

Multivariate Analysis Using Co-Expression Network Modeling Identifies Specific Inflammation and Diffusion MRI Features in Major Depressive Disorder



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BACKGROUND

Major depressive disorder (MDD)

- MDD is the most prevalent psychiatric condition marked by persistent sadness and cognitive impairments.
- Only 50% of the MDD population respond to treatments derived from the monoamine hypothesis, implicating alternative pathophysiological underpinnings.
- Recent research indicates that neuroinflammatory processes play a significant role in its development. Crucially, there are notable sex differences in both the presentation and underlying neuroinflammatory mechanisms.

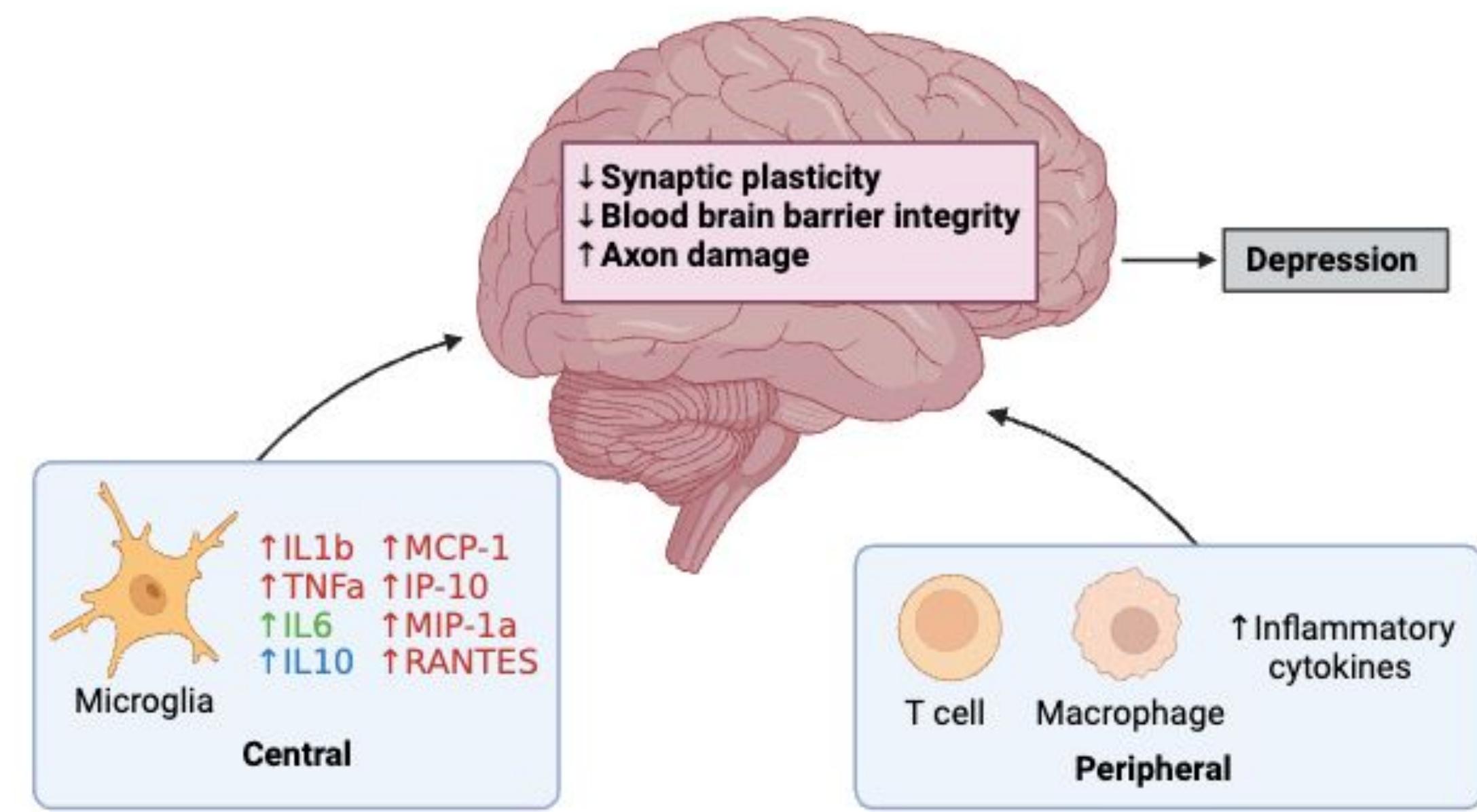


Figure 1. Mechanisms of Neuroinflammation [1]. Red: pro-inflammatory. Blue: anti-inflammatory. Green: both pro- and anti-inflammatory.

Weighted Gene Co-expression Network Analysis (WGCNA)

- Bioinformatics tool used to identify modules or clusters of highly correlated genes across different biological conditions.
- Constructs a network where nodes represent genes and edges represent pairwise correlations between gene expression profiles.
- Unveils biological processes by associating modules with phenotypic traits, clinical outcomes, or experimental conditions.

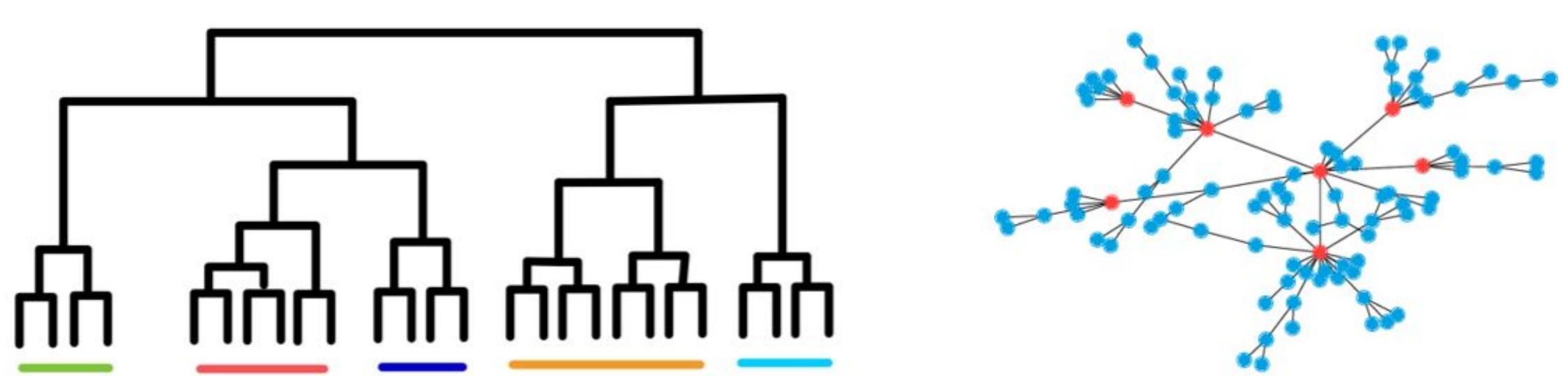


Figure 2. Hierarchical clustering for scale free networks [2-3]

OBJECTIVES

- Identify sex-dependent modules of co-expressed genes associated with inflammatory biomarkers in MDD patients and healthy controls, elucidating shared and distinct networks underlying inflammation in depression.
- Assess the correlation between inflammatory gene expression modules, clinical variables, and neuroimaging markers to elucidate the clinical relevance of immune dysregulation in MDD.

