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Deficits in or Preservation of Basic Number Processing in Parkinson's Disease? A Registered Report

Hannah D. Loenneker[1] | Christina Artemenko[1,2] | Klaus Willmes[3] | Inga Liepelt-Scarfone[4,5,6] | Hans-Christoph Nuerk[1,2,7]

[1]Department of Psychology, University of Tuebingen, Tuebingen, Germany | [2]LEAD Graduate School & Research Network, University of Tuebingen, Tuebingen, Germany | [3]Department of Neurology, RWTH Aachen University, University Hospital, Aachen, Germany | [4]Department of Clinical Neurodegeneration, Hertie Institute for Clinical Brain Research, Tuebingen, Germany | [5]German Centre for Neurodegenerative Diseases, Tuebingen, Germany | [6]IB-Hochschule für Gesundheit und Soziales, Stuttgart, Germany | [7]German Center for Mental Health, Tübingen, Germany

Correspondence: Hannah D. Loenneker (hannah-dorothea.loenneker@uni-tuebingen.de)

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ABSTRACT

Neurodegenerative diseases such as Parkinson's disease (PD) have a huge impact on patients, caregivers, and the health care system. Until now, diagnosis of mild cognitive impairments in PD has been established based on domain-general functions such as executive functions, attention, or working memory. However, specific numerical deficits observed in clinical practice have not yet been systematically investigated. PD-immanent deterioration of domain-general functions and domain-specific numerical areas suggests mechanisms of both primary and secondary dyscalculia. The current study systematically investigated basic number processing performance in PD patients for the first time, targeting domain-specific cognitive representations of numerosity and the influence of domain-general factors. The overall sample consisted of patients with a diagnosis of PD, according to consensus guidelines, and healthy controls. PD patients were stratified into patients with normal cognition (PD-NC) or mild cognitive impairment (level I-PD-MCI based on cognitive screening). Basic number processing was assessed using transcoding, number line estimation, and (non-) symbolic number magnitude comparison tasks. Discriminant analysis was employed to assess whether basic number processing tasks can differentiate between a healthy control group and both PD groups. All participants were subjected to a comprehensive numerical and a neuropsychological test battery, as well as sociodemographic and clinical measures. Results indicate a profile of preserved (verbal representation) and impaired (magnitude representation, place × value activation) function in PD-MCI, hinting at basal ganglia dysfunction affecting numerical cognition in PD. Numerical deficits could not be explained by domain-general cognitive impairments, so that future research needs to incorporate domain-specific tasks of sufficient difficulty.

1 | Introduction

Modern societies currently face the challenges of demographic changes, with age-associated diseases bringing medical, financial, and psychological burdens to patients, caregivers, and the healthcare system. In the elderly population above 60 years of age, the overall prevalence of mild cognitive impairment ranges between 12% and 18% (Petersen 2016) whereas dementia affects 5% to 7% (Prince et al. 2013). Severe cognitive impairment and dementia are associated with a loss of independent functioning and social and legal competence (Sherod et al. 2009). Therefore, supporting active participation in society and functional

Summary

- Numerical activities in daily living are crucial for economic, medical, and legal independence of the elderly.
- As demented patients make errors with money, public transport, or medication early in the disease process, these numerical deficits need to be investigated thoroughly as they negatively impact quality of life, mortality, and caregiver burden.
- Parkinson's disease is an age-related neurodegenerative disease for which little is known about the basic number processing abilities of patients.
- We showed that patients with mild cognitive impairment have deficits in some (comparing numbers, estimating numbers on the number line), but not all numerical tasks.

independence of the elderly (with cognitive deficits) seems to be one of the most crucial challenges.

Parkinson's disease (PD) is characterized by apparent motor deficits like bradykinesia, rigidity, and resting tremor (Postuma et al. 2015). The presence of nonmotor symptoms is common in PD patients and has a substantial impact on their quality of life (Prakash et al. 2016). The development of Parkinson's disease dementia (PDD), especially in more advanced PD disease stages, leads to an increased risk for nursing home placement and mortality (Aarsland et al. 2000; Bjornestad et al. 2017). The presence of mild cognitive impairment in PD patients (PD-MCI) is associated with a shorter window of time before PDD onset and is therefore considered as one of the most important risk factors for dementia (Aarsland et al. 2017). Onset of cognitive dysfunction varies over the disease course and deficits can sometimes already be identified at the time of PD diagnosis using sensitive instruments (Kehagia, Barker, and Robbins 2010; Martinez-Horta and Kulisevsky 2019).

Societal burdens caused by PD on a regional to global scale clearly show the need to develop diagnostic instruments for the disease-immanent cognitive deficits to anticipate the burden on patients and caregivers (Dorsey et al. 2018). Considering the most recent knowledge about PD neuropathology and symptoms, different cognitive biomarkers might serve this purpose (Roheger, Kalbe, and Liepelt-Scarfone 2018).

1.1 | PD—Epidemiology and Clinical Symptoms

PD is the second most common neurodegenerative disease world-wide with over 6 million affected patients globally (Dorsey et al. 2018). Prevalence differs depending on sex and age with a higher incidence in men and the elderly (Hirsch et al. 2016). In terms of cognitive symptoms, the prevalence of PDD in the United States is predicted to at least double between 2015 and 2060 (Savica et al. 2018). All of these epidemiological estimates show that PD already signifies a huge concern for the public health system and will become even more crucial in the future due to demographic changes (Dorsey et al. 2018; Kowal et al. 2013).

The apparent cardinal symptoms of PD are hypo- and bradykinesia alongside at least rigidity and/or resting tremor (Postuma et al. 2015). Nonmotor symptoms can include dysautonomia (e.g., incontinence and sleep disorders) or be psychiatric in nature (e.g., depression; Jankovic 2008). Furthermore, the cognitive symptoms discovered thus far imply deficits in the domains of executive functions, working memory and attention, memory, language, and visuospatial functions (Aarsland et al. 2017; Litvan et al. 2012).

Further differentiation of cognitive deficits in PD can be pursued on a continuum ranging from normal cognition (PD-NC) over the initial stage of clinically significant cognitive disorders (PD-MCI) to PDD, implying a therapeutic indication. Diagnosis of PD-MCI is based on impairments in global cognition or in at least one of the domains of executive functions, working memory and attention, memory, language, and visuospatial functions (Emre et al. 2007; Litvan et al. 2012). Deficits in PDD additionally affect activities of daily living (ADL) such as dressing, housekeeping, and financial management (Christ et al. 2013).

Cognitive disorders in PD patients are characterized by marked heterogeneity, with 30% to 60% moving from PD-NC to PD-MCI or PD-MCI to PDD within 3 to 4 years (Janvin et al. 2006; Lawson et al. 2017). Development of PD-MCI can arise from fronto-striatal malfunctioning (triggered by dopaminergic deficits) and posterior-cortical impairments (caused by Lewy bodies and non-dopaminergic deficits) with the latter being most predictive of PDD (Barker and Williams-Gray 2014). Whether this posterior-cortical profile describes one homogenous etiology is still being investigated (Monchi, Hanganu, and Bellec 2016). Cognition of PD patients is further impacted by factors such as education, aging, comorbidities, and gender (Lin et al. 2018). According to recent findings, one of the most important risk factors for PDD—besides male sex, old age, and severity of motor symptoms—is the occurrence of PD-MCI (Aarsland et al. 2017). Therefore, the development of sensitive instruments for the identification of PD-MCI patients with a high risk of PDD progression is necessary to initiate timely individual and societal compensatory and supportive strategies (Martinez-Horta and Kulisevsky 2019). Surprisingly, the domain of numerical cognition has been neglected despite the apparent deficits of PD patients observed in clinical practice.

At the PD-MCI stage, cognitive deficits are mild enough to be addressed by therapeutic interventions (Leung et al. 2015). The aim of cognitive training is to improve daily functioning and increase self-sufficiency. Within this framework, a very important domain necessary for daily functioning is numerical literacy, including financial capabilities, time management, and household planning. The management of complex numerical and arithmetic processes requires the integration of different basic number processing functions. If these functions are impaired, deficits need to be considered in therapy, remediation, and intervention. However, the lack of research in this field does not allow for any conclusions to be drawn. For this reason, the current study systematically investigated deficits in the basic number processing abilities of PD patients based on established neurocognitive theories.

1.2 | Theories of Basic Number Processing

Possible deficits in the number processing abilities of PD patients can be characterized by looking at the underlying functions of non-pathological numerical cognition. Neurocognitive models of number processing (i.e., the triple code model and its extensions; Dehaene et al. 2003; Dehaene and Cohen 1995; Klein et al. 2016) consider *number magnitude* as the core representation of numerosity, which can be further differentiated. The *approximate number system* (ANS) is supposed to underlie basic numerical operations, whereas *magnitude* is also represented *symbolically* for more accurate processes (Cantlon, Platt, and Brannon 2009; Dehaene 2001, 2009). Whether or not the same number module underlies these two (non-) symbolic number magnitude representations is controversial (Fias et al. 2003; Holloway, Price, and Ansari 2010; Lyons, Ansari, and Beilock 2012; Matejko and Ansari 2016). The acuity of the ANS can be evaluated using nonsymbolic number magnitude comparisons. Both symbolic and nonsymbolic number representations can be addressed by studying distance effects in (non-) symbolic number magnitude comparison tasks.

Furthermore, there are *visuospatial magnitude representations* (Dehaene et al. 2003; Nuerk et al. 2011). These can explain so-called spatial-numerical associations, where different numerical attributes are associated with space (Cipora et al. 2018). Number line estimation can be used to assess this visuospatial representation of magnitude.

An additional prerequisite for the processing of multi-digit numbers is *place × value integration*. For the appropriate magnitude judgment as well as the application of mathematical operations on multi-digit numbers, distinct places and corresponding values need to be identified, manipulated, and/or integrated (Nuerk, Moeller, and Willmes 2015). Place × value integration is revealed by the occurrence of specific errors in transcoding tasks as well as the unit-decade-compatibility effect in symbolic number magnitude comparisons of two-digit Arabic numbers. To investigate all of these representations of number processing, an effect-based approach is preferred over a task-based approach and was used in the current study (Nuerk et al. 2011).

For basic number processing to be performed successfully, both domain-specific numerical and domain-general functions are necessary (covered by the fronto-parietal network of number processing; Klein et al. 2016). On the one hand, deficits in basic number processing can be primarily based on domain-specific numerical functions such as number magnitude representation, place-value integration, or knowledge of mathematical procedures. On the other hand, secondary deficits in basic number processing can also result that are triggered by deficits in domain-general functions such as attention, working memory, or executive functions, as these functions are a prerequisite for successful number processing (Knops, Nuerk, and Göbel 2017). Although there is evidence for domain-general deficits in PD patients (Litvan et al. 2012), the effect of PD-characteristic neurodegeneration on domain-specific numerical cognition was investigated here for the first time.

1.3 | Basic Number Processing and PD

Despite the lack of research on basic number processing of PD patients, hypotheses about lost or preserved functions can be generated based on non-pathological aging effects/deficits in other neurodegenerative diseases such as Alzheimer's disease (AD), and the neuroanatomical and functional overlap between basic number processing and PD neuropathology.

Considering human ontogenesis, number processing changes with age. Domain-general factors such as attention, working memory, processing speed, and executive functions play a role in healthy aging processes concerning number processing (Hinault and Lemaire 2016; Li et al. 2004; Schretlen et al. 2000). Numerical deficits associated with aging were found in the precision of the ANS (Halberda et al. 2012) and in financial abilities (Finke, Howe, and Huston 2017). This illustrates the implications of domain-specific and domain-general deficits in healthy numerical aging processes and is the reason why the current study uses a healthy elderly control group.

Research on AD has already identified several pathophysiological mechanisms and predictive biomarkers. The diversity of the deficits experienced by AD patients indicates there may be heterogeneous profiles in the domain of number processing and the overlap with PDD neuropathology is only partial (e.g., the cholinergic system; Bohnen et al. 2003). Therefore, conclusions from these studies are informative, but limited, for PD (Hugo and Ganguli 2014). Deficits in the number processing abilities of AD patients are unique, with the occurrence of specific intrusion errors in transcoding. For this reason, transcoding tasks are suggested for use as part of the AD diagnostic procedure (Kalbe 1999; Rosselli et al. 1998). AD patients also show compensatory brain activation mechanisms shifting to premotor areas due to parietal dysfunction (Ouchi et al. 2004). This shift in neuronal activation might differ for PD, as neurodegeneration in PD also involves the premotor cortex (Lindenbach and Bishop 2013).

Numerical activities of daily living (NADL) are crucial for the economic and legal literacy of patients affected by neurodegeneration (Sherod et al. 2009). As the ability of AD patients to complete associated tasks such as financial management, public transport, or medication management deteriorates early in the disease process (Martini et al. 2003; Sherod et al. 2009), the systematic investigation of deficits in number processing in the context of neurocognitive diagnoses is needed for medicolegal evaluations (Simpson 2014). In most cases when ADL deficits become apparent in a PD patient, the individual has progressed from a state of PD-MCI to PDD (Emre et al. 2007). Because of their negative impact on quality of life, depression, mortality, and caregiver burden, ADL deficits in PD patients need to be identified as early as possible (Leroi et al. 2012). In order to fully understand the genesis of NADL deficits, basic number processing needs to be investigated thoroughly as it represents an earlier stage of numerical impairment.

Kalbe (1999) showed that PDD patients have impairments in counting, transcoding, and number line estimation. It can only be inferred that some aspects of basic number processing are

impaired in PD at the advanced stage of dementia; however, whether deficits are present at earlier disease stages remains unclear. The task-based approach applied by Kalbe (1999) also does not allow for conclusions regarding representations of basic number processing which could be achieved with an effect-based approach. Additionally, her study was conducted with small sample sizes, decreasing generalizability and focused on the AD group (despite the PDD group showing the worst performance as compared with the control, AD, and vascular dementia groups in 7 out of 14 numerical tests). The comparison of the performance of non-demented PD patients with healthy elderly individuals on complex arithmetic tasks showed the presence of several deficits (Liozidou et al. 2012; Martin et al. 2013; Zamarian et al. 2006). These findings indicate the need to systematically investigate which basic numerical representations might be the underlying cause of complex arithmetic deficits and how the course of degeneration affects both PD-NC and PD-MCI patients.

