

Semiparametric Models for Practice Effects in Longitudinal Cognitive Trajectories: Application to an Aging Cohort Study

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Abstract

Background: True cognitive longitudinal decline can be obscured by repeated testing, which is called practice effects (PEs). We developed a modeling framework that aligns participants by baseline and estimates visit-specific PEs independently of age-related change.

Method: Using real data ($N = 175$), we estimated within-subject correlations via linear mixed-effects modeling and applied these parameters to simulate longitudinal trajectories for healthy controls (HC) and individuals with schizophrenia (SZ). Simulations incorporated aging, diagnostic differences, and cumulative PE indicators. Generalized estimating equations (GEEs) were fit with and without PEs to compare model performance.

Results: Models that ignored PEs inflated estimates of cognitive stability and attenuated HC–SZ group differences. Including visit-specific PEs improved recovery of true trajectories and more accurately distinguished aging effects from learning-related gains. Interaction models further identified that PEs may differ by diagnosis or by age at baseline.

Conclusion: Practice effects meaningfully bias longitudinal estimates if left unmodeled. The proposed alignment-based GEE framework provides a principled method to estimate PEs and improves accuracy in both simulated and real-world settings.

Keywords: practice effects; repeat testing; serial testing; longitudinal testing; mild cognitive impairment; cognitive change.

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1 Introduction

Longitudinal studies are crucial for understanding the course of cognitive impairment in schizophrenia, including whether deficits are static, progressive, or partially reversible with treatment [23, 6, 19]. In clinical studies of cognitive impairments associated with schizophrenia, repeated neuropsychological testing is a key outcome measure used to evaluate both pharmacological and psychosocial interventions. However, it has been shown that improvements in test performance over time are more likely to be due to practice effects (PEs) than to genuine changes in underlying abilities [9, 14, 13]. PEs can therefore distort conclusions about the natural course of schizophrenia and falsify the assessment of a treatment’s effectiveness, especially in studies that use changes in cognitive scores as the primary endpoint.

A substantial body of literature has now confirmed the existence of a practice effect in schizophrenia patients undergoing various cognitive tests. Goldberg’s review indicates that cognitive improvements from targeted training are often underestimated due to confounding factors, and many findings regarding “cognitive enhancement” from antipsychotic drugs can be reinterpreted as training effects or placebo effects [9, 8]. In a study of second-generation antipsychotics in first-episode schizophrenia patients, he noted that the observed cognitive improvement was comparable to the practice effect seen in healthy controls, indicating minimal drug-specific cognitive effects [8]. Meanwhile, Keefe et al. analyzed data from 12 placebo-controlled cognitive studies and found that training effects significantly influenced MATRICS Consensus Cognitive Scale scores, with improvements comparable to those in the placebo group [14]. Collectively, these studies indicate that failing to account for training effects may lead to overestimation of cognitive improvement and misjudgment of the longitudinal stability or improvement of cognitive function in schizophrenia patients.

Practice effects (PEs) are sometimes operationalized as the degree of improvement from baseline to follow-up, but may also manifest as a reduction in the rate of decline. Longitudinal meta-analyses indicate that neuropsychological performance in individuals with schizophrenia often shows only modest improvement or relative stability, even in the presence of expected disease-related and age-related decline [23, 6, 19]. This pattern suggests that practice and related nonspecific factors may mask underlying deterioration, particularly when follow-up intervals are short or subjects undergo multiple testing. For example, Granholm et al. found no neurodegenerative decline in neuropsychological tests administered over multiple years to middle-aged and elderly schizophrenia patients; conversely, aging positively correlated with diminishing gains on repeated tasks, suggesting an interaction between aging, baseline impairment, and practice effects [11]. These findings underscore that practice effects may persist even when observed scores plateau or decline, with their intensity varying across individuals.

Despite this evidence, explicit adjustment for PEs is not a standard approach in schizophrenia research. Many longitudinal and trial analyses implicitly assume that changes of scores reflect the true cognitive change, with practice treated as noise or ignored. There has been relatively limited work modeling visit-specific PEs, examining how PEs evolve across multiple assessments, or testing whether PEs differ by diagnosis or age. Most existing studies focus on short test-retest intervals (weeks to months) rather than multi-year follow-up, and few integrate practice-effect modeling into marginal models of cognitive trajectories in schizophrenia.

In the present work, we address these gaps by developing a generalized estimating equation (GEE) framework that aligns participants by baseline assessment, treats age as a continuous time scale, and incorporates visit-specific indicators to estimate practice effects separately from age-related change. Using both real and simulated data on individuals with schizophrenia and healthy controls, we evaluate how PEs accumulate over repeated assessments, whether their magnitude varies by age or diagnosis, and how failure to model PEs biases estimates of cognitive trajectories. Our overarching goal is to provide a practical approach for incorporating practice effects into longitudinal cognitive analyses in schizophrenia, thereby improving the validity of inferences about disease course and treatment response.

