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Brief Communication

Alzheimer's Polygenic Risk and Clinical Severity Manifest in Greater Cognitive Intra-Individual Variability

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Abstract

Objective: Cognitive intra-individual variability (IIV) is a neuropsychological marker reflecting divergent performance across cognitive domains. In this brief communication, we examined whether clinical severity, apolipoprotein E (*APOE*) ε4 carriers, and higher polygenic risk were associated with higher cognitive IIV, and whether higher polygenic risk and cognitive IIV synergistically influence clinical severity. **Method:** This large study involved up to 24,248 participants (mean age = 72) from the National Alzheimer's Coordinating Center (NACC) and multiple regression controlling for age, sex, and education was used to analyze the data. **Results:** We found that disease severity (B = 0.055, SE = 0.001, $P < 0.001$), *APOE* ε4 carriers (B = 0.02, SE = 0.003, $P < 0.001$), and higher polygenic risk (B = 0.02, SE = 0.004, $P < 0.001$) were associated with higher cognitive IIV. Polygenic risk and cognitive IIV also interacted to influence clinical severity, beyond *APOE* ε4 (B = 0.11, SE = 0.05, $P = 0.02$), such that individuals with high polygenic risk and cognitive IIV had the greatest clinical severity. **Conclusions:** Heightened polygenic risk and increased cross-domain cognitive variation are implicated in dementia and may impact clinical decline in tandem.

Keywords: Polygenic risk score; Apolipoprotein E; Alzheimer's disease; Dementia; Neuropsychology; Cognition

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Statement of Research Significance

Research Question(s) or Topic(s):

This study used data from the National Alzheimer's Coordinating Center and aims to investigate the associations of greater individual variation in performance across neuropsychological tasks with clinical severity and genetic risk.

Main Findings:

Disease severity, APOE ε4 carriers, and higher polygenic risk were associated with higher cognitive intra-individual variability (IIV). Polygenic risk and cognitive IIV also influence clinical severity synergistically, such that individuals with high polygenic risk and cognitive IIV had the greatest clinical severity.

Study Contributions:

Heightened polygenetic risk and increased cross-domain cognitive variation are implicated in dementia and may impact clinical decline in tandem.

Introduction

Cognitive intra-individual variability (IIV) is a neuropsychological dispersion marker that reflects an individual's variation in performance across different cognitive tasks (Salthouse & Soubelet, 2014; Schretlen et al., 2003). Recent meta-analyses suggest that greater cognitive IIV is associated with conversion to mild cognitive impairment (MCI) or dementia (Mumme et al., 2021) and increases as a function of disease severity (Aita et al., 2024). More recently, cognitive IIV was found to be associated with both global and regional magnetic resonance imaging (MRI) measures of neurodegeneration and positron emission tomography (PET) measures of amyloid, tau, and glucose metabolism, highlighting cognitive IIV's strong links to known neuroimaging biomarkers implicated in the Alzheimer's disease (AD) process (Phang & Tan, 2025). Cognitive IIV has also been found to be useful for distinguishing between cognitively normal individuals and those experiencing cognitive impairment as a result of Lewy body disease (Kiselica et al., 2024). While these studies provide valuable insights into the potential utility of cognitive IIV, most of these studies were conducted using data from relatively small cohorts, typically numbering in the hundreds or fewer (Aita et al., 2024). Whether there are differences in cognitive IIV as a function of clinical severity in large cohorts remains unclear.

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Further, the relationship between AD genetic risk and cognitive IIV remains understudied and a recent meta-analysis using a small number of studies did not find any statistically significant relationship between cognitive IIV and apolipoprotein E (*APOE*) ε4 carrier status in cognitively normal individuals (Aita et al., 2024). However, the genetic architecture of late onset AD is polygenic in nature (Lambert et al., 2023; Tan & Desikan, 2018) and polygenic scores have been shown to correlate with Alzheimer's associated biomarkers and prediction of clinical decline (Kauppi et al., 2018; Tan et al., 2019). If indeed greater cognitive IIV reflects the manifestation of AD-related processes, polygenic risk should also contribute to variation in cognitive performance across domains. In this study, using a large sample of participants from the Alzheimer's Disease Research Centers (ADRCs) across the United States, we aimed to elucidate clinical severity group differences and genetic associations with cognitive IIV. We hypothesized that clinical severity, *APOE* ε4 carriers, and higher polygenic risk would be associated with higher cognitive IIV; and that higher polygenic risk and cognitive IIV would synergistically influence clinical severity.