Due to the lack of information on basic number processing in non-demented PD patients, hypotheses to be investigated in the current study can be generated based on the neuroanatomical and functional overlap between basic number processing and the progression of PD neuropathology. The neuropathology of PD is characterized by degeneration of the basal ganglia, which are responsible for dopamine production and are active in neuronal loops of motor control and number processing (Moeller, Willmes, and Klein 2015; Moustafa et al. 2014). Additionally, degeneration occurs in cerebellar and additional subcortical and cortical brain structures, depending on the stage of disease progression (Braak et al. 2003; Caligiore et al. 2016). On the molecular level, an imbalance of the dopaminergic, cholinergic, noradrenergic, and serotonergic systems is accompanied by a characteristic abnormal cortical and subcortical accumulation of protein, the so-called Lewy bodies (Braak et al. 2003). The variety of affected neuronal structures and functions explains diagnostic challenges and the complexity of PD symptoms.

In the course of PD progression, brain areas, which are necessary for basic number processing, become affected sequentially. Several of these areas are involved in domain-specific numerical function so their degeneration implies that patients may exhibit processes of primary dyscalculia. The reduction in acetylcholine production in the nucleus basalis magnocellularis (Braak stage four) is associated with a weakening of projections to the neocortex, such as parietal and temporal areas (Jellinger 2018). This might affect the responsibility of the intraparietal sulcus for (non-)symbolic number magnitude representation and place × value processing as well as superior parietal regions needed for visuospatial representations on a mental number line (Jellinger 2018; Moeller, Willmes, and Klein 2015; Winter et al. 2015). Furthermore, visual number form might be affected and is represented in the temporal cortex (Arsalidou and Taylor 2011; Koob et al. 2014). Inflammation in the angular gyrus and Lewy body-induced degeneration of the hippocampus and posterior cingulate gyrus might affect retrieval from verbal memory and the verbal representation of numerosity (Jellinger 2018; López González et al. 2016; Uribe et al. 2018). Lewy bodies in frontal, cingulate, and the temporal cortex in Braak stage five further impact visuospatial functions and number processing (Arsalidou and Taylor 2011; Collerton et al. 2003; Klein et al. 2016). In Braak stage six, lesions in first order sensory association areas of the neocortex and premotor areas occur, occasionally accompanied by mild changes in primary sensory areas and the primary motor field (Braak et al. 2003). The decrease in dopamine levels further impacts intracortical inhibition in the motor cortex, worsening time estimation (Lindenbach and Bishop 2013). These processes can be linked to deficits in the embodiment of number processing and phonological processing in premotor and supplementary motor areas (Winter et al. 2015). Degeneration of domain-general functions necessary for basic number processing can lead to secondary dyscalculia in PD patients, with degeneration occurring in early disease stages. In Braak stage three, decreased dopamine production in the striatum results in a reduction in the projections to the frontal lobe and consequently deficits in verbal fluency, processing speed, working memory, memory retrieval, attention, and executive functions (Braak et al. 2003; Dirnberger, Frith, and Jahanshahi 2005; Martinez-Horta and Kulisevsky 2019; Rinne et al. 2000).

1.4 | Objectives of the Current Study

The current evidence regarding numerical deficits in PD is scarce, and the differences between PD-NC and PD-MCI have not been investigated at all. Therefore, the aim of the current study is to identify deficits in the basic number processing abilities of PD patients with and without mild cognitive impairment as compared to a healthy control (HC) group. To better understand the underlying mechanisms of behavioral deficits, the influence of both domain-general and domain-specific functions were addressed. The final aim is to investigate whether performance on basic numerical tasks can be used to differentiate between the different cognitive statuses of HC, PD-NC, and PD-MCI and thus be applied in the diagnostic assessment of PD-immanent cognitive disorders.

As level I-PD-MCI based on cognitive screening (level I-PD-MCI) patients are situated at a point of considerable cognitive impairment, they are expected to exhibit worse performance than HC and PD-NC groups. Whether performance of the PD-NC group is closer to the HC or the level I-PD-MCI group was examined.

The above considerations resulted in the following research questions:

1. What effects and representations of basic number processing are impaired in PD patients? (*H1: Basic numerical deficits in PD*)
2. Can basic number processing performance of PD patients be explained by domain-general functions? (*H2: Influence of domain-general functions on basic number processing in PD*)
3. Can basic number processing performance be used to discriminate between HC, PD-NC, and level I-PD-MCI patients? (*H3: Discrimination between the cognitive statuses of PD by tests of basic number cognition*)

Basic numerical processes were investigated with the help of (a) transcoding and (b) number line estimation tasks, and (c) non-symbolic and (d) symbolic number magnitude comparisons.

2 | Methods

2.1 | Statistical Power Analysis and Sample Size Estimation

The sample was composed of the three groups HC, PD-NC, and level I-PD-MCI. Required sample sizes for each hypothesis were computed based on empirical estimates using G*Power (Faul et al. 2007, 2009). Effect sizes were calculated and transformed using Psychometrica (Lenhard and Lenhard 2016).

Systematic studies on the impairment of basic number processing in PD, which can be used for effect size calculations, are scarce. Kalbe (1999) reports differences with large effect sizes between a HC and a PDD group in transcoding ($d = 1.755$), number line estimation ($d = 0.868$), and magnitude comparison ($d = 1.051$). The available effect sizes are expected to be overestimates due to publication bias and the comparison with a cognitively more deteriorated PD patient sample than the ones tested in the current study. Therefore, the smallest effect size was lowered to the conventional effect size for large effects of $d = 0.8$ (Cohen 1992) for separate power analyses estimating the required sample size for the three research questions. Consequently, parameters for the effect size calculations were set to $d = 0.8$, $\alpha = 0.05$, and power = 0.9. In the case of participant exclusion, new participants were recruited for substitution. In case of early ceasing of the testing due to attrition, new participants were recruited, and data of the dropped out patient would only be included in analyses when the patient gave informed consent and has already been assigned to a cognitive group based on the MoCA classification. As performance of PD patients in cognitive tests can be severely affected by other clinical confounders (e.g., age, gender, education, UPDRS-III and/or Hoehn & Yahr staging, disease duration, depression), a maximum of six covariates were be included in the analyses.

2.1.1 | Basic Numerical Deficits in PD (H1)

The ANCOVA sample size was calculated for a comparison between three groups with an effect size of $f = 0.4$ (equivalent to $d = 0.8$) for a maximum of three independent variables assuming a maximum of six clinical confounders. This resulted in a minimum sample size of $n = 111$ participants.

2.1.2 | Influence of Domain-General Functions on Basic Number Processing in PD (H2)

The question of whether performance on numerical tasks can be explained by performance on domain-general tests was addressed with further ANCOVAs. ANCOVA sample size was calculated for a comparison between three groups with an effect size of $f = 0.4$ (equivalent to $d = 0.8$) for a maximum of three independent variables assuming a maximum of six clinical and one cognitive (i.e., seven in total) covariates. This resulted in a minimum sample size of $n = 117$ participants.

2.1.3 | Discrimination Between Cognitive Statuses of PD by Tests of Basic Number Cognition (H3)

The last diagnostic discriminant analysis between HC, PD-NC, and level I-PD-MCI was carried out using a logistic regression. The logistic regression sample size was calculated for an effect size of $OR = 4.27$ (equivalent to $d = 0.8$) for a maximum of 17 predictors assuming normal distributions. This resulted in a minimum sample size of $n = 39$ participants.

For testing all three hypotheses, the same subjects were used with a total sample of $n = 119$ valid data sets (as required for the most complex analysis for Hypothesis 2). Number of patients per group should be approximately n = 39 participants, but this varies slightly due to the recruitment process and the outcome of the cognitive diagnosis based on the neuropsychological test data. We were not able to estimate effect sizes for comparison between the two PD groups, as there are no data published yet on this topic.

2.2 | Participants

This study has been approved by the ethics committee of the University of Tübingen's medical faculty (161/2020BO2) and has been registered at the Deutsches Register für Klinische Studien (DRKS-ID: DRKS00021091) and with the World Health Organization (Universal Trial Number: U1111-1257-2901). Patients were recruited via the PD outpatient clinic and in collaboration with rehabilitation facilities specialized in PD. In addition, previously studied PD patients who gave their consent (Ethical vote: 199/2011BO1) to be contacted in the case of further potential study participation were contacted. Patients' caregivers were recruited as healthy controls according to defined inclusion and exclusion criteria. Furthermore, pensioners' initiatives were contacted for control group recruitment, and the study was advertised using the university mailing system. All participants received monetary compensation. In the recruitment process, participants were matched on the group level according to the following criteria: age ($M \pm 5$ years) and gender (max. 65% male). This resulted in sociodemographic and clinical group means that were as similar as possible. Disease duration cannot be corrected for in this way because cognitive status is confounded with disease duration in PD-MCI patients, who also have a longer PD history as indicated by PD-specific disease progression (Lin et al. 2018). As PD medication can heavily influence experimental performance, all patients were tested in their "on-state" and were allowed to take their regular medication during the session if necessary.

Inclusion and exclusion criteria are listed separately for all three groups in Table 1. Idiopathic PD diagnosis according to the United Kingdom Brain Bank criteria (Hughes et al. 1992) needed to be confirmed by a movement disorder specialist in the outpatient clinic of the University Hospital of Tuebingen. Verification of the diagnosis was required before inclusion in

TABLE 1 | Inclusion and exclusion criteria by cognitive status.

(Sub-)group	Inclusion criteria	Exclusion criteria
General	• ≥60 years of age • (Corrected) hearing and vision • Fluent German skills & German schooling • Informed consent, voluntary participation • Stable health status (i.e., able to conduct the entire testing, comorbidities may be present but do not affect test performance) • Permission to ask a caregiver to verify patients rating on the occurrence of ADL problems	• Further neurological diseases impacting the central nervous system except for damage to intervertebral discs • (History of) substance abuse except for nicotine • BDI-II-Score ≥ 20 indicating major depression • Delirium or acute psychosis • Acute psychiatric diseases • Intake of anti-dementia drugs • History/diagnosis of learning disabilities and developmental disorders (e.g., dyslexia, dyscalculia) • Known genetic diseases and family history of genetic diseases (min. 1 first or min. 2s degree relatives) • Currently undergoing chemotherapy
HC	• Normal cognition (MoCA ≥ 26)	
PD	• Diagnosed idiopathic Parkinson's syndrome	• Severe impulse control disorder, dopamine dysregulation syndrome interacting with the patient's everyday life
PD-NC	• Normal cognition according to MDS Task Force level I diagnosis guidelines (e.g., MoCA ≥ 26)	• Diagnosis of cognitive impairment (level I-PD-MCI based on cognitive screening or PDD; Emre et al. 2007; Litvan et al. 2012)
Level I-PD-MCI based on cognitive screening	• Mild cognitive impairment according to MDS Task Force level I diagnosis guidelines and diagnostic cutoff point based on Hoops et al. (2009; 26 > MoCA > 18)	• Diagnosis of PDD (Emre et al. 2007)

the current study and needed to be documented in a patient's record. The assessment of the UPDRS-III motor examination was conducted based on a training in the PD outpatient clinic. The healthy control group was recruited as similarly as possible to the two PD groups in regard to age, education, and gender. Additionally, a spouse, child, other relative, or friend of legal age of all PD patients who agreed to report on the presence and severity of PD-related ADL problems (see section caregiver assessment) was asked for an assessment of the patient.

The cognitive diagnosis leading to assignment to the PD-NC group, the level I-PD-MCI group, or exclusion in the case of PDD was carried out according to the Level I MDS Task Force criteria for PD-MCI and PDD (Emre et al. 2007; Litvan et al. 2012). This implied a cutoff score of 26 on the screening tool Montréal Cognitive Assessment (MoCA; Nasreddine et al. 2005) to differentiate between PD-NC and level I-PD-MCI and absence of significant ADL impairment impacting everyday life to rule out PDD. The investigator HL verified the diagnosis of each participant based on the MoCA cutoff criteria with the experienced neuropsychologist ILS. Impairment of ADL was operationalized with an FAQ cutoff score of ≥ 3 (see Becker et al. 2021). For the cognitive diagnosis, patients and caregivers were asked whether they have noticed progressive deterioration of the patient's cognitive state. The same MoCA cutoff score was used for the exclusion of individuals with cognitive impairment from the HC group. The MoCA (Nasreddine et al. 2005; Thomann et al. 2018) is a short screening instrument for *global cognitive functions*, evaluating short-term memory, visuospatial and executive functions, attention, language, and orientation to time and space. It has a maximum score of 30 and uses education status correction for patients with 12 years of education or less.

2.3 | Materials

Our materials and programmed experiments are openly available via the Open Science Framework (https://osf.io/ap6je/). If the participants gave their consent for study inclusion, inclusion and exclusion criteria were checked during a clinical visit or via a telephone call using a semi-standardized questionnaire.

2.3.1 | Introductory Interview

An introductory interview was used at the beginning of experimental sessions to acquire information on sociodemographic (age, gender, years of education, handedness, and mother tongue) and clinical variables (diagnosis, age at disease onset, medication for depression and cognition). Furthermore, Levodopa equivalence dose (LEDD; DGN 2016; Tomlinson et al. 2010) was calculated based on current dopaminergic medication and time since last dopaminergic medication intake was recorded. Regarding experience with mathematics, participants were asked for preceding employment and associated mathematical experience (based on The

International Standard Classification of Education ISCED 2011; UNESCO 2012), level of income (below/ above/ average), math-related leisure activities, and self-rating of mathematical skill. For the cognitive diagnosis, patients were asked whether they have noticed a progressive deterioration of their cognition.

