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14. ABSTRACT As the Alzheimer's disease field moves to studies and intervention trials in the preclinical phase and early prodromal period, it will be necessary to measure everyday function in an increasingly more sensitive and sophisticated way to capture more subtle impairments. One approach to increasing sensitivity in functional measures is to use performance based instruments, such as the UCSD Performance-based Skills Assessment (UPSA), in Mild Cognitive Impairment (MCI) or mild Alzheimer's disease (AD) research. In this test patients are observed and their response scored as they actually perform proxies for real world tasks and it contrasts with more typical informant based measures. In a preliminary study we compared patients with MCI, patients with mild AD, and healthy age matched controls on the UPSA. We found that patients with MCI had compromises in everyday functional competence and that the UPSA was strikingly sensitive to these (Goldberg et al, 2010). <i>However, that study was not longitudinal.</i> Therefore, it is important that we obtain data on the longitudinal characteristics of the UPSA in these populations, including psychometric characteristics, size of decline, etc. To date, we have enrolled 23 subjects in the study to date. Preliminary results demonstrate: 1. high test-retest reliability that is greater than .80; 2. large Effect Size differences between healthy controls and a mixed MCI/AD group, greater than 2.2; and 3. excellent validity indicators for our short form. This set of results is in keeping with our predictions					
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Introduction

As the Alzheimer's disease field moves to studies and intervention trials, it will be necessary to measure everyday function in an increasingly more sensitive and sophisticated way to capture more subtle impairments. One approach to increasing sensitivity in functional measures is to use performance based instruments, such as the UCSD Performance-based Skills Assessment (UPSA), in Mild Cognitive Impairment (MCI) or mild Alzheimer's disease (AD) research. In this test patients are observed and their response scored as they actually perform proxies for real world tasks (such as determining which bus route to take, writing a check, planning a trip to the beach, and recalling an appointment's time and place). In a preliminary study we compared patients with MCI, patients with mild AD who by diagnosis have functional impairments, and healthy age matched controls on the UPSA, as well as measures of cognition (e.g., episodic memory, semantic memory, executive function, speed). We found that patients with MCI had compromises in everyday functional competence and that the UPSA was strikingly sensitive to these (Goldberg et al, 2010). *However, that study was not longitudinal.* Therefore, it is important that we obtain data on the longitudinal characteristics of the UPSA in these populations, including the severity of decline in this measure over time, the relationship of decline to cognitive changes in order to determine the validity of the UPSA, and its technical psychometric characteristics (e.g., test-retest reliability). We will longitudinally assess magnitude of decline in the UPSA individuals with MCI and mild AD assessed at baseline, 6 weeks, and 12 months. We will compare and contrast decline in the UPSA with a commonly used measure of function administered to informants (the FAQ) in MCI and AD using Effect Sizes (ES) and mixed model repeated measures. We will determine the cognitive measures that best predict decline in the UPSA. We predict that the UPSA will decline over time in the MCI and AD groups with and demonstrate strong relationships to cognitive decline

Key Research Accomplishments

- In this post start-up period we submitted all necessary protocol related documents to the ORP via Dr. Jeff Stephenson. Our protocol was reviewed and we received notification of its approval on September 21 2012.
- Recruitment of subjects for baseline evaluation and longitudinal follow up. To date 23 subjects have been enrolled (see below).
- Implementation of testing procedures and screening procedures. Entry of data into our database.
- We have hired all necessary personnel, including a psychometrician and a post doctoral fellow (Dr. Jesus Gomar). All staff have been appropriately trained.

Body

Mild Cognitive Impairment (MCI), a relatively newly defined diagnostic entity, is usually considered to be a possible transitional stage between CNS health and Alzheimer's disease (AD); it is thought to be an important locus for intervention, since both cognitive impairment and neuropathology are relatively circumscribed and thus may be more easily modified or arrested. As the field moves to studies and intervention trials, it will be necessary to measure function in an increasingly more sensitive and sophisticated way to capture more subtle impairments and to appreciate psychometric properties that may improve such sensitivity, including lack of ceiling effects or informant mediated biases. In individuals with amnesic MCI, the most widely used criteria (proposed by Petersen) require that functional ability be preserved, yet memory impairment must be at least 1.5 SD below the mean of a control group. Since cognitive impairment has been an important predictor of functional outcome in a wide variety of neuropsychiatric disorders, including traumatic brain injury, epilepsy, schizophrenia, stroke, and AD, there appears to be a paradox. One explanation for this discrepancy might be that the measures commonly used to rate function were designed to assess disability in various stages of AD and so weighted to very simple Activities of Daily Living (ADL) skills, which can be intact in MCI. Thus, it may be the case that if more sensitive measures were used, function would indeed be found to be compromised. An approach to increasing sensitivity in functional measures is to use performance based instruments, such as the UCSD Performance-based Skills Assessment (UPSA), not hitherto applied in MCI or AD research. In this test

patients are observed and their response scored as they actually perform proxies for real world tasks (e.g., such as determining which bus route to take, writing a check, planning a trip to the beach, and recalling an appointment's time and place). In a preliminary study, we compared patients with MCI, patients with mild AD who by diagnosis have functional impairments, and healthy age matched controls on the UPSA, as well as measures of cognition (e.g., episodic memory, semantic memory, executive function, speed). Consistent with our hypothesis, we found that patients with MCI had compromises in everyday functional competence and that the UPSA was strikingly sensitive to these (Goldberg et al, 2010). *However, that study was not longitudinal.* Therefore, it is key that we obtain data on the longitudinal characteristics of the UPSA in these populations, including test-retest reliability and magnitude of decline, and the relationship of decline to cognitive changes in order to determine the validity of the UPSA.

