

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



Lucy Hui, Joanna Chen, Jean Chen

Rotman Research Institute, Baycrest Health Sciences, Toronto, Canada

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.

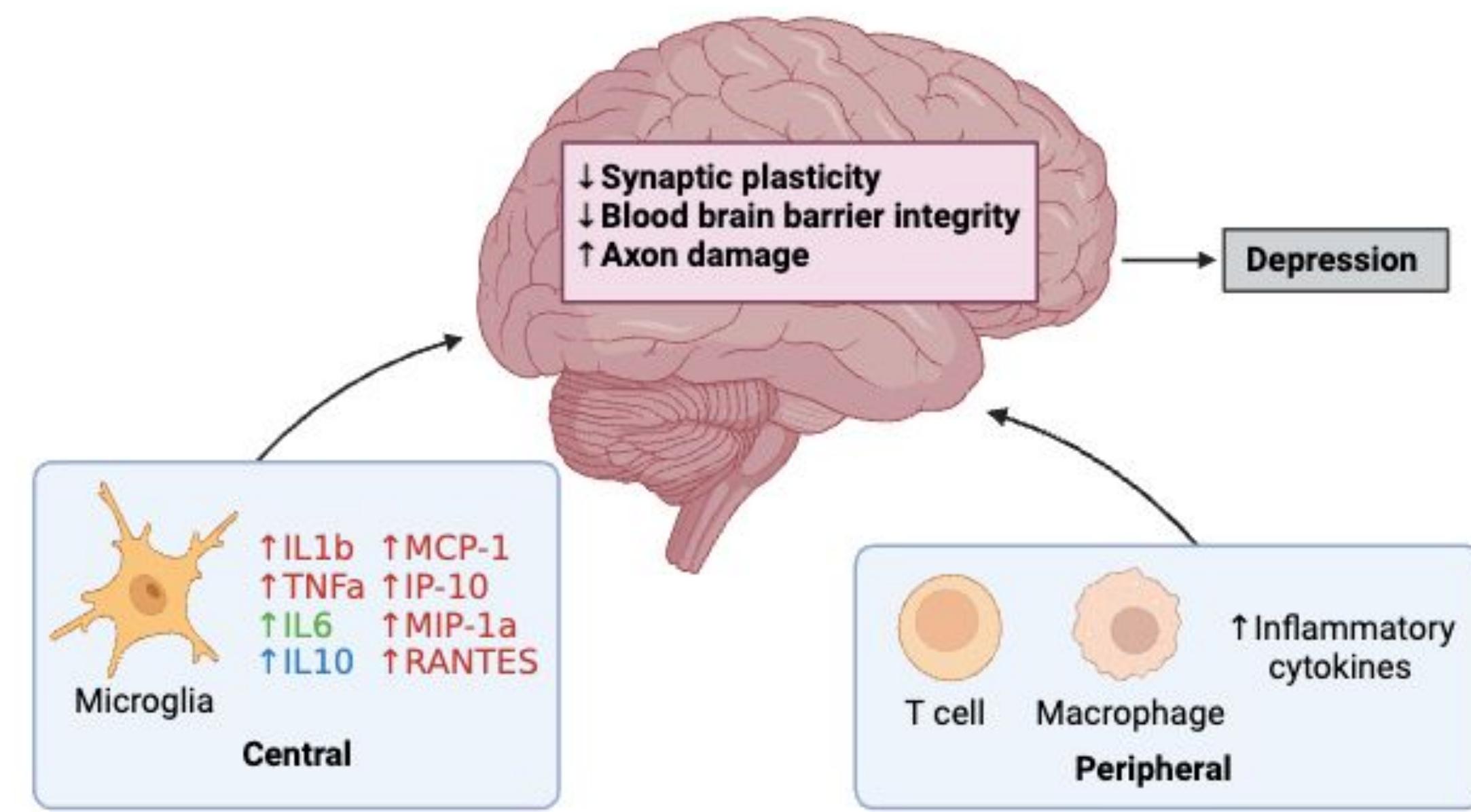


Figure 1. Mechanisms of Neuroinflammation [1]. Red: pro-inflammatory. Blue: anti-inflammatory. Green: both pro- and anti-inflammatory.

