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

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# Author note

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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 of Parkinson’s is substantially lower in women1,2 (at least outside of China and Japan).1,3 The reason is unknown but could include greater male exposure to risk factors (e.g. head injury or occupational use of toxins),4 or protective factors applying differentially to women (e.g. 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 conditions5 and hence observational studies have tested associations between increased hormone exposure and 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,6 most reviews7, large prospective8 or case-control9 studies, and meta-analyses10,11 have shown little support for relationships between any such measures and a lowered risk of Parkinson’s.

Eight studies have examined the effect of parity (number of childbirths) upon the risk of women subsequently developing Parkinson’s.10 Meta-analysis 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).10 Three 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.12–14 That is, although having children might not reduce the risk of Parkinson’s *per se,* it might still slow the pathological process. The associations were surprisingly large and consistent, with symptom onset reported as being later by 2.7 years (95% CI: 0.8 – 4.6, Netherlands, n = 97)12 or 2.6 years per childbirth (95% CI: 0.05 – 5.1, Germany, n = 79)14, or to have a correlation coefficient of 0.35 between parity and onset age (India, n = 81, p = 0.001).13

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, however, defining the predictor as “number of biological children” rather than “number of childbirths” allows men with Parkinson’s to be a suitable control for non-biological explanations. We propose that if the relationship between number of children and onset age is absent in men, it would strengthen claims for a protective female sex hormone effect. Conversely, if that relationship *does* hold for men, it would strongly support the cause being non-biological.

# Methods

## Data sets

*PPMI:* The openly-available Parkinson’s Progressive Marker Initiative15 is a dataset of incident cases, with a mean 7 months between diagnosis and recruitment (see Table 1 and Acknowledgments). Valid data on number of children was available from 421 of PPMI’s 423 idiopathic Parkinson’s cases.

*NZBRI:* At the New Zealand Brain Research Institute, we combined two previously-conducted risk-factor surveys, in which 604 people with idiopathic Parkinson’s provided valid responses on age at diagnosis and number of biological children (Table 1). Cases ranged from recently-diagnosed to those with long-standing disease. Responses were mostly collected online, with some submitting via paper or telephone. Respondents 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. Canterbury respondents had diagnosis confirmed by a neurologist. The remainder required a diagnosis in order to receive care from Parkinson’s New Zealand, which might have been made by a neurologist, other specialist, or general practitioner.

## Analyses

Onset age was defined as when Parkinson’s was diagnosed, because symptom onset age was not collected in the NZBRI nation-wide survey. Data were fit with simple Bayesian linear models, using the R16 package *brms*.17 Weakly-informative Student *t* priors were used for the intercept (df = 3, mean = data mean, scale = 10) and standard deviation of the residuals (df = 3, mean = 0, scale = 10) with rejection sampling used to ensure the standard deviation was non-negative. The scale values were chosen so the prior distributions had moderate probability mass fully covering the range of plausible parameter values. Based upon the three previous studies,12–14 we used a proper informative normal prior (mean = ±2.5, SD = 2) for the effect of the number of children (being positive for the dependent variable of age, and negative for year of birth). We ran four chains of 20 000 iterations each.

When testing hypotheses of associations 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 give the ratio of the likelihood of the data given a model including the number of children, to the likelihood of the data given 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 (credible interval [0.15, 2.1]), being the slope of the line in the upper-right panel of Figure 1B. However, a Bayes factor (BF) of 1.5 indicated very weak evidence for an association compared to the intercept-only model. Stronger results were found for the PPMI men, with a slope of 1.4 years per child [0.4, 2.3], BF = 4.9. That the relationship occurred in men argues against the underlying cause being pregnancy- or birth-related.

For completeness, we also examined whether women did actually have a later age of disease onset. As indicated in Table 1, the mean age at diagnosis was similar between the sexes, occurring earlier for women by just -0.8 [-2.5, 1.0] years.

