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Interpreting Functional Connectivity in Alzheimer's Disease as Cognitive Processes: Multinomial Processing Trees and the Common Model of Cognition

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Abstract

Cognitive process models and brain connectivity analyses both provide a higher resolution into what cognitive functions are engaged during cognitive tasks than traditional methods. However, the two methods are typically applied in isolation. Our goal is to combine them, and ask which impaired cognitive functions are associated with a specific connectivity signature.

Participants were 1,127 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI), of varying cognitive status at their last included time point: Cognitively Normal = 554, Mild Cognitive Impairment = 386, Alzheimer's Disease = 187. We combine Bayesian multinomial processing tree (MPT) cognitive modelling with resting-state functional connectivity analysis guided by the Common Model of Cognition.

MPT modelling showed that Learned and Delayed Retrieval processes had the largest diagnostic differences ($\eta^2 \approx 0.40$), while Short-term Retrieval was unaffected. MPT parameters were correlated with widespread brain connectivity changes. However, brain connectivity changes were collinear, and mostly attributable to the diagnostic group.

The exception was the Delayed Retrieval process parameter, which was associated with functional connectivity between areas associated with Working Memory and areas associated with Long-Term Memory, even when corrected for all other parameters.

Combining the two analyses allowed us to link a function defined at the neural level to a function defined at the behavioral level. This article describes the potential and current limits of joining the two classes of models.

Introduction

Human cognition can be characterized both by the behavior it produces and by the brain activity that underlies it, two levels of description that research ideally relates to one another (Marr & Poggio, 1976). However, models of cognition and analyses of brain data have been developed within largely separate and specialized frameworks. Cognitive models typically focus on estimating latent mechanisms from behavioral data, while neuroimaging approaches focus on patterns of activity or connectivity in the brain and correlate them with summary behavioral outcomes, which limits their ability to attribute an observed connectivity change to any specific cognitive process.

Joint modeling of behavioral and neural data has developed across cognitive neuroscience as a way to give such links cognitive specificity (Forstmann et al., 2016; Turner et al., 2019; Nunez et al., 2024; Schubert et al., 2019).

These approaches combining cognitive processes to brain processes are particularly valuable in contexts such as clinical research, where heterogeneous neurological disorders are tied to complex and dynamic neurological origins and behavioral consequences. By disentangling and mapping these

components, integrated modeling approaches can help explain individual differences in cognitive functioning and support a more precise understanding of complex cognitive impairments.

Cognitive process models can be used to disentangle and measure specific underlying aspects of cognition (Forstmann et al., 2016). The aim of these cognitive process models is to decompose observable behavior into latent mechanisms, the underlying cognitive processes, which give rise to task performance. Specifically, within the memory literature, multinomial processing tree models (MPT) have been used to disentangle memory task performance into various encoding and retrieval processes (Batchelder & Riefer, 1990, 1999; Riefer et al., 2002; Schmidt, Erdfelder, & Heck, 2022). By isolating specific cognitive processes, MPT models yield behavioral descriptions which are well-suited for the integration with neural data, but on their own they do not specify how these processes would be implemented in the brain.

To relate cognitive process estimates to neural systems, a theoretical framework is required which specifies how cognitive functions are organized and interact. The Common Model of Cognition (CMC) provides such a framework (Laird, Lebiere, & Rosenbloom, 2017) by proposing a domain-independent cognitive architecture consisting of interacting functional modules, including Perception, Working Memory, Long-Term Memory, Procedural Memory, and Motor Systems. When applied as an architecture, the CMC allows formalizing cognitive processing in terms of information flow between these modules, thereby generating explicit hypotheses about functional interactions underlying cognition. The CMC thereby functions as a bridge between the latent cognitive processes extracted from MPT models and brain data. Its modules and pathways defined by the CMC can be mapped onto interacting brain systems, which enables the theory-driven interpretation of neural connectivity patterns.

Functional connectivity analyses provide an empirical way of examining the interactions between brain systems proposed by cognitive architectures such as the CMC. By quantifying the statistical dependencies between activity time-series of different brain regions, functional connectivity captures patterns of processing which can reflect the information exchange between cognitive modules. Previous work has linked the CMC to neuroimaging data using approaches such as Dynamic Causal Modeling and Granger causality (Stocco et al., 2021; Hake et al., 2022), providing evidence that its theoretically-driven structure aligns with observed neural interactions. When combined with cognitive models, like the MPT models, functional connectivity analyses potentially allow us to examine how connectivity between CMC-related regions varies as a function of the underlying cognitive processes extracted through the latent variables.

Alzheimer's disease (AD) provides a particularly suitable application for the proposed framework. AD is characterized by a heterogeneous set of cognitive impairments and widespread alterations in brain connectivity. Deficits in memory and learning are some of the most well-described cognitive results of the disease, disrupting encoding, consolidation, and retrieval. At the neural level, AD is associated with distributed, mostly disruptive changes in brain connectivity which can explain the cognitive effects (Badhwar et al., 2017; Brier et al., 2014; Buckner et al., 2009; Greicius et al., 2004). Yet, an overarching

framework linking the affected latent processes underlying behavior to specific affected pathways, therefore characterizing different causes and effects in AD, has not been established. This combination of behavioral heterogeneity, strong alterations in brain connectivity, and the need for a better understanding of disease progression in AD makes it a suitable and demanding test case for evaluating our proposed framework.

We combine multinomial processing tree (MPT) modeling of the verbal learning test, which estimates these processes and allows the others to be controlled, with resting-state functional connectivity analysis structured by the Common Model of Cognition, which groups brain regions into cognitive modules, and ask which cognitive processes are associated with connectivity changes specific to them; we apply this to Alzheimer's disease.

