- Wechsler Test of Adult Reading in Parkinson's: a stable yet imperfect measure of premorbid cognitive function
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14 Abstract

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Purpose. To assess long-term trajectories of Wechsler Test of Adult Reading (WTAR)
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   scores in people with Parkinson's as a function of age. The WTAR has been recommended
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   as a measure of premorbid cognitive function in English speakers with Parkinson's disease
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   and as a reference against which to assess current cognitive status. For this, however, it
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   needs to be shown that WTAR scores remain stable despite the substantial cognitive
   deterioration that can occur in Parkinson's. Methods. From 252 Parkinson's and 57
   Control participants who had completed at least two WTARs, we analyzed scores over time
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   using latent class trajectory modeling. This allows for individual participants to be
   classified into data-driven clusters, depending on the shape of their longitudinal trajectory.
   Results. WTAR scores were quite stable within both Controls and Parkinson's
   participants, even for those who progressed to dementia. This validates it as a research tool
   for comparing premorbid function at a group level. In both Parkinson's and Controls, and
   regardless of current cognitive status, the distribution of scores was, however, higher than
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   expected from the population norms, making it an unreliable benchmark against which to
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   detect cognitive decline at an individual level. Conclusion. The WTAR is stable in
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   Parkinson's even when participants decline from normal cognitive function to early
   dementia. Nonetheless, its apparent over-estimation of premorbid IQ and the
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   impracticality of implementing analogous tests in many other languages makes it
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   poorly-suited for detecting current cognitive impairment in individuals with Parkinson's.
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         Keywords: Parkinson disease, cognitive impairment, dementia, neuropsychology,
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   premorbid function
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Introduction

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The prevalence of Parkinson's is rising,^{1,2} and hence the burden of dementia
associated with the disease will also continue to grow. There is therefore value in detecting
the transitional stage of mild cognitive impairment in Parkinson's, in particular because it
may provide a therapeutic window for future treatments, prior to the irreversible
pathological damage associated with dementia. To provide for consistent delineation of this
transitional state, the International Parkinson and Movement Disorder Society (MDS)
published guidelines in 2012 for the diagnosis of mild cognitive impairment in Parkinson's
(PD-MCI).³

When the diagnosis is based on a comprehensive battery of multiple individual 48 neuropsychological tests (rather than on a single scale of global cognitive ability), the MDS guidelines propose that significant impairment may be determined in three ways. Firstly, current performance on a test can be shown to be below appropriate norms (which may be 51 established either relative to standardized norms for that test, or relative to a local matched control group). This approach has the disadvantage that the cause of poor current performance cannot be distinguished between that due to a recent decline (such as the onset of MCI or dementia), or a long-standing poor level of cognitive ability. To unambiguously detect recent impairment in cognitive status therefore requires some way of demonstrating a decline in function within an individual, rather than simply poor current performance. To achieve this, the guidelines suggest seeking evidence of either a decline in performance on serial testing, or, in the absence of such prior testing, evidence of a decline from an individual's *estimated* premorbid level of function. For pragmatic reasons, however, methods based upon current norms still tend to predominate in research studies.⁴ In practice, one seldom has reference to prior formal serial testing. Even in a well-resourced research setting, serial testing remains somewhat ambiguous, as the first available test session may itself be contaminated by early disease-related cognitive impairment. This would produce a falsely low baseline and thereby impede the ability to detect cognitive decline.

A reliable method of estimating premorbid cognitive function is therefore appealing.

Establishing a person's premorbid ability addresses the shortcomings of both the

current-norms approach (by showing whether current poor performance is indeed a decline

from past status), and the issue with the timing of serial testing (which will usually begin

only after disease diagnosis). The Wechsler Test of Adult Reading (WTAR)⁵ was suggested

in the MDS guidelines as being suitable for this purpose (along with the National Adult

Reading Test, NART).⁶ Both tests are based on the ability to correctly pronounce

phonetically-irregular English words, such as 'porpoise' or 'hyperbole'. Unlike many

neuropsychological functions, this ability has been shown to be preserved in the face of

both normal ageing and a broad range of brain insults.^{5,6}

When the WTAR was initially normed, it was tested in Parkinson's as well as a
number of other neurological or psychiatric disorders, such as Huntington's, schizophrenia,
and traumatic brain injury.⁵ Only in Alzheimer's disease were scores shown to be
significantly lower than in matched controls.^{5,6} Additionally in the Alzheimer's group,
WTAR scores were lower in those with lower overall current cognitive status,⁶ further
indicating that it is not a stable measure of premorbid function in that condition. Those
results were, however, published in 2001, well before the formal MDS guidelines on
diagnosing PD-MCI³ and Parkinson's dementia⁷ were promulgated. It is therefore
unknown to what extent the findings from that sample are valid in the face of the
significant cognitive deterioration that can occur in Parkinson's, as it could not have been
formally diagnosed at the time. Moreover, their Parkinson's sub-sample was also comprised
of only 10 people: given the marked heterogeneity of function in this disorder, this restricts
the validity of generalizing from those findings. We know of only one study in which the

