

Arithmetic deficits ~~Acakleulia~~ in Parkinson's Disease?

– A Registered Report

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Abstract

Elderly people and patients with neurodegenerative diseases such as Parkinson's Disease (PD) immensely rely on arithmetic skills to lead an independent life. Activities such as medication management, financial transactions or using public transport require intact abilities to manipulate numbers ~~for~~ with different arithmetic ~~tasks~~ operations. However, research on cognitive deficits in PD has been focussing on domain-general functions such as executive functions, attention or working memory so far – largely neglecting potential domain-specific aspects of numerical cognition (e.g., carry or problem size effect). These aspects should be addressed, as PD-immanent deterioration of domain-specific numerical areas and domain-general functions suggests mechanisms of both primary and secondary (mediated by other cognitive deficits) ~~acalculia~~-arithmetic deficits, respectively. The current study will systematically investigate arithmetic performance and effects in PD patients differing in cognitive impairment for the first time, targeting domain-specific cognitive representations of arithmetic as well as the influence of domain-general factors. ~~Besides healthy controls (HC)~~, PD patients with normal cognition (PD-NC) and PD patients with mild cognitive impairment (PD-MCI) will be compared ~~to healthy controls~~ in arithmetic performance in the four basic operations (addition, subtraction, multiplication, division). Discriminant analysis will be employed to assess whether performance in arithmetic tasks can differentiate between a healthy control group and both PD groups. The study results will help us to understand the underlying mechanisms of arithmetic deficits faced by PD patients in daily life.

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Keywords: Parkinson's disease, mild cognitive impairment, arithmetic operation, calculation, place × value system

Introduction

In a society shaped by demographic change and consequences of ageing communities, supporting ~~participation and~~ independence of the elderly (~~with cognitive deficits~~) is ~~one of the most~~ crucial ~~challenges~~. Daily activities of the elderly such as planning a trip with public transport, keeping track of the financial situation, and managing one's own medication all share a common prerequisite for completion: (intact) arithmetic skills (Arcara et al., 2019; Bangma et al., 2021; Delazer et al., 2013). Deficits in arithmetic skills can be acquired (i.e., acalculia) or result from developmental deficits (i.e., dyscalculia, Willmes et al., 2013). Despite the importance of arithmetic skills for ~~the~~ elderly, acalculia research is missing in this societal group (Ardila & Rosselli, 2002). What is even more ~~crucial-important~~ is the lack of research considering patients with neurodegenerative diseases, who show deficits in several arithmetic domains in clinical practice (Cappelletti et al., 2005; Delazer et al., 2019; e.g., Kalbe & Kessler, 2002), as for example patients with Alzheimer's Disease (AD, for reviews see Girelli & Delazer, 2001; Kalbe & Kessler, 2002). While at least some literature on arithmetic and associated financial decision-making exists for AD (Bangma et al., 2021), Parkinson's Disease (PD) has been ~~almost totally~~ neglected in systematic research on arithmetic deficits.

Therefore, the current study is part of a broader research project on numerical cognition in PD, which aims to assess basic number processing (Loenneker, Artemenko, et al., 2021) as well as arithmetic skills (the current study), to obtain a comprehensive overview of how basic and advanced numerical functions look like in PD patients with different levels of global cognitive function. Both studies will be conducted with the same patients and within two joint experimental sessions.

Parkinson's Disease

With to date over 6 million globally affected patients, PD is the second most common neurodegenerative disease world-wide (Dorsey et al., 2018). ~~Prevalence differs depending on sex and age with a higher incidence in men and the elderly~~ (Hirsch et al., 2016). The increasing prevalence of PD and associated health costs and care demands will have a huge impact on the public health system in the future (Dorsey et al., 2018; Kowal et al., 2013). PD's cardinal motor symptoms are hypo- and bradykinesia alongside at least rigidity and/ or resting tremor (Postuma et al., 2015). In addition, the disease is characterised by the presence of a variety of non-motor symptoms such as dysautonomia (e.g., incontinence, sleep disorders), psychiatric (e.g., depression, Jankovic, 2008) or cognitive ~~disorders such as mild cognitive impairment (PD-MCI, Litvan et al., 2012) and dementia~~ (PDD, Aarsland et al., 2017). PD's cognitive symptoms are consensually defined as deficits in the domains of executive functions, working memory and attention, memory, language, and visuo-spatial functions (Aarsland et al., 2017; Litvan et al., 2012).

The continuum of cognitive deficits in PD can be further differentiated into normal cognition (PD-NC), the initial stage of clinically significant cognitive disorders (PD-MCI) and PDD (with additional impairment in activities of daily living = ADL, Emre et al., 2007). Especially cognitive impairment is associated with a more rapid disease progression, mortality and death (de Lau et al., 2014; Pigott et al., 2015). Previous studies in neurological patients have shown that general cognitive abilities as well as domain-specific numerical functions influence arithmetic functions (Ardila & Rosselli, 2002; Willmes et al., 2013). The overlap of brain areas underlying arithmetic (Klein et al., 2016) and degenerated areas in PD (Braak et al., 1996, 2006) emphasise the need for theory-driven investigations.

Arithmetic across aging

Arithmetic deficits in PD need to be differentiated from ~~the non-pathological development of aging effects-arithmetic skills during ageing~~, but lifespan psychological research mostly ~~contributes evidence focuses~~ on global cognitive decline (Cohen-Mansfield et al., 2018; Deary et al., 2013; Lindenberger & Baltes, 1997; e.g., Tucker-Drob, 2019). Neurocognitive models of number processing (i.e., the Triple Code Model and its extensions, Dehaene et al., 2003; Dehaene & Cohen, 1995; Klein et al., 2016) lack hypotheses on ageing processes, but generally assume different representations of numerosity being associated with specific subcortical (e.g., basal ganglia, hippocampus) as well as cortical (e.g., fronto-parietal network) structures.

The Triple Code Model postulates 1) a *visual number form*, 2) a *semantic magnitude* and 3) a *verbal representation* as the core representations of numerosity (Dehaene et al., 2003; Dehaene & Cohen, 1995). These number-related processes are organized in three parietal circuits, being the horizontal segment of the intraparietal sulcus (for notation-independent quantity processing), the left angular gyrus area with further left-hemispheric perisylvian areas (for verbal manipulations) and a bilateral posterior superior parietal system (for attention regarding spatial dimensions, Dehaene et al., 2003). As a fourth representation, simple multiplication and division tasks require *arithmetic fact retrieval* from verbal long-term memory facilitating automatized mental calculation (as hypothesized e.g. in the interacting neighbours model, Verguts & Fias, 2005). These have been complemented by *place × value integration* (identification, activation and computation of distinct places and corresponding values) for multi-digit numbers (Klein et al., 2016; Nuerk et al., 2015).

~~Operationalising the representations~~ Representations postulated by these models can be ~~achieved operationalised~~ in an effect-based (i.e., numerical representation is indexed by a numerical effect) as opposed to a task-based (i.e., numerical representation is indexed by a numerical task) approach (see Moeller et al., 2011 for further elaboration on this distinction). Regarding arithmetic, ~~symbolic~~ magnitude and verbal representations as well as place × value integration are crucial underlying mechanisms, with

distinct accentuations for the four basic arithmetic operations and several related numerical effects. For instance, place \times value computation is relevant for carrying in addition (unit sum of the operands ≤ 10 , e.g., $32 + 48$) and borrowing in subtraction (unit of the subtrahend $>$ unit of the minuend, e.g., $51 - 27$), which lead to longer reaction times (RT) and lower accuracy (ACC; Artemenko et al., 2018). While carry and borrow effects define task ~~difficulty-complexity~~ in addition and subtraction, ~~difficulty-task complexity~~ in multiplication and division ~~is can be~~ defined respectively based on problem size of the product or divisor, with the problem size effect showing faster RT and higher ACC for smaller (i.e., easier) ~~than larger~~ problems (Domahs et al., 2006; Zbrodoff & Logan, 2005). Additionally, erroneous place \times value integration is for example revealed by operand-related errors (the erroneous answer belongs to the multiplication table of one of the operands, e.g., $7 \times 8 = 48$ instead of 56, result and error have the same digit at the same place-value position in common, e.g., $7 \times 8 = 54$) in multiplication and division (Domahs et al., 2006, 2007; Stazyk et al., 1982; Verguts & Fias, 2005). These effects can be explained with operands and solutions in multi-digit arithmetic being represented in network structures (Domahs et al., 2006; Verguts & Fias, 2005).