2.3.2 | Motor Performance

Performance concerning PD motor symptoms was evaluated with the sum score of the MDS revision of the Unified Parkinson's Disease Rating Scale Part III and IV and the items *Tremor, Walking and balance* and *Freezing* from Part II (UPDRS II, III & IV; Goetz et al. 2008) and Hoehn & Yahr staging (Hoehn and Yahr 1967). The motor examination of *UPDRS-III* covers the domains speech, facial expression, rigidity of neck and extremities, hand and finger movements, toe tapping, leg agility, rising from a chair, (freezing of) gait, posture and stability, global spontaneity of movement, postural and kinetic tremor of hands, and rest tremor amplitude as well as constancy of rest tremor. Evaluation follows a scale ranging from 0 = normal to 4 = severe, with high values indicating more pronounced motor impairment. A total score maximum of 132 based on 18 items (with several items relating to multiple extremities resulting in 33 scores) was calculated and included in the analysis. The subtest *UPDRS-IV* was carried out to assess dyskinesia, motor fluctuations, and dystonia based on six items with a score ranging from zero to 24 points. The *Hoehn & Yahr score* ranging from one to four (1 = unilateral involvement only; 2 = bilateral involvement without impairment of balance; 3 = mild to moderate involvement, some postural instability, physical independence, and need for assistance in recovery from pull test; 4 = severe disability, and ability to stand and walk unassisted) was assessed as an additional measure for PD severity. Alongside performance on the *UPDRS*-III, the items from *UPDRS-II* are needed to classify patients as being of the *tremor* or *postural instability and gait disorder* (*PIGD*) motor type (Stebbins et al. 2013).

2.3.3 | Neuropsychological Test Battery

Performance in the cognitive domains of executive functions, working memory and attention, verbal memory, language, and visuospatial functions were assessed with at least one test per domain. For each test, raw scores were included as covariate measures.

For *executive functions*, inhibition was assessed with the subtest Go/No Go "2 out of 5" in the test battery of attention (TAP = Testbatterie zur Aufmerksamkeitsprüfung; Zimmermann and Fimm 2017). Participants were required to discriminate five types of stimuli and to react to only two of them. Performance on this test was measured by the number of errors.

Working memory abilities were assessed in a letter span forward and backward task (as in Soltanlou, Pixner, and Nuerk 2015). Participants had to listen to letter strings of increasing length. In the first part, they had to reproduce them in the same order, and in the second part, the letters had to be reproduced in reverse order. The relevant outcome variable was the maximum length of reproduced letter strings backwards. *Visuospatial working memory* was assessed with the Corsi Block-Tapping Test, requiring to mimic a sequence of blocks tapped on by the experimenter in the correct forward and backward order (Corsi 1972; Kessels et al. 2000). Sequences increased starting from two blocks with a maximum of nine, when both items of the same length were correctly reproduced, and the outcome measure was the longest Corsi backward span correctly reproduced. *Attention* was measured with the TAP subtest Alertness (Zimmermann and Fimm 2017). The test required a simple reaction to a visually presented stimulus with or without prior notice via an auditory cue. The median RT in conditions without an auditory cue (as a measure of intrinsic arousal) was used as the outcome variable.

Verbal memory was measured with the Verbaler Lern- und Merkfähigkeitstest (VLMT; Helmstaedter, Lendt, and Lux 2001). Participants had to learn, recall, and recognize super-span lists of words after different time intervals and an intruding list of distractors. The relevant measure of performance was the sum score for delayed recall.

The German version of the WAIS-IV subtest Similarities (Petermann 2012) measured *language* operationalized as the conceptual understanding of two words by indicating what they have in common. The total number of correctly solved items was used as a measure of word knowledge.

The Benton Line Orientation Test (Benton, Varney, and Hamsher 1978) is a measure of *visuospatial function* where two lines of a certain angle and position are presented on a sheet of paper. Patients were supposed to compare these two lines, with 11 lines being arranged in a star-shaped fashion around a centre. Identifying the two lines out of the displayed 11 lines correctly was scored as one point and a maximum sum score of 15 could be achieved.

2.3.4 | Numerical Tasks

Basic number processing was assessed with computerized procedures and a paper-and-pencil test. The tasks were typical tasks used to assess basic number processing and the related numerical representations. The current study design required a detailed assessment instead of an overall screening, and the control group was used to compensate the lack of standardized norms. The required response mode was adjusted to the PD-immanent motor impairments in as much as cards with single-digit numbers were used (transcoding) and responses were given with easier-to-handle mouse keys (magnitude comparisons, number line estimation). There were no time restrictions in any of the tasks, but testing was stopped if a participant could not answer the first five experimental trials of the current task.

The *transcoding* task consisted of transforming auditory number words into written Arabic digits (16 items) and written Arabic digits into written number words (16 items) in a paper-and-pencil format, with the experimenter presenting items and coding responses manually. The experimental items were preceded by a practice block of three trials each. The outcome measures were overall accuracy and number of errors per category (error categories similar to Kalbe 1999; Zuber et al. 2009).

Lexical errors address the meaning of the digit (i.e., 24 ➔ 25, 90 ➔ 91, 90 ➔ 19). Syntactic errors imply the composition of multi-digit numbers (i.e., additive composition: 360 ➔ 30,060, multiplicative composition: 400 ➔ 4100, and inversion ignored: 182 ➔ 128). Dementia-specific errors are intrusion errors with switches of the response modality (i.e., 2007 ➔ 2thousand7) or intrusions from the preceding item. Orthographic errors were categorized as education- and disease-dependent errors.

The accuracy of a range-dependent number-to-space mapping was assessed in a computerized *number line estimation* task. Participants had to locate 20 given numbers per number line (range: small 0–100, large 0–1,000,000) with the mouse cursor. For each range, numbers were equally distributed over the entire number line and the percent absolute error per range was calculated as the measure of (in)accuracy.

The ANS was assessed with a *nonsymbolic number magnitude comparison* task. Two groups of dots were presented simultaneously next to each other for maximally 800 ms. This presentation phase was followed by the participant's response with a left- or right-hand key press to indicate which group of dots was larger. After an inter-stimulus interval of 900 ms, the next trial was presented. Proportions between the two groups of dots comprised four different ratios (1:2, 3:4, 5:6, and 7:8) with 48 trials each and a minimum group size of four. Furthermore, stimuli were manipulated based on the visual attributes total occupied area, individual dot size, convex hull area, and mean occupancy (i.e., the inverse of density) in a balanced design within each ratio (see Guillaume, Schiltz, and Van Rinsveld 2020). The experimental parameters had to be changed compared to Stage 1, as the stimulus presentation time and inter-stimulus interval initially were too short for even young and healthy participants (see detailed report of changes in Supporting Information). Performance was evaluated with average reaction time per ratio and the Weber fraction as a measure of accuracy with small fractions indicating high accuracy and sharper Gaussian tuning curves (as in Dietrich, Huber, and Nuerk 2015). The Weber fraction stems from modeling psychophysical behavior (such as e.g., discriminating two stimuli of different loudness) and is based on signal detection theory (Dehaene 1993; Kingdom and Prins 2010). It has become the dominant method modeling ANS acuity (Krajcsi et al. 2024). In ANS research, the Weber fraction is a measure of task performance grasping the smallest difference between two groups of dots an individual can detect. It can be obtained using the following formula:

$$f_{\text{acc}}(n_1, n_2, w) = 1 - \frac{1}{2}\text{erfc}\left(\frac{|n_1 - n_2|}{\sqrt{2w}\sqrt{{n_1}^2 + {n_2}^2}}\right)$$

where erfc stands for the complementary Gaussian error function, n_1 and n_2 stand for the respective numbers of dots in Groups 1 and 2, and w stands for the Weber fraction (Dietrich, Huber, and Nuerk 2015). A current critical discussion about the advantages and disadvantages of the Weber fraction in ANS research and whether additional parameters should be considered can be found in the consensus paper of Krajcsi et al. (2024), but is beyond the scope of this paper. Here, we use the Weber fraction in its most standard form for ANS research.

A *symbolic number magnitude comparison* task was used to measure the exact magnitude representation. Participants had to respond with the keys of two mice positioned above each other to indicate which of two numbers (presented vertically aligned, one above the other on a screen) is larger. The duration of stimulus presentation was until the participant pressed the response key. Stimuli were manipulated by unit-decade-compatibility (comparison of units and decades separately would have the same result as the whole number) and distance (small $\leq$30, large $\geq$40; as in Moeller et al. 2012). The number pairs consisted of 60 unit-decade-compatible and 60 unit-decade-incompatible two-digit Arabic numbers as well as 120 filler items (numbers within the same decade). The outcome measures were the average reaction times for compatible vs. incompatible trials and small vs. large distances. This allowed for the assessment of the unit-decade-compatibility effect (faster reaction to compatible trials) and the distance effect (faster reaction to large distances; Nuerk, Weger, and Willmes 2001). Furthermore, overall accuracy was calculated.

2.3.5 | Clinical Questionnaires for NonMotor Assessment, ADL, and Quality of Life

In addition to the introductory interview, further clinical variables were assessed with self-report questionnaires. The Nonmotor Symptoms Questionnaire for Parkinson's Disease (NMSQuest; Chaudhuri et al. 2006) is a 30-item screening questionnaire with a categorical answer format of "yes," "no," and "don't know" based on the occurrence of *nonmotor symptoms* in the last month. It allows quantification of sleep disorders, and neuropsychiatric, autonomic, gastrointestinal, sensory, and other symptoms, with the help of a sum score.

Participants' *depressive symptoms* were rated with the Beck Depression Inventory (BDI-II; Hautzinger, Kühner, and Keller 2006) with a cutoff of 20 indicating signs for major depression. The inventory consists of 21 items to be rated for the intensity of occurrence of the symptom on a scale ranging from 0 to 3 (maximum sum score of 63). This questionnaire reflects the patient's feelings during the last 2 weeks.

The Functional Activities Questionnaire (FAQ; Pfeffer et al. 1982) was used to measure current *activities of daily living* in older adults. Participants had to rate their level of performance (ranging from 0 = normal to 3 = dependent) in 10 different daily life activities, resulting in a sum score characterizing ADL.

Health-related quality of life was assessed with the single index score of the 39-item Parkinson's Disease Questionnaire (PDQ-39; Jenkinson et al. 1997). The eight dimensions, such as activities of daily living and social support, were coded on a scale ranging from 0 (= perfect health) to 100 (= worst health).

2.3.6 | Caregiver Assessment

For a broader evaluation of participant ADL, the FAQ was also filled out by a caregiver. Furthermore, caregivers were asked for their relationship with the participant, their demographic data (i.e., age and gender) and the frequency, as well as the intensity,

of contact with the participant. For the cognitive diagnosis, caregivers were asked whether they have noticed a progressive deterioration of the patient's cognitive state.

2.4 | Procedure

Participants gave written informed consent. In the second step, participant eligibility was assessed according to the defined inclusion and exclusion criteria. PD patients were assigned to PD-NC or level I-PD-MCI groups according to their cognitive performance. As the current study belongs to a larger project, the testing was conducted together with further measures which are not included in the current publication (Loenneker et al. 2022). Participants attended two sessions of 1.5 to 2 h each. In order to handle patient attrition, there were breaks within each session when patients needed them. In the first experimental session, the sociodemographic questionnaire, and the numerical tasks transcoding, number line estimation, and nonsymbolic and symbolic number magnitude comparison were carried out in this order. Afterwards, participants and caregivers completed the clinical scales and questionnaires which may also be filled out at home between the first and second session. The second session consisted of the MoCA, clinical variables, motor assessment, and neuropsychological test battery in this order. The two sessions were scheduled 3 weeks apart at maximum.

3 | Data Treatment and Proposed Analysis Pipeline

Data analyses were run with R version 4.2.2 (R Core Team 2014) and JASP version 0.18.1.0 (JASP Team 2018). Data were managed using REDCap electronic data capture tools (Harris et al. 2009). Anonymised data and analyses scripts are freely available on the Open Science Framework (https://osf.io/ap6je/) and PsychArchive (Loenneker 2024). For all inferential statistics, an α-level of 0.05 was assumed and effect sizes were estimated.

3.1 | Data Preprocessing

3.1.1 | Exclusions

Participants with missing data were excluded in a case-wise manner for the analyses including the respective measure. For forced choice format tasks (nonsymbolic number magnitude comparison for the easiest ratio 1:2, symbolic number magnitude comparison, TAP tasks, and Benton line orientation test), participants needed to achieve an accuracy (ACC) of at least 75% to be included in the analysis of the respective measure, while this 75% accuracy threshold relates to the easiest condition (ratio 1:2) in the nonsymbolic magnitude comparison task. In the number line estimation task, understanding of task instruction was checked for by monotony in responses, with participants being excluded if they did not answer overall in a format of numbers ascending from left to right (indicated by a minimum positive space-magnitude correlation of 0.3). Understanding of task instruction in transcoding was assessed with a minimum accuracy of 50% in single-digit trials. Furthermore, participants were excluded from the respective analysis if their performance exceeded 3 *SD* below the group *M*.

3.1.2 | Reaction Times

Data trimming for reaction times (RT) followed Baayen and Milin (2010). After the exclusion of incorrectly solved trials, the RT distribution was inspected with per-subject quantile-quantile plots. This method was pursued to identify the theoretical model for data transformation in order to achieve a normal distribution. The most appropriate distribution was chosen based on the best model fit and used to transform the data. The next step considered two levels of outlier exclusion. Physically impossible RTs were considered to be anticipations faster than 200 ms and were excluded. Then, outliers were excluded based on model criticism. This was achieved with Shapiro tests for normality. Those data points with absolute standardized residuals exceeding 3 were removed. The following, preregistered steps could not be followed (see Supporting Information), as they are incompatible with hypothesis testing using ANCOVAs running on averaged data (only appropriate for generalized linear models considering each observation of each subject): The last step of corrections for temporal dependencies was not applied to the data, including autocorrelation functions by participant and a regression model with a log-transformation for latencies and the covariates trial number and preceding RT. An overview of chosen transformations and excluded observations per preprocessing step can be found in the Supporting Information (Table S2).

3.1.3 | Accuracy

Depending on the best model fit for the empirical distribution of accuracies, these data have either been arcsine- or logit-transformed.

3.1.4 | Assumption Check

After these separate steps of data preprocessing, specific assumptions for statistical hypothesis testing were checked. In the case of a violation of linear model assumptions for the ANCOVA, a robust ANCOVA was conducted. In cases where even after transformations data did not meet all ANCOVA assumptions, parametric ANCOVAs correcting for the confounding variables were conducted on the transformed data which (visually and in terms of reducing skewness) came closest to a normal distribution as well as resampling ANCOVAs with 5000 permutations on untransformed data with the R package permuco (Frossard and Renaud 2021). Predictors of the logistic regression were checked for collinearities based on a variance inflation factor below 10. However, we still need to stress the caveat that the variable group was unbalanced due to unequal group sizes, whereas all within-subjects variables were experimentally manipulated in a balanced design.

