Updated Criteria for the Diagnostic Procedure for Parkinson's Disease Dementia on Level I and their Validity in Deep Brain Stimulation Cohort

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder typically characterized by a progressive onset of motor symptoms, including rigidity, bradykinesia, postural instability and resting tremor. Moreover, patients suffer from a range of non-motor impairments (Postuma et al., 2015), particularly cognitive decline. This factor might result in Parkinson's disease dementia (PDD) in a subset of patients (Meireles & Massano, 2012).

According to a recent meta-analysis, approximately one-quarter of PD patients is likely to be diagnosed with PDD (Sousa et al., 2022). However, reported PDD rate estimates vary widely, ranging from 14% up to 55%, depending on methodological criteria employed (Sousa et al., 2022). Moreover, factors such as patients' sex (Cereda et al., 2016), age and disease duration appear to modulate the risk of cognitive decline and PDD (Oh et al., 2016; Rana et al., 2011).

Despite the clinical relevance of PDD, its diagnosis remains complex. A milestone in research of PDD was the publication of diagnostic criteria established in 2007 by the International Parkinson and Movement Disorder Society (MDS) (Dubois et al., 2007). In these citeria, the MDS introduced a two-levelled system for PDD detection. Level I consists of brief cognitive assessments, while Level II involves comprehensive neuropsychological testing across cognitive domains (Emre et al., 2007).

The original Level I algorithm included eight conditions that had to be satisfied simultaneously in order to diagnose probable PDD. These included: 1) diagnosis of PD proposed by the Queen Square Brain Bank; 2) PD onset prior to the PDD emergence; 3) evidence of global cognitive impairment (MMSE score < 26 points); 4) cognitive deficit interference with the IADL (assessed by the pill questionnaire or caregiver interview); 5) impairment in at least two cognitive domains, namely memory, attention, visuo-constructive abilities and executive functions; 6) there was absence of Major Depressive Disorder; 7) absence of delirium; and 8) exclusion of other abnormalities and potential causes of dementia (Dubois et al., 2007).

Currently, efforts are focused on refining this PDD diagnostic framework. A recent call for a change pinpoints limitations regarding the original criteria and suggest various updates to enhance their utility (Kulisevsky et al., 2024). Proposed suggestions include replacement of Mini Mental State Examination (MMSE) by Montreal Cognitive Assessment (MoCA), which is more sensitive to PD specific cognitive impairment; expansion of instrumental activities of daily living (IADL) evaluation; inclusion of language assessment; recognition of anxiety as one the neuropsychiatric symptoms relevant in PDD; and intergration of biomarkers.

In the light of these proposals, the current study aims to evaluate the diagnostic concordance between the original MDS Level I PDD criteria (Dubois et al., 2007; Emre et al., 2007) and a modified framework based on the recent call for change (Kulisevsky et al., 2024). Furthermore, both Level I diagnostic approaches are compared to PDD diagnosed on Level II. The study aims to address the following research objectives (RO): (RO1) To estimate the PDD rate and evaluate the diagnostic variability and concordance across different PDD criteria. (RO2) To identify specific diagnostic components contributing to PDD classification variability across the applied criteria.

Methods

Participants

This study retrospectively analyzed clinical data from a cohort of patients with PD at the General University Hospital in Prague. All patients were diagnosed with idiopathic PD by a movement disorder specialist according to the MDS Clinical Diagnostic Criteria for PD (Postuma et al., 2015). Clinical records spanning August 2014 to February 2025 were examined. All participants were candidates for for Deep Brain Stimulation (DBS) treatment and underwent neuropsychological evaluation conducted by a trained clinical psychologist (OB) as part of standard preoperative assessments forDBS eligibility at the General University Hospital in Prague.

Neuropsychological Assessment

Cognitive performance was evaluated at both Level I and Level II according to the standard MDS battery for Parkinson's Disease Mild Cognitive Impairment (PD-MCI) Bezdicek et

al. (2017). Cognitive performance at Level I was assessed by the Mini-Mental State Examination (MMSE) (Stepankova et al., 2015; **?**) and the Montreal Cognitive Assessment (MoCA) (Kopecek et al., 2016; Nasreddine et al., 2005). The comprehensive neuropsychological assessment at Level II evaluated five cognitive domains through specific test: attention and working memory assessed by Trail Making Test Part A (TMT-A) (Bezdicek et al., 2012; Reitan, 2004), and WAIS Digit Span Backward (WAIS DSB) (Wechsler, 1997), executive functions by Categorical Verbal Fluency (CF) (Nikolai et al., 2015), and subtest from the Prague Stroop Test – Colors (PST-C) (Bezdíček et al., 2021), language by the WAIS Similarities subtest (Wechsler, 1997), and the Boston Naming Test (BNT-60) (Kaplan et al., 1983; Zemanová et al., 2016), memory by the Rey Auditory Verbal Learning Test (RAVLT) (Bezdicek et al., 2013; Frydrychová et al., 2018; Rey, 1964) delayed recall, and the Brief Visual Memory Test–Revised (BVMTR) (Benedict, 1997; Havlík et al., 2020) delayed recall, or WAIS Family Pictures subtest (Wechsler, 1997) delayed recall, visuospatial function assessed by the Judgment of Line Orientation Test (JoLO) (Benton et al., 1983), and Clock Drawing Test (CLOX) (Royall et al., 1998).

The Functional Activities Questionnaire (FAQ) (Bezdicek et al., 2016; Pfeffer et al., 1982) was administered to assess functional impairment. The Beck Depression Inventory-II (BDI-II) (Beck et al., 1996; Ciharova et al., 2020) and State-Trait Anxiety Inventory (STAI) (Mullner et al., 1980; Spielberger et al., 1983) were used to assess neuropsychiatric status. Psychotic symptoms were assessed through structured psychiatric interviews conducted by a trained psychiatrist.

Diagnostic algorithms for probable Parkinson's Disease Dementia

In this study, we applied three distinct sets of diagnostic algorithms for probable PDD at Level I. The first set was based on the original framework (Dubois et al., 2007), which utilized the Mini-Mental State Examination (MMSE) as a global cognitive screening tool, supplemented by assessments of attention, executive function, visuospatial abilities, and memory. The second set of algorithms was based on the recent call for change of dementia diagnostic guidelines (Kulisevsky et al., 2024), which advocates for more sensitive cognitive domain assessments in the context of PD. This updated approach incorporated specific items from the Montreal Cognitive Assessment

(MoCA). The third approach applied the Czech version of the shortened Montreal Cognitive Assessment (sMoCA) (Bezdicek et al., 2020), a time-efficient modification designed to measure global cognitive performance using a reduced testing protocol that omits items providing redundant information. Lastly, the fourth approach followed the Level II protocol for diagnosis of PDD and Mild Cognitive Impairment in PD (PD-MCI) (Dubois et al., 2007; Litvan et al., 2012). The Level II methodology, including the use of a regression-based normative scoring approach, has been detailed in a prior study (Bezdicek et al., 2017). In this study, the thresholds for cognitive impairment at Level II were set at $z \leq -1.5$. All non-cognitive criteria of probable PDD (i.e., diagnosis of PD that developed before dementia and absence of Major Depression, delirium or other abnormalities that obscure diagnosis) held true for all patients in the sample according to the psychiatric and neurological examinations.

For each of these diagnostic approaches, we applied two operationalizations of deficits in Instrumental Activities of Daily Living (IADL). First, we utilized FAQ item 9, which approximates the pill questionnaire from the original criteria (Dubois et al., 2007) employing a cut-off score of 2 points or higher. Second, we applied the entire Functional Activities Questionnaire (FAQ) as suggested in the call for change (Kulisevsky et al., 2024), employing a cut-off score of 7 points or higher based on Czech normative data (Bezdíček et al., 2011). These methodologies resulted in a total of 68 algorithms, which were distributed across different diagnostic criteria: 4 MMSE-based, 60 MoCA-based, 2 sMoCA-based, and 2 based on the Level II battery (see Table 1 and Appendix Table A1 for the exact specification of each algorithm).

[Insert Table 1 here]

Statistical Analyses

Following the framework proposed by Lundberg et al. (2021), in this study we explicitly connect our research objectives and their corresponding theoretical (i.e., targets of inference) and empirical (i.e., data-driven) estimands to statistical estimates. The theoretical estimand refers to a unit-specific quantity defined over a target population and represents the ideal quantity that would address the research question under optimal conditions, such as access to complete population

data or perfect experimental control. In contrast, the empirical estimand corresponds to the quantity that is actually computable using the available dataset, given real world constraints. The full description of the study's estimands and their relation to our research objectives is presented in the Appendix (see Table A2).

