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The effects of CNS atrophy and ICVD on tests of executive function and functional status are mediated by intelligence

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ABSTRACT

Background: Impairments in executive function (EF) are often attributed to ischemic cerebrovascular disease (ICVD) and frontal circuit pathology. However, EF can be distinguished from general intelligence and the latter is likely to manifest in "executive" measures. We aimed to distinguish the effects of imaging biomarkers on these constructs.

Methods: We tested neuroimaging biomarkers as independent predictors of observed 12 month-prospective cognitive performance by a Multiple Indicators Multiple Causes (MIMIC) model in the Alzheimer's Disease Neuroimaging Initiative (ADNI) ($N \cong 1750$).

Results: ICVD was associated with ''Organization" (ORG) and "Planning" (PLAN) domain scores from the test of Every Day Cognition. Left anterior cingulate (LAC) atrophy was independently associated with Trail-Making part B and Animal Naming. The MIMIC model had excellent fit and tests additional latent variables i.e., EF and dEF (a latent δ homolog derived from Spearman's general intelligence factor, *g*). Only dEF was associated with instrumental activities of daily living (IADL). ICVD and LAC were both associated with observed executive measures *through dEF*. ICVD was independently associated with those same measures through EF.

Conclusions: Observed EF is independently determined by multiple factors. The effects of EF-associated MRI biomarkers can be related to disability and dementia only via their effects on *g*. Because *g* /δ are unlikely to be located within the frontal lobes, the *dementia-specific* variance in executive measures may have little to do with either frontal structure or function. Conversely, *domain-specific* variance in EF may have little to do with either IADL-impairment or dementia.

List of Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's disease neuroimaging initiative; AMOS, analysis of moment structures; animals, categorical fluency (Animals); ATTN, attention domain scores from the ECog; AUC, area under the receiver operating characteristic curve; CDR-SB, clinical dementia rating scale "Sum of Boxes"; CFA, Confirmatory factor analysis; CFI, comparative fit index; CHI SQ, chi square; CNS, central nervous system; CR, critical ratio; CSF, cerebrospinal fluid; DF, degrees of freedom; DMN, default mode network; ECog, test of everyday cognition; EDUC, education (years); EF, executive function; FAQ, functional abilities questionnaire; FIML, full information maximum likelihood; FLAIR, fluid attenuation inversion recovery; GDS, 30 item geriatric depression scale; IADLs, instrumental activities of daily living; ICVD, ischemic cerebrovascular disease; IRB, institutional review boards; LAC, Left anterior cingulate; LMI, Wechsler logical memory immediate paragraph recall; LPC, Left post central grey; MCI, mild cognitive impairment; MIMIC, multiple indicators multiple causes structural model; MOCA, Montreal cognitive assessment; MRI, Magnetic Resonance Imaging; NACC, national Alzheimer's coordinating center; NC, normal controls; ORG, organization domain scores from the ECog; PLAN, panning domain scores from the ECog; RIP, right inferior parietal; RLO, right lateral occipital; RMSEA, root mean square evaluative assessment; ROC, receiver operating characteristic curve; rs-fMRI, resting state functional MRI; SEM, structural equation model; SD, standard deviation; TARCC, Texas Alzheimer's research and care consortium; Trails B, trail making test part B; UDS, Uniform Dataset (NACC); VCD, vascular cognitive disorder(s); VCI, vascular cognitive impairment; WMC, white matter changes.

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1. Introduction

The cognitive correlates of ischemic cerebrovascular disease (ICVD) are multifaceted [1]. ICVD encompasses multiple pathologies including hemorrhagic and non-hemorrhagic cortical and subcortical infarctions, lacunar infarcts and both macro- and microstructural white matter changes (WMC). These in turn, vary in their regional distributions and comorbidities.

Impairment of executive function is often attributed to ICVD and held to be a hallmark of Vascular Cognitive Disorders (VCD) including Vascular Cognitive Impairment (VCI) and Vascular dementia (VaD) [2]. However, executive function itself is a multifaceted construct. Putative "executive" measures load on discriminable factors associated with neuropathologies in distinct regional distributions [3]. While some of those pathologies can be associated with "frontal circuits" [4], lesions outside the frontal circuits are also associated with performance on "executive" measures [5].

The association of ICVD with dementia is particularly ambiguous. Experts have proposed several patterns of "dementing" ischemic lesions, including so-called "critical lesions" [6] but the same patterns are reported among non-demented persons and so they cannot be invoked as *de facto* evidence of a demented presentation. Dementia is necessarily associated with functional disablement [7] but domain-specific cognitive changes, including those associated with ICVD, vary widely in their associations with Instrumental Activities of Daily Living (IADL) and hence dementia [8].

We have developed a new approach to dementia assessment that may have implications for both the association of ICVD with dementia and the executive impairments attributed to it. By a unique confirmatory bifactor model in a structural equation model (SEM) framework, we can isolate the variance in cognitive performance that is empirically related to IADL impairments in a latent variable. The resulting construct (i.e. "δ" for dementia) offers a dementia-specific cognitive phenotype [9].

