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RESEARCH ARTICLE

Examining the role of repeated test exposure over 12 months across ADNI protocols

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Abstract

Objective: Changes to study protocols during longitudinal research may alter cognitive testing schedules over time. Unlike in prior Alzheimer's Disease Neuroimaging Initiative (ADNI) protocols, where testing occurred twice annually, participants enrolled in the ADNI-3 are no longer exposed to cognitive materials at 6 months. This may affect their 12-month performance relative to earlier ADNI cohorts, and potentially confounds data harmonization attempts between earlier and later ADNI protocols. **Method:** Using data from participants enrolled across multiple ADNI protocols, this study investigated whether test exposure during 6-month cognitive evaluation influenced scores on subsequent 12-month evaluation. **Results:** No interaction effects were observed between test exposure group and time at 12 months on cognitive performance. No improvements, and limited declines, were seen between baseline and 12-month follow-up scores on most measures. **Conclusions:** The 6-month testing session had minimal impact on 12-month performance in ADNI. Collapsing longitudinal data across ADNI protocols in future research appears appropriate.

KEYWORDS
ADNI, assessment, longitudinal, neuropsychology, reliable change

1 | INTRODUCTION

The longitudinal multi-center Alzheimer's Disease Neuroimaging Initiative[1] (ADNI) study has profoundly affected Alzheimer's disease (AD) research since its inception in 2003. When including study extension in 2009 (ADNI-GO) and renewals in 2011 (ADNI-2) and 2016 (ADNI-3), cognitive, imaging, genetic, and blood-marker data from these protocols have collectively been responsible for ≈2000 peer-reviewed publications as of 2021 (www.pubmed.org). However, changes to study procedures have arisen over time with respect to

the cognitive measures administered and the frequency of test administration, which has led to some uncertainty about the appropriate procedures for longitudinal analyses. For example, the transition from the ADNI-2 protocol[2] to the ADNI-3 protocol[3] not only resulted in a truncated cognitive battery (eg, eliminating Boston Naming Test from ADNI-3), but also eliminating a 6-month assessment within the first year of the study for newly enrolled participants. Consequently, whereas participants enrolled during ADNI-1, ADNI-GO, or ADNI-2 were administered baseline (BL), 6-month (M06), and 12-month (M12) cognitive batteries within their first year of the study, participants enrolled following the transition to ADNI-3 only completed BL and M12 batteries during the same time frame.

The result of these procedural changes is that participants enrolled in ADNI-3 are exposed to cognitive test materials only once prior to their M12 evaluation, as compared to prior ADNI participants who are exposed to materials twice during that same period. Because repeated exposure to cognitive test materials is known to impact test scores,[4,5] it is unclear whether this differential exposure interferes with the appropriateness of comparing follow-up data between participants in ADNI-1/ADNI-GO/ADNI-2 and ADNI-3. This potential confound to data harmonization has led to various approaches to analyzing longitudinal ADNI data. Some studies, for example, have focused on data collected prior to ADNI-3 to permit the inclusion of the greatest number of participants possible within a particular test-administration schedule.[6] Conversely, others have chosen more labor-intensive approaches, including applying a series of participant matches within each ADNI cohort to reduce variability in follow-up data-collection procedures.[7] To date, no study has directly compared the performance of ADNI participants at follow-up across protocols to determine the appropriateness of pooling the respective cohorts.

To help clarify this harmonization ambiguity, the current study aims to evaluate the impact of the presence or absence of M06 test administration on future cognitive performance in ADNI. As such, we compared the performance of ADNI participants at their M12 cognitive assessment when they were either exposed or not exposed to test stimuli at 6 months. We hypothesized that test-material exposure at 6 months would result in proportionately better cognitive scores during the M12 evaluation, relative to those participants in the ADNI sample not exposed to a M06 evaluation. Such a result would suggest that researchers should caution against pooling study participants across ADNI protocols. Conversely, should minimal or no differences be observed in M12 performance regardless of whether a M06 test administration occurred, this would permit incorporating data across all ADNI protocols in future longitudinal analyses.

RESEARCH IN CONTEXT

1. **Systematic review**: Procedural changes in the Alzheimer's Disease Neuroimaging Initiative (ADNI) have led to different cognitive testing schedules over the first 12-months of enrollment. Specifically, ADNI-1, ADNI-GO, and ADNI-2 participants were exposed to cognitive test materials twice prior to their 12-month evaluation, whereas ADNI-3 participants were exposed only once. When considering data harmonization practices across protocols, no study, to date, has directly evaluated the impact of prior test administration schedules on cognitive performance at 12 months in ADNI.
2. **Interpretation**: In a sample of 436 demographically matched participants enrolled across ADNI protocols, results of both mixed between-within subjects repeated-measures analysis of variance (ANOVA) and linear regression suggest that the 6-month testing session had minimal impact on 12-month performance in the ADNI sample.
3. **Future direction**: This would suggest that it is appropriate to collapse longitudinal participant data across ADNI protocols in future research.