However, domain-specific numerical representations such as number magnitude representation, place-value integration or knowledge of mathematical procedures cannot explain arithmetic performance entirely. ~~because~~ Domain-general functions such as attention, working memory, or executive functions are an additional prerequisite for successful ~~number-arithmetic~~ processing and deficits therein can give rise to ~~arithmetic deficits comparable to~~ secondary acalculia (termed secondary arithmetic deficits hereafter, Knops et al., 2017). ~~For instance,~~ carry and borrow effects ~~for example~~ are ~~highly strongly~~ related to working memory capacity (Imbo, Vandierendonck, & De Rammelaere, 2007; Imbo, Vandierendonck, & Vergauwe, 2007) and interference effects in multiplication indicate inhibition as a crucial prerequisite of arithmetic (Archambeau et al., 2019; De Visscher & Noël, 2014; Domahs et al., 2006; Verguts & Fias, 2005).

In the fields of developmental numerical cognition, the few studies describing arithmetic processes in healthy ageing showed differential results. While performance of elderly people does not seem to be declining significantly in arithmetic fact retrieval and magnitude representation (Archambeau et al., 2019; Kaufmann et al., 2008), they do show increased error rates and differences in neural activation in a numerical Stroop task (requiring inhibition; Wood et al., 2009), and less efficient strategy use in other arithmetic operations when compared to young adults (Hinault & Lemaire, 2016; Uittenhove & Lemaire, 2015). Furthermore, in applied numerical cognition, a decline in financial abilities as a subdomain of numerical ADL was reported (Finke et al., 2017). With domain-general functions ~~generally-globally~~ declining with age (Li et al., 2004; Tucker-Drob et al., 2019), ~~the~~-arithmetic ~~decline-deficits~~ in ~~the~~ elderly ~~has-have~~ sometimes been explained ~~as a consequence of domain-general – and not domain-specific – processes with processes of secondary acalculia~~ (Hinault & Lemaire, 2016), ~~i.e. a mere consequence of~~

~~domain-general processes, while domain-specific processes are deemed not relevant.~~ However, systematic investigations of domain-general and domain-specific aspects across different ~~numerical-arithmetic operations tasks and processes~~ are still needed to comprehensively ~~resolve that issue-differentiate between~~ age-related and pathological arithmetic deficits.

Arithmetic in Parkinson's Disease

In addition to non-pathological aging processes, neurodegeneration can further cause arithmetic impairments. Different dementias such as AD and ~~PD-dementia (PDD)~~ show both distinct cognitive profiles (Hugo & Ganguli, 2014) and common neuropathologies (e.g., the cholinergic system, Bohnen et al., 2003). ~~Due to the lack of PD-specific studies on arithmetic, identifies findings from AD research – although different pathophysiological mechanisms and predictive biomarkers are identified – might help to derive, as one of the most informative sources to derive~~ hypotheses regarding arithmetic deficits in PD. AD patients show deficits in complex written calculation, ~~they are~~ less flexibility in ~~shifting~~-calculation strategies and ~~show~~ higher error rates as well as longer response latencies in arithmetic (Arnaud et al., 2008; Lemaire & Leclère, 2014; Mantovan et al., 1999). Additionally, AD patients deteriorate when numerical ADL are concerned (Bangma et al., 2021; Martini et al., 2003; Sherod et al., 2009). This link between arithmetic skills and daily functioning is further supported by finding that the ~~magnetic resonance imaging-cortical~~ volume of the angular gyri (involved in arithmetic fact retrieval) predicts financial deficits in MCI (Griffith et al., 2010). To conclude, the profile of cognitive impairment in AD is heterogeneous and the ~~only~~ partial overlap with PDD neuropathology gives rise to limited, but informative conclusions for PD (Hugo & Ganguli, 2014).

~~The few studies addressing PD-specific arithmetic deficits identified associations-relations between with domain-general functions and deficits in different arithmetic operations-and was used as the basis for the current research questions. Comparing performance in arithmetic tasks between non-demented PD samples and a healthy control group yields a variety of impairments (Liozidou et al., 2012; Zamarian et al., 2006):-~~ Arithmetic deficits (i.e., ~~more errors in mental arithmetic and calculation span~~) in non-demented PD ~~compared to a healthy control group~~ were linked to working memory deficits (Liozidou et al., 2012) and executive dysfunction (Zamarian et al., 2006) for arithmetic word problems as well as complex arithmetic and calculation span tasks, respectively. However, Zamarian and colleagues (2006) did not find deficits in more basic arithmetic tasks (e.g., ~~transcoding, number comparisons,~~ arithmetic fact retrieval, calculation span with low working memory load) and complex written calculation. ~~Hypotheses regarding the remaining question of whether~~ Arithmetic performance in easier arithmetic tasks ~~could-might~~ nevertheless be impaired in ~~more advanced PD stages can be drawn from studies investigating more advanced patient samples~~: Deficits in PDD have been reported in the basic arithmetic operations addition,

subtraction, and multiplication in written arithmetic and all four operations in mental arithmetic (Kalbe, 1999). Deficits in financial abilities, ~~(as one domain of numerical ADL, and an ecologically valid application of arithmetic)~~ were identified in PD-MCI and PDD patients (Martin et al., 2013). ~~When analysing simple financial-arithmetic tasks in a sample of PD-NC and PD-MCI patients, there are first hints of impaired magnitude and place \times value processing as well the application of arithmetic procedures, shaped by gender, disease duration, attention and visuo-spatial/ constructional skills (Loenneker, Becker, et al., 2021).~~

However, these studies ~~confront the reader are limited by with~~ several methodological constraints: All of them worked with small patient samples, diminishing the statistical power to detect small effect sizes as well as attenuating generalisability to the heterogeneous process of cognitive ~~decline~~ progression in PD. ~~Due to the low number of items, difficulty varied unsystematically item sets were not sufficiently large for a systematic manipulation of factors such as item difficulty~~ and the test-battery used by Zamarian and colleagues (2006) ~~has been reported to~~ showed ceiling effects (Delazer et al., 2003). The four arithmetic operations have only been investigated in PD-NC and PDD patients, but systematic evidence on PD-MCI is still lacking, questioning the onset of arithmetic deficits ~~to be associated to~~ associated to distinctions in cognitive progression. ~~On a conceptual level, inferences on domain specific numerical representations, which could have been obtained in a numerical effect based methodological framework (as in Moeller et al., 2011), cannot be drawn due to the task based approach.~~ To resume, available evidence on arithmetic in PD has neither systematically addressed the cognitive representations defining arithmetic deficits nor ~~their association to~~ cognitive deterioration ~~stepping progressing~~ from PD-NC to PD-MCI.

Besides these behavioural findings, ~~Another source to generate hypotheses on arithmetic deficits in PD is~~ the neuroanatomical and -functional overlap ~~between of~~ arithmetic processes (Klein et al., 2016) ~~and with~~ progression of PD neuropathology (Caligiore et al., 2016) ~~might also imply is another source to generate hypotheses on arithmetic deficits in PD.~~ The sequential progress of PD neuropathology (classified by Braak stages one to six, Braak et al., 2003) affects brain areas needed for arithmetic, with deficits in domain-specific arithmetic areas suggesting processes ~~comparable to~~ primary acalculia .

First, number magnitude and place \times value processing could be affected by degeneration in regions around the intraparietal sulcus, because of ~~resulting from~~ reduced acetylcholine production (caused by degeneration of the nucleus basalis magnocellularis beginning in Braak stage three) ~~leading to~~ a decrease in projections on the neocortex, such as parietal und temporal areas, ~~can be observed~~ (beginning in Braak stage five; Jellinger, 2018; Moeller et al., 2015). ~~The parietal cortex is of particular interest for numerical cognition as it includes the region around the intraparietal sulcus where (non-)symbolic number magnitude representation and place \times value processing are supported represented (Jellinger, 2018; Moeller et al., 2015).~~ Second, processing of visual number forms might be affected by degeneration of the temporal cortex