WTAR has actually been used as a criterion against which to establish mild cognitive impairment in Parkinson's. The proportion classified as PD-MCI using WTAR-estimated premorbid functioning was strikingly higher than when using the more conventional method of comparing current performance against norms (79% vs 33%). This naturally leads to questions about whether the WTAR is in fact a valid measure to be used for cognitive classification in Parkinson's. In particular, if using the WTAR leads to most people with Parkinson's being classified as having MCI, does that result in a category that no longer has any prognostic or discriminative utility?

Performance on the WTAR is known to be impacted negatively by Alzheimer's 98 dementia, but as noted the initial claim of stability in Parkinson's was based on very 99 limited evidence.⁵ We therefore sought to examine WTAR scores longitudinally in a large 100 and cognitively formally-characterized cohort that spanned the range from normal function 101 through to mild cognitive impairment and dementia. We included only those participants 102 who had completed a minimum of two WTARs, so that the trajectory of the measure 103 within individuals over time could be examined. To do this, we used latent class trajectory 104 analysis⁹. This allows for detecting heterogeneous patterns of change over time in a 105 data-driven fashion, rather than assigning individuals to a priori sub-groups. That is, we 106 combined both Control and Parkinson's participants in a single pool. The modeling 107 process examines individual subjects and assigns them into clusters depending on 108 similarities in their longitudinal trajectories. If the presence of either Parkinson's or 109 cognitive impairment affects longitudinal WTAR scores, this should be reflected by 110 differential membership across groups in the resulting data-driven trajectory clusters. For example, Parkinson's participants with normal cognition might cluster together with most 112 of the Controls in a "flat" trajectory class, while those showing cognitive impairment might cluster in one or more trajectory classes showing decline over time. Conversely, if the WTAR is truly stable in people with Parkinson's, we would expect them to cluster 115 together with controls in relatively flat trajectory classes, regardless of their current level of cognitive function. In particular, we sought to examine whether WTAR performance
declines in the dementia due to Parkinson's, as it does in Alzheimer's. If so, this would
impact its usefulness in estimating premorbid function in the way proposed in the MDS
guidelines for cognitive diagnosis.

121 Methods

Participants

The New Zealand Parkinson's Progression Programme (NZP³) is a longitudinal study 123 of a convenience prevalence sample of idiopathic Parkinson's participants, ¹⁰ largely 124 recruited from the specialist Movement Disorders Clinic at the New Zealand Brain Research 125 Institute (NZBRI). Ethical approval was granted by the Southern Health and Disability 126 Ethics Committee of the New Zealand Ministry of Health. The ongoing recruitment 127 commenced in 2007, and includes patients ranging from the recently-diagnosed to those 128 with advanced disease. Inclusion and exclusion criteria have been described previously. 11 129 For this analysis, we selected data from the 252 Parkinson's and 57 Control participants 130 who had completed at least two WTARs (range 2-8, mean =3.70, total number of 131 measures = 1155). The period between successive WTAR assessments was multi-modal, 132 mostly clustering around intervals of one and two years, due to varying follow-up periods 133 over the course of the wider study (see Supplementary Material). Of the Parkinson's 134 participants, the mean duration since diagnosis at the first WTAR assessment was 5.0 135 years (range 0-23) and the mean duration of follow-up was a further 4.6 years (range 0-11). All participants were classified as having normal cognition, mild cognitive impairment, 137 or dementia via a comprehensive Level II neuropsychological battery, 11,12 administered in 138 accordance with MDS guidelines.^{3,7} A PD-MCI classification was based on at least two test 139 scores falling ≥ 1.5 standard deviations below norms in at least one cognitive domain, 140 without significant impairment in activities of daily living. For PD dementia, a significant

impairment (≥ 2.0 standard deviations below normative data) in at least two cognitive 142 domains was required, as well as evidence of significant impairment in activities of daily 143 living. 11,12 The WTAR itself was not used in the cognitive diagnostic classification 144 procedures. Characteristics of the sample are shown in Table 1. All participants were 145 speakers of New Zealand English, and were assessed against the US norms of the WTAR, 146 corrected for age, sex, and years of education. The provided ethnicity classifications are not 147 applicable in a New Zealand context and all participants were assessed against norms for 148 "Whites". Of the 249 Parkinson's participants with a recorded ethnicity, 240 (96.4%) 149 identified as Pākehā (New Zealand European), 2 as Māori, 1 as Samoan, 1 as Indian, and 5 150 were 'Other'. Of the Controls, 56 (98.2%) identified as Pākehā and 1 was 'Other'. 151