Table 1. Demographics

	(n = 24,248)
Age (M, SD)	71.97 (10.2)
Years of education (M, SD)	15.2 (3.2)
Sex (Female *n*, %)	13,886 (57.3)
APOE ε4 carriers (n, %)[#]	7883 (39.2)
APOE ε4 dosage (*n*, 0/1/2)[#]	12,238/6638/1245
Polygenic hazard score (M, SD)*	0.44 (0.88)
CN/Questionable dementia/AD dementia (*n*)	11,032/9656/3560
Cognitive intra-individual variability by clinical severity group (M)	0.62/0.67/0.77
Derived NIH race definitions	
White (*n*, %)	19,516 (80.5)
Black or African American (*n*, %)	3051 (12.6)
American Indian or Alaska Native (*n*, %)	132 (0.54)
Native Hawaiian or Pacific Islander (*n*, %)	17 (0.07)
Asian (*n*, %)	462 (1.91)
Multiracial (*n*, %)	833 (3.44)
Geriatric depression total score (M, SD)	2.09 (2.59)
Diabetes (*n*, Active vs. Absent/Inactive)	3027/21150
Hypertension (*n*, Active vs. Absent/Inactive)	11,893/12275
Hypercholesterolemia (*n*, Active vs. Absent/Inactive)	11,872/12091

Note: [#]n = 20,121, *n = 2,375.

Method

We evaluated 24,248 participants from the National Alzheimer's Coordinating Center (NACC) with complete demographic, neuropsychological, and clinical severity quantified by the CDR® Dementia Staging Instrument scores. Participants were classified as cognitive normal (CN), questionable dementia, or dementia based on a CDR global score of 0, 0.5 and >0.5 respectively. Participants' characteristics are summarized in Table 1. Intra-individual cognitive variability was computed by first standardizing each participant's performance on the following neuropsychological tests assessing multidomain cognition available in UDS 2.0: Logical memory, forward and backward Digit Span, Animals and Vegetables verbal fluency, Trail-making tests A and B, Wechsler Adult Intelligence Scale–Revised (WAIS-R) Digit Symbol Test, and the Boston Naming Test. Next, the standard deviation of all the standardized test scores of each participant was computed to derive the final cognitive IIV measure. This method of deriving dispersion-based cognitive IIV has been previously described (Holtzer et al., 2008; Phang & Tan, 2025). *APOE* ε4 carrier status was binarized and the data was only available in a subset of 20,121 participants. AD polygenic hazard score (PHS) was computed based on 31 AD-associated single nucleotide polymorphisms (SNPs) as previously described and validated (Desikan et al., 2017; Tan et al., 2017). These polygenic data were only available in a subset of participants (n = 2,375). Participants selection flowchart can be found in Supplementary Figure 1 and were included based on data availability on the respective measures of interest to maximize statistical power. The research was completed in accordance with the Helsinki Declaration. Informed consent and ethics approval were obtained by the individual ADRCs.

We first evaluated whether there were clinical severity categorical group differences (CN vs. Questionable dementia vs. Dementia) in cognitive IIV using multiple regression. We additionally evaluated whether higher continuous CDR-Sum of Boxes (CDRSB) was associated with higher cognitive IIV. We further controlled for performance on the Mini-mental state examination (MMSE) to exclude the possibility that the association was simply driven by general cognitive function. Next, we investigated whether *APOE* ε4 carrier status was associated with higher cognitive IIV. We further tested whether higher polygenic risk as quantified by PHS was associated with higher cognitive IIV, even after controlling *APOE* ε4 carrier status. Lastly, we used multiple regression to investigate whether PHS interacted with cognitive IIV to influence clinical severity quantified using CDRSB. In all analyses, we controlled for age, sex, and years of education. Several sensitivity analyses were also conducted, including controlling for categorical *APOE* ε4 dosage, derived National Institutes of Health (NIH) race categories (White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Asian, Multiracial), mood (Geriatric Depression Scale total score), and vascular risk factors (Active vs. absence/inactive diabetes, hypertension, and hypercholesterolemia). All statistical analyses were conducted using R 4.4.3.

Results

Greater clinical severity is associated with higher cognitive IIV

Across all participants in the we found that cognitive IIV increases as a function of the 3 clinical severity groups (Figure 1A). Compared to CN individuals, participants with questionable dementia (B = 0.06, SE = 0.003, $P < 0.001$) and dementia had higher cognitive IIV (B = 0.15, SE = 0.004, $P < 0.001$). Likewise, participants with dementia also had higher cognitive IIV than those with questionable dementia (B = 0.10, SE = 0.004, $P < 0.001$). When using continuous CDRSB, we found converging evidence such that higher CDRSB was associated with higher cognitive IIV (B = 0.055, SE = 0.001, $P < 0.001$). Notably, this association remained statistically significant (B = 0.027, SE = 0.001, $P < 0.001$) even after controlling for general cognitive performance on the MMSE.