Methods

Alzheimer’s Disease Neuroimaging Initiative (ADNI)

Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI 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 Alzheimer’s disease (AD). For up-to-date information, see www.adni-info.org.

The data used in this article was downloaded from the ADNI database in October of 2024. Participants are between 55 and 90 years of age, and are grouped into Normal, MCI, and AD subjects. Inclusion in subgroups is based on MMSE scores. Specifically, this indicates that the diagnosis was not based on the verbal learning test and MRI data, but rather on MMSE scores.

Task-free fMRI data

For a subset of participants in ADNI, 10-minute-long task-free fMRI scans using a variety of 3T MRI scanners were acquired. Participants were asked to lie down in an MRI scanner with their eyes being kept open. A further subset utilized ADNI’s advanced protocol, which generally uses a Repetition Time of 600 ms and has generally higher spatial resolutions, although specifics depend on the scanner. The

number of sessions per participant varies from 1 to 13, with healthy controls only having one session and patients having one or more sessions, distributed over a different number of years.

After standard quality control procedures, scans from 1,136 participants were retained for analysis. The sample included 581 cognitively normal participants (mean = 2.16 sessions each, range = 1–9), 371 participants with Mild Cognitive Impairment (mean = 2.4 sessions each, range = 1–10), and 184 participants diagnosed with Alzheimer's Disease (mean = 1.97 sessions each, range = 1–7).

The raw, unpreprocessed functional and anatomical data was converted to the Brain Imaging Data Structure (BIDS) format (Gorgolewski et al., 2016) using Clinica (Routier et al., 2021; Samper-González et al., 2018). They were preprocessed and denoised using the default CONN preprocessing and denoising pipelines (Nieto-Castanon, 2020), including realignment and unwarping, slice-timing correction, outlier detection using ART, normalization to MNI space using SPM unified segmentation, resampling to 2mm isotropic voxels, and spatial smoothing with an 8mm FWHM Gaussian kernel. Denoising was performed including regression of white matter and cerebrospinal fluid noise components, motion parameters and their derivatives, outlier scans, session effects, and linear trends. Residual BOLD time series were band-pass filtered between 0.01 and 0.1 Hz.

Verbal learning test data

As part of the ADNI dataset, a verbal learning test was given to participants in a larger ADAS-cog test battery. This test consisted of 3 immediate trials of 10 words, presented sequentially in differing orders across trials, but in the same orders between participants. In each trial, the participant was asked to recall as many words as possible. Two different tasks followed, after which a delayed trial was given without the words presented, where the participant had to recall as many words of the earlier list as possible. Each assessment and diagnosis was paired, as they were conducted within a few months of each other.

The data initially included 1908 participants, spanning 7733 total assessments. We removed incomplete data and only used participants with fMRI data available, leaving 1127 individuals, spanning 3976 assessments. Finally, while the data is longitudinal, we only used the assessment data from individuals on their furthest disease progression diagnosis, so if an individual has 3 assessments while cognitively normal and 2 while having Alzheimer's, we will only use the Alzheimer's data points. Note that we used only the furthest disease progression for which fMRI data was available, as there was less fMRI data than task data available, and then removed data from other disease stages for that person. Filtering the data in this way leaves us with 1127 individuals, spanning 3976 assessments. For the specific demographic information, consult Table 1 below.

Table 1
Demographic information on CN, MCI, and AD individuals.

N	**Cognitively Normal**	**Mild Cognitive Impairment**	**Alzheimer's Disease**
	554	**386**	**187**
Number of Sessions Total	1953	1540	483
Mean follow-up age (years)* mean ± SD range	74.39 ± 7.22 50.58–95.66	74.79 ± 8.09 55.58–97.33	76.52 ± 8.07 55.5-95.92
Education, mean ± SD, y	16.69 ± 2.44	16.12 ± 2.85	15.62 ± 2.61
% Female	59.03%	45.34%	43.32%

*The mean age across this diagnosis' included assessments

Multinomial Processing Tree structure

The model we used is based on an application of a multinomial processing tree model to the verbal learning test (VLT) paradigm (Alexander et al. 2016), restructured to estimate process scores per individual rather than item position effects (Potthoff et al., 2023; Fig. 1). The model aims to separate cognitive processes contributing to VLT performance into three retrieval processes (namely: short-term retrieval, learned retrieval, delayed retrieval) and four learning-related processes (namely: one-shot learning, partial learning, consolidation, and testing effect). The model script in its entirety is available on the project's OSF page at https://osf.io/3v6ek.

Functional connectivity analyses using the Common Model of Cognition

While previous research has mapped the CMC onto the brain using directed methods such as Dynamic Causal Modeling and Granger causality (Stocco et al., 2021; Hake et al., 2022), reliably specifying those directed pathways requires a level of fidelity that, given the diverse population tested, cannot be assumed here. We therefore measured undirected functional connectivity over the same CMC-defined modules, using the CONN toolbox for Matlab at the cluster level, with clusters defined as groups of brain regions assigned to theoretically derived modules of the Common Model of Cognition (CMC). Brain regions were identified using the Harvard-Oxford parcellation provided in CONN, with selected regions subsequently grouped into CMC modules based on previous findings (Hake et al., 2022; Steine-Hanson et al., 2018; see Appendix for details). Grouping regions into CMC modules, rather than into an

atheoretical functional atlas, labels the connectivity nodes by cognitive function, so that connectivity can be interpreted in the same terms as the MPT process parameters.

