PSG
PARKINSON STUDY GROUP

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WORKING GROUP ACTIVITY SUMMARY
2018-2019

COGNITIVE / PSYCHIATRIC (BEHAVIOR) WORKING GROUP

Leadership: Greg Pontone, PhD, Chair; Kelly Mills, MD and Roseanne Dobkin, PhD, Co-Chairs

Parkinson's psychosis scale (Greg Pontone)
  -reviewed common phenomenology within psychosis to establish consensus on component sxs
  -reviewed/compared: NINDS PDP criteria vs. DSM 5 schizophrenia criteria
  -challenges to PD psychosis scale
      -content validity – extent to which a measure represents all facets of construct
      -misattribution and phenocopies
      -heterogeneity of psychosis in PD
      -scale thresholds for diagnosis, severity, treatment (e.g. insight)
  -reviewed psychosis subtypes (Factor et al. Eur J Neurol) 2017
  -approach to scale development: revising SAPS-PD vs. *de novo*
  -Melissa Nirenberg – update on eSAPS-PD
      -description of development from SAPS-PD
      -examples of improvements over prior
  -next steps
      -email Greg about collaboration on moving forward
      -inquire with members of MDS working group regarding collaboration on any efforts
  -deliverables
      -consensus / opinion paper on need to establish new scale
      -interim phone conference to discuss working group on psychosis scale

Telemedicine and psychotherapy (Roseanne Dobkin)
  -reviewed goal of spurring collaboration on dissemination of telehealth
  -reviewed prior trials showing efficacy of CBT in PD depression
  -Next steps
      -how to scale this?
      -collaboration for a larger protocol?
      -needs larger multi-center feasibility study (efficacy already establish)
          -outside VA network?

Cognitive dysfunction in PD (Daniel Martinez-Ramirez)
  -background on PD MCI -> PDD and risk factors for PDD
  -analysis of predictors of cognitive impairment across 5 centers

-cross-sectional analysis showed possible association of MAOB-I with reduced odds of cognitive
     impairment
-Next steps
        -larger observational study of association between MAOB-I and cognition
        -implications for treatment trial?

BIOMARKERS WORKING GROUP

Leadership: Roy Alcalay, MD, Chair; Liana Rosenthal, MD and Paul Tuite, MD, Co-Chairs

We had a busy working group meeting. Roughly 30 members participated in the meeting. We heard 3 presentations on biomarkers research being performed by PSG members.

1. Dr. Liana Rosenthal spoke about poly-ADP-ribose (PAR) as a possible biomarker of PD diagnosis and progression. She presented some published data showing that CSF PAR levels separated out individuals with PD and controls in the Johns Hopkins Parkinson's Disease Biomarker Program (PDBP) and Cleveland Clinic cohort. Dr. Rosenthal also reported on some preliminary data indicating that higher CSF PAR levels predicted higher MDS-UPDRS part III scores though were inversely related to cognitive status. Additional research is needed to validate CSF PAR levels as a PD biomarker.

2. Dr. Kathleen Poston presented a web-presentation. She discussed the fMRI scans performed as part of the PPMI investigation and her efforts to make the data more usable to other researchers. Others have noted specific connectivity changes that occur among individuals with PD and changes in this connectivity when in the on-medication state compared to the off medication state. Within PPMI, there have been a total of 342 resting state fMRI scans in 183 unique individuals. Dr. Poston's analysis determined that many of the scans were unusable due to head motion, with the number of unusable scans varying depending on the cutoff used for quality control. Moreover, scans were obtained in a mixture of de Novo, on meds and off meds. This pre-processed data will be made available for the entire dataset with category documentation.

3. Dr. Bodis-Wollner presented data on retinal imaging as a biomarker for PD. Using optical coherence tomography (OCT). a-syn stains cells in the retina of patients with PD. He proposes a symmetric change in fovea. Using mathematical models, they can distinguish between PD and controls (70%) using symmetry and breath measurements. This is consistent with PM data showing decreased retinal dopamine in PD cases

Action items and suggestions for the coming year:
1. Members requested to hear about the role of biomarkers in the PSG lead clinical trials, specifically, for inosine and isradipine.
2. Members requested that the WG meeting would not overlap with mentorship sessions, so they could attend both meetings.
3. We have not finished discussing plans for the coming year, and may schedule a follow up conference call for interested members.