2 | METHOD

2.1 | Participants

All participant data in the current study was obtained from ADNI. Please see the ADNI website (http://adni.loni.usc.edu) for a thorough review of the study resources and data publicly available. The primary goal of ADNI—led by principal investigator Michael W. Weiner, MD—has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. For up-to-date information, see www.adni-info.org. Institutional review board approval has been obtained for each of the multi-center sites, and informed consent was obtained in written form from study participants or their authorized representatives.

As of April 26th, 2021, cognitive data were available for 2366 ADNI participants across ADNI protocols, with enrolled participants being followed cognitively for up to 180 months. Inclusion for ADNI involved being between the ages of 55 to 90 at baseline; having at least 6 years of education and having a reliable study partner; being free of significant head trauma, depression, or neurologic disease; being stable on permitted medications; and being fluent in either English or Spanish.[2,3,8,9] For the current study, 712 participants were excluded for possessing missing cognitive data or consensus diagnosis at BL or M12, resulting in a total of 1654 participants remaining. Participants were subsequently matched for age, education, diagnosis, sex, race, and premorbid intellect at a 1:1 ratio for those participants receiving an M06 cognitive evaluation (YES M06 group) relative to those without (NO M06 group). The final sample included 218 participants that received BL, M06, and M12 cognitive evaluations over their first year of ADNI enrollment, and 218 participants who received only BL and M12 cognitive evaluations over that same time frame, for a total sample of 436 participants.

ADNI classification of participants into diagnostic categories has been documented previously.[2,3,8,9] In the current sample, 143 participants were classified as being of normal cognition (NC), 231 were classified as having MCI, and 62 were classified as having AD. Briefly, Logical Memory from the Wechsler Memory Scale—Revised[10] (WMS-R), the Mini-Mental State Examination[11] (MMSE), and the Clinical Dementia Rating (CDR) scale[12] were used to determine diagnostic classifications. These diagnostic classifications were divided evenly among test administration groups; all three were included in the current study to broaden conclusions across the entire diagnostic spectrum of ADNI participants, instead of limiting conclusions to cognitively normal participants.

The current sample's mean age was 72.12 (SD = 6.7, range = 55 to 90) years old and mean years of education was 16.17 (SD = 2.6, range = 8 to 20). The sample of participants was mostly White (89.7%) and consisted of slightly more men (55.7%). Mean premorbid intellect at BL was estimated to be high average according to the American National Adult Reading Test[13] (AMNART; Verbal Intellect standard score: mean = 117.50, SD = 9.8, range = 86 to 131). Self-reported depression was generally low (mean = 1.32, SD = 1.4, range = 0 to 7) according to the 15-item Geriatric Depression Scale[14] (GDS; cut-off is a score ≥5, with higher scores indicating greater self-reported depression-burden).

2.2 | Procedure

All participants underwent a standard neuropsychological battery at a baseline visit regardless of the ADNI protocol in which a participant enrolled. Readers are referred to ADNI protocols[2,3,8,9] for neuropsychological test descriptions and psychometric properties. The neuropsychological measures used in the current study were as follows: Rey Auditory Verbal Learning Test (RAVLT) Total Recall and Delayed Recall, Trail Making Test Parts A and B (TMT-A and TMT-B), Category Fluency—Animals, Clock Drawing Test (CDT) and Clock Copy Test (CCT), AMNART, Alzheimer's Disease Assessment Scale—Cognitive Subscale—13 (ADAS-Cog), Montreal Cognitive Assessment (MoCA), and the 15-item GDS. All values used were raw scores. Higher scores indicated better performance for RAVLT Total Recall and Delayed Recall, Category Fluency—Animals, CDT and CCT, AMNART, MMSE, and MoCA. Lower scores indicated better performance for TMT-A and TMT-B and ADAS-Cog.

For half the sample (n = 218; NO M06 group), the RAVLT, CDT, CCT, Animals, TMT-A, TMT-B, ADAS-Cog, and MoCA (hereafter referred to as the "repeated cognitive battery") were repeated after 12 months. For the other half of the sample (n = 218; YES M06 group), the cognitive battery was repeated after both 6 months and 12 months. The same version of the measure was administered for all tasks in ADNI—including the RAVLT—with the exception of a word list from the ADAS-Cog according to ADNI protocols.[2,3,8,9] The AMNART and GDS were administered only at baseline.