Latent class trajectory modeling

We fitted latent class trajectory models using the hlme function from the lcmm 153 package⁹ (version 2.0.0), running in the R statistical environment¹³ (version 4.2.1), and 154 used the tidyverse constellation of packages¹⁴ for data manipulation and vizualisation. The 155 dependent variable was WTAR-estimated premorbid IQ, initially modeled within each 156 subject as a polynomial (cubic) function of age, to allow for non-linear trajectories. The 157 resulting trajectories were close to straight lines (see Supplementary Material) so we 158 simplified the models to be a linear function of age. The models were not informed by any 150 other variables (such as the diagnostic categories of PD-MCI or dementia). We used age 160 rather than disease duration as the time metric to allow for direct comparison against any 161 aging effect in controls. 162

A latent class model is fitted by first specifying an *a priori* number of classes

(i.e. clusters) into which the participants can be divided. For example, if just one cluster is

specified, then the trajectory that is produced will simply describe the average change in

score over time for all participants, disregarding any possible sub-groups. If two classes are

specified, then the model will determine two trajectories that optimally separate the total

sample into two clusters, on the basis of differing performance over time. Multiple 168 independent models are fitted, with increasing numbers of classes. Those models are then 169 compared to see which produces the best description of the data. The classes are termed 170 'latent' as they are not known a priori, but instead arise from the data. The resulting 171 classes can, however, then be compared to known groupings (such as Parkinson's vs 172 Controls). This allows us to examine to what extent performance over time might be 173 driven by known factors. For example, if Control and Parkinson's participants perform 174 differently over time, they should fall unequally into the various latent classes (for models 175 with more than one class). 176

We fitted five separate models, with the specified number of latent classes ranging 177 from 1 to 5. The gridsearch function of the lcmm package was used to run 500 departures from random initial values for each multi-class model, using the one-class model from which to generate the starting values. The maximum number of iterations within the hlmefunction was set at 1000. Parameters corresponding to the best log-likelihood were used as 181 initial values for the final estimation of the parameters⁹. The optimal model of the five 182 candidates was selected on the basis of it converging and having the lowest BIC (Bayesian 183 information criterion). That is, this allowed us to determine whether longitudinal 184 performance on the WTAR was best described by the participants falling into either 1, 2, 185 3, 4, or 5 underlying trajectory classes. 186

When reporting values from the chosen model, we formed the interval in brackets following the maximum likelihood estimate (MLE) by subtracting and adding 1.96 times the standard error given by *hlme* to the MLE.

190 Reproducibility

The code and anonymised dataset extracts sufficient to reproduce the analyses and generate this manuscript are publicly available at github.com/nzbri/wtar-trajectory. There

are a number of decisions that can affect the outcome of a latent class modeling analysis 193 and for reproducibility in the Supplementary Material we therefore report our performance 194 against the 16-item checklist "Guidelines for Reporting on Latent Trajectory Studies". 15 195

Results 196

Distribution of scores

The distributions of all WTAR-estimated IQ scores for the Parkinson's and Control 198 participants are shown in Figure 1. The mean of the latest score for participants in each of 199 the groups is given in Table 1, with both being well above the expected population norm 200 mean IQ score of 100. The population distribution of IQ should be symmetrical about 100, 201 yet in our sample, 87.0% of Parkinson's WTAR scores were greater than or equal to 100, as 202 were 92.5% of Control scores. 203

Longitudinal trajectories

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The raw data showed that WTAR scores within individuals were relatively constant 205 over time (Figure 2A). This was evident even in participants whose overall cognitive 206 performance declined substantially, as they progressed to PD-MCI or dementia (Figure 207 2B). We modeled WTAR scores as a linear function of age, with repeated measures within 208 individuals, and fitted candidate models that ranged from having one to five latent 209 trajectory classes. We selected the two-class model on the basis of it having the lowest BIC 210 value. Full details on the modeling process are provided in the Supplementary Material. 211 Individuals were assigned to the class for which they had the highest posterior 212 classification probability. The mean assigned probability was 0.91 (SD 0.14), with a value 213 of 0.7 being regarded as acceptable model performance. 16 The two trajectories are depicted 214 superimposed upon the raw data in Figure 2A. We labeled the first trajectory 'Typical', as 215 this class captured 78% of all participants (81% of the PD and 65% of Control