Aim 1. We will longitudinally assess magnitude of decline in the UPSA individuals with MCI and mild AD assessed at baseline, 6 weeks, and 12 months. We will compare and contrast decline in the UPSA with FAQ in MCI and AD using Effect Sizes (ES) and mixed model repeated measures. We will determine the cognitive measures that best predict decline in the UPSA using regression models. In an exploratory analysis we will assess reliable decline at the level of individual cases using RCI statistics. We predict that the UPSA will decline over time in the MCI and AD groups with ESs in the medium to large range and demonstrate robust relationships to cognitive decline.

Aim 2. We will determine the psychometric properties of the UPSA, including test-retest reliability (baseline-6 weeks) in MCI, as well as the HC and AD groups. Critically, we will examine the possibility of ceiling effects in the MCI and HC groups for various measures, and possible floor effects in the AD group. We will also assess kurtosis, skewness, and coefficient of variation. We predict that the UPSA will exhibit excellent psychometric properties.

Aim 3. We will assess the utility of a short form of the UPSA consisting of the Comprehension/Planning and Communication subtests that was developed by us in a prior study in each of the above contexts.

Subject Recruitment

Recruitment began September 21, 2012 with North Shore-LIJ IRB and ORP approval. In the approximately 6 months since, we have recruited 23 subjects. These included 11 healthy controls, 6 MCI subjects, and 6 AD subjects. Twelve of these individuals have received 6 week follow-ups. (Over the next month 8 more subjects are scheduled to receive their follow up.)

Preliminary Data Analyses

We first examined effect size differences at baseline between healthy controls (HCs) and a mixed group of patients with MCI or AD. Effect sizes for both the full UPSA and the short-form UPSA were large and in keeping with our predictions. The ES differences are shown in Figure 1.

In keeping with our Aims, we also examined test- retest reliability. We found that baseline-time 2 reliabilities were high for both the full UPSA (.91) and the UPSA short form (.89). A scatter plot for the full UPSA is shown in Figure 2.

In the healthy control group skewness was .16; kurtosis was .14; and CV was 3.41. In the mixed MCI/AD group skewness was -.33; kurtosis was -1.27; and CV was 29.8.

Reportable Outcomes

We are beginning to prepare our initial data for use in an abstract for presentation at a scientific meeting (e.g., ACNP, AAIC).

Conclusion

Our recruitment of subjects who are being assessed on the UPSA (and cognitive measures) is proceeding well. We have enrolled both healthy controls and MCI and AD subjects. Preliminary data are encouraging and in keeping with our main hypothesis. First we have found that test-retest reliability of the UPSA is high ($>.80$). Second we have found that UPSA performance in a mixed group of MCI and AD subjects is impaired when contrasted to healthy subjects, with an effect size difference of approximately 2.2.

References

Goldberg TE, Koppel J, Keehlisen L, Christen E, Werringloer U, Conejero-Goldberg C, Gordon ML, Davies P. Performance-based measures of everyday function in Mild Cognitive Impairment. *Am J Psychiatry*. 2010 Jul;167(7):845-53.

Gomar J, Bobes T, Davies P, Goldberg TE. Development of an UPSA short form for use in Mild Cognitive Impairment and Alzheimer's disease. *Am J Geriatric Psychiatry*. 2011 Nov;19(11):915-22

Supporting Data

Figure 1

UPSA and UPSA Short Effect Sizes
(Cohen's d) for HC v. MCI/AD Contrasts

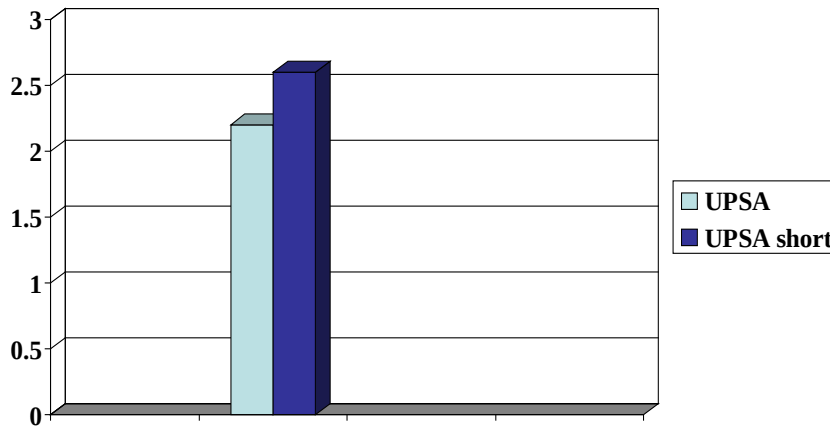


Figure 2

Test-Retest Reliability of UPSA