To address study objectives, we started by repeatedly assigning each patient the diagnosis of probable PDD based on each PDD algorithm listed in Table 1 (see also Table A1) resulting in a 204 (patients) × 68 (algorithms) matrix where each cell indicates whether a patient (row) meets criteria for probable PDD according to an algorithm (column)[1]. PDD rate estimates were computed as $\frac{N_{PDD}}{N_{total}}$ separately for each algortihm. The predictive value of age and sex was then evaluated by fitting a set of logistic regressions, one for each algorithm for probable PDD, whereby the probable PDD was predicted by age, sex and their interaction.

Next, a set of two class cross-tabulations with associated statistics was computed for each pair of algorithms via the `confusionMatrix()` function from the R package *caret* (Kuhn, 2008). For each pair of algorithms, the analysis was repeated twice such that each variable of the pair served once as the reference and once as the predictor. Following measures were used to evaluate pairwise concordance between different algorithms for probable PDD: 1) Cohen's κ with its 95% confidence interval (CI) computed via the `cohen.kappa()` function from the R package *psych* (William Revelle, 2024); 2) Accuracy (i.e., the proportion of correct predictions, both true positives and true negatives, among the total number of cases) with its 95% CI; 3) Sensitivity/Recall (i.e., the proportion of true positives); and 4) Specificity (i.e., the proportion of true negatives).

Finally, the No Information Rate (NIR) was calculated for each pair of algorithms. NIR is the accuracy that could be obtained by always predicting the majority class and in our case it is equivalent to the complement of the PDD rate estimate according to the reference algorithm. Accuracy of prediction was compared to the NIR via a one-sided Exact Binomial Test as

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[1] **JM: This could and should be shared most likely, as long, as we anonymize properly. Let's ask Oto Mestek and the NPO team how and if is it possible.**

implemented by the `binom.test()` R stats function. Reference/predictor pairs associated with p < .05 were considered to show significantly better accuracy than NIR. In other words, for reference/predictor pairs associated with p < .05, we conclude that knowing the probable PDD status according to the predictor algorithm helps to estimate the probable PDD status according to the reference algorithm and the two algorithms thus show substantial concordance.

Data wrangling and visualizations were done in the *tidyverse* package (Wickham et al., 2019) and tables were formatted in the *gt* package (Iannone et al., 2024). All analyses were conducted within the R (version 4.4.1) software environment for statistical computing (R Core Team, 2024). The software code supporting this article is available at https://github.com/josefmana/DemCr1t.git.[2]

Results

Sample Description

A total of 204 patients were included. The sample included 126 (62%) men, with an average of 58.96 (SD = 8.35) years of age, 13.75 (SD = 3.07) years of education, 10.79 (SD = 4.23) years of disease duration, 37.43 (SD = 13.04) Unified Parkinson Disease Rating Scale (UPDRS), part III in medication OFF state and 15.97 (SD = 8.25) UPDRS III in medication ON state. Cognitive characteristics of the sample are summarized in Table 2.

[Insert Table 2 here]

PDD Rate Estimates

Algorithm-wise rate of PDD estimates are presented in Table A3. On average, estimated PDD rate was 6.03% (SD = 3.46, Md = 3.94, range 2.00-16.75). Notably, the estimates were substantially lower when FAQ item 9 was used as a criterion of IADL deficit (M = 3.11% SD = 0.48, Md = 2.96, range 2.00-3.94) compared to using total FAQ score criterion (M = 8.95% SD = 2.54, Md = 9.11, range 3.50-16.75) as demonstrated also in Figure 1. Neither age nor sex or their interaction (*p*s ≥ .110) reliably predicted probable PDD classification across algorithms (see

[2] **JM: Do not forget to make it public before submitted!**

Figure A1 and Figure A2).

[Insert Figure 1 here]

Concordance between Algorithms

Results of the analyses of prediction Accuracy, Cohen's κ, Sensitivity and Specificity are presented in Figure 2, Figure A3, Figure A4 and Figure A5 respectively. **Numerical results are available at …** [3]. Generally, algorithms that employed the same operationalization of IADL deficit showed substantial pairwise concordance, however, algorithms that operationalized IADL deficit differently did not. Whereas among algorithms with identical IADL deficit operationalization, the agreement judged by Cohen's κ was moderately high (operationalization by FAQ total score: $\kappa = 0.75$, SD = 0.13; operationalization by FAQ item 9: $\kappa = 0.86$, SD = 0.09), among algorithms that differ in IADL deficit operationalization it was low ($\kappa = 0.34$, SD = 0.08).

[Insert Figure 2 here]

Prediction of Level II Criteria

For easier interpretability of our results, we next examine cases where Level II algorithms served as a reference and Level I algorithms as a predictor. Table 3 shows five Level I algorithms with the highest and five with the lowest accuracy in predicting Level II classification of probable PDD.

When IADL deficit was defined by total FAQ score, the Level II estimate of PDD rate was 10.71%. All five Level I algorithms that approximated the Level II classification most accurately were MoCA-based and defined Executive Function deficit by Clock drawing rather than Lexical fluency test. On the other hand, two out of the five Level I algorithms with the lowest accuracy were MMSE-based, whereas the remaining three were MoCA-based and defined Executive Function deficit by Lexical fluency test.

When IADL deficit was defined by FAQ item 9 score, the Level II estimate of PDD rate was 3.57%. Overall, the difference between the most accurate and the least accurate Level I

[3] **JM: Should provide an excel sheet or html table the readers could go through by themselves.**

algorithms was lower than in the case of IADL deficit being defined by FAQ total score (see Table 3). The five most accurate algorithms were all MoCA-based, defined Executive Function deficit by Clock drawing (with threshold < 2) and in majority of cases defined Language deficit by Animal naming. Two out of the five Level I algorithms with the lowest accuracy were MMSE-based, whereas the remaining three were MoCA-based and defined Executive Function deficit by Clock drawing (with threshold < 3) and Language deficit by Abstraction.

Finally, if the predictors are sorted by their balanced accuracy (i.e., average of sensitivity and specificity) instead of raw accuracy, the results are similar with the exception that for prediction of Level II with total FAQ score algorithm for probable PDD, the highest balanced accuracy was achieved by the sMoCA algorithm with sensitivity 0.95 and specificity 0.93 (see Table A4).

Discussion

This study systematically investigated the application of multiple Level I diagnostic criteria for PDD. Our results show variability in PDD rate estimates, strongly influenced by the choice of cognitive screening instruments (MMSE, MoCA and sMoCA) and the operationalization of functional impairment. The divergence observed across algorithms demonstrates the sensitivity of diagnostic outcomes to seemingly negligible methodological choices.

Variability in PDD Rate Estimates

Our results showed a wide range in estimated PDD rate across algorithms, ranging from 2.00% to 16.75%. Estimates reached lower rates when using solely FAQ item 9 (as an approximation of the pill questionnaire suggested by Dubois et al. (2007)) in comparison with the full FAQ scale. This discrepancy highlights the diagnostic importance of how IADLs are assessed.

Our overall PDD rates were consistently lower than previous studies regarding PDD among PD patients, demonstrating wide variability based on various criteria used. For instance, a retrospective study reported a PDD rate of 19.7% (Rana et al., 2011), while other clinical investigation found even higher rate, reaching up to 30% (Aarsland et al., 2005). A recent complex meta-analysis synthesizing global data placed the expected PDD rate in PD at 26.30%

(Sousa et al., 2022). Compared to these estimates, our study reports generally lower PDD rates, likely reflecting differences in diagnostic criteria, methodology and sample characteristics. Specifically, age was repeatedly shown to be a strong predictor of PDD across studies(Rana et al., 2011; Sousa et al., 2022). In our sample, we did not observe age-related PDD rate within our cohort, likely due to low age variability.

Concordance Between Diagnostic Algorithms

Pairwise comparisons of diagnostic algorithms showed that agreement was notably stronger among those using the same IADL operationalization compared to those using different IADL definitions. Moreover, the agreement was slightly higher between algorithms that defined IADL deficit by FAQ item 9 compared to algorithms that defined it using the full FAQ scale. One possible explanation of this difference follows from the observation that algorithms using the full-scale definition yielded higher PDD rate estimates. Because there was a higher probability of being diagnosed with IADL deficit based on the full FAQ scale, there was also a bigger room for disagreement in the Cognitive Impairment status when different indexes were used (e.g. by defining executive deficit via clock drawing vs. lexical fluency).