participants). The intercept of the Typical trajectory, representing the estimated WTAR 217 score of a person at the mean age of assessment (70.7 years) was 107.6 [105.9, 109.2]. 218 Scores then gently declined at a rate of -1.2 [-1.9, -0.6] IQ points per decade. The second 219 trajectory we labeled 'High performers'. This class, capturing the remaining 22% of all 220 participants, had an intercept of 121.0 [118.9, 123.1] and a slope of -0.2 [-1.2, 0.8] points 221 per decade (effectively flat). That is, both trajectories were relatively stable over time, and 222 were separated primarily due to the initial scores of their respective clusters of participants. 223 We make no strong claims as to the number of classes. For example a single trajectory 224 model, somewhat intermediate between the two reported here, would also describe the data 225 relatively well, and a single trajectory was the optimal model when cubic rather than linear 226 trajectories were specified (see Supplementary Material). The key findings are that the 227 trajectories are relatively flat, and do not separate performance between the Parkinson's and Control participants, nor between people with preserved versus impaired cognitive 229 function.

231 Discussion

Unlike the progression to Alzheimer's dementia, we found that WTAR scores were 232 quite stable over time in Parkinson's, despite many of our participants undergoing 233 substantial decline in overall cognitive performance over the course of the study, including 234 to dementia (Figure 2B). Latent class analysis revealed that in our sample people were best 235 classified into two trajectory classes. These appeared to be largely driven by two clusters of 236 performance at baseline, rather than being trajectories that substantially differed longitudinally. Those with very high initial WTAR scores (the 'High performers' class) 238 maintained high scores (Figure 2A), even if they subsequently developed dementia (Figure 2B). The remaining 78% of participants (the 'Typical' class) had a wider range of initial scores, but were again relatively stable, showing an estimated decline of only -1.2 points 241 per decade. If the WTAR was used to assess disparities between current cognitive

performance and a premorbid level of function, a decadal decline of that magnitude would be unlikely to influence assignment to clinical categories like MCI and dementia.

Measures of premorbid function are closely tied to the concept of cognitive reserve. 19 245 For example, higher NART scores have been associated with better current 246 neuropsychological test performance in people with Parkinson's, ²⁰ indicating that higher 247 cognitive reserve may be protective against subsequent cognitive decline. This could, 248 however, lead to circular reasoning if the premorbid measure was not reliable, because if 240 the disease process also reduces current performance on that measure, then inferring poorer 250 cognitive reserve would not be valid. That is, due to current impairments, we would be 251 estimating a lower level of premorbid function than the person actually had. Our findings, 252 of stable WTAR scores despite substantial current cognitive decline, provide support for 253 the WTAR being a stable indicator of cognitive reserve in Parkinson's. 254

We retain reservations about the use of the WTAR, however. Although still in wide 255 use, it is outdated, inasmuch as it was originally devised to estimate premorbid IQ scores 256 from the WAIS-III (Wechsler Adult Intelligence Scale III, released in 1997).⁵ The WAIS-IV 257 was released in 2008) and is now in widespread use, while the WAIS-V is currently under 258 development. The TOPF (Test of Premorbid Function) estimates WAIS-IV IQ and was 250 designed as a successor to the WTAR, but has had limited uptake in the Parkinson's 260 literature.²¹ This perhaps reflects the inertia of substantial research studies (including our 261 own), in which investigators have a natural desire to retain backwards compatibility with 262 measures that they have gathered over a long period of time. The age of an IQ-related test 263 is particularly important. The Flynn effect²² is the robust finding that cohort IQ scores have increased substantially over time (by up to 1 standard deviation per generation). Our sample would (on average) have been born well after their age-matched WAIS-III normative sample group and that might partly explain their above-average estimated IQ 267 levels. Another possibility for the high scores that we observed is that those who volunteer 268 for research are unlikely to be representative of their respective populations. Such a

self-selection effect, however, applies more to the controls than to the Parkinson's group, 270 particularly because our controls were excluded (at study entry only) if they showed 271 cognitive impairment. This restriction did not apply to the Parkinson's participants, but 272 again, as research volunteers, they may not be representative of the Parkinson's population 273 at large. As shown in Table 1, the mean education level for both the Controls and 274 Parkinson's participants was close to that of a complete New Zealand high school education 275 (13 years). Although a selection bias is undoubtedly a factor in the NZP³ sample, we do 276 not believe it could account for the predominance of estimated IQ scores above the 277 putative population norm of 100 (87.0% of Parkinson's scores and 92.5% of Control scores). 278