MOTOR WORKING GROUP

Leadership: Tiago Mestre, MD, MSC, Chair, Zoltan Mari, MD, Co-Chair, Aristide Merola, MD, Junior Co-Chair

In the inaugural meeting of the newly formed Motor Working Group (WG), there was a brief welcoming followed by an introduction of the members of the WG attending the meeting.

1.   The new Motor Working group:

The chairs of the Motor Working Group presented this new PSG WG stemming from a survey conducted to the PSG members and the history of the Classic Motor WG.

The new Motor WG will have as main mission to foster development and use of health technology to characterize, measure and intervene on the motor phenotype in PD. The field of technology applied to PD is an expanding field that so far failed to deliver a widely accepted measure for the above purposes. The group felt that the PSG can offer an excellent environment to achieve this goal, as a network of excellence PD centers. Following the tradition of the precedent Classic Motor WG, the group is also open to develop novel, promising interventions that can improve motor symptoms of PD at its different stages. The two roles may overlap as technologies may be used to help tracking a therapeutic response, for example.

2.   Planning of activities for the Motor Working Group:

We discussed what could be the role of the group in this context. A rich discussion took place in which various avenues were considered: 1) the conduction of clinical studies involving technology development within PSG, 2) contribute to the incorporation of technology-based outcomes into 'classical' pharmacological clinical trials, 3) conduct a survey on view, opinions and needs for use of technology across the PSG membership to inform a sustained and successful activity planning by the WG, 4) establish regular calls for the Motor WG, 5) contact other chairs of PSG WGs to establish strategic collaborations.

3.   Individual Research Projects:

This part of the meeting was dedicated to the presentation of projects that focused on technology development for the motor phenotype in PD conducted or planned by PSG members at their own institutions to inform WG members, and to lead a discussion on how future studies could be developed or promoted by the WG.

Jamie Adams represented the group of the University of Rochester led by Ray Dorsey on the project of Quantification of motor symptoms in Parkinson via smartphones and wearables. Ray Dorsey's group is currently partnering with PSG in the study WATCH-PD.

Aristide Merola from the University of Cincinnati presented a proposal for a study on motor phenotyping entitled: "Very Slow Progressive (Benign) versus Rapidly Progressive (Malignant) Parkinson disease: Multicenter clinical epidemiology and genetic study. The idea of creating a survey as a feasibility to identify the extreme PD motor phenotypes across PSG sites was considered.

Raja Mehanna from the University of Texas Health Care Science Center presented his study on the use of the PersonalKineticGraph wearable device to evaluate treating uncontrolled patients with Parkinson's Disease.

**4.	Action items for year 2019-2020:**

At the meeting's closure, the group established immediate actions:
1. Draft a needs and views survey on technology for the wide PSG membership.
2. Establish contact with other PSG WG chairs (Biomarkers, Functional Surgery).
3. Request PSG Annual Meeting organizers to schedule WG meetings so that chairs of the various WG with shared research interests can co-attend each WG meeting.
4. Consider the feasibility of regular WG calls to boost participation in the WG activities and attract participation among PSG members.
5. Inform PSG leadership on the motor WG meeting to obtain guidance on how to establish contact with technology developers interested in partnering the PSG in developing outcomes to characterize motor phenotype in PD.

ATYPICAL PARKINSONIAN DISORDERS WORKING GROUP

Leadership: Anne-Marie Wills, Co-Chair; Irene Litvan Co-Chair

1) **Introduction to the Atypical Parkinsonian Disorders Working Group** (Anne-Marie Wills, MGH): presentation of the survey data of participating sites, including numbers of PSP patients and numbers of clinical trials at each site. Several sites with large PSP and MSA populations are not participating currently in any trials.

2) **State of research in PSP, recent activities of CurePSP** (Larry Golbe, RWJMS and CurePSP): Dr. Golbe discussed the goals and research interests of CurePSP. This led to discussion of possible collaborative research topics for the working group including: 1) starting a RedCap database for researchers across our sites to be able to enter their clinic patients for observational studies; 2) Survey sites on the frequency of sleep disorders in PSP (OSA in particular) and whether this is a premorbid sign; 3) clinical trials of symptomatic treatments, such as treatment of dizziness in PSP. We plan to discuss these and other possible research topics in a phone conference follow-up call.