Overall, when the same IADL definitions were used across algorithms, we observed concordance levels varying from moderate (using FAQ total score) to strong (using FAQ item 9), consistent with inter-rater reliability analysis (McHugh, 2012). Contrarily, the concordance between algorithms using different IADL deficit definitions was equivalent to minimal agreement. This demonstrates that even slight methodological differences can yield divergent diagnostic outcomes. Such findings are critical for clinicians relying on Level I criteria for eligibility decisions, as the choice of algorithm could lead to contradictory classifications of PDD.

Predictive Validity Comparison With Level II Criteria

Using Level II diagnosis as the reference, MoCA-based Level I algorithms, particularly those using Clock Drawing to assess executive function, demonstrated the highest predictive accuracy. This supports recent proposals to modernize PDD diagnostic frameworks (Kulisevsky et al., 2024), favouring MoCA-derived components and broader functional assessment tools. In

contrast, MMSE-based algorithms consistently underperformed, suggesting limited sensitivity in capturing cognitive deficits typical in PDD.

The advantage of MoCA-based algorithm was evident in combination with using the FAQ total score, reaching accuracy rates of 94–99%, along with high sensitivity and specificity. Furthermore, in the algorithm using sMoCA, the raw accuracy was moderate, however, the balanced accuracy (i.e. combined sensitivity and specificity) was robust. These findings imply that simplified tools such as sMoCA may be a promising tool for heightening efficiency of the assessment while maintaining diagnostic accuracy.

Limitations and Future Directions

This study's generalizability is limited by its retrospective design and the homogeneity of the patient cohort, which may not reflect broader PD populations with varying cognitive profiles. Specifically, the younger age of the sample and possible lack of high-risk phenotypes for PDD compared to the general population of people with PD might have been responsible for comparatively lower PDD rate estimates in our study.

Nevertheless, the analysis of the algorithm concordance might not be affected by the sample to the same degree allowing for a broader generalization. Future studies should aim to replicate our results on larger and different cohorts of PD patients. To make this process easier, the code used to generate our results is publicly available and easily applicable to similarly structured data.

Furthermore, another limitation is the use of the FAQ questionnaire for IADL assessment. FAQ is highly subjective and informant-reliant, which may result in biased data. We recommend the use of more objective, modernized tools for IADl assessment, such as performance-based methods(Schmitter-Edgecombe et al., 2020) or questionnaire adaptation including questions regarding gadgets use and digital literacy (Postema et al., 2024). Our results emphasise the importance of IADL deficit for the PDD diagnosis, therefore, we advocate for using more reliable tools with high ecological validity.

Conclusions

Our study highlights the variability in PDD classification across Level I diagnostic algorithms, heavily influenced by IADL operationalization and the choice of cognitive screening tools. The findings support the call for a change of the current diagnostic criteria (Kulisevsky et al., 2024), favouring the use of MoCA-based components and comprehensive IADL assessments.

Conservative criteria, such as reliance on pill questionnaire (i.e. FAQ item 9 equivalence), may fail to detect functional decline and thus under-identify true cases of PDD. Importantly, concordance across algorithms rises significantly, reaching moderate to high values, when the same definition of IADL is used (either FAQ total or FAQ item 9). Moreover, when using MoCA-based algorithms instead of MMSE-based ones, we can observe better approximations to the Level II battery.

Future research should validate these strategies longitudinally and explore the possible integration of biomarkers, neuropsychiatric variables (e.g. anxiety profile) and modernised IADL methods to further improve diagnostic reliability, accuracy and consistency of PDD diagnostics.

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Table 1

Summary of probable PDD operationalizations compared in the study.

Type	Global functioning	Attention	Executive Function
MMSE-based	MMSE < 26	Sevens backwards < 4	Clock drawing < 2 OR Lexical fluency (S) < 10
MoCA-based	MoCA < 27	Sevens backwards < 3	Clock drawing < {2, 3} OR Lexical fluency (K) <
sMoca-based	sMoCA < 13	-	-
Level II	-	TMT A & WAIS DSB	CF A & PST C

[a]The visual memory was evaluated based on WMS-III Family Pictures or BVMTR depending on which test was used in the assessment. This lead to no missing values because each patient underwent assessment via one of these tests.

Note. MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; sMoCA: short version of the MoCA; TMT A: Trail Making Test, Part A; WAIS DSB: Wechsler Adult Intelligence Scale Digit Span, Backwards; CF A: Categorical Verbal Fluency, Animals; PST C: Prague Stroop Test, Colours; WAIS Similarities: Wechsler Adult Intelligence Scale, Similarities; BNT 60: Boston Naming Test; RAVLT delayed recall: Rey Auditory Verbal Learning Test, Delayed Recall; BVMTR delayed recall: Brief Verbal Memory Test, Delayed Recall; WMS-III Family Pictures: Wechsler Memory Scale Family Pictures; JoLO: Boston Judgement of Line Orientation; CLOX: Clock Drawing Test. The OR operator implies that exactly one of the criteria listed is utilized within a single operationalization; the & operator implies that both criteria are used at the same time within a single operationalization; each threshold value within the set brackets {} was used to define probable PDD once in combination with all the other criteria on the same row.

Table 2

Cognitive characteristics of the sample.

	N	Md	Min-max	M	SD
MMSE					
Total score (Range 0-30)	203	27	15-30	26.69	2.22
Sevens (Range 0-5)	1/2/8/20/34/139	-	-	-	-
VF S (Number of Words per Minute)	202	15	1-34	14.95	5.80
Clock Drawing (Range 0-2)	26/91/86	-	-	-	-
Pentagons (Range 0-1)	187 (92%)	-	-	-	-
Three words (Range 0-3)	5/14/60/124	-	-	-	-
MoCA					
Total score (Range 0-30)	203	24	9-30	24.07	3.48
sMoCA total score (Range 0-16)	203	11	1-16	11.26	2.74
Sevens (Range 0-3)	1/2/29/171	-	-	-	-
VF K (Number of Words per Minute)	204	16	0-29	15.50	5.34
Clock drawing (Range 0-3)	24/83/96	-	-	-	-
Cube drawing (Range 0-1)	164 (81%)	-	-	-	-
Five words (Range 0-5)	69/19/29/39/22/25	-	-	-	-
Animal naming (Range 0-3)	10/193	-	-	-	-
Abstraction (Range 0-2)	7/72/124	-	-	-	-
Affect					
BDI (Range 0-63)	203	10	0-34	10.79	7.02
STAI X1 (Range 0-80)	188	39	20-72	38.96	8.93
STAI X2 (Range 0-80)	186	40	22-63	40.38	7.77
IADL					
FAQ (Range 0-30)	203	2	0-25	4.05	4.89
FAQ 9 (Range 0-1)	144/48/10/1	-	-	-	-

Table 3

Level I algorithms for probable PDD as predictors of Level II classification as the reference.

Level II (1)[a]						Level II (2)[b]				
Predictor	κ	Accuracy	p	Sensitivity	Specificity	Predictor	κ	Accuracy	p	Sensiti
			Top five							
MoCA (3)	0.64	0.94	.010	0.52	0.99	MoCA (12)	0.85	0.99	.028	0.8
MoCA (51)	0.70	0.94	.010	0.71	0.97	MoCA (16)	0.85	0.99	.028	0.8
MoCA (11)	0.63	0.94	.019	0.57	0.98	MoCA (2)	0.83	0.99	.028	0.7
MoCA (13)	0.68	0.94	.019	0.71	0.97	MoCA (20)	0.85	0.99	.028	0.8
MoCA (15)	0.63	0.94	.019	0.57	0.98	MoCA (4)	0.83	0.99	.028	0.7
			Bottom five							
MMSE (1)	0.53	0.93	.061	0.43	0.99	MoCA (50)	0.70	0.98	.168	0.7
MoCA (25)	0.57	0.92	.098	0.57	0.97	MoCA (54)	0.70	0.98	.168	0.7
MoCA (35)	0.53	0.92	.098	0.48	0.98	MoCA (58)	0.70	0.98	.168	0.7
MMSE (3)	0.41	0.92	.143	0.30	0.99	MMSE (2)	0.66	0.98	.168	0.5
MoCA (39)	0.51	0.92	.148	0.48	0.97	MMSE (4)	0.53	0.97	.296	0.4