To provide evidence of cognitive decline, scores on the tests from a 279 neuropsychological test battery must fall below some reference value. If the WTAR was 280 used as an individualized premorbid reference for those scores, rather than a per-test 281 z-score norm of zero, we would expect to see inflated numbers of participants being 282 classified as MCI, because of the over-estimation of premorbid function. The PD-MCI 283 guidelines do not actually formalize how the results of premorbid function tests should be 284 used in practice to demonstrate decline in cognitive functioning.^{23,24} We are aware of only 285 one study⁸ that has compared the norms-based vs premorbid estimation approaches to 286 establishing cognitive impairment. They converted the WTAR-estimated full-scale IQ to a 287 z-score and used that as the reference against which to test each individual 288 neuropsychological test z-score. Any test of current performance that was lower by more 289 than 1.5 SD from the estimated premorbid level was deemed impaired. Of their sample of 290 139 non-demented people with Parkinson's, as noted earlier, the WTAR method classified many more of them as having PD-MCI (79%) than did a norms-based classification method (33%). Marras et al. interpreted this as evidence that most people with Parkinson's have undergone at least some decline relative to their premorbid function, with the WTAR providing a sensitive method to detect it. Conversely, however, that finding 295 might support our contention that the WTAR simply over-estimates a person's premorbid

level of function – just as in our sample, where the distribution of estimated IQ values was skewed well above the supposed population mean of 100.

The WTAR (and similar tests such as the NART and TOPF) are also limited in that 299 they are inherently tied to peculiarities of written and spoken English. The orthography 300 (writing system) of a language can be described as deep/opaque when it contains many 301 irregularities in its mappings of graphemes to phonemes, or shallow/transparent when the 302 mappings are largely regular.²⁵ In a quantitative analysis of 17 orthographies,²⁶ the reading 303 of English words stood out as particularly opaque, whereas by comparison Arabic, Finnish, 304 Korean, Serbo-Croatian, and Turkish were highly transparent. Attempting to devise 305 analogues of tests like the WTAR for speakers of languages with transparent orthographies 306 is unlikely to be fruitful. 307

Even across varieties of English, both between and within countries, the US- and 308 UK-based selection of words can be problematic. For example, the TOPF was found to not 309 reliably predict WAIS-IV IQ in New Zealand English speakers of Māori ethnicitv.²⁷ A word 310 like 'porpoise', ranked in the TOPF as relatively simple (28th of 70 items), resulted in 311 more errors than a word like 'plethora' (ranked 42nd of 70), likely reflecting different word 312 frequencies between North American and New Zealand English. After the commencement 313 of our study, a New Zealand Adult Reading Test (NZART) was created²⁸, with a more 314 culturally-relevant selection of words, but this will require further development to supplant 315 the established international tests. Neuropsychological screening tests developed in the 316 "Anglosphere" have been shown to have poor cross-cultural validity in Parkinson's.²⁹ This 317 extends even to visuoperceptual and non-verbal executive tasks previously assumed to be "culture fair". 30 It is perhaps therefore not surprising that an inherently language-based 319 test faces issues with cross-cultural applicability. In subsequent revisions of the PD-MCI diagnostic criteria, if premorbid measures continue to be advocated, more consideration 321 could be given to alternative techniques³¹ that could have improved validity in a wider 322 international and cross-cultural context.

In summary, the WTAR is a measure that is stable over time in people with 324 Parkinson's, even in the face of a marked decline in current cognitive performance. This 325 makes it a valid research tool to probe cognitive reserve and premorbid function differences 326 across groups. In absolute terms, however, it likely overestimates premorbid IQ, making it 327 unsuitable to use as a benchmark to establish a decline in function within individuals. All 328 such measures likely suffer from cross-cultural word choice issues, even across different 329 varieties of English. More importantly, analogous tests are not even able to be created for 330 languages that do not share the orthographic peculiarities of English. The strikingly stable 331 recall of atypical pronunciation should not be thought of as a fundamental 332 neuropsychological function, but rather a phenomenon that is only evident in particular 333 linguistic and cultural populations. Therefore, in future revisions of the international 334 guidelines for classifying cognitive impairment in Parkinson's, we believe that a test of 335 premorbid function like the WTAR should no longer be recommended as one of the means of formally establishing cognitive decline at an individual level. Due to its remarkable 337 stability in Parkinson's despite substantial cognitive impairment, this and related measures 338 will, however, remain a valuable research tool in the Anglosphere, at least for testing groups 339 for differences on premorbid functioning. The absolute estimation of premorbid function in Parkinson's should be determined for newer tests such as the TOPF and its successors. 341 With newer norms, they may address the over-estimation we found with the WTAR. 342

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Table 1

Demographics of the Parkinson's and Control groups,
and cognitive status as at their latest assessment.