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.

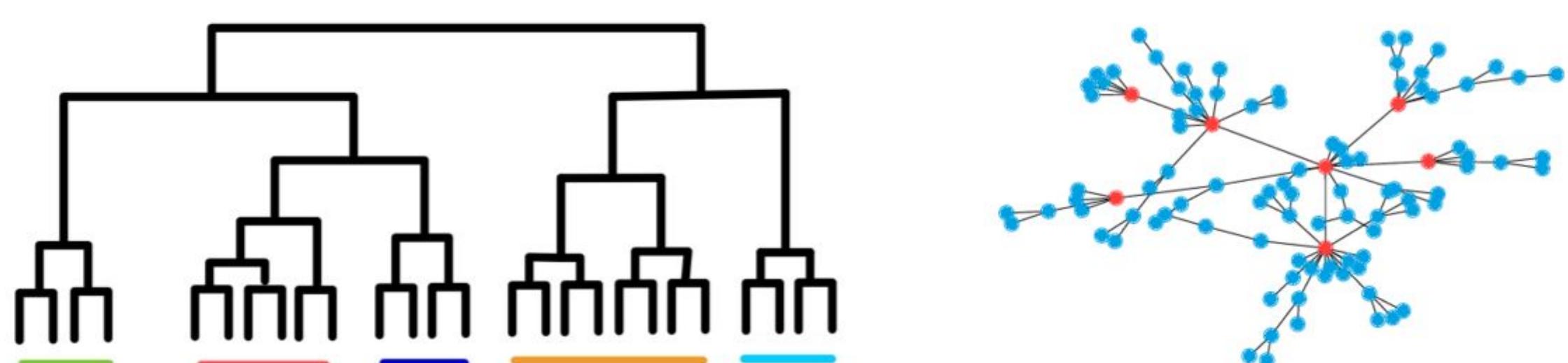


Figure 2. Hierarchical clustering for scale free networks [2-3]

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

- Miller, A., Raison, C. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* 16, 22–34 (2016). <https://doi.org/10.1038/nri.2015.5>
- Kim, E. How to find the optimal number of clusters with R? *Medium* (2022). <https://medium.com/@chewin5555/how-to-find-the-optimal-number-of-clusters-with-r-dbf8498388b8>
- Wurzburg, J. Synchrony Measurement and Connectivity Estimation of Parallel Spike Trains from *in vitro* Neuronal Networks (2020). DOI:10.25972/OPUS-22364