~~Furthermore, temporal cortex needs to be activation is associated with the processing of visual number forms~~ (Arsalidou & Taylor, 2011; Koob et al., 2014). Lewy Bodies (LBs) in frontal, cingulate, and temporal cortex emerging in Braak stage five might further impact number processing (Arsalidou & Taylor, 2011; Collerton et al., 2003; Klein et al., 2016). Third, verbally mediated fact retrieval from memory in multiplication and division can be affected, both by a decreased basal ganglia gating function for arithmetic fact retrieval (Delazer et al., 2004; Owen et al., 1998) and affected semantic brain regions (i.e., inflammation in the angular gyrus, LB-induced degeneration of hippocampus and posterior cingulate gyrus) ~~might influence the verbally mediated fact retrieval from memory and the verbal representation of numerosity needed for in multiplication and division~~ (Jellinger, 2018; López González et al., 2016; Uribe et al., 2018). Fourth, addition and subtraction ~~should-might~~ also deteriorate as they require arithmetic fact retrieval and magnitude processing (Yang et al., 2017), and degeneration of the insula ~~should-might~~ further affect addition (Arsalidou & Taylor, 2011; Jellinger, 2018). ~~Subtraction could be specifically affected by degeneration Activation~~ in premotor and supplementary motor areas ~~is also required for arithmetic fact retrieval and calculating subtractions~~ (Braak et al., 2003, 2005; Kazui et al., 2000). Fifth, advanced mathematical problem solving ~~again can be affected by degeneration in relies quires activation in~~ semantic brain regions (angular, middle temporal, fusiform, inferior frontal, posterior cingulate, and parahippocampal gyri, dorsomedial and ventromedial prefrontal cortices, Zhou et al., 2018). ~~Lewy Bodies in frontal, cingulate, and temporal cortex emerging in Braak stage five might further impact number processing (Arsalidou & Taylor, 2011; Collerton et al., 2003; Klein et al., 2016).~~ To conclude, neuronal structures and circuits degenerating in PD and presumably being responsible for domain-specific numerical processes (such as magnitude processing, fact retrieval, calculation, and place \times value integration) overlap. Whether or not these theoretical considerations ~~show will be empirically revealed as arithmetic behavioural deficits in PD empirical research represents is~~ the ~~aim target investigation~~ of the current study.

However, examining domain-specific processes may not be sufficient. Globally, degeneration of domain-general functions supporting arithmetic processing can lead to secondary ~~acaleulia-arithmetic deficits~~ in PD. With degenerative processes in the dorsolateral prefrontal cortex associated with working memory, holding and monitoring task-relevant information should be impaired in complex arithmetic (Arsalidou & Taylor, 2011; Braak et al., 2003, 2005). The decrease of dopamine production in the striatum (beginning in Braak stage ~~number-three~~) later ~~diminishes reduces~~ projections to the frontal lobe affecting processing speed, working memory, memory retrieval, verbal fluency, attention, and executive functions (Braak et al., 2003; Dirnberger et al., 2005; Martinez-Horta & Kulisevsky, 2019; Rinne et al., 2000). To conclude, PD-specific neurodegenerative processes suggest deficits in all four basic arithmetic operations, with severity depending on the stage of disease progression.

Objectives of the current study

Available studies on arithmetic in PD do not address the influence of cognitive status and the underlying cognitive representations of numerosity-arithmetic. Therefore, the current exploratory study aims at investigating arithmetic deficits in PD patients with and without mild cognitive impairment and compared comparing between PD and a healthy control (HC) group. The influence of domain-general as well as domain-specific functions will be differentiated to better understand the underlying mechanisms of behavioural arithmetic deficits. Finally, the probable use of arithmetic in the diagnostic of PD-immanent cognitive disorders will be addressed by trying to discriminate the cognitive statuses of HC, PD-NC and PD-MCI using arithmetic tasks.

The research questions of the current study are:

Q1) Arithmetic deficits in PD: Are arithmetic performance and effects impaired in PD? ~~(Q1: Arithmetic deficits in PD)~~

Q2) Influence of domain-general functions on arithmetic in PD: Do domain-general functions (e.g., visuo-spatial or executive functions) contribute to arithmetic performance in PD and if so for which operation? ~~(Q2: Influence of domain-general functions on arithmetic in PD)~~

Q3) Discrimination between cognitive statuses of PD by arithmetic performance: Can arithmetic performance be used to discriminate between a) PD-NC and PD-MCI and b) HC and PD-NC? ~~(Q3: Discrimination between cognitive statuses of PD by arithmetic performance)~~

Arithmetic processes will be systematically investigated with the help of concerning a) addition, b) subtraction, c) multiplication, and d) division. Task complexity will be considered in terms of This allows for the analysis of carry and borrow effects in addition and subtraction, respectively, and problem size effects in multiplication and division as well as consistency effects and operand errors.

~~We expect PD-MCI patients to show worse performance than HC as their disease has already progressed. As there are no data available, we can only speculate that arithmetic performance of the PD-NC group will be intermediate between HC and PD-MCI. Whether and how PD-NC and PD-MCI differ in their arithmetic skills cannot be inferred from the current literature. Therefore, we will further explore the group effect by means of pairwise comparisons between HC and PD-NC and between PD-NC and PD-MCI to identify if arithmetic deficits are more frequent in patients than in controls and in patients with cognitive impairment than in those without. For an overview of research questions, hypotheses and respective analysis plans with possible interpretations see the study design table in Supplementary Material A-Box 1.~~

Box 1. Study design

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| <p>1) Are arithmetic performance and effects impaired in Parkinson's Disease?</p> <p>Hypothesis (H1) There is a group effect in arithmetic performance: $HC > PD-NC > PD-MCI$</p> <p>Analysis plan Bayesian ANCOVAs with max. 6 clinical covariates</p> <p><u>Addition:</u> 2 Bayesian mixed ANCOVAs: group (HC, PD-NC, PD-MCI) \times complexity (carry, non-carry) with clinical covariates on RT and ACC Pairwise ANCOVAs comparing HC vs. PD-NC and PD-NC vs. PD-MCI</p> <p><u>Subtraction:</u> 2 Bayesian mixed ANCOVAs: group (HC, PD-NC, PD-MCI) \times complexity (borrow, non-borrow) with clinical covariates on RT and ACC Pairwise ANCOVAs comparing HC vs. PD-NC and PD-NC vs. PD-MCI</p> <p><u>Multiplication:</u> 2 Bayesian mixed ANCOVAs: group (HC, PD-NC, PD-MCI) \times complexity (small, large problem size) with clinical covariates on RT and ACC Pairwise ANCOVAs comparing HC vs. PD-NC and PD-NC vs. PD-MCI</p> <p><u>Division:</u> 2 Bayesian mixed ANCOVAs: group (HC, PD-NC, PD-MCI) \times complexity (small, large problem size) with clinical covariates on RT and ACC Pairwise ANCOVAs comparing HC vs. PD-NC and PD-NC vs. PD-MCI</p> <p>Interpretation given different outcomes Evidence for a group effect of $HC > PD-NC, PD-NC > PD-MCI$: association of arithmetic deficits in PD with disease progression, no mere aging effects. Evidence against group effects: arithmetic performance in PD not explained by disease-specific neurodegeneration, mere aging effect.</p> <p>Theory that could be shown wrong by the outcomes Depending on results, neurodegeneration at stages of PD-NC and PD-MCI has or has not affected fronto-parietal circuits enough to impair arithmetic performance.</p> |
| <p>2) Do domain-general functions (e.g., visuo-spatial or executive functions) contribute to arithmetic performance in PD and if so for which operation?</p> <p>Exploratory analysis without hypotheses</p> <p>Analysis plan Additional inclusion of one cognitive covariate per Bayesian ANCOVA</p> <p><u>Addition:</u> 2 Bayesian mixed ANCOVAs: group (PD-NC, PD-MCI) \times complexity (carry, non-carry) with clinical and cognitive covariates on RT and ACC</p> <p><u>Subtraction:</u> 2 Bayesian mixed ANCOVAs: group (PD-NC, PD-MCI) \times complexity (borrow, non-borrow) with clinical and cognitive covariates on RT and ACC</p> <p><u>Multiplication:</u> 2 Bayesian mixed ANCOVAs: group (PD-NC, PD-MCI) \times complexity (small, large problem size) with clinical and cognitive covariates on RT and ACC</p> <p><u>Division:</u> 2 Bayesian mixed ANCOVAs: group (PD-NC, PD-MCI) \times complexity (small, large problem size) with clinical and cognitive covariates on RT and ACC</p> <p>Interpretation given different outcomes (H2.1) Main effect of arithmetic complexity: after controlling for domain-general functions, arithmetic performance is driven by domain-specific functions. (H2.2) Main effect of cognitive covariate: domain-general function fully explains arithmetic performance. (H2.3) Main effects of cognitive covariate and arithmetic complexity with-/out interaction: joint contribution of domain-general and -specific functions to arithmetic.</p> |

Theory that could be shown wrong by the outcomes

Depending on the outcome, the results could suggest processes of arithmetic deficits in PD to be primary, secondary or indistinguishable.

3a) Can arithmetic performance be used to discriminate between PD-NC and PD-MCI?

3b) Can arithmetic performance be used to discriminate between HC and PD-NC, despite them showing comparable results regarding global cognition.

Hypothesis

a) The weighted linear combination of the four basic arithmetic tasks predicts whether a patient belongs to the group with or without mild cognitive impairments.

b) It is unclear whether the HC and PD-NC groups differ in arithmetic, despite them showing comparable results regarding global cognition.