	Control	Parkinson's
n	57	252
Male	63.2%	69.4%
Age (SD)	76.1 (7.9)	72.7 (7.0)
Years of education (SD)	13.6 (2.7)	12.7(2.6)
WTAR (SD)	112.6 (9.5)	108.9 (9.3)
Normal cognition	94.7%	41.3%
MCI	3.5%	34.9%
Dementia	1.8%	23.8%

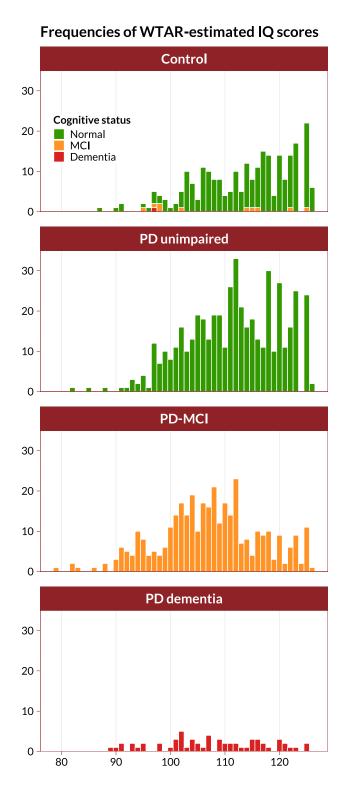


Figure 1. The distribution of WTAR-estimated IQ scores across all participants (containing at least two observations from each). Observations are color-coded by the participant's cognitive status at each session. Regardless of current cognitive status, WTAR scores span a wide range. For each cognitive classification, the center of distribution is shifted well above the population norm mean of 100. Figure available under an open CC-BY licence.¹⁷

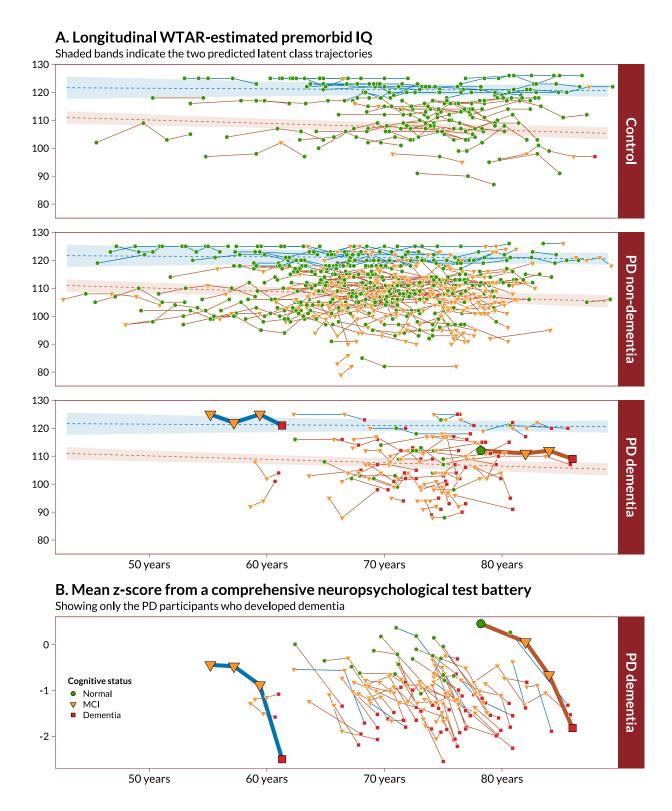


Figure 2. (A) Longitudinal WTAR score trajectories for all individuals, divided into Controls, Parkinson's participants who remained dementia-free, and those who developed dementia. Superimposed are the two predicted latent class trajectories (blue ribbon = Highperformers, brown ribbon = Typical). Blue and brown connecting lines link observations from individuals from each class. (B) Mean z-score from multiple tests in a comprehensive

Appendix

Supplementary Material

- Horne et. al., "Wechsler Test of Adult Reading in Parkinson's: a stable yet imperfect
 measure of premorbid cognitive function."
- Here we report the analysis of the above paper against the following checklist for reporting latent class trajectory analyses:
- van de Schoot, R., Sijbrandij, M., Winter, S. D., Depaoli, S., & Vermunt, J. K.
- 411 (2017). The GRoLTS-checklist: Guidelines for reporting on latent trajectory studies.
- Structural Equation Modeling: A Multidisciplinary Journal, 24, 451–467.
- https://doi.org/10.1080/10705511.2016.1247646

1. Is the metric of time used in the statistical model reported?

- We used age as the time metric (in years to one decimal place). This was to allow for
- direct comparison against controls (which would not be possible with disease duration).
- 417 Follow-up time within the study was also not considered, as participants can enter the
- 418 study at arbitrary points (in terms of both age and disease duration).
- To avoid instabilities in the cubic models, age was standardised by subtracting the
- global mean age at assessment and dividing by ten. For comparability, this was also done
- for the linear models. In the visualisations, predictions were projected back into
- untransformed age in years.

2. Is information presented about the mean and variance of time within a

424 wave?