3) **Postural Instability and TMS in PSP** (Marian Dale, MUSC): in a pilot study of TMS to the cerebellum and frontal lobe of PSP patients for balance and postural instability, Dr. Dale found a marked improvement in the bradyphasia/bradyphrenia and dysmetric/scanning speech of 1 patient and a modest improvement in the second. She requests interest from other WG sites to expand this study. Please reach out to Dr. Dale at dalem@musc.edu if you have TMS capabilities and are interested in participating. We will discuss this study at the next phone conference call.

GENETICS AND ENVIRONMENTAL RISK FACTORS IN PD WORKING GROUP

Leadership: Xiang Gao, Chair; Anne-Marie Wills, Co-chair

1) Results from the PD Twin Studies (Carlie Tanner, UCSF): Dr. Tanner presented the 20 year update from the National Academy of Sciences Twin Registry (just published). Concordance rates were 0.67 in monozygotic vs 0.20 in dizygotic twins with age of onset <50, but only 0.14 in monozygotic vs 0.1 in dizygotic twins with onset >50. The somewhat elevated dizygotic concordance rate leads Dr. Tanner to hypothesize that there is a shared environmental risk as well.
2) Presentation of the Parkinson's Foundation Genetics Initiative (Jim Beck, Parkinson's Foundation): Dr. Beck talked about the new PD GENEration initiative to genotype several thousand PD patients at PF and PSG sites. PD GENEration will genotype GBA, LRRK2, SNCA, VPS35, PRKN, PINK 1, PARK7 (results returned) as well as perform exome sequencing (results not returned). Pilot study is about to start.
3) Genetic determinants of Uric Acid levels (Alberto Ascherio, Harvard School of Public Health): Dr.

Ascherio spoke more generally about bias in geneXenvironment studies, and about mendelian randomization. He discussed the lack of an association between the genetic variants which determine uric acid levels and Parkinson's disease.

NON-MOTOR FEATURES OF PD WORKING GROUP

Leadership: Pinky Agarwal, Chair; Leslie Cloud and David Shprecher, Co-Chairs

In attendance: Pinky Agarwal, David Shprecher, Leslie Cloud, Aleks Videnovic, Cyndy McRae, Nati Stover, Danny Bega, Richard Doty, Sana Aslam, Jamie Hamilton, Thyagarajan Subramanian, & David Song.

1. Cyndy McRae proposed that the group data mine the Fetal Transplant Data from the Columbia-Colorado Study. There are two data mining projects linked to the Columbia-Colorado fetal transplant study conducted between 1995 and 1999 that are of some interest to neurologists today. These projects are: 1) Exploration of very long-term data of participants from 1995 to 2015 that might inform selection of future candidates for stem cell transplants; and 2) Investigation of expectancies and the placebo effect based on the one-year period of the double-blind. The following data sets are available: Demographic, Neurological, PET, Motor Physiology, Neuropsychological, Personality, Psychosocial and Quality of Life, Interview, and Care Partner.

Action item: The group requested that Cyndy circulate more information re: exactly what variables are contained within the available datasets so that the group could better determine the potential utility and relevance to the working group.

2. Leslie Cloud discussed her current multiple study of RQ10 for gastroparesis and constipation in PD (funded by MJFF). Enrollment anticipated ending this summer. If trial results are positive, a multicenter phase II trial will likely follow, which could be executed through the NMS working group. She also discussed the possibility of a multi-center validation study of a GI symptoms scale for which she has done the preliminary validation work.

Action item: Leslie will update the group when RQ10 trial results are available and will send additional emails later this year re: the GI scale.

3. David Shprecher discussed the data mining opportunities in the AZ Brain & Body Donation Program. NMS data included in the dataset: ESS, SCOPA-AUT, Mayo Sleep, UPSIT. More information is available at: https://www.brainandbodydonationregistration.org/.

