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Reply to "Studying reproducibility of data-driven Parkinson's disease subtypes"

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We would like to thank van Rooden et al. for their interest in our work and thoughtful comments expressed in their letter entitled "*Studying reproducibility of data-driven Parkinson's disease subtypes*". van Rooden et al. make the case that the assessment of reproducibility may be unsuccessful due to the methodology followed in replication studies. Specifically, the use of different scales to measure the same construct, the use of distinct cluster analyses methods, and non-matching use of variables to identify and comprehensively characterize Parkinson's disease (PD) subtypes are listed as missing steps that may justify the lack of reproducibility we reported when attempting to replicate the original PD subtype study by van Rooden et al. [2] in our test cohort, the Longitudinal and Biomarker Study in Parkinson's Disease (LABS-PD) [1,3].

Establishing reproducibility of subtyping classification systems is complex. For example, van Rooden et al. state that their PD subtype classification system was well reproduced in the Spanish ELEP cohort. We inspected the heat maps that van Rooden et al. used to present the similarities between generated PD subtype systems in their two cohorts. Based on our experience in using similar heat maps to compare PD subtype solutions, it is our impression that if the data presented by van Rooden et al. were to be presented to our Delphi panel it would be found not to reproduce well. This observation shows how currently there is a lack of standards to define what is an acceptable level of reproducibility in a PD subtype classification system. We agree that the original and replication studies need to share some common features regarding study population, study design, and data analysis plan. Accordingly, in our study, we only included studies for which there was confidence about having access to similar data (even with different scales) in LABS-PD and the ability to reproduce to a large extent the methodology followed in each of the included studies. We would also argue, however, that reproducibility despite the presence of heterogeneity between cohorts is desirable. A PD subtype classification system found to be valid in these circumstances is likely more robust. The use of an alternate statistical method of generating clusters would be an example of this. We adopted the use of k-means for all our cluster analyses as this clustering method was used in the majority of the included studies, thus providing consistency in the replication of the different studies. In addition, k-means cluster analyses allowed us to pre-define the same number of clusters or PD subtypes reported in the initial studies, assuring that we would obtain the same number of clusters in LABS-PD. In the letter by van Rooden et al., it is pointed out that there is a need to discriminate between variables used to identify PD subtypes in cluster analyses and those used to further characterize the identified PD subtypes. We would like to clarify that, although it was not explicitly described in our published report, we did make this differentiation for all cluster analyses including the one conducted using the data reported by van Rooden et al. [2]. We used the same variables as were used in each paper or substitute variables/scales that measure similar constructs, and we also included additional descriptive variables in the tables we presented, though we did not make a distinction between them in the report.

The points raised by van Rooden et al. highlight the sensitivity of currently described PD subtypes to methodologic variations such as different PD populations, use of different scales that measure a given construct or slightly different data analyses algorithms. Such lack of reproducibility is a major impediment to the use of PD subtypes in clinical research.

Finally, we conceptualize a PD subtype ideally as a trait identifier that can be linked to an individual (or group of individuals) throughout their natural history of PD. The ability to characterize a PD subtype at different time points of disease progression is essential but should be ideally evaluated in a longitudinal study design. The inference of disease progression from a cross-sectional evaluation has a weak correlation with a more appropriate longitudinal assessment [4]. In our opinion, PD subtype instability is a significant limitation in many of the currently reported PD subtype classification systems and deserves to be assessed systematically in future studies.

We agree with van Rooden et al. that the critical appraisal of PD subtype studies is fundamental and thank them for providing further insight based on their own experience. International leaders in PD subtypes are coming together in a Task Force endorsed by the International Parkinson's disease and Movement Disorders Society to develop standards and guidelines to design, conduct and evaluate the results of PD subtypes studies. We believe that such work is fundamental to allow this exciting field to move forward and be applied in a

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meaningfully way to clinical research, namely in drug discovery programs.

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