## NZBRI sample

In the NZBRI sample, the slope for women was only 0.5 years per child [-0.5, 1.4], with a Bayes factor of 0.2 indicating strong evidence against an association. The results were similar for men, with a slope of 0.4 years per child [-0.3, 1.1], BF = 0.1.

The NZBRI mean age at diagnosis was again similar between the sexes, occurring earlier for women by just -0.5 years [-1.9, 0.9].

## Testing a non-biological alternative explanation

In many countries, due to late twentieth-century societal changes, 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. We then modelled how many years earlier we would expect a patient to have been born, given how many children they had. The coefficients are negative, as, for consistency across studies with recruitment at different times, we modeled year of birth rather than age. *PPMI study.* Women: -1.2 years per child, credible interval [-2.19, -0.2], BF = 1.7. Men: -1.4 years per child [-2.38, -0.4], BF = 5.1. *NZBRI study.* Women: -0.6 years per child, [-1.43, 0.1], BF = 0.3 (although the association was not present in this sample, we know that the population fertility for New Zealand women did indeed decline markedly in the late twentieth century.18) Men: -1.0 years per child [-1.54, -0.4], BF = 14.3.

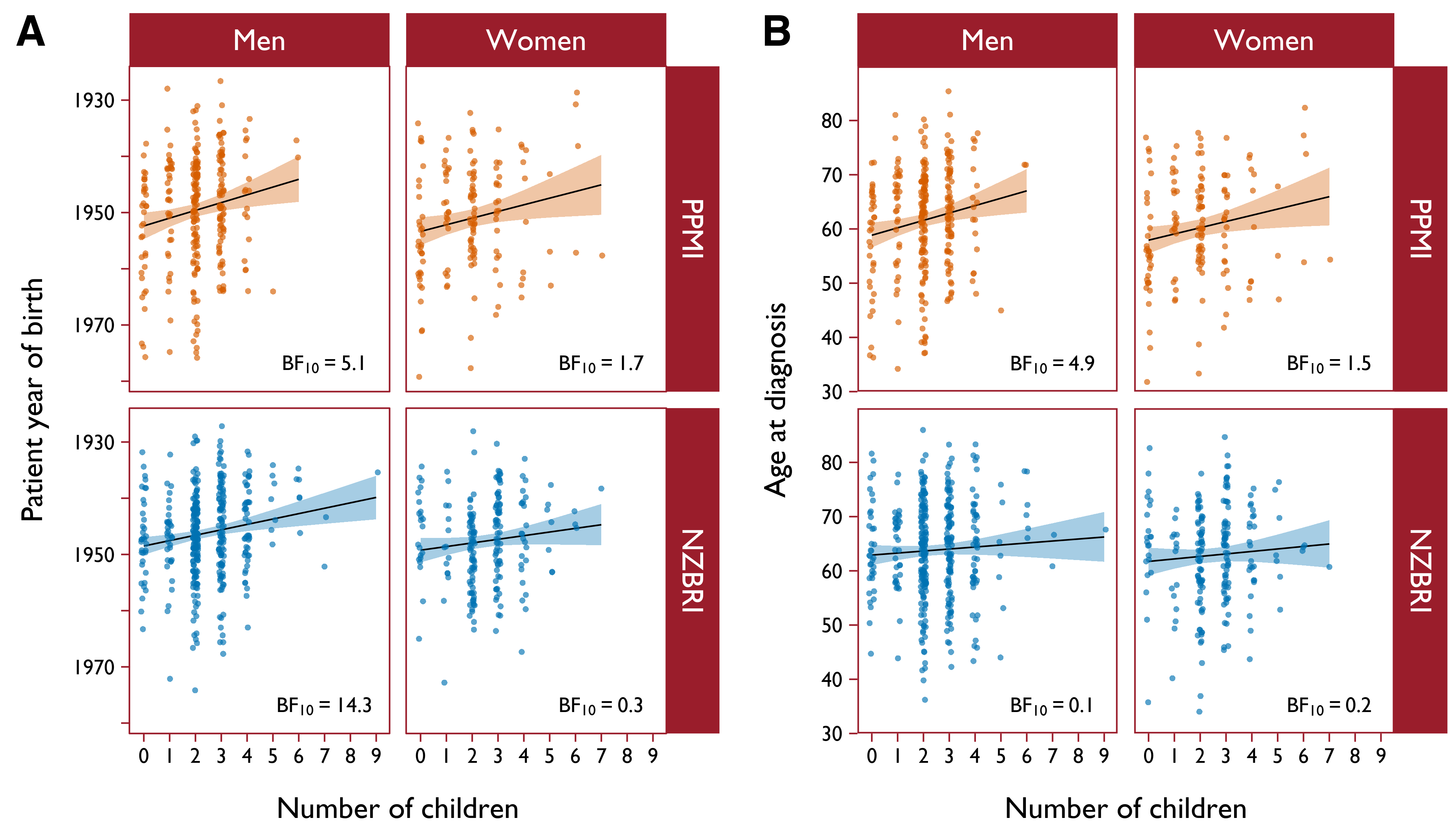


Figure 1: **(A).** In the PPMI (orange) and NZBRI (blue) studies, there was a background cohort effect in which older patients tended to have had more children than had patients who were born more recently (for ease of comparison with the age-of-onset associations, we plot number of children on the x-axis, although this does not reflect the direction of causality). 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 association was more strongly evident in men than in women in these samples. **(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 BF (Bayes factor) values). Figure by MacAskill (2019), distributed at <https://doi.org/10.6084/m9.figshare.9928460> under an open CC-BY 4.0 license.

# Discussion

The PPMI men showed a clear association between having more children and later disease onset (although the dataset is limited by having few patients with more than four children). This is sufficient to discount the proposed hormonal cause for this relationship, previously reported in women only.12–14 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 a near-perfect correlation between patient age and age of diagnosis. Accordingly, the diagnosis-age effect in the PPMI study (top row, Figure 1B) very closely resembles the simple background generational cohort effect (top row, 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.19. As patient age and age-of-onset are almost perfectly correlated in this study, it is not possible to use age to statistically “correct for” generational membership.

