

Arithmetic deficits in Parkinson's Disease? A registered report

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Submitted by Hannah Dorothea Loenneker 29 Jun 2021 19:23

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 with different arithmetic 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) 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 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.

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

Round #2

by Zoltan Dienes, 09 Nov 2021 09:24

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Dear Zoltan, der Reviewers,

Thanks again for this valuable experience of constructive peer review. We learnt a lot and believe that it improved our study greatly. We have now implemented your remaining minor revisions as suggested.

We are looking forward to hearing back from you.

Hannah Loenneker
On behalf of all authors

minor revision

The reviewers are very happy with your revisions. Roshtein asks you to consider some possible additional control groups; you can decide the feasibility of this.

One further point. Exploratory analyses are not pre-registered in Stage 1. In your design table you list one set of analyses as exploratory and without hypotheses; yet your interpretation involves conclusions about substantial theory. In what sense do you mean they are exploratory? If you mean you see analytic and interpretative flexibility, then they should not be registered in the Stage 1; but you are free to perform them at Stage 2 in a non-pre-registered section. I am not sure you mean this, as it seems there is clear theory at stake and you can specify the analyses and the interpretation. Please clarify.

Thanks a lot for pointing out this important inconsistency in our manuscript. We agree with the reviewers' position that the term "Exploratory analysis" is not correct for our specific analysis. Indeed, we have already given interpretations for different outcomes, but not formulated the corresponding hypotheses. For our research question 2 we formulated three different hypotheses, which correspond to the previously given interpretations for different outcomes (which remained unchanged) and also match our previously formulated analysis plan (also unchanged) with hypotheses and conclusions. We revised both the manuscript and the design table in the Supplementary Material to specify our hypotheses more clearly:

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

Exploratory analysis without hypotheses

Parallel Hypotheses

(H2.1) There is only a main effect of arithmetic complexity.

(H2.2) There is only a main effect of cognitive covariate.

(H2.3) There are main effects of cognitive covariate and arithmetic complexity with-/out interaction.

Analysis plan

Additional inclusion of one cognitive covariate per Bayesian ANCOVA

Addition:

2 Bayesian mixed ANCOVAs: group (PD-NC, PD-MCI) \times complexity (carry, non-carry) with clinical and cognitive covariates on RT and ACC

Subtraction:

2 Bayesian mixed ANCOVAs: group (PD-NC, PD-MCI) \times complexity (borrow, non-borrow) with clinical and cognitive covariates on RT and ACC

Multiplication:

2 Bayesian mixed ANCOVAs: group (PD-NC, PD-MCI) \times complexity (small, large problem size) with clinical and cognitive covariates on RT and ACC

Division:

2 Bayesian mixed ANCOVAs: group (PD-NC, PD-MCI) \times complexity (small, large problem size) with clinical and cognitive covariates on RT and ACC

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.

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.

This change also applies to the section on Hypotheses testing in “Data treatment and proposed analysis pipeline”:

“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. **The factor group will be split among two chains of separate pairwise analyses, comparing HC with PD-NC and PD-NC with PD-MCI.** *Addition* will be analysed by two Bayesian mixed ANCOVAs with the factors group (HC vs. PD-NC/ **PD-NC vs. 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 vs. PD-NC/ **PD-NC vs. 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 vs. PD-NC/ **PD-NC vs. 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 vs. PD-NC/ **PD-NC vs. PD-MCI**) and complexity (small, large problem size) on RT and ACC. (H1) We expect the HC group to perform better than the PD-NC and PD-MCI groups, and the PD-NC group than the PD-MCI group. The group comparisons will be conducted by pairwise ANCOVAs that include the covariates of the respective analysis.”

You could also simplify in another way: You propose for some analyses to first do an omnibus ANOVA and then the planned contrasts; but conclusions follow only from the contrasts, which also define the stopping rule. You need therefore only perform the contrasts. You might wish to have a separate row for each contrast to indicate what theoretical claim precisely is at stake for each contrast. At the moment it is not clear what follows from one contrast showing an effect and the other showing no effect.

We considered your methodological approach in research question 1, as research questions 2 and 3 already include only pairwise comparisons. We changed the analysis plan accordingly:

1) Are arithmetic performance and effects impaired in Parkinson’s Disease?

Hypothesis

(H1.1) There is a group effect in arithmetic performance: $HC > PD-NC > PD-MCI$

(H1.2) There is a group effect in arithmetic performance: $PD-NC > PD-MCI$

Analysis plan

Bayesian ANCOVAs with max. 6 clinical covariates

Addition:

2 **pairwise** Bayesian mixed ANCOVAs: group (HC, PD-NC, ~~PD-MCI~~) \times complexity (carry, non-carry) with clinical covariates on RT and ACC

2 pairwise Bayesian mixed ANCOVAs: group (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~~

Subtraction:

2 pairwise Bayesian mixed ANCOVAs: group (HC, PD-NC, ~~PD-MCI~~) \times complexity (borrow, non-borrow) with clinical covariates on RT and ACC

2 pairwise Bayesian mixed ANCOVAs: group (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~~

Multiplication:

2 pairwise Bayesian mixed ANCOVAs: group (HC, PD-NC, ~~PD-MCI~~) \times complexity (small, large problem size) with clinical covariates on RT and ACC

2 pairwise Bayesian mixed ANCOVAs: group (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~~

Division:

2 pairwise Bayesian mixed ANCOVAs: group (HC, PD-NC, ~~PD-MCI~~) \times complexity (small, large problem size) with clinical covariates on RT and ACC

2 pairwise Bayesian mixed ANCOVAs: group (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~~

Interpretation given different outcomes

(H1.1) Evidence for a group effect of HC > PD-NC, ~~PD-NC > PD-MCI~~: association of arithmetic deficits in PD with disease ~~progression~~ pathology, no mere aging effects.