2.3 | Analyses

One-way analysis of variance (ANOVA) was used to compare continuous demographic variables (eg, age, education, premorbid intellect) and baseline performance between participants who received BL and M12 assessments (NO M06 group) and those who received BL, M06, and M12 assessments (YES M06 group). Similarly, chi-square analyses were conducted between the two groups to compare categorical demographic variables (eg, sex, ethnicity, diagnostic classification). Bivariate correlations were conducted to examine the relationship between BL cognitive measures and demographic variables (ie, age, education, premorbid intellect sex, ethnicity) across assessment groups to determine the appropriateness of covariates.

2.4 | Primary analyses

To compare the impact of an additional exposure of test material at 6 months post-baseline, a series of mixed between-within subjects repeated-measures analyses of covariance (ANCOVAs) was conducted on participants' BL and M12 performances for each of the repeated measures in the cognitive battery. For these mixed repeated-measures ANCOVA, the interaction effect between cognitive change over time * assessment group (YES M06 and NO M06 groups) was determined by a significant Wilks' lambda value for the omnibus analysis.[15] The main effect for performance change over time was determined by a significant Wilks' lambda value for the tests of within-subject effects, and the main effect for assessment group was determined by a significant *P*-value for the tests of between-subject effects. Analyses were additionally conducted within individual diagnostic groups (NC, MCI, and AD). In addition, Δ change scores were calculated from BL and M12 performances for each cognitive measure, and then two-way (M06 assessment group by diagnosis) between-group ANCOVAs were conducted to identify Δ score differences. Finally, hierarchical linear regression was conducted to determine the incremental contribution of M06 assessment on M12 scores for both the total sample, and stratified for diagnostic subsamples, after accounting for demographic variables; specifically, age, education, premorbid intellect, sex, and BL cognitive performance were entered as Step 1 into a model, and M06 assessment was entered as Step 2. Incremental contribution of M06 assessment was determined by *F* Change tests—related to R^2 change—between Steps 1 and 2 in the overall models.

Measures of effect size were expressed throughout as partial eta squared (η^2) values for ANCOVA, *phi* values for chi-square analyses, and R^2 for regression analyses. Small, medium, and large effect sizes for η^2 and R^2 are considered 0.04, 0.25, and 0.64, respectively.[16] Small, medium, and large effect sizes for *phi* are considered 0.20, 0.40, and 0.70, respectively.[17] To account for multiple comparisons, Bonferroni correction of nine outcome variables suggested that a two-tailed alpha level should be set at .0055 for all statistical analyses.

TABLE 1 Demographic characteristics of the current sample

Variable	NO M06 group	YES M06 group
N	218	218
Age (years)	72.00 (7.8)	72.23 (5.3)
Education (years)	16.33 (2.4)	16.01 (2.8)
Sex (%)		
Female	45.9	42.7
Male	54.1	57.3
Ethnicity (%)		
Caucasian/Non-Hispanic	87.6	91.7
Non-Caucasian/Hispanic	12.4	8.3
Diagnosis (%)		
Normal Cognition	32.1	33.5
Mild Cognitive Impairment	51.8	54.1
Alzheimer's disease	16.1	12.4
AMNART—Verbal Intellect (*SS*)	117.30 (10.3)	117.70 (9.4)
M12 Retest Interval (days)	379.48 (34.3)	372.78 (36.9)
Montreal Cognitive Assessment	23.03 (4.5)	23.99 (3.6)
Geriatric Depression Scale	1.35 (1.4)	1.30 (1.3)

Note: AMNART = American National Adult Reading Test, *SS* = *Standard Score*. All values reflect mean (*SD*) unless otherwise noted. All values for cognitive tests reflect performance at baseline. No differences were observed between groups, $P > .0055$.

3 | RESULTS

Table 1 reflects demographic characteristics of participants in the current sample. Consistent with their demographic matching, no differences were observed between participants in the NO M06 and YES M06 groups for age: $F(1, 434) = 0.13$, $P = .72$, $\eta^2 = .001$; education: $F(1, 434) = 1.68$, $P = .20$, $\eta^2 = .04$; AMNART premorbid verbal intellect: $F(1, 423) = 0.17$, $P = .68$, $\eta^2 = .001$; M12 retest interval: $F(1, 433) = 3.85$, $P = .05$, $\eta^2 = .01$; sex: χ^2 (1) = 0.34, $P = .56$, *phi* = -0.03; ethnicity: χ^2 (1) = 1.59, $P = .21$, *phi* = -0.07; or diagnostic classification: χ^2 (2) = 1.20, $P = .55$, *phi* = 0.05.

The degree to which demographic variables accounted for BL cognitive performances when collapsing across diagnostic and assessment groups is shown in Table 2. The demographic variables of education and premorbid intellect were consistently significantly related to BL cognitive performance across measures, age was significantly correlated with four of nine measures, and sex was significantly correlated with two of nine measures. Ethnicity was not significantly related to baseline cognitive performance. As a result, education, premorbid intellect, age, and sex were used as covariates in the subsequent analyses.