2 Methods

2.1 Study Sample

Participants were drawn from an ongoing longitudinal study of psychosis and aging conducted at the University of California San Diego. The study follows adults with schizophrenia (SZ) and demographically similar healthy controls (HC) to characterize cognitive aging across midlife and later adulthood. Individuals with SZ were recruited through outpatient psychiatric clinics and community mental health programs, whereas HC participants were recruited through community advertisements and referral networks. All participants were fluent in English and had sufficient sensory and motor ability to complete neuropsychological testing.

At baseline, 175 participants completed cognitive assessments, including 90 SZ and 85 HC, and were between 26.2–49.8 years of age (mean = 39.2, SD = 7.0). Participants returned for follow-up evaluations approximately every 12 months, with up to six repeated assessments per individual. Demographic characteristics, psychiatric diagnoses, medication history, and medical comorbidities were collected at each visit. Cognitive performance was assessed using a standardized battery, and a composite score was derived to summarize global cognitive functioning. Participants were excluded if they had a neurological disorder, intellectual disability, uncontrolled medical illness affecting cognition, or recent substance dependence. The analytic sample included individuals with at least one post-baseline cognitive assessment. All procedures were approved by the UC San Diego Human Research Protections Program (IRB Protocol #101631), and written informed consent was obtained from all participants.

2.2 Statistical Analysis

Alignment of Assessment Time to Estimate Practice Effects

In this study, subjects are assessed approximately every 12 months (there is some deviation for some subjects, but we treat assessments as 12 months apart for analytic purposes). Thus, we can estimate practice effects (PEs) for the 1st, 2nd, 3rd, etc. reassessments. For simplicity, we focus on the practice effect for the 1st reassessment.

Because there are 12 months between consecutive assessments, we can estimate the practice effect for the 1st reassessment at 12 months. We partition the sample into the following subsamples.

We model practice effects by examining the difference in mean between the red values (2nd assessment, or 1st reassessment) and the black values (1st assessment). By including an interaction

Age at visit for each observed subject			PE for each age aligned on 1 st reassessment		
Age at enrollment	1st visit	2nd visit			
26	26	27	26	27	
27	27	28	27	28	
28	28	29	28	29	
29	29	30	29	30	
:	:	:	:	:	:

Figure 1: Left: observed ages at enrollment and first two study visits. Right: practice effect illustration obtained by aligning assessments on the first reassessment; red values represent performance at the reassessment.

between practice effect and age at visit, we can also test whether practice effects change as age increases.

We dummy-code age at visit and practice-effect indicators so that we do not impose a specific functional form on the relationship between the cognitive outcome, age at visit, and practice effect. We first included age at visit as 28, 29, 30, etc. as single-year indicators; because results were unstable, we then grouped age at visit into 5-year bins so that the model provides the mean cognitive outcome for each age bin and a practice effect for each age bin. The results for EXCOMP2 showed that, without controlling for practice effects, EXCOMP2 appeared to increase over age, but after adjusting for practice effects, the mean of EXCOMP2 decreased with age.

Generalized Estimating Equation Models

Models Without Practice Effects

We first estimated a GEE model that omitted explicit practice effects. Let i index subjects and j index assessment times. Let Y_{ij} denote the observed response (dependent variable) and W_{ij} the vector of all explanatory variables, including age at visit, diagnostic group dx_i , and other baseline covariates (e.g., gender, education, race). Time since baseline is represented by t_{ij} in years, where j indexes the j th visit and $t_{i1} = 0$ at baseline. Age at visit, agevisit_{ij} , is defined as the subject i 's age at visit j , and age_{i1} is the age of subject i at the baseline visit.

The model without PEs can be written as

$$\mathbb{E}[Y_{ij} | W_{ij}] = \beta_0 + \beta_1 \text{agevisit}_{ij} + \beta_2 dx_i + \beta_3 t_{ij} dx_i + X_i^\top \beta_4, \quad (1)$$

which is equivalent to

$$\mathbb{E}[Y_{ij} | W_{ij}] = \beta_0 + \beta_1 (\text{age}_{i1} + t_{ij}) + \beta_2 dx_i + \beta_3 t_{ij} dx_i + X_i^\top \beta_4. \quad (2)$$

This model serves as the baseline against which PE-adjusted models are compared, allowing us to quantify the extent to which ignoring repeated-test gains may bias longitudinal estimates.