3.2 | Group Characteristics

Sociodemographic, clinical, and cognitive variables were compared between the three groups in order to identify possible

TABLE 2 | Sociodemographic and clinical characteristics per group.

	HC ($n=40$)	PD-NC ($n=50$)	HC vs. PD-NC p (BF_{10})	Level-I PD-MCI ($n=29$)	PD-NC vs. Level-I PD-MCI p (BF_{10})
Sociodemographic					
Age *M* (*SD*)	68.8 (5.80)	69.6 (6.11)	0.524 (0.27)	70.9 (5.82)	0.356 (0.35)
Gender (female) *n* (%)	20 (50.0%)	22 (44.0%)	0.723 (0.44)	7 (24.1%)	0.128 (1.74)
Education years *M* (*SD*)	17.0 (2.92)	15.3 (3.75)	**0.013 (3.01)**	13.3 (3.58)	**0.022** (2.33)
Clinical					
Disease duration *M* (*SD*)		7.45 (4.88)		9.27 (5.22)	0.133 (0.68)
Age at onset *M* (*SD*)		62.1 (7.37)		61.6 (6.38)	0.739 (0.26)
LEDD *M* (*SD*)	0[a]	648 (435)	**<0.001 (>1000)**	997 (656)	**0.014 (7.18)**
Antidepressants *n* (%)	0[a]	8 (16.0%)	**0.023 (9.21)**	3 (10.3%)	0.717 (0.33)
Motor symptoms (UPDRS-III) *M* (*SD*)	1.30 (1.54)	26.3 (12.7)	**<0.001 (4.48)**	32.7 (11.0)	**0.020** (2.21)
Hoehn & Yahr *n* (%)					**0.039 (4.44)**
0		0		0	
1		11 (22.0%)		0 (0%)	
2		31 (62.0%)		21 (72.4%)	
3		7 (14.0%)		6 (20.7%)	
4		1 (2.0%)		2 (6.9%)	
Motor type *n* (%)					0.388 (0.36)
Tremor		17 (34.0%)		6 (20.7%)	
PIGD		26 (52.0%)		19 (65.5%)	
Mixed		7 (14.0%)		3 (10.3%)	
Depression (BDI-II) *M* (*SD*)	3.08 (3.78)	7.83 (5.12)	**<0.001 (>1000)**	8.71 (4.71)	0.449 (0.31)

Note: Two-sided Welch two sample *t*-test for independent samples and Bayesian *t*-tests with $r=0.707$ and JZS prior distribution for continuous variables, Pearson's chi-squared test with Yates' continuity correction and Bayesian contingency tables with joint multinomial sampling for categorical variables. Values marked in bold font represent significance levels of $p<0.05$ and BF10 > 3.0.
Abbreviation: PIGD, postural instability and gait disorder.
[a]Intake of both antidepressants and dopaminergic medication is an exclusion criterion for the control group.

confounding differences between them (see Table 2). The categorical variables gender, motor type, and Hoehn & Yahr staging were characterized as total amount per category and corresponding percentage and compared with chi-squared tests between HC and PD-NC and between PD-NC and level I-PD-MCI groups. Continuous variables were described with *M* (SD) and compared between HC and PD-NC groups and between PD-NC and level I-PD-MCI groups with an independent samples *t*-test. The frequentist group comparisons were supported with the calculation of Bayes factors. These variables are sociodemographic (age and education years) and clinical (disease duration, age at onset, LEDD, and intake of antidepressants) variables. Furthermore, motor (UPDRS-III & IV, motor type) and cognitive function were compared. The last group comparison addressed sum scores of completed questionnaires (nonmotor symptoms: NMSQuest, depression: BDI-II, ADL self-report & caregiver report: FAQ, health-related quality of life: PDQ-39). At this point, we reported the number of HC, PD-NC, and level I-PD-MCI participants being impaired in any of the cognitive measures (see Table S4).

3.3 | Hypothesis Testing

The three groups were first compared regarding sociodemographic and clinical variables. We had planned to include a maximum number of six clinical covariates in all models. The maximum number of covariates were set to seven for the analysis of Hypothesis 2, allowing the additional integration of the cognitive variable with the largest association (minimum correlation of 0.3) for each numerical task separately. We expected to find an ordinal trend of the HC group outperforming both PD-NC and level I-PD-MCI groups, and the PD-NC group outperforming the level I-PD-MCI group. The groups significantly differed in education years, severity of motor symptoms

(UPDRS-III), and depression (BDI-II), which were therefore included as confounding variables in the reported analysis (see Table 2). To avoid multicollinearity with the UPDRS-III, the LEDD was not included as an additional covariate in the models. For all numerical tasks concerning Hypotheses 1 and 2, the ordinal trend of performance decreasing from HC over PD-NC to level I-PD-MCI groups was tested with pairwise ANCOVAs that include the covariates of the respective analysis.

3.3.1 | Basic Numerical Deficits in PD (H1)

The *transcoding* task was analyzed using an ANCOVA with the factor group (HC, PD-NC, or level I-PD-MCI) and the dependent variable ACC. Error categories (lexical errors, syntactic errors, dementia-specific errors, and education- and disease-dependent errors; no rest category) were compared between groups (HC vs. PD-NC, PD-NC vs. level I-PD-MCI, and HC vs. level I-PD-MCI) with chi-squared tests. Performance in *number line estimation* was assessed with a 3 (group: HC, PD-NC, and level I-PD-MCI) × 2 (range: small vs. large)-ANCOVA with percent absolute deviation as the dependent variable. *Nonsymbolic number magnitude comparison* was evaluated with two separate ANCOVAs of the factor group (HC, PD-NC, and level I-PD-MCI) on the dependent variables Weber fraction and overall ACC. Analysis of *symbolic number magnitude comparison* was conducted both for the dependent variables RT and ACC by separate 3 (group: HC, PD-NC, and level I-PD-MCI) × 2 (distance: small vs. large) × 2 (unit-decade compatibility: compatible vs. incompatible)-ANCOVAs. Following this frequentist approach, Bayesian ANCOVAs were calculated to allow for further conclusions on the presence or absence of effects.

3.3.2 | Influence of Domain-General Functions on Basic Number Processing in PD (H2)

The question of whether numerical task performance can be explained by performance on domain-general tests was addressed with further ANCOVAs. ANCOVAs were carried out twice—once in a task-based and once in an effect-based approach. These lines of analysis were preceded by correlational analyses of numerical performance and numerical effect (differing significantly between groups for H1) with possible covariates (executive functions, working memory, attention, verbal memory, language or visuospatial function and motor symptoms and depression). For each numerical task/numerical effect (differing between groups), the cognitive covariate with the highest association was included in the respective model, adding up to a maximum of three covariates including confounders identified for H1. For the task-based approach, this preliminary step is followed by separate ANCOVAs with the factor group (HC, PD-NC, or level I-PD-MCI) and the respective covariates for each numerical task. These ANCOVAs were conducted for ACC (transcoding and (non-)symbolic number magnitude comparison) or percent absolute error (number line estimation). For the effect-based approach, this preliminary step is followed by separate ANCOVAs with the factor group (HC, PD-NC, or level I-PD-MCI) and the respective covariates for each numerical task. These ANCOVAs were conducted on RTs for the respective effects. Following this frequentist approach, Bayesian ANCOVAs were calculated to allow for further conclusions on the presence or absence of effects.

3.3.3 | Discrimination Between Cognitive Statuses of PD Patients by Tests of Basic Number Cognition (H3)

The following analysis was planned in Stage 1: "*The last diagnostic research question will be answered using logistic regression. This discriminant analysis with multiple predictors will be conducted on z-standardized performance scores for tasks differing between groups (i.e., transcoding, number line estimation, nonsymbolic, and/or symbolic number magnitude comparison) as well as significant numerical effects (i.e., Weber fraction, distance effect, and/or unit-decade compatibility effect) with the dependent variable of cognitive status (HC, PD-NC, or level I-PD-MCI). Covariates included in the preceding analyses will also be included in the model (i.e., a maximum of six clinical confounders and four cognitive covariates). The probability for members of the three groups to be (correctly or falsely) assigned to each group will be calculated based on the regression as a measure of prognostic value*." However, as only one task differentiated PD-NC and PD-MCI group, H3 was turned into an exploratory research question for Stage 2 as described in the results section.

4 | Results

4.1 | Sample Characteristics

Participants were tested between during the pandemic, with recurring pandemic-related closures of laboratories in order to create a safe testing environment for this vulnerable sample slowing recruitment. Overall, $N = 150$ participants were tested, of which $N = 119$ ($n = 40$ HC, $n = 50$ PD-NC, $n = 29$ level I-PD-MCI) were included in analyses. Despite numerous, widespread and intensive efforts in recruitment, similar sample sizes of the level I-PD-MCI and PD-NC groups could not be fully reached as preregistered. Poor performance in the MoCA was the main exclusion criteria for patients (score < 19, $n = 3$) and HC (score < 26, $n = 20$), followed by comorbid psychiatric disease for patients (major depression, BDI-II > 19, $n = 6$) and HC ($n = 1$). In addition, presence of other neurologic diagnoses (stroke, $n = 1$) and intake of dementia medication (PD, $n = 3$) and drop-out for medical reasons ($n = 1$) lead to exclusion in the PD patient groups. For some participants, multiple reasons apply.

As shown in Table 2, education years, severity of motor symptoms (UPDRS-III), and depression (BDI-II) were included as confounding variables in the reported analyses. Descriptive information of group performance in numerical tasks, cognitive tasks, and math-related characteristics can be found in the Supporting Information (see Tables S1, S3 and S4).

4.2 | H1) Basic Numerical Deficits in PD—Confirmatory Analyses

4.2.1 | 1a) Transcoding

For transcoding orally dictated number words to written Arabic digits, the ANCOVAs on accuracy correcting for education years, motor symptoms, and depression did not show significant group effects (see Table 3A, Figure 1). In the permuted ANCOVAs, motor symptoms had a significant effect on the performance in

TABLE 3 | ANCOVA models for transcoding.

	Df	Sum of squares	*F*	$p_{parametric}$	$p_{permuted}$	BF_{incl}
(A) Auditory[a]						
Education years	1	2.12	0.55	0.459	0.216	0.44
Motor symptoms (UPDRS-III)	1	15.05	3.91	0.051	**0.039**	**7.06**
Depression (BDI-II)	1	13.45	3.50	0.064	0.147	0.99
Group	2	6.40	0.83	0.438	0.484	0.39
Residuals	104	400.16				
(B) Written[a]						
Education years	1	0.25	4.75	**0.031**	**0.038**	**3.22**
Motor symptoms (UPDRS-III)	1	0.11	2.11	0.150	0.114	**3.74**
Depression (BDI-II)	1	0.04	0.83	0.366	0.603	0.43
Group	2	0.21	1.94	0.150	0.254	1.56
Residuals	105	5.57				

Note: Type III sum of squares ANCOVAs with parametric *p*-values on logit-transformed data for auditory and arcsine transformed data for written transcoding and *p*-values based on permutation testing using untransformed data. BF_{incl} = how much more probable are the observed data under models with the respective predictor, than under models without that predictor, averaged across all models, and using transformed data. Values marked in bold font represent significance levels of $p < 0.05$ and $BF10 > 3.0$.

[a]6 observations less due to missing BDI-II questionnaires.

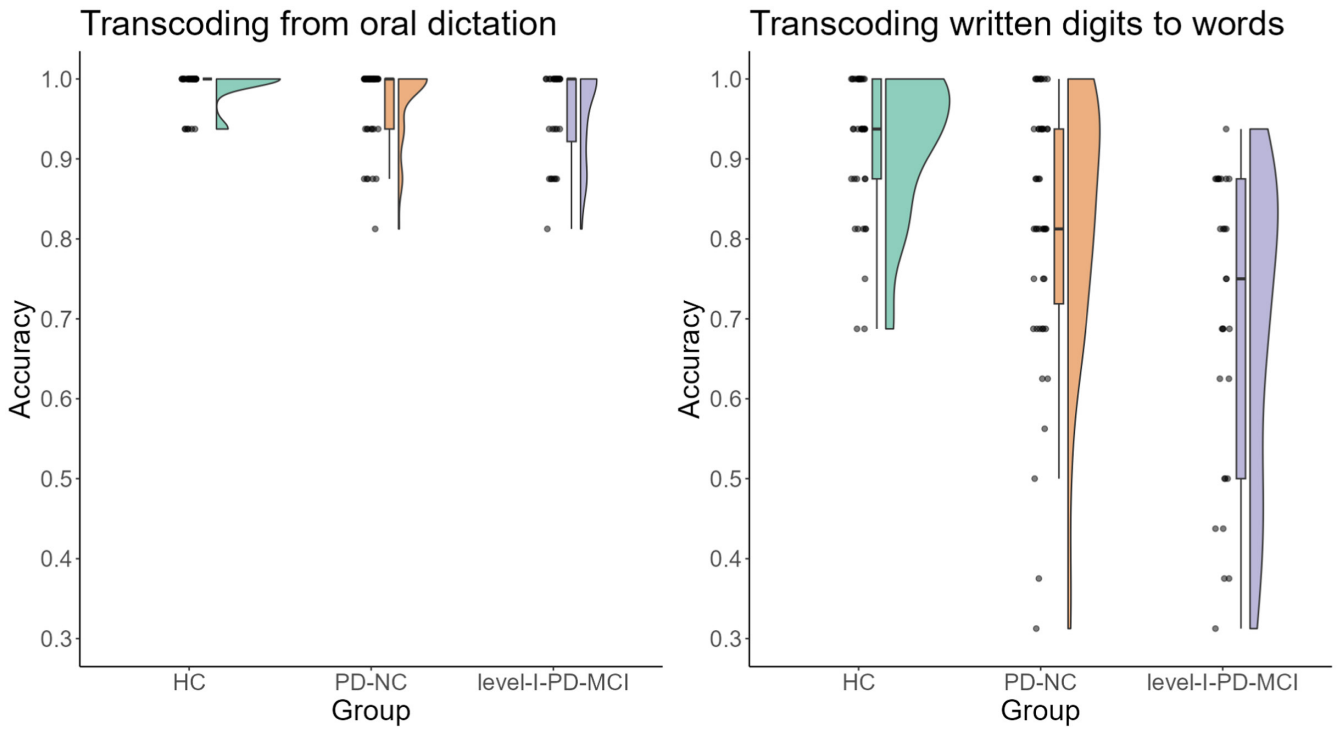

FIGURE 1 | Accuracy in transcoding from oral dictation and written transcoding per group.

auditory transcoding (with moderate Bayesian evidence). The main error categories (lexical, syntactical, memory, dementia-specific and multiple) neither differed significantly between HC and PD-NC, $\chi^2(4) = 4.56$, $p = 0.335$, nor between PD-NC and level-I PD-MCI, $\chi^2(3) = 6.25$, $p = 0.102$, but between HC and level-IPD-MCI, $\chi^2(4) = 9.58$, $p = 0.048$ (see Table 4 and for German examples see Table S13).

