PRE-PROPOSAL TEMPLATE – FALL 2017

Principal Investigator: Samantha Holden, MD
Institution/Company: University of Colorado Denver
Project Title: Can Baseline Functional Abilities Predict Future Cognitive Decline in Parkinson Disease?

Background and Preliminary Data:

We propose a clinical longitudinal study of functional ability related to cognition, as measured by a performance-based assessment, and its relationship to future cognitive decline in Parkinson's disease (PD). Our recently completed validation study of the UCSD Performance-Based Skills Assessment (UPSA) in PD, funded by the Michael J. Fox Foundation, has demonstrated that UPSA scores correlate strongly with measures of global cognition (DRS-2, r=0.62, p<0.0001*)*.[1] This supports the hypothesis that the UPSA is measuring functional impairment related to cognition, as opposed to being related to motor symptoms. The UPSA also demonstrates strong internal consistency (Cronbach's α=0.82) and retest reliability (r=0.89). The UPSA discriminates demented from non-demented with a sensitivity of 80% and specificity of 89% (AUC=0.91). As this study has progressed, we have noted that participants who are borderline cognitively impaired, but not meeting strict diagnostic criteria by neuropsychological testing, are performing worse on the UPSA than those who are clearly cognitively normal. Also, within the normal cognition subset, participants with subjective cognitive complaints (n=23) are performing worse on the UPSA than those without complaints (n=16), with a mean difference in UPSA score of 5.2 points (p=0.03), despite similar neuropsychological testing scores. This observation has raised the possibility that assessments of functional ability related to cognition may be picking up subtle cognitive impairments not detected by traditional neuropsychological testing alone. If true, testing of functional abilities related to cognition could detect impending cognitive decline earlier than pure cognitive measures, allowing for earlier intervention. Though activities of daily living (ADLs) have generally been considered intact in non-demented patients, impairments in cognitively demanding instrumental ADLs (iADLs) have been found in individuals with normal cognition and mild cognitive impairment (MCI) in the general population,[2] as well as in PD.[3,4] Several large longitudinal studies of aging in a general population have found increased risk of future dementia with baseline iADL impairment, present up to 10 years prior to diagnosis, as well as a risk of more rapid deterioration over time.[5,6] However, the literature on longitudinal changes in iADL performance is limited and has not been studied in PD. The proposed study would be the first longitudinal study of functional ability related to cognition in PD and seeks to determine if an increased risk of future cognitive impairment exists when baseline iADL impairment, as identified by the UPSA, is present.

Study Design:

The overall objective of this application is to delineate risk factors of future cognitive decline in PD through a prospective study, continuing to follow our well-defined cohort of non-demented PD participants from our UPSA validation study. These cognitively classified participants will repeat our thorough cognitive and functional testing battery annually, over an additional three-year period, timed from their initial UPSA validation study visit. Our earliest participants have already started returning for their first annual follow-up visits at this time, providing a significant starting point for the proposed study. My central hypothesis is that baseline functional abilities related to cognition, as measured by the UPSA, are more predictive of future cognitive and functional decline in PD than baseline pure cognitive abilities, as measured by neuropsychological test scores. My long-term goal is to clearly define the earliest cognitive changes in PD and ensure that patient priorities and experiences are integrated into the interpretation of cognitive outcome measures used in both clinical and research settings. The rationale for the proposed research is that regular assessment of functional abilities related to cognition could not only identify those at risk for future dementia earlier than neuropsychological testing alone, but also allow for the development of focused interventions for identified functional impairments, ensuring personally meaningful and practical treatment benefits for people with PD.

