Large-scale Network Connectivity as a Predictor of Age: Evidence Across the Lifespan from the Cam-CAN Dataset

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Introduction

- Changes in brain connectivity patterns as a function of age have been recently proposed to underlie differences in cognitive abilities between young and older adults[1].
- A prioritization of fluid cognition in young adulthood progressively gives its place to crystalized knowledge and an emphasis on semantic cognition in older adulthood, shifts that take place along with changes in functional connectivity between executive (ECN) and default mode (DMN) network areas.
- The **default-executive coupling hypothesis** posits that aging is marked by network dedifferentiation, leading to *increased connectivity between* ECN & DMN and *decreased connectivity within* these networks as a function of age[1].
- It is possible that the previously observed aging effects on default and executive connectivity are further modulated by the salience network, which plays a a crucial role in the dynamic interplay between ECN and DMN[2].
- Although past research has used these patterns to account for performance differences among age groups, here, we focus on the reverse question, namely **whether changes in brain network organization, as reflected in resting-state functional connectivity measures, can predict age variability.**

Hypotheses:

- We predicted that connectivity between ECN and DMN regions, especially within prefrontal cortex, would explain much of age variability and that the inclusion of the salience network would improve these predictions.
- We further anticipated that the examination of the strength and direction of these relationships by age cohort would reveal that they change dynamically across the lifespan.

Participants & Methods

- 547 participants (ages 18-88 years old) from Cambridge Centre for Ageing and Neuroscience (Cam-CAN) dataset[3,4] were included, if they had no history of stroke or other brain injury and had complete structural and functional neuroimaging.

Table 1.
Demographic and Neuropsychological Characteristics of Sample by Age Cohort (N = 547)

	Younger (18-39)	Middle aged (40-64)	Older (65-88)	*p*
N	140	223	184	
Age in years	30.91 (5.71)	51.77 (7.34)	74.58 (5.92)	< .001
Male/Female	63/73	107/116	98/86	.500
ACE-R	96.63 (3.44)	95.57 (3.60)	92.57 (5.41)	< .001
Cattell Fluid Intelligence	37.25 (4.10)	33.41 (4.82)	26.33 (6.10)	< .001

Methods:

- A series of ROIs were defined based on prior models of cognitive control[5] with MNI coordinates derived from prior resting-state imaging studies[2,6].
- For each seed-to-seed connection, bi-variate correlations were calculated and transformed into Z-scores, using Fisher transformation for each participant and used in subsequent linear regression analyses.
- Our linear regression analyses are outlined below:

Analysis 1:
Determine which seeds within and between the DMN & ECN significantly predict age.