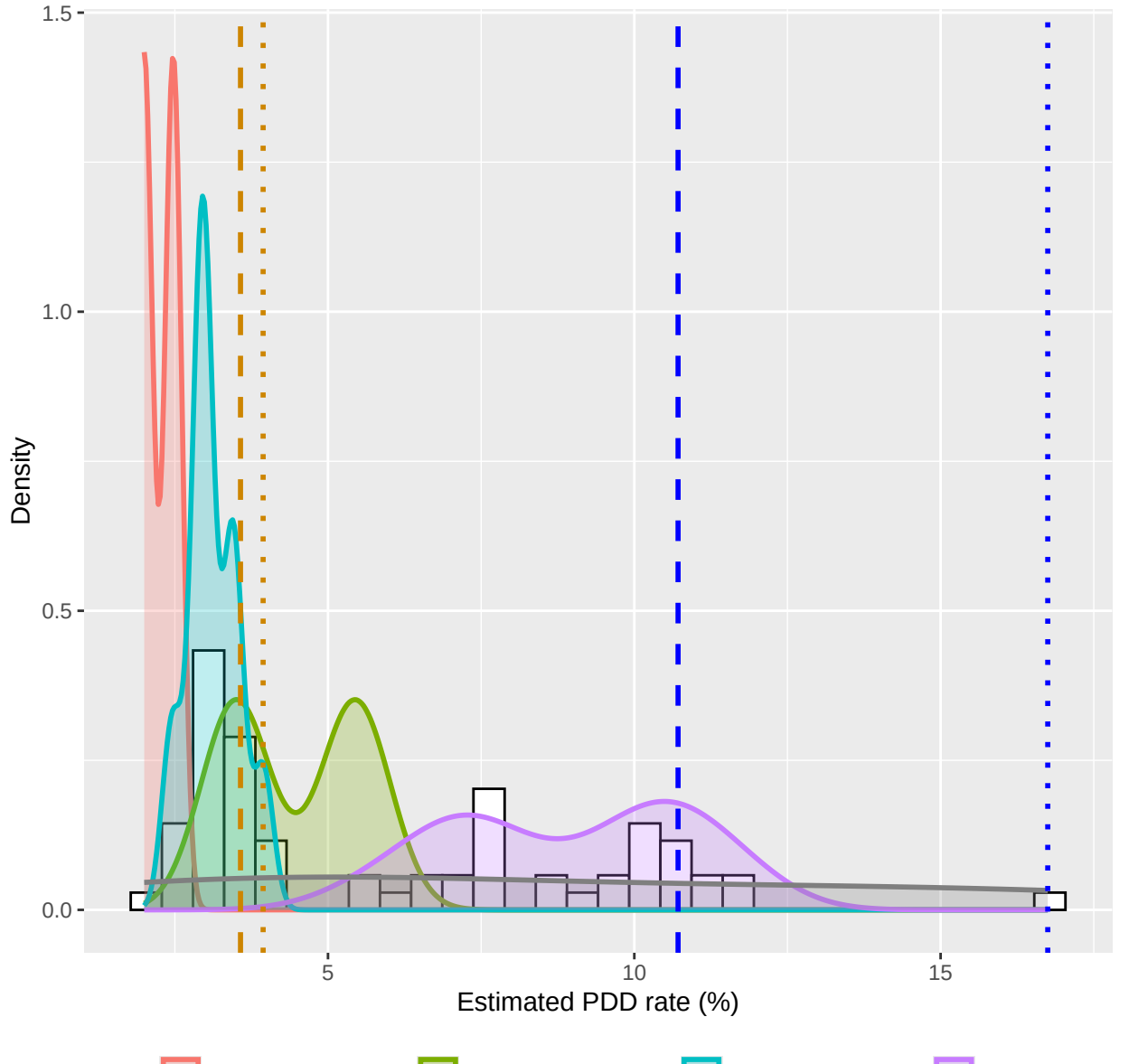
[a]IADL deficite was defined as FAQ (total score) > 7

[b]IADL deficite was defined as FAQ (item 9) > 1

κ: Cohen's κ; p: p-value associated with a one-sided Exact Binomial Test comparing the Accuracy to the No Information Rate; The table shows five most accurate (Top five) and five least accurate (Bottom five) Level I algrithms for Parkinson's Disease Dementia (PDD) in predicting Level II classficiation of PDD. The algorithms were grouped by their definition of the deficit in Instrumental Activities of Daily Living (IADLs). The items comprising each listed algorithm can be found in Table A1.

Figure 1

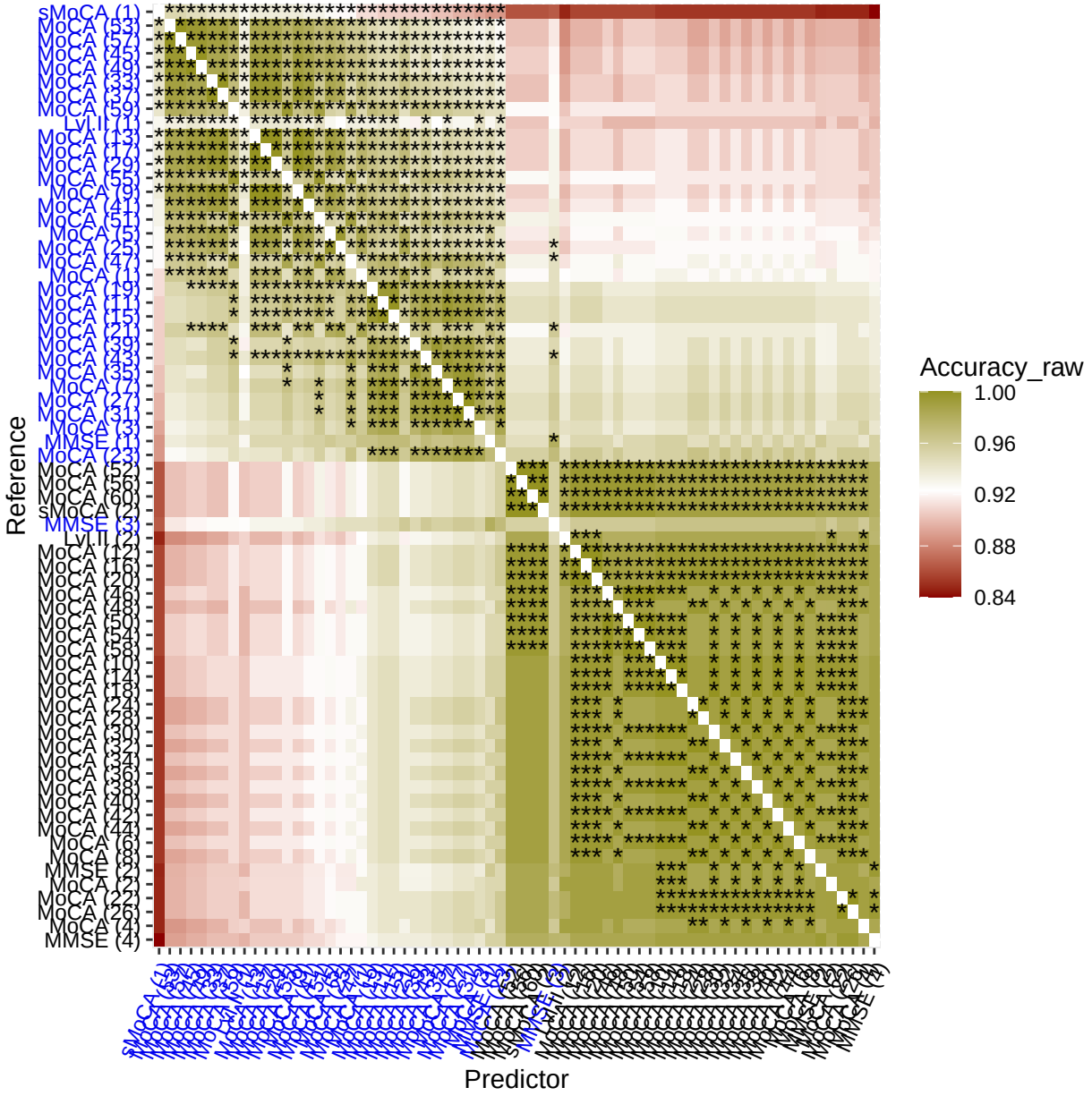
Summary of the estimates of probable PDD rate.



Note. Vertical lines represent estimates arrived at by using sMoCA (dotted) or Level II (dashed) with FAQ item 9 (orange) or FAQ total score (blue) as criteria for probable PDD.

Figure 2

Prediction accuracy matrix.



Note. The matrix depicts classification accuracy of algorithms for PDD depicted on x-axis in predicting outcomes based on algorithms on the y-axis. Algorithms printed in blue defined IADL deficit by FAQ total score, algorithms printed in black defined IADL deficit by FAQ item 9 response. Cases with asterisk indicate predictive accuracy statistically significantly higher than the No Information Rate.

