in school-based screenings and community health programs. These tools aim to be accessible, culturally relevant, and tailored to diverse populations, enhancing early detection, informing personalized interventions, and supporting scalable clinical applications. DISCUSSION/SIGNIFICANCE OF IMPACT: This study explores links between early adversity, biological aging, and mental health, advancing understanding of adolescent depression. Epigenetic biomarkers could improve risk detection and guide tailored interventions in schools and community settings, enhancing access and reducing disparities.

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Universal representation of human diseases using large language models

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OBJECTIVES/GOALS: Understanding the interconnections among over 20,000 human diseases spanning organ systems could inform more precise diagnosis and treatment of diseases. Here, we examine whether the ability of large language models (LLMs) to learn universal representations of concepts can be leveraged to discover complex relationships across human diseases. METHODS/STUDY POPULATION: To address the challenge of computationally representing thousands diseases spanning multiple organ systems, we used internal representations of concepts by LLMs to encode diseases based on their descriptions from standard disease ontologies (ICD10 and Phecodes). To do this, we leveraged application programming interfaces (APIs) of three LLMs-GPT3.5, Mistral and Voyage to encode disease relationships. We then performed unsupervised clustering of the diseases using their encodings (embeddings) from each LLM to determine whether the resulting clusters reflect disease relationships. To enable deeper exploration of disease relationships, we developed interactive plots that provide a system level view of the relationships between thousands of diseases and their association with specific organ systems. RESULTS/ANTICIPATED RESULTS: We found that unsupervised analysis of disease relationships using the LLM encodings reveal high similarities among diseases based on organ systems they affect. All the LLMs clustered diseases into groups largely defined by the organ systems they affect without being trained to specifically classify diseases into their corresponding organ system classification. An exception to this was tumors in which we observed that most tumors cluster together as a group irrespective of the organs they affect. Interestingly, we found that tumors affecting anatomically related organs show higher similarity to each other than to those affecting distantly related organs. In addition to anatomical relationships between diseases, we found that the LLM embeddings capture genetic relationships between diseases. DISCUSSION/SIGNIFICANCE OF IMPACT: Overall, we found that the LLM-derived encodings uphold biologically and clinically significant relationships across organ systems and disease types. These results suggest that LLM encodings could provide a universal framework for representing diseases as computable phenotypes and enable the discovery of complex disease relationships.

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Localization of critical speech areas in glioma-infiltrated brain cortex using local neuronal field potentials via electrocorticography (ECOG)*

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OBJECTIVES/GOALS: The standard care for malignant gliomas includes maximal tumor resection, but challenges arise near functional (speech) areas. Direct cortical stimulation (DCS) identifies functional (nonresectable) cortex. We aim to identify electrophysiologic (via subdural electrode recordings [ECOG]) biomarkers of DCS-positive (functional) areas. METHODS/STUDY POPULATION: Our lab maintains one of the largest datasets of electrophysiology analysis of glioma infiltrated brain cortex in the USA. Recordings of intraoperative brain mapping were analyzed to identify cortical sites that were found to be positive (functional) during DCS. DCS positive and negative (nonfunctional) sites were aligned to corresponding subdural electrodes. Future analysis: We plan to compare the temporal and spectral electrophysiologic variations associated with cortical sites found to be DCS positive versus negative during brain mapping. We plan to train machine learning classifiers that utilize these electrophysiologic biomarkers to discriminate between DCS positive and negative sites. RESULTS/ANTICIPATED RESULTS: In total, our database comprised of 110 resections with brain mapping (DCS) and ECOG, including 4 patients who underwent a second procedure for resection. Eight patients were excluded as their resections were for brain metastases, not glioma. Our final cohort was comprised of 98 glioma resections, including 4 patients who underwent surgery twice for recurrence. During these resections, a total of 1393 sites were mapped via DCS for language function (including picture naming, word reading, and sentence syntax tasks). Of these 1393 sites, 100 sites were found to be DCS positive (7.1% positivity rate). (Currently in the process of conducting analysis comparing electrophysiologic features and biomarkers of DCS positive versus negative sites.) DISCUSSION/SIGNIFICANCE OF IMPACT: This research is ongoing. Identifying electrophysiologic biomarkers of critical DCS-positive regions may provide a durable alternative to stimulation mapping. Due to its resource intensity, DCS has access barriers. Future neurosurgeons may use biomarkers from subdural electrode recordings to plan safer cortical resections.

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Uncovering links between innate immunity, DNA repair, and cognitive health in aging populations

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OBJECTIVES/GOALS: Neurodegenerative diseases involve progressive neuronal loss or dysfunction, often due to accumulated

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