Models With Practice Effects

To estimate PEs explicitly, we extended the GEE model by introducing visit-specific indicator variables. Let $I(j = k)$ be an indicator function that equals 1 if visit j corresponds to the k th

assessment and 0 otherwise. Incorporating these indicators, the model becomes

$$\begin{aligned}\mathbb{E}[Y_{ij} | W_{ij}] &= \beta_0 + \beta_1 \text{agevisit}_{ij} + \beta_2 dx_i + \beta_3 t_{ij} dx_i + X_i^\top \beta_4 + \sum_{k=2}^5 \beta_{5k} I(j = k) \\ &\quad + \sum_{k=2}^5 \beta_{6k} I(j = k) dx_i,\end{aligned}\tag{3}$$

or equivalently,

$$\begin{aligned}\mathbb{E}[Y_{ij} | W_{ij}] &= \beta_0 + \beta_1 (\text{age}_{i1} + t_{ij}) + \beta_2 dx_i + \beta_3 t_{ij} dx_i + X_i^\top \beta_4 + \sum_{k=2}^5 \beta_{5k} I(j = k) \\ &\quad + \sum_{k=2}^5 \beta_{6k} I(j = k) dx_i.\end{aligned}\tag{4}$$

Here, β_{5k} captures the PE at visit k ($2 \leq k \leq 5$), and the interaction coefficients β_{6k} capture group differences in PEs between healthy controls and individuals with schizophrenia.

2.3 Simulation Study

A simulation study was conducted to evaluate the performance of the aligned GEE framework under controlled conditions and to examine how failing to model PEs can bias estimates of longitudinal cognitive trajectories.

2.3.1 Estimating the Correlation Structure

We first estimated the within-subject correlation structure from real longitudinal cognitive data. Participants with at least one post-baseline visit were retained, and up to six visits per subject were used. Time since baseline was derived from days-since-baseline and converted to years. Subjects without a baseline assessment were excluded to maintain proper alignment. A linear mixed-effects model was fit to these data to estimate the intra-class correlation (ICC):

$$Y_{ij} = \beta_0 + \beta_1 \text{agevisit}_{ij} + \beta_2 dx_i + \beta_3 t_{ij} dx_i + X_i^\top \beta_4 + b_i + \epsilon_{ij},\tag{5}$$

$$b_i \sim \mathcal{N}(0, \sigma_b^2), \quad \epsilon_{ij} \sim \mathcal{N}(0, \sigma_e^2),\tag{6}$$

or equivalently,

$$Y_{ij} = \beta_0 + \beta_1 (\text{age}_{i1} + t_{ij}) + \beta_2 dx_i + \beta_3 t_{ij} dx_i + X_i^\top \beta_4 + b_i + \epsilon_{ij},\tag{7}$$

$$b_i \sim \mathcal{N}(0, \sigma_b^2), \quad \epsilon_{ij} \sim \mathcal{N}(0, \sigma_e^2).\tag{8}$$

Here b_i and ϵ_{ij} denote the subject-specific random intercept and residual error, respectively. The fitted model produced the following parameter estimates:

$$\begin{aligned}\beta_0 &= 0.333, \quad \beta_1 = -0.006, \quad \beta_2 = -0.803, \quad \beta_3 = 0.018, \\ \beta_4 &= [0.093, 0.091, -0.078]^\top, \quad \sigma^2 = (0.312)^2, \quad \rho = 0.753.\end{aligned}$$

The ICC was calculated as

$$\text{ICC} = \frac{\sigma_b^2}{\sigma_b^2 + \sigma_e^2},$$

and this value was subsequently used to calibrate the copula-based dependence structure in the simulated data.

Using both real and simulated datasets, we examined longitudinal outcome trajectories for individuals in the Healthy Control (HC) and Schizophrenia (SZ) groups, comparing scenarios that included practice effects with those that did not. To generate within-subject dependence that better resembled real cognitive data, we employed a copula-based approach to model the correlation structure. Marginal mean trajectories were then estimated with generalized estimating equations (GEE), which provided a population-level view of how outcomes evolved over time under each modeling condition.

2.3.2 Simulation With No Practice Effects (No PE)

To create a more realistic scenario and decouple practice effects from time, we simulated data for $n = 500$ subjects in five waves of enrollment. Let t_{ij} denote the time in years at the j th visit with $t_{i1} = 0$ ($1 \leq i \leq n$, $1 \leq j \leq J$). For our simulation study, we set

$$\begin{aligned}\beta_0 &= 0.326, \quad \beta_1 = -0.007, \quad \beta_2 = -0.782, \quad \beta_3 = 0.013, \quad \boldsymbol{\beta}_4 = [0.098, 0.034, -0.077], \\ n &= 500, \quad J = 5, \quad t_{ij} = 1 \times (j - 1), \quad \sigma^2 = (0.155)^2.\end{aligned}$$

Thus the five assessment times occurred at

$$t_{i1} = 0, \quad t_{i2} = 1, \quad t_{i3} = 2, \quad t_{i4} = 3, \quad t_{i5} = 4, \quad t_{i6} = 5.$$