For transcoding written Arabic digits into handwritten number words, the ANCOVAs on accuracy correcting for education years, motor symptoms, and depression did not show significant group effects, but a significant effect of education (see Table 3B, Figure 1). The main error categories (syntactical, dementia-specific, orthographic, and multiple) neither differed significantly between HC and PD-NC, $\chi^2(3) = 5.34$, $p = 0.149$,

TABLE 4 | Error categories in transcoding oral dictation to written Arabic digits.

Modality	Category	HC	PD-NC	Level-I PD-MCI	Subtypes
Oral dictation to written Arabic digits	Lexical	3 (50.00%)	9 (45.0%)	2 (10.0%)	Wrong value
	Syntactic	2 (33.3%)	7 (35.0%)	12 (60.0%)	Additive multiplication Inversion Omission
	Memory	0	1 (5.0%)	2 (10.0%)	No answer
	Dementia-specific	1 (16.7%)	0	0	Perseveration
	Multiple: Syntactic & dementia-specific	0	1 (5.0%)	1 (5.0%)	Inversion & perseveration
	Multiple: Syntactic & Lexical	0	2 (10.0%)	3 (15.0%)	Inversion & wrong value Intrusion place & value
		6	20	20	
Written Arabic digits to handwritten number words	Syntactic	6 (11.8%)	13 (8.2%)	19 (13.6%)	Omission Wrong place Wrong construction
	Dementia-specific	0	0	1 (0.7%)	Notational intrusion
	Orthographic	41 (80.4%)	108 (68.4%)	90 (64.3%)	
	Transcoded partially	0	2 (1.3%)	2 (1.4%)	
	Multiple: Lexical & other	0	2 (1.3%)	1 (0.7%)	Wrong value & orthographic
	Multiple: Syntactical & other	2 (4.0%)	11 (6.9%)	10 (7.1%)	Inversion & orthographic Omission & orthographic Step-wise composition & orthographic Zero intrusion, transcoded partially & orthographic Zero intrusion, notational intrusion & orthographic
	Multiple: Dementia-specific & other	0	1 (0.6%)	5 (3.5%)	Notational intrusion & perseveration Syntactic perseveration and wrong place Lexical perseveration & orthographic Notational intrusion, lexical perseveration & orthographic
	Multiple: multiple orthographic	2 (3.9%)	17 (10.8%)	12 (8.5%)	
	Multiple: transcoded partially & other	0	4 (2.5%)	0	Transcoded partially & orthographic
		51	158	140	

nor between PD-NC and level-I PD-MCI, $\chi^2(3) = 2.47$, $p = 0.480$, or between HC and level-I PD-MCI, $\chi^2(3) = 5.90$, $p = 0.117$ (see Table 4 and for German examples see Table S13).

4.2.2 | 1b) Number Line Estimation

The ANCOVA on logit-transformed percent absolute deviation (PAE) data and the bootstrapped ANCOVA on raw data correcting for education years, motor symptoms, and depression did not show a significant group effect, but a main effect of range indicating the large range 0–1,000,000 to be more difficult than the small range 0–100 (with substantial Bayesian evidence, see Table 5A, Figure 2). The ANCOVA on Tukey ladder of power transformed reaction time data and the bootstrapped ANCOVA on raw data correcting for education years, motor symptoms, and depression did not show a significant group effect, but a main effect of range and an interaction of group with range (with small to moderate Bayesian evidence, see Table 5B, Figure 2). Post hoc tests indicated that this interaction is only present in the model subsuming HC and level-I PD-MCI groups ($p_{parametric} = 0.002$, $p_{permuted} = 0.008$, $BF_{incl} = 15.10$, see Supporting Information Table S5) with the level-I PD-MCI group showing a larger range effect than the HC group. Interestingly, level-I PD-MCI patients were faster in the more difficult range 0–1,000,000 than in the easier range 0–100. Motor symptoms were a significant predictor for both dependent variables in number line estimation (with moderate and substantial Bayesian evidence for accuracy and reaction time, respectively).

4.2.3 | 1c) NonSymbolic Magnitude Comparison

The parametric ANCOVA on log-transformed Weber fraction data and bootstrapped ANCOVA on raw Weber fraction data indicated a significant effect of group (with inconclusive Bayesian evidence, see Table 6A, Figure 3), which was shown to delve from differences between PD-NC and level-I PD-MCI groups in post hoc tests ($p_{parametric} = 0.019$, $p_{permuted} = 0.017$, $BF_{incl} = 3.31$, see Supporting Information Table S6). The level-I PD-MCI group showing on average larger Weber fractions indicated less accurate approximate number representations in this group. The parametric and bootstrapped ANCOVAs on untransformed accuracy data correcting for education years, motor symptoms, and depression did not show a significant group effect but an effect of ratio (with substantial Bayesian evidence, see Table 6B, Figure 3), indicating a group-independent decrease in accuracy from the easiest ratio 1:2 up to the most difficult ratio 7:8. The ANCOVA on log-transformed reaction time data and the bootstrapped ANCOVA on raw data correcting for education years, motor symptoms, and depression did not show a significant group

TABLE 5 | ANCOVA models for number line estimation.

	Df	Sum of squares	*F*	$p_{parametric}$	$p_{permuted}$	BF_{incl}
(A) PAE						
Education years	1	1.28	2.32	0.131	**0.029**	0.69
Motor symptoms (UPDRS-III)	1	2.96	5.34	**0.023**	0.171	**10.58**
Depression (BDI-II)	1	1.21	2.17	0.143	0.055	0.63
Group	2	1.77	1.60	0.207	0.730	0.28
Residuals	104	57.67				
Range	1	27.46	60.89	**< 0.001**	**< 0.001**	**> 1000**
Group × Range	2	1.41	1.56	0.215	0.122	0.28
Residuals	107					
(B) Reaction time						
Education years	1	0.00	0.00	0.944	0.672	0.19
Motor symptoms (UPDRS-III)	1	0.00	14.05	**< 0.001**	**< 0.001**	**> 1000**
Depression (BDI-II)	1	0.00	0.06	0.806	0.331	0.19
Group	2	0.00	0.81	0.447	0.264	0.62
Residuals	104	0.00				
Range	1	0.00	9.82	**0.002**	**0.018**	**3.18**
Group × Range	2	0.00	5.49	**0.005**	**0.023**	**5.78**
Residuals	107	0.00				

Note: Type III sum of squares ANCOVAs with parametric *p*-values on logit-transformed data for PAE and Tukey ladder of power transformed data for RT and *p*-values based on permutation testing using untransformed data. BF_{incl} = how much more probable are the observed data under models with the respective predictor, than under models without that predictor, averaged across matched models and using transformed data. Post hoc ANCOVAs indicated that the interaction between group and range in the reaction time model stems from a smaller range effect in the HC than in the level-I PD-MCI group. Values marked in bold font represent significance levels of $p < 0.05$ and $BF10 > 3.0$.

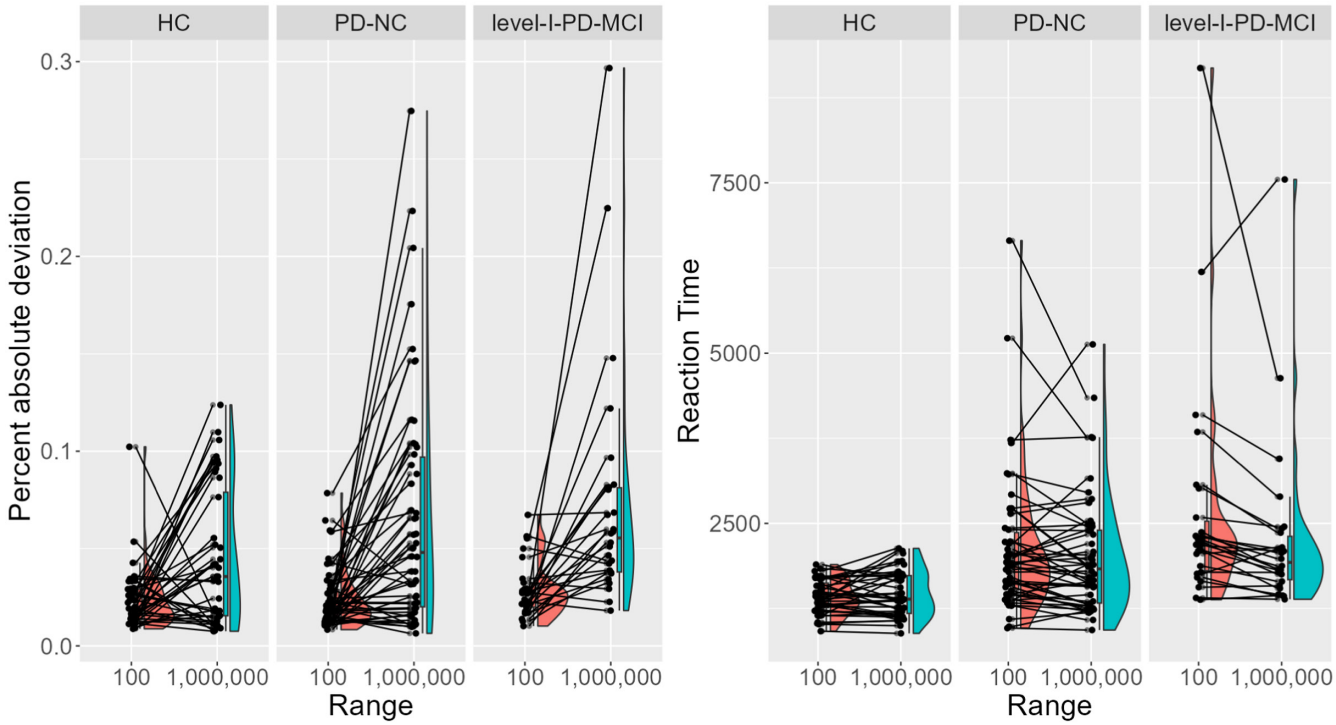

FIGURE 2 | Percent absolute deviation and reaction time in number line estimation by range and group.

effect, but a main effect of ratio (with substantial Bayesian evidence), and the parametric ANCOVA on log-transformed data showed an interaction of group with ratio (with inconclusive Bayesian evidence, see Table 6C, Figure 3). Post hoc tests indicated that this interaction is only present in the model subsuming HC and level-I PD-MCI groups ($p_{\text{parametric}} = 0.007$, $p_{\text{permuted}} = 0.090$, $\text{BF}_{\text{incl}} = 7.77$, see Supporting Information Table S7), where HC had a larger ratio effect than level-I PD-MCI (see also Figure 3), meaning HC profited more from the easiest 1:2 condition. Motor symptoms were only significant in the parametric nonsymbolic magnitude comparison model on log-transformed Weber fraction data (with inconclusive Bayesian evidence), but not in any of the models using the dependent variables overall accuracy and reaction time.

4.2.4 | 1d) Symbolic Magnitude Comparison

The ANCOVA on logit-transformed accuracy data and the bootstrapped ANCOVA on raw data correcting for education years, motor symptoms, and depression showed significant effects of group (with inconclusive Bayesian evidence) and compatibility (with moderate Bayesian evidence), while the bootstrapped ANCOVA also indicated an effect of distance (with inconclusive Bayesian evidence, see Table 7A, Figure 4). Post hoc tests show that the group effect arises from comparing the PD-NC and level-I PD-MCI groups ($p_{\text{parametric}} = 0.018$, $p_{\text{permuted}} = 0.007$, $\text{BF}_{\text{incl}} = 3.06$, see Supporting Information Table S8), while distance is only a significant predictor in the model analyzing HC and PD-NC groups ($p_{\text{parametric}} = 0.029$, $p_{\text{permuted}} = 0.010$, $BF_{incl} = 1.64$, see Supporting Information S8). The ANCOVA on log-transformed reaction time data and the bootstrapped ANCOVA on raw data correcting for education years, motor symptoms, and depression showed a significant group effect (with substantial Bayesian evidence, see Table 7B, Figure 4), which, according to post hoc tests, is anchored in differences between PD-NC and level-I PD-MCI ($p_{\text{parametric}} = 0.002$, $p_{\text{permuted}} = 0.001$, $BF_{incl} = 27.45$, see Supporting Information Table S9). There was a significant main effect of motor symptoms on accuracy (with substantial Bayesian evidence) and on reaction time (with inconclusive Bayesian evidence on the overall ANCOVA, but substantial evidence in pairwise post hoc comparisons) in symbolic magnitude comparison.

4.3 | H2) Influence of Domain-General Functions on Basic Number Processing in PD

Table 8 provides an overview of correlation coefficients between domain-general cognitive and domain-specific numerical measures. Only those tasks from H1 indicating a group difference in numerical performance or in a numerical effect were analyzed for H2 (for complete ANCOVA models, see Supporting Information Tables S10–S12) with only the most highly associated domain-general cognitive measure identified in the correlation analysis being added to the ANCOVA models. When incorporating language (i.e., verbal reasoning) in a model on the dependent variable range effect for reaction time of number line estimation, the group effect remained significant while verbal reasoning was not a significant predictor. In the nonsymbolic magnitude comparison, the group effect was not significant anymore when adding visuospatial working memory to the Weber fraction model, while visuospatial working memory was not a significant predictor. Regarding symbolic magnitude comparison, adding language to accuracy and reaction time models did not change results and this additional covariate was not significant.

TABLE 6 | ANCOVA models for nonsymbolic magnitude comparison.