Aim 1: Determine the predictive ability of a performance-based cognitive functional assessment for cognitive decline in Parkinson's disease

Hypothesis: Lower baseline scores on the UPSA will be associated with decline in cognitive and functional abilities over time, even when controlling for baseline global cognitive and motor abilities.
Approach: 80 non-demented PD participants, who have undergone thorough baseline cognitive and functional evaluations in our validation study, will repeat these assessments annually, following for decline over time. An average of the z-scores of each of the 10 neuropsychological tests in out neuropsychological battery will be calculated to create a composite cognitive score. Cognitive decline will be defined as a reduction in this composite cognitive score over time, with a change of -1.0 SD in one year defined as significant cognitive decline. We will model cognitive decline as a continuous variable with UPSA score as a predictor, controlling for DRS-2 and UPDRS Part III scores.

Aim 2: Determine which cognitive functional abilities are most vulnerable to decline over time in Parkinson's disease and evaluate their impact on patient-reported outcomes of functionality and quality of life

Hypothesis: Particular cognitive functional abilities, such as financial skills, will decline more rapidly in PD, and will correlate with participants' subjective report of disability and overall wellbeing, allowing for future development of targeted therapies to improve functionality and quality of life.
Approach: Utilizing a mixed-methods approach, individual subdomains of the UPSA will be assessed for rates of decline and correlated with participants' self-reports of cognitive and functional impairment. Mixed linear regression models will be used to determine which UPSA subdomains demonstrate a significant decline from baseline and their rate of decline. Identified vulnerable subdomains will be correlated with patient reports of disability and quality of life, using both questionnaire-based assessments (PDAQ, PD-CFRS, PDQ-39) and semi-structured interviews. Interviews will be conducted with a subset of 20 participants to elicit their perspectives on cognitive functional ability: which of the UPSA subdomain tasks were most relevant to their daily lives; which did they think they had the most trouble with from a cognitive standpoint; and what kind of therapies would help them perform these tasks better.

Project Timeline:

Prior to Funding Period:	**Month 1-6** Oct 2017-Mar 2018	**Month 6-12** Apr 2018-Sep 2018	**Month 12-18** Oct 2018-Mar 2019	**Month 18-24** Apr 2019-Sep 2019
- Continue Year 1 visits for earliest UPSA validation study participants	- Continue Year 1 visits - Data analysis for Baseline to Year 1 - Semi-structured interviews with 10 participants	- Start Year 2 visits - Abstract preparation for Baseline to Year 1 data - Semi-structured interviews with another 10 participants	- Continue Year 2 visits - Data analysis for Baseline to Year 2 - Data analysis for qualitative data (Aim 2) - Start manuscript preparation for Baseline to Year 2 data	- Start Year 3 visits - Submit manuscript for Baseline to Year 2 data - Submit manuscript for qualitative data (Aim 2) - Start Baseline to Year 3 analysis

Preparatory Work:

An amendment to the IRB protocol for the UPSA validation study has already been approved, allowing for re-evaluation of participants at yearly intervals. Five participants have already returned for their Year 1 return visits and completed the testing protocol. Another six participants are already scheduled for their Year 1 visits over the next several weeks. 100% of contacted participants have agreed to return so far. Regardless, an additional 10 participants will be recruited for their initial visits on a yearly basis to account for attrition.

Career Development:

An NINDS K23 mentored patient-oriented research career development award is being prepared, proposing extension of this longitudinal study to a total of up to 7 years from the first baseline visits (January 2016). This will allow for adequate statistical power to capture conversion to dementia, rather than cognitive decline, assuming an annual conversion rate of 10-15%. It will also provide a rich database of longitudinal cognitive and functional data, both quantitative and qualitative, in PD. An additional aim of the K23 proposal is to define the minimal clinically important difference (MCID) for the UPSA, using an anchor-based method. For this aim, care partners will be formally asked to participate in assessments. Participants and their partners will complete Clinical Global Impression of Change (CGIC) scales and provide subjective feedback through semi-structured interviews. Both the UPSA and more traditional neuropsychological test scores will be compared to CGIC scores, in order to determine which assessment method better captures patient and partner experience. Defining psychometric properties such as the MCID will aid in the design and interpretation of future treatment trials for cognitive impairment in PD.