A new cohort of 100 individuals of the same age in months was then randomly assigned to either the schizophrenia (SZ) or healthy control (HC) group, with their first assessment at $j = 1$ and $t_{i1} = 0$. The outcome Y_{ij} for subject i at visit j was generated as:

$$Y_{ij} = \mu_{ij} + \epsilon_{ij}, \quad \mu_{ij} = \beta_0 + \beta_1 \text{agevisit}_{ij} + \beta_2 d_{x_i} + \beta_3 t_{ij} d_{x_i} + \mathbf{X}_i^\top \boldsymbol{\beta}_4, \quad (9)$$

or equivalently,

$$\mu_{ij} = \beta_0 + \beta_1 (\text{age}_{i1} + t_{ij}) + \beta_2 d_{x_i} + \beta_3 t_{ij} d_{x_i} + \mathbf{X}_i^\top \boldsymbol{\beta}_4,$$

where $d_{x_i} = 1$ for SZ and 0 for HC, and age_{i1} denotes the age (in years) of the i th subject at baseline ($j = 1$, $t_{i1} = 0$). We set age_{i1} for each cohort as:

$$\text{age}_{i1} = \begin{cases} 25 & \text{Cohort 1,} \\ 30 & \text{Cohort 2,} \\ 35 & \text{Cohort 3,} \\ 40 & \text{Cohort 4,} \\ 45 & \text{Cohort 5.} \end{cases}$$

In model (1),

$$\text{agevisit}_{ij} = \text{age}_{i1} + t_{ij}$$

is the age of subject i at visit j , and β_1 is the aging effect. We can also model aging effects as a categorical variable using:

$$Y_{ij} = \mu_{ij} + \epsilon_{ij}, \quad \mu_{ij} = \beta_0 + \sum_{k=1}^6 \mathbf{1}(5(k-1) + 25 \leq \text{agevisit}_{ij} \leq 5k + 25) \beta_1 + \beta_2 d_{x_i} + \beta_3 t_{ij} d_{x_i} + \mathbf{X}_i^\top \boldsymbol{\beta}_4, \quad (10)$$

2.3.3 Simulation With Practice Effects (PE)

To incorporate cumulative practice effects, we extended the simulation framework by adding five indicator variables, `prac1plus` through `prac5plus`, denoting whether a subject had completed at least one through five previous assessments. These indicators were included as main effects and in interaction with diagnosis.

The linear predictor for subject i at visit j was specified as:

$$Y_{ij} = \mu_{ij} + \epsilon_{ij},$$

with

$$\mu_{ij} = \beta_0 + \beta_1 \text{agevisit}_{ij} + \beta_2 d_i + \beta_3 t_{ij} d_i + \mathbf{X}_i^\top \beta_4 + \sum_{k=2}^6 \beta_{5k} I(j=k),$$

or equivalently,

$$\mu_{ij} = \beta_0 + \beta_1 (\text{age}_{i1} + t_j) + \beta_2 d_i + \beta_3 t_{ij} d_i + \mathbf{X}_i^\top \beta_4 + \sum_{k=2}^6 \beta_{5k} I(j=k).$$

Here, β_{5k} represents the increase in performance due to practice at visit k , with

$$\beta_{52} \leq \beta_{53} \leq \beta_{54} \leq \beta_{55} = \beta_{56},$$

and we set

$$\beta_{52} = 0.2, \quad \beta_{53} = 0.3, \quad \beta_{54} = 0.4, \quad \beta_{55} = \beta_{56} = 0.5.$$

*Differential Practice Effects by Diagnosis

To evaluate group differences in practice effects between schizophrenia (SZ) and healthy control (HC) participants, we used:

$$\begin{aligned} Y_{ij} &= \mu_{ij} + \epsilon_{ij}, \\ \mu_{ij} &= \beta_0 + \beta_1 \text{agevisit}_{ij} + \beta_2 d_i + \beta_3 t_{ij} d_i + \mathbf{X}_i^\top \beta_4 + \sum_{k=2}^5 \beta_{5k} I(j=k) + \sum_{k=2}^5 \beta_{6k} I(j=k) d_i, \end{aligned}$$

or

$$\mu_{ij} = \beta_0 + \beta_1 (\text{age}_{i1} + t_j) + \beta_2 d_i + \beta_3 t_{ij} d_i + \mathbf{X}_i^\top \beta_4 + \sum_{k=2}^5 \beta_{5k} I(j=k) + \sum_{k=2}^5 \beta_{6k} I(j=k) d_i.$$

Here, β_{6k} represents the differential practice effect for SZ relative to HC at visit k .