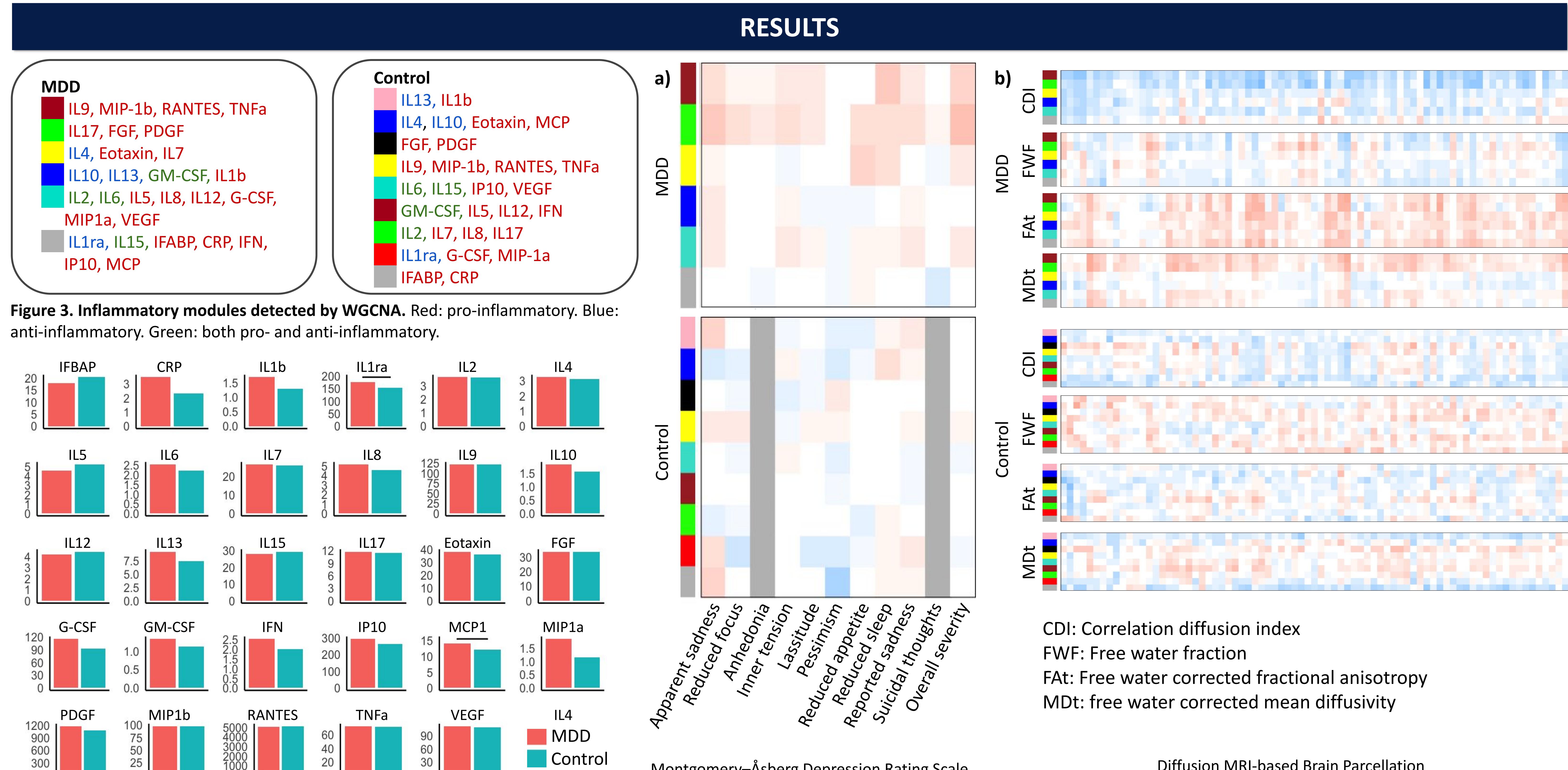
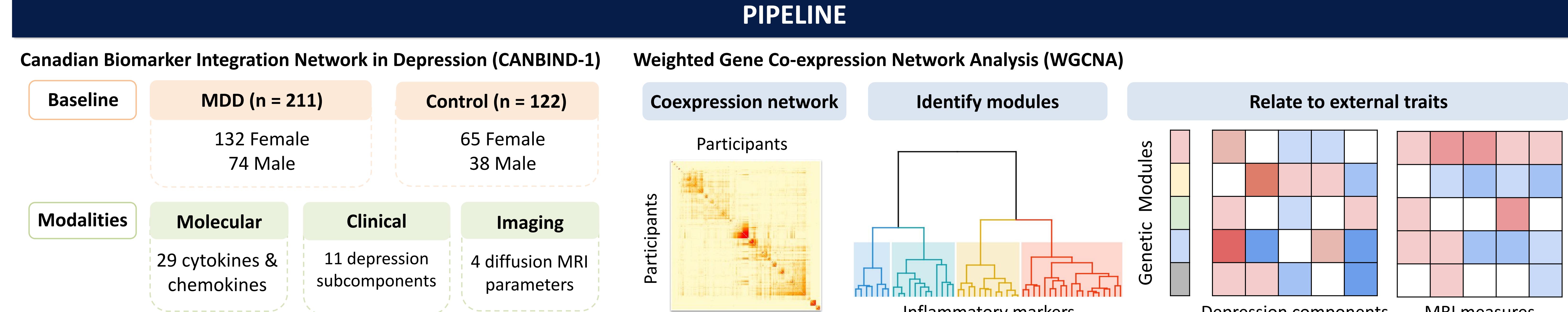