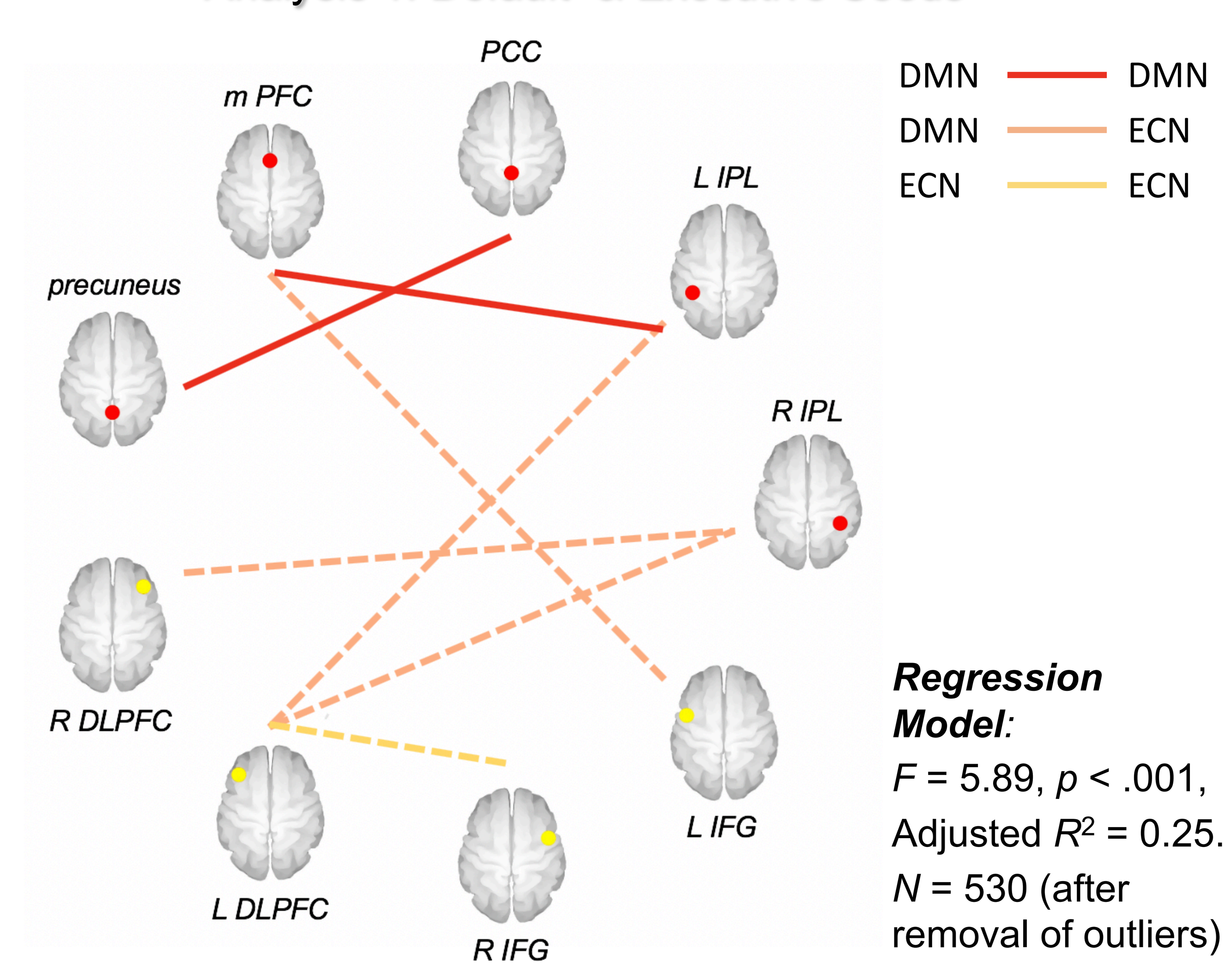
Analysis 1 Seeds	
DMN	**ECN**
R IPL	R DLPFC
L IPL	L DLPFC
mPFC	R IFG
Precuneus	L IFG
PCC	

Analysis 2:
Use significant seeds from Analysis 1 with the addition of salience network seeds to determine whether addition of salience network improves predictive power of model.

Analysis 2 Seeds		
DMN	**ECN**	**Salience**
R IPL	R DLPFC	R Ant. Insula
L IPL	L DLPFC	L Ant. Insula
mPFC	R IFG	R OFI
Precuneus	L IFG	L OFI
		ACC