*Differential Practice Effects by Age

To evaluate whether practice effects vary by age, we used:

$$\begin{aligned} Y_{ij} &= \mu_{ij} + \epsilon_{ij}, \\ \mu_{ij} &= \beta_0 + \beta_1 \text{agevisit}_{ij} + \beta_2 d_i + \beta_3 t_{ij} d_i + \mathbf{X}_i^\top \beta_4 + \sum_{k=2}^5 \beta_{5k} I(j=k) + \sum_{k=2}^5 \beta_{7k} I(j=k) \text{agevisit}_{ij}, \end{aligned}$$

or

$$\mu_{ij} = \beta_0 + \beta_1(\text{age}_{i1} + t_j) + \beta_2 d_i + \beta_3 t_{ij} d_i + \mathbf{X}_i^\top \boldsymbol{\beta}_4 + \sum_{k=2}^5 \beta_{5k} I(j=k) + \sum_{k=2}^5 \beta_{7k} I(j=k)(\text{age}_{i1} + t_j).$$

Here, β_{7k} quantifies the change in practice-related improvement per additional year of age at visit k . As in earlier sections, aging effects can alternatively be modeled using categorical age groups.

3 Results

Baseline demographic characteristics were comparable between groups (Table 1). The schizophrenia group included a slightly higher proportion of males (53% vs. 45% in controls) and had fewer years of education (median 12 vs. 15). Median baseline age was similar across groups—40 years for schizophrenia and 38 years for healthy controls. Racial/ethnic distributions did not differ substantially, with most participants identifying as Caucasian, followed by Hispanic and African American.

Table 1: Baseline characteristics of study participants

Characteristic	Healthy controls (n = 85)	Schizophrenia (n = 90)
Sex , male, n (%)	38 (45%)	48 (53%)
Age at baseline , median (Q1, Q3), years	38 (32, 46)	40 (34, 46)
Years of education , median (Q1, Q3)	15 (13, 16)	12 (11, 13)
Race/ethnicity , n (%)		
Caucasian	49 (58%)	38 (42%)
African American	11 (13%)	12 (13%)
Hispanic	21 (25%)	31 (34%)
Asian	3 (3.5%)	4 (4.4%)
Native Hawaiian / Pacific Islander	0 (0%)	1 (1.1%)
Multiracial	1 (1.2%)	4 (4.4%)

Table 2 summarizes the linear mixed-effects model fit to the observed data. Cognitive performance was substantially lower in SZ compared with HC ($\beta = -0.803$, $p < 0.0001$). Higher educational attainment was associated with better performance ($\beta = 0.093$, $p = 0.0001$), whereas age at visit was not statistically significant ($p = 0.34$). A significant diagnosis-by-time interaction ($\beta = 0.018$, $p = 0.0037$) indicated differing longitudinal trajectories between groups.

To evaluate whether these estimates reflected practice effects, simulated datasets were generated using the real-data parameter values but without practice effects. As shown in Tables 3 and 4, the schizophrenia effect remained similar ($\beta \approx -0.78$, $p < 2 \times 10^{-16}$), and age demonstrated a small, negative slope ($\beta \approx -0.007$, $p < 0.001$), confirming that the simulation accurately reproduced the empirical effect structure.

Table 6 presents GEE estimates from simulations incorporating practice effects. Large gains were observed at early reassessments (e.g., prac1 : $\beta = 0.305$, $p < 2 \times 10^{-16}$), with diminishing increases thereafter. When practice effects were modeled, the expected age-related decline re-emerged

$(\beta = -0.006, p = 0.0006)$, demonstrating that unmodeled practice effects can mask true cognitive deterioration.

Figures 2 and 3 illustrate these patterns: parameter estimates were consistent across analytic frameworks, and trajectories that appeared stable without adjustment showed clear decline once practice effects were accounted for.

Table 2: Linear Mixed Effects Model for Correlation (Real Data)

Fixed Effect	Estimate	Std. Error	DF	t-value	p-value
(Intercept)	0.333	0.515	397	0.65	0.5177
agevisit	-0.006	0.006	397	-0.95	0.3424
dxgroup	-0.803	0.109	170	-7.39	< 0.0001
educ	0.093	0.022	170	4.16	0.0001
gender	0.091	0.089	170	1.02	0.3071
race_lat	-0.078	0.034	170	-2.30	0.0228
dxgroup:yearsbl	0.018	0.006	397	2.92	0.0037

Table 3: Linear Mixed Effects Model (Simulated Data, Without Practice Effect)

Fixed Effect	Estimate	Std. Error	DF	t-value	p-value
(Intercept)	0.319	0.0932	1519	3.42	0.0006
age_visit	-0.007	0.0015	1519	-4.79	0.0000
dx_bin	-0.782	0.0252	495	-30.99	0.0000
educ	0.099	0.0049	495	20.11	0.0000
gen	0.035	0.0247	495	1.40	0.1632
race_lat	-0.077	0.0092	495	-8.29	0.0000
dx_bin:t	0.013	0.0035	1519	3.71	0.0002