δ is empirically strongly related to dementia severity [as measured by the Clinical Dementia Rating scale "Sum of Boxes" (CDR-SB)] [10], both cross-sectionally and longitudinally [9,11,12]. This has been independently confirmed in the National Alzheimer's Coordinating Center (NACC)'s Uniform Dataset (UDS) ($N = 26{,}606$) [11] and in well characterized European [13] and Austral-Asian [14,15] samples.

δ can be "reified" as a factor composite and assigned to individuals as a "d-score". Because d-scores are continuously distributed, δ effectively converts dementia from a *category* to a *dimension*. This improves statistical power to detect effects [16].

Because δ is derived from Spearman's general intelligence factor, "*g*" [17], it can be distinguished from domain-specific cognitive performance including the domains of frontal /EF [18]. *g* is not likely to be so localized. It manifests in every cognitive performance measure including both those that purport to measure EF and those that don't. Studies of ICVD's impact on *g* and on *g*-adjusted domain-specific factors are rare. Only one study has previously associated δ with empiric assessments of ICVD [19]. In that study, a latent construct indicated by multiple ICVD-related autopsy findings had no association with δ, independent of Alzheimer's Disease (AD)-specific lesions. However, the study was conducted among *decedents with pathologically confirmed AD* i.e., in cases selected against the full range of ICVD-related pathology. No study has associated ICVD-related neuroimaging biomarkers with δ. We aimed to distinguish the effects of imaging biomarkers on these constructs. Making that distinction may advance our understanding of ICVD's contributions to disablement and dementia and offer insights into its modulation.

2. Materials and methods

2.1. Subjects

The present study is a secondary analysis of data collected by ADNI. Informed consent was obtained from all participants (or their legally authorized proxies) before data collection, and both studies are approved by their respective Institutional Review Boards (IRB).

2.1.1. ADNI

ADNI is a well-characterized longitudinal convenience sample intended to validate the magnetic resonance, PET, cerebrospinal fluid (CSF) and genetic biomarkers of AD [20]. The initial 5-year study, ADNI-1, enrolled cognitively normal, mild cognitive impairment (MCI) and AD subjects, and subsequent studies (ADNI-GO and ADNI-2) added early- and late-MCI cohorts. In ADNI's combined sample ($N = 1738$) $N = 342$ were diagnosed with AD, $N = 978$ with MCI and $N = 417$ as NC. For this analysis, all MCI subtypes were combined, including ADNI-GO participants with "Subjective cognitive impairment (SCI)".

2.1.2. Clinical variables

2.1.2.1. The dEF δ homolog. δ is derived from Spearman's "*g*" factor. [17]. As *g* is thought to contribute to all cognitive measures, it has proven feasible to construct δ from a wide range of measures /batteries. Ideally, δ's indicators should represent a broad range of cognitive domains. However, our interest here was to concentrate on so-called "executive" measures. ADNI's dataset includes several putative executive measures, including the Attention (ATN), Planning (PLAN) and Organization (ORG) constructs from the Test of Everyday Cognition (ECog) [21], Categorical Fluency (Animals) [22], and Trail-Making Part B (TrailsB) [23]. Self-rated rather than informant-rated ECog scores were used. The Functional Assessment Questionnaire (FAQ) [24] was selected for d's "Target Indicator".

We also constructed a latent variable measuring "Executive Function" (EF). EF was also indicated by the executive measures listed above. EF was regressed onto the FAQ so its δ-independent effects on IADL might be assessed. This introduced several obstacles to the model's construction and interpretation. First, it becomes necessary to disambiguate EF and dEF. While EF should comprise variance shared across our battery of executive measures (essentially providing a "measurement model" of EF [25]) dEF, being a derivative of *g*, might be indicated by any number of additional non-executive measures. We therefore added a more general measure of cognition to the model (i.e., the Montreal Cognitive Assessment (MOCA) [26]. MOCA was constrained to be an indicator of dEF but not EF. Thus, dEF was indicated by both executive and non-executive measures while EF is indicated solely by executive measures. Because dEF is associated with all of EF's executive indicators, the EF construct is effectively adjusted for dEF's effect and the two latent constructs are orthogonal.

It might be suggested that our choice of the MOCA as dEF's distinguishing non-executive indicator is inadequate because of the MOCA's widely held perception as an "executive" measure. We would counter that the assertion has never been tested while adjusting for g's contribution to the observed MOCA score. Regardless, we fit an alternative model substituting immediate paragraph recall [i.e., logical memory I (LMI) from the Weschler Memory Scale] [27] for MOCA.

2.1.2.2. Covariates. The observed indicators were adjusted for age, education and the Geriatric Depression Scale (GDS) [28]. Each of those covariates has been previously associated with dementia-severity as measured by δ. However, we are interested in the unique effect of the selected biomarkers and their covariate independent associations with cognitive performance. We did not adjust the models for gender as there is a statistically strong association between male gender and higher levels of ICVD in ADNI, as might be expected. Any gender-specific effects on cognitive performance unrelated to ICVD are likely to be relatively trivial.