Results

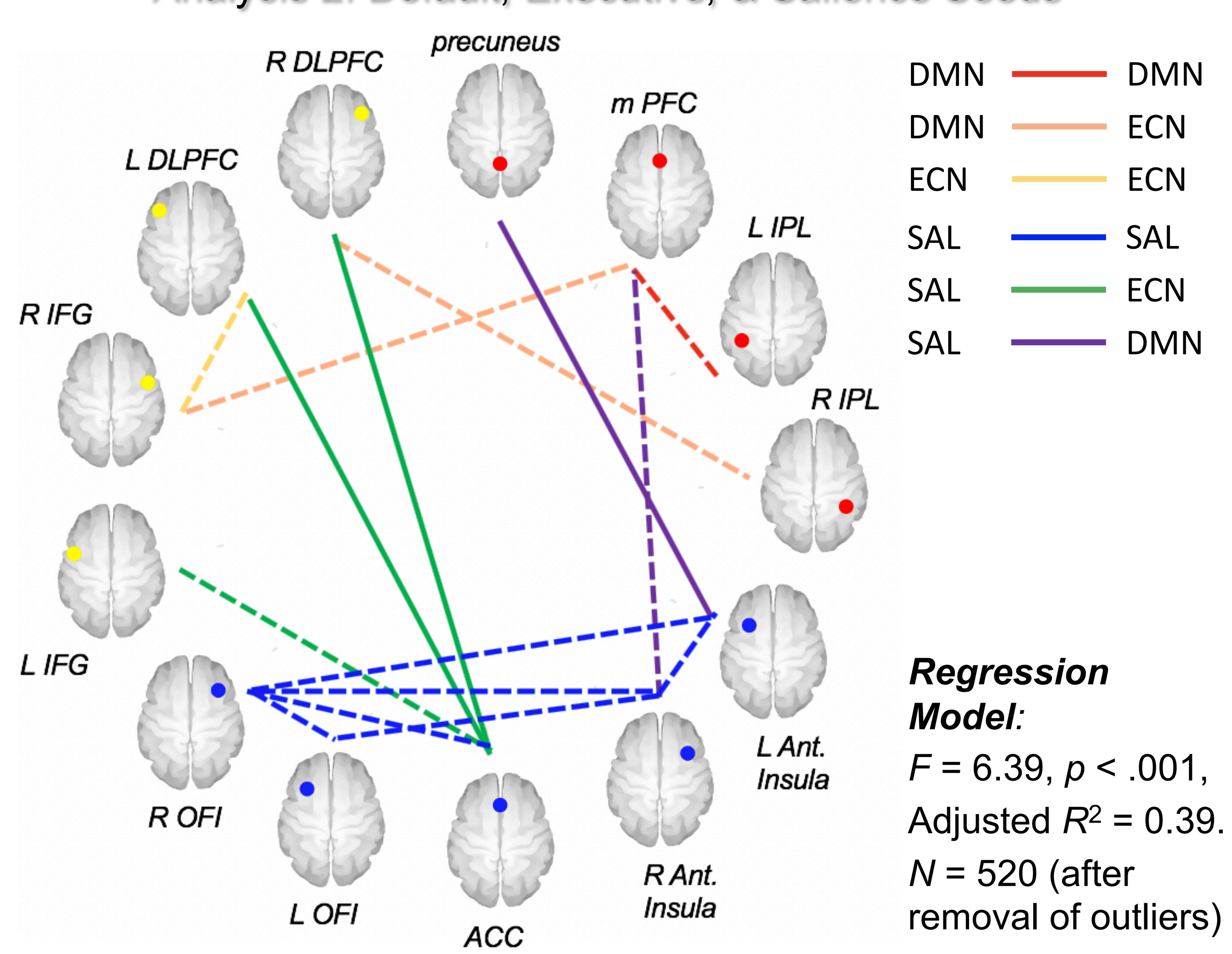
Analysis 1: Default & Executive Seeds



Regression Model:
$F = 5.89$, $p < .001$,
Adjusted $R^2 = 0.25$.
$N = 530$ (after removal of outliers)

Figure 1. Significant predictors of age from regression analysis of DMN and ECN (above) and for DMN, ECN, and salience (SAL) networks (below). Solid lines indicate a positive correlation between seed pairs and age, dashed lines indicate a negative correlation between seed pairs and age.

Analysis 2: Default, Executive, & Salience Seeds



Regression Model:
$F = 6.39$, $p < .001$,
Adjusted $R^2 = 0.39$.
$N = 520$ (after removal of outliers)