Some of the established five CMC modules were subdivided into multiple clusters to reflect distinct subprocesses per module. For example, Working Memory was separated into frontal and parietal clusters, and Perception was divided into auditory, tactile, and primary, as well as secondary visual (V1/V2) clusters. In addition, the hippocampus was included as a dedicated episodic memory cluster, consistent with prior literature highlighting its importance in Alzheimer's disease and proposing its addition to the CMC. Procedural Memory, Long-Term Memory, and Motor Areas were each modeled as single clusters. The final model can be seen in Fig. 2.

Connectivity was tested between all possible pairs of connections and clusters using Fisher-transformed bivariate correlations, implemented in the CONN general linear model framework (Whitfield-Gabrieli & Nieto-Castanon, 2012). While the CMC posits specific and directional pathways, which can be formally assessed using methods such as Dynamic Causal Modeling (DCM), functional connectivity is inherently undirected. It only indicates whether two clusters are statistically related, without implying direct anatomical connections or directionality, as observed relationships may be mediated by intermediate regions or pathways (Reid et al., 2019).

For statistical inference, a connection-level threshold of $p < 0.05$ (uncorrected) was applied. At the cluster level, results were tested using an MVPA omnibus test with false discovery rate (FDR) correction ($p < 0.05$), thereby controlling for multiple testing (Benjamini & Hochberg, 1995).

Combined analysis using Partial Least Squares regression

When combining the MPT estimated cognitive processes to functional connectivity analysis, we use the mean estimate for each process per individual. Since we do not use the full range of the posterior distribution in modeling (cf. Potthoff et al, 2026a), we should carefully interpret findings for non-retrieval parameters (Potthoff et al., 2026b).

For each of the MPT parameters, we integrated the parameter values into the functional connectivity analyses as predictors of changes in brain connectivity. In this framework, parameter scores were used to model stronger or weaker connections between regions or clusters as a function of individual differences.

Beyond testing the raw effect of each parameter, we additionally constructed models with covariates to evaluate the unique contribution of each parameter. Specifically, we controlled for: 1. The other MPT parameters; 2. Original test results (immediate and delayed summary scores for each participant); and 3. Diagnostic group (CN, MCI, AD). This approach allowed us to assess whether the parameters explained connectivity changes beyond related behavioral or clinical measures, and to clarify which latent concepts they may load onto.

To further investigate the validity and structure of the MPT parameters, we conducted Partial Least Squares (PLS) regression using the plsregress function in Matlab R2024b, asking whether the parameters correspond to separable processes or to a single shared factor. PLS extracts latent variables, which are the weighted combinations of the MPT parameters covarying with the connectivity data. Each parameter's loading is the weight it receives. We further report Variable Importance in Projection (VIP) scores to identify which parameters contributed meaningfully to the prediction.

Results

Diagnostic Group Differences in Verbal Learning and MPT Parameters

Verbal learning task performance declined with disease progression, as expected (Fig. 3). These findings are confirmed by linear mixed-effects models, which we show in Supplement S1.

ANOVA tests on the posterior samples for estimated cognitive process scores showed strong evidence for group differences in five parameters (significant in ≥ 95% of samples): Learned retrieval ($\eta^2 = 0.40$ [0.37, 0.43]) and delayed retrieval ($\eta^2 = 0.40$ [0.36, 0.43]) had the largest effects, with other significant effects found in partial learning ($\eta^2 = 0.02$ [0.01, 0.04]), consolidation learning ($\eta^2 = 0.03$ [0.01, 0.05]) and one-shot learning ($\eta^2 = 0.05$ [0.03, 0.08]). Testing effect showed weak evidence of group differences ($\eta^2 = 0.01$ [0.00, 0.02], 84.1% of samples), while short-term retrieval showed no evidence ($\eta^2 = 0.002$ [0.000, 0.008], 15% of samples). There was a consistent pattern of Normal > MCI > AD performance. The MPT findings are visualized in Fig. 4, and further explained in Supplement 2 with paired t-tests.

Functional Connectivity Across Subjects and Diagnoses

Functional connectivity analyses revealed synchronized activity between all CMC clusters. Changes in functional connectivity across diagnostic groups were in line with previous studies. AD patients showed mostly weaker connectivity across networks compared to CN, with few connections being stronger. Further, the disease progression from CN via MCI to AD was in line with expectations, with MCI showing a mix of stronger and weaker connectivity compared to CN, while AD exclusively showed weaker connectivity compared to MCI.

Effect of Cognitive Process Parameters on Functional Connectivity

We examined the relationship between MPT-derived parameters and functional connectivity. The analyses primarily focused on identifying connectivity changes associated with each parameter, and explored whether these effects align with pathways proposed in the CMC. For each parameter, the effect on the functional connectivity was tested: (1) as raw, uncontrolled effect, (2) controlled for the other

respective parameters (3) when controlling for clinical diagnosis, and (4), when controlling for test performance.

Six of the parameters showed strong changes in connectivity patterns, with higher parameter scores being linked to both systematic increases and decreases in pathway connection strengths, as shown in Fig. 5. These connectivity changes were visibly correlated with one another, mirroring the correlations amongst the original parameters themselves. Correcting for the other parameters, only one connectivity change remained significant, being associated with the parameter Delayed Word Retrieval (Fig. 6 (1)). This reflects both an increase of connectivity strength between frontal Working Memory and Long-Term Memory areas, as well as weakened within-Working Memory connectivity. Overall, the six parameters showed strong overlap in their connectivity effects.