REFERENCES

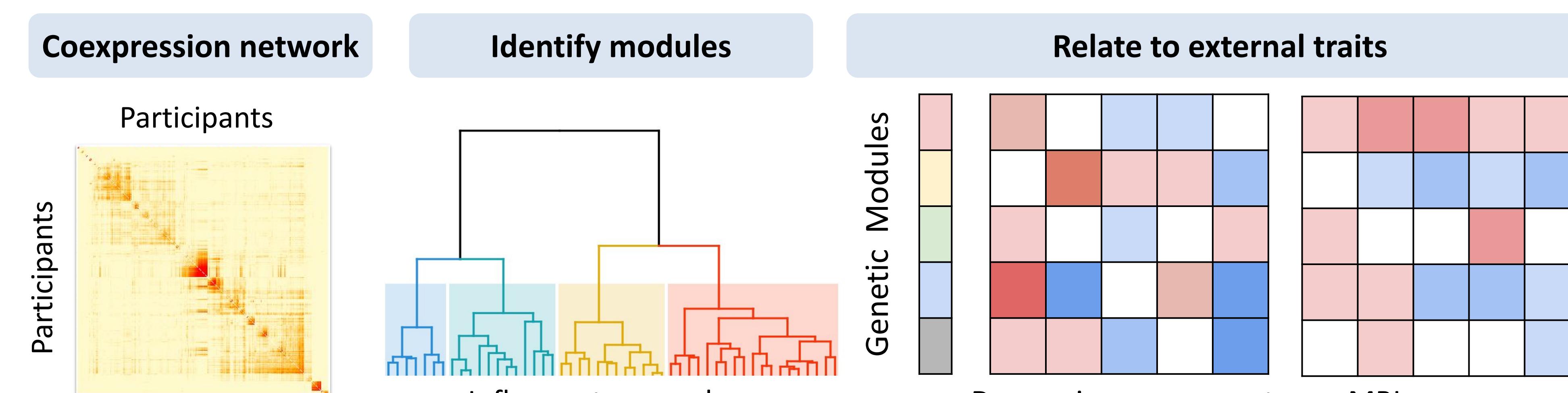
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Pipeline

Canadian Biomarker Integration Network in Depression (CANBIND-1)

Baseline	MDD (n = 211)	Control (n = 122)	
	132 Female 74 Male	65 Female 38 Male	
Modalities	Molecular	Clinical	Imaging
	29 cytokines & chemokines	11 depression subcomponents	4 diffusion MRI parameters

Weighted Gene Co-expression Network Analysis (WGCNA)



RESULTS

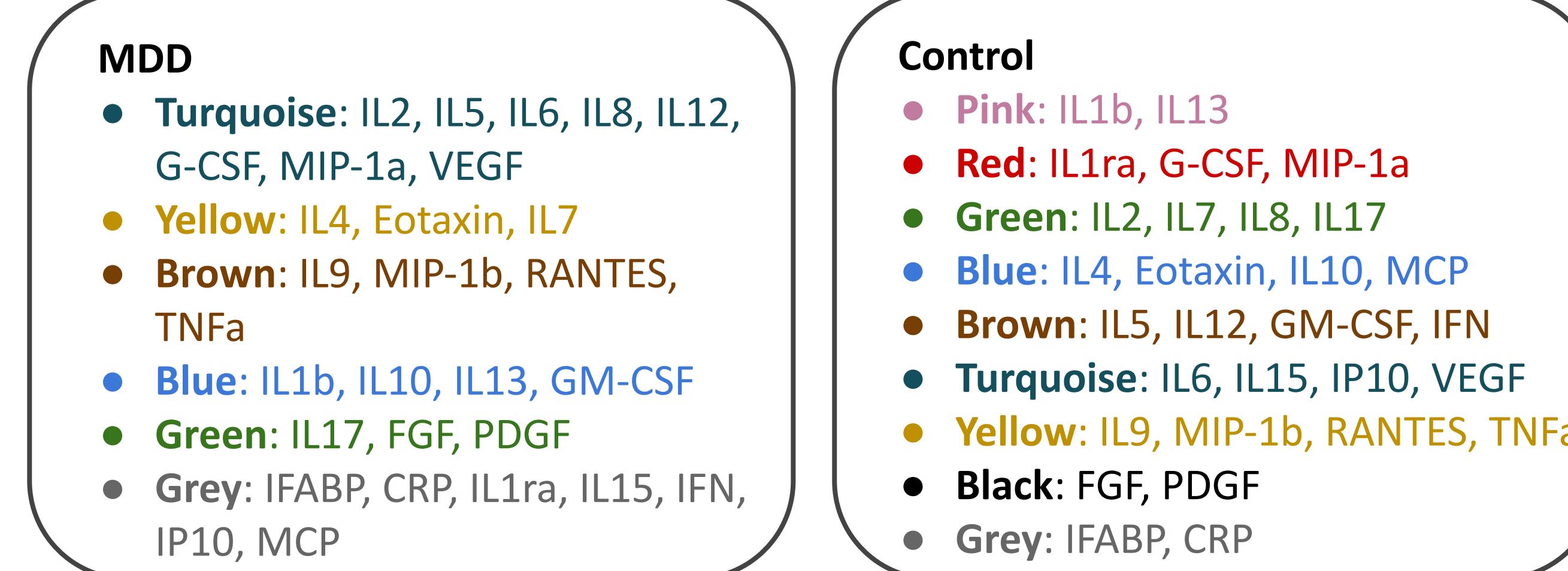


Figure 3. Inflammatory modules detected by WGCNA in MDD and control subjects.