BL performances were compared for each measure in the repeated cognitive battery for the NO M06 and YES M06 groups. As seen in Table 3, a significant difference was observed between groups on the ADAS-Cog total score—$F(1, 415) = 18.85$, $P < .001$, $\eta^2 = .04$—such that the NO MO6 Group performed worse at BL. Conversely, no differences between groups were observed for BL performance on the remainder of measures in the repeated battery: (F's(1, 419) = .01 to 5.79, p's = .02 to .97, η^2s = .00 to .01). When considering diagnostic subsamples separately, a significant difference was observed between groups on the ADAS-Cog total score for both NC, $F(1, 135) = 38.73$, $P < .001$, $\eta^2 = .22$, and MCI groups, $F(1, 213) = 10.52$, $P = .001$, $\eta^2 = .05$, such that the NO MO6 Group performed worse at BL. The AD subsample did not differ between groups on the ADAS-Cog, $F(1, 55) = 0.55$, $P = .46$, $\eta^2 = .01$, and no differences between groups were observed for NC, MCI, or AD diagnostic samples BL performances on the remainder of measures in the repeated battery (F's(1, 56 to 1, 215) = .01 to 4.70, p's = .03 to .99, η^2s = .001 to .02).

3.1 | Primary analyses

The current study compared the impact of the administration of a 6-month assessment (M06) on 12-month (M12) performance for the repeated cognitive battery using a series of mixed between-within subjects repeated-measures ANCOVAs. As seen in Table 3 and Figure 1, there were no significant interactions between group status (NO M06 and YES M06 groups) and cognitive performance over time (BL and M12 performances) for any of the variables in the cognitive battery (Wilks' lambda = 0.99 to 1.00, F's = 0.01 to 4.39, p's = .05 to .94, η^2s = .001 to .010). Similarly, after accounting for demographic covariates, there was no significant main effect for time observed for any of the cognitive variables (Wilks' lambda = 0.99 to 1.00, F's(1, 419) = 0.09 to 5.82, p's = .02 to .76, η^2s = .001 to .01). The main effect comparing cognitive performance across test-exposure groups was significant for ADAS-Cog, $F(1, 411) = 18.02$, $P < .001$, $\eta^2 = .042$, where the NO M06 group performed worse across both BL and M12 assessments. No other main effects for time were observed with the remaining eight variables in the repeated cognitive battery (F's(1, 418) = 0.03 to 6.75, p's = .01 to .87, η^2s = .001 to .02).

When considering analyses examining M12 performances across each of the NC, MCI, and AD groups, the results were generally comparable to those obtained for the total sample. After accounting for demographic variables, no interaction effects were observed across any cognitive measures in any diagnostic group (Wilks' lambda = 0.96 to 1.00, F's(1, 44 to 1, 136) = 0.01 to 6.39, p's = .01 to .94, η^2s = .001 to .04). Although a trend of greater improvement was seen between BL and M12 assessment for NO M06 participants than YES M06 participants on RAVLT Delayed Recall, this did not remain significant after controlling for multiple comparisons (Wilks' lambda = 0.96, $F(1, 136) = 6.39$, $P = .01$, $\eta^2 = .04$). Significant main effects for time were observed for the AD group for the CCT (Wilks' lambda = 0.87, $F(1, 55) = 8.45$, $P = .005$, $\eta^2 = .13$), where performance for both groups declined between BL and M12 assessments. No other main effects for time were observed for any other cognitive measure across NC, MCI, or AD subsamples (Wilks' lambda = 0.85 to 1.00, F's(1, 44 to 1, 215) = 0.02 to 7.98, P's = .01 to .90, η^2s = .001 to .15). Main effects for cognitive performance across M06 assessment groups were observed for the NC and MCI groups for ADAS-Cog, $F(1, 133) = 64.52$, $P < .001$, $\eta^2 = .33$, and

TABLE 2 Bivariate correlations (and *P* values) between baseline scores and demographic variables across the total sample (n = 436)