After controlling for diagnosis, the majority of significant effects for all parameters disappeared. The two exceptions were the Testing Effect, Fig. 6 (2), where multiple connections remained significantly correlated with the parameter, even when the diagnosis was accounted for, and the within-Procedural Memory connectivity of Learned Word Retrieval. The connections remaining for Testing Effect were:

Working Memory - Episodic Memory

Working Memory - Visual Perception

Within-Perception connectivity across different modalities

Within-Procedural memory connectivity

Finally, when controlling for the original test results as covariates, only one of the connectivity changes remained significant, again linked to the Testing Effect (Fig. 6 (3)).This indicates that the majority of observed effects can be explained equally well by the pure performance of participants on the original test. The exception is the connection between Parietal Working Memory and Secondary Visual Perception areas, strongly increasing with a higher value of the Testing Effect parameter.

The only parameter showing no significant relation to brain connectivity in any of the tests was Short-Term Retrieval. Even where similar tendencies in connectivity were visible, any underlying effects on connectivity were too weak to pass the significance threshold.

PLS Multicollinearity Test

The previous results indicate high multicollinearity among the parameters. This suggests that the parameters capture overlapping aspects of variability in brain connectivity. Two main possibilities arise: The parameters might capture distinct neural processes or networks in the brain, with each of them loading on multiple of them, or they share one, singular, underlying mechanism. To address this question, a Partial Least Squares Regression (PLS) was employed. This makes it possible to identify latent variables which explain the variance in brain network connectivity based on the parameter values derived

from the MPT model. Each latent variable should, in principle, reflect one distinct process, and PLS determines both its impact on brain connectivity variance, as well as the individual load of each parameter on it.

Given the inherently noisy nature of brain data, the overall proportion of variance explained was relatively low. The first latent variable accounted for approximately 0.5% of the variance in brain connectivity, with the contribution of the remaining latent variables strongly leveling off (Fig. 7 (1)). This suggests that the explanatory power is concentrated in a single latent variable, with the remaining components likely capturing noise.

Further, the contribution of individual parameters to this primary latent variable was examined, with the same six parameters previously identified as exhibiting similar patterns in functional connectivity loading strongly onto it (Fig. 7 (2)). A Variable Importance in Projection (VIP) test determined three of the seven parameters to be important for explaining the variance in brain connectivity data: Learned Word Retrieval, Delayed Word Retrieval, and Testing Effect (Fig. 7 (3)). These are the same three showing the strongest effect on functional connectivity, as well as showing any patterns when corrections for test results, diagnosis, or other parameters are made.

The presence of one relatively strong latent variable, combined with the consistent loading of all parameters except Short Term Retrieval suggests that the relationship between the MPT model parameters and brain connectivity may be largely mediated by diagnostic group membership.

Discussion

Both our multinomial processing tree analysis and functional connectivity showed differences between diagnostic groups. When combining the two approaches, however, we were unable to reliably map the specific cognitive changes suggested by the model to individual connections of the functional connectivity map. Instead, across the combined analysis, most cognitive processes were associated with collinear connectivity changes that were largely attributable to diagnostic group; only delayed retrieval remained associated with a specific connectivity change after the other processes were controlled, an increase in connectivity between regions of the Working Memory and Long-Term Memory modules.

The contribution of this study is methodological: it links process-level cognitive modeling to functional connectivity through a cognitive architecture, so that connectivity changes can be interpreted in terms of specific cognitive processes. This combined approach let us evaluate how specific cognitive processes relate to resting-state neural connectivity.

Consistent with expectations, we found progressively lower task performance from CN to MCI and AD patients, which our MPT models specified as large deficits to learned and delayed retrieval, as well as smaller deficits to learning processes (one-shot learning, partial learning, and consolidation).These findings align with earlier applications of the MPT model (Lee et al., 2020; Bock et al., 2021). Likewise,

the functional connectivity analyses showed strong alterations across the three diagnostic groups (CN, MCI, and AD), reflecting progressive disruptions of the networks. Both the mixed patterns of hyper- and hypoconnectivity in MCI compared to CN, as well as the strong development of hypoconnectivity in AD, are in line with previous findings (Badhwar et al., 2017).

We combined the analyses to investigate whether the cognitive processes isolated with the MPT model explained connectivity changes between brain regions. The results indicate that the cognitive processes assessed are closely linked to widespread and strong alterations in large-scale brain connectivity, with all but one MPT parameter showing robust associations with functional connectivity patterns. The results also showed that the diagnostic group accounted for the majority of the variance in connectivity changes, which suggests that the disease stage and its associated effects on brain connectivity are the main aspect captured by the model. This interpretation is further supported by the PLS analysis, showing that all six relevant parameters loaded strongly onto a single latent variable, indicating that they largely reflect a shared, underlying dimension, rather than distinct processes. Additionally, the MPT parameters provided little additional explanatory power beyond the clinical test results the MPT is fitted on, implying that the disruptions can mostly be captured by the assessment itself.

Two notable exceptions to this pattern emerged, illustrating how the framework can be used to distinguish between shared and parameter-specific effects.

First, Delayed Word Retrieval exhibited unique associations with functional connectivity, which persisted even after controlling for all other MPT parameters. Better delayed retrieval performance was linked to strengthened connectivity between frontal areas of Working Memory and Long-Term Memory, as well as weakened connectivity within frontal Working memory regions themselves. Theoretically, this might reflect the capacity to retrieve declarative memories from storage into Working Memory, as the second functions as a hub in the Common Model of Cognition. This process might be captured in the different modalities of task-free fMRI and memory tasks, as it might be both involved in explicit task-related retrievals, as well as retrieval related to intrinsic processing, such as spontaneous thought. Although Delayed Word Retrieval was not indicated as a distinct, relevant latent factor in the PLS analysis, it nevertheless displayed the strongest loading on the shared primary latent factor, suggesting that it may capture a subtly different cognitive mechanism than the other parameters, which would be reflected in its unique neural signature.