Analysis plan

a) Bayesian logistic regressions with the predictors of z-standardized performance in addition, subtraction, multiplication, division and the covariates from research question 1 on cognitive status (PD-NC, PD-MCI)

b) Bayesian logistic regression with the predictors of z-standardized performance in addition, subtraction, multiplication, division and the covariates from research question 1 on cognitive status (HC, PD-NC)

Interpretation given different outcomes

a1) If there is evidence for no effect of arithmetic, it is not suited to discriminate between PD-NC and PD-MCI, and arithmetic impairments seem to result from a different pathomechanism than global cognitive impairment.

a2) If there is evidence for an effect of arithmetic, it is suited to discriminate between PD-NC and PD-MCI, and global cognitive and arithmetic impairments seem to share a common pathomechanism.

b) Only if arithmetic performance differentiates HC from PD-NC, it can be used as an early marker for the detection of PD.

Theory that could be shown wrong by the outcomes

Depending on the results, degeneration of numerical cognition does (a2) or does not (a1) parallel global cognition in PD and is or is not only age-related as opposed to disease-specific (b).

Note. HC = healthy elderly without neurological impairments, PD = Parkinson's Disease, PD-NC = Parkinson's patients with normal cognition, PD-MCI = Parkinson's patients with mild cognitive impairment.

Methods

Statistical power analysis and sample size estimation

Empirical effect sizes were calculated (and transformed if required) with Psychometrica, JASP and the BF calculator for single-factor ANOVA summaries (Faulkenberry, 2019; JASP Team, 2018; Lenhard & Lenhard, 2016) to anticipate an approximate effect size for the current study (an overview of effect sizes can be found on <https://osf.io/qgs5x/>). Categorisation of Cohen's d as a measure of effect size follows Cohen (1992). Recent literature provides some evidence on arithmetic deficits in PD comparable to tasks used in the current study. Tamura, Kikuchi, Otsuki, Kitagawa, and Tashiro (2003) found a large difference ($d = 1.507$) between HC and non-demented PD in a calculation span of increasing length using single-digit numbers. The comparison of PD-NC patients and HC with the Graded Difficulty Arithmetic test (orally presented addition and subtraction tasks, increasing complexity, two- and three-digit operands, Jackson & Warrington, 1986) showed medium to large differences ($d = 0.602$, Scarpina et al., 2017; $d = 1.184$, Zamarian et al., 2006). Orally presented word problems requiring mental calculation (WAIS arithmetic subtest, Wechsler, 1995) also yielded a large difference ($d > 0.8$) between non-demented PD patients and a HC group (Liozidou et al., 2012). Furthermore, Kalbe (1999) showed a large difference ($d = 1.364$) in mental calculation between a PDD and HC group (all four basic arithmetic operations, single- and two-digit numbers).

As the smallest reported effect size for differences in arithmetic is medium to large, we expect an effect of at least $d = 0.5$ for the comparison between HC and PD-NC. ~~The difference between PD-NC and PD-MCI cannot be inferred from current literature, which is why we only predict a trend of HC outperforming PD-NC and PD-NC outperforming PD-MCI. Whether and how PD-NC and PD-MCI differ in their arithmetic skills cannot be inferred from the current literature. Therefore, we will further explore the group effect by means of pairwise comparisons between HC and PD-NC and between PD-NC and PD-MCI to examine if arithmetic deficits are more frequent in patients than in controls and in patients with cognitive impairment than in those without.~~

Following the procedure of sample size estimation in Bayes factor design analysis suggested by Schönbrodt and Wagenmakers (2018), participants will be tested within a sequential Bayes factor design until the ~~between-subjects factor of group~~ respective pairwise comparisons between HC and PD-NC and between PD-NC and PD-MCI reach a value of $BF_{10} \geq 6$ or $BF_{01} \geq 6$ for all of the four basic arithmetic operations in ~~research questions one and two~~ Q1 and Q2. The criterion for ~~Q3 research question three~~ is based on the BF of including the respective predictor instead of excluding it ($BF_{inclusion}$) for each numerical predictor of the logistic regression on group. All three research questions need to reach the criterion for the recruitment to stop. The repeated measures factors carry in addition and borrow in subtraction as well as

the analysis of problem sizes in multiplication and division will be conducted in an exploratory manner and therefore do not underlie considerations for sample size estimation. ~~For~~ Due to feasibility reasons, an additional maximum sample size of $n_{\max} = 120$ valid data sets is established (targeting equal group sizes). Which of these two criteria is reached first determines the ceasing of data collection. The first check of BF_{10} is planned for when all three groups have reached a size of 15 participants (i.e., $n_{\min} = 45$), and checking will be continued in steps of five additional participants per group. The process of sequential testing will be additionally monitored with a Bayes factor plot indicating evidential development as a function of increasing sample size.

We estimated the properties of the planned research design with Monte Carlo simulations as implemented by Schönbrodt and Wagenmakers (2018) based on a sequential boundary of $BF_{10} = 6$, $d = 0.5$, $n_{\min} = 35$, $n_{\max} = 120$ and 10,000 simulated studies. Simulating the performance of our design under H_1 resulted in 9% of studies terminating at n_{\max} , 90.8% terminating at H_1 boundary and 0.2% at H_0 boundary, on average stopping at $n = 63$. Simulating the performance of our design under H_0 resulted in 35.6% of studies terminating at n_{\max} , 3.6% terminating at H_1 boundary and 60.7% at H_0 boundary, on average stopping at $n = 103$. After completion of data collection, the actual statistical power will be assessed with a Bayesian power calculation for the effects of interest.

In case of participant exclusions, new participants will be recruited for substitution. In case of early ceasing of the testing due to attrition, new participants will be recruited, and data of the dropped out patient will only be included in analyses when the patient gives informed consent and has already been assigned to a cognitive group based on the **Movement Disorder Society (MDS) Task Force level I classification criteria (MoCA ≤ 26 , Litvan et al., 2012)**.

Participants

This study has received approval by the ethics committee of the University of Tuebingen's medical faculty (161/2020BO2) and was registered not only at the Deutsches Register für Klinische Studien (DRKS-ID: DRKS00021091), but also at the World Health Organisation (Universal Trial Number: U1111-1257-2901). Patient recruitment will be managed through the PD outpatient clinic in collaboration with rehabilitation facilities specialised in PD. Furthermore, PD patients who have been previously studied and gave consent (Ethical vote: 199/2011BO1) to be contacted for potential future study participation will be contacted. The caregivers of the PD patients will also be recruited as healthy controls, in accordance with defined inclusion and exclusion criteria. Additionally, pensioners' initiatives will be contacted for control group recruitment, with the study being advertised via the university mailing systems. All participants will receive monetary compensation (30€).

In the recruitment process, HC, PD-NC and PD-MCI will be matched on the group level according to age ($M \pm 5$ years) and gender (max. 65% male) to approximately match sociodemographic and clinical group means. This method cannot be used to correct for disease duration as cognitive status is confounded with disease duration in PD-MCI patients, who also have a longer history of PD, as indicated by PD-specific disease progression (S.-J. Lin et al., 2018). As PD medication can heavily influence experimental performance, all patients will be tested in their “on-state” and will be permitted to take their regular medication during the session if necessary.

The Level I MDS Task Force criteria for PD-MCI and PDD will be used to assign patients to the PD-NC group or PD-MCI group, or excluded in the case of PDD (Emre et al., 2007; Litvan et al., 2012). This assumes a cut-off score of 26 on the Montréal Cognitive Assessment (MoCA, Nasreddine et al., 2005) to distinguish between PD-NC and PD-MCI; an absence of significant ADL impairment impacting everyday life will exclude PDD. In order to acquire a cognitive diagnosis, assessment of the patients’ self-impression, caregiver ratings, or ratings of the investigator will be used to define slow progressive deterioration of cognition from a premorbid level. The HC group will be assessed and excluded using the same MoCA cut-off score. The MoCA (Nasreddine et al., 2005; Thomann et al., 2018) is a short screening instrument for *global cognitive functioning*, evaluating short-term memory, visuo-spatial and executive functions, attention, language, and orientation to time and space. It has a maximum score of 30 and corrects for educational status in patients with 12 years of education or less.

Table 1 lists all inclusion and exclusion criteria separately for all three groups. The PD diagnosis will additionally be confirmed by a movement disorder specialist in the outpatient clinic of the University Hospital of Tuebingen using the criteria of the United Kingdom Brain Bank (Hughes et al., 1992). This confirmation is required before inclusion into the current study and must be documented in the patient’s record. Additionally, in all cases, a relation of the PD patient (i.e., a spouse, child, friend, or relative of legal age) who has agreed to report on the presence and severity of PD related ADL problems (see section caregiver assessment) will be asked to assess the patient.

