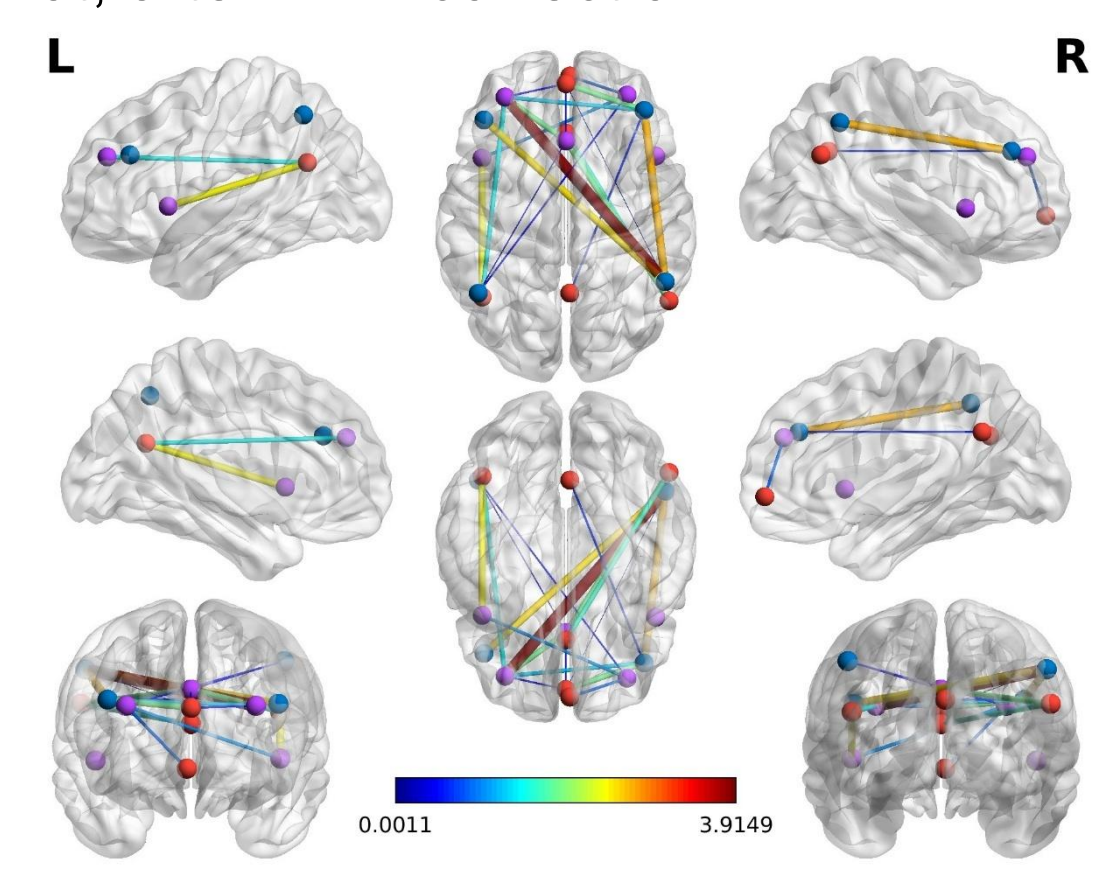
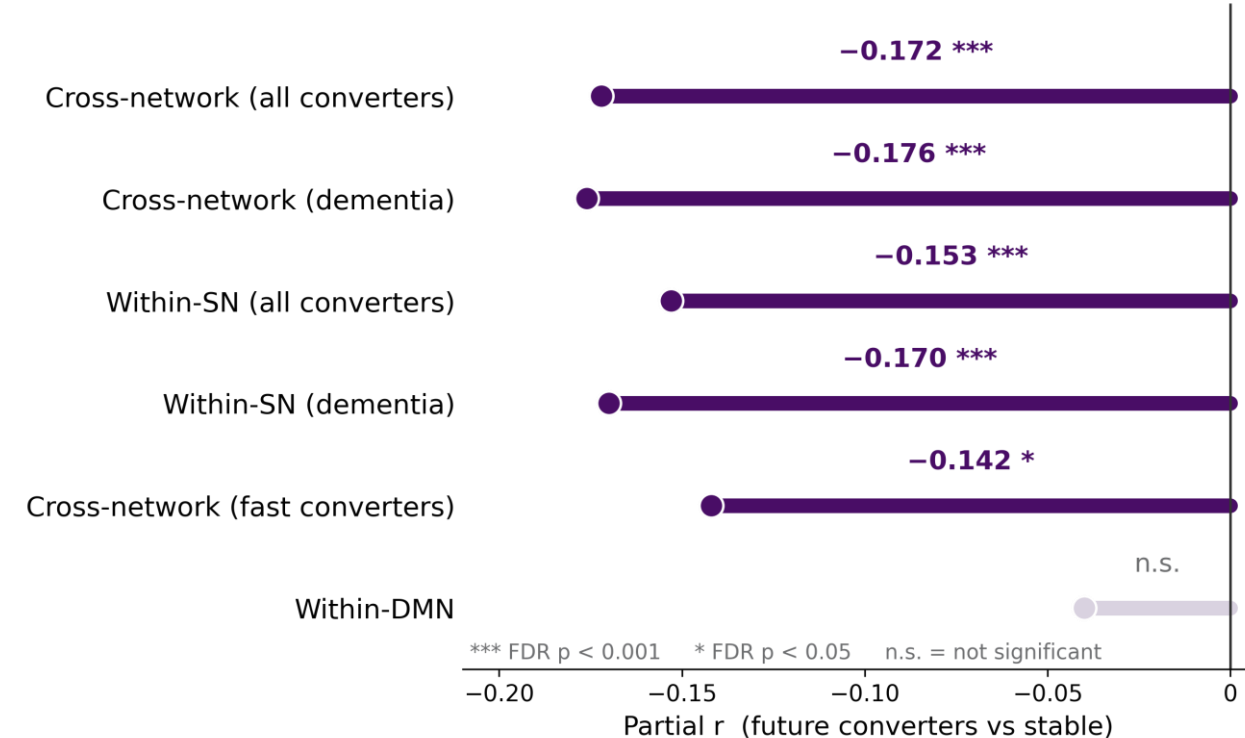


Triple-network effective connectivity is reduced years before dementia onset in cognitively normal adults

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Salience- and cross-network effective connectivity weaken in cognitively normal adults a decade or more before they convert to MCI or dementia.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Alzheimer's disease is increasingly viewed as a "dysconnectivity syndrome": network breakdown begins before symptoms and is often entrenched by diagnosis [1]. The triple-network model. Three hub networks are especially vulnerable to early AD: the default-mode (DMN; memory), executive-control (ECN; cognitive control), and salience (SN) networks [2]. The SN switches between them [3] and, as a high-traffic hub, is disproportionately exposed to amyloid and tau. Why effective connectivity? Functional connectivity only shows co-activation. Spectral DCM (spDCM) estimates directed, causal coupling from resting-state fMRI [4,5]. Gap & hypothesis. No study has mapped <i>directed</i> triple-network interactions in cognitively normal adults who later convert. We hypothesised that baseline connectivity is already attenuated in future converters, with greater reductions closer to conversion.	Cohort (OASIS-3) [6] 647 cognitively normal adults at baseline 146 future converters (92 MCI , 54 dementia) 10.3 yr median converter follow-up Imaging & preprocessing. 3T resting-state fMRI, preprocessed in SPM12 (realignment, slice-timing, MNI normalisation, 6 mm smoothing). Triple-network model. 15 canonical ROIs (DMN 6, SN 5, ECN 4) Effective connectivity. Spectral DCM (spDCM) estimated a full 15 × 15 matrix of directed connections per participant. Statistics. <i>Group:</i> PEB with Bayesian Model Reduction & Averaging [7]. <i>Subject:</i> within-/between-network coupling by GLM (covariates: age, sex, education, mean FD); converter-stable difference as partial r, FDR-corrected.	