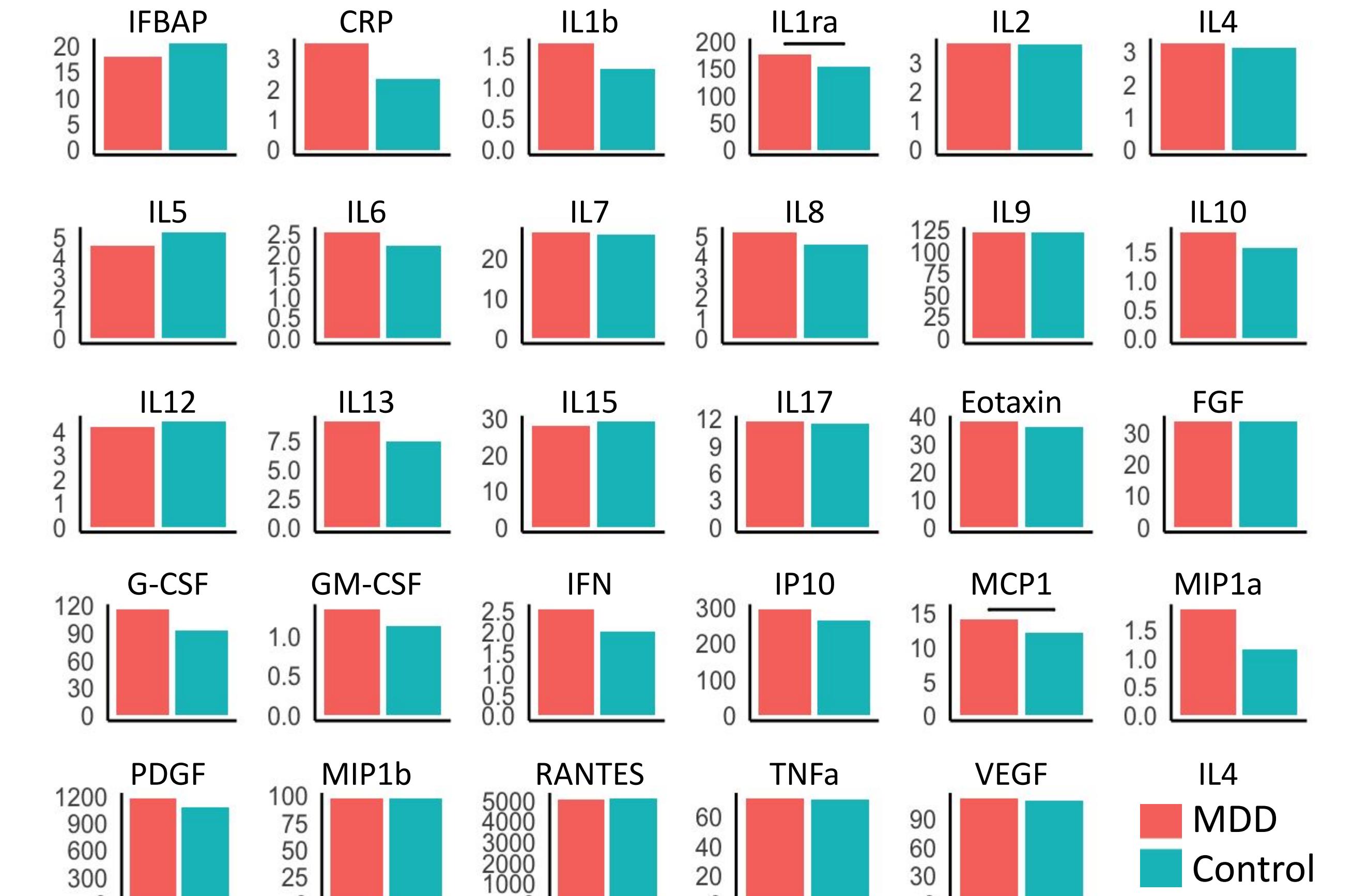
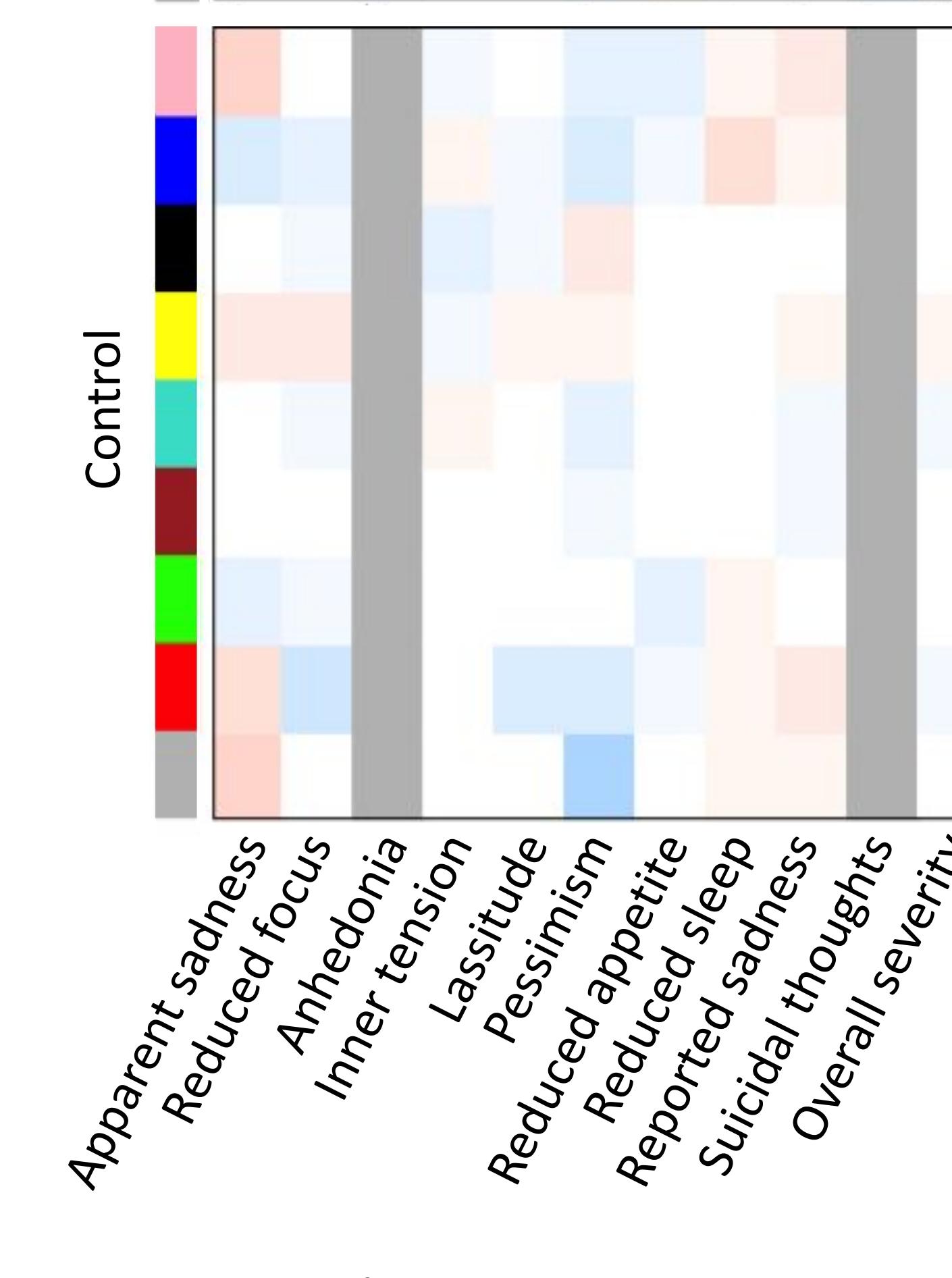
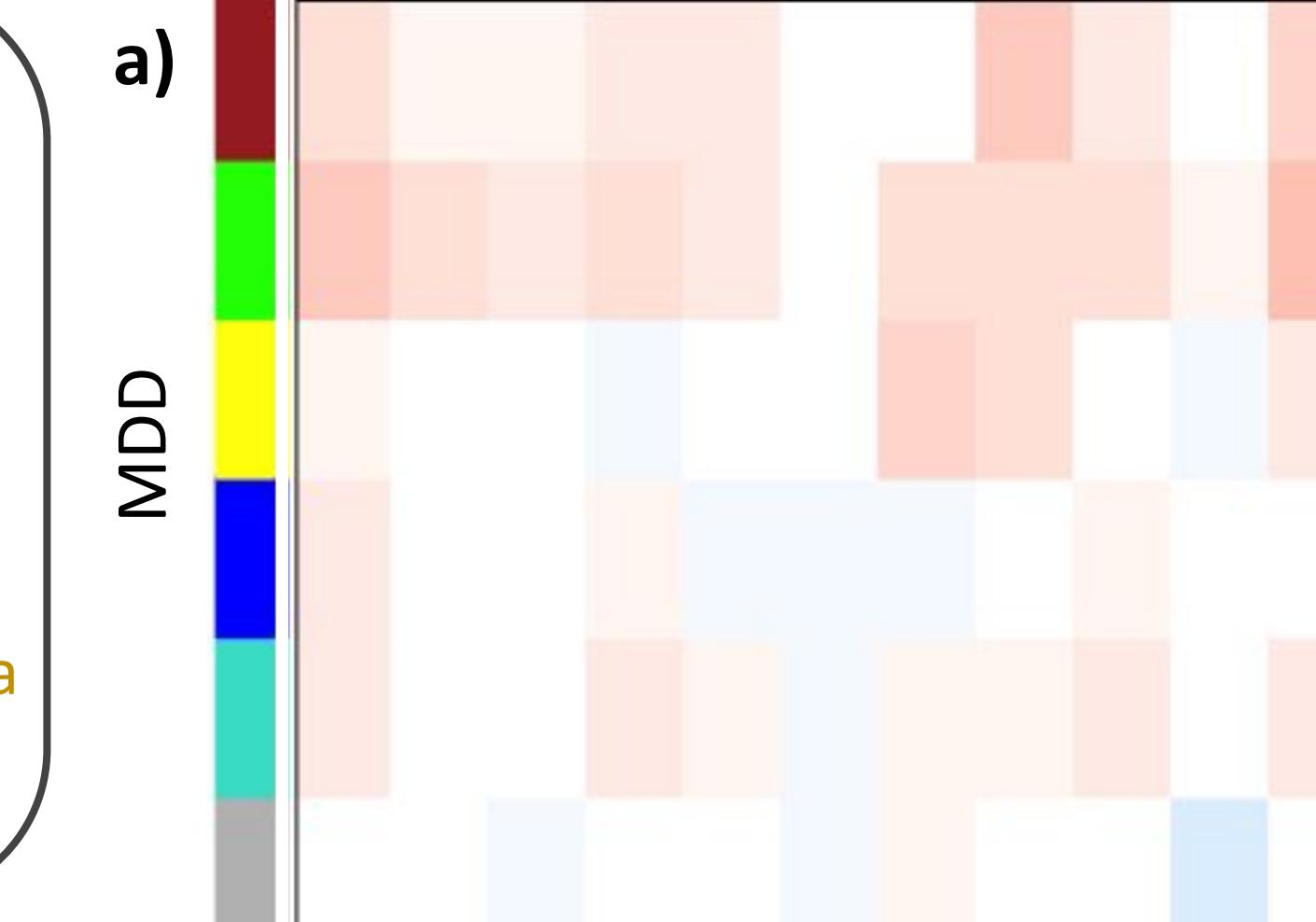