2.1.3. Imaging biomarkers

1.5T (ADNI 1) and 3T (ADNI GO, ADNI 2, ADNI 3) MRI were obtained at baseline, six months and annually thereafter. We used baseline data in this analysis. Image quality and pre-processing was performed at a designated MRI center. [29] Standardized MRI imaging datasets have been developed to ensure consistency across ADNI collection sites, imaging platforms and serial assessments. [30] Because of technical issues, 3.0-T images from sites with single-channel coils were excluded from the standardized sets. 1.5T and multichannel 3T scans are included, and involve a volumetric T1-weighted scan, with an accelerated T1-weighted volumetric scan, a fluid attenuation inversion recovery (FLAIR), and a T2*-weighted gradient echo. Each image has undergone specific image pre-processing as follows:

1. Gradwarp: gradwarp is a system-specific correction of image geometry distortion due to gradient non-linearity.
2. B1 non-uniformity: this procedure corrects the image intensity non-uniformity that results when RF transmission is performed with a more uniform body coil while reception is performed with a less uniform head coil.
3. N3: N3 is a histogram peak sharpening algorithm that reduces intensity non-uniformity. It is applied to all images after grad warp and B1 correction.

The ADNI standardized dataset also contains derived cortical and subcortical regional volumetric masures computed using FreeSurfer [31] on the pre-processed T1-weighted MR images. WMH were detected by co-registered T1-, T2-, and proton density (PD) weighted images using an automated protocol. [32]

2.2. Statistical analyses

These analyses were conducted a combined sample of ADNI-1, ADNI-2, and ADNI-GO data ($N = 1737$). The analysis was performed using Analysis of Moment Structures (AMOS) software [33]. The maximum likelihood estimator was chosen for these models. Covariances between the residuals were allowed to be estimated if they were significant and improved model fit.

The observed variables were fit to a linear confirmatory bifactor model. Measurement errors are assumed uncorrelated and the latent variables means and variances were fixed to 0 and 1 respectively allowing all loadings to be freely estimated.

A Multiple Indicators and Multiple Causes (MIMIC) model was specified to investigate the potential association between imaging biomarkers and the observed executive measures. Here, two latent variables (EF & dEF) intervene between biomarkers predicting the observed cognitive and functional status measures [34–36], independently testing dEF and g' as mediators of the biomarker's associations with cognitive test performance. Three sets of relationships can then be evaluated) (1) the measurement models, where the relationships between the latent variables (EF and dEF) and their indicators are were observed (2) the structural regression equations, where the relationships among the biomarkers and the latent constructs are observed and (3) the direct effects, where the relationships between the biomarkers and the observed measures are observed.

The MIMIC model also offers an opportunity to test EF and dEF as competing mediators of the unadjusted direct effects of observed imaging biomarkers on observed measures of cognitive performance and IADL. We modeled imaging biomarkers observed at baseline as predictors of cognitive performance and IADL observed 12 months later. So, the resulting longitudinal mediation affects can be interpreted causally [37]. Finally, we estimated the significance and impact of the mediation effects by MacKinnon's method [38]. It may also be of interest that the direct effects and the mediation effects are mutually adjusted and can be interpreted as independent effects of the imaging biomarkers.

All the confirmatory factor analysis (CFA) and MIMIC analyses were performed using AMOS [33]. Co-variances between the residuals were allowed to be estimated if they were significant and improved model fit. The latent variable of interest has been validated as predictors of observed TARCC outcomes in multivariate regression models and by receiver operating characteristic (ROC) analyses [39].

2.2.1. Missing data

We used Full Information Maximum Likelihood (FIML) methods to address missing data. FIML uses the entire observed data matrix to estimate parameters with missing data. In contrast to listwise or pairwise deletion, FIML yields unbiased parameter estimates and preserves the overall power of the analysis [40,41].

2.2.2. Fit indices

The validity of structural models was assessed using three common test statistics. A non-significant chi-square signifies that the data are consistent with the model [42]. However, with large samples chi-square will often be significant, even for models which fit the data well. Therefore, the ratio of the chi-square to the degrees of freedom in the model is also of interest. A CMIN/DF ratio < 5.0 suggests an adequate fit to the data. The CFI, with values ranging from between 0 and 1, compares the specified model with a model of no change [43]. CFI values below 0.95 suggest model misspecification. Values of 0.95 or greater indicate adequate to excellent fit. An RMSEA of 0.05 or less indicates a close fit to the data, with models below 0.05 considered "good" fit, and up to 0.08 as "acceptable" [44]. All three fit statistics should be simultaneously considered to assess the adequacy of the models to the data.

3. Theory

General intelligence manifests in *all* observed cognitive performance measures and seems unlikely to be regionally localizable. ADNI's ICVD measure is referenced across multiple regions of interest, making it more likely to impact *g*/δ. ADNI's measures of regional atrophy are not. If the association between regional frontal lobe atrophy is related to observed performance in executive measures through *g*/δ, then it may relate to other domains of cognitive performance as well. Conversely, if frontal lobe atrophy relates specifically to frontal /executive function, then it may not be mediated through g/δ and should not be disabling /dementing. Similarly, if the association between regional atrophy and observed executive measures is mediated by g/δ, then it may not matter which brain region is being tested, as has been observed for WML [45]. As a test of that hypothesis, we repeat the analysis above using three structures thought unlikely to contribute to EF, i.e. right lateral occipital (RLO), left post central gray (LPC), and right inferior parietal (RIP).

