

BACKGROUND

Frontotemporal dementia (FTD) is highly heritable, with autosomal dominant mutations in *C9orf72*, *GRN*, or *MAPT* as the most frequent genetic causes. The salience network, anchored in the anterior cingulate and insular cortices, is hypothesized to underlie the social and behavioural deficits characteristic of bvFTD [1]. Reliable biomarkers sensitive at presymptomatic stages are urgently needed for emerging disease-modifying therapies.

Objectives:

1. Characterize longitudinal functional connectivity (FC) changes in presymptomatic and symptomatic genetic FTD carriers compared to non-mutation carrier controls
2. Identify gene-specific patterns of network vulnerability
3. Determine whether specific network FCs associate with cognitive-behavioral measures and whether this pattern differs by genetic groups

METHODS

Analysis was based on a cohort of 959 participants from the GENetic Frontotemporal dementia Initiative (GENFI) [2], which included individuals with FTD-causing mutations and their non-carrier family members, and consisted of 362 non-carrier controls, and presymptomatic (n = 400) and symptomatic (n = 197) carriers of *C9orf72*, *GRN*, and *MAPT* mutations.

Longitudinal resting state fMRI was acquired across multiple sites. fMRIPrep (v24.1.1)[3] was used for spatial preprocessing. Temporal preprocessing involved ICA-based denoising. Data was harmonized using longCombat. Networks were derived from the Gordon atlas (333 nodes).

We used linear mixed-effects models to assess the main effects and interaction between time from baseline visit versus clinical & genetic status of the participant within seven major resting-state networks. Covariates included age, sex, grey matter volume, and mean framewise displacement. Years of education was an additional covariate in association analyses. Random effects modeled subjects nested within families.

RESULTS

Table 1. Participant demographic characteristics

	Presymptomatic				Symptomatic			p-value ²
	Control N = 362 ¹	<i>C9orf72</i> N = 168 ¹	<i>GRN</i> N = 165 ¹	<i>MAPT</i> N = 67 ¹	<i>C9orf72</i> N = 101 ¹	<i>GRN</i> N = 62 ¹	<i>MAPT</i> N = 34 ¹	
Demographics								
Age (years)	45.84 (13.17)	44.20 (11.62)	46.23 (11.55)	39.52 (11.25)	63.73 (7.36)	64.73 (8.13)	55.65 (9.81)	<0.001
Education (years)	14.40 (3.38)	14.27 (3.11)	15.02 (3.56)	14.33 (3.06)	12.55 (3.71)	11.71 (3.94)	13.47 (3.55)	<0.001
Sex								<0.001
Female	206 (57%)	95 (57%)	101 (61%)	36 (54%)	34 (34%)	33 (53%)	12 (35%)	
Male	156 (43%)	73 (43%)	64 (39%)	31 (46%)	67 (66%)	29 (47%)	22 (65%)	
Clinical								
CDR® NACC FTLD-SOB	0.29 (0.79)	0.37 (0.88)	0.28 (0.72)	0.36 (0.66)	10.56 (7.22)	11.15 (7.50)	8.03 (6.56)	<0.001
Cambridge Behavioral Inventory	4.53 (6.76)	6.53 (7.86)	4.25 (7.84)	8.59 (14.11)	64.72 (30.18)	59.79 (32.07)	54.45 (33.22)	<0.001
Mini Mental State Examination	29.39 (1.07)	29.13 (1.24)	29.39 (0.91)	29.40 (1.29)	23.58 (5.24)	19.23 (7.51)	24.93 (4.67)	<0.001
Imaging								
Gray Matter Volume (mL)	588 (67)	567 (69)	585 (58)	596 (70)	478 (66)	455 (66)	500 (49)	<0.001
Mean Framewise Displacement (mm)	0.15 (0.12)	0.15 (0.12)	0.15 (0.09)	0.13 (0.07)	0.23 (0.16)	0.24 (0.18)	0.26 (0.32)	<0.001