Figure 4. Average inflammatory marker levels (mg/L) in MDD and control subjects. Horizontal bar depicts $p < 0.05$.

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

This project is supported by the Data Sciences Institute, University of Toronto



git lucy-mhui

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



Lucy Hui, Joanna Chen, Jean Chen

Rotman Research Institute, Baycrest Health Sciences, Toronto, Canada

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.

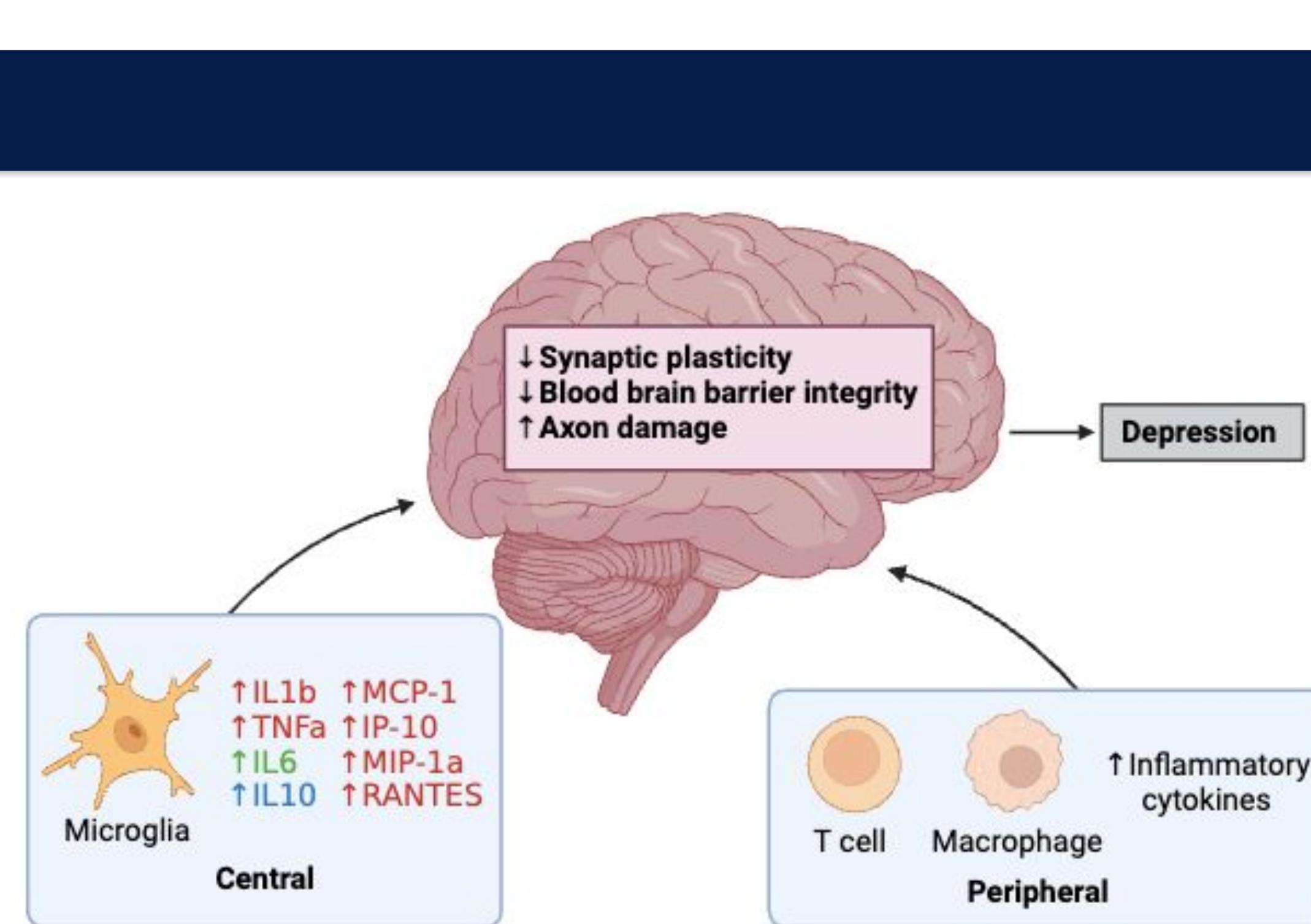


Figure 1. Mechanisms of Neuroinflammation [1]. Red: pro-inflammatory. Blue: anti-inflammatory. Green: both pro- and anti-inflammatory.

MDD						
IL9, MIP-1b, RANTES, TNFa						
IL17, FGF, PDGF						
IL4, Eotaxin, IL7						
IL10, IL13, GM-CSF, IL1b						
IL2, IL6, IL5, IL8, IL12, G-CSF, MIP1a, VEGF						
IL1ra, IL15, IFABP, CRP, IFN, IP10, MCP						

Figure 2. Inflammatory modules detected by WGCNA. Red: pro-inflammatory. Blue: anti-inflammatory. Green: both pro- and anti-inflammatory.