Cross-network coupling. Converters show reduced global cross-network connectivity (combined $r = -0.172$; dementia $r = -0.176$; FDR $p < 0.001$). Salience network. Within-SN coupling was reduced (combined $r = -0.153$; dementia $r = -0.170$); the SN's directed exchanges with both DMN and ECN were consistently weakened. Dose-response. Fast converters showed significant reductions (cross-network $r = -0.142$); slow converters did not, after FDR correction.  Figure 1. Directed connections best distinguishing converters from non-converters. Node colour = network (DMN red, SN purple, ECN blue). Edge thickness $\propto \Delta$ connectivity; edge colour = feature importance (blue low $\rightarrow$ red high). Only connections with posterior probability > 0.99 shown. L = left, R = right.	 Figure 2. Baseline connectivity is reduced in future converters. Partial r (adjusted for age, education, mean FD); negative = weaker coupling in converters vs stable non-converters. *** FDR $p < 0.001$, * $p < 0.05$, n.s. = not significant. - Directed triple-network connectivity is attenuated years before conversion to MCI or dementia. - The most reliable signatures, point to early failure of network switching, not a network-local abnormality. - Effect sizes ($r \approx -0.12$ to -0.18) are small and may complement established preclinical plasma biomarkers (GFAP, NfL, pTau181) [8]. - Combined with molecular and genetic markers, directed rs-fMRI connectivity could support earlier biological staging and prodromal-phase trials.	1. Ereira S, et al. Nat Ment Health. 2024;2:787–800. doi:10.1038/s44220-024-00259-5 2. Menon V. Trends Cogn Sci. 2011;15:483–506. doi:10.1016/j.tics.2011.08.003 3. Sridharan D, et al. PNAS. 2008;105:12569–12574. doi:10.1073/pnas.0800005105 4. Friston KJ. Brain Connect. 2011;1:13–36. doi:10.1089/brain.2011.0008 5. Razi A, et al. NeuroImage. 2015;106:1–14. doi:10.1016/j.neuroimage.2014.11.027 6. LaMontagne PJ, et al. medRxiv. 2019. doi:10.1101/2019.12.13.19014902 7. Zeidman P, et al. NeuroImage. 2019;200:12–25. doi:10.1016/j.neuroimage.2019.06.032 8. Chatterjee P, et al. Alzheimers Dement. 2022;18:1141–1154. doi:10.1002/alz.12447
				CONTACT  Zhen Xuen Brandon Low Monash University Malaysia zlow0014@student.monash.edu Code: github.com/zxKyouma/trinet-dcm 