their cognitive status going into surgery. The neuroanatomy of the disease, age and developmental level, and cultural and language differences can all influence patients' performance during brain mapping and impact surgical decision making. The purpose of this session is to discuss the importance of taking a highly individualized approach to brain mapping, focusing on anatomical considerations and individual patient differences in task selection and data interpretation. We will cover language mapping in patients who speak more than one language. Practical information will be provided to help guide informed task selection through illustrative case presentations that highlight the need for individualized brain mapping.
Upon conclusion of this course, learners will be able to:
1. Discuss informed task selection based on cortical and subcortical functional neuroanatomy
2. Explain how functional maps change with normal development and factors that should be considered when interpreting results for presurgical planning
3. Assess differences between the bilingual and monolingual brain, factors that modulate the neuroanatomical representation of language in bilinguals and strategies in mapping multiple languages for surgical planning

Symposium 08: Neuropsychological Considerations for Alzheimer's Disease Clinical Trials

10:15 - 11:40am
Friday, 3rd February, 2023
Town & Country Ballroom B

Chair

Andrew Kiselica
University of Missouri, Columbia, USA

Discussant

Kevin Duff
Oregon Health Science Center, Portland, USA

Summary Abstract:

The 2011 National Institute on Aging and Alzheimer's Association (NIA-AA) criteria for the diagnosis of Alzheimer's disease (AD) focused on clinical signs and symptoms to make a diagnosis of probable or possible AD. Under these criteria, emphasis was placed on gathering objective evidence of cognitive decline, which gave neuropsychologists a central role as diagnosticians in AD clinical trials. The release of the 2018 NIA-AA research framework put greater emphasis on the use of biomarkers, especially measures of amyloid, tau, and neurodegeneration, to define AD. Once AD is defined based on these biomarkers, it is staged via clinical signs and symptoms. Thus, the role of neuropsychologists has shifted from being central to diagnosis to a possibly more ancillary role of staging the disease once it is determined to be present. The move away from clinical signs towards biomarkers only became more prominent with the recent, controversial Food and Drug Administration approval of Aducanumab as an AD treatment based on evidence of change in biomarkers without clear evidence of clinical benefit. In this landscape, the fit of neuropsychologists in AD clinical trial research has become less clear.
This symposium will address the role of neuropsychologists in modern AD clinical trial research. The presenters will highlight varied ways in which neuropsychologists can enrich and improve AD clinical trials. First, Dr. Dustin Hammers from Indiana University will discuss how neuropsychological methods can help us to understand which participants do, and perhaps more importantly, do not get enrolled in clinical trials. Second, Dr. Mirella Diaz-Santos from the University of California Los Angeles will summarize her work to enroll Hispanic individuals in the Human Connectome Project, improving inclusivity. Third, Dr. Tamar Gollan from the University of California San Diego will summarize her work on novel behavioral markers of AD risk discovered from the study of Spanish-English bilingual patients. Fourth, Dr. Andrew Kiselica from the University of Missouri will highlight psychometric considerations in interpreting clinically meaningfully change in AD clinical trials using data from the National Alzheimer's Coordinating Center. Fifth, Dr. Samantha John from the University of Nevada at Las Vegas will discuss the influence of

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race/ethnicity on how clinically meaningful change is defined using data from a diverse cohort.
Dr. Kevin Duff will serve as discussant for this series of studies. He will highlight the important roles that neuropsychologists can play in improving AD clinical trial screening processes, expanding inclusion of diverse patients into trials, and enhancing interpretation of the clinical meaningfulness of trial results. He will also reflect on the future of neuropsychology's role in the AD clinical trial landscape and encourage audience questions and responses to the research presented.
Keyword 1: dementia - Alzheimer's disease
Keyword 2: cross-cultural issues
Keyword 3: psychometrics

1 Clinically Meaningful Change in Alzheimer's Disease Depends on Anchor Agreement and Disease Severity

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Objective: Measures of clinical significance are critical for meaningful interpretation of treatment outcome research on Alzheimer's disease. A common method of quantifying clinical significance is to calculate a minimal clinically important difference (MCID), which represents the smallest numerical change on an outcome measure that corresponds to an added benefit in a patient's life. Often the MCID is calculated based on an anchor response. Individuals who report a meaningful change serve as the "anchors", and the mean level of change for this group serves as the MCID. In research on Alzheimer's disease, there are several possible raters to provide anchors, including patients, family observers, and clinicians, who may or may not agree on whether there has been a meaningful change in outcome. The goal of this study was to examine the extent to which agreement among anchors impacts MCID estimation and whether this relationship is moderated by cognitive severity status.
Participants and Methods: Analyses were completed on a longitudinal sample of 2,247 adults, age 50-103, from the Uniform Data Set 3.0. Outcome measures included the Clinical Dementia Rating – Sum of Boxes (CDR-SB), Functional Activities Questionnaire, and Montreal Cognitive Assessment.
Results: For all of the outcomes, the MCID estimate was significantly higher when meaningful decline was endorsed by all of the raters compared to situations in which there was disagreement among the raters. For example, on the CDR-SB, agreement significantly impacted MCID estimates ($F(1, 2241)=168.80$, $p<0.001$; partial $h2 = 0.07$), such that the agreement group had greater CDR-SB change score (mean=1.29, SD1.98) than the no agreement group (mean=0.37, SD=1.38; Tukey HSD: $p<0.001$). In addition, the MCID estimate increased with increasing levels of cognitive impairment. For instance, on the CDR-SB, MCID estimates were significantly different across the severity groups ($F(2, 2241)=138.27$, $p<0.001$; partial $h2 = 0.11$), such that increase in CDR-SB was highest for the mild dementia group (mean=1.84, SD=2.42), moderate in the MCI group (mean=0.71, SD=1.30), and lowest for the cognitively normal group (mean=0.07, SD=0.55; Tukey HSD; all p's < 0.001). Finally, cognitive severity status moderated the influence of agreement among raters on MCID estimation for the CDR-SB and FAQ, such that rater agreement demonstrated less influence on the MCID as disease severity increased. For example, on the CDR-SB, post-hoc tests revealed that there was a significant difference across agreement groups in the cognitively normal ($p<0.001$; Cohen's $d = 0.96$) and MCI groups ($p<0.001$; Cohen's $d = 0.49$), but agreement did not impact MCID estimates for the mild dementia group ($p=0.065$).
Conclusions: MCID estimates based on one anchor may underestimate meaningful change, and researchers should consider the viewpoints of multiple raters in constructing MCIDs. Consideration of agreement appears most important in the early stages of cognitive decline, which are the focus of most modern clinical trials.

Categories: Dementia (Alzheimer's Disease)
Keyword 1: dementia - Alzheimer's disease
Keyword 2: cross-cultural issues