¹Mean (SD); n (%)
²One-way analysis of means; Pearson's Chi-squared test

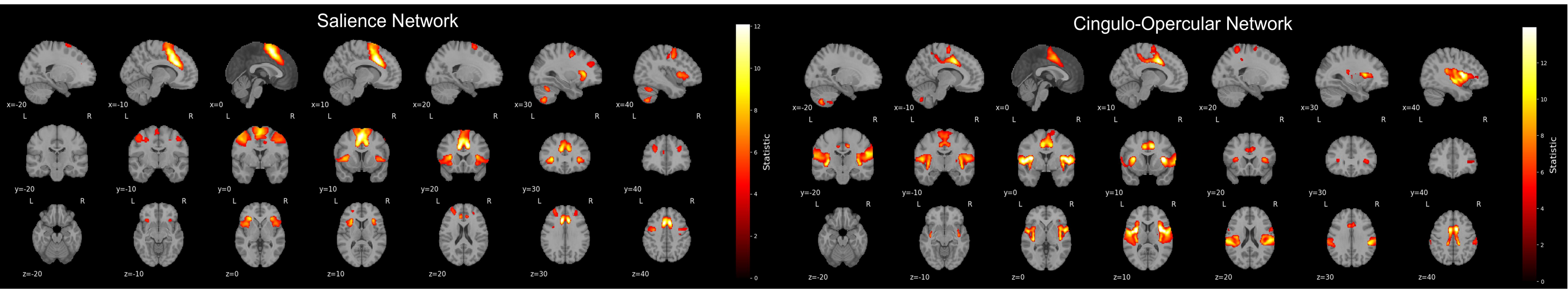


Figure 1. GroupICA derived components confirming salience and cingulo-opercular network definitions in the genetic FTD cohort.