Figure 4. Average inflammatory marker levels (mg/L) in MDD and control subjects. Horizontal bar depicts $p < 0.05$.



Montgomery–Åsberg Depression Rating Scale

Figure 5. Module-Trait correlations for (a) depression (b) and MRI. Red: $r^2 > 0$. White: $r^2 = 0$. Blue: $r^2 < 0$. Grey: missing values.

DISCUSSION

- WGCNA-derived brown and green inflammatory modules revealed positive correlations with the traits of depression, fractional anisotropy, and mean diffusivity in MDD.
- The simultaneous reduction of fractional anisotropy with mean diffusivity in MDD suggests the presence of cytotoxic edema and neurodegeneration.
- Moreover, MDD inflammatory modules are negatively correlated with correlation diffusion index in white matter tracts, implying decreased white matter integrity.

ACKNOWLEDGEMENTS

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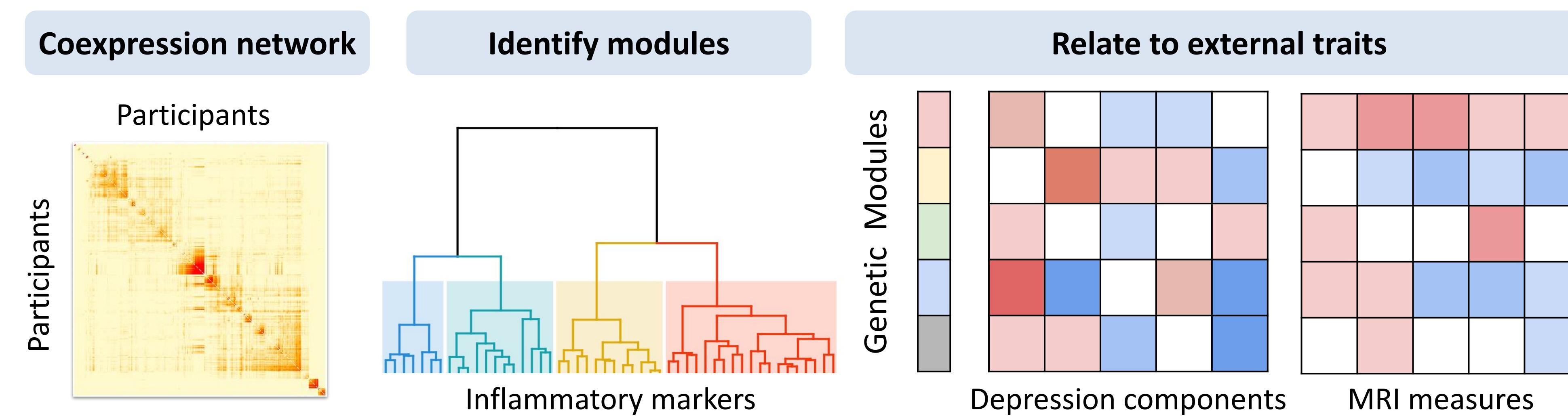