4. Pinky Agarwal discussed some of the lesser-known autonomic in PD such as rhinorrhea and sweating. She is planning a project to estimate the prevalence of rhinorrhea in PD. The group discussed other existing datasets that may be available in order to estimate the prevalence of these symptoms. The group also decided that a position paper or consensus guidelines on the management of these rare autonomic symptoms would be an excellent group project for this year.

Action item: Pinky and Leslie will spearhead the consensus guideline effort with a goal of publishing the manuscript before next year's meeting.

5. The group also discussed a potential collaborative project related to levodopa intolerance. This topic was discussed more extensively last year when the group had a lengthy talk about the EDS that is a common central side effect of levodopa. Due to time limitations, the group did not have time to further develop plans for this topic at this year's meeting, but everyone agreed it is a topic of interest to the group for future work.

FUNCTIONAL NEUROSURGICAL FEATURES OF PD WORKING GROUP

Leadership: Jason Schwalb, Chair; Joohi Jimenez-Shahed and Mustafa Siddiqui, Co-Chairs

Ongoing projects:
1. RAD-PD (Registry for the Advancement of DBS in Parkinson's Disease): This project launched in October 2018 and the first patient was enrolled in March 2019. We currently have 9 sites activated with one slot remaining for Year 1 activation. Sites offered Year 2 activation are obtaining relevant materials to facilitate activation at the beginning of Year 2 (October 2019) for a competitive site activation process. The Scientific Review Committee, Publications Committee, Data Use and Access Committee and Safety Committee have all been populated. The first Quality Improvement Network call was held in July 2019. We will hold our first Neurosurgery engagement meeting at the Congress of Neurologic Surgeons Annual Meeting, also in October 2019 and will benchmark our first round of baseline data at that time, which will characterize the cohort of patients with PD being evaluated for DBS surgeries in a real-world setting. Multiple additional projects are anticipated to stem from this data repository.
2. DBS practices survey (Cabrera): this project has begun to collect initial data and was reviewed by the PSG Scientific Review Committee. A survey for distribution within the FNSWG is planned and will assess attitudes and perceptions about patient selection criteria, factors involved in considering DBS, attitudes towards the earlier use of DBS taking into account the expanded FDA approval.

Proposed projects:
1. Registry for lesional surgeries (PI: Siddiqui): a survey will be disseminated to WG members by Dr Siddiqui to determine the number of sites actively offering lesional surgeries and what kinds. Feasibility and further work will be determined by the results of the survey.
2. Other neurosurgical interventions for PD: Dr. Schwalb reviewed the status of this type of treatment for PD. The group discussed pursuing conversations with industry and international partners in order to determine if the FNSWG can partner on clinical trials or other investigations.

HEALTH/CARE OUTCOMES & DISPARITIES OF PD WORKING GROUP

 Leadership: Allison Willis, MD, MS, Chair, Jay Nutt, MD, Co-chair

Summary: The Health Care Outcomes and Disparities Working group had a productive year. Below we describe what we worked on in the 2018-2019 year.

- Collaboration with RAD-PD. We completed our primary research/writing activities on an outcomes study of DBS.   The national study was performed in collaboration with the Functional Neurosurgery Group, as they work to plan a PSG DBS registry (the RAD-PD project). The manuscript from this project is currently under review for publication in a scientific journal.

- Determinants of Research Participation- collaboration with Mentoring Group. In a true example of the impact and importance of the PSG for developing collaborative relationships among academic PD researchers that lead to high impact studies, the HCODWG has begun a study of determinants of research participation. IN this multi institution study, which samples adequate numbers of women and minorities to allow for race-sex comparisons, we will examine the extent to which individual and study design characteristics predict participation in each of three hypothetical PD studies -1) a phase 3a/3b study of a neuroprotective drug, 2) an observational study which collects imaging, blood, and CSF data over time and 3) an observational study which seeks to understand genetic risk factors for PD. This study will provide previous unmeasured data on potential barriers to trial

participants and will include adequate numbers of groups that are typically underrepresented in PD research (women, race/ethnic minorities).

- FIRE-UP PD- we had an outstanding presentation from the leaders of the FIRE-UP PD project. The HCODWG leadership will share survey instruments to FIREUP-PD sites, and include these data in future analyses.