Childbirth and delayed Parkinson’s onset: a reproducible non-biological artefact of societal change.

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| Michael R. MacAskill, PhD1,2, Daniel J. Myall, PhD1, Reza Shoorangiz, PhD1, Tim J. Anderson, MD, FRACP1,2,3,4, & Toni L. Pitcher, PhD1,2,3 |
| 1 New Zealand Brain Research Institute, 66 Stewart St, Christchurch, New Zealand |
| 2 Department of Medicine, University of Otago, Christchurch; Christchurch, New Zealand |
| 3 Brain Research New Zealand, Rangahau Roro Aotearoa |
| 4 Department of Neurology, Christchurch Hospital, Christchurch, New Zealand |
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# Author note

Correspondence concerning this article should be addressed to Michael R. MacAskill, PhD, 66 Stewart St, Christchurch 8011, New Zealand. E-mail: [michael.macaskill@nzbri.org](mailto:michael.macaskill@nzbri.org)

Abstract

**Background:** Uncontrolled studies have reported associations between later Parkinson’s onset in women and a history of giving birth, with age of onset delayed by nearly three years per child.

**Objectives:** We tested this association in two independent datasets but, as a control to test for non-biological explanations, also included men with Parkinson’s.

**Methods:** We analysed valid cases from the Parkinson’s Progressive Markers Initiative incident sample (PPMI: 145 women, 276 men) and a prevalent sample surveyed by the New Zealand Brain Research Institute (NZBRI: 210 women, 394 men).

**Results:** The association was present in both women and men in the PPMI study, and absent in both in the NZBRI study. This is consistent with generational differences, common to men and women, which confound with age of onset in incident-dominant samples.

**Conclusion:** Despite being replicable in certain circumstances, associations between childbirth and later Parkinson’s onset are an artefact of generational cohort differences.

*Keywords:* Parkinson disease, sex differences, pregnancy, epidemiology, cohort effects, sex hormones

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# Introduction

The incidence and prevalence of Parkinson’s are substantially lower in women.1,2 The cause is unknown but could include greater male exposure to risk factors, such as head injury or occupational use of toxins.3 Conversely, protective factors might apply differentially to women, possibly including greater exposure to hormones like œstrogens and progestogens.

Plausible mechanisms have been proposed for how female sex hormones could play a neuroprotective role in neurodegenerative conditions4 and observational human studies have examined whether increased hormone exposure is associated with protection against Parkinson’s. Lifetime hormonal exposure has been operationalised using endogenous measures such as fertile life span (the duration between age at menarche and at menopause), or exogenous exposure through oral contraceptives or hormone replacement therapy. Despite some positive findings,5 however, most reviews,6 large prospective7 or case-control8 studies, and meta-analyses9,10 have shown little support for relationships between any such measures and a lowered risk of Parkinson’s.

Lv *et al.’s* meta-analysis9 included an examination of five case-control and three cohort studies of the effect of parity (number of childbirths) upon the risk of women subsequently developing Parkinson’s. This showed no effect, with the relative risk of Parkinson’s between the highest and lowest number of births being 0.99 (95% CI: 0.79–1.25). Two studies have, however, independently reported another childbirth-related association not specifically addressed in that meta-analysis: among women diagnosed with Parkinson’s, they found that a history of childbirth was associated with later age of onset.11,12 That is, although having children might not reduce the risk of Parkinson’s *per se,* it might still slow the pathological process, resulting in later onset. The associations were surprisingly large: Haaxma *et al.* found symptom onset to be later by 2.7 years per childbirth (95% CI: 0.8 – 4.6)11 while Frentzel *et al.* independently found a delay of 2.6 years per birth (95% CI: 0.05 – 5.1).12 In neither study was the effect as linear as these single coefficients might imply, however.

A challenge in such observational studies is applying valid control comparisons. Women without Parkinson’s lack the disease outcome measures (such as age of onset), while men with Parkinson’s lack the predictor hormonal measures. For this specific association between number of children and age of onset, however, men with Parkinson’s are a suitable control to test for non-biological explanations. We proposed that if the relationship is absent in men, it would provide stronger evidence for a protective hormonal effect, specific to women. Conversely, if that relationship does hold for men, it would strongly support the cause being non-biological, and common to both sexes.

# Methods

## Data sets

*PPMI:* We downloaded the openly-available Parkinson’s Progressive Marker Initiative dataset (see Acknowledgments). PPMI is an incident case study, with a mean 7 months between diagnosis and study entry (see Table 1). Valid data on number of children was available from 421 of the study’s 423 idiopathic Parkinson’s cases.