PIPELINE

Canadian Biomarker Integration Network in Depression (CANBIND-1)

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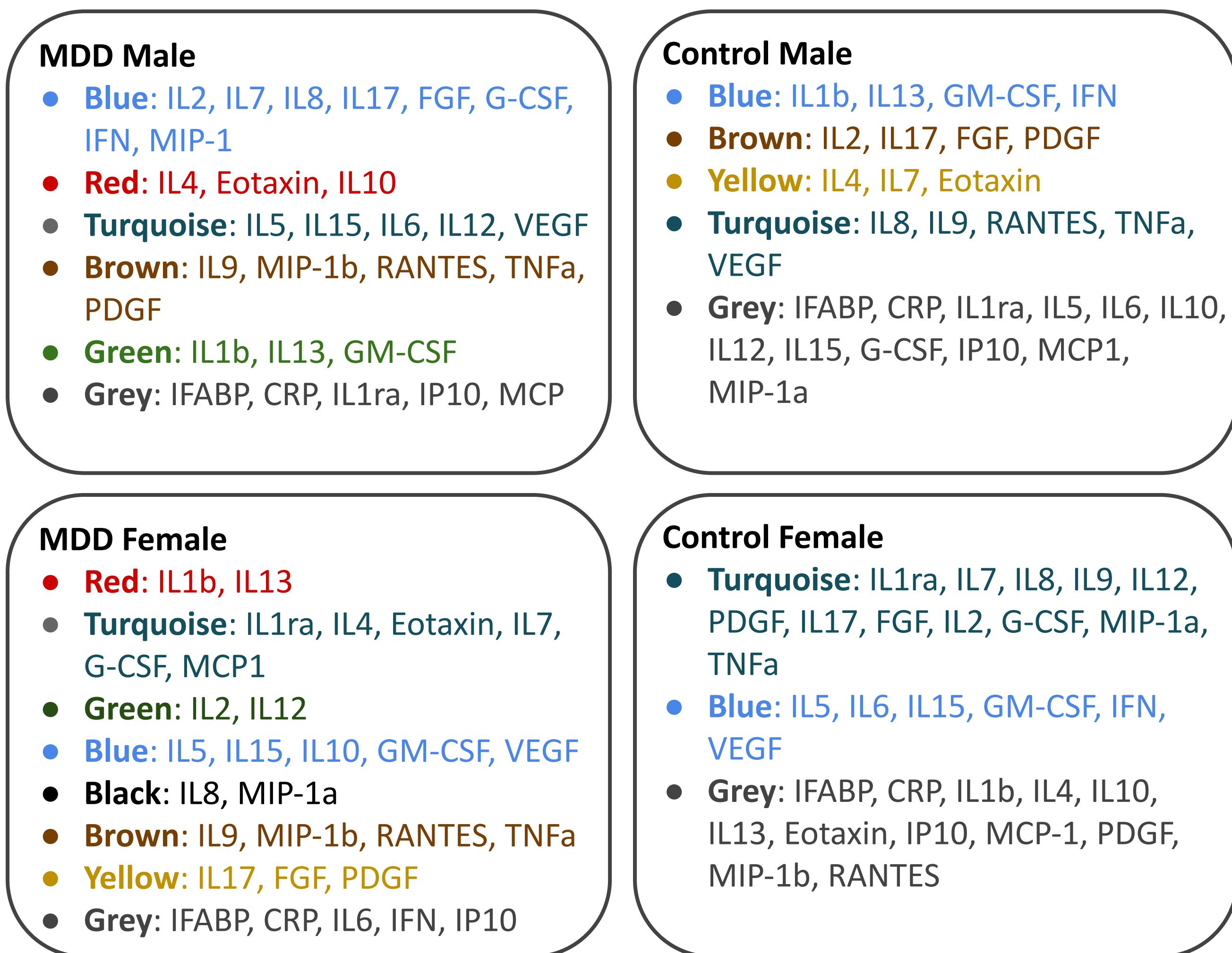


Figure 1. Inflammatory modules detected by WGCNA.