- The metric was age rather than intended study time points. The overall goal in the
- study was to follow-up participants two-yearly, however, the interval between follow-up
- times was multi-modal and varied both within and across participants (see Figure A1).

This variability was due to both changing study demands (such as recruiting participants for sub-studies) and participant health and availability.

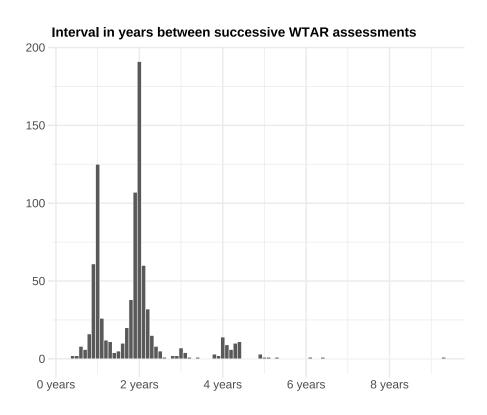


Figure A1. Frequencies of the interval between successive WTAR assessments.

3a. Is the missing data mechanism reported?

Data was not missing at random: participants are more likely to drop out of the study due to increasing disease severity, other health issues, and old age. As shown in Figure 2, however, many remained in the study until the end point of WTAR collection (the onset of dementia). Those participants did not show a decline in WTAR performance relative to other participants. Due to the findings of this study (that the WTAR is relatively stable throughout the disease course), differential drop-out is unlikely to affect the results.

- 3b. Is a description provided of what variables are related to attrition/missing data?
- They are speculated upon in 3a above.
- 3c. Is a description provided of how missing data in the analyses were dealt with?
- As noted in 3a above, missing data was not thought to be problematic in this analysis and was not included explicitly in the modeling process.
- 44. Is information about the distribution of the observed variables included?
- In Figure ?? in the accompanying manuscript, we show the distribution of the
 WTAR-estimated IQ scores in each group, showing the cognitive status at each observation.
- 5. Is the software mentioned?
- See the Methods section in the accompanying manuscript.
- 6a. Are alternative specifications of within-class heterogeneity considered (e.g., LGCA vs. LGMM) and clearly documented? If not, was sufficient justification
- provided as to eliminate certain specifications from consideration?
- An LGMM which includes a varying intercept and slope by participant was used in this analysis and, given the nature of the within-subject variance in the data, is more appropriate than an LGCA.

- 6b. Are alternative specifications of the between-class differences in variance—covariance matrix structure considered and clearly documented? If not, was sufficient justification provided as to eliminate certain specifications from consideration?
- The variance-covariance matrix was allowed to vary by a class-specific proportional parameter. The more restrictive case of restricting all classes to a common variance-covariance matrix structure was not considered.

7. Are alternative shape/functional forms of the trajectories described?

We initially modeled the trajectories using a cubic function, to allow for the depiction
of any curvilinear decline in performance. The resulting trajectory in the one-class cubic
model (which had the lowest BIC) was effectively flat, and hence we moved to linear
modeling for the ease of interpretation of the model coefficients.

8. If covariates have been used, can analyses still be replicated?

Not applicable: age was the only predictor in the models.

9. Is information reported about the number of random start values and final iterations included?

The gridsearch() function of the lcmm package was used to run 500 departures from random initial values for each multi-class model, using the one-class model to generate those starting values from. The maximum number of iterations within the hlme() function was set at 1000.

10. Are the model comparison (and selection) tools described from a statistical perspective?

We selected the two-class linear model on the basis of it converging and having the lowest BIC value.

11. Are the total number of fitted models reported, including a one-class solution?

For both linear and cubic trajectories, models were fitted with one through five classes. See the model comparison tables in Tables A1 and A2.

[tbp]

Table A1

Comparison of hlme models with G = 1 to 5 linear latent trajectory classes.

G	loglik	converged	BIC	entropy	%class1	%class2	%class3	%class4	%class5
1	-3,116.9	yes	6,268.2	1.00	100.0				
2	-3,102.4	yes	6,262.2	0.71	78.3	21.7			
3	-3,092.6	yes	6,265.5	0.64	44.0	40.5	15.5		
4	-3,086.2	yes	6,275.5	0.69	30.4	9.7	46.9	12.9	
5	-3,082.3	yes	6,290.8	0.68	27.5	48.9	15.5	2.3	5.8

[tbp]

Table A2

Comparison of hlme models with G = 1 to 5 cubic latent trajectory classes.