Appendix

Derivation of the Algorithms Set

Both, the original PDD criteria (Dubois et al., 2007) and the call for their change (Kulisevsky et al., 2024) allow for several distinct combinations of items to be used to define cognitive impairment. Consequently, in this study we derived all algorithms for probable PDD on Level I that are in line with published criteria. This procedure parallel the diagnostic algorithm outlined in Table 2 of Dubois et al. (2007). Specifically, in this study, we varied the exact specification of items 3-5 of this table (i.e., the measure of global cognitive impairment, the measure of the impact on IADLs and the measures of impaired cognition).

For each set of criteria (MMSE-based, MoCA-based, sMoCA-based and Level II), we first specified the items and then the thresholds for each item used to define probable PDD. If more than one option was present in either the choice of the item or the choice of the threshold, we created an algorithm for each choice in turn. The final set of algorithms was arrived at by computing the Cartesian product of all possibilities provided by varying items and thresholds. All combinations are presented in Table A1.

For MMSE-based algorithms, the following sets of items served as the basis:

$Global = \{MMSE < 26\}$

$Attention = \{Sevens\ backwards < 4\}$

$Executive = \{Clock\ drawing < 2, Lexical\ fluency\ (S) < 10\}$

$Construction = \{Pentagons < 1\}$

$Memory = \{Three\text{-}words\ recall < 3\}$

$IADL = \{FAQ > 7, FAQ\ (it.9) > 1\}$

The ensuing Cartesian product $Global \times Attention \times Executive \times Construction \times Memory \times IADL$ results in $1 \times 1 \times 2 \times 1 \times 1 \times 2 = 4$ MMSE-based algorithms for probable PDD.

For MoCA-based algorithms, the following sets of items served as the basis:

$Global = \{MoCA < 26\}$

$Attention = \{Sevens\ backwards < 3\}$

$Executive = \{Clock\ drawing < 2, Clock\ drawing < 3, Lexical\ fluency\ (K) < 11\}$

$Construction = \{Cube\ drawing < 1\}$

$Memory = \{Five\text{-}words\ recall < 1, Five\text{-}words\ recall < 2, Five\text{-}words\ recall < 3, Five\text{-}words\ recall < 4, Five\text{-}words\ recall < 5\}$

$Language = \{Abstraction < 2, Animal\ naming < 3\}$

$IADL = \{FAQ > 7, FAQ\ (it.9) > 1\}$

Note that the additional language domain adds complexity to establishing a diagnostic algorithm because simply by adding it to the set of items, the number of potential algorithms doubles. Further complexity is added by the fact that there are so far no guidelines for selecting a diagnostic threshold for Clock drawing and Five-words recall tests, both of which differ from their counterparts used by Dubois et al. (2007). Finally, although the Sevens backwards item has different thresholds in MoCA-based compared to MMSE-based algorithms, this difference is solely due to a difference in scoring whereby 3 points in MoCA correspond to 4 or 5 points in MMSE. The Seven backwards item threshold for MoCA-based algorithms used in this study is thus equivalent to its MMSE-based counterpart.

Computing the Cartesian product $Global \times Attention \times Executive \times Construction \times Memory \times Language \times IADL$ yields $1 \times 1 \times 3 \times 1 \times 5 \times 2 \times 2 = 60$ distinct MoCA-based algorithms for probable PDD.

For sMoCA-based algorithms, the following sets of items served as the basis:

$Global = \{sMoCA < 13\}$

$IADL = \{FAQ > 7, FAQ\ (it.9) > 1\}$

yielding $Global \times IADL$, i.e., $1 \times 2 = 2$ distinct sMoCA-based algorithms for probable PDD.

Finally, the Level II algorithms were based on the following sets of items:

$Attention = \{z(TMT\ A) < -1.5\ \cup z(WAIS\ DSB) < -1.5\}$

$$Executive = \{z(CF\ A) < -1.5\ \cup z(PST\ C) < -1.5\}$$

$$Construction = \{z(JoLO) < -1.5\ \cup z(CLOXI) < -1.5\}$$

$$Memory = \{z(RAVLT\ DR) < -1.5\ \cup z(BVMTR\ DR) < -1.5\ \cup z(WMS\text{-}III\ Family\ Pictures) < -1.5\}$$

$$Language = \{z(WAIS\ Similarities) < -1.5\ \cup z(BNT\ 60) < -1.5\}$$

$$IADL = \{FAQ > 7, FAQ\ (it.9) > 1\}$$

where $z()$ denotes calculation of age, sex and education adjusted z-score. This yields $1 \times 1 \times 1 \times 1 \times 1 \times 2 = 2$ distinct Level II algorithms for probable PDD in the current study. All but the BNT 60 item were evaluated using regression norms published by Bezdicek et al. (2017). Since the original article used BNT 30 instead of BNT 60, we approximated the deficit in BNT 60 by comparing patients' raw score to age- and education-specific normative values reported by Zemanová et al. (2016). Specifically, patients whose BNT 60 score fell below 5th percentile of their demographic group in Table 6 of Zemanová et al. (2016) were considered to show signs of impaired performance.

Operationalization of Impaired Cognition

In the original criteria, item 4 of Level I criteria, i.e., impaired cognition, was defined as follows: *"The proposed diagnostic criteria require a profile of cognitive deficits, typical of those described for PD-D, in two or more of four domains."* (Dubois et al., 2007, p. 2316) Consequently, we defined impaired cognition as a deficit in two or more domains of four in MMSE-based criteria and as a deficit in two or more of five domains in MoCA-based criteria. sMoCA-based criteria omitted the "impaired cognition" item altogether because they were intended as a shorter screening alternative to classical Level I assessment. Finally, for the Level II criteria, we employed standard definition of impaired cognition as the *"[i]mpairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains."* (Litvan et al., 2012, Table 1)

Theoretical and Empirical Estimands

In this study, we follow the framework proposed by Lundberg et al. (2021) for specifying targets of inference (i.e., the estimands) in qunatitative sciences to increase transparency and connect statistical evidence to relevant theory. Table A2 contains verbal description of the components relating to each of our proclaimed research objectives and map them to the population quantity of interest (the theoretical estimand), data-dependent quantity that could be estimated (the empirical estimand) and quantities that are reported in the study (statistical estimates).

The RO1 - to estimate the PDD rate and evaluate the diagnostic variability and concordance across different algorithms of probable PDD - was divided into four distinct research objectives:

- to estimate the rate of PDD within PD (RO1.1),
- to estimated variability of this rate (RO1.2),
- to evaluate predictive value of demographic variables for probable PDD classification (RO1.3) and
- to evaluate concordance between different probable PDD operationalizations and criteria (RO1.4).

Estimates relating to RO1.1 and RO1.3 cannot be safely generalized beyond a population of PD patients that are candidates for DBS due to the systematic differences between DBS candidates pool and general PD population (such as the lower age of DBS candidates compared to the general PD population). On the other hand, the estimates relating to RO1.4 (and to a lesser degree to RO1.2[4]) may not be substantially influenced by the sample at hand as the primary

[4] Because the quantity of interest is a rate and could thus be though of as a sum of binomially distributed PDD occurences divided by the total number of patients, its variance will likely systematically vary with its mean. Specifically, as the rate goes from extremes to 0.5, the variance increases. Consequently, if our estimate of the rate was lower than the true population rate, e.g., because our sample includes younger patients compared to the general PD population, our estimate of variance would also lower than the true variance of PDD rate in the general PD

source of their variance might come from variability in measures employed (e.g., MMSE vs MoCA to assess global cognitive performance) rather than variability in patients' performance. Assuming that there is no substantial Differential Item Functioning for DBS candidates compared to a broader population of patients with PD, the estimates relating to RO1.4 can be cautiously generalized beyond the current sample.

Finally, for the RO2, the theoretical estimand is defined as the set of diagnostic components whose variation systematically alters the probability of a probable PDD diagnosis. This aspect of the study is exploratory in nature. Empirically, we assess the contribution of each diagnostic feature by examining how variations in operational definitions (e.g., domain-specific thresholds, criteria for functional impairment) influence the statistical estimates derived for the first objective. This allows us to identify the diagnostic elements most responsible for between-algorithm discrepancies.

