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INTRODUCTION

Metabolic syndrome (MetS) [1], defined as the clustering of three or more vascular risk factors (RFs), is a growing problem in the aging US population and leads to accelerated brain aging and increased risk for dementia. While the relationship between isolated RFs and brain structure and function have been previously examined, very little is known about how the shared contribution of RFs in MetS disrupts functional organization and temporal dependency across core brain networks. We hypothesize that the shared underlying pathophysiological mechanisms of the co-occurring RFs in MetS interrupting neural metabolic health (i.e., cerebrovascular functioning) also disrupt structural and functional integrity in the brain, specifically, among the networks belonging to attentional and executive control domains. Results from our analyses will provide valuable information on the mechanisms by which comorbid vascular risks influence the integrity of core functional networks that are critical for cognition.

METHODS

Participants

Total: 78 participants
MetS (i.e., three or more RFs): 27 (age (mean ± SD): 65.70 ± 7.87, 3 females)
Non-MetS (less than 3 RFs): 51 (age (mean ± SD): 59.63 ± 8.60, 19 females)

Metabolic Syndrome (MetS) Criteria:

- Waist circumference ≥102/88 cm (male/female)
- Triglycerides ≥150 mg/dL or drug treatment
- HDL-C <40/50 mg/dL (male/female) or drug treatment
- Systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or drug treatment
- Fasting plasma glucose ≥100 mg/dL or drug treatment

Imaging Parameter (3T Siemens Prisma)

- 3D MPRAGE: TR=2530 ms, TE=3.35 ms, voxel size=1x1x1 mm, 176 slices.
- Resting-state EPI: TR=4000 ms, TE=31 ms, voxel size=2x2x2.5 mm, 55 axial slices.

fMRI Data Preprocessing

- Cortical surface reconstructed from T1-weighted MRI volume using FreeSurfer.
- Resting state fMRI data were preprocessed using a standard FSL stream [http://freesurfer.net/fswiki/FsFast]
- The 7-network surface-based functional parcellation published by Yeo et al. [2] were used to extract individual cluster time series associated with the core networks.
- The spatially averaged time series of each of these 7 regions served as seeds for whole-brain voxel-wise correlation (functional connectivity, FC) maps in each individual.

Statistical Analyses: Group Difference (Figure 1)

- Group differences were computed using FreeSurfer's `mri_glmfit` function.
 - Nuisance regressors of age, sex and scanner were included.
- Corrections for multiple comparisons were performed using FreeSurfer's `mri_glmfit-sim` function ($p < 0.05$).

Within- and between- network FC effects (Figure 2)

- Within-network effects were computed as the total count of vertices belonging to the same network seed region.
- Between-network effects were computed as the count of vertices belonging to regions outside of the network seed.
- Finally, the percentage of within- and between-seed FC effects were computed relative to the total count of vertices within the seed (network) region.

RESULTS

Group difference in functional connectivity (FC)

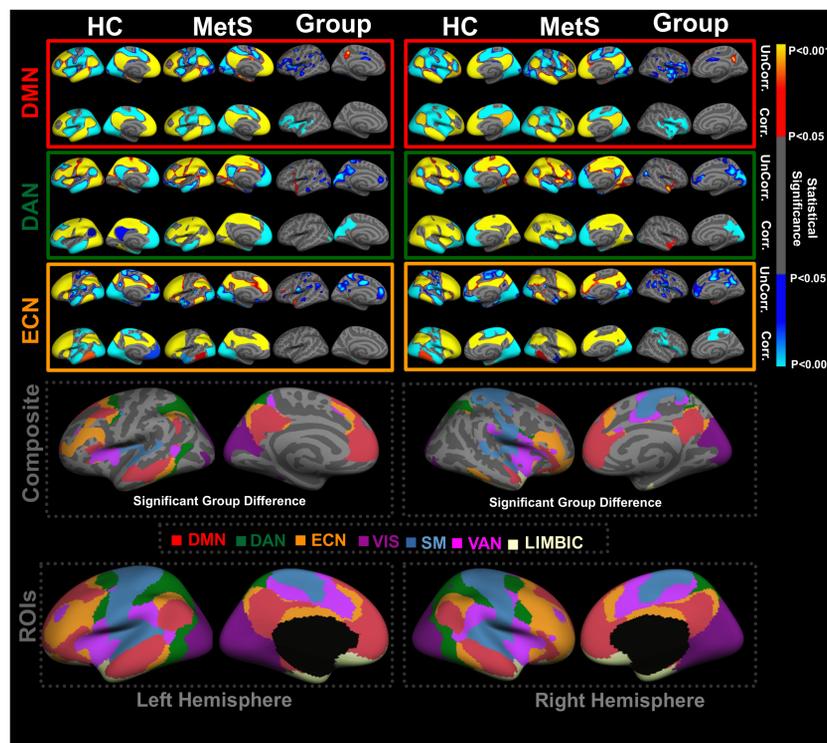


Figure 1: For each seed and for each hemisphere, the uncorrected and corrected for multiple comparisons ($p < 0.05$) results from the GLM analysis showing the (i) one-sample group mean (OSGM) measures of FC in non-MetS and MetS groups, and (ii) the group differences in FC of the seed to the rest of the brain regions, after regressing out scanner-, age- and sex-effects. Only the results from DMN, DAN and ECN are highlighted for convenience. The composite ROI maps provide an overview of how much significant group-related effects were found across each hemisphere for all seven seeds (i.e., effects are color-coded based on the underlying seed regions).

