Cognitive profiles of patients with mild cognitive impairment due to Alzheimer’s versus Parkinson’s disease defined using a base rate approach: Implications for neuropsychological assessments

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Abstract

Introduction: Large studies on cognitive profiles of patients with mild cognitive impairment (MCI) due to Alzheimer’s disease (AD-MCI) compared to Parkinson’s disease (PD-MCI) are rare.

Methods: Data from two multicenter cohort studies in AD and PD were merged using a unified base rate approach for the MCI diagnosis. Cognitive profiles were compared using scores derived from the Consortium to Establish a Registry for Alzheimer’s Disease battery.

Results: Patients with AD-MCI showed lower standardized scores on all memory test scores and a language test. Patients with PD-MCI showed lower standardized scores in a set-shifting measure as an executive task. A cross-validated logistic regression with test scores as predictors was able to classify 72% of patients correctly to AD-MCI versus PD-MCI.

Discussion: The applied test battery successfully discriminated between AD-MCI and PD-MCI. Neuropsychological test batteries in clinical practice should always include a broad spectrum of cognitive domains to capture any cognitive changes.

KEYWORDS Alzheimer’s disease, Consortium to establish a registry for Alzheimer’s disease test battery, cognitive profiles, mild cognitive impairment, neuropsychological assessment, Parkinson’s disease

1 | INTRODUCTION

Cognitive decline is common in both Alzheimer’s disease (AD) and Parkinson’s disease (PD), representing the two most frequently occurring neurodegenerative disorders associated with older age. Several studies have revealed differential patterns of cognitive deficits between patients with AD compared to patients with PD, which is thought to reflect differential neuropathological processes. Memory deficits rather depend on cortical dysfunctions, which are typically associated with the AD pathology, whereas fronto-striatal dysfunctions resulting in the impairment of executive function, working memory, and attention rather depend on dopaminergic imbalances, which are typically associated with PD. However, according to the dual syndrome hypothesis regarding cognitive impairment in PD, cognitive deficits in PD are highly heterogeneous. Some patients may display an “Alzheimer-typical” pattern, associated with prominent amnestic dysfunctions, and possibly associated with a higher risk of the progression of cognitive decline to dementia.

To date, only a few studies have provided direct comparisons between AD and PD samples across different levels of cognitive impairment. Overall, the expected cognitive patterns have been confirmed, with more severe levels of cognitive impairment identified in AD compared to PD, and memory and language deficits were particularly more pronounced in patients with AD compared to those in patients with PD. In PD, the observed deficits were more severe in executive, attentional, and visuo-cognitive tasks. One limitation of these prior publications has been the rarity of biomarker-based etiological AD diagnoses. Furthermore, existing studies comparing the two etiologies during the mild cognitive impairment (MCI) stage (AD-MCI vs. PD-MCI) have been based on relatively small or strongly imbalanced...
sample sizes. Another limitation associated with existing comparisons during the MCI stage has been the use of inhomogeneous MCI criteria across AD-MCI and PD-MCI samples within one study; for example, differences in the cutoff scores applied for impaired cognitive test performance (e.g., \( \leq -1 \) standard deviation [SD] vs. \( \leq -1.5 \) SD) and differences in the numbers of impaired tests required to diagnose objective cognitive impairment (e.g., 2 vs. 1) have been reported. Therefore, the observed differences might be at least partially due to divergent MCI criteria rather than differences in etiologies.

One method for overcoming this problem may be the application of a base rate approach to the neuropsychological definition of MCI. This approach recognizes that cognitive variability among healthy older adults can result in low test scores when multiple tests are administered, even in the absence of any clinically relevant objective cognitive impairment. The most common base rate approach described in the literature is to diagnose MCI, when the number of cognitive tests on which impaired performance is shown equals or exceeds the number of cognitive tests on which impaired performance is shown by the worst-performing 10% of a non-impaired control group, as defined by established diagnostic criteria. So far, to the authors’ best knowledge, the base rate approach has only been applied in the AD context but has never been used across different etiologies.