	Age	Education	Premorbid Intellect	Sex	Ethnicity
RAVLT					
Total Recall	−.16 (*P* = .001) *	.21 (*P* < .001) *	.34 (*P* < .001) *	.24 (*P* < .001) *	.09 (*P* = .07)
Delayed Recall	−.12 (*P* = .01)	.19 (*P* < .001) *	.28 (*P* < .001) *	.15 (*P* = .002) *	.04 (*P* = .38)
Clock Drawing	−.03 (*P* = .52)	.14 (*P* = .004) *	.25 (*P* < .001) *	.00 (*P* = .99)	.10 (*P* = .05)
Clock Copy	.07 (*P* = .14)	.03 (*P* = .47)	.12 (*P* = .02)	−.02 (*P* = .62)	.07 (*P* = .13)
Category Fluency – Animals	−.14 (*P* = .004) *	.24 (*P* < .001) *	.33 (*P* < .001) *	.04 (*P* = .38)	−.06 (*P* = .25)
Trail Making Test					
Part A	.11 (*P* = .03)	−.12 (*P* = .02)	−.15 (*P* = .003) *	−.01 (*P* = .90)	−.02 (*P* = .70)
Part B	.14 (*P* = .003) *	−.26 (*P* < .001) *	−.31 (*P* < .001) *	.05 (*P* = .35)	.04 (*P* = .37)
ADAS−Cog	.12 (*P* = .02)	−.18 (*P* < .001) *	−.35 (*P* < .001) *	−.07 (*P* = .16)	−.03 (*P* = .48)
MoCA	−.16 (*P* = .005) *	.28 (*P* < .001) *	.42 (*P* < .001) *	.01 (*P* = .92)	−.06 (*P* = .27)

Note: RAVLT = Rey Auditory Verbal Learning Test, ADAS-Cog = Alzheimer's Disease Assessment Scale−Cognitive subscale 13, and MoCA = Montreal Cognitive Assessment.
*To account for multiple comparisons, a Bonferroni correction of *P* < .0055 was significant.

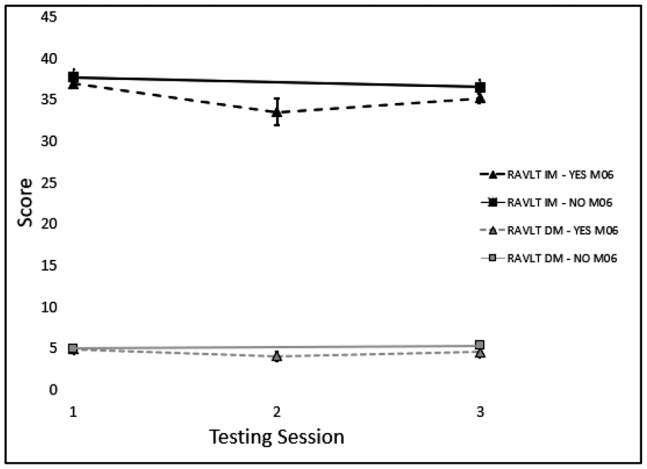
TABLE 3 Baseline, M06, and M12 scores between participants with and without a M06 test administration across the total sample (n = 436)

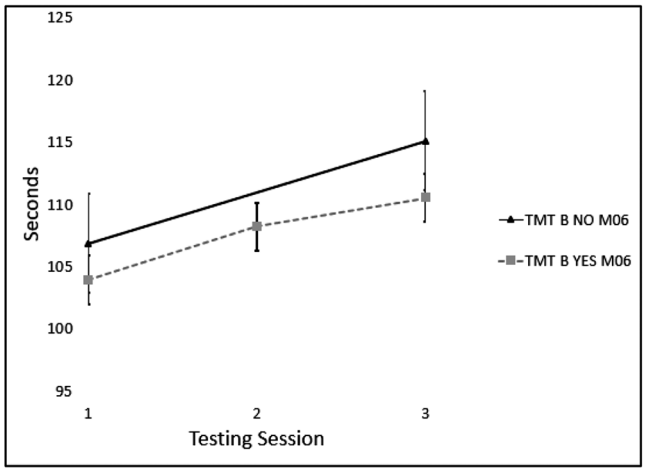
	NO M06 Group				YES M06 Group			
	Baseline Score	M06 Score	M12 Score	M12 to BL Δ	Baseline Score	M06 Score	M12 Score	M12 to BL Δ
RAVLT								
Total Recall	37.68 (13.0)	–	36.55 (14.1)	−1.13 (8.0)	36.92 (11.0)	33.49 (11.5)	35.16 (11.8)	−1.77 (7.3)
Delayed Recall	4.95 (4.2)	–	5.25 (5.1)	0.30 (3.9)	4.83 (4.1)	4.00 (4.0)	4.48 (4.54)	−0.36 (2.8)
Clock Drawing	4.30 (1.0)	–	4.38 (1.0)	0.08 (0.9)	4.46 (1.0)	4.32 (1.0)	4.39 (1.0)	−0.07 (0.8)
Clock Copy	4.60 (0.8)	–	4.56 (0.9)	−0.05 (0.8)	4.78 (0.6)	4.71 (0.7)	4.72 (0.6)	−0.06 (0.6)
Category Fluency - Animals	17.96 (5.8)	–	17.71 (6.0)	−0.25 (4.3)	18.11 (6.0)	18.07 (6.0)	17.50 (6.1)	−0.61 (4.3)
Trail Making Test								
Part A	41.04 (22.2)	–	44.45 (37.0)	3.41 (31.3)	39.01 (18.1)	39.21 (20.5)	40.13 (20.3)	1.12 (14.2)
Part B	106.86 (67.8)	–	115.10 (75.8)	8.24 (47.5)	103.92 (61.6)	108.21 (70.7)	110.51 (75.0)	6.59 (52.3)
ADAS-Cog 13[a]	18.52 (8.5)	–	19.57 (10.2)	1.06 (4.2)	15.25 (8.6)	15.92 (9.5)	15.70 (10.6)	0.45 (4.8)
MoCA	23.22 (4.3)	–	22.94 (5.2)	−0.28 (2.7)	24.17 (3.4)	23.98 (3.7)	24.14 (4.1)	−0.03 (2.6)