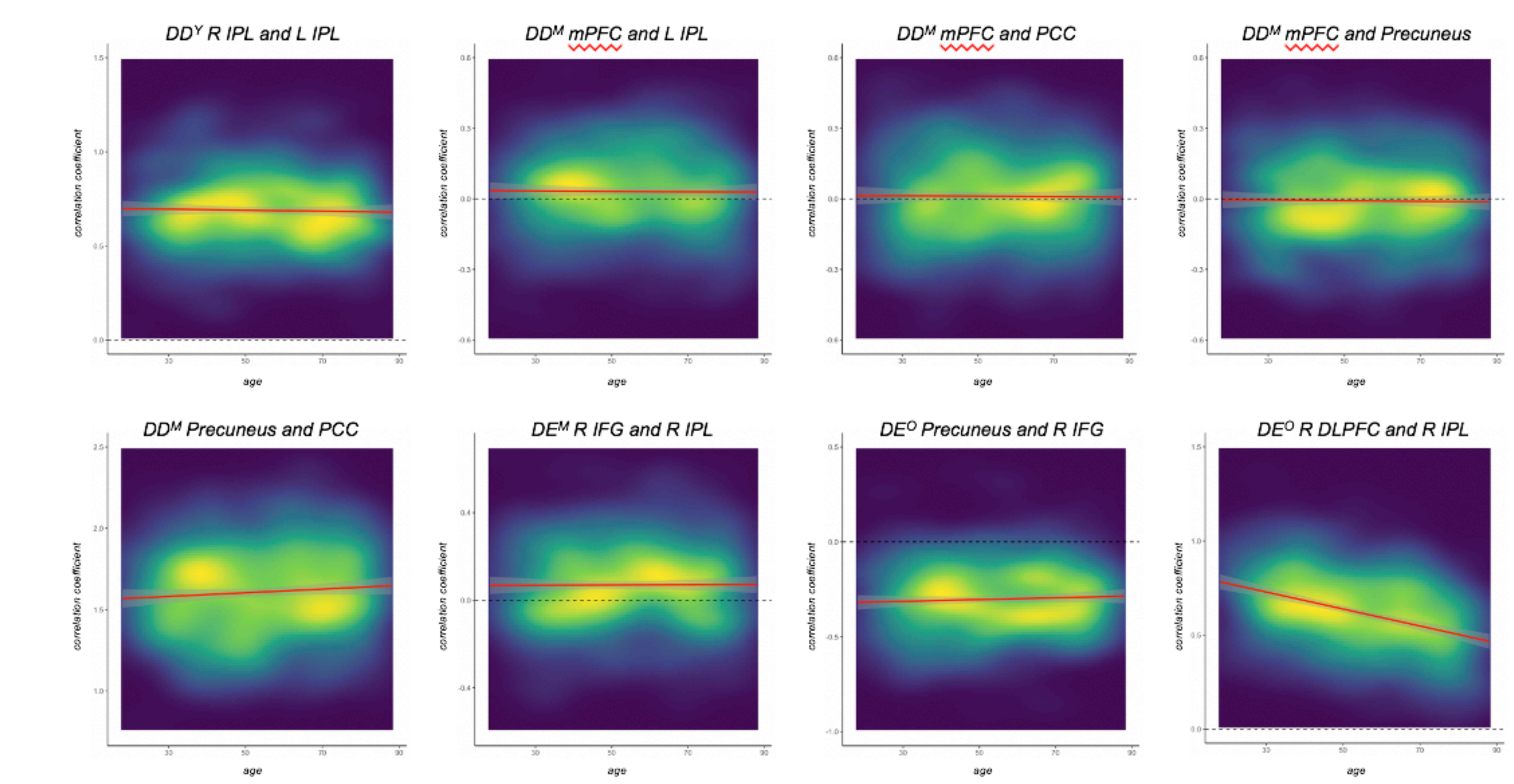
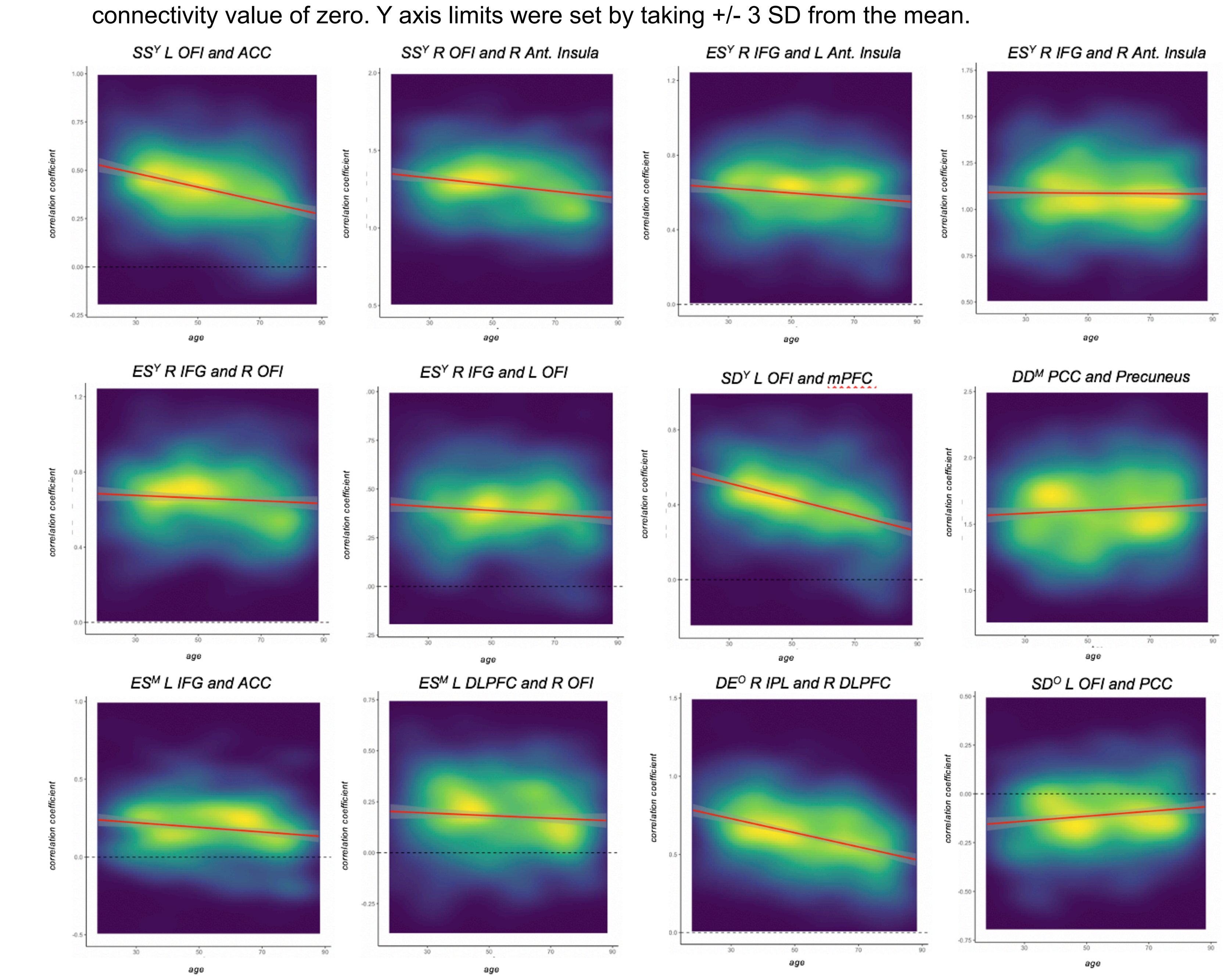


Figure 2. ROI seed pairings for the executive (E) default (D), and salience (S) network combinations that were significant predictors of age for each cohort (Y = young, M = Middle, O = Old). The top plot demonstrates significant pairings in the default and executive only analysis. The bottom panel demonstrates how inclusion of the salience network improves the amount of variance explained. Density plots visualize the distribution of the data (yellow = dense) and the direction of network connections relationship with age. The linear regression line is presented in red, dotted horizontal line indicates a connectivity value of zero. Y axis limits were set by taking +/- 3 SD from the mean.



Conclusions

- We examined how intrinsic functional connectivity relates to healthy aging, by examining resting state functional connectivity across the lifespan independent of task performance.
- A series of multiple regression analyses revealed that connectivity between dorsolateral and ventromedial prefrontal cortex and parietal regions, including the precuneus, accounted for a significant portion of age variability. The inclusion of the salience network improved the models' explanatory power.
- Follow-up age cohort analyses showed that these relationships dynamically change across the lifespan, providing snapshots of the brain's changing intrinsic architecture.
- Overall, these findings support the default-executive coupling hypothesis for aging.[1] They further suggest that the relationship between these two networks might be more complex and mitigated by salience network contributions, as well as changes in the intrinsic connectivity within the salience network itself.

References

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