Table 4: GEE Results (Simulated Data, Without Practice Effect)

Term	Estimate	Std. Err	Wald	p-value
(Intercept)	0.32629	0.09170	12.66	0.00037
age_visit	-0.00754	0.00150	25.19	5.2×10^{-7}
dx_bin	-0.78211	0.02510	970.66	$< 2 \times 10^{-16}$
educ	0.09886	0.00499	390.98	$< 2 \times 10^{-16}$
gen	0.03441	0.02450	1.97	0.16014
race_lat	-0.07660	0.00790	94.10	$< 2 \times 10^{-16}$
dx_bin:t	0.01304	0.00329	15.68	7.5×10^{-5}

Table 5: GEE Model Results (Simulated Data, Age Binned Without Practice Effect)

Term	Estimate	Std. Error	Wald	p-value
(Intercept)	0.09193	0.07428	1.53	0.2159
age_band_kband2	-0.00241	0.01746	0.02	0.8903
age_band_kband3	-0.04653	0.02128	4.78	0.0288
age_band_kband4	-0.09214	0.02349	15.39	8.8×10^{-5}
age_band_kband5	-0.11568	0.02780	17.31	3.2×10^{-5}
dx_bin	-0.77973	0.02527	952.40	$< 2 \times 10^{-16}$
educ	0.09885	0.00503	385.76	$< 2 \times 10^{-16}$
gen	0.03588	0.02450	2.14	0.1431
race_lat	-0.07673	0.00788	94.88	$< 2 \times 10^{-16}$
dx_bin:t	0.00973	0.00300	10.29	0.0013

Table 6: GEE Model Results (Simulated Data, With Practice Effect)

Term	Estimate	Std. Error	Wald	p-value
(Intercept)	0.28374	0.09455	9.01	0.00269
age_visit	-0.00622	0.00182	11.65	0.00064
dx_bin	-0.79729	0.02704	869.34	$< 2 \times 10^{-16}$
practiceprac1	0.20589	0.01082	362.13	$< 2 \times 10^{-16}$
practiceprac2	0.30321	0.01220	617.46	$< 2 \times 10^{-16}$
practiceprac3	0.38135	0.01414	727.41	$< 2 \times 10^{-16}$
practiceprac4	0.51345	0.01584	1050.84	$< 2 \times 10^{-16}$
practiceprac5	0.50425	0.01892	710.67	$< 2 \times 10^{-16}$
educ	0.09547	0.00535	318.25	$< 2 \times 10^{-16}$
gen	0.13455	0.02605	26.68	2.4×10^{-7}
race_lat	-0.07779	0.00861	81.54	$< 2 \times 10^{-16}$
dx_bin:t	0.01414	0.00450	9.86	0.00169

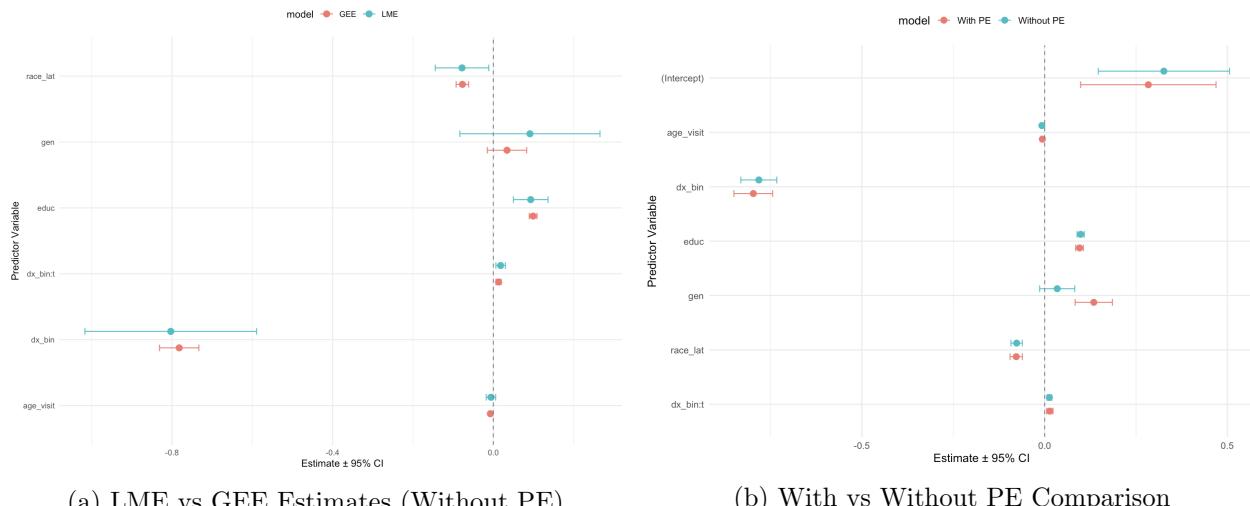


Figure 2: Model comparison plots. Left: LME vs GEE. Right: With vs Without Practice Effects.