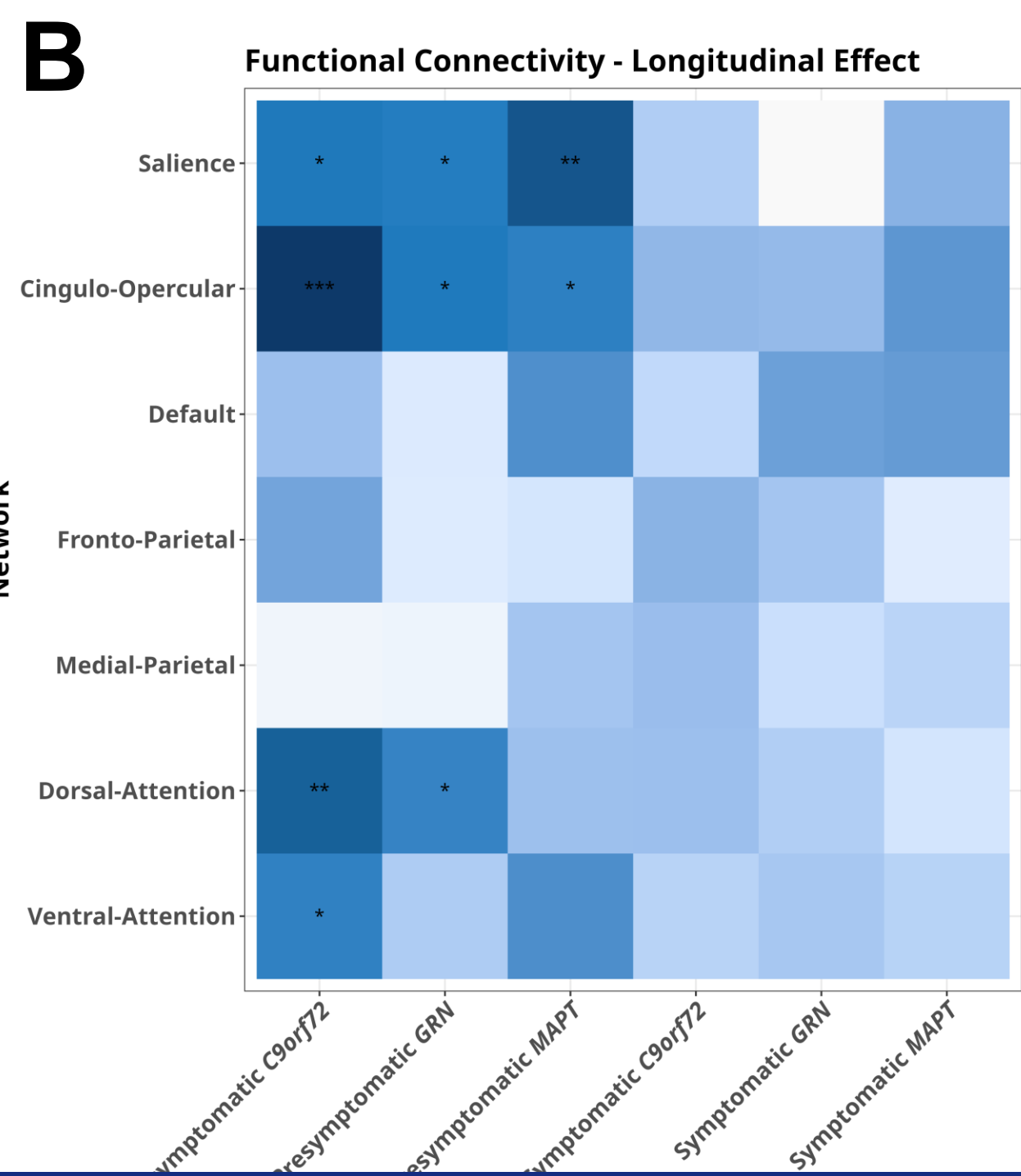
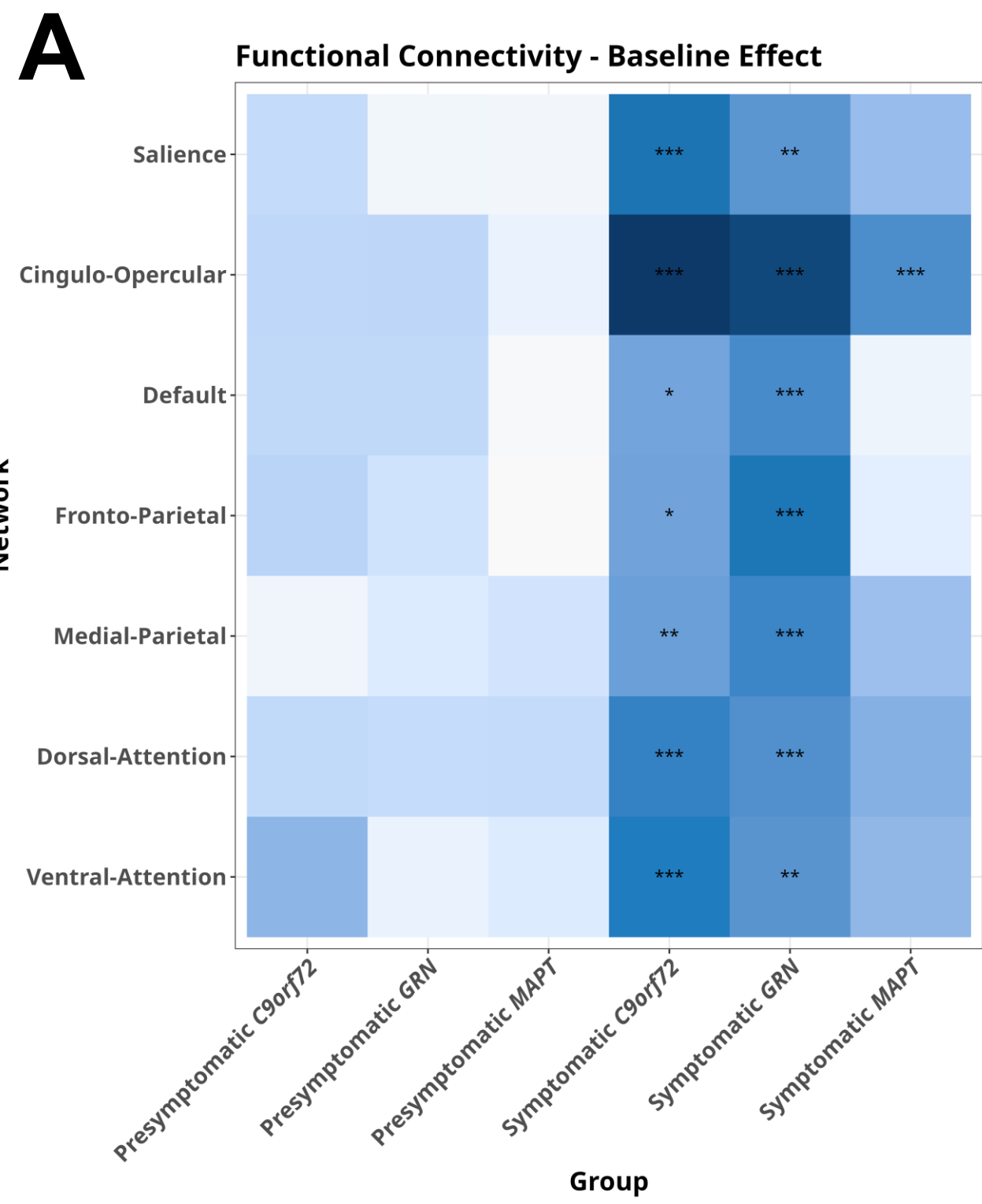