Differential cognitive profiles associated with the two different etiologies might strongly influence diagnostic accuracy when applying neuropsychological screening instruments or test batteries. For example, the well-established Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) test battery may fail to capture relevant changes in PD-specific fronto-striatal cognitive functions. Those functions tend to be underrepresented in the CERAD test battery, which features a substantial majority of subscores designed to represent amnestic functions (e.g., Word List Learning, Recall, and Recognition; Figure Recall and Savings). In German-speaking countries, the augmentation of the original CERAD test battery has been suggested through the inclusion of additional subtests designed to assess processing speed and executive functions. The resulting CERAD-Plus test battery has been demonstrated to display strongly improved diagnostic accuracy for identifying dementia associated with non-AD etiologies. By gauging detailed cognitive profiles obtained from broad neuropsychological test batteries, clinicians are better able to draw inferences regarding the underlying etiologies and accelerate the diagnostic workflow during the crucial MCI state.

Therefore, our aim was to outline the cognitive profiles of patients with AD-MCI and PD-MCI in a large dataset and examine the diagnostic utility of different tests derived from the CERAD-Plus to differentiate between the two diagnoses. The baseline data from two large, prospective, multicenter observational cohort studies, the German Dementia Competence Network (DCN) study and the Dementia and Parkinson’s Disease (DEMPARK) consortium’s LANDSCAPE study, were merged using a base rate approach for the neuropsychological MCI diagnosis. Based on existing evidence, we hypothesize a higher severity of memory and language deficits in the AD-MCI sample compared to the PD-MCI sample, whereas patients with PD-MCI are expected to be more impaired in executive tasks. Consequently, deficits in these respective domains should be more predictive for the corresponding diagnoses.

## METHODS

### 2.1 Patients

Baseline data of patients with AD-MCI were obtained from the DCN study, which recruited participants from 14 specialized outpatient memory clinics of university hospitals across Germany between 2003 and 2007. Data of patients with PD-MCI were drawn from the DEM-PARK/LANDSCAPE study, which recruited participants from nine specialized outpatient movement disorder centers across Germany between 2009 and 2013. Figure 1 visualizes the participant selection process from the original studies to the final AD-MCI and PD-MCI sample evaluated for the present profile comparison.

#### 2.1.1 Dementia Competence Network

The general inclusion and exclusion criteria for participation in the DCN study have previously been reported in detail. At baseline, \( n = 813 \) patients with MCI were included in the study. The clinical MCI...
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**2.1.2 DEMPARK/LANDSCAPE**

The general inclusion and exclusion criteria for participation in the DEMPARK/LANDSCAPE study have previously been reported in detail. At baseline, \( n = 314 \) patients with MCI were included in the study. Patients were diagnosed with “idiopathic PD” according to the UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria. The diagnosis of PD-MCI was performed according to the established MCI criteria available at the time of study design, as proposed by Petersen: (1) self-reported subjective cognitive dysfunctions, according to medical history; (2) no significant impairment in activities of daily living according to medical history; and (3) evidence of objective cognitive impairment, operationalized by impaired test performance (< -1.5 SD below published normative data) in at least one test of the investigated domains (memory, executive function, attention, visuospatial functions, and language).

For the present profile comparison, we used a subsample of DEMPARK/LANDSCAPE patients with PD-MCI. After imputing Trail Making Test (TMT) data for at least one of the subtests for 5.7% of patients with PD-MCI, the subsample from the DEMPARK/LANDSCAPE study consisted of \( n = 312 \) patients with PD-MCI, which was further reduced after unification of MCI criteria as described below.

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We had to cope with several missing values in the Trail Making Test (TMT) A and B. As described by Schmid et al., severely cognitively impaired patients did not complete the TMT subtests. Therefore, we substituted missing values for the TMT-A and TMT-B using the lowest possible value (TMT-A: 180 seconds, TMT-B: 300 seconds) to ensure a non-random penalty for the non-completion of these subtests.
2.2 | Clinical and neuropsychological assessment