Note: M12 to BL Δ = M12 score minus BL score, RAVLT = Rey Auditory Verbal Learning Test, ADAS-Cog 13 = Alzheimer's Disease Assessment Scale − Cognitive subscale 13, and MoCA = Montreal Cognitive Assessment. Higher scores reflect improvement over time in all variables except Trail Making Test Parts A and B, and ADAS-Cog—where higher scores reflect decline over time.
[a]Denotes difference between NO M06 and YES M06 groups at baseline, *P* < .001.

F(1, 212) = 10.16, *P* = .002, η^2 = .05, respectively; for both diagnostic subsamples, the NO M06 group performed worse than the YES M06 group across both BL and M12 assessments. No other main effects for assessment group were observed for any other cognitive measure across NC, MCI, or AD subsamples: *F's*(1, 211 to 1, 215) = 0.06 to 5.13, *p's* = .03 to .81, η^2s = .001 to .02.

To examine the change from BL to M12 for each cognitive measure more closely, a change or Δ variable was calculated to reflect M12 score minus BL score for each measure. Consistent with our lack of interaction effects observed using mixed between-within subjects repeated-measures ANCOVA across diagnostic subsamples, when conducting two-way between-groups ANCOVA for each cognitive measure, no interaction effects were observed between M06 assessment group and diagnosis. This means that the influence of assessment group on Δ scores did not differ by diagnostic subsample: *F's*(2, 411) = 0.28 to 2.21, *p's* = .11 to .76, η^2s = .001 to .01. The main effects for assessment group were all non-significant, meaning that Δ scores did not differ significantly for NO M06 and YES M06 groups for any of the cognitive measures: *F's*(1, 414) = 0.06 to 4.51, *p's* = .03 to .80, η^2s = .001 to .01. Main effects for diagnostic group were significant for ADAS-Cog: *F*(2, 407) = 11.80, *P* < .001, η^2 = .06; CCT: *F*(2, 414) = 11.59, *P* < .001, η^2 = .05; and MoCA: *F*(2, 281) = 7.06, *P* = .001, η^2 = .05. In each case, the Δ change score was greater for NC and MCI groups than for AD. No main effect differences for diagnosis were observed for





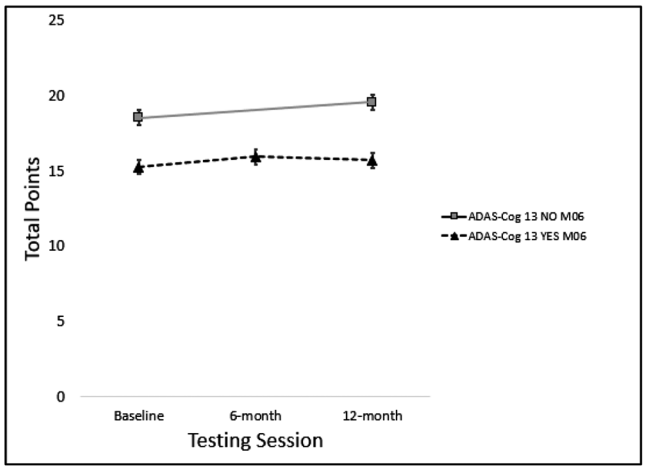


FIGURE 1 Baseline, 6-month, and 12-month performances between participants with and without a 6-month administration across the total sample ($n = 436$) for select measures

any of the remaining cognitive measures: $F's(2, 414 \text{ to } 2, 415) = 1.53$ to 3.87, $p's = .02$ to .22, η^2s = .005 to .007.