Second, the Testing Effect showed multiple associations with brain connectivity, even when controlled for the clinical diagnosis and overall test performance of subjects. However, these associations were fully accounted for by the remaining MPT parameters, raising uncertainty regarding their interpretability. Rather than reflecting a distinct cognitive mechanism, these effects may capture shared variance represented at the model level beyond diagnosis.

Consistent with this interpretation, the PLS analysis did not support a strong, independent latent variable corresponding to this parameter. As such, this finding shows the framework's capacity to identify

whether apparent parameter-specific associations are better explained by shared structure across cognitive processes.

Our findings directly address limitations identified in previous research where brain connectivity changes have been examined primarily in relation to neuropsychological summary scores, such as the ADAS (Lin et al., 2018), rather than specific cognitive processes. Our MPT decomposition validates concerns raised about traditional neuropsychological assessment (Weintraub et al., 2012) while supporting arguments that sum scores obscure important distinctions between cognitive processes (Rouder & Mehrvarz, 2024). In an independent cohort, a multinomial processing tree model of a recognition memory task likewise outperformed traditional summary scores in detecting amyloid and tau pathology in older adults without cognitive decline (Vanderlip et al., 2024).

Properly interpreting functional connectivity changes in relation to cognitive processes remains a significant challenge. While we demonstrate that MPT parameters, in some cases, correspond to specific connectivity patterns, these findings are limited by high collinearity between the parameters, and resting-state connectivity is itself low-dimensional, which may bound how separable the parameters' signatures can be (Marrelec et al., 2016). The Common Model of Cognition contributes here by labelling the connectivity nodes in cognitive terms, letting behavioral and neural measures be read in a shared vocabulary; because functional connectivity is undirected and was tested across all module pairs, however, the analysis does not test the architecture's directional pathways, and these results should be read as cognitively-labelled associations rather than confirmation of those pathways. Because a single joint model of cognitive and connectivity data is difficult to specify and estimate in a sample this large and heterogeneous, we related posterior parameter means to connectivity in a two-stage analysis, which necessarily loses some sensitivity (Ghaderi-Kangavari et al., 2023). The mechanistic relationships between specific cognitive processes and brain network changes require further theoretical development.

While the data for both the MPT model, as well as the brain data, were acquired from participants during the same sessions, fMRI data was not taken during the performance of the task, but instead during a task-free part. While this minimizes confounds which would occur with the task engagement and movement of dementia patients, it does mean that changes detected between groups in the connectivity data might be related to different cognitive processing than would be the case related to the task. Because the Common Model of Cognition is intended as a domain-general architecture (Stocco et al., 2021; Hake et al., 2022), it may generalize across task domains, although the specific connections involved can differ. Therefore, no 1–1 mapping of involved regions can be assumed.

Our approach of only using furthest disease progression in each individual, despite using longitudinal data, limits our understanding of how cognitive processes and brain connectivity correlate over disease progression. Future studies should examine within-individual changes in both cognitive parameters and connectivity patterns to better understand causal relationships. Similarly, extending our approach to

additional cognitive domains and neuropsychological tests would validate the generalizability of this combined method.

The integration of process-level cognitive modeling with other neuroimaging approaches, such as structural MRI or task-based fMRI, could provide evidence for the brain-behavior relationships identified through resting-state connectivity. Additionally, investigating whether similar process-level advantages emerge in other neurodegenerative conditions would help establish the broader utility of this approach.

Cognitive process modeling and functional connectivity analysis together show which cognitive processes have a connectivity signature specific to them and which reflect variance shared across processes and tied to disease stage, clarifying both the potential and the current limits of joining these two classes of models.

Declarations

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Ethics Approval

This study used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI protocols were approved by all the Institutional Review Boards of the participating institutions. Only data from volunteers who had provided written informed consent were used to complete these analyses.

Consent to Participate

Written informed consent was obtained from all individual participants (or their authorized representatives) at the respective ADNI clinical sites prior to their enrolment in the study. The authors did not have contact with participants and accessed only de-identified data.

Consent to Publish

This article does not contain any individual person's identifiable data in any form. Consent for publication of the de-identified data was obtained by ADNI as part of the original informed consent procedure at the participating clinical sites.

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Author Contribution

All authors contributed to the conceptualization of this manuscript. S.S. and R.P. prepared the manuscript and data analysis. S.S oversaw functional connectivity analysis. R. P. oversaw cognitive modelling analysis. All authors reviewed and approved the final manuscript.

Data Availability

The datasets analyzed during the current study are available on the Alzheimer's Disease Neuroimaging Initiative website at https://adni.loni.usc.edu/data-samples/adni-data/. The data used in this analysis was downloaded on the 21st of November 2024.

Code availability

The cognitive model and script to analyze the cognitive model outcomes are both available publicly on the OSF at https://osf.io/3v6ek. Further analyses are available upon reasonable request.