G	loglik	converged	BIC	entropy	%class1	%class2	%class3	%class4	%class5
1	-3,108.2	yes	6,302.4	1.00	100.0				
2	-3,093.6	yes	6,307.6	0.77	81.2	18.8			
3	-3,083.0	yes	6,320.9	0.75	61.8	13.3	24.9		
4	-3,076.4	yes	6,342.0	0.68	23.6	23.9	22.7	29.8	
5	-3,069.0	yes	6,361.7	0.71	21.7	3.2	18.8	24.6	31.7

[tbp]

Table A3

Number within each class in the selected model.

	Typical	High
N	242	67
%	78.32	21.68

- 12. Are the number of cases per class reported for each model (absolute
- sample size, or proportion)?
- The number of cases within each class of the selected model is shown in Table A3.
- See Tables A1 and A2 for the percentage of cases within each class in all candidate models.

13. If classification of cases in a trajectory is the goal, is entropy reported?

Classification of cases was not a goal of the analysis. However, entropy-related measures are shown in Tables A4 and A5.

[tbp]

Table A4

Confidence of assignment
to each class within the
selected model.

	prob1	prob2
Typical	0.96	0.04
High	0.29	0.71

[tbp]

Table A5

Levels of classification

confidence for each class

within the selected model.

	Typical	High
prob>0.7	93.39	64.18
prob>0.8	91.32	7.46
prob>0.9	86.78	0.00

⁴⁹⁰ 14a. Is a plot included with the estimated mean trajectories of the final ⁴⁹¹ solution?

The trajectories are depicted within Figure 2 of the accompanying manuscript, and in isolation in Figure A2.

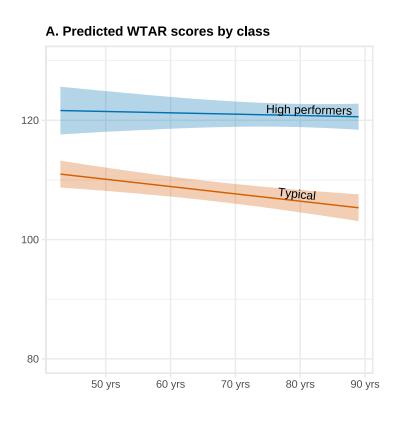


Figure A2. The predicted trajectories of the chosen two-class linear model.

14b. Are plots included with the estimated mean trajectories for each model?

Figure A3 shows the predicted trajectories of all 5 candidate linear and cubic models, as tabulated in Tables A1 and A2.

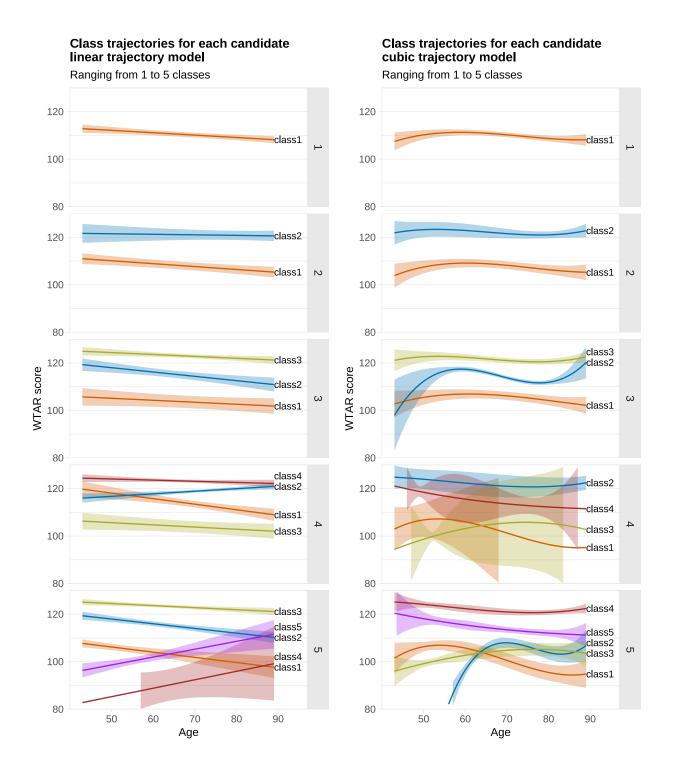


Figure A3. The predicted trajectories of all candidate latent trajectory models (the selected one was the two-class linear trajectory model, as shown in Figure A2). The percentage of participants assigned to each class in each model can be found in Tables A1 and A2.

- 14c. Is a plot included of the combination of estimated means of the final
 model and the observed individual trajectories split out for each latent class?
- This is shown in Figure 2 of the accompanying manuscript.
- 15.Are characteristics of the final class solution numerically described (i.e., means, SD/SE, n, CI, etc.)?
- Yes, see the Results section of the accompanying manuscript.
- 16. Are the syntax files available (either in the appendix, supplementary materials, or from the authors)?
- Yes, they are publicly available at github.com/nzbri/wtar-trajectory.