	Df	Sum of squares	F	$p_{parametric}$	$p_{permuted}$	BF_{incl}
(A) Weber fraction						
Education years	1	0.01	0.06	0.806	0.608	0.28
Motor symptoms (UPDRS-III)	1	0.41	4.29	**0.041**	0.055	2.37
Depression (BDI-II)	1	0.06	0.65	0.420	0.516	0.35
Group	2	0.61	3.19	**0.045**	**0.042**	1.94
Residuals	104	9.98				
(B) Accuracy						
Education years	1	0.00	0.01	0.919	0.923	0.26
Motor symptoms (UPDRS-III)	1	0.05	3.84	0.053	0.053	1.64
Depression (BDI-II)	1	0.01	0.52	0.471	0.461	0.30
Group	2	0.07	2.72	0.070	0.074	1.17
Residuals	104	1.29				
Ratio	3	3.14	309.13	**< 0.001**	**< 0.001**	**> 1000**
Group × Ratio	6	0.02	1.03	0.403	0.407	0.04
Residuals	321	1.09				
(C) Reaction time						
Education years	1	0.00	0.01	0.918	0.791	0.67
Motor symptoms (UPDRS-III)	1	0.02	0.30	0.582	0.708	0.70
Depression (BDI-II)	1	0.00	0.01	0.924	0.683	0.66
Group	2	0.01	0.09	0.916	0.916	0.50
Residuals	104	5.73				
Ratio	3	0.20	117.50	**< 0.001**	**< 0.001**	**> 1000**
Group × Ratio	6	0.01	2.20	**0.043**	0.324	0.49
Residuals	321	0.19				

Note: Type III sum of squares ANCOVAs with parametric *p*-values on log-transformed data for Weber fraction, untransformed data for accuracy and log-transformed data for RT and *p*-values based on permutation testing using untransformed data. BF_{incl} = how much more probable are the observed data under models with the respective predictor, than under models without that predictor, averaged across matched models, and using transformed data. The interaction group × ratio in reaction time was further differentiated in post hoc ANCOVAs, indicating a larger ratio effect in HC than in level-I PD-MCI as HC are relatively faster in the ratio 1:2. The group effect in Weber fractions resulted from more accurate discriminatory performances in the PD-NC than in the level-I PD-MCI group.

4.4 | H3 Exploratory) Discrimination Between Cognitive Statuses of PD by Tests of Basic Number Cognition

The originally preregistered analysis for Hypothesis 3 could not be conducted meaningfully, as there was only one numerical task showing significant group differences in accuracy and reaction time as shown by ANCOVA models. Therefore, in order to explore discriminatory strength of the numerical tasks, two binomial regressions were calculated, one predicting group membership of HC vs. PD-NC and one of PD-NC vs. level-I PD-MCI for both accuracy and reaction time of all numerical measures (see Table 9). For accuracy, written transcoding discriminated between HC and PD-NC, while there was no numerical variable discriminating between PD-NC and level-I PD-MCI. Regarding reaction time, number line estimation performance discriminated between HC and PD-NC, while performance in the symbolic magnitude comparison task discriminated between PD-NC and level-I PD-MCI. Descriptively, there was no obvious pattern of clustered numerical impairment or subgroups (see Figures S1 and S2 in Supporting Information). A summary of the main findings of all three hypotheses can be found in Box 1 in the Discussion section.

5 | Discussion

This study investigated basic number processing in patients with PD. The current research design allows to grasp the effect of Parkinsonian pathology on numerical cognition based on two variables operationalizing distinct aspects of the disease: While the variable group simultaneously grasps the transition from a neurologically healthy old-aged person to a person diagnosed with PD and from normal cognition to mild cognitive

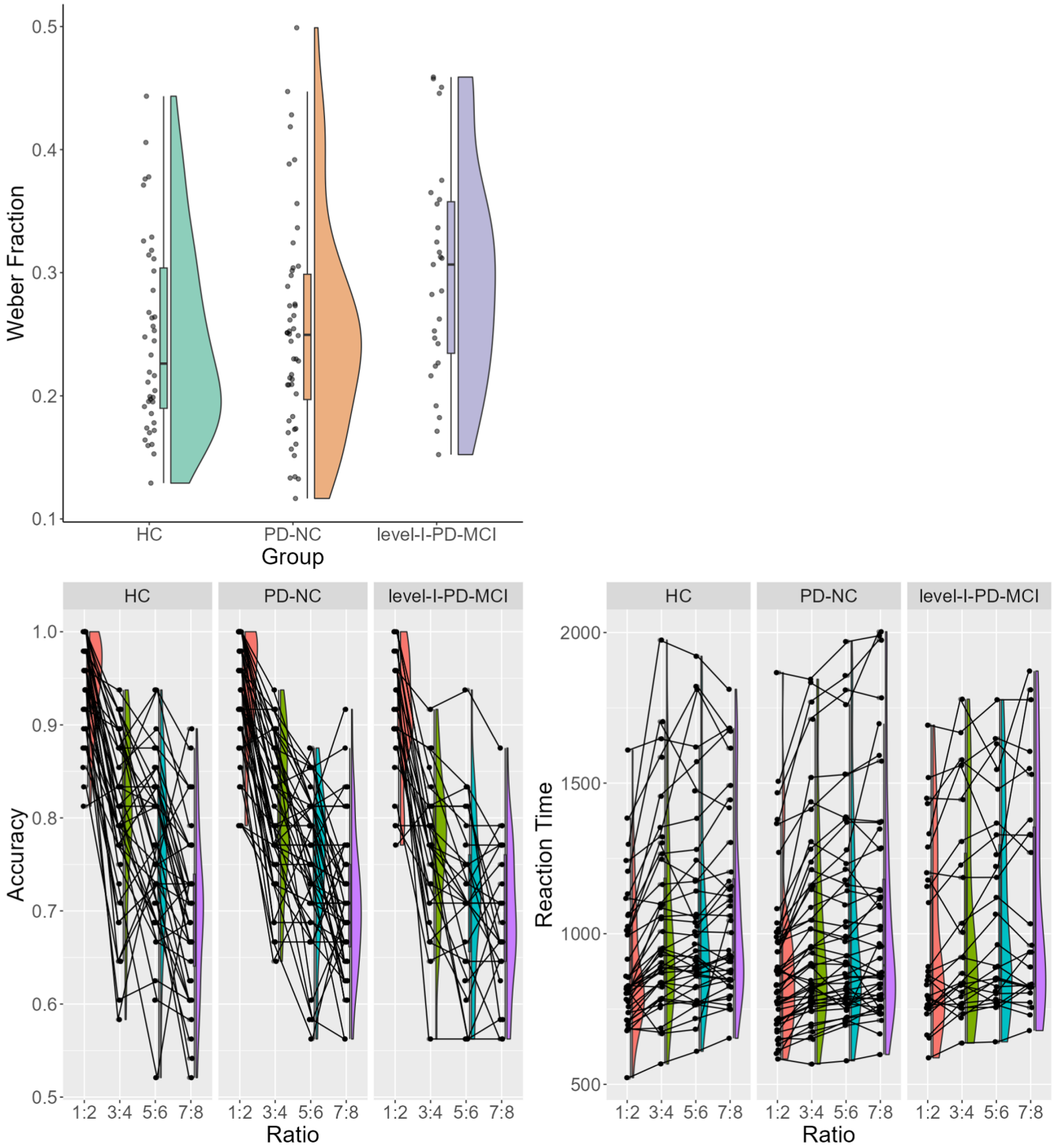

FIGURE 3 | Weber fraction per group and accuracy and reaction time per ratio and group in nonsymbolic magnitude comparison.

impairment within PD progression, the variable motor symptoms (UPDRS-III) assesses the progression of disease severity using the description of PD-specific motor symptoms. Overall, the results paint a complex picture (see Box 1), as PD-related performance depends on the respective basic numerical task and within the task on the experimental conditions, error types, and outcome measures (reaction time, accuracy, and Weber fraction). An influence of motor symptoms as well as domain-general cognitive tasks on basic number processing was identified, discussed in detail below. Interestingly, no direct influence of the severity of depressive symptoms on the evaluated number cognition tasks were pointed out and education affected performance only in some models such as accuracy in written transcoding and percent absolute deviation in number line estimation. Therefore, we disambiguate these distinct results per task and relate them to different aspects of the system-level disorder PD (Caligiore et al. 2016) and theoretical neurocognitive takes on basic numerical cognition (Dehaene et al. 2003; Klein et al. 2016; Nuerk, Moeller, and Willmes 2015).

TABLE 7 | ANCOVA models for symbolic magnitude comparison.

	Df	Sum of squares	*F*	$p_{parametric}$	$p_{permuted}$	BF_{incl}
(A) Accuracy						
Education years	1	2.52	0.42	0.518	0.235	0.21
Motor symptoms (UPDRS-III)	1	76.07	12.75	**0.001**	**0.012**	**256.86**
Depression (BDI-II)	1	1.20	0.20	0.655	0.348	0.19
Group	2	46.35	3.88	**0.024**	**0.004**	2.03
Residuals	105	626.70				
Compatibility	1	23.35	7.81	**0.006**	**0.018**	**8.56**
Group × Compatibility	2	1.05	0.17	0.840	0.820	0.06
Residuals	108	323.0				
Distance	1	10.81	3.42	0.067	**0.032**	1.09
Group × Distance	2	2.92	0.46	0.631	0.679	0.08
Residuals	108	341.80				
(B) Reaction time						
Education years	1	0.05	2.11	0.150	0.201	0.63
Motor symptoms (UPDRS-III)	1	0.20	7.73	**0.006**	**0.008**	0.88
Depression (BDI-II)	1	0.02	0.84	0.361	0.377	0.89
Group	2	0.30	5.93	**0.004**	**0.003**	**18.76**
Residuals	105	2.70				
Compatibility	1	0.00	0.08	0.777	0.580	0.13
Group × Compatibility	2	0.00	0.84	0.436	0.492	0.08
Residuals	108	0.01				
Distance	1	0.00	1.19	0.278	0.211	0.15
Group × Distance	2	0.00	0.16	0.849	0.828	0.06
Residuals	108	0.01				

Note: Type III sum of squares ANCOVAs with parametric *p*-values on logit-transformed data for accuracy and log-transformed data for RT and *p*-values based on permutation testing using untransformed data. BF_{incl} = how much more probable are the observed data under models with the respective predictor, than under models without that predictor, averaged across matched models, and using transformed data. Post hoc ANCOVAs that the group effects resulted from more accurate and faster responses in the PD-NC compared to the level-I PD-MCI group. Values marked in bold font represent significance levels of $p < 0.05$ and $BF10 > 3.0$.

5.1 | Profile of Distinct Preserved and Impaired Basic Numerical Functions in PD

The current research design allows to investigate specificities in numerical representations of PD patients (1) by detecting general deficits in task performance, (2) by categorizing errors produced in transcoding tasks according to taxonomies established by research on cognitive development and dementia (Bahnmueller, Nuerk, and Moeller 2018; Kalbe 1999; Zuber et al. 2009), and (3) by analyzing differences in the manipulated numerical effects of the respective task between groups (Nuerk, Moeller, and Willmes 2015). First, looking at the impairment or preservation of the different numerical constructs, the current study found an impaired magnitude representation in level-I PD-MCI, operationalized by group differences in accuracy and reaction time of symbolic magnitude comparison and Weber fraction of nonsymbolic magnitude comparison. Second, there seems to be a group-specific spatial-numerical representation, operationalized by a smaller range effect in the healthy control group than in the level-I-PD-MCI group in number line estimation. Third, the place-value representation also seems to be impaired, operationalized by group differences in error categories in transcoding in the level-I-PD-MCI group. Finally, the verbal representation itself does not seem to be impaired as there were no overall group differences in the two transcoding tasks. This profile of impairment and preservation is explained per numerical representation in the following.

5.1.1 | Impaired Magnitude Representation

The most reliable finding of an existent group difference can be found in *symbolic magnitude comparison*. While there was no difference to the HC group, PD-NC and level-I-PD-MCI patients

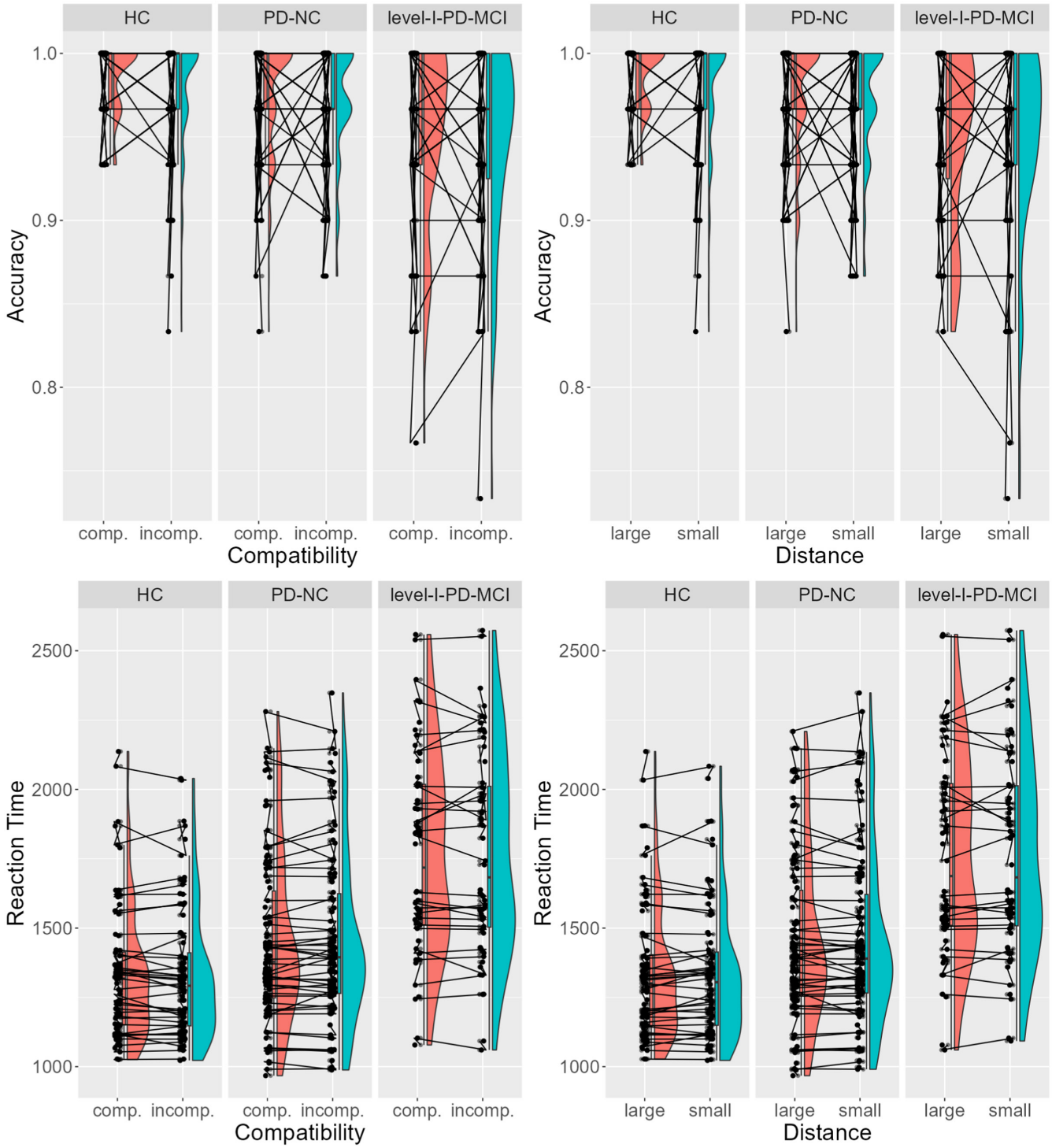

FIGURE 4 | Accuracy and reaction time in symbolic magnitude comparison per compatibility, distance, and group.