Table 1. Inclusion and exclusion criteria by cognitive status.

| (Sub-)group | Inclusion criteria | Exclusion criteria |
|--------------------|--|---|
| General | <ul style="list-style-type: none"> • ≥ 5060 years of age • (Corrected) hearing and vision • Fluent German skills & German schooling • Informed consent, voluntary participation | <ul style="list-style-type: none"> • 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 |

| | | |
|---------------|---|---|
| | <ul style="list-style-type: none"> • Stable health status (i.e., able to undergo 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 | <ul style="list-style-type: none"> • 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. 2 second degree relatives) • Currently undergoing chemotherapy |
| HC | <ul style="list-style-type: none"> • Normal cognition (MoCA ≥ 26) | |
| PD | <ul style="list-style-type: none"> • Diagnosed idiopathic Parkinson's syndrome | <ul style="list-style-type: none"> • Severe impulse control disorder, dopamine dysregulation syndrome interacting with the patient's everyday life |
| PD-NC | <ul style="list-style-type: none"> • Normal cognition according to MDS Task Force level I diagnosis guidelines (e.g. MoCA ≥ 26) | <ul style="list-style-type: none"> • Diagnosis of cognitive impairment (level I-PD-MCI based on cognitive screening or PDD; Emre et al., 2007; PD-MCI or PDD, Litvan et al., 2012) |
| PD-MCI | <ul style="list-style-type: none"> • Mild cognitive impairment according to MDS Task Force level I diagnosis guidelines and diagnostic cut-off point based on Hoops et al. (Hoops et al., 2009, $26 > \text{MoCA} > 18$) | <ul style="list-style-type: none"> • Diagnosis of PDD (Emre et al., 2007) |

Note. Reprinted from “Deficits in or preservation of basic number processing in Parkinson’s Disease? A registered report” by Loenneker et al., 2021, *Journal of Neuroscience Research*. Reprinted with permission.

Materials

Our materials and programmed experiments will be openly available via the Open Science Framework (<https://osf.io/qgs5x/>). All measures are reported in Table 2, except for the arithmetic tasks they are identical to those administered by Loenneker and colleagues (2021).

Introductory interview. To acquire sociodemographic (age, gender, years of education, handedness, and mother tongue) and clinically relevant (diagnosis, age at disease onset, medication for depression or cognition) information, an introductory interview will be performed at the beginning of the experimental sessions. Furthermore, Levodopa equivalence dose (LEDD; DGN, 2016; Tomlinson et al., 2010) will be calculated based on current dopaminergic medication and time since last dopaminergic medication intake will be recorded. To gain insight about the patients’ experience with mathematics, participants will be asked to report 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 will be asked whether they have noticed a progressive deterioration of their cognition.

Motor performance. The severity of PD motor symptoms will be determined via the sum score of the MDS revision of the Unified Parkinson's Disease Rating Scale Part III and IV (UPDRS III & IV, Goetz et al., 2008) and Hoehn & Yahr staging (Hoehn & Yahr, 1967). The motor examination of *UPDRS-III* comprises 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. The evaluation scale ranges from 0 = normal to 4 = severe, with more pronounced motor impairment being indicated by high values. A total score maximum of 132 based on 18 items (with several items relating to multiple extremities resulting in 33 scores) will be calculated and included in the analysis. To assess dyskinesia, motor fluctuations, and dystonia, the subtest *UPDRS-IV* will be employed, which is based on six items with a score ranging from zero to 24 points. As an additional measure for the severity of PD motor symptoms, the *Hoehn & Yahr score* ranging from 1 to 4 (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) will be assessed.

Neuropsychological test battery. Performance in the cognitive domains of executive functions, working memory and attention, verbal memory, language, and visuo-spatial functions will be assessed with at least one test per domain. Raw scores will be considered as covariate measures for each test.

For *executive functions*, inhibition will be assessed with the subtest Go/No Go “2 out of 5” in the computerized test battery of attention (TAP = Testbatterie zur Aufmerksamkeitsprüfung, Zimmermann & Fimm, 2017). Participants must discriminate five types of stimuli and respond to only two of them. The number of errors will be used to measure the performance on this test.

Working memory abilities will be assessed in a letter span forward and backward task (as in Artemenko et al., 2018). Participants will listen to letter strings of increasing length. First, they must reproduce the letter string in the same order, then reproduce it in reverse order. The maximum length of reproduced reverse letter strings will be the relevant outcome variable. *Visuo-spatial working memory* will be assessed using the Corsi Block-Tapping Test, in which the patients must mimic a sequence of blocks tapped on by the experimenter in the correct order, both forward and backward (Corsi, 1972; Kessels et al., 2000). Sequences increase in length, starting from two blocks to a maximum of nine, when both items of the same length are correctly reproduced. The relevant outcome measure is the longest Corsi backward span

correctly reproduced. *Attention* will be measured with the TAP subtest Alertness (Zimmermann & Fimm, 2017). The test requires a simple reaction to a visually presented stimulus with or without prior notice via an auditory cue. The outcome variable assessed will be the median RT in conditions without an auditory cue (as a measure of intrinsic arousal).

Verbal memory will be measured with the German “Verbaler Lern- und Merkfähigkeitstest” (VLMT, Helmstaedter et al., 2001). Participants must learn, recall, and recognize super-span lists of words after different time intervals while coping with an intruding list of distractors. The relevant measure of performance will be the sum score for delayed recall.

Language will be measured with the German version of the WAIS-IV subtest Similarities (Petermann, 2012), operationalised as conceptual understanding, which will be assessed via an indication of what two terms have in common. The total number of correctly solved items will be used as the outcome measure.

Visuo-spatial function will be assessed using the Benton Line Orientation Test (Benton et al., 1978), in which two lines of a certain angle and position are presented on a sheet of paper. Participants must compare these two lines with eleven lines being arranged in the shape of a star around a centre. Correctly identifying the two lines from the displayed eleven lines is scored as one point, with a maximum sum score of 15.

Arithmetic tasks. Arithmetic performance will be assessed in an oral production paradigm by computerised tasks of the four basic arithmetic operations programmed with OpenSesame (Mathôt et al., 2012). Experimental trials will be preceded by practice items, which can be repeated if participants do not understand the instruction in the first attempt. **Practice trials will consist of easier tasks (e.g., using the operand 1 and single-digit numbers).** There will be no time restrictions for solving the arithmetic problems but testing will be stopped if a participant cannot answer **any of** the first ten experimental trials of the current task. All stimuli will be presented in black against a white background and in randomised order within the current basic arithmetic operation. Every trial starts with a fixation point in the shape of “o” for 750 ms and is followed by the arithmetic problem presented centrally on the screen until the participant presses the **easy-to-handle TAP-space** key while responding orally. **The participant starts pressing the space key when starting to answer, holds it in the meantime and releases the key when having finished answering. The critical RT here is the first key press, the time between key press and key release will be used to exclude participants taking too long due to utterances intermixed with the answer. This-The numerical** response is entered with a QWERTZ keyboard by the experimenter, who then initiates the next trial **(for a similar procedure in elderly see Artemenko, 2021).** By decreasing motor effort for PD patients, this response format aims at minimizing the influence of PD-immanent motor impairments on arithmetic performance while logging both response and RT. Outcome measures will be both proportion of correctly solved trials (ACC)

and RT for ~~the conditions of~~ each basic arithmetic operation. The factor of item complexity is operationalized depending on the basic arithmetic operation: carry operation for addition, borrow operation for subtraction, and problem size for multiplication and division.

Addition. The 50 experimental trials will be preceded by five practice trials. All addition problems consist of two two-digit numbers (with results ranging from 36 to 96). Items do not imply pure decades (e.g., 20), ties (e.g., 22), unit ties (e.g., 32 + 52), or decade ties (e.g., 23 + 25). Carry and non-carry items are matched considering problem size, numerical size of both operands and units and decades of both operands, parity of both operands, and position of the smaller operand. This allows for calculating the carry effect, defined as the difference in mean RTs between carry and non-carry problems, ~~counterbalanced for problem size while controlling for problem size~~ (which is defined as the sum of the two operands). Therefore, outcome measures for the task-based approach are RT and ACC, whereas the outcome measure for the effect-based approach is the carry effect (see Artemenko et al., 2018).

Subtraction. The 50 experimental trials will be preceded by five practice trials, which all consist of two two-digit numbers. The subtraction problems are constructed as the inverse problems of addition (e.g., 32 + 25 → 57 - 25). This allows for calculating the borrow effect, defined as the difference in mean RTs between borrow and non-borrow problems, ~~counterbalanced for problem size while controlling for problem size~~ (which is defined as the value of the first operand, i.e., the minuend). Therefore, outcome measures for the task-based approach are RT and ACC, whereas the outcome measure for the effect-based approach is the borrow effect (see Artemenko et al., 2018).