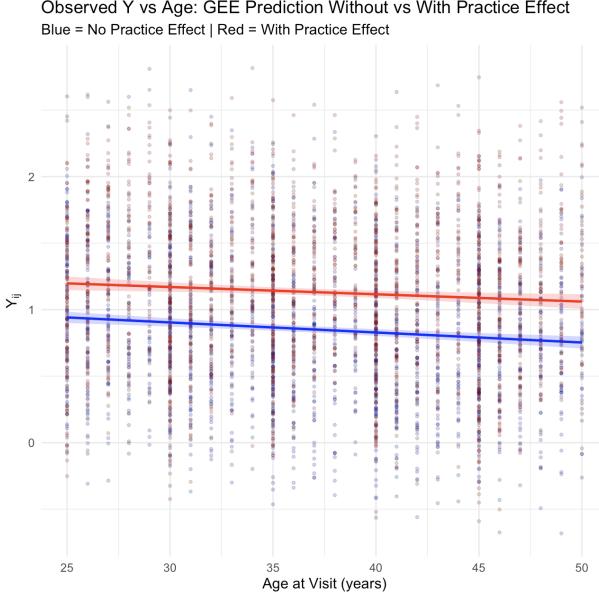


Figure 3: Plot of Outcome Y over Age at Visit

4 Discussion

Longitudinal cognitive data reflect the combined influence of true temporal change and improvements driven by repeated test exposure. Extensive work has shown that practice effects (PE) can inflate performance, particularly early in follow-up, and may obscure or even reverse evidence of cognitive decline [20, 12, 10]. In aging and psychiatric research, failure to account for PE risks mischaracterizing disease progression, treatment response, and group differences [18, 2]. The present study directly addressed this challenge by developing and evaluating a modeling framework that separates practice-related gains from aging-related change.

A central contribution of this work is the explicit specification of visit-level PE indicators, allowing practice gains to vary across assessments rather than assuming a constant or linear effect. This structure aligns with empirical patterns reported in neuropsychological cohorts, where the largest gains typically occur between the first and second assessments before plateauing [4, 1]. By estimating PE alongside demographic and diagnostic predictors, the model improves interpretability and reduces the risk that attenuated aging slopes are mistakenly attributed to preserved cognition.

The simulation findings further reinforce the importance of explicitly modeling PE. When practice effects were embedded in the data-generating process but omitted from analysis, aging-related decline was underestimated and diagnostic differences were muted—consistent with concerns raised in prior methodological evaluations [15, 24]. Incorporating PE restored the expected negative association between age and cognition and recovered group contrasts, demonstrating that conventional longitudinal models may yield misleading inferences when practice effects are ignored.

Another strength of the approach is the use of a flexible copula-based dependence structure to generate simulated data. This framework allows realistic within-subject correlation without imposing restrictive assumptions about temporal autocorrelation [5, 17]. The use of both linear mixed-effects models and generalized estimating equations ensured that conclusions were not tied to a single analytic framework, consistent with recommendations for longitudinal cognitive research [7].

Several limitations warrant consideration. Practice effects were modeled as monotonic and positive, yet PEs may diminish, reverse, or vary across cognitive domains, diagnostic groups, or testing intervals [22]. Future work may evaluate spline-based, nonlinear, or domain-specific PE structures. The simulations did not incorporate additional real-world complexities such as alternate test forms, contextual influences, or informative dropout. Finally, the empirical dataset consisted of midlife adults from a single research program, potentially limiting generalizability to older populations or community-based samples.

Overall, these findings underscore the necessity of accounting for practice effects when interpreting longitudinal cognitive trajectories. The modeling strategy developed here offers a scalable, transparent, and empirically grounded approach for separating practice-related improvements from aging-related change. As repeated cognitive testing becomes increasingly common in clinical trials, epidemiologic studies, and preventative interventions, routine consideration of practice effects will be essential for accurate characterization of cognitive health across adulthood.