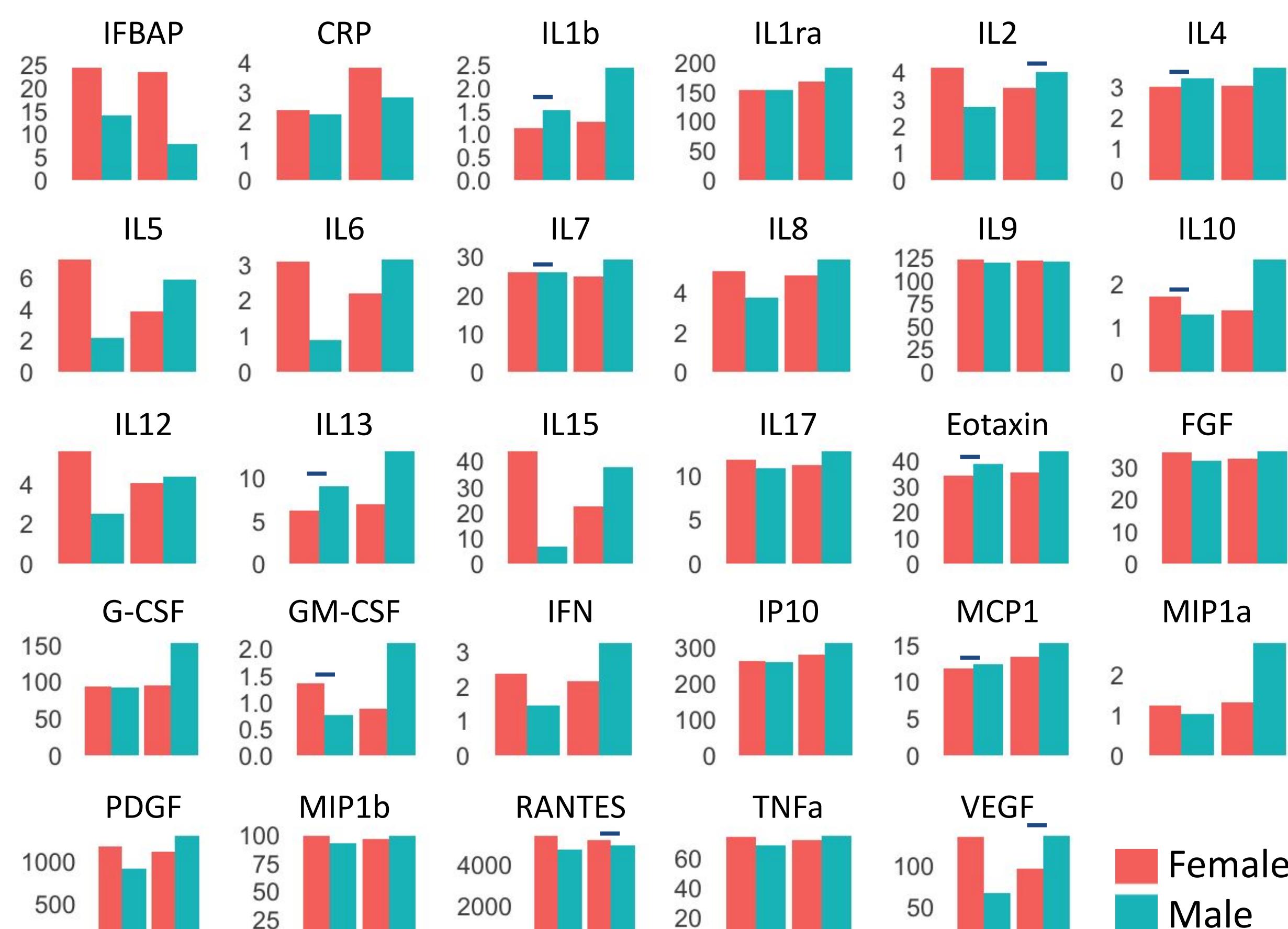


Figure 2. Average marker levels (mg/L) in MDD (left) and control (right).

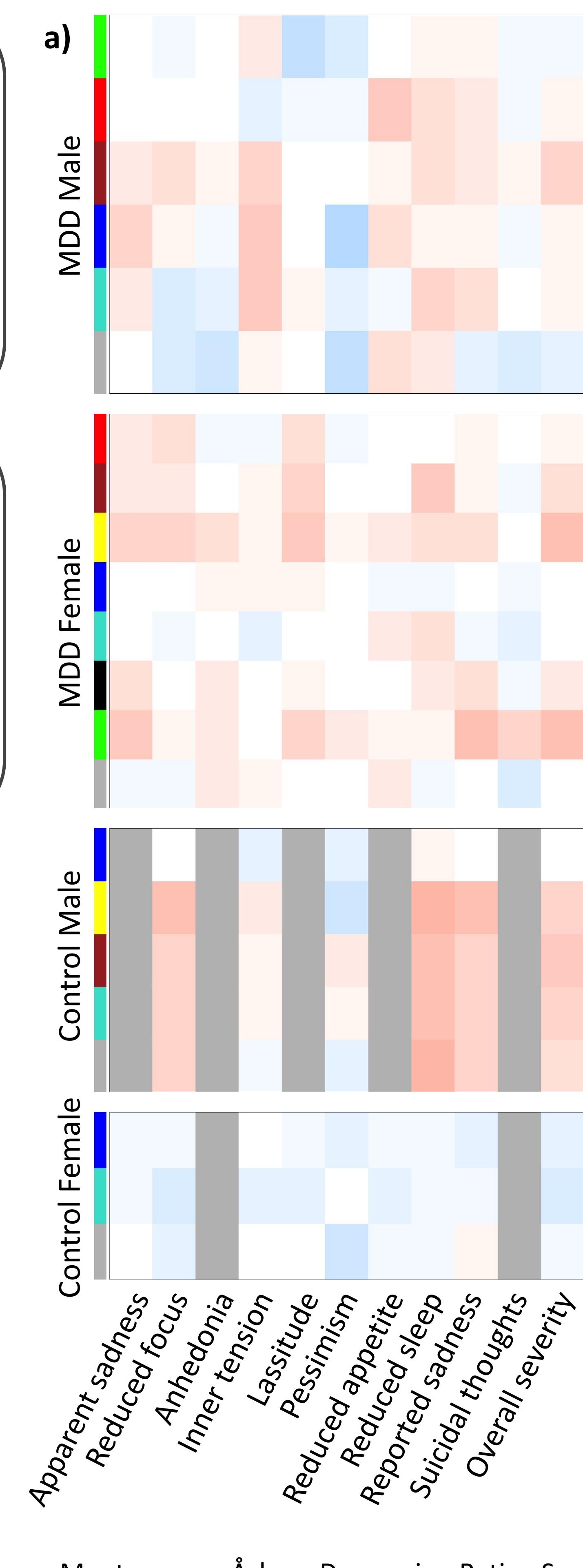


Figure 3. Module-Trait correlations for (a) depression (b) and MRI. Red: $r^2 > 0$. White: $r^2 = 0$. Blue: $r^2 < 0$. Grey: missing values.

CDI: Correlation diffusion index
FWF: Free water fraction
FAt: Free water corrected fractional anisotropy
MDt: free water corrected mean diffusivity