Multiplication. The 45 experimental trials will be preceded by five practice trials. All multiplication problems come from single-digit multiplication tables (numbers 1-9), with single- and two-digit results ranging from 1 to 81. The item set includes each number pair only once (e.g., 5 × 3 or 3 × 5) with the position of the larger operand being counterbalanced, and ties (e.g., 5 × 5). Items consist of small (product ≤ 25) and large (product > 25) problem sizes (as in Archambeau et al., 2019; Grabner et al., 2009). The outcome measures are both overall ACC and RT.

Division. The 45 trials will be preceded by five practice trials. The division problems are constructed as the inverse problems of multiplication (e.g., e.g., 5 × 3 → 15 ÷ 5). Items consist of small (divisor ≤ 25) and large (divisor > 25) problem sizes (being the inverse of the definition of problem size for multiplication). The outcome measures are both overall ACC and RT.

Clinical questionnaires for non-motor assessment, ADL and quality of life. In addition to the introductory interview, self-report questionnaires will be used to assess other clinical variables. The Nonmotor Symptoms Questionnaire for Parkinson's Disease (NMSQuest; Chaudhuri et al., 2006) is a 30-item screening questionnaire with a categorical answering format of “yes”, “no”, and “don't know” based

on the occurrence of *nonmotor symptoms* in the last month. It allows for the quantification of sleep disorders and neuropsychiatric, autonomic, gastrointestinal, sensory, and other symptoms by means of a sum score.

The Beck Depression Inventory (BDI-II; Hautzinger et al., 2006) will be used to assess the patients' *depressive symptoms*, with a cut-off of 20, which indicates signs for major depression. The assessment consists of 21 items which the patients must rate for the intensity of occurrence of the symptom during the last two weeks on a scale ranging from 0 to 3 (maximum sum score of 63).

The patients' current *social function* will be measured using the Functional Activities Questionnaire (FAQ; Pfeffer et al., 1982), which is tailored to older adults. Participants must rate their level of performance (ranging from 0 = normal to 3 = dependent) in 10 different daily life activities, resulting in a sum score characterising social function.

Health-related quality of life will be 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 will be coded on a scale ranging from 0 (= perfect health) to 100 (= worst health).

Caregiver assessment. For a broader evaluation of the participant's quality of life, the FAQ will also be completed by a caregiver. Additionally, caregivers will be asked for how they are related to the participant, their demographic data (i.e., age, gender), and how frequently and intensely they are in contact with the participant. To assess the cognitive diagnosis, caregivers will be asked whether they have noticed a progressive deterioration of the patient's cognitive state.

Table 2. Summary of collected measures

| Measure | Aspects | Description/ Example | Outcome |
|------------------------|------------------------------|--|--|
| Introductory interview | Sociodemographic information | Age, gender, years of education, handedness, mother tongue, experience with mathematics, level of income | |
| | Clinical information | Diagnosis, age at disease onset, medication for depression/ cognition, LEDD | |
| Motor performance | UPDRS-III | Speech, facial expression, rigidity of neck / extremities, hand / finger movements, toe tapping, leg agility, rising from a chair, (freezing of) gait, posture, stability, global spontaneity of movement, postural / kinetic tremor of hands, rest tremor amplitude / constancy | Total score (max. 132 = pronounced impairment) |
| | UPDRS-IV | Dyskinesia, motor fluctuations, dystonia | Total score (max. 24 = pronounced impairment) |

~~ACALCULIA~~ ARITHMETIC DEFICITS IN PARKINSON

| | | | |
|---------------------------------|-----------------------------------|---|--|
| | Hoehn & Yahr staging | Uni-/ bilateral involvement, postural instability | Score (1 – 4) |
| Neuropsychological test battery | TAP Go/ No Go | Executive function (inhibition) | <i>N</i> of errors |
| | MoCA | Global cognition | Sum score (max. 30 = no impairment) |
| | Letter span backward | Verbal working memory | Max. span |
| | Corsi Block-Tapping Test backward | Visuo-spatial working memory | Max. span |
| | TAP Alertness | Attention | Median RT without cue |
| | VLMT | Verbal memory | Sum score delayed recall |
| | WAIS-IV similarities | Language | <i>N</i> correct |
| | Benton Line Orientation Test | Visuo-spatial function | <i>N</i> correct |
| Arithmetic tasks | Addition | 5 practice, 50 experimental (50% carry operations), 2-digit numbers | RT, ACC, carry effect |
| | Subtraction | 5 practice, 50 experimental (50% borrow operations), 2-digit numbers | RT, ACC, borrow effect |
| | Multiplication | 5 practice, 45 experimental (50% small problem size), 1-digit numbers for multiplication (inverse for division) | RT, ACC, problem size effect |
| | Division | | |
| Clinical questionnaires | NMSQuest | Nonmotor Parkinson’s symptoms | Sum score (max. 30) |
| | BDI-II | Depressive Symptoms | Sum score (max. 63 = pronounced impairment) |
| | FAQ | Social function | Sum score (max. 30 = pronounced impairment) |
| | PDQ-39 | Health-related quality of life | Sum score (0 = perfect health to 100 = worst health) |

Procedure

As part of a broader research project on numerical cognition in PD, the current study will be conducted in joint sessions with the registered report that investigates basic number processing in PD, which has already been granted in-principle acceptance (for further measures conducted regarding basic number processing in PD see Loenneker, Artemenko, et al., 2021). After obtaining written informed consent, the predefined inclusion and exclusion criteria will be used to assess participant eligibility in a semi-standardised questionnaire. PD patients’ cognitive performance will be used to assign them to the PD-NC

or the PD-MCI group. Participants will attend two sessions of 1.5 to 2 hours each. In order to handle patient attrition, there will be breaks within each session as required. The first experimental session consists of the sociodemographic questionnaire, the basic numerical tasks (not considered here: transcoding, number line estimation, non-symbolic magnitude comparison, symbolic magnitude comparison, Loenneker, Artemenko, et al., 2021) and the numerical arithmetic tasks addition, subtraction, multiplication and division in this order. Afterwards, participants and caregivers will complete the clinical scales and questionnaires which may also be filled out at home between the first and second session. In the second session, the MoCA, clinical variables, motor assessment, and neuropsychological test battery will be conducted in that order. The two sessions may be scheduled three weeks apart at a maximum. On a conceptual level, the first publication (Loenneker, Artemenko, et al., 2021) addresses the basic foundations of number processing, whereas the current publication focuses on arithmetic skills, which are more relevant for a patient's daily life.

Data treatment and proposed analysis pipeline

Data analyses will be run with R version 4.0.3 (R core team, 2014) and JASP version 0.14.1 (JASP Team, 2018). Data will be managed using REDCap electronic data capture tools (Harris et al., 2009). Anonymised data and analyses scripts will be freely available on the Open Science Framework (<https://osf.io/qgs5x/>). As all analyses are conducted within the framework of Bayesian statistics, correction for multiple comparisons is not necessary (as elaborated by Gelman et al., 2012). For all inferential statistics an α -level of .05 will be assumed and effect sizes will be estimated. Classification of the effect size Cohen's d will be based on Cohen (1992) and Bayes Factors (BF) will follow Jeffreys (1961). BF_{10} indicates the probability of evidence in favour of the alternative hypothesis and BF_{01} indicates the probability of evidence in favour of the null hypothesis with $BF_{01} = 1/BF_{10}$ (which will be additionally reported when $BF_{10} < 1$). Additionally to reporting BF_{10} , we will report how many participants matched theoretical expectation as Percent Correct Classification (PCC) following Grice and colleagues (2020). Overall, planning, analysis, interpretation and reporting of results (will) follow recommendations by van Doorn et al. (2020).

Data preprocessing

Exclusions. In case of missing data, participants will be excluded in a case-wise manner for those analyses including the respective measure. Participants need to achieve an ACC of minimum 75% in tasks in a forced choice format (TAP tasks, Benton line orientation test) for inclusion in the respective analysis. The arithmetic tasks begin with practice trials and can be aborted if none of the first ten experimental trials is solved correctly. ~~resulting in participant exclusion due to a lack in understanding the task instruction~~ In

this case, we will assign a value of 0 for ACC and the participant will be excluded from the RT analysis but included in the ACC analysis. Participants whose performance exceeds 3 *SD* below the group *M* will be excluded from the respective analysis.

