron size, clustering, eccentricity, field fraction and polarity. This algorithm was applied to temporal cortex with a pathological diagnosis of focal cortical dysplasia (FCD); obtained from patients undergoing temporal lobectomy epilepsy surgery and to temporal cortex from post-mortem control samples. Segmentation analyses of diagnostic groups (normal vs. FCD), using t-Distributed Stochastic Neighbor Embedding (tSNE) revealed patterns within the high-dimensional data suggesting that non-random associations were detectable.

These results indicate that data-driven algorithms may be capable of distinguishing dysplastic from normal cortex on the basis of automated segmentations.

This represents a foundational step in developing pathology driven MRI detection of subtle FCD lesions.

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Presenter's Name: Courchesne, Marc

Additional Authors: Khazaee R, Nygard K, Cumming R

Abstract Title: Examining the Spatial Expression of P66Shc within Brain Tissues of Healthy and Transgenic Alzheimer's Disease Mice

Introduction: Alzheimer's disease (AD) is a neurodegenerative disorder resulting in gradual cognitive dysfunction and memory loss. A major pathogenic factor in AD is oxidative stress triggered by the progressive deposition of toxic amyloid-beta (Aß) plaques. The p66Shc adaptor protein has been implicated in potentiating Aß-induced oxidative stress by increasing reactive oxygen species generation and repressing antioxidant defense. In this study, we are attempting to determine the cell type specificity, subcellular localization, and regional distribution of p66Shc expression and activation in the rodent brain.

Methods: The spatial expression of p66Shc in transgenic AD mice and healthy mice will be determined using p66Shc specific, cell-type specific, and mitochondrion-specific antibodies combined with immunofluorescence (IF) microscopy. If staining and imaging of healthy and AD brain tissues from both sexes have been completed. The levels of p66Shc that are colocalized with cell-type and mitochondrion-specific signals are currently being quantified.

Expected Results: We expect that p66Shc expression and activation will be elevated in the brains of AD mice compared to healthy mice for all cell types, especially in neurons due to higher susceptibility to oxidative stress. The localization of p66Shc within the mitochondria is also expected.

Discussion: The results of this study should reveal which cell types in the brains of healthy and AD mice are involved with p66Shc activity, as well as subcellular localization. This study could then provide novel insight into the mechanism of p66Shc in healthy and transgenic AD mouse brains. Elucidating the role that p66Shc plays in the pathogenesis of AD for both sexes could validate p66Shc as a potential therapeutic target.

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Presenter's Name: Gaur, Amish

Additional Authors: Van Hedger S, Johnsrude IS

Abstract Title: The Effects of Degraded Speech on Long-Term Memory in Individuals with Mild-Moderate Sensorineural Hearing Loss

Introduction: Sensorineural hearing loss (SNHL) is a common form of hearing impairment in which individuals have difficulties in understanding speech sounds. These difficulties are especially prevalent in challenging listening environments (e.g., speech in background noise). It has been suggested that an increased effort required to understand speech in these challenging listening environments may result in a depletion of cognitive resources and can manifest as cognitive decline in the long-term (Rabbit, 1968; Wingfield et al., 2005). This 'effortfulness hypothesis' would thus provide a direct link between hearing loss and cognitive decline. However, research supporting this theory has for the most part been limited to simple materials (e.g., spoken digits). Speech in real life is often more descriptive and meaningful to a listener. Therefore, an increased amount of effort required to understand degraded meaningful speech may actually facilitate a more semantic form of processing (Craik & Lockhart, 1972). In fact, recent research in our laboratory has shown that long-term memory (LTM) for degraded meaningful speech is greater than that for clear speech in normal hearing individuals, provided the speech remains intelligible. Moreover, we have found that the memory benefit for degraded sentences is greater than that for degraded words—suggesting that contextually rich meaningful speech is more available to a greater depth of processing. This study looks to extend these findings by investigating LTM for perceptually degraded speech compared to clear speech in individuals with SNHL.

Methods: We are currently recruiting participants with mild-moderate SNHL and an age matched normal-hearing control group to take part in an online behavioural experiment. In this experiment, participants will listen to two blocks of 48 sentences and 48 words as part of the encoding phase. Half of the materials in each block are degraded with background noise, and the other half is presented in the clear. Intelligibility for the speech materials is assessed in the encoding phase via self-report. Participants are then asked to complete a memory recognition task in which they are presented visually with two blocks of 48 sentences and two blocks of 48 words, half of which are presented for the first time (i.e., "foils"). They are to report if they recognize each presented stimulus from the encoding phase. Memory recognition scores will then be analyzed using a three-factor mixed ANOVA: (noise/clear), (sentence/word), and (SNHL/control).

Results: As of now, 11 SNHL and 11 age-matched control participants have been recruited for this study. We expect that memory for degraded speech will be greater than that for clear speech in individuals with SNHL. We also expect to see a greater memory benefit for contextually rich degraded sentences compared to words. In addition, we do not expect to see a significant difference in results in individuals with SNHL and control participants.