4. Results

Fig. 1 presents multivariate regression models of the two imaging biomarkers as predictors of the observed 12-month prospective performance on cognitive and IADL measures, adjusted for covariates. While several significant associations are observed, the model's fit was inadequate (probably because it does not specify any latent constructs and the residuals are uncorrelated) [i.e. CHI SQ = 2058.78 (26), $p < 0.001$; CFI = 0.430; RMSEA = 0.212]. Regardless, ICVD predicted PLAN and ORG independently of anterior cingulate volume. Conversely, anterior cingulate volume predicted Animals and Trails B independently of ICVD. Although the model does not fit well, those findings are consistent with regression analyses in the literature which do not test fit. We therefore used these unadjusted direct effects in constructing the four mediation models Table 1.

In contrast to multivariate regression, the MIMIC model had excellent fit [i.e. CHI SQ = 77.85 (16), $p < 0.001$; CFI = 0.983; RMSEA = 0.047] (Fig. 2). Both latent constructs (i.e. EF and dEF) were significantly associated with their indicators (Table 2). Since dEF had effects on observed executive measures independent of EF, this reiterates that

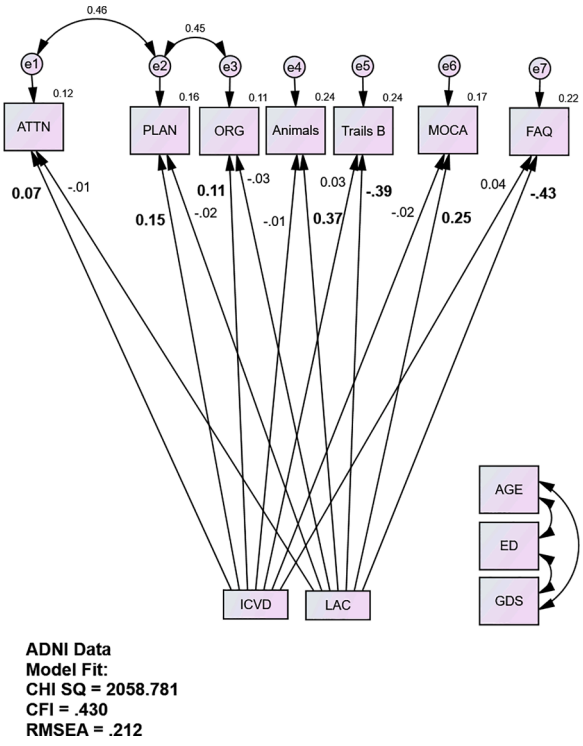

Fig. 1. Multivariate Regressions*.
*Baseline biomarkers are being regressed onto Month 12 observed variables adjusted for covariates. Significant associations are in bold. Nb poor fit indices. ADNI = Alzheimer's Disease Neuroimaging Initiative; Animals = Categorical Fluency (Animals); ATTN = Attention; ED = years of education; FAQ = Functional Abilities Questionnaire; GDS = Geriatric Depression Scale; ICVD = Ischemic Cerebrovascular Disease; LAC = left rostral anterior cingulate; MOCA = Montreal Cognitive Assessment; ORG = Organization; PLAN = Planning; SD = standard deviation; Trails *B* = Trail Making Test Part B.

intelligence's impact on observed cognitive measures is independent of their putative domain-specific designations, and is confirmed here by the model's improved fit relative to Fig. 1, i.e., to an identical set of variables modeled without latent contributions to their variance.

Both imaging biomarkers were independently associated with dEF, but only ICVD was associated with EF (Table 3). The LAC's lack of an association with EF eliminates that domain as a potential mediator of the LAC's unadjusted effects on observed Animals and Trails B (in Fig. 1). The only viable mediation paths for those effects are through dEF (Table 4). Moreover, we note that the LAC had a significant residual direct effect on Trails B but not Animals (Table 2). This suggests that the LAC's significant unadjusted association with Animals in Fig. 1 has been fully attenuated by dEF (Table 3). Both EF and dEF were significant mediators of ICVD's unadjusted associations with PLAN and ORG (Tables 3 and 4). ICVD's significant unadjusted effect on PLAN was partially mediated by the independent effects of dEF and EF. Its effect on ORG was fully attenuated (Table 2).

Finally, EF had no effect on IADL, as measured by the FAQ, independent of dEF's statistically strong association (Table 2). This means that even though ICVD had EF-mediated indirect effects on PLAN and ORG, and an independent direct effect on PLAN, none of those influences on observed cognitive performance were associated with changes in functional status and might thereby be invoked as explanations for ICVD's association with dementia. Only by their effects on δ might either ICVD or LAC atrophy be related to IADL. Thus, none of the domain-specific EF variation in this battery of observed "executive" measures is related to functional outcomes i.e., the disability that defines dementing processes.

Fig. 2 does not model direct effects on the FAQ, independent of dEF.

Table 1
Descriptive statistics.