Greater genetic risk is associated with higher cognitive IIV and interacts to influence CDRSB

APOE ε4 carriers had higher cognitive IIV (B = 0.02, SE = 0.003, $P < 0.001$) compared to non-carriers. Individuals with higher AD

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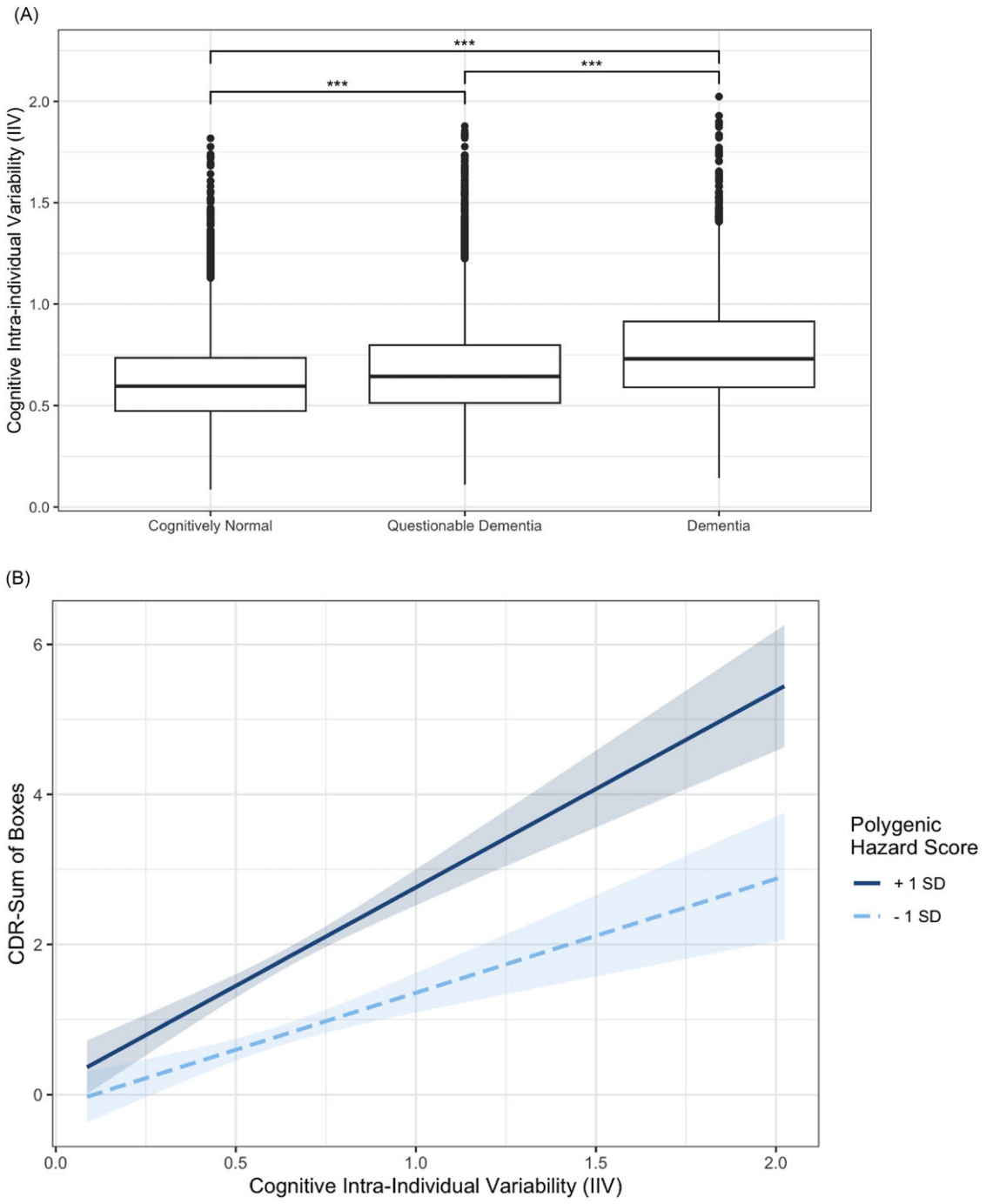

Figure 1. (A) cognitive intra-individual variability (IIV) increases as a function of clinical severity assessed using clinical dementia rating (CDR). (B) individuals with high polygenic risk and cognitive IIV showed the greatest clinical severity.

polygenic risk i.e. PHS, also had higher cognitive IIV (B = 0.02, SE = 0.004, $P < 0.001$) and this association remained statistically significant even when controlling for *APOE* ε4 carrier status (B = 0.016, SE = 0.006, $P = 0.006$). Lastly, we found an interaction between PHS and cognitive IIV on CDRSB (B = 0.13, SE = 0.05, $P = 0.01$, Figure 1B), which remained statistically significant even after accounting for *APOE* ε4 carrier status (B = 0.11, SE = 0.05, $P = 0.02$). Simple slopes analysis revealed that in individuals with high PHS, higher cognitive IIV was most strongly associated with greater clinical severity (B = 0.56, SE = 0.06, $P < 0.001$). For individuals with lower PHS, the association between cognitive IIV and clinical severity was attenuated but remained statistically significant (B = 0.32, SE = 0.06, $P < 0.001$).