The details regarding the diagnostic procedures of the DCN\(^23\) and the DEMPARK/LANDSCAPE study\(^24\) have been described previously. For both studies, in addition to other tests, the CERAD test battery\(^20,22\) extended by TMT-A and TMT-B was applied, resulting in 12 test scores obtained from nine tests: the Boston Naming Test (BNT), Figure Copy, Figure Recall, Figure Savings, Word List Learning, Word List Recall, Word List Recognition, Word List Intrusions, Animal Fluency, TMT-B/A (TMT-B divided by TMT-A), TMT-A, and TMT-B. For the CERAD test battery extended by the TMT-A and TMT-B, normative data correcting for age, sex, and education were available.\(^22\) All patients were cognitively screened using the Mini-Mental State Examination (MMSE),\(^29\) and an established CERAD total score, based on the formula established by Chandler et al.,\(^30\) was computed. Additionally, patients with PD were screened with the Parkinson Neuropsychometric Dementia Assessment (PANDA).\(^31\) Depressive symptoms were assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS)\(^32\) in the DCN study and the Geriatric Depression Scale (GDS)\(^33\) in the DEMPARK/LANDSCAPE study. For patients with PD-MCI, motor symptom severity was assessed with the Unified Parkinson’s Disease Rating Scale Part 3 (UPDRS-3)\(^34\) and the Levodopa Equivalent Daily Dose (LEDD) was reported. For patients with AD-MCI the biomarker levels of CSF A\(_{\beta}42\), CSF tau, and CSF p-tau\(_{181}\) (phosphorylated tau 181) were stated.

2.3 | Definition of MCI

In the initial datasets, MCI was diagnosed according to the established diagnostic criteria for MCI at the time of each respective study design.\(^25,28\) However, the neuropsychological tests used, the definition of cognitive domains considered relevant for MCI diagnosis, the cutoff scores that were used to define impaired test performance ($\leq -1$ SD vs. $\leq -1.5$ SD), and the numbers of impaired tests that were considered necessary to diagnose objective cognitive impairment (2 vs. 1) differed between the two studies.

Therefore, we applied a base rate approach\(^14–19\) to the neuropsychological MCI definition. Patients were diagnosed as cognitively impaired when the number of cognitive tests indicating impaired performance was equal to or greater than the number of cognitive tests indicating impaired performance obtained by the worst-performing 10% of a healthy control group. The DCN study included $n = 234$ healthy older adults without evidence of relevant neurological diseases\(^23\) and with complete neuropsychological data in the CERAD test battery;\(^20,22\) this group was defined as the non-impaired control group for the base rate approach. Twelve test scores per participant, based on the nine tests of the CERAD test battery including TMT-A and TMT-B, were used for the base rate analysis approach.

We compared the base rates between the two commonly applied cutoff values for impaired test performance ($\leq -1$ SD and $\leq -1.5$ SD) for increasing numbers of impaired tests. With $\geq$ three cognitive tests being impaired at a cutoff of $\leq -1.5$ SD below the mean of published normative data, 9.4% of DCN healthy controls were still classified as cognitively impaired. These cutoff specifications yielded the closest results to the 10% mark\(^14–19\) (for details, see Table 1). Using them, $n = 103$ (80.5%) patients originally diagnosed with AD-MCI and $n = 136$ (43.6%) patients originally diagnosed with PD-MCI were classified as cognitively impaired. Therefore, the applied MCI criteria for inclusion in this profile comparison included the original criteria of (1) a self-report of cognitive dysfunctions; (2) no significant impairment in activities of daily living; and (3) evidence of objective cognitive impairment, as determined using the described base rate approach.

2.4 | Standard protocol approvals, registrations, and patient consents

The underlying study protocols were conducted in compliance with the World Medical Association Declaration of Helsinki. The study protocol for the DCN study\(^23\) was approved by the Ethics Review Board of the Erlangen Medical Faculty and by local ethics committees of all participating study centers. The DEMPARK/LANDSCAPE\(^24\) study was approved by the Ethics Committee of Philipps University Marburg and the local ethics committees of all participating centers. All participants provided written informed consent for participation before the baseline assessment of both studies.

2.5 | Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics 26 for Mac. Prior to analyses, all test scores of the CERAD test battery, TMT-A, TMT-B, and TMT-B/A were standardized into $z$-values correcting...
for age, sex, and education using published normative data for the CERAD.\(^2\) For comparisons between AD-MCI and PD-MCI, independent samples t-tests were conducted, with group (AD-MCI vs. PD-MCI) as the independent variable and demographic, clinical, and neuropsychological data (including the 12 CERAD test scores) as dependent variables. To ensure the normal distribution of continuous data, these variables were previously inspected by Shapiro-Wilk tests. Cohen's \(d\) was reported as the effect size, indicating small (\(d \geq 0.2\)), moderate (\(d \geq 0.5\), or strong (\(d \geq 0.8\)) effects. Chi-square (\(\chi^2\))-tests were used to compare the distributions of categorical data (sex, presence of depressive symptoms, percentage of patients with impaired cognitive test performance) between the AD-MCI and PD-MCI samples.