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Figures

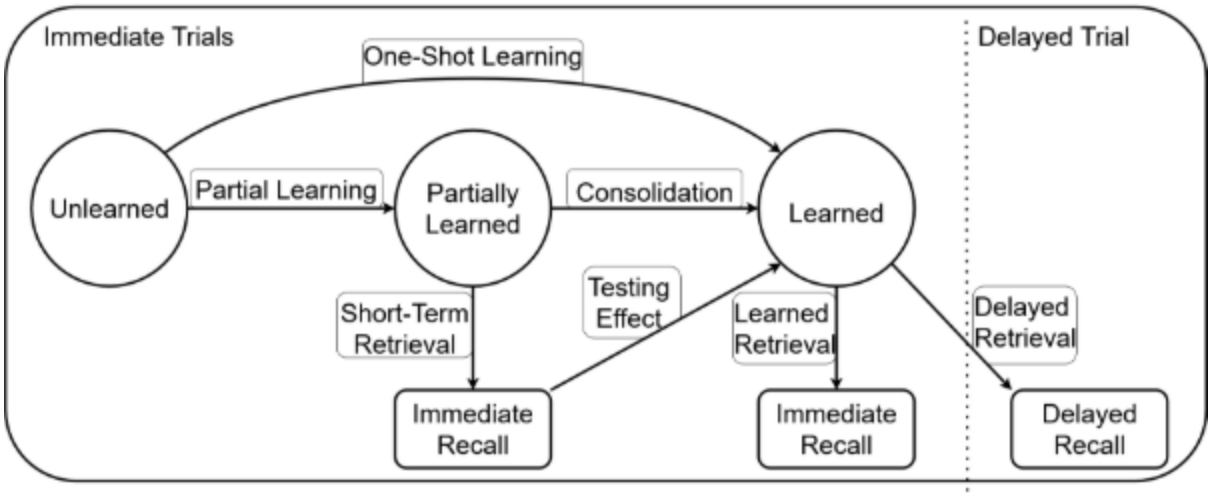


Figure 1

MPT model schematic, based on the work by Alexander et al. (2016). Each circle represents a state in which a word can be, and all words start in the unlearned state. After each trial, the learning processes can move a word between states, and the retrieval processes can attempt to retrieve the word.

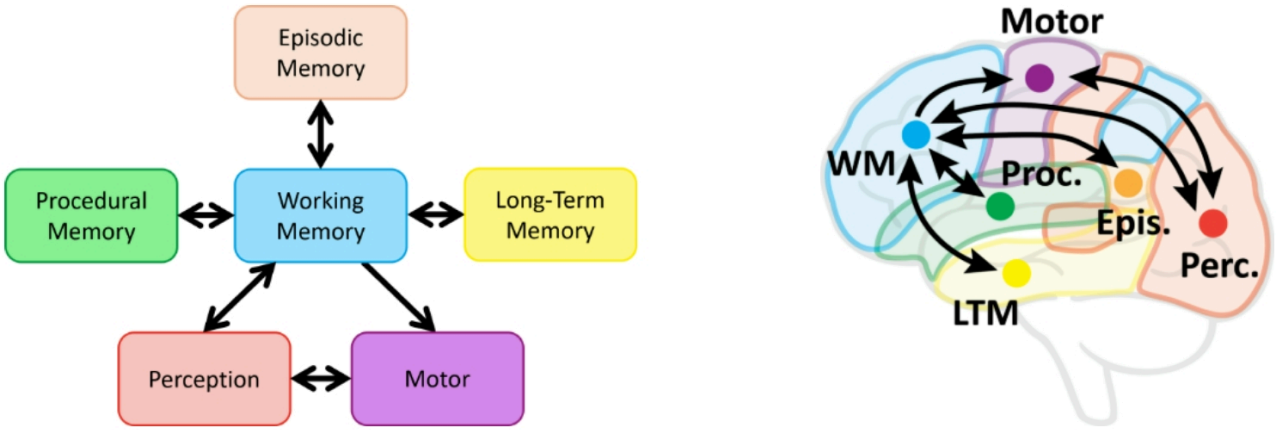


Figure 2

The Common Model of Cognition (CMC), extended with a dedicated Episodic Memory module located in the Hippocampus. The CMC is used to define the connectivity clusters. Arrows indicate the pathways proposed by the architecture. Region-to-module assignments are listed in Appendix A2.

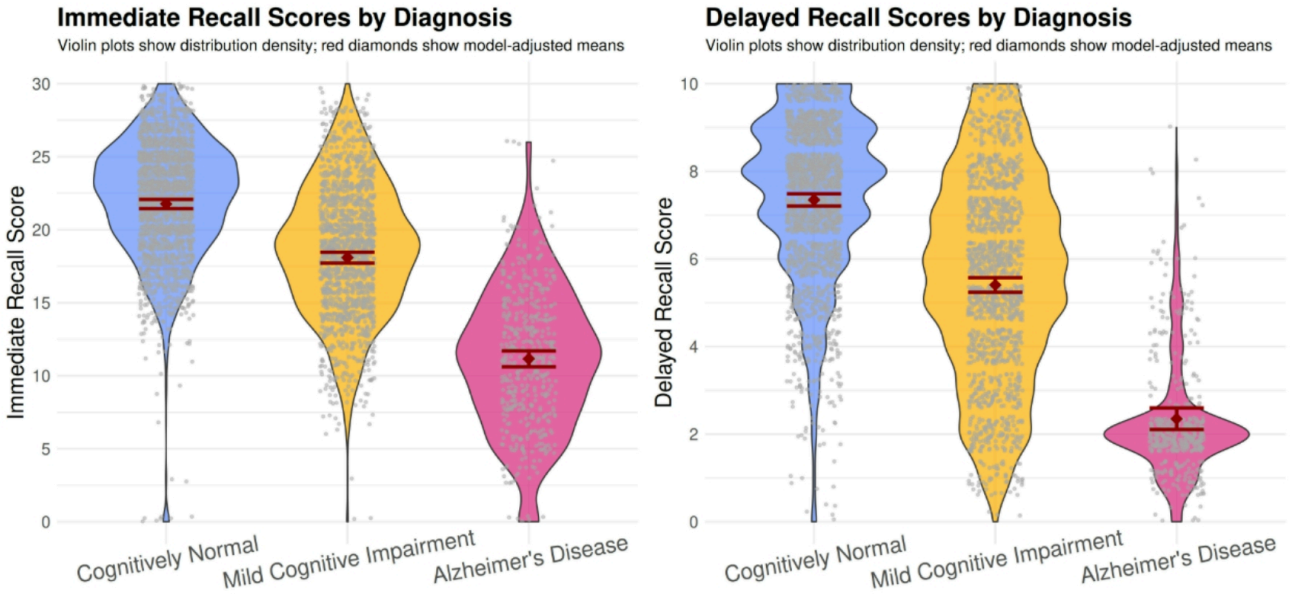


Figure 3

Violin plot showing the distribution of sum scores per diagnosis per assessment on the delayed verbal learning trial. As a majority of individuals had repeated measures taken, we also show a linear mixed effects model mean estimate, which corrects for these repeated measures.

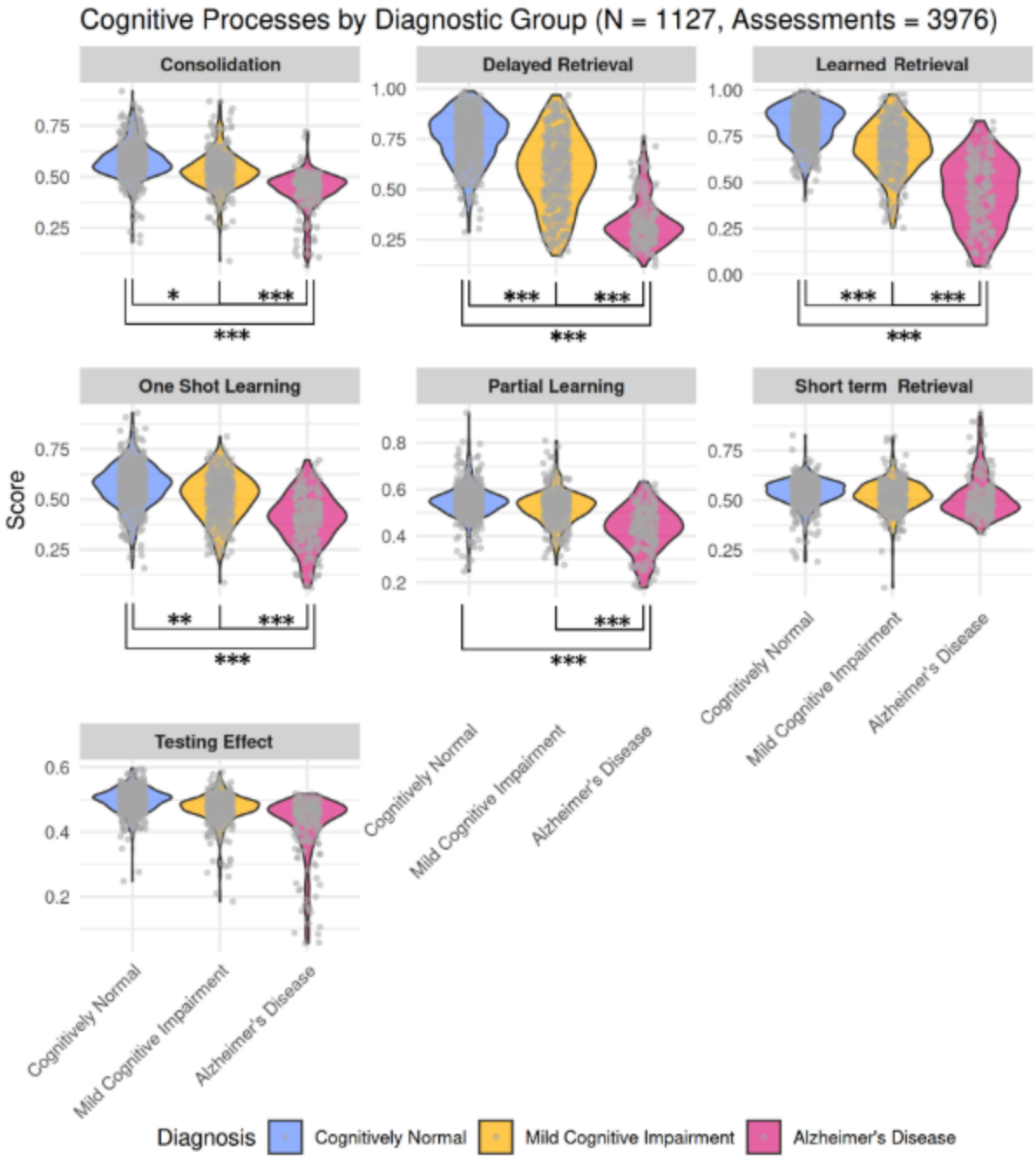


Figure 4

Violin plots showing mean distributions of cognitive process estimations for cognitively normal, mild cognitive impairment and Alzheimer groups, based on their first diagnosis. ** Indicates Benjamini-Hochberg corrected p-values of <.01, *** indicates Benjamini-Hochberg corrected p-values of <.001.

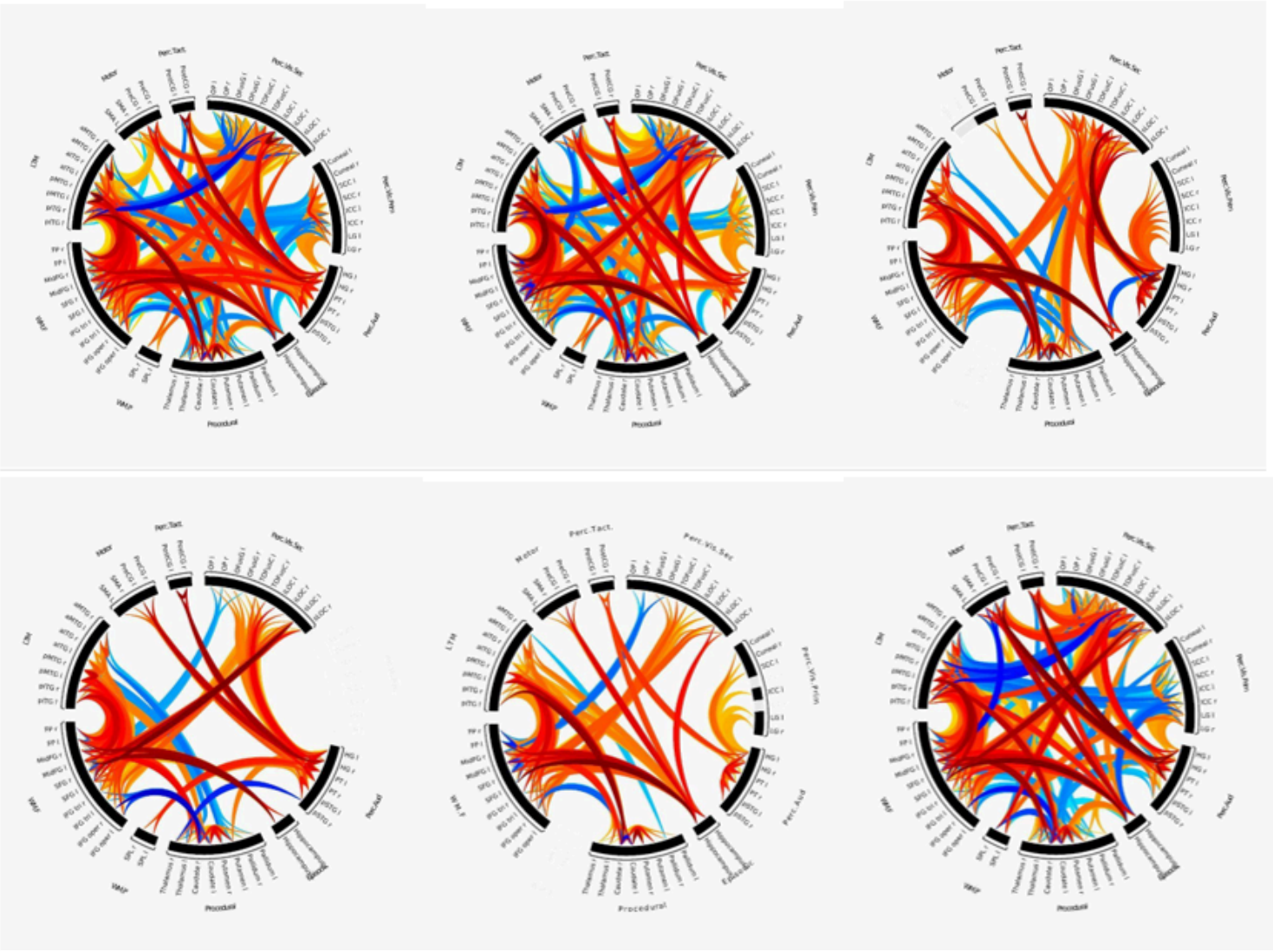


Figure 5

Effect of Parameters on Functional Connectivity. Order from left top to right bottom: Learned Word Retrieval, Delayed Word Retrieval, Partial Learning, One Shot Learning, Consolidation Learning, Testing Effect.



Figure 6

MPT Parameter Effects controlled for Covariates. Left to right: (1) Delayed Word Retrieval - Functional Connectivity when corrected for other MPT parameters. (2) Testing Effect - Functional Connectivity when corrected for clinical diagnosis. (3) Testing Effect - Functional Connectivity when corrected for test results.

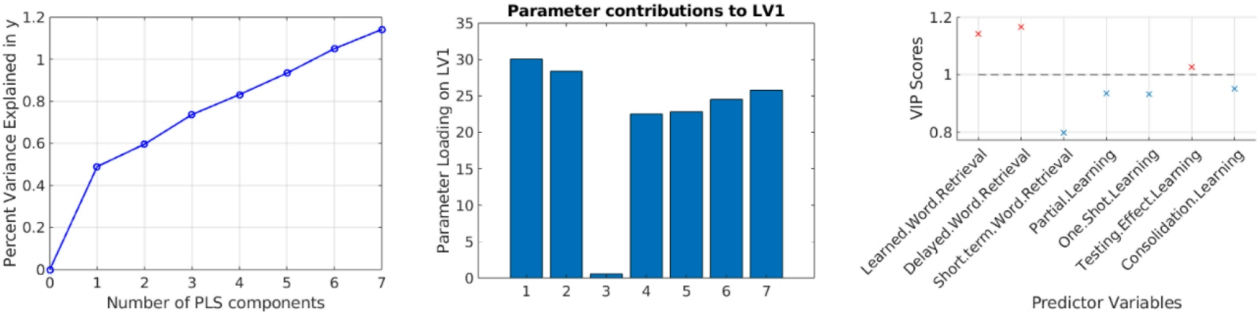


Figure 7

PLS Results for MPT Parameters. Left to right: (1) Explained Variance in Brain Data per extracted component. (2) Load of each MPT parameter on the first Latent Variable. (3) Predictor Importance test for all MPT parameters.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 20260909RubenSnkeTwoModelApproachSupplement.docx