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The Role of TCF7L2 in Hepatic Metabolic Zonation

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OBJECTIVES/GOALS: Single nucleotide polymorphisms in the transcription factor 7-like 2 (TCF7L2) gene are associated with Type 2 Diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD). The metabolic function of TCF7L2 in the liver remains to be fully elucidated, but we hypothesized that TCF7L2 contributes to NAFLD through regulation of zonal metabolic pathways. METHODS/STUDY POPULATION: Using single nuclei RNA sequencing, we examined Tcf7l2 expression in periportal (PP) hepatocytes around the portal triad and pericentral (PC) hepatocytes surrounding the central vein of the liver. To visualize TCF7L2 transcriptional activity we used a TCF reporter mice, which expresses an H2B-eGFP fusion protein downstream of the conserved TCF DNA binding site. We disrupted Tcf7l2 transcriptional activity in mouse liver by breeding mice with a floxed Tcf7l2 exon 11, which encodes part of the DNA binding domain (DBD), to albumin-Cre mice (Hep-TCF7L2Î”DBD). Eight-week-old mice were fed a choline-deficient amino acid-defined high fat (CDAHFD) diet for 8 weeks. In liver samples harvested from these mice, we examined disruption to several key zonated metabolic pathways, and quantified the development of fibrosis. RESULTS/ANTICIPATED RESULTS: Single nuclei analysis revealed that Tcf7l2 mRNA was expressed primarily in parenchymal cells of the liver but was ubiquitous across the liver lobule. However, in immunofluorescence analysis of TCF reporter mice, the transcriptional activity of TCF7L2 was highly restricted to PC hepatocytes. Classic PC hepatocyte markers, including glutamine synthetase (Glul), were absent in Hep-TCF7L2Î”DBD mice. Following the CDAHFD, Hep-TCF7L2Î”DBD mice developed more severe fibrosis in histological analysis, and expressed elevated levels of genes involved in fibrogenesis, collagen synthesis and TGFβsignaling. Hep-TCF7L2Î”DBD mice also displayed hepatic cholesterol accumulation following the CDAHFD, which was likely the result of impaired pericentral bile acid synthesis. DISCUSSION/SIGNIFICANCE: Our results suggest that TCF7L2 plays an important role in the regulation of zonated metabolic pathways, which may contribute to the development of fibrosis. Ongoing analyses are exploring the mechanisms regulating the zonal transcriptional activity of TCF7L2.

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The tradeoff between kinematic and muscular control of reaching as a potential biomarker of motor performance in stroke

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OBJECTIVES/GOALS: Nearly 3 million Americans live with arm impairment following stroke. While as many as 20% of patients fully recover, individual differences in recovery make one-size-fits-all rehabilitation approaches suboptimal. The goal of this study was to use our custom rehabilitation platform to identify neuromuscular biomarkers of arm control in stroke. METHODS/STUDY POPULATION: Chronic stroke survivors (N = 10) reached for targets in a virtual reality environment using both hands. They completed 162 reaches divided into 3 blocks. Following baseline, we used our custom exoskeletons to provide 50% arm weight assistance to the impaired limb and 50% arm weight resistance to the non-impaired limb. We removed the exoskeletons during the retention block. We used electromyography to approximate muscle activity in the anterior deltoids. Relative contribution (RC) was calculated as the displacement of the impaired arm divided by the sum of displacements for both arms. Muscle contribution (MC) was calculated as the root mean square of impaired arm muscle activity divided by the sum of activity for both deltoids, normalized to maximum voluntary contraction. RESULTS/ANTICIPATED RESULTS: During baseline, RC of the impaired limb was 43%; patients reached significantly less with their impaired arm compared to their non-impaired arm ($p = 0.02$). MC of the impaired deltoid was 56% and was similar between arms ($p = 0.5$). During loading, RC did not change relative to baseline ($p = 0.87$), but MC tended to decrease by 11% ($p = 0.12$). These results suggest a tradeoff between kinematic and muscular control of reaching. This new finding closely matches our previous work in 12 healthy controls, where we found a 2% increase in RC and a 11% decrease in MC. Importantly, 4/10 patients exhibited an inverse tradeoff (i.e., decrease in RC and/or increase in MC). We will analyze neuroimaging data to determine the role lesion size and location play in predicting an individual's response to gravity compensation. DISCUSSION/SIGNIFICANCE: Our tradeoff analysis serves as a potential neuromuscular biomarker of stroke survivors' responsiveness to gravity compensation. This forms the basis for personalized technologies for stroke rehabilitation. With further development, clinicians can use our platform to fine-tune compensation levels based on the individual needs of the patient.

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Translating a precision dosing approach for opioid use disorder in Puerto Rico: Pilot testing of the clinical utility and patient/provider acceptability

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OBJECTIVES/GOALS: The purpose of this pilot study is to evaluate the clinical utility and patient/provider acceptability of a buprenorphine (bup) precision dosing approach for opioid use disorder (OUD) in Puerto Rico (PR) to in estimate the most adequate bup dosing regimen based on the unique pharmacological and clinical characteristics of these patients. METHODS/STUDY POPULATION: The goal of this pilot study is to evaluate the extent to which people delivering (providers) or receiving (patients) opioid use disorder care in PR consider our 'bup precision dosing approach' to be appropriate, based on anticipated or experienced cognitive and emotional responses. We will use the Theoretical Framework of Acceptability (TFA) to conduct this evaluation. We expect to generate a baseline understanding of the acceptability

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