Evidence against group effect HC > PD-NC: arithmetic performance in PD not explained by disease-specific neurodegeneration, mere aging effect.

(H1.2) 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 effect PD-NC > PD-MCI: arithmetic performance in PD does not parallel global cognitive decline associated to disease progression.

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.

This change also applies to the section on Hypotheses testing in “Data treatment and proposed analysis pipeline”:

“We expect to find differences of at least medium to large effect sizes between the HC and PD-NC and between the PD-NC 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.~~”

I won't be sending back to review in order for you to obtain IPA, as the reviewers are very positive; I will make that decision myself.

Reviews

Reviewed by Stephanie Rossit, 05 Nov 2021 14:04

Dear Editors, I am very happy to endorse the publication of this manuscript and have no further comments as the authors have done a fabulous job at revising. I look forward to learning about the results of the study in due course and wish the authors the best of luck!

Thank you.

Reviewed by Pia Rotshtein, 08 Nov 2021 07:17

I first like to thank the authors again for a very thorough and thoughtful work and response to our comments. I also apologize for the delay in reviewing the paper.

While the work is excellent and thorough it is also very complex. I fear this will be a future barrier for readers to appreciate the quality, especially if you want to communicate the results to medical and clinicians. I am not sure what the authors can do to simplify it, but maybe it is something to be minded in the report of the results.

Thanks you for this comment. We agree with Ms. Rotshtein that this is a true caveat we need to keep in mind, as we also want to use our work to inform practitioners about probable arithmetic deficits in Parkinson's Disease. We are aware that our research design is complex and might be hard to understand. We will make the following adaptations to enhance accessibility to the data.

We are planning to present our results as straightforward and structured as possible. This will be achieved by using subheadings corresponding to the research questions laid out in the methods section as well as interim summaries linking the results to our main hypotheses. Additionally, we will use accessible and intuitive visualizations of the data and move details of minor importance to the Supplementary Material. Finally, the conclusions of this study will provide a summary of the most important findings written in a simplified way so that the findings can be understood by practitioners. By these means, we will be able to communicate our research project to both a scientific and a clinical target audience.

Two final thoughts:

Control group:

1) I appreciate that an MCI control group is likely to be heterogeneous and may include some overlapping PD-like etiology. Please make sure you bring it up in study limitation - that difference between PD-MCI vs. PD-NC may reflect comorbidity with other degeneration symptoms rather than relates to PD severity per se.

Thanks for this valuable comment. We added the following sentence to the limitation section where we discuss the heterogeneity of cognitive impairment in PD:

“Differences between PD-NC and PD-MCI do not necessarily relate to PD severity per se, but might also possibly result from further neuropathological processes associated to alteration in patient's cognitive performance.”

2) Given the potential difference in socio-demographics between PD-NC and PD-MCI, maybe include to healthy control groups with a match to each group. or based on the adapt analysis approach using two t-tests: PD-NC vs HC, PD-MCI vs PD-NC, than make sure the HC matches the PD-NC better.

We agree that the characteristic of the control group is a crucial point regarding the interpretation of our results. As we discussed in the limitation section, recruiting participants during a pandemic (who additionally belong to the risk group) is not easy. We state in the Methods: “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.”

To make this issue more present, we added the following sentence in the Participants section of our manuscript: “The caregivers of the PD patients will also be recruited as healthy controls, in accordance with defined inclusion and exclusion criteria, to make the HC group as comparable as possible considering sociodemographic background to both PD-NC and PD-MCI.”

Overall, our aim is to recruit a heterogeneous control group and to statistically account for differences between HC and PD-NC which do not stem PD by including these variables as covariates. This is already addressed in our limitations section and expanded in the most recent manuscript version:

“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 comparison. If matching is not perfect, we will try to control for differences in these variables between groups by using them as covariates and partialling their variance out. Additionally, this issue will be addressed in the limitation section, because there might be non-linear relations between variables, interactions or in the worst case, too many confounding variables to control for all of them with the given degrees of freedom. Note, however, that in this case, the Bayes factor still allows interpreting how likely the hypothesis is given the data. We will clearly outline the limitations of our study in such a case and make clear that 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.”

Thank you

PS, Zoltan I do not need to review it again, I am happy with whatever decision you will make regarding the authors responses.

We wish to thank for the trust Ms. Rotshtein put into us and tried to accommodate her comments as carefully as we do in all other cases.

Additionally, due to the Covid19 situation, we slightly altered our "Further procedure" section:

"Testing ~~is planned to begin~~ has begun in September 2021 after critical revisions of the registered report. However, experiments can only ~~start~~ be conducted when the current Covid-19 situation permits human-to-human testing with elderly participants. Recruitment and testing phase are estimated to last ~~9~~ 12 months."