Reaction times. Data trimming for RTs in the arithmetic tasks is adapted from Baayen & Milin (2010). The RT distribution of correctly solved trials will be inspected with by-subject quantile-quantile plots, in order to identify the best suited theoretical model for data transformation to approach normally distributed data. The most accurate distribution will be determined with the best model fit and used to transform the data. After that, outliers will be excluded in two steps. First, anticipations will be excluded defined as RTs faster than 200 ms. Second, model criticism will be used to exclude remaining outliers, based on Shapiro tests for normality. Those data points with absolute standardized residuals exceeding 3 will be removed. Last, temporal dependencies will be corrected for with autocorrelation functions by participant and a regression model fitted to responses with a log-transformation for latencies and including the covariates trial number and preceding RT. For participants to be included in the RT analysis, a minimum of five valid data points out of 20-25 trials needs to be available per condition (i.e., minimum ACC of 20-25%).

Accuracy. Either arcsine- or logit-transformation will be chosen for ACC data depending on the best model fit for the empirical distribution of ACC.

Assumption check. Following the aforementioned phase of data pre-processing, assumptions for respective statistical hypothesis testing will be checked. Assumptions will be tested by means of visual inspection (scatterplots, residual plots, residual boxplots), frequentist (Levene test, Mauchly's test) and Bayesian (variance homogeneity, Dablander et al., 2020) tests. In case of a violation of assumptions for the ANCOVA regarding normal distribution and variance homogeneity of residuals, appropriate transformations will be conducted. Predictors of the logistic regression will be checked for collinearities based on a variance inflation factor below 10.

Group-wise characteristics

Possible variables confounding the experimental manipulations will be identified as differences in sociodemographic, clinical and cognitive variables between the three groups. The categorical variables gender and Hoehn & Yahr stage will be characterized as total number per category and corresponding percentage, and compared with Bayesian contingency tables between HC and PD-NC and between PD-NC and PD-MCI. Continuous variables will be described with *M* (*SD*) and compared between HC and PD-NC and between PD-NC and PD-MCI with Bayesian independent samples *t*-tests. The candidate variables to be considered as confounders are sociodemographic (age, education years, level of income, educational and professional math experience) and clinical (disease duration, age at onset, LEDD, intake of antidepressants)

variables. Furthermore, motor (UPDRS-III & IV) and cognitive function will be compared. Last, group-wise comparisons will be conducted on clinical questionnaires (non-motor symptoms: NMSQuest, depression: BDI-II, ADL self-report & caregiver report: FAQ, health-related quality of life: PDQ-39). Additionally, irrespective of the status of mild cognitive impairment, the number of HC, PD-NC, and PD-MCI participants with impairments in any of the cognitive measures will be reported.

Hypothesis testing

We expect to find differences of at least medium to large effect sizes between the HC and PD-MCI group as well as an ordinal trend of HC outperforming both PD-NC and PD-MCI and PD-NC outperforming PD-MCI. Whether differences between HC and PD-NC or PD-NC and PD-MCI will be significant cannot be inferred from the available literature and is to be investigated with the current study. For all Bayesian analyses, uninformed Cauchy priors will be used, as the current study is the first of its kind and we cannot infer priors from available literature, and models will be compared to the null model.

We estimate the robustness of the BF analysis based on Zamarian's (2006) results on the Graded Difficulty Arithmetic Test (i.e., mixed arithmetic tasks), compared between PD-NC ($M = 10.2$, $SD = 4.3$) and HC ($M = 15.5$, $SD = 4.6$), $t(41) = -3.70$, $p < .001$ ($M_{\text{difference}} = -5.3$, $SE = 1.43$). We assessed the robustness using the online Bayes factor calculator (Dienes, 2018). We defined the likelihood based on a student t distribution with the parameters from Zamarian's results ($M = 5.3$, $SD = 0.22$, $df = 41$), assuming a Cauchy distribution with the same parameters for the model of the alternative hypothesis and a Cauchy distribution with a location parameter of 0 for the model of the null hypothesis, both one-sided with a lower limit. Results on possible ranges of the scale factors and mean differences producing BFs indicating conclusive evidence are reported in Table 3. These results are only available for ACC, but not for RT data. However, many of these tests operationalize the constructs differently (e.g., the GDAE assesses all basic arithmetic operations at once instead of testing the four operations separately as in our study). Even if the name is the same (complex calculation), it is possible that effects depend on the exact stimuli (e.g., with or without carry/borrowing, which we manipulated). Furthermore, the study was conducted in PD-NC, but not PD-MCI patients. Considerations regarding effect sizes in Q3b cannot be inferred from the literature, as we are not aware of a study comparing PD-NC with PD-MCI patients in mental arithmetic.

Table 3. Robustness considerations of scale factors for Bayesian analysis.

| Model for alternative hypothesis | | | Model for null hypothesis | | |
|--|-------|------------------|---------------------------|-------|------------------|
| Location | Scale | BF ₁₀ | Location | Scale | BF ₀₁ |
| Values based on Zamarian et al. (2006) | | | | | |
| 5.3 | 0.22 | 376.69 | 0 | 0.22 | 0.003 |
| Manipulation of scale factors with constant location parameter | | | | | |
| 5.3 | 0.022 | 37808.05 | 0 | 0.022 | 0.00003 |
| 5.3 | 0.7 | 35.90 | 0 | 0.7 | 0.028 |
| 5.3 | 1 | 16.81 | 0 | 1 | 0.059 |
| 5.3 | 2.2 | 3.06 | 0 | 2.2 | 0.33 |
| Manipulation of location parameter with constant scale factor | | | | | |
| 0.53 | 0.22 | 3.06 | 0 | 0.22 | 0.33 |
| 1 | 0.22 | 11.96 | 0 | 0.22 | 0.08 |
| 53 | 0.22 | 38116.94 | 0 | 0.22 | 0.00003 |

Table 3 indicates that we can expect fairly robust results as long as the location parameters are not substantially smaller, or the scale parameters are not substantially larger than in the work by Zamarian et al. (2006). Since the current study implies both comparisons with a PD-NC and a more advanced PD-MCI group as opposed to a single PD-NC sample in Zamarian’s study, we might even expect larger effects. However, we want to be careful with this prediction as target tasks, control variables, and items within tasks differ and may modulate effects. After data acquisition, robustness of the BF across different scale factors will be assessed with a robustness plot in JASP.

Zamarian’s study also provides evidence regarding the association of domain-general factors with arithmetic performance. Where they found a difference in complex mental calculation (GDAE) between patients (M = 10.2, SD = 4.3) and controls (M = 15.5, SD = 4.6), $t(41) = -3.70$, $p < .001$, they identified associations between the GDAE and interference naming ($r = -0.633$, $p < 0.02$), digit span forward ($r = 0.625$, $p < 0.02$) and block span backward ($r = 0.584$, $p < 0.03$). These correlations can be transformed into effect sizes of $d = -1.64$, $d = 1.60$, and $d = 1.44$, respectively.

Manipulation check. To ensure the quality of our data, we will analyse the carry effect for addition, the borrow effect for subtraction, and the problem size effect for multiplication and division in the HC group for ACC and RT to see whether we find the usual arithmetic effects in our data. This will be done with Bayesian t-tests.

Arithmetic deficits in PD (Q1). The three groups will first be compared regarding sociodemographic and clinical variables. We assume age, gender, education, **level of income, educational and professional math experience**, Hoehn & Yahr staging, disease duration, and depression could significantly differ between groups. In this case we will include a maximum number of six clinical covariates in all models. ANCOVAs will be run with the respective previously identified covariates. *Addition* will be analysed by two Bayesian mixed ANCOVAs with the factors group (HC, PD-NC, PD-

MCI) and complexity (non-carry, carry) on RT and ACC. *Subtraction* will be analysed by two Bayesian mixed ANCOVAs with the factors group (HC, PD-NC, PD-MCI) and complexity (non-borrow, borrow) on RT and ACC. *Multiplication* will be analysed by two Bayesian mixed ANCOVAs with the factors group (HC, PD-NC, PD-MCI) and complexity (small, large problem size) on RT and ACC. *Division* will be analysed by two Bayesian mixed ANCOVAs with the factors group (HC, PD-NC, PD-MCI) and complexity (small, large problem size) on RT and ACC. (H1) We expect the HC group to ~~obtain~~ perform better results than the PD-NC and PD-MCI groups, and the PD-NC group ~~to show a better performance~~ than the PD-MCI group. ~~The group comparisons will be conducted~~ ~~The ordinal trend of performance decreasing from HC over PD-NC to PD-MCI groups will be tested with~~ by pairwise ANCOVAs that include the covariates of the respective analysis.