differed in both accuracy and reaction times, indicating that performance in comparing two-digit numbers is affected by PD-MCI. Even when controlling for language (i.e., verbal reasoning), the cognitive function showing the highest association to this task, the group differences did only change slightly, while the influence of language performance itself was not significant. These findings are in line with Zamarian et al. (2006) who did not find group differences between HC and PD-NC for symbolic magnitude comparison for single-digit numbers, as the current study only found impairments to occur at the stage of level-I PD-MCI. Surprisingly, Kalbe (1999) did not report impaired symbolic number comparison in a sample of PDD patients. This absence of impairment in a PDD sample can be due to limited task difficulty in Kalbe's (1999) $n = 8$ stimuli having very large distances between the numbers and often even a different amount of digits. Independent of group, we observed the domain-specific distance effect (e.g., Artemenko, Giannouli, and Nuerk 2024). We conclude that symbolic magnitude representation of two-digit numbers is affected by PD-immanent mild cognitive impairment.

TABLE 8 | Spearman rank correlations between numerical tasks and cognitive domains.

	Auditory transcoding	Written transcoding	Number line estimation			Nonsymbolic magnitude comparison			Symbolic magnitude comparison	
	$N=116$	$N=117$	$N=116$			$N=115$			$N=117$	
	ACC	ACC	PAE	RT	Range effect RT	ACC	Weber	RT	ACC	RT
Executive functions	−0.27*	−0.20*	0.33*	0.17	0.01	−0.10	0.07	−0.01	−0.30*	0.16
	0.003	0.035	<0.001	0.069	0.926	0.292	0.481	0.924	0.001	0.077
	$n=114$	$n=114$	$n=115$	$n=115$	$n=115$	$n=114$	$n=114$	$n=114$	$n=116$	$n=116$
Verbal working memory	0.30*	0.28*	−0.32*	−0.13	0.09	0.15	−0.17	**0.19***	0.21*	−0.31*
	<0.001	0.002	<0.001	0.153	0.336	0.119	0.062	**0.047**	0.022	0.001
	$n=115$	$n=116$	$n=116$	$n=116$	$n=116$	$n=115$	$n=115$	$n=\mathbf{115}$	$n=117$	$n=117$
Visuospatial working memory	0.28*	0.13	−0.34*	−0.19*	0.17	0.18*	**−0.24***	0.04	0.24*	−0.40*
	0.002	0.177	<0.001	0.044	0.068	0.049	**0.010**	0.639	0.009	<0.001
	$n=116$	$n=117$	$n=116$	$n=116$	$n=116$	$n=115$	$n=\mathbf{115}$	$n=115$	$n=117$	$n=117$
Attention	−0.25*	−0.14	0.29*	0.16	−0.20*	**−0.23***	0.21*	0.07	−0.22*	0.40*
	0.006	0.137	0.002	0.088	0.030	**0.012**	0.026	0.453	0.020	<0.001
	$n=114$	$n=115$	$n=115$	$n=115$	$n=115$	$n=\mathbf{114}$	$n=114$	$n=114$	$n=116$	$n=116$
Verbal memory	**0.37***	0.32*	−0.23*	−0.12*	0.16	0.14	−0.14	0.14	0.21*	−0.28*
	<0.001	<0.001	0.015	0.026	0.092	0.126	0.138	0.149	0.024	0.003
	$n=\mathbf{113}$	$n=114$	$n=114$	$n=114$	$n=114$	$n=113$	$n=113$	$n=113$	$n=115$	$n=115$
Language/verbal reasoning	0.33*	**0.58***	−0.36*	**−0.27***	0.20*	0.15	−0.17	0.14	**0.38***	**−0.42***
	<0.001	**<0.001**	<0.001	**0.004**	0.035	0.115	0.076	0.143	**<0.001**	**<0.001**
	$n=115$	$n=\mathbf{116}$	$n=116$	$n=\mathbf{116}$	$n=116$	$n=115$	$n=115$	$n=115$	$n=\mathbf{117}$	$n=\mathbf{117}$
Visuospatial function	0.17	0.31*	**−0.42***	−0.01	0.11	0.17	−0.17	0.13	0.27*	−0.23*
	0.073	<0.001	**<0.001**	0.883	0.239	0.077	0.066	0.181	0.003	0.012
	$n=116$	$n=117$	$n=\mathbf{116}$	$n=116$	$n=116$	$n=115$	$n=115$	$n=115$	$n=117$	$n=117$

Note: N = overall sample size indicating the number of participants in all three groups solving the task with sufficient accuracy to ensure task understanding. Values marked as bold indicate the correlation of highest magnitude for the respective numerical task. Tasks and dependent variables highlighted in gray indicate those analyses with a significant group effect in Hypothesis 1—the other tasks were not addressed in Hypothesis 2.
*Significant correlation.

TABLE 9 | Exploratory pairwise logistic regressions on accuracy and reaction time data, discriminating HC, PD-NC, and level-I PD-MCI groups using basic numerical cognition tasks.

	β	SE	z	p	OR	CI	VIF
Accuracy							
HC vs. PD-NC: $R^2_{\text{McFadden}} = 0.14$, $AIC = 111.36$							
Intercept	0.75	0.33	2.30	**0.022**	2.13	0.16; 1.47	
Transcoding auditory	−0.14	0.45	−0.32	0.749	0.87	−1.11; 0.89	1.09
Transcoding written	−1.08	0.43	−2.49	**0.013**	0.34	−2.01; −0.30	1.13
Number line	0.06	0.29	0.19	0.850	1.06	−0.50; 0.66	1.14
Nonsymbolic	0.00	0.25	0.02	0.987	1.00	−0.50; 0.50	1.01
Symbolic	−0.51	0.38	−1.34	0.182	0.60	−1.29; 0.22	1.10
PD-NC vs. level-I PD-MCI: $R^2_{\text{McFadden}} = 0.14$, $AIC = 86.58$							
Intercept	−1.06	0.31	−3.41	**< 0.001**	0.35	−1.71; −0.48	
Transcoding auditory	−0.26	0.28	−0.94	0.347	0.77	−0.83; 0.28	1.21
Transcoding written	−0.18	0.28	−0.64	0.525	0.84	−0.74; 0.38	1.12
Number line	0.00	0.29	−0.02	0.988	1.00	−0.61; 0.55	1.17
Nonsymbolic	−0.33	0.32	−1.03	0.302	0.72	−1.01; 0.28	1.18
Symbolic	−0.57	0.32	−1.77	0.077	0.57	−1.24; 0.05	1.25
Reaction time							
HC vs. PD-NC: $R^2_{\text{McFadden}} = 0.23$, $AIC = 99.92$							
Intercept	1.21	0.41	2.95	**0.003**	3.36	0.48; 2.11	
Number line	2.67	0.75	3.56	**< 0.001**	14.39	1.35; 4.30	1.01
Nonsymbolic	−0.23	0.29	−0.77	0.439	0.80	−0.82; 0.34	1.01
Symbolic	0.53	0.38	1.41	0.158	1.70	−0.19; 1.32	1.00
PD-NC vs. level-I PD-MCI: $R^2_{\text{McFadden}} = 0.11$, $AIC = 87.32$							
Intercept	−0.99	0.30	−3.37	**< 0.001**	0.37	−1.61; −0.44	
Number line	0.14	0.23	0.62	0.534	1.16	−0.32; 0.63	1.09
Nonsymbolic	0.10	0.25	0.38	0.702	1.10	−0.42; 0.59	1.03
Symbolic	0.72	0.28	2.56	**0.011**	2.05	0.19; 1.30	1.07

Note: Values marked in bold font represent significance levels of $p < 0.05$ and BF10 > 3.0.

Likewise, a group difference between PD-NC and level-I PD-MCI was observed in *nonsymbolic magnitude comparison* when considering the typical outcome measure Weber fraction, indicating a less accurate nonsymbolic magnitude representation related to PD-immanent mild cognitive impairment. When controlling for visuospatial working memory, the group effect changed significance, which cannot be meaningfully interpreted due to the small numerical change. In nonsymbolic magnitude comparison, a significant effect of ratio indicated that responses became increasingly less accurate and slower going from ratios 1:2, over 3:4 and 5:6 to 7:8. This ratio effect in reaction time further differed between HC and level-I PD-MCI which might be caused by faster HC than level-I-PD-MCI reactions to the easiest ratio 1:2, which still resulted in a larger difference between ratio 1:2 and 7:8 even though the HC group also reacted faster to ratio 7:8. This decline of the Weber fraction in level-I PD-MCI is in line with aging affecting the overall precision of the approximate number system (captured in the Weber fraction, Halberda et al. 2012) or performance in incongruent trials of nonsymbolic numerosity estimation related to inhibitory deficits (Cappelletti et al. 2014). This aging effect might further decrease across the disease course as indicated by general MCI (i.e., a process unrelated to PD pathology) impairing performance in nonsymbolic magnitude comparison (Benavides-Varela et al. 2015). The presence of Weber fraction differences between PD-NC and level-I PD-MCI in the current study relates to the absence of group differences between HC and PD-NC in the literature, where patients were at an earlier disease stage (according to disease duration, Hoehn & Yahr stage, and global cognitive state) and the task design was less complex (smaller numerosity, successive presentation, paper-and-pencil test, Dormal et al. 2012;

BOX 1 | Summary of empirical findings.

Auditory transcoding	Written transcoding	Number line estimation	Nonsymbolic magnitude comparison	Symbolic magnitude comparison
H1: *Which effects and representations of basic number processing are impaired in PD patients?*				
ACC HC = PD-NC PD-NC = level-I PD-MCI & motor symptoms* **Error types** HC: mostly lexical PD-NC: lexical & syntactic level-I PD-MCI: mostly syntactic	**ACC** HC = PD-NC PD-NC = level-I PD-MCI & education*	**PAE** HC = PD-NC PD-NC = level-I PD-MCI & range effect* & motor symptoms* & education* **RT** HC = PD-NC PD-NC = level-I PD-MCI range effect HC < level-I-PD-MCI* *& motor symptoms**	**Weber fraction** HC = PD-NC PD-NC < level-I-PD-MCI#* *& motor symptoms** **ACC** HC = PD-NC PD-NC = level-I PD-MCI & ratio effect* **RT** HC = PD-NC PD-NC = level-I PD-MCI & ratio effect* ratio effect HC>level-I PD-MCI*	**ACC** HC = PD-NC PD-NC > level-I-PD-MCI* & compatibility effect* & distance effect* & motor symptoms* **RT** HC = PD-NC PD-NC < level-I-PD-MCI* & motor symptoms*
H2: *Can basic number processing performance of PD patients be explained by domain-general functions?*				
		RT range effect + verbal reasoning HC = PD-NC PD-NC = level-I PD-MCI HC < level-I-PD-MCI	**Weber fraction** + visual working memory HC = PD-NC *PD-NC = level-I PD-MCI#*	**ACC** + verbal reasoning HC = PD-NC PD-NC > level-I-PD-MCI* & compatibility effect* & distance effect* & motor symptoms* **RT** + verbal reasoning HC = PD-NC PD-NC < level-I-PD-MCI* & motor symptoms*
H3 exploratory*: Can basic number processing performance be used to discriminate between HC, PD-NC and level I-PD-MCI patients?*				
ACC HC vs. PD-NC: Written transcoding PD-NC vs. level-I PD-MCI: none **RT** HC vs. PD-NC: Number line estimation PD-NC vs. level-I PD-MCI: Symbolic magnitude comparison				

Note: The columns summarize ANCOVA results per numerical task; the rows represent the three research questions. Higher accuracy (ACC) indicates more correct answers (i.e., PD-NC>level-I PD-MCI); smaller reaction time (RT) indicates faster responses (i.e., PD-NC<level-I PD-MCI). #A smaller Weber fraction indicates better acuity. Models for H1 and H2 include the covariates education, motor symptoms, and depression. *Significant predictor in the respective model. Effects changing between H1 and H2 are marked in italics. Significant group effects and interactions with group are marked in gray.

Semenza et al. 2014). Taken together, not only symbolic but also nonsymbolic magnitude representations are affected by PD-immanent mild cognitive impairment.

These findings of an MCI-related impaired magnitude representation in PD can be linked to neuronal network models postulating a crucial role of the basal ganglia in both symbolic and nonsymbolic magnitude comparison (Conrad et al. 2020). The association between symbolic and nonsymbolic magnitude representations has been discussed controversially (Krajcsi, Lengyel, and Kojouharova 2018; Nieder 2005), as there seem to be both distinct and shared neural underpinnings (Conrad et al. 2020; Sokolowski et al. 2017). While both neural networks of symbolic and nonsymbolic magnitude comparison include the basal ganglia, other parts of the (non-) symbolic magnitude network which are affected by PD include the thalamus, prefrontal and parietal regions, sensorimotor network, hippocampus, nucleus accumbens (Aarsland et al. 2021; Caligiore et al. 2016; Conrad et al. 2020), and cerebellum (Kaufmann et al. 2006, 2008; Li, Le, and Jankovic 2023; Vandervert 2017). Additionally, impaired magnitude processing in the level-I-PD-MCI group might point at an involvement of the intraparietal sulcus in PD-MCI pathology (Klein and Knops 2023).