Highlights from these results include:

- **Default mode network (DMN):** Relative to the non-MetS group, the MetS group demonstrated significantly greater within-DMN FC in the left hemisphere and significantly greater FC between DMN and SM and ECN regions in the right hemisphere.
- **Dorsal attention network (DAN):** The MetS group demonstrated significantly greater FC between the DAN and VIS regions across both hemispheres, and lower FC between the DAN and DMN regions in the right hemisphere compared to the non-MetS group.
- **Executive control network (ECN):** The MetS group demonstrated greater FC between ECN and VAN and SM in the right hemisphere, relative to the non-MetS group. No significant clusters exhibiting group differences were identified in the left hemisphere.
- **Visual network (VIS):** Relative to non-MetS, the MetS group exhibited greater FC between the VIS and DAN regions in the left hemisphere, and the greater FC between the VIS and LIMBIC regions in the right hemisphere.
- **Sensorimotor network (SM):** Relative to non-MetS, the MetS group exhibited greater FC between SM and several DAN regions across both hemispheres.
- **Ventral attention network (VAN):** The MetS group exhibited greater FC between the VAN and VIS regions in the left hemisphere and the VAN and DMN regions across both hemispheres.
- **Limbic network (LIMBIC):** For the right hemisphere, the within-LIMBIC FC was greater in MetS group. No significant clusters exhibiting group differences were identified in the left hemisphere.

Within- and between-network effects

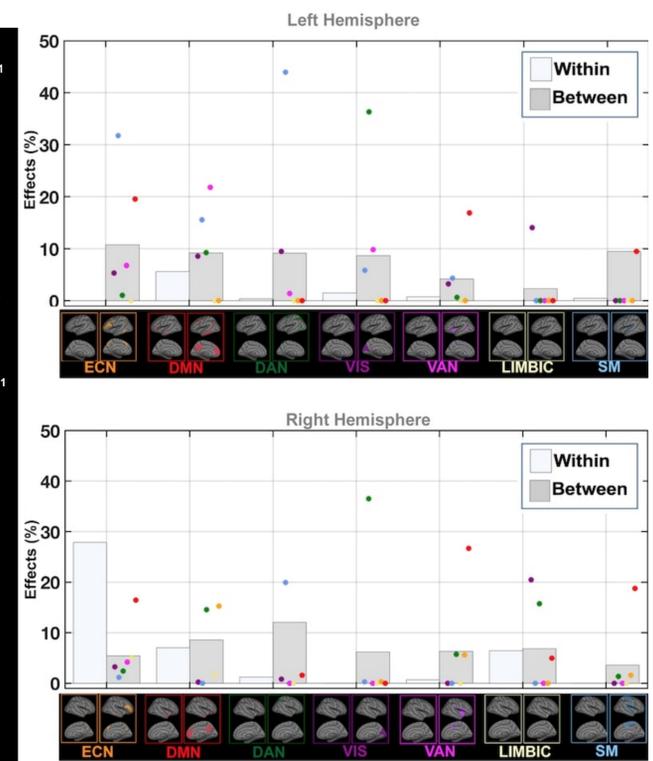


Figure 2: The within- and between-network effects for each hemisphere. Bar plots showing MetS-related significant within- and between-network effects (%) in functional connectivity (FC) across functional brain networks. Each dot is colored based on the associated seed region for a specific network (e.g., red dot=default mode network), and represents the effects of MetS in FC between a particular seed region and that network. Except for few seed regions, most between-network effects were observed across both hemispheres. In the left hemisphere, the ECN, DMN, DAN and VIS seed regions showed higher between-seed effects, ranging from 8.7-10.8%, with only DMN exhibiting relatively greater within-DMN effects (5.6%) compared to other brain networks. Interestingly, in the right hemisphere, the ECN seed showed greater within-ECN effect (27.9%), and the DMN seed showed similar within-DMN (7%) and between-DMN (8.5%) effects. The LIMBIC seed also showed similar within-LIMBIC (6.4%) and between-LIMBIC (6.8%) effects in the right hemisphere. Other seed regions showed consistent patterns of relatively higher between-seed effects in the right hemisphere.

SUMMARY

In summary, MetS is associated with disrupted functional connectivity (FC) within and between core brain networks, including the DMN, ECN and attention (i.e., DAN and VAN) networks. Moreover, the effects of MetS are more prominent across the between-network FC measures. Future directions will explore how these findings relate to neuropsychological performance.

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- [2] Thomas Yeo, B., et al., *The organization of the human cerebral cortex estimated by intrinsic functional connectivity*. *Journal of neurophysiology*, 2011, 106(3): p. 1125-1165.