Supplementary Presentation of Results

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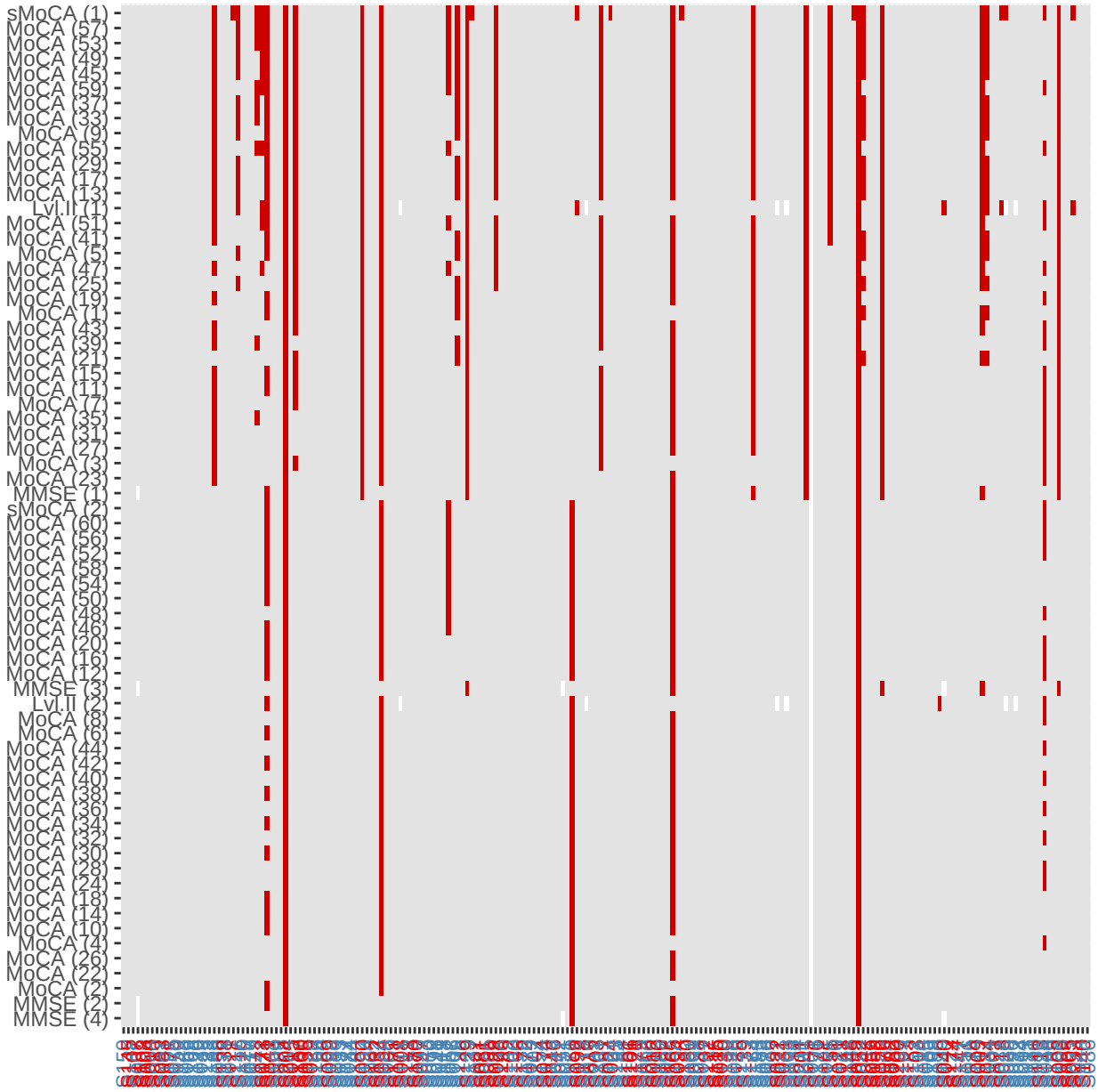
population. Nonetheless, the between-algorithm variability may not be affected by this phenomenon as unlike variability of PDD rate, we do not have reason to assume it comes about by summing independent binomial events

Figure A1

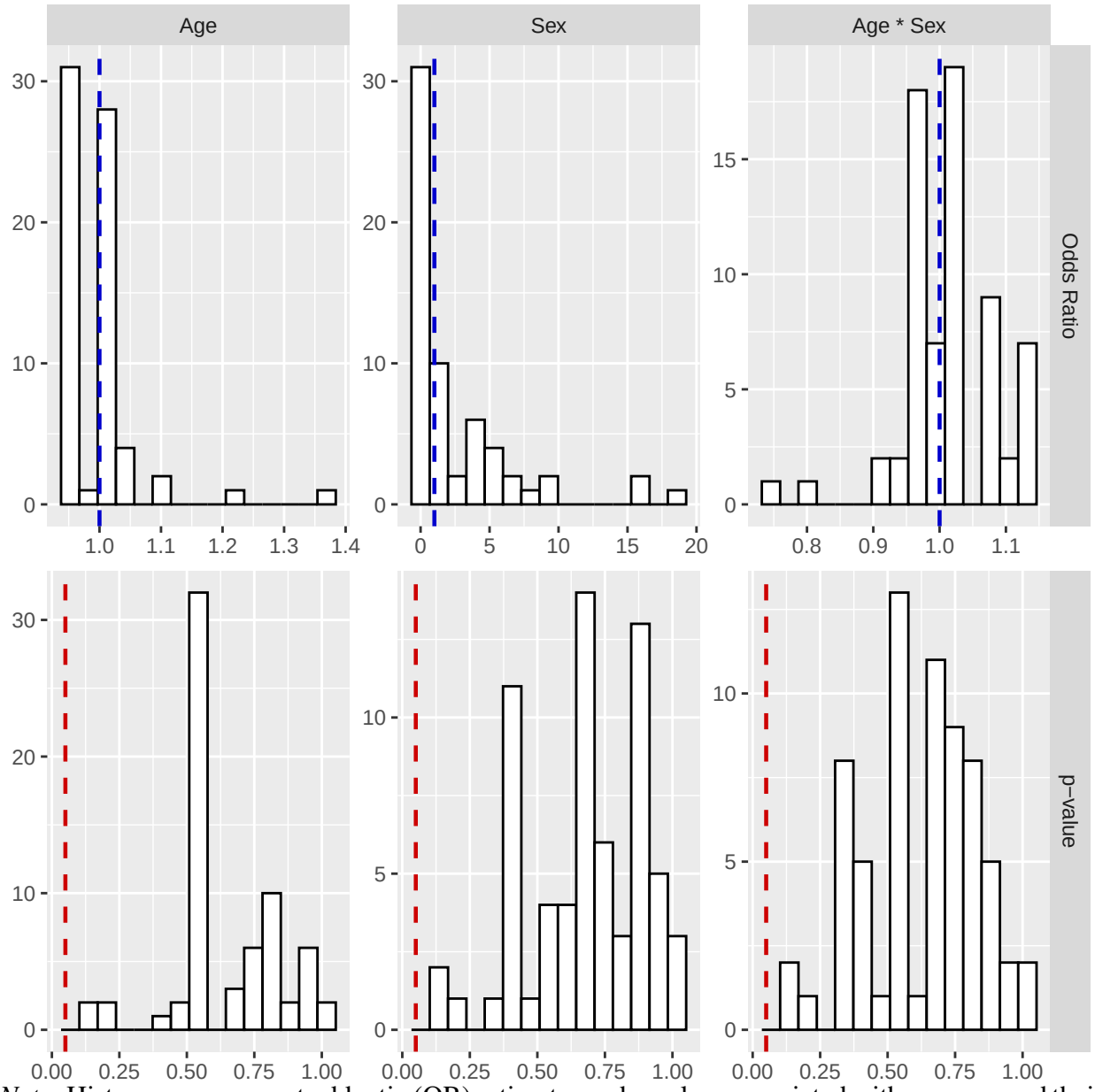
Representation of study data.



Note. The figure shows whether patients (x-axis) ordered from the youngest (left) to the oldest (right) were classified as probable PDD by each tested algorithm (y-axis) ordered from the one with the lowest (bottom) to the highest (top) PDD rate estimate. Patients printed in red are women, patients printed in blue are men. Red cells indicate probable PDD diagnosis, grey cells indicate non-PDD diagnosis and white cells indicate missing diagnosis.

Figure A2

Summary of logistic regressions parameters prediction probable PDD by age and sex.



Note. Histograms represent odd ratio (OR) estimates and p-values associated with age, sex, and their interaction as predictors of each of the 68 probable PDD classification. In the case of parameters for sex, values higher than 20 were omitted for clarity. Vertical lines indicate OR = 1 and p = .05.

Table A1

Summary of all algortihms for probable PDD used in the study.

