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.

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2 Reading Aloud Elicits Connected Speech and Autocorrection: a Novel Marker of Alzheimer's Disease and Risk

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Objective: Spontaneous speech involves tight coordination of a constellation of cognitive mechanisms (including planning, lexical selection, grammatical encoding, internal & external monitoring). Recent years brought a flurry of interest in detailed analysis of spontaneous speech in search of markers of prodromal Alzheimer's disease. This work dates back to the nun studies by Snowdon et al (1996) and reveals promise for early detection through identification of subtle but significant changes in the nature of speech output years prior to diagnosis of dementia.
A major challenge for neuropsychology is to develop methods to harness the potential sensitivity of language to subtle cognitive changes when testing individuals in clinical settings. In this talk I will present two lines of research that illustrate how reading aloud can be used to engage the cognitive mechanisms of spontaneous speech production in a manner that provides an easily accessible measure of Alzheimer's disease/risk.
Participants and Methods: In the first study, Spanish-English bilinguals with mild-to-moderate Alzheimer's disease (n=20) and proficiency matched controls (n=29) read aloud mixed-language paragraphs with a small number of language-switched words, and we recorded the number of times they automatically translated switch words by accident (e.g., saying pero instead of but; effectively autocorrecting language switches to avoid producing switches overtly). In the second study, cognitively normal monolinguals at risk for AD based on CSF biomarkers (n=14) and controls (n=50) read aloud short paragraphs in which ten critical target words were replaced with autocorrect targets (e.g., The player who scored that final [paint] for the local team reported [him] experience). Participants were instructed to avoid autocorrecting (e.g., avoid saying point instead of paint or his instead of him), and we recorded the number of times they autocorrected by accident.
Results: Bilinguals with AD translated switch words more often than controls, and ROC curves revealed good-to-excellent discrimination between patients and controls based solely on the number of errors produced during reading aloud (AUC or Area Under the Curve values ranged from .71-.92). In the second study, cognitively normal monolinguals with high CSF Tau/Aβ42 (i.e., an AD-like biomarker profile) produced more autocorrect errors (e.g., saying point instead of paint)than those below the biomarker threshold, and autocorrection errors showed potential for discriminating individuals with higher AD risk from controls (AUC=.76; 95%CI .62-.90).
Conclusions: Difficulty stopping automatic translation of language switch words and autocorrection during reading aloud reveals promise as a diagnostic tool. Reading aloud elicits rapid production of hundreds of words while maintaining tight experimental control over the content of speech and harnessing the power and complexity of language to enable detection of very subtle cognitive changes through simple analysis of critical targets. I will discuss the theoretical implications of this work for understanding how bilinguals choose a single language for production, the nature of cognitive impairments in early AD and areas of need for further research to maximize the potential utility of reading aloud for detection of cognitive impairment.

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3 Ethnoracial Differences in Anchor Agreement and MCID Estimation in Alzheimer's Disease

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