N = 1737	
	N (%)
AD cases	342 (19.7)
MCI cases	978 (56.3)
NC	417 (24.8)
Gender (♀)	780 (44.9)
	Mean (SD)
Age	73.77 (7.20)
Education	15.91 (2.86)
GDS	1.42 (1.40)
PLAN	1.41 (0.55)
ORG	1.52 (0.62)
Animals	17.15 (5.93)
Trails B (*s*)	122.23 (75.78)
MOCA	23.15 (4.28)
FAQ	4.26 (6.26)
ICVD	1,531,370.581 (166,604.1861)
LAC	0.002 (0.0003)
LPC	0.006 (0.0007)
RLO	0.007 (0.0009)
RIP	0.009 (0.0013)

AD = Alzheimer's Disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; Animals = Animal Naming; FAQ = Functional Abilities Questionnaire; ICVD = Ischemic Cerebrovascular Disease; LAC = left rostral anterior cingulate; LPC = left paracentral; MCI = Mild Cognitive Impairment; MOCA = Montreal Cognitive Assessment; NC = normal controls(RIP = right inferior parietal; RLO = right lateral occipital; SD = standard deviation; Trails *B* = Trail Making Test Part B.
* Scaled scores.

When these were added, neither path was significant and model fit suffered (data not shown). This suggests that LAC's association with the FAQ in Fig. 1 has been fully attenuated by dEF and that the only path from either ICVD or LAC atrophy to IADL impairment would again by through their effects on δ */g*.

The above findings suggest that the only path from LAC atrophy to disability and dementia is through general intelligence. Ancillary Table 1a provides data on alternative structures (RLO, LPC and RIP). In each case, those measures of regional atrophy were related to dEF and through it to all observed cognitive measures and functional status. No non-frontal measure of atrophy was related to EF. ICVD remained a significant predictor of EF, but that construct was shown above to have no association with IADL. So, ICVD's effect on observed executive measures via domain-specific EF is neither disabling nor dementing while the effects of atrophy in non-frontal regions on those same measures is through intelligence and is both disabling and dementing.

In our alternative model using LMI instead of the MOCA, model fit was essentially unchanged [i.e. CHI SQ = 66.39 (16), $p < 0.001$; CFI = 0.987; RMSEA = 0.049]. ICVD and LAC were again significantly associated with dEF, but ICVD lost its formerly significant association with EF (Supplementary Table 1). So, once again, these imaging biomarkers had no paths to IADL except via δ/*g* and their associations with multiple observed executive measures were not significantly mediated through domain-specific executive variance.

5. Discussion

We have found that neuroimaging biomarkers of ICVD and frontal lobe atrophy have few effects on observed executive measures independent of their associations with general intelligence. As intelligence is unlikely to be regionally localized (because it manifests in so many cognitive measures) we were also able to show that atrophy in many non-frontal structures is also related to the observed variation in "executive" measures through intelligence. Moreover, although a latent

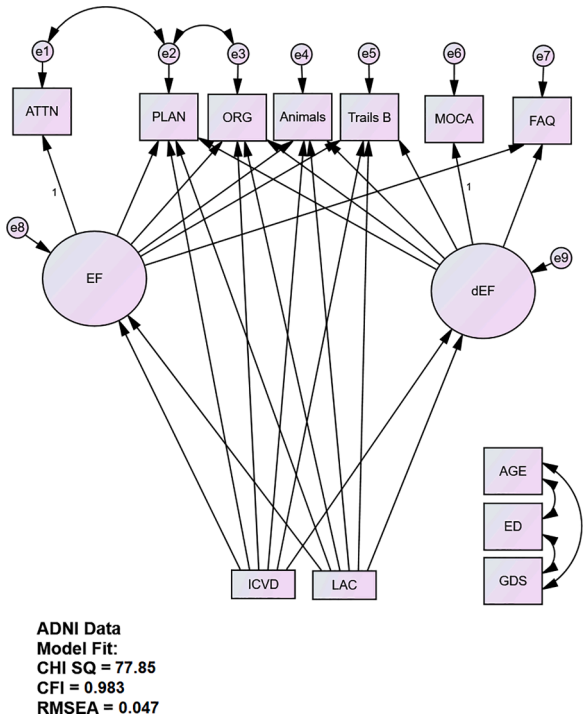

Fig. 2. MIMIC model.
*Baseline biomarkers are again being regressed onto Month 12 observed variables adjusted for covariates. However, the MIMIC approach models both direct and indirect associations mediated through latent constructs (i.e. EF and dEF). Nb improved fit to the identical set of observed measures presented in Fig. 1. Model parameters are presented in Table 2. ADNI = Alzheimer's Disease Neuroimaging Initiative; Animals = Categorical Fluency (Animals); ATTN = Attention; ED = years of education; FAQ = Functional Abilities Questionnaire; GDS = Geriatric Depression Scale; ICVD = Ischemic Cerebrovascular Disease; LAC = left rostral anterior cingulate; MOCA = Montreal Cognitive Assessment; ORG = Organization; PLAN = Planning; SD = standard deviation; Trails *B* = Trail Making Test Part B.

domain-specific EF factor impacts observed executive measures independently of general intelligence, it is not independently associated with IADL and cannot then be invoked to explain the observed associations between executive measures and dementia. The associations between observed executive measures and IADL /dementia are mediated instead by δ. Strengths of our analysis include the relatively large sample, longitudinal data, and the use of latent constructs, which are continuously distributed, improve statistical power and are relatively unbiased compared with dichotomous /categorical clinical diagnoses (for example). These findings suggest that general intelligence, manifesting through "domain-specific" cognitive measures, may be the primary driver of observed associations between various central nervous system (CNS) structural changes and IADL impairment /dementia.