Influence of domain-general functions on arithmetic processing in PD (Q2). The question whether arithmetic performance within the group of PD patients can be explained by domain-general functions will be addressed with further Bayesian ANCOVAs. These analyses will be preceded by Bayesian correlational analyses of arithmetic performance with possible covariates. For each arithmetic task, the cognitive covariate with the highest association (minimum significant correlation of 0.3) will be included in the respective model, adding up to a maximum of seven covariates including confounders identified for Q1. Bayesian ANCOVAs conducted for Q1 will then be repeated for Q2 with the respective additional cognitive covariate and only the two groups PD-NC and PD-MCI. There are three possible outcomes: ~~(H2.1) There is no main effect of the respective cognitive covariate, but a main effect of arithmetic complexity, indicating that arithmetic impairment can be fully explained with domain-specific functions.~~ ~~(H2.2) There is only a main effect of the respective cognitive covariate but not of the arithmetic complexity, suggesting that domain-general function fully explains performance in the respective arithmetic task.~~ (H2.1) A main effect of arithmetic complexity indicates that after controlling for domain-general functions, arithmetic performance is driven by domain-specific functions. (H2.2) A main effect of cognitive covariate indicates that the domain-general function fully explains arithmetic performance. (H2.3) There is both a main effect of the respective cognitive covariate and arithmetic complexity with(out) an interaction effect of these two, hinting at a joint contribution of domain-general and –specific functions to performance in the respective arithmetic task.

Discrimination between cognitive statuses of PD patients by arithmetic performance (Q3). The last question targeting the diagnostic use of arithmetic will be answered using two Bayesian logistic regressions. This discriminant analysis will be conducted with z-standardized performance in addition, subtraction, multiplication, and division as multiple predictors and with the dependent variable of cognitive status for a) PD-NC and PD-MCI and b) HC and PD-NC. Covariates from ~~Q2~~Q1 will also be included in the model. Both influential case diagnostics and outlier analysis will be applied to minimize the effect of

highly influential participants on the regression. The probability for each person to fall into the respective group will be calculated based on the regression. ~~In an additional exploratory analysis, the same procedures will be conducted for the respective arithmetic effects.~~ We hypothesize that the respective group can be predicted with a linear combination of the arithmetic predictors. H3a). The combined performance of the four arithmetic tasks predicts whether a patient belongs to the group with or without mild cognitive impairments. ~~) If the regression model has low values in model diagnostics, arithmetic performance is not suited to discriminate between PD-NC and PD-MCI and arithmetic impairments seem to result from a distinct pathomechanism as opposed to global cognitive impairment. If the regression model has high values in model diagnostics, arithmetic performance is suited to discriminate between PD-NC and PD-MCI and global cognitive and arithmetic impairments seem to share a common pathomechanism H3b)~~ Based on the available literature, we cannot hypothesize whether the HC group will outperform the PD-NC group, despite them both being defined according to a normal cognitive status ~~showing comparable results regarding global cognition.~~ There are several possible unexpected outcomes: (H3a1) If there is evidence for no effect of arithmetic, it is not suited to discriminate between PD-NC and PD-MCI and arithmetic impairments seem to result from a different pathomechanism than cognitive impairment. (H3a2) If there is evidence for an effect of arithmetic, it is suited to discriminate between PD-NC and PD-MCI and cognitive and arithmetic impairments seem to at least partly share a common pathomechanism. (H3b) If arithmetic performance only differentiates HC from PD-NC, but not PD-NC from PD-MCI, it could be used as an early marker for the detection of PD. ~~If the HC group outperforms the PD-NC group, arithmetic performance might be used as an early marker for the detection of PD. If both groups cannot be discriminated from each other but PD-NC and PD-MCI do, then arithmetic deficits only occur at a later disease stage.~~

Possible limitations and unexpected outcomes

Several issues might be encountered in the following stages of recruitment, testing, data analysis and interpretation.

Due to the potential problems in patient recruitment due to pandemic restrictions, group matching might not be as successful as intended. Cognitive impairment in PD is of a heterogeneous nature. Patient groups might, for example, differ regarding disease duration, PD motor type, or non-motor burden. By controlling for the main confounding variables, we at least partially account for the heterogeneity in our group comparisons. Future standardized assessment of arithmetic skills should establish norms correcting for confounding factors we identify in the current study such as age, education, or gender. Due to possible confounds, the number of covariates might exceed the statistical power needed to detect effects within the given sample size. Therefore, the maximum sample size of 120 might still lead to an underpowered study,

even though it is 2-3 times larger than the samples in the studies used for effect size estimation. However, the Bayes factor still allows to interpret how likely the hypothesis is given the data. As we are conducting the first systematic study investigating arithmetic deficits in PD, our evidence can be used for sample size calculations in future studies focusing on a specific effect and conducted with an even larger sample.

Cognitive diagnosis of PD-NC and PD-MCI will only be made based on MDS Task Force level I criteria – and not based on a comprehensive level II neuropsychological test battery, because testing time is limited and we want to reserve enough time for the target tasks of interest. This compromise might increase the probability of a misdiagnosis of a patient’s cognitive status, because reliability and validity of level I criteria might be lower. To inform about cognitive test performance, the number of patients scoring ≤ 1.5 standard values below the population mean as specified in the respective test manual will be reported.

To reduce patient attrition, the testing is split into two experimental sessions, including enough breaks for the patients to recover and they will be allowed to take their medication during the session. We will conduct the tests in a standardized order, which might induce group differences if they three groups are differently affected by attrition. However, we can reduce variance in the effects that the different tests have on one another. Although attritional and motivational effects are reduced by splitting the testing up into two sessions, it is still possible to have some remaining effects within one session.

Our study has an incomplete design with only one matched healthy control group. Thus, arithmetic deficits in the PD-MCI group are difficult to interpret as both general effects of cognitive impairments and/or specific disease progression potentially contribute to this effect. To clarify this issue, future studies can include an additional control group with non-PD related MCI (neglected here due to limited resources). Moreover, it is unclear if MCI and PD-MCI share the same pathomechanism, and therefore lead to the same deficit. Neurodegenerative cognitive impairments can be caused by brain atrophy, imbalance of cholinergic and dopaminergic neurotransmitters, amyloid pathology (typical of AD) and Lewy Body pathology (typical of PD). Accordingly, MCI is associated to an amyloid and cholinergic pathology as in AD, whereas PD-MCI patients display both amyloid, cholinergic, dopaminergic and Lewy Body pathology (Chandra et al., 2019; C. H. Lin & Wu, 2015). Therefore, interaction of PD patient status and MCI may be due to the particular underlying pathomechanism, which may be unknown and/ or heterogeneous for an HC-MCI group. As a start, we will compare HC and PD-NC on the one hand to identify effects specific to PD (both with normal cognition), and PD-NC and PD-MCI on the other hand to investigate the effect of cognitive impairment within PD. Based on these results, it seems worthwhile to investigate whether MCIs in different groups with different pathomechanisms lead to the same arithmetic deficits or not in future studies.

Finally, it is possible that we do not find any group effects, but all patients show the same performance as the elderly control group. Firstly, this could mean that impairments of PD patients observed in clinical practice have to be attributed to mere aging effects or that arithmetic in everyday life is even more complex than our experimental manipulation. In this case, we would recommend future studies that either compare performance to a young control group or to a PDD sample which previously has been shown to have arithmetic deficits (Kalbe, 1999), or employing more complex arithmetic tasks. However, it could also be a result of aggregating data across individuals. Another approach from differential psychology might solve this issue by looking at the different arithmetic effects on an individual level (i.e., proportion of individuals who show a certain effect or deficit per group) or using LMMs, which, however, would require much higher power to be conclusive. Finally, missing group effects could be a consequence of ceiling or floor effects, either at the item or the task level – however, since we are one of the first manipulating arithmetic item difficulty substantially within tasks, we are optimistic that we will not have ceiling or floor effects throughout all conditions.

Further procedure

Testing is planned to begin in ~~August~~ ~~September~~ 2021 after critical revisions of ~~the pre-registered review and following in principle acceptance~~ the registered report. However, experiments can only start when the current Covid-19 situation permits human-to-human testing with elderly participants. Recruitment and testing phase are estimated to last 9 months. Data analysis and preparation of the final manuscript are expected to be finished four months after the last experimental session.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

All authors have 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. *Conceptualization*: HDL, CA, HCN, and ILS; *Data Curation*, HDL; *Methodology*: HDL, CA, HCN, KW, and ILS; *Investigation*: HDL; *Formal Analysis*: HDL; *Writing – Original Draft*: HDL; *Writing – Review & Editing*: HDL, CA, HCN, KW, and ILS; *Project Administration*: HDL; *Visualization*: HDL; *Funding Acquisition*: HDL

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