Algorithm	Global deficit	Attention	Executive function	
Lvl.II (1)	-	TMT A < -1.5 OR WAIS DS < -1.5	CF A < -1.5 OR PST C < -1.5	Jo
Lvl.II (2)	-	TMT A < -1.5 OR WAIS DS < -1.5	CF A < -1.5 OR PST C < -1.5	Jo
MMSE (1)	Total score < 26	Sevens < 4	Clock Drawing < 2	
MMSE (2)	Total score < 26	Sevens < 4	Clock Drawing < 2	
MMSE (3)	Total score < 26	Sevens < 4	VF S < 10	
MMSE (4)	Total score < 26	Sevens < 4	VF S < 10	
MoCA (1)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (10)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (11)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (12)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (13)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (14)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (15)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (16)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (17)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (18)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (19)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (2)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (20)	Total score < 26	Sevens < 3	Clock drawing < 2	
MoCA (21)	Total score < 26	Sevens < 3	VF K < 11	
MoCA (22)	Total score < 26	Sevens < 3	VF K < 11	
MoCA (23)	Total score < 26	Sevens < 3	VF K < 11	
MoCA (24)	Total score < 26	Sevens < 3	VF K < 11	
MoCA (25)	Total score < 26	Sevens < 3	VF K < 11	
MoCA (26)	Total score < 26	Sevens < 3	VF K < 11	

Table A2

Mapping between research objectives and quantities of interest in the current study.

To estimate the rate of PDD within PD.
To assess variability of PDD diagnosis depending on the algorithm applied.
To evaluate predictive information provided by demographic variables for probable PDD diagnosis.
To evaluate the diagnostic concordance between different PDD algorithms within and between PDD criteria.
To identify algorithms' components that contribute to variability in probable PDD diagnosis within and across cr

Table A3

Estimates of the rate of probable PDD in the sample.

Algorithm	N	Rate
sMoCA (1)	203	34 (16.75%)
MoCA (53)	203	24 (11.82%)
MoCA (57)	203	24 (11.82%)
MoCA (45)	203	23 (11.33%)
MoCA (49)	203	23 (11.33%)
MoCA (33)	203	22 (10.84%)
MoCA (37)	203	22 (10.84%)
MoCA (59)	203	22 (10.84%)
Lvl.II (1)	196	21 (10.71%)
MoCA (13)	203	21 (10.34%)
MoCA (17)	203	21 (10.34%)
MoCA (29)	203	21 (10.34%)
MoCA (55)	203	21 (10.34%)
MoCA (9)	203	21 (10.34%)
MoCA (41)	203	20 (9.85%)
MoCA (51)	203	20 (9.85%)
MoCA (5)	203	19 (9.36%)
MoCA (25)	203	18 (8.87%)
MoCA (47)	203	18 (8.87%)
MoCA (1)	203	16 (7.88%)
MoCA (19)	203	16 (7.88%)
MoCA (11)	203	15 (7.39%)
MoCA (15)	203	15 (7.39%)
MoCA (21)	203	15 (7.39%)
MoCA (39)	203	15 (7.39%)
MoCA (43)	203	15 (7.39%)

Table A4

Level I algorithms for probable PDD as predictors of Level II classification as the reference arranged by their balanced accuracy score.

Level II (1)[a]						Level II (2)[b]				
Predictor	κ	Accuracy	p	Sensitivity	Specificity	Predictor	κ	Accuracy	p	Sensiti
Top five										
sMoCA (1)	0.70	0.93	.061	0.95	0.93	MoCA (12)	0.85	0.99	.028	0.8
MoCA (45)	0.69	0.94	.019	0.76	0.96	MoCA (16)	0.85	0.99	.028	0.8
MoCA (49)	0.69	0.94	.019	0.76	0.96	MoCA (20)	0.85	0.99	.028	0.8
MoCA (53)	0.67	0.93	.035	0.76	0.95	MoCA (52)	0.79	0.98	.078	0.8
MoCA (57)	0.67	0.93	.035	0.76	0.95	MoCA (56)	0.79	0.98	.078	0.8
Bottom five										
MoCA (31)	0.55	0.93	.061	0.48	0.98	MoCA (58)	0.70	0.98	.168	0.7
MoCA (35)	0.53	0.92	.098	0.48	0.98	MoCA (22)	0.66	0.98	.168	0.5
MoCA (39)	0.51	0.92	.148	0.48	0.97	MoCA (26)	0.66	0.98	.168	0.5
MMSE (1)	0.53	0.93	.061	0.43	0.99	MMSE (2)	0.66	0.98	.168	0.5
MMSE (3)	0.41	0.92	.143	0.30	0.99	MMSE (4)	0.53	0.97	.296	0.4

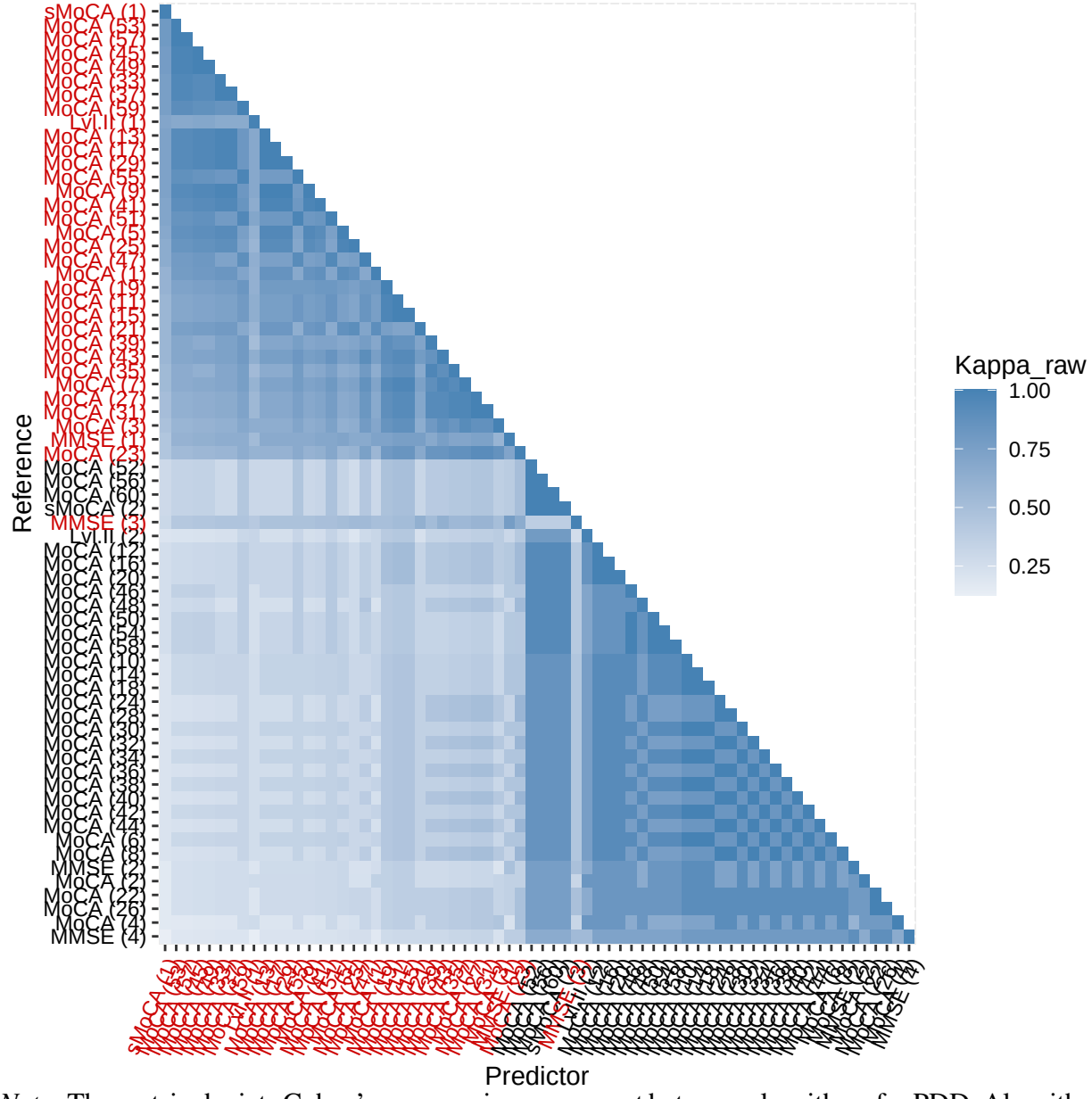
[a]IADL deficite was defined as FAQ (total score) > 7

[b]IADL deficite was defined as FAQ (item 9) > 1

κ: Cohen's κ; p: p-value associated with a one-sided Exact Binomial Test comparing the Accuracy to the No Information Rate; The table shows five most accurate (Top five) and five least accurate (Bottom five) Level I algrithms for Parkinson's Disease Dementia (PDD) in predicting Level II classficiation of PDD. The algorithms were grouped by their definition of the deficit in Instrumental Activities of Daily Living (IADLs). The items comprising each listed algorithm can be found in Table A1.