Diffusion MRI-based Brain Parcellation



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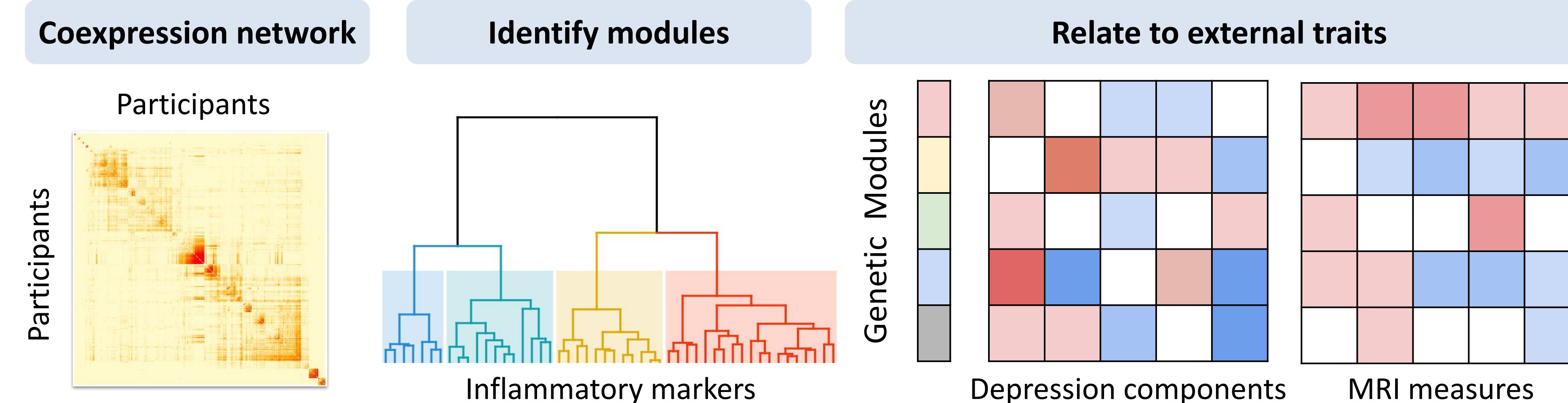
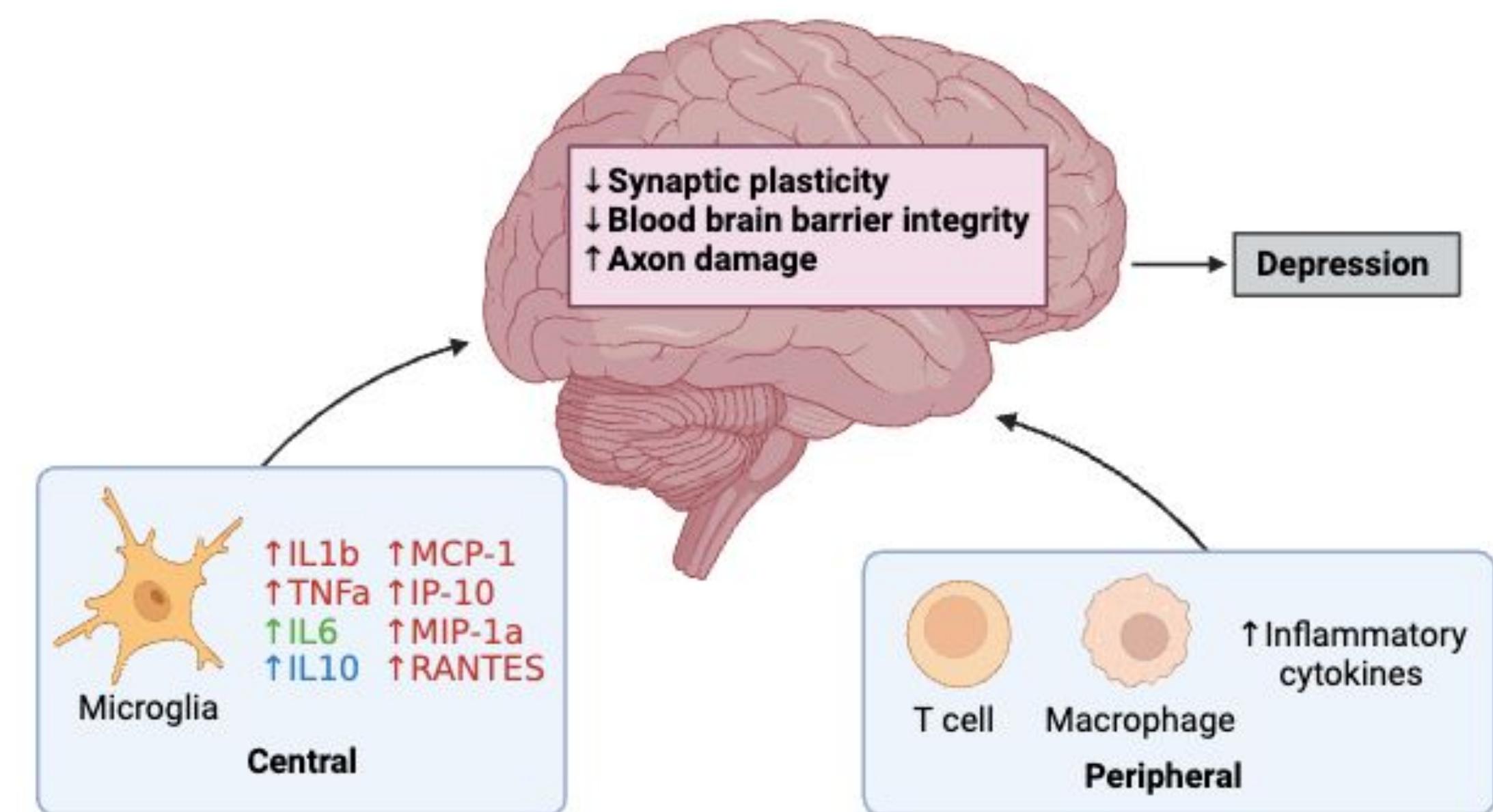
Weighted Gene Co-expression Network Analysis (WGCNA)**RESULTS**

Figure 1. Mechanisms of Neuroinflammation [1]. Red: pro-inflammatory. Blue: anti-inflammatory. Green: both pro- and anti-inflammatory.

MDD

- Turquoise: IL2, IL5, IL6, IL8, IL12, G-CSF, MIP-1a, VEGF
- Yellow: IL4, Eotaxin, IL7
- Brown: IL9, MIP-1b, RANTES, TNFa
- Blue: IL1b, IL10, IL13, GM-CSF
- Green: IL17, FGF, PDGF
- Grey: IFABP, CRP, IL1ra, IL15, IFN, IP10, MCP

Figure 2. Inflammatory modules detected by WGCNA.