Associations between number of children and diagnosis age were absent in both sexes in the NZBRI study (bottom row, Figure 1B), although the background generational effect (bottom row, Figure 1A) was similar to that in the PPMI study. This is consistent, because in a prevalence sample, people with long-standing disease somewhat de-couple the relationship between patient age and their age of diagnosis. Consider one person diagnosed at age 50 and another at 75. In an incident study, with recruitment soon after diagnosis, these people would necessarily come from different generations. In a prevalent sample, however, this relationship can break down. They could even be the same age, if one was recently diagnosed at age 75, while the other, also currently aged 75, had a 25 year history of disease. Artefactual associations between number of children and age of onset are therefore most likely 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). Two of the previous studies defined disease duration from symptom onset: with mean durations of 2.5 years12 and 5.8 years,14 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). The third study had a median disease duration of 5 years although it was not specified if that was defined from symptom onset or diagnosis.13 The magnitude of the effect we found (approximately one year later onset per child) was smaller than in the previous studies. This is consistent with the complex web of social, cultural, financial, and health factors that influence family size, with generational cohort being only one contributor (evident in the large variability in Figure 1A).

If there was a causal association between childbirth and delayed disease onset, women’s mean onset age should be measurably later than men’s (unless some other competing female risk factors could somehow balance the putative protective childbirth effect). We found male and female onset age was similar, in both the PPMI and NZBRI samples. In the previous studies, women’s onset age (57.1) was either similar to men’s (57.3),14 or non-significantly later (53.4 vs 51.3, p = 0.06)12 (the remaining study13 had no male comparison). That is, not only is the association between childbirth and later disease onset artefactual, there is likely no female age-of-onset advantage in need of explanation.

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# Authors’ Roles

MacAskill: Research project: conception. Statistical analysis: design, execution. Manuscript: writing of each 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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