The alpha-level was set at \(\alpha = 0.05\). To counteract the problem of multiple comparisons within the CERAD test battery, the \(P\)-values of independent samples t-tests calculated for CERAD subscores and the \(\chi^2\)-tests examining the incidence of impaired CERAD test performance at \(\leq -1.5\ SD\) were corrected using the Bonferroni-Holm method.

Furthermore, to obtain a global estimate of the differences in the cognitive profiles between AD-MCI and PD-MCI and to identify cognitive tests that can predict the underlying etiological diagnosis, a cross-validated logistic regression analysis was performed with AD-MCI (\(F = 0\)) versus PD-MCI (\(F = 1\)) as the dependent variable, and the z-scores of the 12 CERAD test scores as predictors. The stratified 10-time repeated 10-fold cross-validation was applied to gain a more accurate estimate of the true classification performance of the model.

## RESULTS

### 3.1 Demographic and clinical characteristics

Patients with AD-MCI and patients with PD-MCI did not significantly differ in terms of age or total years of education. Whereas the sex ratio was balanced in the AD-MCI sample, there were significantly more men than women in the PD-MCI sample. The prevalence of depressive symptoms according to the respective cutoff criteria for the applied screening tools was higher among patients with AD-MCI than among patients with PD-MCI. Compared to patients with AD-MCI, patients with PD-MCI showed higher scores for the MMSE and CERAD total scale. For further details, see Table 2.

### 3.2 Cognitive profile comparison

Descriptively, the scores for patients with AD-MCI were lower than those for patients with PD-MCI for all subscores except for Figure Copy, TMT-B, and TMT B/A. These differences were significant for the BNT, with a small effect size, and for Figure Recall, Figure Savings, Word List Learning, Word List Recall, and Word List Recognition subscores with moderate to strong effect sizes. Patients with PD-MCI showed significantly lower standardized test scores compared to those of patients with AD-MCI in the TMT-B/A measure, with a small effect size. Further details can be obtained from Table 3 and Figure 2.
TABLE 3 Performance and percentage of impaired performance at ≤ −1.5 SD in CERAD subtests

| Test                          | AD-MCI n = 103 | PD-MCI n = 136 | Cohen’s d | $P$-test/$\chi^2$-test | $\eta^2$ | P ANCOVA |
|-------------------------------|----------------|----------------|-----------|-------------------------|---------|----------|
| Boston Naming Test            | −0.60 (1.28)  | −0.11 (1.14)  | 0.41      | .014*                   | .294    | .020 .031*|
| Figure Copy                   | −0.55 (1.40)  | −0.34 (1.32)  | 0.07      | .745                    | .570    | .012 .440 |
| Figure Recall                 | −2.08 (1.38)  | −1.49 (1.37)  | 0.29      | .009*                   | .264    | .002 .025*|
| Figure Savings                | −1.68 (1.22)  | −1.02 (1.12)  | 0.57      | ≤ .001***               | .036    | .003**    |
| Word List Learning            | −2.17 (1.56)  | −1.49 (1.28)  | 0.34      | .002**                  | .075    | .016 .053 |
| Word List Recall              | −1.93 (0.95)  | −1.06 (1.18)  | 0.15      | ≤ .001***               | .097    | ≤ .001*** |
| Word List Recognition         | −1.38 (1.41)  | −0.72 (1.26)  | 0.40      | ≤ .001***               | .038    | .033*     |
| Word List Intrusions          | −0.94 (1.24)  | −0.74 (1.39)  | 0.39      | ≤ .001***               | .006    | .657      |
| Semantic Verbal Fluency       | −0.95 (1.11)  | −0.63 (0.98)  | 0.29      | .081                    | .082    | 0.008 .648|
| TMT-A                         | −1.18 (1.37)  | −0.97 (1.32)  | 0.34      | .082                    | .082    | 0.008 .648|
| TMT-B                         | −1.37 (0.98)  | −1.47 (1.08)  | 0.34      | .075                    | .075    | 0.006 .657|
| TMT-B/A                       | −0.23 (1.31)  | −0.65 (1.12)  | 0.29      | .043*                   | .715    | 0.021 .048*|

Note: Data are mean (standard deviation) and percentage of patients with impaired test performance ≤ −1.5 SD below the mean of published normative data of the German CERAD-Plus test battery. Bonferroni-Holmes corrected $P$-values of independent sample $t$-tests with group (AD-MCI vs. PD-MCI) as independent variable and the respective CERAD score as dependent variable and $\chi^2$-tests comparing the percentage of patients with impaired cognitive test performance between the AD-MCI and PD-MCI are reported. Due to significant group differences in global cognitive functioning assessed with the MMSE, univariate ANCOVAs with MMSE score as covariate were conducted. Partial $\eta^2$ ($\eta^2_p$) and Bonferroni-Holmes corrected $P$-values are reported for the main effect of group.