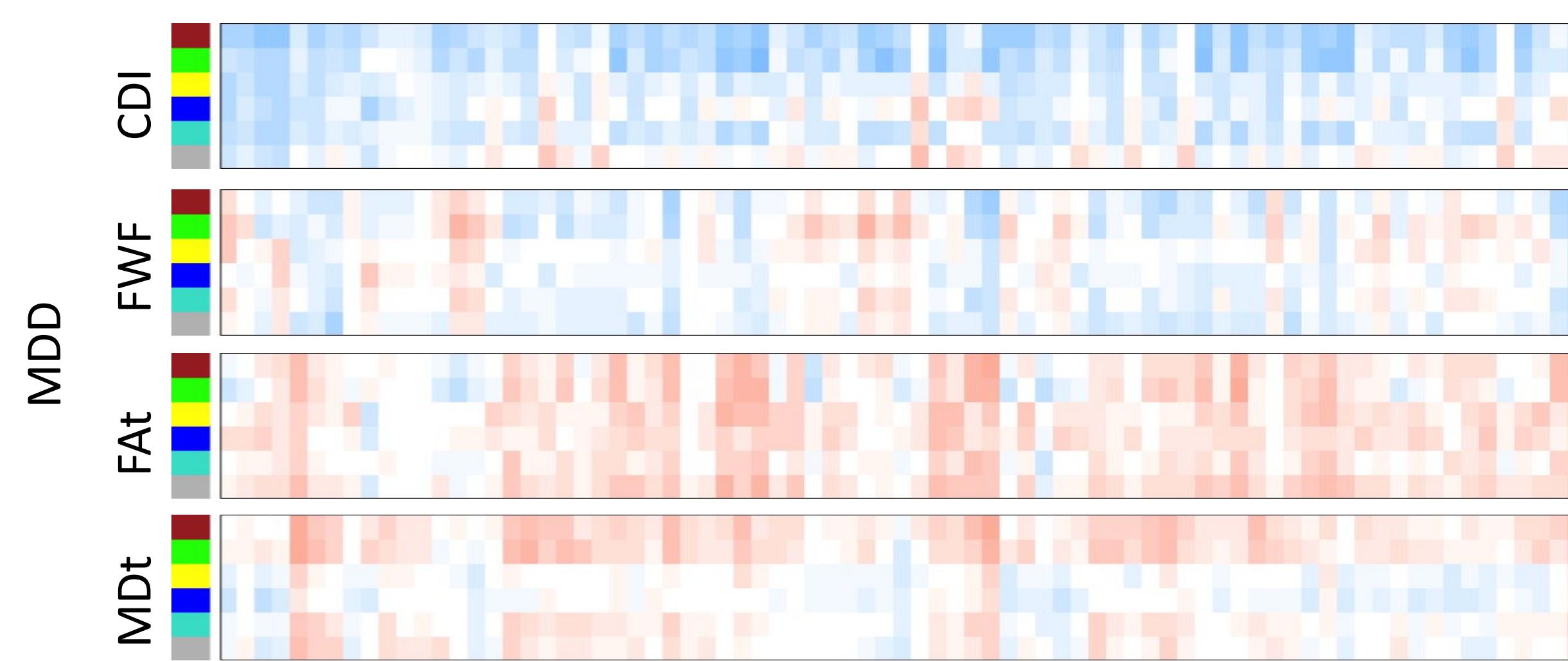
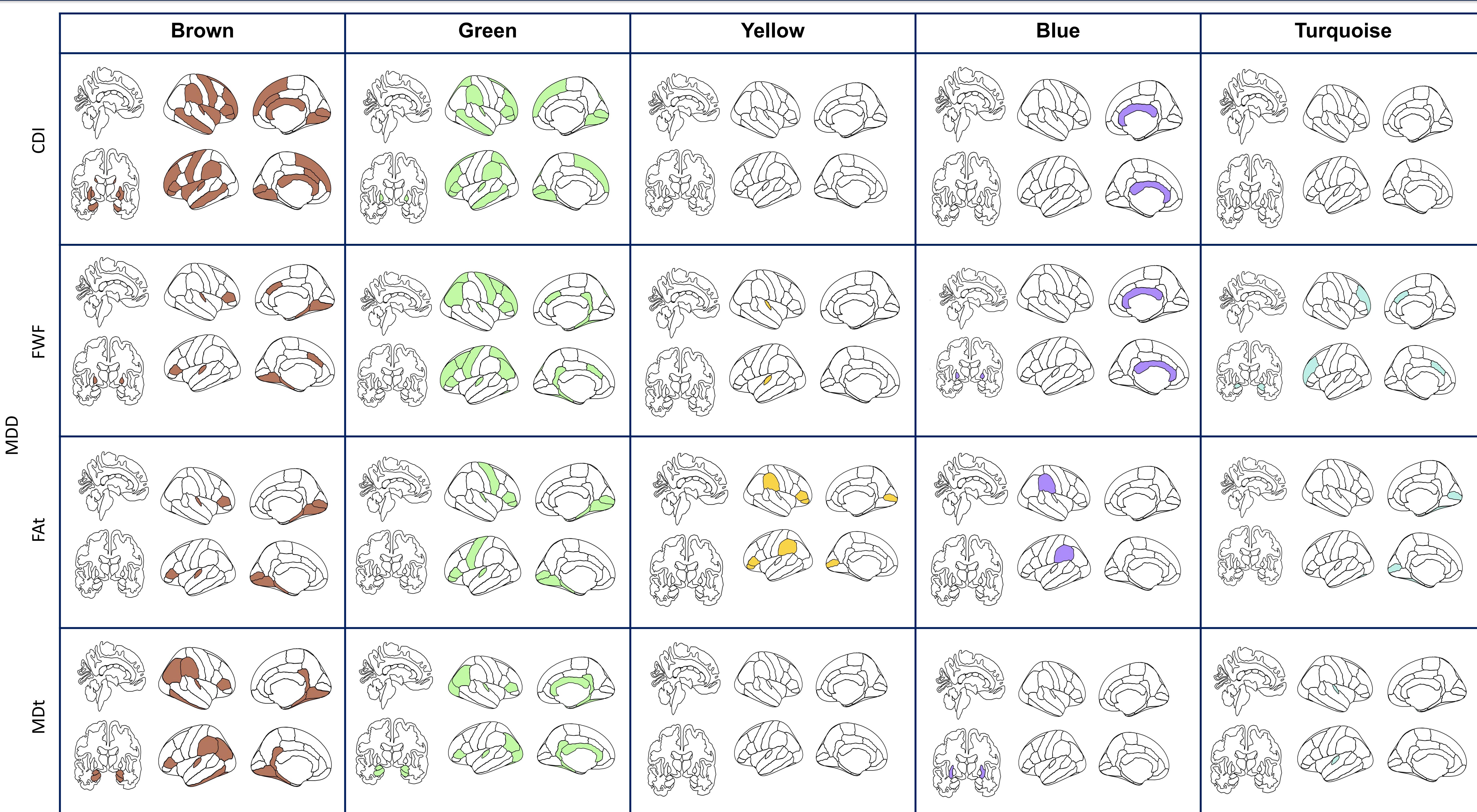


Figure 3. Module-Trait correlations for MRI. Red: $r^2 > 0$. White: $r^2 = 0$. Blue: $r^2 < 0$. Grey: missing values.



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Figure 4. Diffusion tensor imaging correlates with inflammatory modules of depression.



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