Discussion: These results would suggest that individuals with SNHL may process degraded speech in a similar manner to individuals without clinical hearing loss. Furthermore, these findings would be in contrast to the effortfulness hypothesis and may provide alternative insight on the link between hearing loss and cognitive decline. Thus, we hope that this research will provide valuable knowledge that can be used in the management of hearing loss and cognitive function in the clinic.

POSTER PRESENTATIONS 2
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Presenter's Name: Goldberg, Polina

Additional Authors: Duennwald M, McDonald D

Abstract Title: Aberrant Mitochondrial Transfer-RNAs contribute to the Pathogenesis of Neurodegenerative Diseases

Introduction: Mitochondria are semi-autonomous organelles as they contain their own circular genomes. Previous research implicates variant mitochondrial tRNA (mt-tRNA) in a number of human pathologies, mainly those involving post-mitotic cells such as neurons. Mutated tRNA-modifying enzymes have also been implicated in human disorders, and the presence of mutated tRNA-modifying enzymes has been to shown to cause protein aggregation in yeast cells. These findings have led our lab to investigate the potential role of mistranslating mt-tRNAs and mutated tRNA-modifying enzymes in the pathogeneses of neurodegenerative diseases. Neurodegenerative diseases are a group of disorders that result in a progressive loss of neural structure and function. Protein aggregation is a hallmark pathology of all neurodegenerative diseases, and a mitochondrial role for this pathology has been proposed.

Methods: The organization of mt-tRNAs in mitochondrial genomes (mitogenomes) of several key model organisms will be compared to establish that mt-tRNAs are evolutionary conserved. The incidence of polymorphisms in tRNA-modifying genes and tRNA-specific aminoacyl synthetases will be investigated in clinical cases of neurodegenerative diseases. Finally, we will investigate whether four mistranslating tRNA variants cause protein aggregation in Saccharomyces cerevisiae using the Hsp104-YFP reporter system.

Results: The number and relative organization of mt-tRNAs in mitogenomes of key model organisms are conserved. Furthermore, there are numerous identified mutations in both mt-tRNA-modifying genes and mt-tRNA aminoacyl synthetases that have been implicated in human neurodegenerative diseases. Finally, no significant increase in protein aggregation in S. cerevisiae was observed when co-expressing any of the four mistranslating tRNA variants.

Discussion: This study is an in-depth investigation into the role of both variant tRNAs and variant tRNA-associated enzymes in the context of neurodegenerative diseases. This study also investigates whether or not mistranslating tRNA may contribute to protein misfolding, a hallmark feature of neurodegenerative diseases.

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Presenter's Name: Liu, Peter

Additional Authors: Zhao C, Alturkusrttani M, Ang LC, Zhang Q

Abstract Title: Charactering the Regional Heterogeneity of Adult-Onset Leukoencephalopathy with Axonal Spheroids (ALAS): A High-Plex and High-Throughput Digital Spatial Profiling Study

Introduction: Adult-onset leukoencephalopathy with axonal spheroids (ALAS) is a group of hereditary, progressive, neurodegetative disorders involving primarily the central nervous system white matter (WM). ALAS is characterized by patchy, asymmetrical myelin loss and axonal destruction in the WM, predominantly involving the frontoparietal regions. The subcortical U-fibers are usually spared. The discovery of mutations in colony stimulating factor 1 receptor (CSF1R) gene suggests microgliopathy as a potential mechanism for this disease. However, the asymmetrical and heterogenous involvement of different brain regions remains poorly characterized.

Methods: In this study, five autopsy-confirmed ALAS cases were examined. Nanostring GeoMX Digital Spatial Profiling (DSP) was performed to investigate the region-specific expressions of 60 proteins, across neural cell profiling, glial cell subtyping, immune activation status, autophagy and MAP kinase signaling. The region of interests (ROIs) were selected based on the expression of myelin basic protein (MBP) and Luxol Fast Blue (LFB) stain, representing subcortical U-fiber (ROI-1), immediate microenvironment (ROI-2), WM with extensive degeneration (ROI-3), WM with no or mild degeneration (ROI-4), cerebral cortex above ROI-3 (ROI-5), and cerebral cortex above ROI-4 (ROI-6).

Results: Homeostatic/resting microglia marker (TMEM119) was significantly higher in ROI-1 and ROI-4 (U-fiber and WM with no/mild degeneration, respectively), whereas the polarized markers (CD80, CD163, GPMBP, SPP1, and CD44) are enriched in ROI-3 (WM with severe degeneration). CD9, a tetraspanin protein expressed by oligodendrocyte progenitor cells and pre-myelinating oligodendrocytes, shows increased expression in ROI-1 (U-fiber). BAG3, an antiapoptotic and co-chaperone protein, is highly expressed in ROI-3. There are no significant differences identified between the cortical ROIs.