Figure 2. Functional connectivity changes in the genetic FTD cohort. Heatmaps linear mixed effects baseline effects (A) and longitudinal effects (B) are shown for all networks, with color coding representing the magnitude of the t-statistic for the given cell, with darker blue indicating greater more negative (decline) effect. Significant effects are indicated by asterisks within the cells.

* p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001.

SUMMARY & CONCLUSIONS

Longitudinal FC decline in salience, cingulo-opercular, and attention networks marks early connectivity loss in genetic FTD. FC changes precede symptoms and differentiate genetic subtypes. FC-cognitive-behavioral associations exist in *C9orf72* and *GRN* symptomatic individuals in general agreement with the hypothesized roles of each network. FC is a potential sensitive, non-invasive biomarker for presymptomatic disease tracking and therapeutic trial design in genetic FTD.

REFERENCES

1. Seeley WW. The salience network: A neural system for perceiving and responding to homeostatic demands. The Journal of Neuroscience 2019;39(50):9878–9882.
2. Rohrer JD, Nicholas JM, Cash DM, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the genetic frontotemporal dementia initiative (GENFI) study: A cross-sectional analysis. The Lancet. Neurology 2015;14(3):253–62.
3. Esteban O, Markiewicz CJ, Blair RW, et al. fMRIPrep: A robust preprocessing pipeline for functional MRI. Nature methods 2019;16(1):111–116.