Abbreviations: AD-MCI, mild cognitive impairment with probable Alzheimer’s Disease; ANCOVA, analysis of covariance; MMSE, Mini-Mental State Examination; PD-MCI, Parkinson’s Disease with mild cognitive impairment; SD, standard deviation; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; TMT-B/A, Trail Making Test Part B divided by Part A.

Due to significant group differences in the global cognitive scores (MMSE and CERAD total), we exploratively investigated whether the observed group differences between AD-MCI and PD-MCI would persist if group comparisons were controlled for global cognition. Univariate analyses of covariance (ANCOVAs), with the CERAD subscores as dependent variable, group (AD-MCI vs. PD-MCI) as the independent variable, and the MMSE score as a covariate continued to identify significant group differences for the BNT, Figure Recall, Figure Savings, Word List Recall, Word List Recognition, and the TMT-B/A, similar to the uncontrolled comparison. Only Word List Learning was no longer significantly different between groups when controlling for global cognition.

Comparing the frequencies of patients with impaired test performance, as defined by a performance of ≤ −1.5 SD below the mean of published normative data for each test score, significant differences were only observed for Figure Savings and Word List Recall, indicating that significantly more patients with AD-MCI were impaired than patients with PD-MCI. Further details can be obtained from Table 3.

3.3 Logistic regression

The logistic regression analysis for predicting the etiological diagnosis using the 12 CERAD subscores as predictors is displayed in Table 4. The cross-validation of the model ($\chi^2[12] = 75.50, P ≤ .001$, $R^2_{Nagelkerke} = 0.36$) revealed a mean classification accuracy of 75.8% in the training datasets and a 72.0% accuracy in the testing datasets. Lower $z$-scores in the BNT, Word List Recall, and TMT-B tests were significant predictors of the AD-MCI diagnosis, whereas lower $z$-scores on TMT-A and TMT-B/A were significant predictors for the PD-MCI diagnosis.

4 Discussion

The present analyses aimed to outline the differential cognitive profiles AD-MCI and PD-MCI using a large dataset of patients and applying a uniform MCI definition. We found that (1) patients with AD-MCI...
FIGURE 2  Standardized cognitive test performance of patients with mild cognitive impairment (MCI) due to Alzheimer's disease (AD-MCI, n = 103) versus MCI due to Parkinson's disease (PD-MCI, n = 136)

TABLE 4  Logistic regression analyses to predict the MCI underlying diagnosis (AD vs. PD)

| Predictor                | b     | SE    | P      | Odds ratio (95%CI) |
|--------------------------|-------|-------|--------|--------------------|
| Constant                 | 2.25  | 0.45  | ≤ .001*** | 9.49               |
| Boston Naming Test       | 0.29  | 0.14  | .042*  | 1.34 (1.01; 1.77)   |
| Figure Copy              | −0.07 | 0.16  | .699   | 0.93 (0.68; 1.28)   |
| Figure Recall            | 0.03  | 0.39  | .941   | 1.03 (0.48; 2.19)   |
| Figure Savings           | 0.36  | 0.44  | .414   | 1.43 (0.61; 3.35)   |
| Word List Learning       | −0.06 | 0.14  | .658   | 0.94 (0.72; 1.24)   |
| Word List Recall         | 0.79  | 0.22  | ≤ .001*** | 2.21 (1.44; 4.40)   |
| Word List Intrusions     | 0.14  | 0.13  | .571   | 1.08 (0.84; 1.38)   |
| Animal Fluency           | 0.19  | 0.17  | .258   | 1.21 (0.87; 1.69)   |
| TMT-A                    | −1.52 | 0.59  | .010** | 0.22 (0.07; 0.69)   |
| TMT-B                    | 1.70  | 0.66  | .010** | 5.50 (1.51; 20.07)  |
| TMT-B/A                  | −1.92 | 0.61  | .002** | 0.15 (0.05; 0.48)   |

Notes: Based on using the z-scores (lower score = less performance) and dummy-coding of the dependent variable (AD = 0, PD = 1), results can be interpreted as follows: For scores with a significant odds ratio > 1, lower z-score performance is predictive (i.e., associated with an increased likelihood) for belonging to the AD group, for scores with a significant odds ratio < 1, lower z-score performance is predictive for belonging to the PD group. 10-times 10-fold cross-validation revealed a classification accuracy of 75.8% in the training samples and 72.0% in the testing samples. Abbreviations: AD, Alzheimer's disease; CI, confidence interval; MCI, mild cognitive impairment; PD, Parkinson's disease; SE, standard error; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; TMT-B/A, Trail Making Test Part B divided by Part A.
evaluate whether the suggested discriminative neuropsychological tests can be used to differentiate the two etiologies equally well when cognitive decline is more subtle.

Overall, we were able to confirm our hypotheses regarding the existence of differential cognitive profiles between AD-MCI and PD-MCI. The cross-validated logistic regression model was able to classify 72% of patients correctly in the testing datasets, which were not used to train the model. This indicates that the neuropsychological profiles based on cognitive test scores that were included in the model substantially differed between AD-MCI and PD-MCI, suggesting that our model might be valid beyond the training datasets. The 28% misclassification rate may be due to the significant overlap in amnestic dysfunctions between patients with AD-MCI and PD-MCI that may occur during the transition from PD-MCI to PD dementia. Furthermore, due to the heterogeneity of cognitive decline reported among PD patients, some patients with PD-MCI may display rather "AD-typical" cognitive profiles during early disease stages.6

As expected,11–13 patients with AD-MCI showed worse performance than patients with PD-MCI in the memory domain across all applied tests and subscores. Furthermore, patients with AD-MCI obtained lower scores in the BNT, a language assessment. Most of these differences, including the difference in the TMT-B/A discussed below, persisted when we controlled for global cognition, indicating that the differential cognitive profiles between patients with AD-MCI versus PD-MCI exist beyond differences in global cognition. However, differences in the assessed global cognition measures should be interpreted cautiously, as the memory domain is overrepresented within both the MMSE and the CERAD total score, relative to other cognitive domains (e.g., executive functions). Due to evidence suggesting a more severe memory impairment among patients with AD-MCI compared to patients with PD-MCI, the group differences in these global cognition scores may be biased by their different cognitive profiles.

Patients with PD-MCI obtained significantly lower scores than patients with AD-MCI only for the TMT-B/A executive function set-shifting measure and on a descriptive level in the Figure Copy test. The lack of other statistically significant differences is likely associated with the overall composition of the applied test battery, as several tests are based on the recruitment of resources from a broad spectrum of cognitive domains. For example, although verbal fluency measures are well-established neuropsychological assessments for executive functions, semantic fluency tests, such as Animal Fluency, are also considered to reflect strong language and semantic memory components.36 A similar pattern is discussed for Word List Intrusions, which can reflect executive deficits in monitoring and inhibition and may also indicate semantic memory deficits.37 Therefore, deficits in one cognitive domain might be compensated by stronger performance in another domain involved in a specific task, which could potentially explain a lack of overall differences between AD-MCI and PD-MCI in some test scores. However, the underlying mechanisms that result in similar deficits might differ between the two diagnoses.

A double dissociation could also be observed for the TMT measures. Patients with AD-MCI performed descriptively worse in the TMT-A (measuring processing speed), whereas patients with PD-MCI performed worse in the TMT-B (additional set-shifting) and even significantly worse in the TMT-B/A. The latter ratio reflects a purer measure of set-shifting and cognitive flexibility by diminishing the influence of psychomotor demands,38 which might be particularly impaired in patients with PD-MCI. Therefore, impairments in the TMT-B observed among patients with PD-MCI might be more strongly influenced by deficits in set-shifting, which constitutes an executive function, whereas it might be more influenced by general deficits in processing speed among patients with AD-MCI.38

A descriptively reduced performance for the PD-MCI group compared to the AD-MCI group was observed for the Figure Copy task, whereas the ratio was reversed for the Figure Recall and Savings tasks. These findings highlight the presence of memory deficits across modalities for the AD-MCI sample and suggest that visuo-cognitive deficits may be more prominent in PD-MCI for an ongoing systematic review in this context, see PROSPERO ID: CRD42018088244).