Finally, hierarchical linear regression analyses were conducted assess the impact of M06 assessment by regressing M12 scores on BL scores and the presence or absence of the M06 assessment, after accounting for demographic variables (Table 4). Although BL performance significantly predicted M12 performance for each measure in the repeated cognitive battery, $F's(5, 418) = 40.00$ to 401.15, $p's < .001$, R^2s = .32 to .83, in no circumstance did the addition of M06 assessment status statistically contribute to the model (F Changes (1, 417) = 0.28 to 4.68, $p's = .03$ to .65, η^2s = .001 to .01). In particular, the incremental R^2 values (ie, R^2 change values) for the addition of M06 assessment status ranged from .00 to .005, suggesting that the M06 group status accounted for 0 to 0.5% of the variance in M12 performances. When stratifying these linear regression analyses into individual diagnostic groups, the incremental R^2 values (ie, R^2 change values) for the addition of M06 assessment status remained non-significant across cognitive measures for NC (F Changes = 0.00 to 0.008, $p's = .28$ to .99, η^2s = .001), MCI (F Changes = 0.00 to 3.14, $p's = .08$ to .72, η^2s = .001 to .01), and AD (F Changes = 0.00 to 1.14, $p's = .29$ to .99, η^2s = .001 to .01) subsamples.

4 | DISCUSSION

To our knowledge, this is the first study to evaluate the impact of prior test administration at an intermediate time point (ie, at 6 months) on cognitive performance at 12 months in ADNI, which can provide information on the appropriateness of data harmonization across ADNI longitudinal analyses. The current study's results suggested that the presence of a 6-month cognitive assessment did not influence performance over 1 year for any of the measures administered in the repeated cognitive battery, after accounting for demographic variables. Specifically, using mixed between-within subjects repeated-measures ANOVA, the current study observed that no significant interaction effects were observed between M06 assessment status and cognitive performance over time. Comparable results were seen in analyses examining these effects within subpopulations of NC, MCI, and AD participants. In addition, the calculation of Δ change scores between BL and M12 similarly indicated no difference between M06 assessment status groups, and the interaction between M06 assessment status and diagnostic subsample was also non-significant. This latter finding suggests that the influence of M06 assessment group status (NO M06 vs YES M06 groups) on Δ scores did not differ by diagnostic subsample. Furthermore, when entered into a regression model with BL performance and demographic variables, M06 assessment status accounted for only an additional 0 to 0.5% of the variance in the prediction M12 performance across cognitive measures examined. These results are counter to our hypotheses because it was anticipated that additional exposure to test materials at M06 months would result in subsequently enhanced performance at M12 months. In fact, non-significant trends across some measures in Table 2 and Figure 1 suggest that exposure to M06 test materials was associated with a *reduced* M12 performance relative to those not assessed at 6 months. These trends were unexpected, as such a finding would make sense if exposure to test stimuli at M06 was retroactively interfering with performance at M12. However, retroactive interference requires test questions/materials to differ over time, which is not the case across measures in the ADNI protocols[2,3,8,9] for

TABLE 4 Incremental contribution of 6-month assessment predicting 12-month assessment beyond baseline performances across ADNI measures (n = 436)

	Total Model F(df), p, r^2	Incremental r^2 change, *P*
RAVLT Total Recall	F(6, 417) = 146.08, *P* < .001, r^2 = .67	
Step 1: Baseline Assessment + Demographics		r^2 = .67, *P* < .001
Step 2: 6-month Assessment		r^2 = .001, *P* = .26
RAVLT Delayed Recall	F(6, 417) = 79.70, *P* < .001, r^2 = .52	
Step 1: Baseline Assessment + Demographics		r^2 = .52, *P* < .001
Step 2: 6-month Assessment		r^2 = .005, *P* = .03
Clock Drawing	F(6, 417) = 33.56, *P* < .001, r^2 = .32	
Step 1: Baseline Assessment + Demographics		r^2 = .32, *P* < .001
Step 2: 6-month Assessment		r^2 = .002, *P* = .27
Clock Copy	F(6, 417) = 41.69, *P* < .001, r^2 = .37	
Step 1: Baseline Assessment + Demographics		r^2 = .37, *P* < .001
Step 2: 6-month Assessment		r^2 = .001, *P* = .34
Category Fluency - Animals	F(6, 417) = 91.04, *P* < .001, r^2 = .56	
Step 1: Baseline Assessment + Demographics		r^2 = .56, *P* < .001
Step 2: 6-month Assessment		r^2 = .001, *P* = .32
Trail Making Test Part A	F(6, 414) = 38.51, *P* < .001, r^2 = .36	
Step 1: Baseline Assessment + Demographics		r^2 = .36, *P* < .001
Step 2: 6-month Assessment		r^2 = .003, *P* = .18
Trail Making Test Part B	F(6, 402) = 96.70, *P* < .001, r^2 = .59	
Step 1: Baseline Assessment + Demographics		r^2 = .59, *P* < .001
Step 2: 6-month Assessment		r^2 = .000, *P* = .60
ADAS-Cog	F(6, 410) = 333.72, *P* < .001, r^2 = .83	
Step 1: Baseline Assessment + Demographics		r^2 = .83, *P* < .001
Step 2: 6-month Assessment		r^2 = .000, *P* = .63
MoCA	F(6, 284) = 121.33, *P* < .001, r^2 = .72	
Step 1: Baseline Assessment + Demographics		r^2 = .72, *P* < .001
Step 2: 6-month Assessment		r^2 = .000, *P* = .65