Budget Justification:

Personnel:

Samantha Holden, MD (Principal Investigator): 10% effort, Months 1-24

Funds requested in the amount of $19,840 per year in salary support plus fringe benefits for Dr. Holden is to support 10% of her total time commitment to research-related activities outlined in this proposal. Dr. Holden will personally oversee all aspects of the project, including design, execution, data analysis and manuscript preparation. She will recruit subjects from the movement disorders clinic at University of Colorado Hospital, and perform motor examinations, functional interviews, and mood assessments on participants.

Luis Medina, PhD (Neuropsychologist): 10% effort, Months 1-24

Funds requested in the amount of $6,400 per year in salary support plus fringe benefits for Dr. Medina. Dr. Medina will assist in the scoring and performing normalization and interpretation of neuropsychological testing results, as well as lead consensus conferences for cognitive classification. He will be available for questions regarding neuropsychological testing administration. He will contribute to the interpretation of data and preparation of abstracts and manuscripts.

Stefan Sillau, PhD, (Biostatistician): 5% effort, Months 1-24

Funds requested in the amount of $4,800 per year in salary support plus fringe benefits for Dr. Sillau, who will provide statistical support for this project, as well as contribute to manuscript preparation.

Abby Simpson, BS (Professional Research Assistant): 50% effort, Months 1-24

Funds requested in the amount of $26,880 per year in salary support plus fringe benefits for Ms. Simpson to support her contributions to this project. Ms. Simpson has participated in the initial validation study of the UPSA in PD and will be able to translate her knowledge and skills directly to the proposed longitudinal project. She is trained in administration of the entire testing battery, as well as in its scoring. She will also assist in the recruitment, scheduling and coordination of study visits.

Other Direct Costs:

Supplies: Formal neuropsychological testing will be performed by our professional research assistant, Abby Simpson, BS, with her budgeted salary covering the cost of these responsibilities. Requested costs for neuropsychological testing reflect only that for testing materials ($50 per participant, 80 participants each year, $8000 total). To conduct semi-structured interviews, Dr. Holden and Ms. Simpson will use a recording device and microphone ($150).

Participant Reimbursement: We will offer reimbursement to participants for their time, as the testing will take up to four hours to complete, as well as travel, as many of our clinic patients live outside of the immediate Denver area ($50 each participant, 80 participants/year, total $8,000). Parking passes for the University campus will also be provided to participants for the day of their visit ($5 each, 80 participants/year, total $800)

References

1. Holden SK, Medina LD, Hoyt B, et al. Validation of a performance-based assessment of functional ability related to cognition in Parkinson's disease [abstract]. *Mov Disord.* 2017;32(2).
2. Reppermund S, Brodaty H, Crawford JD, et al. Impairment in instrumental activities of daily living with high cognitive demand is an early marker of mild cognitive impairment: the Sydney memory and ageing study. *Psychological medicine.* 2013;43(11):2437-2445.
3. Rosenthal E, Brennan L, Xie S, et al. Association between cognition and function in patients with Parkinson disease with and without dementia. *Mov Disord.* 2010;25(9):1170-1176.
4. Pirogovsky E, Schiehser DM, Obtera KM, et al. Instrumental activities of daily living are impaired in Parkinson's disease patients with mild cognitive impairment. *Neuropsychology.* 2014;28(2):229-237.
5. Peres K, Helmer C, Amieva H, et al. Natural history of decline in instrumental activities of daily living performance over the 10 years preceding the clinical diagnosis of dementia: a prospective population-based study. *Journal of the American Geriatrics Society.* 2008;56(1):37-44.
6. Fauth EB, Schwartz S, Tschanz JT, Ostbye T, Corcoran C, Norton MC. Baseline disability in activities of daily living predicts dementia risk even after controlling for baseline global cognitive ability and depressive symptoms. *International journal of geriatric psychiatry.* 2013;28(6):597-606.