These findings, in addition to the results of the logistic regression analysis, which provided a global estimate of the predictive accuracy of cognitive profiles to differentiate between AD-MCI and PD-MCI, highlight the importance of applying neuropsychological test batteries capable of assessing a broad spectrum of functions during clinical practice. The subscores derived from the TMT emerged as valuable predictors for the underlying diagnosis of both AD-MCI and PD-MCI in the logistic regression analysis, which supports the extension of the established CERAD test battery20,22 to the CERAD-Plus.21 However, this extension has only been well established in the German-speaking market thus far. By gauging such detailed cognitive profiles, clinicians might be able to capture relevant cognitive impairment both early and broadly. This may facilitate the drawing of inferences regarding the progress of cognitive decline across diagnoses and accelerate the diagnostic workflow during the crucial MCI state. Furthermore, a detailed cognitive examination is fundamental for the development of individualized and disease-specific treatment approaches and the promotion of precision medicine approaches for the prevention and therapy of cognitive decline, including pharmacological and non-pharmacological (e.g., cognitive training and rehabilitation39,40) interventions.

Important limitations of this profile comparison include the likely specificity of our findings to moderate and severe MCI stages and the limited number of available neuropsychological tests to assess some of the cognitive domains under investigation (e.g., only one test was used to assess visuo-construction). The latter resulted in the decision not to attempt any domain-wise analysis. Furthermore, this type of analysis would have required the assignment of cognitive tests to single cognitive domains and a more comprehensive discussion regarding the factor-structure of cognition,41 which we were unable to adequately address given the tests available in our samples. Furthermore, although we unified the inclusion and exclusion criteria of the MCI diagnosis across the two studies on a conceptual level, differences in the concrete assessment of the presence of subjective cognitive decline and everyday functioning remain. Future research may also investigate the usefulness of the base rate approach for identifying patients with MCI, regardless of further supporting MCI criteria (i.e., the
presence of subjective cognitive complaints and preserved everyday functioning).

The strengths of this profile comparison include a large, balanced sample size of reliable MCI cases and the careful application of the base rate criteria to unify the cognitive criteria of the MCI diagnoses across two different etiologies. Further strengths include the robust results within the analyses, which persisted even when controlling for global cognition, and the cross-validation procedure used for the logistic regression analysis. Additionally, this study only included those patients with AD-MCI that were supported by a biomarker-based AD profile. Another strength of this profile comparison was that all test scores were standardized using published normative data correcting for age, sex, and education. Accordingly, the results of the reported cognitive profile comparison can be considered to be valid despite etiology-dependent observed (and expected) differences in sex distribution that may otherwise bias cognitive outcomes.

In conclusion, patients with AD-MCI were more impaired in measures of memory and language, whereas patients with PD-MCI were more impaired in a measure of executive function. Furthermore, we found some evidence that similar levels of impairment in one cognitive test might be attributable to differential underlying mechanisms, reflecting the differential influence of contributing cognitive functions. Future data-driven approaches may be able to shed further light on this aspect. Finally, neuropsychological test batteries in clinical practice should include a broad spectrum of cognitive domains to capture any cognitive changes.

ACKNOWLEDGMENTS
The authors thank all patients participating in the two studies and all staff members in the recruiting centers who contributed to the study. The German Dementia Competence Network (DCN) study has been supported by a grant from the German Federal Ministry of Education and Research (BMBF; project number 01GI0420). The DEMPARK study was funded by an unrestricted grant from Novartis and a grant from the International Parkinson Fonds (Deutschland) GmbH (IPD). The continuation of the DEMPARK study (LANDSCAPE) was part of the Competence Network Degenerative Dementias and is funded by the BMBF (project number 01GI1008C).

DATA AVAILABILITY STATEMENT
The data are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST
AO, SW, SR, AP, ASp have nothing to disclose. LF received consulting honoraria or lecture fees from Abbvie, Biogen, and Roche, outside the submitted work; received grant support/case payment for work in clinical trials from Biogen, Roche, Novartis, Janssen, Pharmatrophix, Eisai, and Fujifilm, outside the submitted work. AR, JW, have nothing to disclose. ILS reports grants from International Parkinson Fonds (Deutschland) GmbH (IPD), grants from Johnson & Johnson, a grant from the Michael J. Fox Foundation, grants from European Commission, H2020-TWINN-2015, outside the submitted work. SB, DB, JBS, KR, JW, have nothing to disclose. JKa has received fees as speaker and/or advisor from UCB Pharma, Desitin, Novartis, Bial, Zambon, Medtronic, Desitin, AbbVie, NeuroDerm, and Teva Pharmaceuticals. AST, MBG, RHR have nothing to disclose. KW reports personal fees from BIAL, personal fees from Desitin, personal fees from UCB, personal fees from Stadapharm, outside the submitted work. BM, CT, HUW, OR have nothing to disclose. RD reports personal fees from AbbVie, personal fees and non-financial support from Axon Neuroscience, non-financial support from Akademie für medizinische Fortbildung, personal fees from Agentur Süh, personal fees and non-financial support from Bayer, grants from Baxter, personal fees from Bial, personal fees and non-financial support from Biogen, personal fees and non-financial support from Bayer Vital, personal fees and non-financial support from BB-Biotech, grants and non-financial support from Deutsche Gesellschaft für Neurologie, non-financial support from Deutscher Hausärztekammer, personal fees from Deutsches Zentrum für neurodegenerative Erkrankungen, grants and non-financial support from Deutsche Parkinson Vereinigung, non-financial support from Deutsche Gesellschaft Parkinson, personal fees and non-financial support from Desitin, non-financial support from European Brain Council, grants from EU-Horizon, personal fees and non-financial support from Eisai, personal fees from Elsevier, grants from Ernst und Margot Faber Stiftung, personal fees and non-financial support from Gemeinsamer Bundesausschuss, personal fees and non-financial support from GE Healthcare, grants from GE Healthcare General Electric, personal fees and non-financial support from International Parkinson and Movement Disorder Society, personal fees and non-financial support from Institut für häusärztliche Fortbildung im Deutschen Hausärztekammer, personal fees and non-financial support from IAK+, personal fees and non-financial support from Johanniter, personal fees from Kohlhammer, grants and personal fees from Lilly, grants from Michael J. Fox Foundation, grants, personal fees and non-financial support from Novartis, personal fees from Ono Pharma, personal fees and non-financial support from Pfizer, personal fees and non-financial support from Paul-Martini-Stiftung, non-financial support from Programm Demenz, personal fees and non-financial support from Roche, personal fees and non-financial support from Schwabe, personal fees from Springer Verlag, grants from Stichting International Parkinson Fonds, personal fees from Thieme Verlag, personal fees and non-financial support from UCB Pharma, personal fees from Hummingbird, grants from BMBF, outside the submitted work; in addition, Dr. Dodel has a patent Alpha-Synuclein Epitopbereiche (Bindungsstellen) natürlich vorkommender humane Alpha-Synuclein Autoantikörper zur Diagnostik und Therapie von Morbus Alzheimer und anderen neurodegenerativen Erkrankungen issued, a patent Diagnosis of Alzheimer’s Disease and other...
neurodementia diseases of AD-type and AD-therapeutic application issued, a patent Diagnosis, Prohylaxis and Therapy of Alzheimer’s Disease and other neurodementing disorders issued, a patent ELISA-Test zur Bestimmung von Amyloid Beta Auto-Antikörpern in humanen Serum-/Plasma-/CSF-Proben issued, a patent Herstellung von oligomeren (trimeren) beta-Amyloid Molekülen mittels spezifischer Mutationen issued, a patent Künstliche Mini-Amyloide zur Diagnose und Behandlung der Alzheimer Demenz issued, a patent Naturally occurring autoantibodies against alpha-synuclein that inhibit the aggregation and cytotoxicity of alpha-synuclein mit Dr. Rentschler Holding GmbH & Co KG issued, and a patent Verfahren, insbesondere Enzyme-linked Immunosorbenz Assay (ELISA) zum in vitro Nachweis von Amyloid beta Auto-Antikörpern, Mikrotiterplatte und Testkit issued. MW has nothing to disclose. EK reports grants.

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How to cite this article: Ophey A, Wolfsgruber S, Roeske S, et al. Cognitive profiles of patients with mild cognitive impairment due to Alzheimer’s versus Parkinson’s disease defined using a base rate approach: Implications for neuropsychological assessments. Alzheimer’s Dement. 2021;13:e12223. https://doi.org/10.1002/dad2.12223