Another strength of this analysis was our use of latent variables (i.e., *g*/δ) to indicate intelligence, as opposed to observed measures. So-called "intelligence tests" or indices created from them, are not derived by factor analysis but are instead chosen because of their relatively strong loadings on intelligence factor scores. This is a convenience that relieves the clinician of having to collect an entire battery of measures. Regardless, like any observed cognitive measure, only a fraction of an intelligence test's variance can be explicitly attributed to that construct. Our SEM approach makes this obvious. The variance in our observed "EF" measures is attributable to δ, to *g*', to EF and to yet other unaccounted influences, via their residuals.

Our analysis had several weaknesses. First, frontal structures have been related to at least three "executive" domains, i.e., inhibiting prepotent responses (inhibiting) shifting mental sets (shifting) and updating working memory (updating) [3,46]. The ADNI battery does not directly assess any of these, although many putative "executive" measures, including Trails B and Animals, are presumed to depend on them. Our *ad hoc* battery of "executive" measures is unlikely to correspond to any one of those primary executive constructs and the resulting factor we labeled "EF" may inadequately account for them.

On the other hand, Friedman et al. [47] have associated the three primary "executive" factors with measures of global cognition. Only one of the three (Updating) was associated with intelligence and it was associated with both fluid and crystalline intelligence. However, that was not by a bifactor model. The executive factors were not orthogonal to each other, likely because *g*'s contribution to their indicators was not explicitly modeled and adjusted for. Instead, the resulting "EF" factors correlated strongly with each other. It should not be surprising then if one claimed *g*'s contribution and was strongly associated with intelligence while the others made little contribution independently of *g*.

Second, the range of ICVD pathology in this sample is limited. ADNI is a convenience sample focused on AD and imposes selection biases against many ICVD-associated presentations. Gavett et al. [19] previously failed to associate ICVD neuropathology with δ in a similarly selected panel of autopsy proven AD cases. ICVD burdens are likely to be reduced in such cases [48]. Regardless, the present analysis adds more specific detail to the cognitive features that mediate the association between ICVD and observed cognitive performance. No MRI-rated ICVD changes have been previously associated with δ homologs, especially in MIMIC models.

Finally, ADNI's regional atrophy measures were not adjusted for their shared variance (i.e. global atrophy). Global atrophy seems much more likely to be associated with *g* /δ than might be any residual regional change. It is associated both with IQ tests in adults [49,50] and with functional status [51]. Had we adjusted our regional biomarkers for global atrophy, a more specific association between the LAC and EF might have emerged while the LAC's statistically weak association with dEF might have been attenuated. However, even if EF replaced dEF as the mediator of the LAC's (global atrophy-adjusted) association with observed executive measures, EF still had no independent impact on IADL, confirming what we have previously reported in another cohort by second δ homolog [52]. That would leave global atrophy-adjusted LAC changes with no clear pathway to dementia.

Similarly, global ratings of ICVD may be more clinically salient [53]. The observation that, regardless of their location, WML impair performance on EF measures is consistent with an impact on *g* /δ and with our finding that regional atrophy impairs performance on EF measures (through dEF) regardless of its location. Measures of global ICVD are already in use clinically, as operationalized in the Fazekas system [54] and others [55]. Our finding replicates Hamilton et al.'s recent analysis of data from the Lothian Birth Cohort 1936. [56] Global ICVD burden predicted prospective change in general intelligence, but had no independent associations with changes in domain-specific measures of processing speed, verbal memory or visuospatial ability. EF was not specifically modeled. Similarly, Gavett et al. [57] have used bifactor CFI to better precise the association between regional atrophy and prospective cognitive performance, including global cognitive change (i.e. Δ*g*). Atrophy in orthogonal global ($\beta = 0.43$) temporolimbic ($\beta = 0.28$) and medial temporal ($\beta = 0.24$) factors contributed independently to variance in Δ*g*. Frontal structures made no independent contribution.

Global ICVD ratings had effects on EF that survived adjustment for dEF and a direct effect on PLAN that survived adjustment for both EF and dEF. Regional assessments of ICVD among structures participating in frontal networks might have had effects on EF that would survive adjustment for dEF, or even direct residual effects on executive measures that survive adjustment from both dEF and EF. Regardless, EF had no association with IADL independent of dEF. So, it seems unlikely that the impact regional frontal system ICVD on EF would be associated with IADL and thereby contribute to dementia.

On the other hand, regional atrophy in the hubs of the default mode

Table 2
Regression weights.