*NZBRI:* At the New Zealand Brain Research Institute (NZBRI) we conducted two online risk-factor surveys, from which 604 people with idiopathic Parkinson’s provided valid data on age at diagnosis and number of biological children (Table 1). Cases ranged from recently-diagnosed to those with long-standing disease. Those with dementia had assistance to complete the questions. One survey (192 valid cases) recruited from our ongoing longitudinal study of a convenience sample of prevalent cases in the local Canterbury region. The other (412 valid cases) was nation-wide, recruiting from the membership (excluding Canterbury) of the Parkinson’s New Zealand charitable trust. Age at diagnosis was self-reported in the national survey and confirmed from clinical records in the Canterbury survey.

## Analyses

Disease onset was defined as the age at which a formal diagnosis of Parkinson’s was made, as symptom onset age was not included in the NZBRI national survey. Data were fit with simple Bayesian linear models, using the R13 package *brms*.14 Parameters were given default weakly-informative priors. Four chains of 4000 iterations each were run.

When testing hypotheses of an association between the number of children and age of onset (or year of birth), in each case we compared a model containing the number of children as a predictor to an intercept-only model (i.e. a model of no association). Bayes factors indicated how much more likely it was that incorporating the number of children as a predictor provided a better fit to the data than an intercept-only (“flat-line”) model.

## Reproducibility

The code and the anonymised dataset extracts used to conduct the analyses and generate this manuscript are available at <https://github.com/nzbri/pd-parity>.

Table 1: Demographic characteristics of the PPMI and NZBRI samples.

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| --- | --- | --- | --- | --- | --- |
| Study | Sex | n | Mean age | Mean age at diagnosis | Mean years disease duration |
| PPMI | Men | 276 | 62.2 (9.7) | 61.6 (9.7) | 0.5 (0.5) |
| PPMI | Women | 145 | 60.7 (9.6) | 60.1 (9.6) | 0.6 (0.6) |
| NZBRI | Men | 394 | 71.7 (7.5) | 63.8 (9) | 7.9 (5.8) |
| NZBRI | Women | 210 | 70.3 (7.3) | 62.9 (9) | 7.5 (5.8) |

# Results

## PPMI sample

We first attempted to replicate the association between number of children and later disease onset in the PPMI women. The linearly-modelled delay in diagnosis was 1.1 years per child (uncertainty interval [0.05, 2.1]). This is the slope of the line in the upper-right panel of Figure 1B. A Bayes factor of 0.4 indicated substantial evidence for an association, compared to the intercept-only model. Similar results were, however, found for the PPMI men, with a slope of 1.3 years per child [0.3, 2.3] and a Bayes factor of 1. As the relationship was not unique to women, this strongly argues against the underlying cause being pregnancy- or birth-related.

For completeness, we also tested whether women did actually have a later age of disease onset. As indicated in Table 1, the mean age at diagnosis was actually slightly *earlier* for women, by -1.5 [-3.4, 0.4] years, with a posterior probability of only 6% of a later onset in the population.

## NZBRI sample

In the NZBRI sample, the slope for women was only 0.3 years per child [-0.6, 1.3], with a Bayes factor of 0.1 indicating no evidence for a positive association. The results were similar for men, with a slope of 0.3 years per child [-0.4, 1.0] and a Bayes factor of 0.0.

The NZBRI mean age at diagnosis was again marginally earlier for women, by -0.9 years [-2.5, 0.6], with a posterior probability of 12% of onset actually being later in the population.

## Testing a non-biological alternative explanation

In many countries, late twentieth-century societal changes mean that older people on average had larger families than people born more recently. Figure 1A shows such effects for the men and women in both studies (for ease of comparison with the age-of-onset associations, we plot number of children on the *x*-axis, although this does not reflect the direction of causality). We then modelled how many years earlier we would expect a patient to have been born, given how many children they had. *PPMI study.* Women: -1.1 years per child, uncertainty interval [-2.14, -0.1], Bayes factor 0. Men: -1.3 years per child [-2.32, -0.3], Bayes factor 1. *NZBRI study.* Women: -0.6 years per child, [-1.38, 0.2], Bayes factor 0.1 (although the evidence for this association was not strong in this sample, we know that the population fertility for New Zealand women did indeed decline markedly in the late twentieth century.15) Men: -0.9 years per child [-1.51, -0.3], Bayes factor 4. The coefficients are negative, as, for consistency across studies with recruitment at different times, we modeled year of birth rather than age.