Figure A3

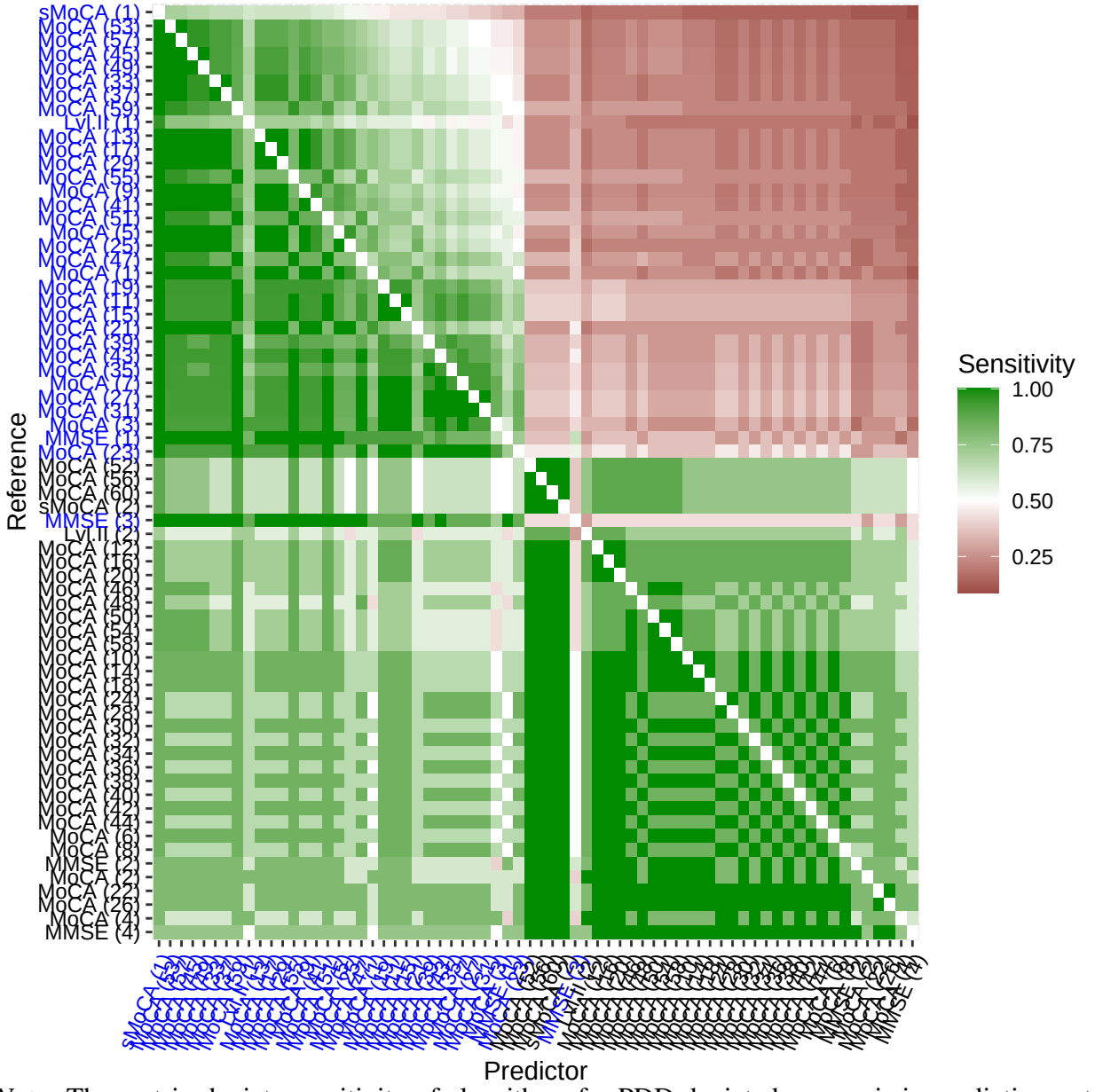
Cohen's κ matrix.



Note. The matrix depicts Cohen's κ measuring agreement between algorithms for PDD. Algorithms printed in red defined IADL deficit by FAQ total score, algorithms printed in black defined IADL deficit by FAQ item 9 response.

Figure A4

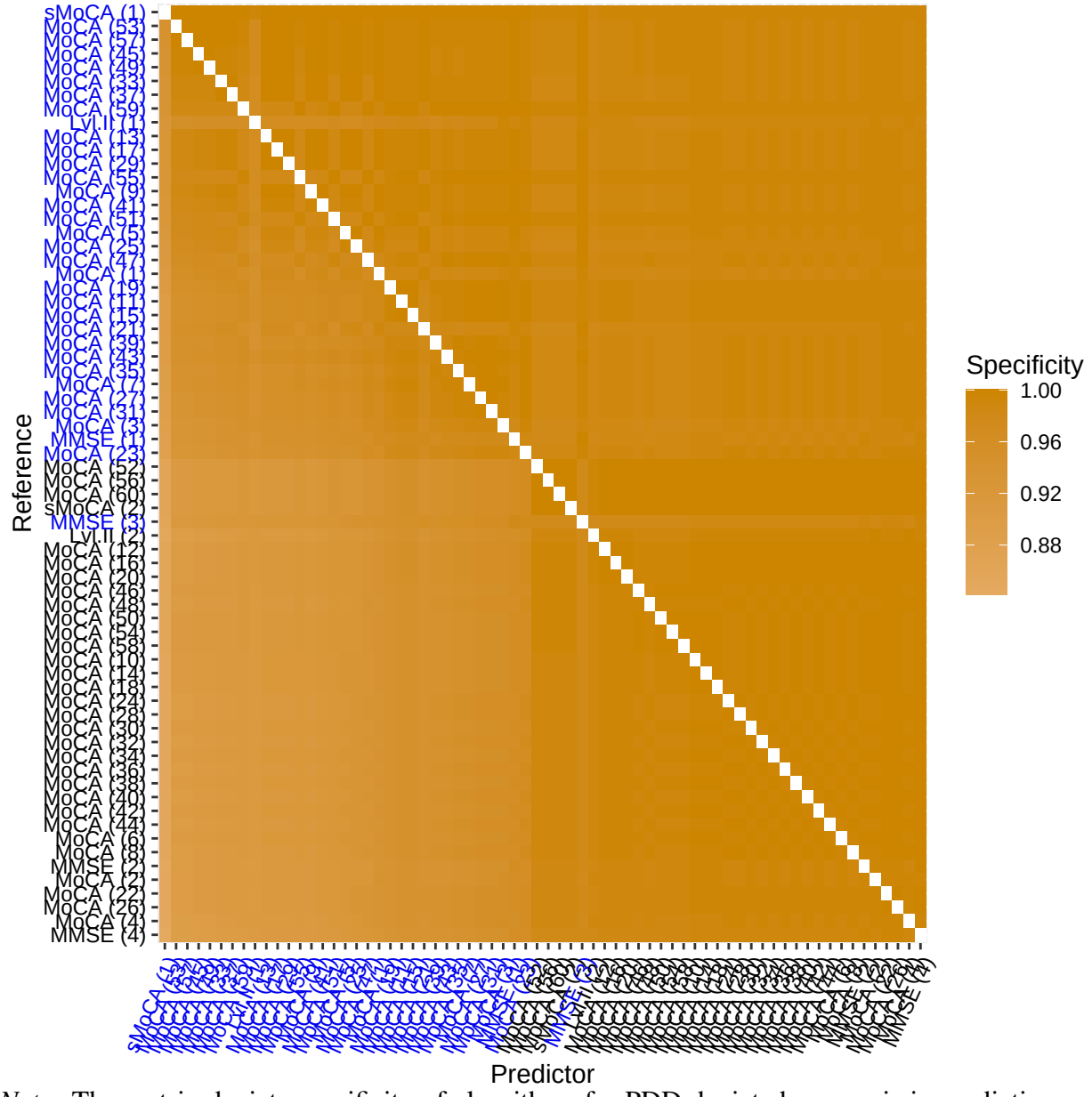
Sensitivity matrix.



Note. The matrix depicts sensitivity of algorithms for PDD depicted on x-axis in predicting outcomes based on algorithms on the y-axis. Algorithms printed in blue defined IADL deficit by FAQ total score, algorithms printed in black defined IADL deficit by FAQ item 9 response.

Figure A5

Specificity matrix.



Note. The matrix depicts specificity of algorithms for PDD depicted on x-axis in predicting outcomes based on algorithms on the y-axis. Algorithms printed in blue defined IADL deficit by FAQ total score, algorithms printed in black defined IADL deficit by FAQ item 9 response.