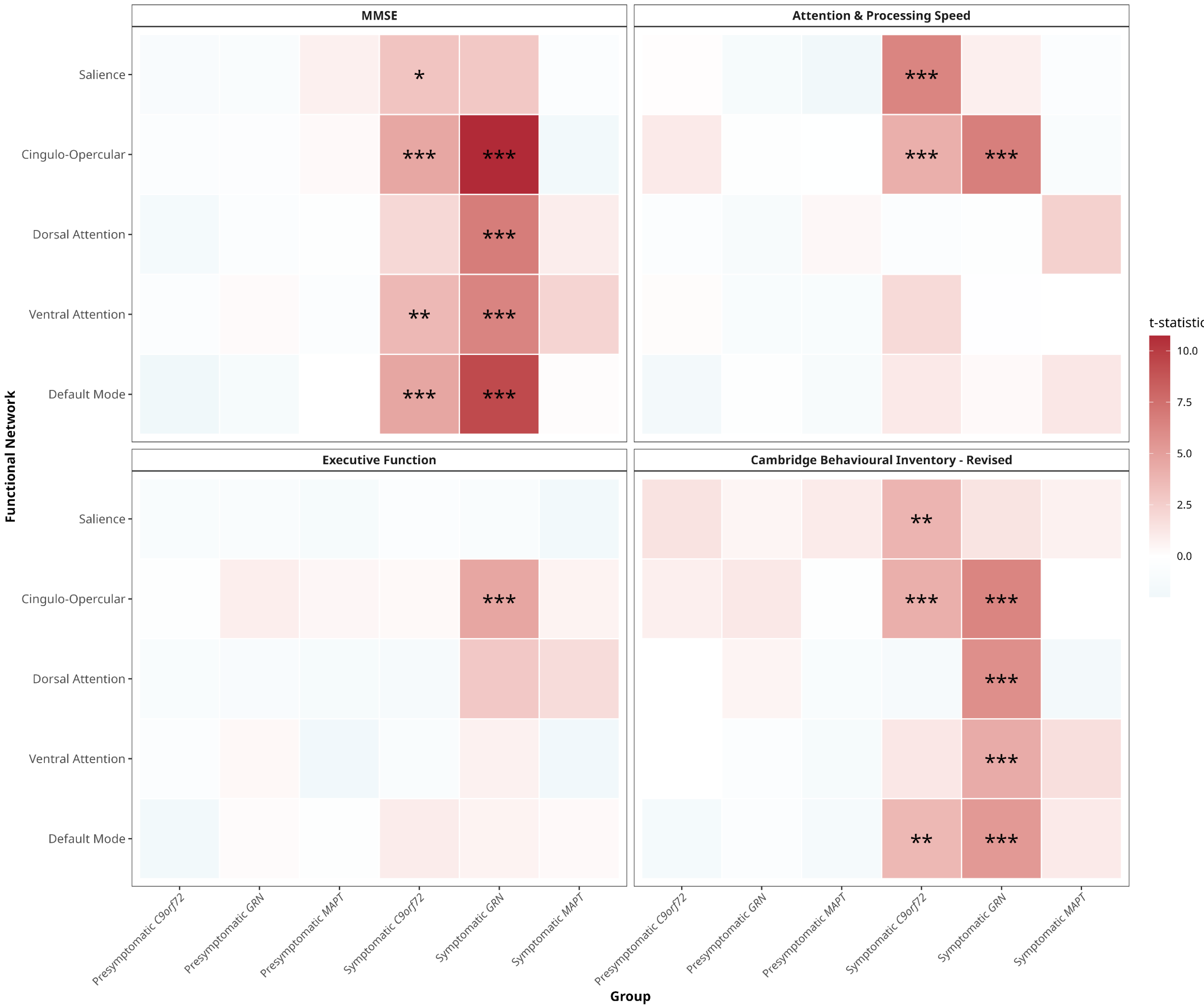


Figure 3. Heatmaps of *post-hoc* linear mixed effects estimated marginal trends measuring functional connectivity association with cognitive-behavioral measures. Cell color coding represents the t-statistic of the trend being greater than zero. Significant effects are indicated by asterisks within the cells.
* p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001.

AFFILIATIONS

(1) Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada; (2) Hurvitz Brain Sciences Research Program, Division of Neurology, Department of Medicine, Sunnybrook Research Institute, Toronto, Ontario, Canada; (3) Department of Clinical Neurosciences, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom; (4) Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, England, United Kingdom; (5) Department of Neurology, Erasmus Medical Center, Rotterdam, South Holland, Netherlands; (6) Alzheimer's Disease and Other Cognitive Disorders Unit, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain; (7) Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, CHU de Québec, Faculty of Medicine Université Laval, Québec, Québec, Canada; (8) Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Stockholm, Sweden; (9) Unit for Hereditary Dementia, Theme Aging, Karolinska University Hospital-Solna, Stockholm, Stockholm County, Sweden; (10) Neurodegenerative Diseases Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Lombardy, Italy; (11) Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Flemish Brabant, Belgium; (12) Faculty of Medicine, University of Lisbon, Lisbon Region, Portugal; (13) Division of Neurology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Lombardy, Italy; (14) Faculty of Medicine, University of Coimbra, Coimbra, Coimbra District, Portugal; (15) Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, Greater Manchester; (16) Departments of Geriatric Medicine and Nuclear Medicine, University of Duisburg-Essen, Essen, North Rhine-Westphalia, Germany; (17) Department of Neurology, Ludwig-Maximilians Universität München, Munich, Bavaria, Germany; (18) German Center for Neurodegenerative Diseases (DZNE), Munich, Bavaria, Germany; (19) Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Tuscany, Italy; (20) Department of Neurofarba, IRCCS Fondazione Don Carlo Gnocchi, Milan, Lombardy, Italy; (21) Department of Neurology, University of Ulm, Ulm, Baden-Württemberg, Germany; (22) Lille Neuroscience & Cognition, Institut national de la santé et de la recherche médicale U1172, University of Lille, Lille, Hauts-de-France, France; (23) Department of Psychiatry, McGill University, Montreal, Quebec, Canada; (24) Medical Sciences Division, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, Oxfordshire, United Kingdom; (25) Department of Brain Sciences, Imperial College London, London, Greater London, United Kingdom; (26) Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada; (27) Timm Center for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada; (28) German Center for Neurodegenerative Diseases (DZNE), Tübingen, Baden-Württemberg, Germany; (29) Department of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Baden-Württemberg, Germany; (30) Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastián, Basque Country, Spain; (31) Group of Neurodegenerative Diseases, Neurosciences Area, Instituto de Investigación Sanitaria Bioparizkou, San Sebastián, Basque Country, Spain; (32) Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Lombardy, Italy; (33) Molecular Markers Laboratory, IRCCS Istituto Centro San Giovanni di Dio, Fatebenefratelli, Brescia, Lombardy, Italy; (34) Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada; (35) Research Imaging Centre, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada