



Integrity of Memory Networks in the Alzheimer’s Disease Continuum

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Background

Memory, the earliest affected cognitive function in Alzheimer’s Disease (AD), has been fractionated into more granular processes and networks. This has shed light on the limited sensitivity of traditional assessments relative to recent theory-driven tests in preclinical AD, such as those assessing conjunctive and associative memory. Didic et al. (2011) proposed that Medial Temporal Lobe (MTL) networks underpinning such functions, namely the Anterior (ANT) and Posterior (PTN) networks, respectively, show AD pathology at different stages of its continuum (i.e., ANT affected earlier). We tested this hypothesis.

Methods

The GERO (Forno et al., 2021), Cognitive Reserve (Parra et al., 2024), and AD Neuroimaging Cohort (Cecchini et al., 2021) contributed data which were grouped into Cognitively Unimpaired Controls (CUC: n=87, age: M=70.17± 6.16), Prodromal (Subjective and Objective Cognitive Decline; n= 177, age: M=75.56± 4.97), and AD Clinical Syndrome (ADCS: n= 47, age: M=75.60±7.87) (N=311; 69% female) (see Table 2). Volumetric measures (FreeSurfer 8.0.0) were harmonised using Neuro-ComBat (Fortin et al. 2018) and used to extract regions of the ANT and PTN networks within and outside the MTL (see operational framework below). We used a linear mixed-effects model (LMEM) with fixed effects of group, network, medial temporal location, and their interactions, and random intercepts for participant and brain region, with regions modelled as nested within networks to account for the hierarchical structure of the data.

Table 1. Operational framework used to allocate regions to the ANT and PTN networks within and outside the MTL.

Framework Pillar	Operational question	Implication for network allocation	Predicted earliest memory consequence
1. Neuropathological staging of AD	Does the region relate to the anterior sub-hippocampal territory affected during the trans-entorhinal sub-hippocampal stage, or to the hippocampal territory affected later?	Regions connecting to anterior MTL circuitry (perirhinal/entorhinal) should be prioritised as candidate early nodes; hippocampal and posterior medial regions may reflect subsequent propagation or downstream disconnection.	Early disruption of object-based, context-light memory may precede clear deficits in context-rich episodic recollection.
2. Information-processing bias	Does the region preferentially process objects, entities and item features, or scenes, spatial context and relations?	Ventral-stream and anterior-temporal linked regions are weighted toward the anterior MTL network; dorsal-stream and posterior-medial linked regions are weighted toward the posterior MTL network.	Object recognition, familiarity, item-based associative processing, or object-in-context integration may be affected before full episodic-spatial impairment.
3. Challenge to hippocampocentrism	Is a deficit likely to arise from compromised pre-hippocampal cortical binding computations linked to integrative functions (i.e., unitization) rather than from hippocampal binding per se (i.e., relational representation subserving associative episodic (working) memory)?	Regions may be considered functionally integral to memory networks even if they are not hippocampal, provided their dysfunction degrades the representations (unitization) the hippocampus must bind within episodic memories.	Subtle impairments in familiarity, object discrimination, object-location integration, or context-free associative memory may provide earlier behavioural signals than standard episodic tasks.

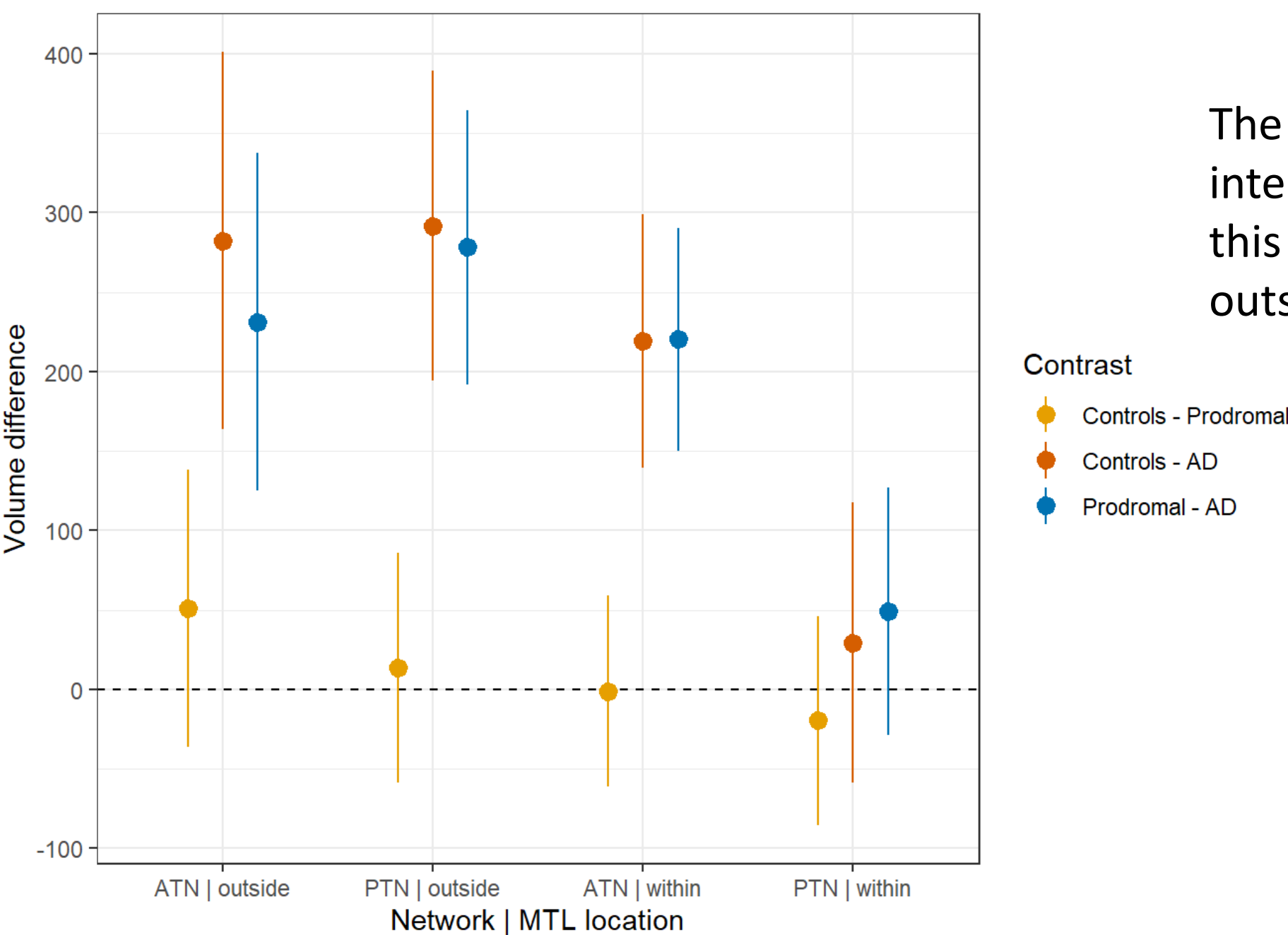
References

Cecchini et al. (2021). Brain and Cognition, 152, 105749.
Didic et al. (2011). Journal of Alzheimers Disease, 27(1):11-22.
Forno et al. (2022). Neuropsychology, 37(7):753–768.
Parra et al. (2024). The Journal of Prevention of Alzheimer's Disease, 11(2):339–347.

Results

We first explored whether diagnosis-related differences in brain region volumes varied between the ANT and PTN networks and location relative to the MTL (within or outside) using linear mixed-effects models that retained region-level measurements rather than averaging volumes within networks.

Figure 1. Mean regional volumes across Diagnosis x Network x Location.



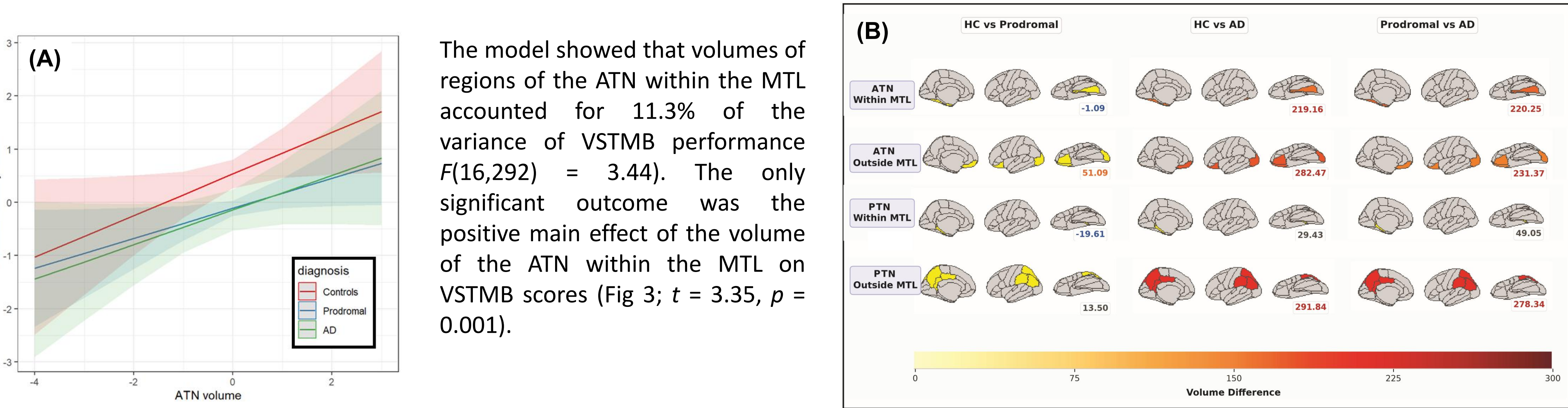
The linear mixed-effects model controlling for demographics revealed a significant 3-way interaction (Diagnosis x Network x Location: $t(22630) = -3.174, p = 0.002$). Table 3 shows this was driven by reduced volumes in the ANT more than the PTN network, mainly outside the MTL.

Table 3. Follow-up contrast to explore outcomes from the interaction models.

Contrast	Network	Location	CI	Z ratio	p-value	Cohen's d
Controls - Prodromal	ATN	outside	-36.3 138.5	1.37	0.357	0.016
Controls - AD	ATN	outside	163.8 401.1	5.58	< .001	0.091
Prodromal - AD	ATN	outside	125.4 337.4	5.115	< .001	0.075
Controls - Prodromal	PTN	outside	-58.9 85.9	0.437	0.9	0.004
Controls - AD	PTN	outside	194.4 389.2	7.023	< .001	0.094
Prodromal - AD	PTN	outside	191.9 364.8	7.549	< .001	0.090
Controls - Prodromal	ATN	within	-61.2 59.0	-0.043	0.999	0.000
Controls - AD	ATN	within	139.3 299.1	6.429	< .001	0.071
Prodromal - AD	ATN	within	150.1 290.4	7.36	< .001	0.071
Controls - Prodromal	PTN	within	-85.6 46.4	-0.697	0.765	-0.006
Controls - AD	PTN	within	-58.9 117.7	0.781	0.714	0.009
Prodromal - AD	PTN	within	-28.9 127.0	1.475	0.303	0.016

Second, regional volumes were averaged within each Network x Location (ATN/PTN x within/outside MTL) and Z-scored across participants to create continuous brain predictors (e.g., ATN-within, ATN-outside) used to model memory performance and diagnosis interactions.

Figure 3. (A) Main effect of ATN within the MTL on VSTMB scores. (B) Topographical representation of the regions where the above-reported effects (Table 3) were found.



The model showed that volumes of regions of the ATN within the MTL accounted for 11.3% of the variance of VSTMB performance $F(16,292) = 3.44$). The only significant outcome was the positive main effect of the volume of the ATN within the MTL on VSTMB scores (Fig 3; $t = 3.35, p = 0.001$).

Conclusions

Our hypothesis proved valid. AD differentially affects the ATN and PTN as the disease progresses, with regions of the former network being affected earlier than the latter. Interestingly, such a dissociation was more pronounced neuroanatomically outside the MTL from the prodromal stages. However, when performance on the VSTMB entered the model as the dependent variables, only regions of the ATN within the MTL accounted for a significant proportion of variance regardless of the disease stages, an observation that remained unchanged when hippocampal regions were excluded from the predicting volumes. These results represent the first add-hoc approach to this hypothesis confirming that the hippocampocentrism (i.e., PTN notion) of memory assessments for AD requires a paradigm shift, with future assessments targeting the anatomical and functional integrity of the ATN. The VSTMBT meets that aim.