*Dependent		Independent**	Estimate***	SE	CR	p
Structural Associations						
EF	←	ICVD	0.127	0.000	2.276	0.023
dEF	←	ICVD	−0.066	0.000	−2.322	0.020
EF	←	LAC	0.037	0.0633	−0.333	0.527
dEF	←	LAC	0.129	631.890	3.249	0.001
Factor Loadings						
ATTN	←	EF	0.625			
PLAN	←	EF	0.505	0.205	2.803	0.005
ORG	←	EF	0.902	0.339	3.443	<0.001
Animals	←	EF	−0.088	0.366	−3.016	0.003
Trails B	←	EF	0.086	4.955	2.802	0.005
FAQ	←	EF	0.032	0.411	1.156	0.248
PLAN	←	dEF	−0.154	0.004	−5.379	<0.001
ORG	←	dEF	−0.103	0.005	−3.418	<0.001
Animals	←	dEF	0.646	0.041	23.751	<0.001
Trails B	←	dEF	−0.591	0.522	−21.913	<0.001
MOCA	←	dEF	0.870			
FAQ	←	dEF	−0.747	0.052	−25.843	<0.001
Direct Effects						
PLAN	←	ICVD	0.071	0.000	2.050	0.040
ORG	←	ICVD	−0.001	0.000	−0.025	0.980
Animals	←	ICVD	0.038	0.000	1.902	0.057
Trails B	←	ICVD	−0.011	0.000	−0.508	0.612
PLAN	←	LAC	0.029	62.108	0.986	0.324
ORG	←	LAC	−0.015	103.594	−0.349	0.728
Animals	←	LAC	−0.011	648.972	−0.405	0.686
Trails B	←	LAC	−0.064	8767.629	−2.178	0.029
Covariates						
ATTN	←	AGE	−0.070	0.004	−1.996	0.046
PLAN	←	AGE	0.013	0.003	0.391	0.696
ORG	←	AGE	0.026	0.003	0.745	0.456
Animals	←	AGE	−0.178	0.019	−7.816	<0.001
Trails B	←	AGE	0.179	0.247	7.761	<0.001
MOCA	←	AGE	−0.156	0.018	−5.510	<0.001
FAQ	←	AGE	0.089	0.024	3.783	<0.001
ATTN	←	EDUC	0.014	0.009	0.397	0.763
PLAN	←	EDUC	−0.122	0.007	−3.581	<0.001
ORG	←	EDUC	−0.044	0.008	−1.265	0.206
Animals	←	EDUC	0.244	0.048	10.758	<0.001
Trails B	←	EDUC	−0.195	0.622	−8.508	<0.001
MOCA	←	EDUC	0.228	0.046	8.079	<0.001
FAQ	←	EDUC	−0.122	0.059	−5.164	<0.001
ATTN	←	GDS	0.324	0.019	9.305	<0.001
PLAN	←	GDS	0.316	0.013	9.250	<0.001
ORG	←	GDS	0.308	0.015	8.866	<0.001
Animals	←	GDS	−0.110	0.098	−4.824	<0.001
Trails B	←	GDS	0.088	1.268	3.830	<0.001
MOCA	←	GDS	−0.110	0.093	−3.886	<0.001
FAQ	←	GDS	0.117	0.121	4.982	<0.001

AD = Alzheimer's Disease; ADNI= Alzheimer's Disease Neuroimaging Initiative; Animals = Categorical Fluency (Animals); ATTN = Attention; ED = years of education; FAQ = Functional Abilities Questionnaire; GDS = Geriatric Depression Scale; ICVD = Ischemic Cerebrovascular Disease; LAC = left rostral anterior cingulate; MOCA = Montreal Cognitive Assessment; ORG = Organization; PLAN = Planning; SD = standard deviation; Trails *B* = Trail Making Test Part B.
*At Month 12.
**At baseline.
***Standardized parameters.

Table 3
dEF's mediation effects*.

Effect*	z-value*	Mediation (%)
ICVD > PLAN	76.97	4.2
ICVD > ORG	145.39	58.3
ICVD > Animals	N/A	Insignificant Path a
ICVD > Trails B	N/A	Insignificant Path a
LAC > PLAN	N/A	Insignificant Path a
LAC > ORG	N/A	Insignificant Path a
LAC > Animals	12.18	100
LAC > Trails B	−11.07	54.4

*On observed 12 month prospective executive function adjusted for EF's effect and covariates.
**z values > 1.96 are sig at $p \leq 0.05$.

network (DMN) has been associated with δ [58]. The DMN is among the most highly connected of CNS networks [59]. Another highly connected structure is the thalamus, a "strategic" region implicated in VCD [60].

We may have to distinguish intra-network connectivity (i.e. "local efficiency" in graph theory) [61] from a network's contribution to global connectivity (i.e. "global efficiency") to find *g*/δ's specific imaging biomarkers. A graph theory analysis of resting state fMRI data has associated intra-network modularity in specific nodes and between module connectivity with IQ measures [62,63]. While the associations were weak-moderate, the nodes overlapped with those of the DMN. Moreover, even weak influences on the d-score may be clinically significant. We have shown that 5-year prospective clinician ratings of dementia severity to be almost entirely explained by baseline d-scores and the d-score's interval change [12]. Each quintile increase in the d-scores of non-demented controls increases the risk of incident

Table 4
EF's mediation effects*.

Effect*	z-value*	Mediation (%)
ICVD > PLAN	1.96	52.4
ICVD > ORG	2.00	100
ICVD > Animals	N/A	Insignificant Path a
ICVD > Trails B	N/A	Insignificant Path a
LAC > PLAN	N/A	Insignificant Path a
LAC > ORG	N/A	Insignificant Path a
LAC > Animals	N/A	Insignificant Path c
LAC > Trails B	N/A	Insignificant Path c

Animals = Animal Naming; ED = years of education; FAQ = Functional Abilities Questionnaire; GDS = Geriatric Depression Scale; ICVD = Ischemic Cerebrovascular Disease; LAC = left rostral anterior cingulate; ORG = Organization; PLAN = Planning; SD = standard deviation; Trails *B* = Trail Making Test Part B.
*On observed 12 month prospective executive function adjusted for dEF's effect and covariates.
**z values > 1.96 are sig at $p \leq 0.05$.

conversion by 50 %. The quintile-specific risk in cases with MCI is increased nearly threefold [64].

The association between intelligence and the connectivity of specific highly connected nodes may explain the prominence of such structures among the so-called "strategic lesions" of ICVD [65]. Regardless, it remains to be seen how δ itself relates to connectivity measures. Gray matter atrophy (which we have related here to δ) and connectivity have different temporo-spatial trends [66]. The association between regional atrophy and dEF might not be mediated through changes in connectivity.

Apart from strategic lesions, the effects of regional ICVD on cognitive performance may merely distinguish that pathology from disorders affecting other structures and /or cognitive domains. The disease-specific relevance of residual cognitive variance (in δ-adjusted models) is supported by findings from the NACC. In $N = 26{,}606$ NACC participants with a wide range of conditions, δ had a high AUC for the diagnosis of all cause dementia (i.e. 0.96) [11], but it could not distinguish any two diagnostic entities. In contrast, observed patterns of cognitive performance distinguished them [67]. These findings suggest first that impairment of δ is dementia's *essential* clinical feature manifesting across all dementing conditions and second that residual variance in cognitive performance, orthogonal to δ and thus unlikely to be functionally-salient, explains disease-specific cognitive signatures.

Loss of connectivity in the DMN and amyloid-β deposition are both observed in cognitively normal persons and therefore do not provide *apriori* evidence of a dementia presentation [68,69]. Regardless, δ also varies among cognitively normal persons and, as a dementia-specific dimension of cognitive performance, may be responsible for cognitive "reserve" which would explain intelligence's association with that construct [70]. In contrast, disease-specific cognitive signatures would be orthogonal to δ and therefore could not be invoked as explanations for the disablement arising from those conditions nor offer protection against that disablement. Similarly, the biomarkers of disease-specific signatures may not be functionally-salient, and intervention on them may have no impact on functional outcomes [71].

6. Conclusions

To summarize, we have found that observed performance on executive measures is independently determined by multiple sources of variance. The effects of executive function-associated MRI biomarkers can be related to disability and dementia only via their effects on *g* via a *g*-derived δ homolog. Because *g*/δ are unlikely to be located within the frontal lobes or related frontal circuits, the dementia-specific variance in so-called executive measures may have little to do with either frontal structure or function.

Ethics approval and consent to participate

ADNI data collection was approved by each site's respective Institutional Review Boards (IRB). Informed consent was obtained from all participants (or their legally authorized proxies) before data collection. This is a secondary analysis of deidentified data.

Consent for publication

Not applicable.

Ancillary Table 1a
Regression weights for selected non-frontal structures. All are associated with executive measures through dEF.

*Dependent		Independent**	Estimate***	SE	CR	p
Structural Associations (RLO)						
EF	←	ICVD	3.899×10^{-8}	1.612×10^{-8}	2.418	0.016
dEF	←	ICVD	-1.148×10^{-7}	6.762×10^{-8}	−1.698	0.090
EF	←	RLO	28.685	31.032	0.924	0.355
dEF	←	RLO	1141.346	168.037	6.792	<0.001
Model Fit:						
CHI SQ = 124.435 (16) p <0.001(CFI = 0.970(RMSEA = 0.062						
Structural Associations (LPC)						
EF	←	ICVD	3.920×10^{-8}	1.612×10^{-8}	2.431	0.015
dEF	←	ICVD	-1.265×10^{-7}	6.824×10^{-8}	−1.854	0.064
EF	←	LPC	77.255	91.582	0.844	0.399
dEF	←	LPC	2364.155	506.243	4.670	<0.001
Model Fit)						
CHI SQ = 107.184 (16) p <0.001(CFI = 0.975(RMSEA = 0.057						
Structural Associations (RIP)						
EF	←	ICVD	3.403×10^{-8}	1.612×10^{-8}	2.112	0.035
dEF	←	ICVD	-5.335×10^{-8}	6.574×10^{-8}	−0.812	0.417
EF	←	RIP	−22.206	21.632	−1.027	0.305
dEF	←	RIP	1320.087	109.407	12.066	<0.001
Model Fit:						
CHI SQ = 122.794 (16) p <0.001(CFI = 0.971(RMSEA = 0.062						

CFI = comparative fit index; CHI SQ = Chi Square; CR = critical ratio; EF = Executive Function; ICVD = Ischemic Cerebrovascular Disease; LPC = left paracentral; RIP = right inferior parietal; RLO = right lateral occipital; RMSEA = root mean square error of approximation; SE = standard error.
*At Month 12.
**At baseline.
***Standardized parameters.

Availability of data and materials

This is a secondary analysis of deidentified ADNI data. ADNI data are available to qualified investigators in the same manner by which the authors obtained it. Requests for ADNI data should be made to http://adni.loni.usc.edu.

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CRediT authorship contribution statement

Donald R. Royall: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **Raymond F. Palmer:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors have no competing interests to declare.

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Supplementary materials

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