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Considerations in the use of MDS research criteria for prodromal Parkinson's in RBD and population cohorts. (Response to letter by Mahlknecht et al)

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We welcome the remarks of Mahlknecht and colleagues regarding the practical application of the MDS research criteria for prodromal Parkinson's Disease. Before commenting further on our own use of these, it is worth revisiting how and why these criteria were established.

The MDS criteria were devised as a data-driven, objective method of estimating an individual's *absolute* probability of being in the prodromal phase of Parksinson's Disease (PD)[1] by incorporating a range of risk factors and prodromal markers. The weighting assigned to each variable is determined solely from the evidence of its predictive value. The criteria can be used with as much or as little data as one has available; the accuracy will improve the more variables are included. Importantly, the purpose is to estimate *whether* prodromal neurodegeneration is present, not *when* an individual will convert to PD.

In light of this, it is clear that in a cohort with polysomnographically proven RBD we would expect ≥75% of patients to fulfil these criteria, given the known long term risk in this population[2-4]. The high likelihood ratio (LR) attributed to RBD reflects this and, as acknowledged in our original discussion[5], the high probabilities seen in RBD cohorts are largely accounted for by the presence of RBD itself. We agree that many of the other risk factors have a negligible effect in comparison, but we do not consider this a weakness of the criteria *per se*, as it simply reflects the clinical reality.

It is clear that excluding the most important marker of prodromal PD will dramatically reduce the accuracy of an individual's probability estimate. Mahlknecht and colleagues nicely illustrate this in their letter as excluding RBD in their case series (20 patients) results in just 10% of individuals meeting criteria for probable prodromal PD. This is very similar to what we reported in our original paper, where amongst our cohort of 171 RBD patients only 12% (95% confidence interval 7.8-18.2%) met criteria for probable prodromal PD without the PSG-confirmed-RBD LR[5]. The mean probability in this case is 30.6% (standard deviation 30.6, median 17.0%). These are likely to be substantial underestimates of the long term risk, as attested by the study of Fereshtehnejad and colleagues, where the sensitivity of the MDS criteria fell to 14.6% when excluding RBD status[6].

We do not agree that this renders the inclusion of PSG futile, but it does highlight the importance of using models in their appropriate context. Within a cohort of patients with

PSG-proven RBD it makes no difference to between-patient stratification whether the LR for PSG is included or not, since all subjects test positive for this (one would simply need to adjust the probability threshold used). However, it is important to note that we do not know the extent to which RBD interacts with other risk factors or neurodegenerative markers. We therefore are more cautious in making any assumptions as to the effects of removing RBD from the equation when applying MDS criteria to RBD patients. This caveat applies to control-RBD comparisons as much as to RBD patient stratification. For example, we have shown that RBD is strongly associated with many non-motor features that are included in the MDS criteria, perhaps to an even greater extent than early PD overall[5]. This suggests that RBD patients may represent the prodromal phase of a subtype of Parkinsonism with higher MDS probability scores than prodromal patients in general, even without the PSG LR. It would therefore be wrong to assume that one could directly compare RBD patients with population cohorts using MDS criteria simply by removing the RBD weighting. It may be that the LRs taken from population-based studies are not generalizable for RBD cohorts and hence the derived probabilities may be misleading.

One must be equally cautious when attempting to estimate sensitivity and specificity for conversion within an RBD cohort, as Mahlknecht et al have done with our data. The gold standard outcome to be used in such calculations against the MDS criteria estimates is life time development of PD/DLB, and not merely early conversion. As acknowledged in the original paper by Berg and colleagues, short duration studies like ours will substantially underestimate the specificity in particular[1].

We do not view the comparison between RBD patients and controls as the primary measure of interest with regards to the application of the MDS criteria in our own analyses. Nevertheless, the lack of PSG in controls is unlikely to have made a significant difference to this since RBD is rare in the general population and even if a few cases of true RBD were inadvertently included in the control group, there would be little effect on the median probability reported. We presume that similar reasoning was used by the Sleep Innsbruck Barcelona Group to justify the inclusion of dopamine transporter imaging in RBD patients but not controls in their recent dataset[7].

The comparison between RBD and PD is also not relevant here, since we already know that the true probability in PD patients is 100%. Rather than looking at between-group comparisons, the motivation for including the MDS criteria in our analysis was to illustrate the following three points: firstly, the estimated prevalence of probable prodromal PD in our RBD cohort (74% of patients meeting criteria) is in line with expected long term outcomes. Secondly, using simple clinical measures in control participants, the false positive rate is estimated to be low. This is important since large scale screening will only be possible with simple measures, and a low false positive rate will be desirable in the design of neuroprotective trials. Thirdly, without additional invasive (and costly) investigations, the sensitivity is estimated to be low, given the result in our early, untreated PD cohort. It is likely, therefore, that a two-step screening process would be required at the population level, starting with simple, accessible tests followed by more expensive and invasive investigations such as PSG and dopaminergic neuroimaging.

In response to the other queries raised: a temporal association between RBD onset and initiation of antidepressants was an exclusion criterion for our study. The mean interval between RBD symptom onset and inclusion was 7.1 years (SD 6.3), and between RBD diagnosis and inclusion was 1.9 years (SD 2.1). Epworth Sleepiness Scale (ESS) scores for the three groups were as follows: control participants, mean 5.7 (SD 3.7); RBD patients, mean 7.2 (SD 4.7); PD patients, mean 6.2 (SD 4.1). Adjusting for age and gender in a linear regression model, the difference in ESS scores between controls and RBD patients was significant ($p = 0.002$) whilst other pairwise comparisons were not.

To conclude, the caveats raised by Mahlknecht and colleagues, along with many others acknowledged in the original MDS criteria paper, are important to consider when assessing for the presence of prodromal PD. We must also, however, be wary of modifying the MDS criteria without a sound evidence base. Further risk stratification models are likely to be needed in RBD cohorts, particularly given the wide variation in lead times to conversion. These may include the rates at which markers change over time in addition to absolute values[8]. DAT SPECT imaging might indeed be an important contributor to such models, and collection of this alongside other imaging data is underway in our cohort. Ultimately,

accumulation of longitudinal data will be the crucial factor in accurately evaluating and refining any risk stratification tool.

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