References

- [1] Bartels, C., Wegrzyn, M., Wiedl, A., Ackermann, V., & Ehrenreich, H. (2010). Practice effects in healthy adults: A longitudinal study on frequent repetitive cognitive testing. *BMC Neuroscience*, 11, 118.
- [2] Calamia, M., Markon, K., & Tranel, D. (2012). Scoring higher the second time around: Meta-analyses of practice effects in neuropsychological assessment. *The Clinical Neuropsychologist*, 26(4), 543–570.
- [3] Duff, K. (2012). Evidence-based indicators of neuropsychological change in the individual patient: Relevant concepts and methods. *Archives of Clinical Neuropsychology*, 27(3), 248–261.
- [4] Duff, K., Beglinger, L. J., Schultz, S. K., et al. (2012). Practice effects in the prediction of long-term cognitive outcome in three patient samples. *Archives of Clinical Neuropsychology*, 27(4), 374–382.
- [5] Fieberg, J., Vitense, K., & Johnson, D. H. (2020). Resampling-based methods for biologists. *Ecology Letters*, 23(1), 4–18.
- [6] Fioravanti, M., Bianchi, V., & Cinti, M. E. (2012). Cognitive deficits in schizophrenia: An updated review. *Clinical Neuropsychiatry*, 9, 202–216.
- [7] Fitzmaurice, G. M., Laird, N. M., & Ware, J. H. (2012). *Applied longitudinal analysis* (2nd ed.). Wiley.
- [8] Goldberg, T. E., Goldman, R. S., Burdick, K. E., et al. (2007). Cognitive improvement after treatment with second-generation antipsychotic medications: Is it a practice effect? *Archives of General Psychiatry*, 64(5), 507–518.
- [9] Goldberg, T. E., & Weinberger, D. R. (2010). Cognitive improvement in schizophrenia: Practice effects or true cognitive change? *Schizophrenia Bulletin*, 36(4), 787–789.
- [10] Goldberg, T. E., Harvey, P. D., Hoyos, C., Korducki, M., & Miller, M. W. (2015). Practice effects due to serial cognitive assessment: Implications for preclinical Alzheimer's disease randomized controlled trials. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 1(1), 103–111.
- [11] Granholm, E., Holden, J., Link, P. C., & McQuaid, J. R. (2010). Randomized clinical trial of cognitive behavioral social skills training for middle-aged and older outpatients with schizophrenia: Age-defining factors and practice effects. *American Journal of Psychiatry*, 167(8), 845–854.
- [12] Hausknecht, J. P., Halpert, J. A., Di Paolo, N. T., & Gerrard, M. O. (2007). Retesting in selection: A meta-analysis of coaching and practice effects for tests of cognitive ability. *Journal of Applied Psychology*, 92(2), 373–385.
- [13] Hill, S. K., Bishop, J. R., Palumbo, D., & Sweeney, J. A. (2010). Effect of second-generation antipsychotics on cognition: Current issues and future challenges. *Expert Review of Neurotherapeutics*, 10(1), 43–57.

- [14] Keefe, R. S. E., Kraemer, H. C., Epstein, R. S., et al. (2017). Placebo response and practice effects in schizophrenia: Analysis of cognitive trials with the MCCB. *JAMA Psychiatry*, *74*(8), 1–10.
- [15] McArdle, J. J., & Hamagami, F. (2001). Modeling longitudinal data when retest effects are present. *Multivariate Behavioral Research*, *36*(1), 1–31.
- [16] McArdle, J. J., Fisher, G. G., & Kadlec, K. M. (2009). Latent variable analyses of age trends of cognition in the Health and Retirement Study, 1992–2004. *Psychology and Aging*, *24*(3), 544–566.
- [17] Nikoloulopoulos, A. K. (2018). A multivariate logistic regression model with application to clustered data. *Biometrical Journal*, *60*(3), 480–492.
- [18] Rabbitt, P., Diggle, P., Holland, F., & McInnes, L. (1993). Practice and drop-out effects during a 17-year longitudinal study of cognitive aging. *Journal of Gerontology*, *48*(4), P84–P97.
- [19] Rund, B. R. (1998). A review of longitudinal studies of cognitive functions in schizophrenia patients. *Schizophrenia Bulletin*, *24*(3), 425–435.
- [20] Salthouse, T. A. (2010). Selective review of cognitive aging. *Journal of the International Neuropsychological Society*, *16*(5), 754–760.
- [21] Salthouse, T. A. (2010). Influence of age on practice effects in longitudinal cognitive studies. *Neuropsychology*, *24*(5), 563–572.
- [22] Salthouse, T. A. (2016). Continuity of cognitive change across adulthood. *Psychonomic Bulletin & Review*, *23*(3), 932–939.
- [23] Szöke, A., Trandafir, A., Dupont, M.-E., Méary, A., Schürhoff, F., & Leboyer, M. (2008). Longitudinal studies of cognition in schizophrenia: Meta-analysis. *British Journal of Psychiatry*, *192*(3), 248–257.
- [24] Wilson, R. S., Beckett, L. A., Barnes, L. L., Schneider, J. A., Bach, J., Evans, D. A., & Bennett, D. A. (2002). Individual differences in rates of change in cognitive abilities of older persons. *Psychology and Aging*, *17*(2), 179–193.