Regarding domain-general late-life memory performance, dopaminergic and cholinergic brain regions and their associations to prefrontal and hippocampal processing are, despite their tight interconnection, distinctly associated to mnestic subdomains (Briand et al. 2007; Dahl et al. 2023; Sara 2009). PD patients show both dopaminergic and cholinergic dysfunction (Caligiore et al. 2016), which might affect numerical performance involving memory functions. In healthy aging, intact working memory (partly operationalized with a letter span task) was linked to dopaminergic substantia nigra areas, while episodic memory (partly operationalized with delayed verbal memory) relied on an intact cholinergic brainstem locus coeruleus (Dahl et al. 2023). First but scarce insights identified the amino acid Gamma-aminobutyric acid (GABA) as a crucial neurotransmitter in parietal regions in young adults (Zacharopoulos et al. 2021) and distinct Catechol-O-methyltransferase polymorphisms (important for dopamine metabolism) to affect magnitude processing in children (Júlio-Costa et al. 2013). However, there is no empirical evidence on related mechanisms or the specific roles of amine neurotransmitters dopamine and acetylcholine in neurodegeneration of numerical cognition. These patterns identify several potential neuronal causes for impaired (non-) symbolic magnitude processing in PD, indicating the need for future neuroimaging studies looking at functional and structural connectivity, α-synuclein deposition as well as neurotransmitter systems. One caveat in the above interpretation of possibly involved brain regions is that most studies on the neural correlates of numerical cognition use samples of young adults—but even the neural representations in the healthy aging brain might differ (Learmonth et al. 2017; Lövdén et al. 2010). Therefore, future imaging studies need to describe PD-specific brain activation of numerical cognition, which could be influenced by processes of dysfunction and compensation (as suggested by Burgio et al. 2022). As the current analysis did not differentiate nonsymbolic magnitude comparison according to congruency, future analyses should also address the effect of congruence between visual size and numerosity in PD patients with visuospatial and executive deficits separately, as it might explain the absence of group differences for overall accuracy and reaction times in the current study (see preregistration of secondary data analysis https://osf.io/3nkj4).

5.1.2 | Group-Specific Spatial-Numerical Representation

In *number line estimation*, a significant effect of range indicated that the estimation of numbers was less precise in the number range to 1,000,000 than to 100 in all groups. While the HC group showed comparable reaction time distributions between the two ranges, the level-I-PD-MCI group responded significantly faster in the large range on average, where accuracy was much worse though, with these differences in responding strategies hinting at processes of resignation facing excessive demand of the more difficult experimental condition. In the aphasia literature, this pattern is termed "mode of failure" responding where overstrain resulting from task difficulty results in faster reactions as the participant does not feel capable of answering correctly and therefore answers less conscientiously and faster (cf. W. Huber, Springer, and Willmes 1993). Supporting the current results, empirical findings hint at preserved number line estimation skills in PD patients without dementia (Burgio et al. 2022; Semenza et al. 2014; Zamarian et al. 2006), while PDD patients show impairments (Kalbe 1999). However, MCI without PD has been shown to impair number line estimation performance in the range 0–100 (Benavides-Varela et al. 2015). To conclude, MCI and the motor challenge of fine-grained movements with a computer mouse affect the spatial-numerical representation of large numbers.

Research on the neural underpinnings of number line estimation identified the following areas and networks as crucial: visuospatial areas (i.e., posterior superior parietal lobules) controlling attentional orientation on the mental number line (Dehaene et al. 2003), the medial wall of the intraparietal sulcus (Chen and Verguts 2010), bilateral parietal–frontal networks, right cerebellum, left insula, and supplementary motor area (Liu et al. 2019). Alterations in these areas and networks might cause impairments for large numbers in PD-MCI patients.

Interindividual differences in lateralized dominance of PD pathology have been shown to lead to biased response tendencies in opposing directions in spatial judgments, depending on the side of the body where PD pathology began (Arshad et al. 2017). This dynamic might cause effects to cancel each other out when left- and right-lateralized patients are combined for analysis as in the current study; thus, future studies investigating number line estimation need to accentuate the current findings by considering these PD-specific spatial-numerical biases. Future research might also delve into modeling the underlying mapping of numbers to space and strategies used to see whether PD patients rely on a logarithmic or linear representation, as research on dyscalculic adults has identified deficits in mapping numbers onto space (Huber et al. 2015).

5.1.3 | Impaired Place × Value Representation

Transcoding orally dictated number words to written Arabic digits using number plates was descriptively less prone to errors in HC who majorly produced lexical errors (i.e., value omissions or wrong values). PD-NC showed both lexical and syntactical errors (i.e., composition errors, inversions, omission of place or "and," wrong place), as well as multiple errors within one transcoded number. Level-I PD-MCI showed mostly syntactical and multiple errors, which parallels linguistic impairments being predominantly syntactical in non-demented PD patients and associated to dopaminergic pathology (Johari et al. 2019). Memory errors in the current sample only occurred in the patient group where numbers were not (fully) remembered after oral presentation. While cognitively healthy old-aged participants occasionally confused the value of digits, conceptual understanding of multi-digit numbers (indicated by frequently occurring syntactical errors) seems to be affected in PD. These error patterns hint at more severe impairments in place-value representation with only patients showing multiple errors in a single number. Error categories did not differ between groups for the task to *transcode written Arabic digits into handwritten number words*.

These findings hint at impaired place × value processing in PD when producing multi-digit numbers. This corroborates previous findings of frequently occurring place × value errors in a simple arithmetic task in a financial context in PD (Loenneker et al. 2021). According to Nuerk, Moeller, and Willmes (2015), transcoding of multi-digit numbers requires place identification, which is the lowest level of place × value processing. On the next level of place × value processing, the comparison of multi-digit numbers does require place × value activation, as indicated by the compatibility effect. As the compatibility effect in symbolic magnitude comparison is stable (in accuracy) and comparable (in accuracy and reaction time) across all groups, place × value activation seems to be equally important for both PD patients and HC and a highly automatized process (Kallai and Tzelgov 2012) because of lifelong experience up to old age. We conclude that place × value activation is not affected by PD, and impaired place identification can only be seen in different transcoding errors committed between groups—but not in transcoding performance per se. Relating the current empirical pattern to the multiroute model by Cipolotti and Butterworth (1995), PD patients in the current study might show impaired direct translations from one modality to the other when the task requires high working memory capacities due to multi-digit numbers, but they should still be able to identify the respective places of the digits within a multi-digit number. As syntactical errors in the patient groups indicate mild impairments of place identification, this processes might show more severe deficits during disease progression.

5.1.4 | Preserved Verbal Number Representation?

The verbal number representation can be operationalized with transcoding tasks. Both transcoding tasks not showing group differences between HC, PD-NC and level-I PD-MCI is in line with other studies not finding differences in transcoding between HC and PD patients without dementia (Burgio et al. 2022; Semenza et al. 2014; Zamarian et al. 2006), while these impairments have been shown in PDD patients (Kalbe 1999). However, MCI unrelated to PD pathology has been shown to lower performance in transcoding (Benavides-Varela et al. 2015). As motor symptoms significantly affected performance in auditory transcoding in the current study, we see first signs of PD disease progression impairing the verbal number representation which might be fully impaired in the stage of PDD, where overall language impairments are frequent (Aarsland et al. 2021). Additionally, the symbolic magnitude comparison requires processing of both magnitude and verbal information, so that group differences in this task cannot be assigned to verbal impairments per se. Therefore, integrating the evidence from the current study with the literature does not allow straightforward conclusions on an impaired verbal number representation.

5.2 | Basic Numerical Deficits in PD Cannot Be Fully Explained by Domain-General Deficits

In our study, there was no basic numerical task in which domain-general function fully explained performance; indeed, there was only one task where group differences became insignificant by adding the cognitive covariate. The pattern of associations found between numerical and global cognitive factors validates the integrity of the current data, because they relate to conceptual links typically described in studies of numerical cognition and impaired PD cognition (Burgio et al. 2022; Muslimovic et al. 2007). This points at numerical deficits in addition to other cognitive deficits in PD, especially when MCI occurs during disease progression.

This does not inevitably mean that domain-general function alone explains numerical impairments, but both cognitive domains might depend on the same underlying mechanism like dopaminergic and later cholinergic dysfunction, as specific numerical factors still explained performance after controlling for domain-general function. Consequently, it does not suffice to use domain-general tests of working memory, executive function or language to investigate numerical deficits, but domain-specific numerical tasks need to be used. Therefore, future studies are needed to get insight into the overlapping underlying pathology of domain-general cognitive and domain-specific numerical representations in early and more advanced disease stages in PD.

5.3 | Effect of Disease Severity on Basic Numerical Cognition

Overall, UPDRS-III affected performance in all numerical tasks except for written transcoding, indicating that basic numerical performance declines along the process of motor disease progression. We interpret this as an association between disease severity (operationalized as UPDRS-III score) and basic numerical cognition, but we need neuroimaging studies targeting the striatal system and Lewy Body pathology to further understand the pathological mechanisms. This approach would mean a renaissance of evaluating the role basal ganglia play for numerical cognition, as well as of cortical areas linked to movement and the cerebellum (Kaufmann et al. 2006, 2008). Cerebellum is already involved in early PD pathology stages as it is linked to the basal ganglia by dopaminergic projections and presents with α-synucleinopathy, affecting both motor and cognitive symptoms (Li, Le, and Jankovic 2023). Moreover, cerebellar crus I and II project to prefrontal and parietal cortices which again are involved in number processing, and there is evidence for both pathological and compensatory processes in the cerebellum of PD patients (Klein et al. 2016; Li, Le, and Jankovic 2023). Consequently, disease severity operationalized as the sum of PD-specific motor symptoms already affects performance in basic numerical functions and not only more complex numerical tasks like, for example, multi-digit arithmetic.

5.4 | Basic Numerical Functions Discriminate HC, PD-NC, and Level-I PD-MCI, but Cannot Serve as Biomarkers of Cognitive Progression

The third hypothesis aimed at exploratorily investigating whether tasks of basic numerical cognition might be candidates to discriminate between HC and PD-NC, as well as between PD-NC and level-I PD-MCI, because progression markers for

cognitive decline are needed for patient care and better identification of especially valuable patients with a prognosis for rapid decline (Roheger, Kalbe, and Liepelt-Scarfone 2018). First, as written transcoding accuracy discriminated between HC and PD-NC group and frequency of error types in auditory transcoding was distinct between PD-NC and level-I-PD-MCI groups, transcoding deficits can already be an early marker of PD-like neurodegenerative processes. Relatedly, transcoding has been described as impaired in PDD patients (Kalbe 1999) and linguistic syntactical errors predict the development of PDD (Galtier et al. 2023; Johari et al. 2019). Furthermore, reaction times in number line estimation discriminated between HC and PD-NC. Second, performance in symbolic magnitude estimation discriminated between PD-NC and level-I PD-MCI. These results hint at impaired place × value and magnitude processing indicating a beginning process of PD-related dementia. Therefore, tasks assessing the magnitude representation with sufficient difficulty (i.e., multi-digit numbers) can be targets for identifying patients at risk of cognitive deterioration.

To fully understand the prognostic value of basic numerical cognition, longitudinal research is needed to extend the findings from the current cross-sectional project. This longitudinal research should further incorporate PD subtypes, with candidates such as postural instability and gait disorder showing a higher prevalence of cognitive decline across the disease course (Michels et al. 2022). The current study did not investigate effects of the motor types tremor-, PIGD-dominant and mixed as these categories were not distinctly distributed between the PD-NC and level-I-PD-MCI groups and therefore not included as covariates. The current work focused on basic number processing, which could explain impairments occurring only at the later stage of PD-MCI, while more complex numerical tasks like multi-digit arithmetic might be already impaired in earlier stages of PD-NC (for an investigation on mental arithmetic in PD see Loenneker et al. 2022).

6 | Conclusion

Just as PD is a system-level disorder (Caligiore et al. 2016) and related cognitive impairments result from various neuropathological processes (Aarsland et al. 2021), so is numerical cognition represented in a network of brain areas associated with domain-general cognitive and domain-specific numeric processes (e.g., Barrouillet et al. 2004; Dehaene et al. 2003; Klein and Knops 2023; Krajcsi, Fedele, and Reynvoet 2023; McCloskey, Caramazza, and Basili 1985). Combining these two research fields leads to the following insights: (1) Even basic numerical tasks can be impaired in the MCI stage of PD, hinting at impaired symbolic and nonsymbolic magnitude representations, as well as place × value processing in PD. (2) These impairments cannot be explained by domain-general cognitive deficits. (3) Basic numerical tasks cannot serve as biomarkers as too many patients in the pre-dementia stage can still easily solve them. (4) Looking at task characteristics, research on numerical cognition in PD has to incorporate different levels of difficulty in a wide range of numerical domains, so that patients from the entire continuum will be able to solve at least some tasks while eliminating ceiling effects as much as possible. (5) However, we need neuroimaging studies targeting the striatal system and Lewy Body pathology to further understand the pathological mechanisms and to evaluate the role basal ganglia and the cerebellum play for numerical cognition. By studying the mechanisms underlying PD and numerical cognition, we can further understand why even performance in basic numerical tasks is affected during neurodegeneration.

Author Contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. H.D.L., C.A., H.-C.N., and I.L.-S. contributed to conceptualization. H.D.L. contributed to data curation. H.D.L., C.A., H.-C.N., K.W., and I.L.-S. contributed to methodology. H.D.L. contributed to investigation. H.D.L. contributed to formal analysis. H.D.L. contributed to writing – original draft. H.D.L., C.A., H.-C.N., K.W., and I.L.-S. contributed to writing – review and editing. H.D.L. contributed to project administration. H.D.L. contributed to visualization. H.D.L. contributed to funding acquisition.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Anonymized data, own materials, programmed experiments, and analyses scripts are freely available on the Open Science Framework (https://osf.io/ap6je/) and PsychArchive (Loenneker 2024, https://doi.org/10.23668/psycharchives.15511).

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Declaration of Transparency

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.