associated with increased odds of having a reported parkinsonism/PD diagnosis. Next steps include examination of the contribution of traumatic brain injury and other sources of RHI (e.g., soccer, military service).

Categories: Neurodegenerative Disorders
Keyword 1: Parkinson's disease
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Early Career Award Presentation

Speaker: Yakeel Quiroz

Taking it to the extreme: The search for determinants of cognitive vulnerability and resilience in children with autosomal dominant Alzheimer's disease

4:00 - 4:30pm
Thursday, 2nd February, 2023
Pacific Ballroom E

Abstract:
Presenilin-1 (PSEN1) mutations predispose individuals to develop autosomal-dominant Alzheimer's disease (ADAD) in middle adulthood. While the pathogenesis of ADAD may be different from late-onset sporadic AD (e.g., differences in disease etiology, age of disease onset, etc), these conditions share many characteristics, including similar abnormalities in amyloid and tau biomarkers, brain structure and brain activity, and clinical features (Quiroz et al., 2010, Quiroz et al., 2011, Quiroz et al. 2018). Biomarker investigations of families with ADAD have already shed light on the trajectory of some AD-related brain changes, especially prior to the onset of clinical symptoms.
We have been studying a Colombian kindred with a genetic form of AD caused by a single genetic mutation in the PSEN1 (E280A), which serves as a unique model for preclinical AD. Because of a well-defined age at clinical onset, and near 100% penetrance, this kindred provides important information about the time course and relationships between physiological mechanisms and cognitive changes, and in so doing, it has yielded new insights about presymptomatic AD that will enhance future prevention trials for AD, including primary prevention trials.
The well-characterized clinical trajectory of these PSEN1 E280A mutation carriers allow us to examine brain function in children, more than three decades before the average age of onset of mild cognitive impairment (MCI) and dementia in this cohort (45 years for MCI, 50 years for dementia). This is giving us the unique opportunity to characterize the cognitive and behavioral profiles of children genetically determined to develop dementia in their forties, and is helping us improve our understanding of the impact of ADAD mutations in early life cognitive and brain functioning, as well as its potential impact on learning, academic performance and educational attainment.
We previously studied 20 PSEN1 E280A carriers and 20 non-carriers aged 9 to 17 years from the Colombian ADAD cohort and showed that mutation-carrying children were distinguished from non-carriers by plasma biomarker findings consistent with Aβ1-42 overproduction, as well as by increased functional connectivity of the posterior cingulate cortex with medial temporal lobe regions (Quiroz et al 2015). More recently, we used the WISC-IV, a measure of general intellectual abilities to examine cognitive abilities in these children. We reported in 265 children with the E280A mutation and 1089 non-carriers that they did not differ on any of the WISC-IV indices. Surprisingly, male carriers performed slightly worse than female carriers on working memory (mean difference = −4.97; P = .001) (Fox-Fuller et al., 2021). Some of our ongoing work includes comprehensive examinations of social, educational and developmental histories along with functional brain networks, as markers of synaptic dysfunction in individuals with ADAD, as this is particularly relevant to understanding the impact of PSEN1 mutations on the developing brain and subsequent neurodegenerative changes seen later in life, without the confounds of aging and age-related comorbidities that often exist in late-onset sporadic AD.
Disclosures: Financial: Dr. Quiroz receives a consulting fee from Biogen. Non-Financial: Dr. Quiroz is a Hispanic Neuropsychological Society Member-At-Large and serves as the INS Teleneuropsychology Special Interest Group Chair

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