Note: Demographics = age, education, premorbid intellect, and sex, RAVLT = Rey Auditory Verbal Learning Test, ADAS-Cog = Alzheimer's Disease Assessment Scale—Cognitive subscale, and MoCA = Montreal Cognitive Assessment.

most measures (with the exception the ADAS-Cog word list on the subtest Word Recall). Similarly, this result appears to hold across diagnostic sub-classifications; therefore this does not seem to reflect a disproportionate recruitment of less-severe participants into ADNI-3 and the "rich getting richer" effect (ie, greater benefit from prior test exposure as a result of stronger baseline performance[18]).

In addition, our analyses indicated that although a single main effect for time was observed in our analyses (for the CCT variable in the AD group), this reflected a significant decline between baseline and 12 months. As in, no improvements were observed across the sample over 12 months . Similarly, we observed that in three variables (ADAS-Cog, MoCA, and CCT) Δ scores were larger in the NC and MCI group than in the AD groups, although this appeared to reflect consistent declines in the AD group over time, as compared to improvements in the NC and MCI groups. These findings are likely explained by the older average age of participants in ADNI, as age has been shown consistently to have a negative impact both on cognitive performance and benefit from practice upon repeat assessment.[19] Specifically, Calamia et al. meta-analytically derived regression-based prediction equations[20] have shown that the ability to benefit from practice is reduced by 51% in the average age of our sample (ie, 71 years old). Similarly, this result is consistent with the failure to observe a benefit from prior test exposure that has been evident in some large-scale longitudinal research using the National Alzheimer's Coordinating Center database[21,22] across a host of cognitive domains when assessed twice over 6 to 24 months. In addition, our difference in Δ scores across groups is consistent with long-standing research suggesting that patients with AD and other severe cognitive compromise are less capable of benefiting from repeated exposure to test material.[20,23]

As a result of these findings, it appears that an acceptable practice would be to collapse longitudinal participant data across ADNI protocols. Previously, differences in ADNI rate of assessment led to a

variety of methods to avoid pooling across protocols,[6,7] based on the presumption that the absence of an M06 assessment rendered ADNI-3 participants incomparable to participants from ADNI-1, ADNI-GO, and ADNI-2. Given the relatively smaller number of participants matriculating in ADNI-3 relative to the prior protocols—due to the recency of initiating ADNI-3—this has been a limitation on including ADNI-3 data in longitudinal research. However, this result suggests that participant data across ADNI cohorts can be included in future endeavors, which will benefit future research on ADNI longitudinal data.

The current study is not without limitations. First, these findings are specific to the cognitive measures administered in this battery over retest intervals of 6 and 12 months therefore it is not necessarily assumed that the results can generalize to other measures of the same cognitive domains, different retest intervals, or use of alternative forms.[20] Second, these results are specific to participants in ADNI, therefore they may not generalize to more heterogeneous participants regarding premorbid functioning, education, ethnicity, or disease state. That said, because ADNI is generally considered to be a high-functioning and educated cohort, it could be argued that such a cohort may be more susceptible to benefiting from prior exposure[18]—which is counter to our findings. Relatedly, ADNI employs rigorous exclusion criteria typical of clinical trials; therefore our study cohort might not be representative of the general population. Third, the measures comprising the repeated cognitive battery were constrained by their needing to be administered both in ADNI-3 and previous ADNI protocols. As such, measures that were discontinued in ADNI-3—like Digit Span, Digit Symbol Substitution Test, and Boston Naming Test—could not be included in the current analyses because they were never assessed in a protocol that excluded an M06 assessment. Fourth, the lack of post-baseline mood assessment may have contributed unaccounted variance to our analyses. Despite these limitations, however, the results indicate no differential impact of M06 test exposure on 12-month longitudinal performance in ADNI. Subsequently, our findings suggest the appropriateness of collapsing longitudinal participant data across ADNI protocols, which will permit a greater breadth of data that can be applied to future ADNI-3 longitudinal research.

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DISCLOSURE

Authors Hammers, Duff, Kostadinova, and Apostolova have no relationships/activities/interests to disclose related to the content of this submission.

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APPENDIX

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