Sensitivity analysis

When treating *APOE* ε4 as 3 categorical groups (0/1/2 copies of ε4 alleles), similar results were found – all post-hoc Tukey-adjusted comparisons showed that increasing number of ε4 alleles was associated greater cognitive IIV. Specifically, individuals 2 copies of ε4 alleles had higher cognitive IIV than those with 1 copy (B = 0.021, SE = 0.007, $P = 0.007$) and those without (B = 0.038, SE =

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0.007, $P < 0.001$). Individuals with 1 copy also had higher cognitive IIV than those without (B = 0.017, SE = 0.003, $P < 0.001$).

When controlling for race based on the derived NIH race definitions, conclusions were likewise unchanged. Higher CDRSB (B = 0.06, SE = 0.001, $P < 0.001$), *APOE* ε4 carriers (B = 0.02, SE = 0.003, $P < 0.001$), higher PHS (B = 0.02, SE = 0.004, $P < 0.001$) were all associated with higher cognitive IIV, including the interaction analyses (B = 0.13, SE = 0.05, $P = 0.01$). When accounting for mood and vascular risk factors, higher CDRSB (B = 0.05, SE = 0.002, $P < 0.001$), *APOE* ε4 carriers (B = 0.02, SE = 0.003, $P < 0.001$), higher PHS (B = 0.02, SE = 0.004, $P < 0.001$) were all associated with higher cognitive IIV, including the interaction analyses (B = 0.11, SE = 0.05, $P = 0.02$).

Discussion

In this large NACC cohort study, we demonstrated that variation in performance across cognitive domains increases as a function of clinical severity, escalating evidently from cognitively normal individuals to questionable dementia and to dementia. In addition, we found that *APOE* ε4 carriers and higher AD polygenic risk were associated with greater cognitive IIV, highlighting that genetic risk also contributes to greater cross-domain cognitive variation in AD. Lastly, interaction analysis revealed that individuals with high polygenetic risk in conjunction with increased cognitive IIV had the worst CDRSB scores. Taken together, our results provides evidence that elevated cognitive variation reflects the manifestation of AD-associated polygenic risk with clear impact on clinical severity.

To our knowledge, this is the single largest study to demonstrate that higher dispersion-based cognitive IIV increases as a function of clinical severity. In addition, we demonstrate that greater continuous CDRSB was associated with elevated cognitive IIV, even after accounting for general cognitive performance on the MMSE. These results suggest that cognitive variation and dynamicity in cross-domain cognitive performance likely contains predictive utility beyond overall or absolute measures of cognitive function, aligning with the multifactorial and heterogeneous nature of AD and related dementias (Avelar-Pereira et al., 2023; Devi & Scheltens, 2018).

Studies have also found associations of cognitive IIV with known AD biomarkers (Holmqvist et al., 2023; Meeker et al., 2021; Phang & Tan, 2025), with the strongest Aβ effects in the frontal regions while tau and neurodegenerative effects were most evident in the temporal regions (Phang & Tan, 2025). The presence of heterogeneity in amyloid and tau spatial deposition across individuals, in conjunction with downstream differential regional neurodegeneration may account for the greater cross-domain variability in cognitive performance. Non-AD specific dysfunction in neural networks (Lin & McDonough, 2022), presence of concomitant cerebrovascular disease (Tan et al., 2022), and/or other types of dementia (Webber et al., 2022) may also contribute to heterogeneity in disease presentation and progression that may manifest as greater cognitive IIV.

In this study, higher genetic risk (*APOE* ε4 and PHS) was associated with higher cognitive IIV. Importantly, polygenic risk was associated with cognitive IIV beyond *APOE* ε4 suggesting that polygenic scores such as PHS captures a greater diversity of genetic risk variants that may better emulate the heterogeneous AD pathobiological and consequent cognitive decline process. Further, PHS interacted with cognitive IIV to influence CDRSB, even after accounting for *APOE* ε4, suggesting that the combination of these measures may be useful for enhancing risk stratification. These results were robust to several sensitivity analyses, even when controlling for *APOE* ε4 dosage, race, mood, and vascular risk factors.

The cross-sectional nature of the study limits our ability to make longitudinal predictions. In addition, PHS data was only available in a much smaller subset of the larger NACC sample and may not be generalizable to the entire cohort or to community populations. However, these limitations are mitigated by the large sample size and novel polygenic findings with cognitive IIV. AD is a complex disease and precision medicine approaches towards understanding disease risk and progression may benefit from leveraging intra-individual cognitive variation that may reflect underlying polygenic risk and neurobiological dysfunctions.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617725101252.

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