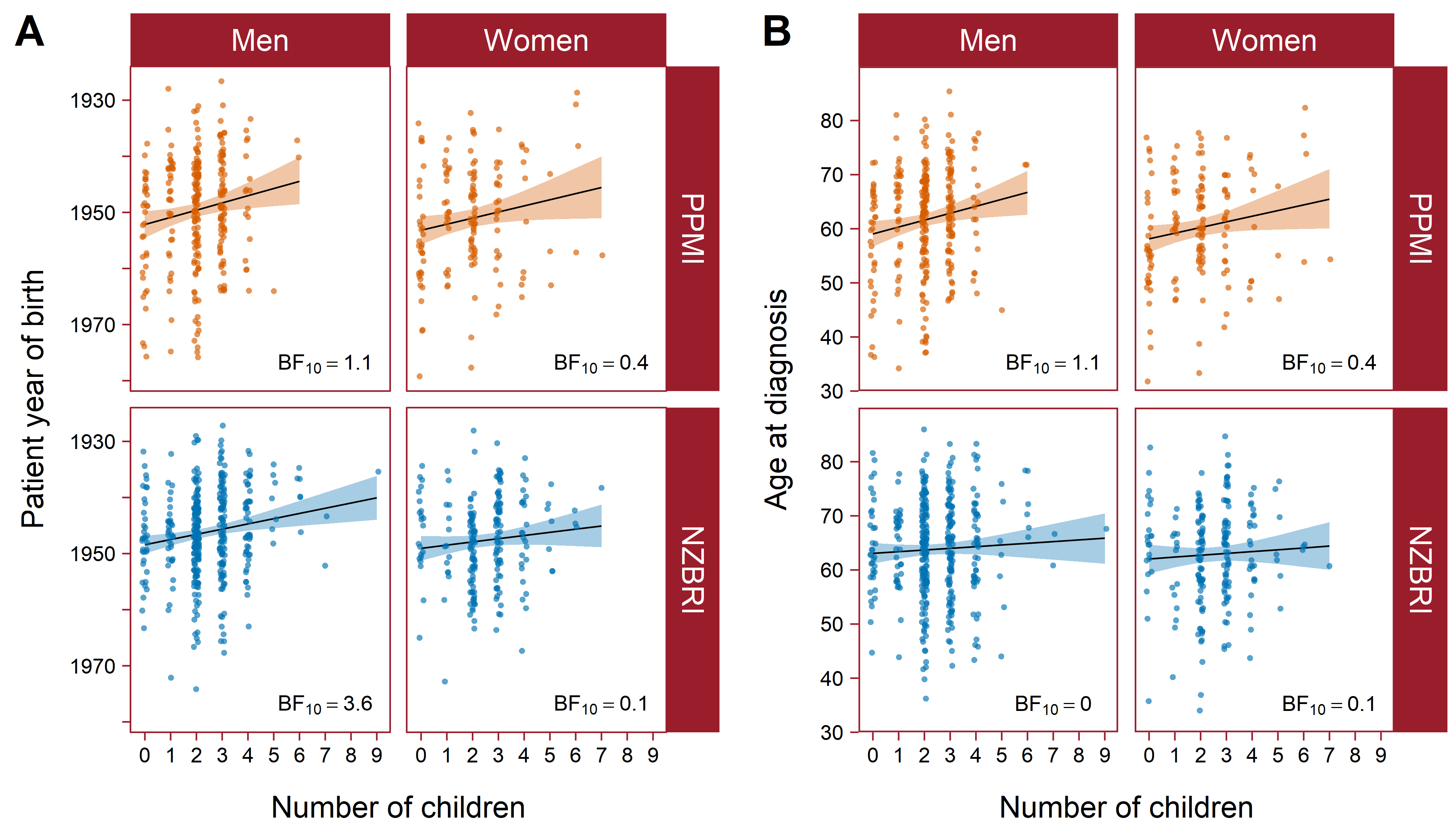


Figure 1: **(A).** In both the PPMI (orange) and NZBRI (blue) studies, in both men and women, there was a background cohort effect in which older patients tended to have had more children than had patients who were born more recently. The magnitude of this effect (i.e. the slope of each line) was such that each additional child was associated with the average patient having been born (approximately) one year earlier. The Bayes factor (BF) labels indicate how many times more likely the data was better fit by each model, compared to the null hypothesis of there being no association (i.e. a flat line). **(B).** PPMI is an incident study and hence patient age and age-of-diagnosis are tightly correlated. Accordingly, the PPMI age-of-diagnosis association almost perfectly reflects the underlying background societal association of older people having more children (at a similar magnitude of approximately one year per child). By contrast, the NZBRI survey was of a prevalent sample, in which a patient’s current age and their age of diagnosis are no longer necessarily coupled. That is, a patient of a given age might have been recently diagnosed, or they could have long-standing disease. Accordingly, the age-of-diagnosis association was absent for both the NZBRI men and women (as indicated by the small Bayes factors). Figure by MacAskill (2019), distributed at <https://doi.org/10.6084/m9.figshare.9928460> under an open CC-BY 4.0 license.

# Discussion

The men of the PPMI sample showed a clear association between having more children and later disease onset. This is sufficient to discount the proposed hormonal cause for this relationship previously reported in women only.11,12 We tested a non-biological explanation, common to both men and women, in which older patients are simply more likely than younger ones to have had larger families. In incident studies like PPMI, there is an almost perfect correlation between patient age and age of diagnosis. Accordingly, the diagnosis-age effect in the PPMI study (top row of Figure 1B) almost perfectly resembles the simple background generational cohort effect (top row of Figure 1A). The previously reported associations are therefore likely an example of the classic epidemiological trap of mistaking an age effect for a generational cohort one.16

The association between number of children and diagnosis age was not found in either sex in the NZBRI study (bottom row of Figure 1B), although the background generational effect (bottom row of Figure 1A) was similar to that in the PPMI study. This is consistent, because in a prevalence sample the relationship between patient age and their age of diagnosis becomes de-coupled, because the sample includes many people with long-standing disease. Take, for example, a pair of people, one diagnosed at 50 and another at 75. In an incident study, participants are recruited soon after diagnosis, and such a pair would necessarily come from different