Conclusions: Using a high-plex and high-throughput method, we provide evidence of regional heterogeneity in ALAS, particularly involving key markers of microglia composition, glial cell subtype and macroautophagy.

POSTER PRESENTATIONS 2
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Presenter's Name: Twible, Carolyn

Additional Authors: Zhang, Q

Abstract Title: Elucidating the pathological mechanisms behind no-HS subtype of hippocampal sclerosis in temporal lobe epilepsy patients

Introduction: Hippocampal sclerosis (HS) is the most common pathology finding for drug resistant temporal lobe epilepsy (TLE) and is characterized by neuronal loss and gliotic Cornu Ammonis. The hippocampal dentate gyrus and granule cell layer (GCL) are often overlooked by pathologists. Nearly 20% of the surgical specimens obtained from drug-resistant TLE surgery patients contain "normal" populations of neurons yet still benefit from their surgical resection, possibly pointing to a neuropathological explanation for the epileptogenic focus present in the resected tissue that is not able to be detected through standard diagnostic practices. The overall goals of this project are to add to the neuropathological understanding of drug resistant TLE, and to elucidate the structural and molecular changes of HS and no-HS, with a focus on the GCL. We expect to identify different histopathological features and differentially expressed genes between HS and no-HS.

Methods: In this study, 21 TLE surgical resection cases were examined, including 14 HS and 7 no-HS cases, to investigate morphometry of the GCL. Information on histopathological diagnosis and post-operative outcome were included in a clinicopathological correlation database. The digital image analysis software QuPath was used to perform cell detection analysis on the GCL. Measures including Delaunay mean and cell density were analyzed. Six TLE, including 3 HS and 3 no-HS, surgical resection cases were selected for gene expression profiling using the NanoString Neuroinflammatory panel.

Results: HS patients show a significant increase in granule cell spacing and decrease in granule cell density within the granule cell layer compared to no-HS patients. Similarly, HS and no-HS patients that were able to achieve seizure freedom post-operatively demonstrated an increase in granule cell spacing and decrease in granule cell density in comparison to cases that did not achieve seizure freedom post-operatively. We have also observed several disease-dependent differentially expressed genes, including GRIA1, HIST1H1D, ATG14, MBD2 and FYN, and differentially expressed cellular pathways within the dentate gyrus, including autophagy, matrix remodeling, oligodendrocyte function and Wnt signaling.

Discussion: HS and no-HS diagnosis groups have distinct dentate gyrus morphometry and gene expression profile. These results contribute to alleviating the knowledge gap surrounding the no-HS diagnosis group and may hold prognostic value for HS and no-HS patients.

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Presenter's Name: Zhao, Chelsey

Additional Authors: Yan L, He W, Ang LC, Zhang Q

Abstract Title: Corticobasal Degeneration and Progressive Supranuclear Palsy Have Distinct Tau Burden in the Subcoritcal Regions but Not Brainstem

Introduction: Parkinsonism is a clinical syndrome manifested by resting tremor, rigidity, bradykinesia, and postural instability. As the two tauopathies commonly presented with Parkinsonism, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) overlap both clinically and pathologically. In the present study, we are exploring the extent of phosphorylated tau (p-tau) burden in different brain regions, with a focus on basal ganglia, thalamus and brain stem.

Methods: In this study, 30 neuropathology confirmed tauopathy autopsy cases were examined, including 10 PSP, 8 CBD and 12 Alzheimer disease (AD) cases (6 AD-high level, 6 AD-intermediate level). All PSP and CBD cases have parkinsonism during the course of disease. There is no movement disorder reported in the 12 AD cases. The digital image analysis software QuPath was used to quantify p-tau burden on scanned whole slide images. Sixteen brain regions were analyzed, including putamen, external and internal division of globus pallidus (GPe and GPi), claustrum, anterior limb and posterior limb of internal capsule (ICa and ICp), subthalamic nucleus (STN), substantia nigra, midbrain, pons, cerebellar dentate, and various nuclei of the thalamus including anterior, medial dorsal, intralaminar, ventral lateral, and zona incerta.

Results: Among these 3 groups, CBD had high p-tau pathology in almost all regions explored with the highest p-tau pathology in basal ganglia in general. In comparison with PSP, CBD cases demonstrate higher p-tau accumulation in both globus pallidus and putamen, with the difference more significant in putamen. Surprisingly, when compared with AD-H, PSP cases have a lower p-tau burden in putamen, claustrum and anterior thalamic nucleus. There is no p-tau expression difference detected in claustrum between CBD and AD-H. Both CBD and PSP have a higher p-tau burden in STN, midbrain, and pons, in comparison with AD-H. Except a slightly higher p-tau pathology in the STN in CBD, there is no difference between CBD and PSP in these brainstem regions.

Discussion: PSP and CBD share an overlapping but distinct p-tau pathology pattern.