generations. In a prevalent sample, however, that relationship breaks down. Both patients could even be the same age: one recently diagnosed at age 75, while the other, also currently aged 75, would have a 25 year history of disease. Artefactual associations between number of children and the age of Parkinson’s onset are therefore most likely to be observed in samples with a preponderance of incident cases. In a pure incident sample, the magnitude of the association should closely match the background societal association between age and family size (as shown in the roughly one-year-per-child associations in the PPMI sample). The two previous studies defined disease duration from symptom onset, so with durations of 2.5 years11 and 5.8 years,12 this indeed places them closer to the PPMI incident study (2.1 years mean female symptom duration) than to the NZBRI prevalent sample (where the mean duration since diagnosis was 7.5 years, implying a much longer time relative to symptom onset).

Lastly, we found that women’s age of onset was marginally *earlier* compared to men. This is not inconsistent with the two previous studies, where the women’s age of onset (57.1) was either similar to the men’s (57.3),12 or non-significantly later (53.4 vs 51.3, p = 0.06).11 Remembering that the representative population age will be far older than in studies with actively-participating patients, further analysis of our previously-reported national-level pharmaco-epidemiology study of 10 500 [10 300, 10 700] incident cases of Parkinson’s2,17 found the standardised age of onset for women was again, if anything, minimally earlier (69.8 [69.6, 70.0]) compared to men (70.5 [70.5, 70.6]). That is, not only is the association between childbirth and later disease onset artefactual, but there might not even be a female advantage for it to explain.

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# Authors’ Roles

MacAskill: Research project: conception. Statistical analysis: design, execution. Manuscript: writing of first draft. Myall: Research project: execution. Statistical analysis: design, review. Manuscript: review and critique. Shoorangiz: Statistical analysis: design, review. Manuscript: review and critique. Anderson: Manuscript: review and critique. Pitcher: Research project: conception, execution. Manuscript: review and critique.

# Relevant conflicts of interest/financial disclosures

Authors report no conflicts of interest. MacAskill, Anderson, and Pitcher are employed by the University of Otago. Myall and Shoorangiz are employed by the New Zealand Brain Research Institute. No other funding was obtained to carry out this specific project. The authors have jointly received funding for other projects in the past 12 months from the Neurological Foundation of New Zealand, New Zealand Brain Research Institute, Canterbury Medical Research Foundation, the University of Otago, and Brain Research New Zealand, Rangahau Roro Aotearoa.

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