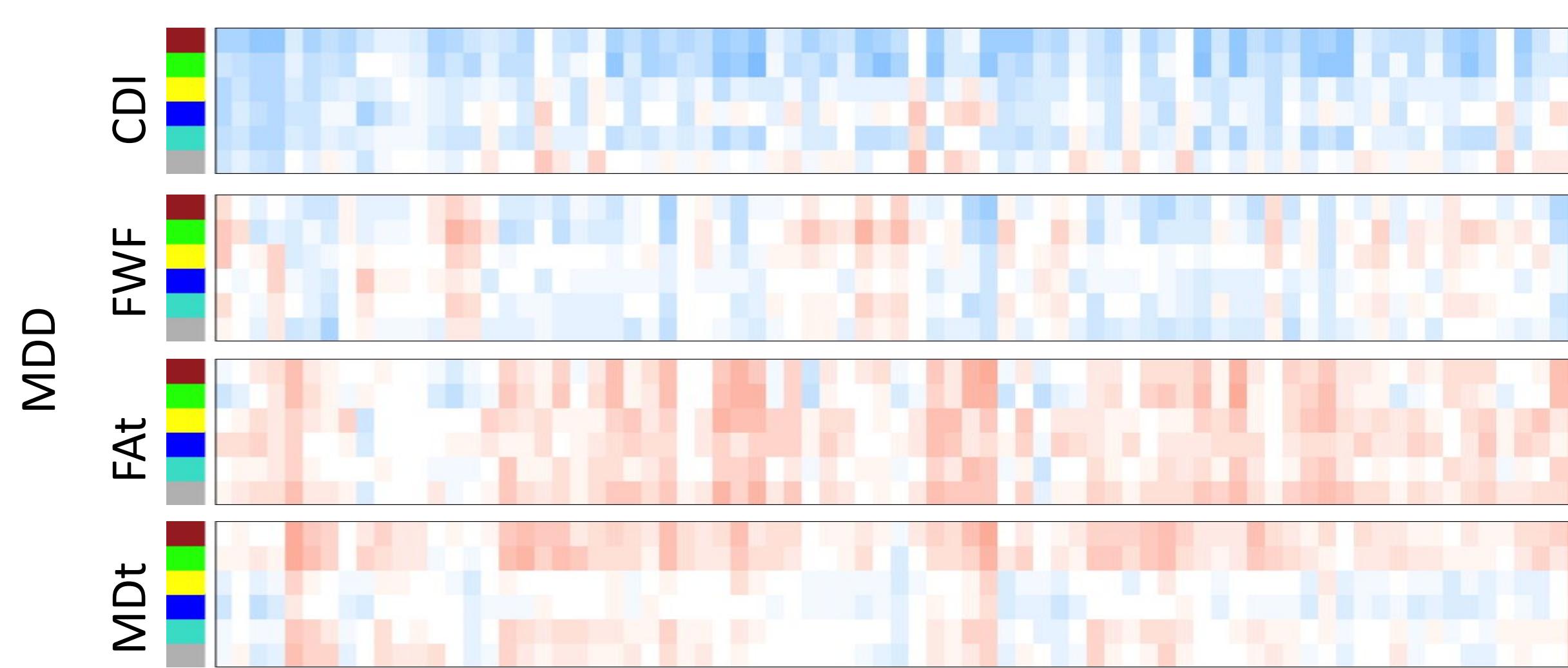


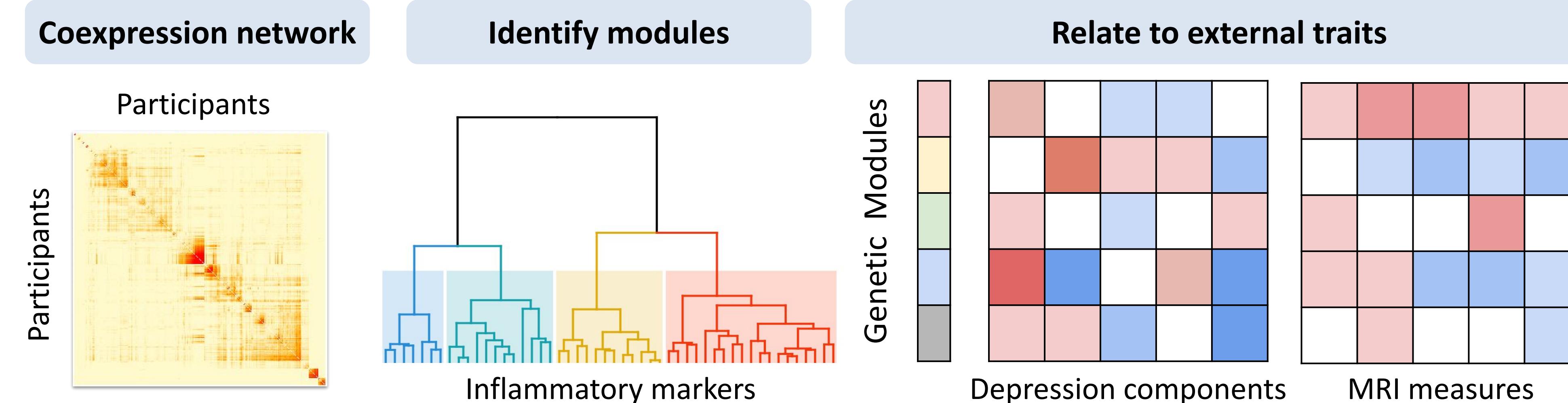
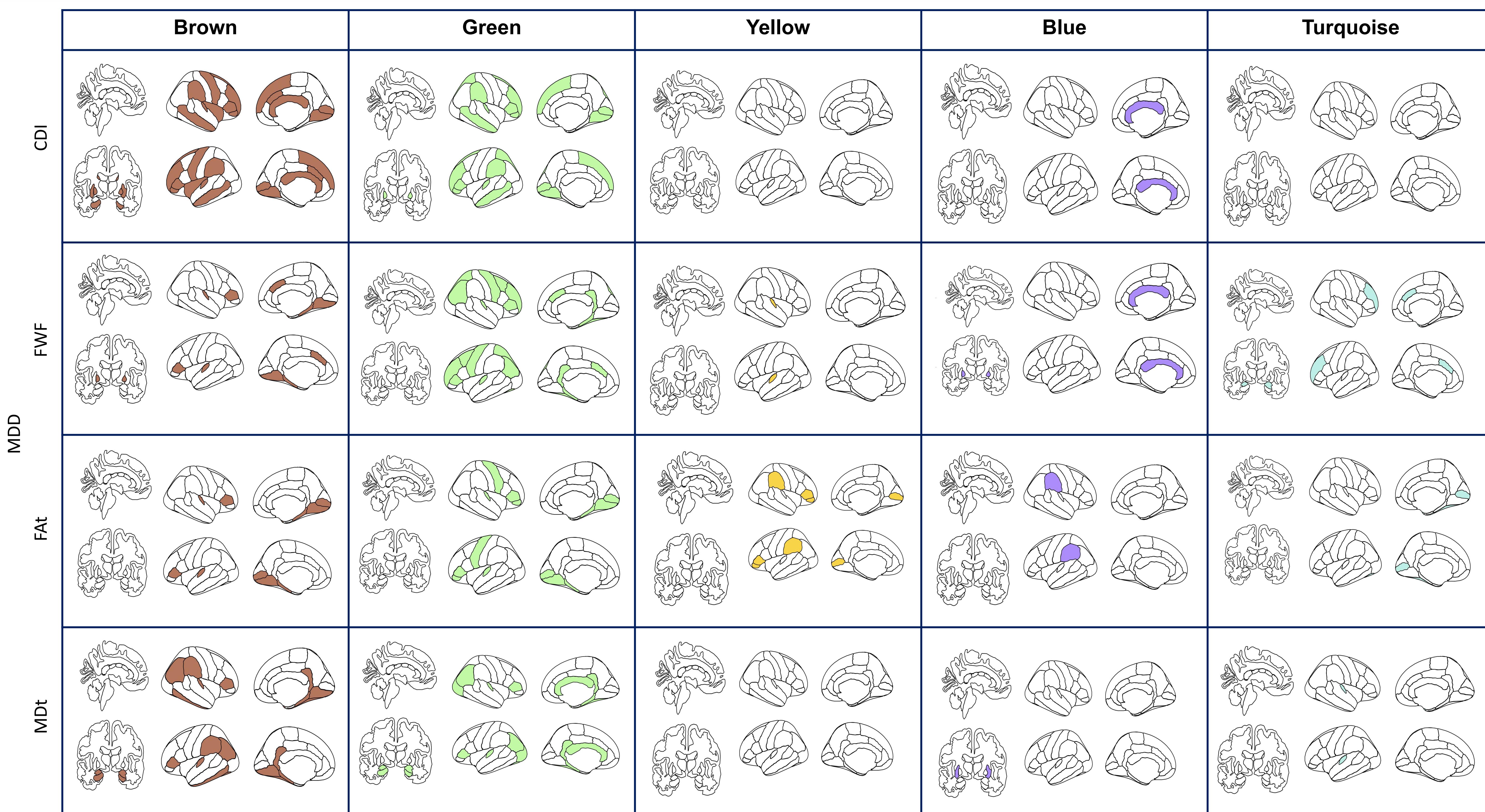
Figure 3. Module-Trait correlations for MRI. Red: $r^2 > 0$. White: $r^2 = 0$. Blue: $r^2 < 0$. Grey: missing values.

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 29 cytokines & chemokines	Clinical 11 depression subcomponents
		Imaging 4 diffusion MRI parameters

Weighted Gene Co-expression Network Analysis (WGCNA)

**RESULTS**

CDI: Correlation diffusion index

FWF: Free water fraction

FAt: Free water corrected fractional anisotropy

MDt: free water corrected mean diffusivity

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

git lucy-mhui

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

Lucy Hui, Joanna Chen, Jean Chen

Rotman Research Institute, Baycrest Health Sciences, Toronto, Canada

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.

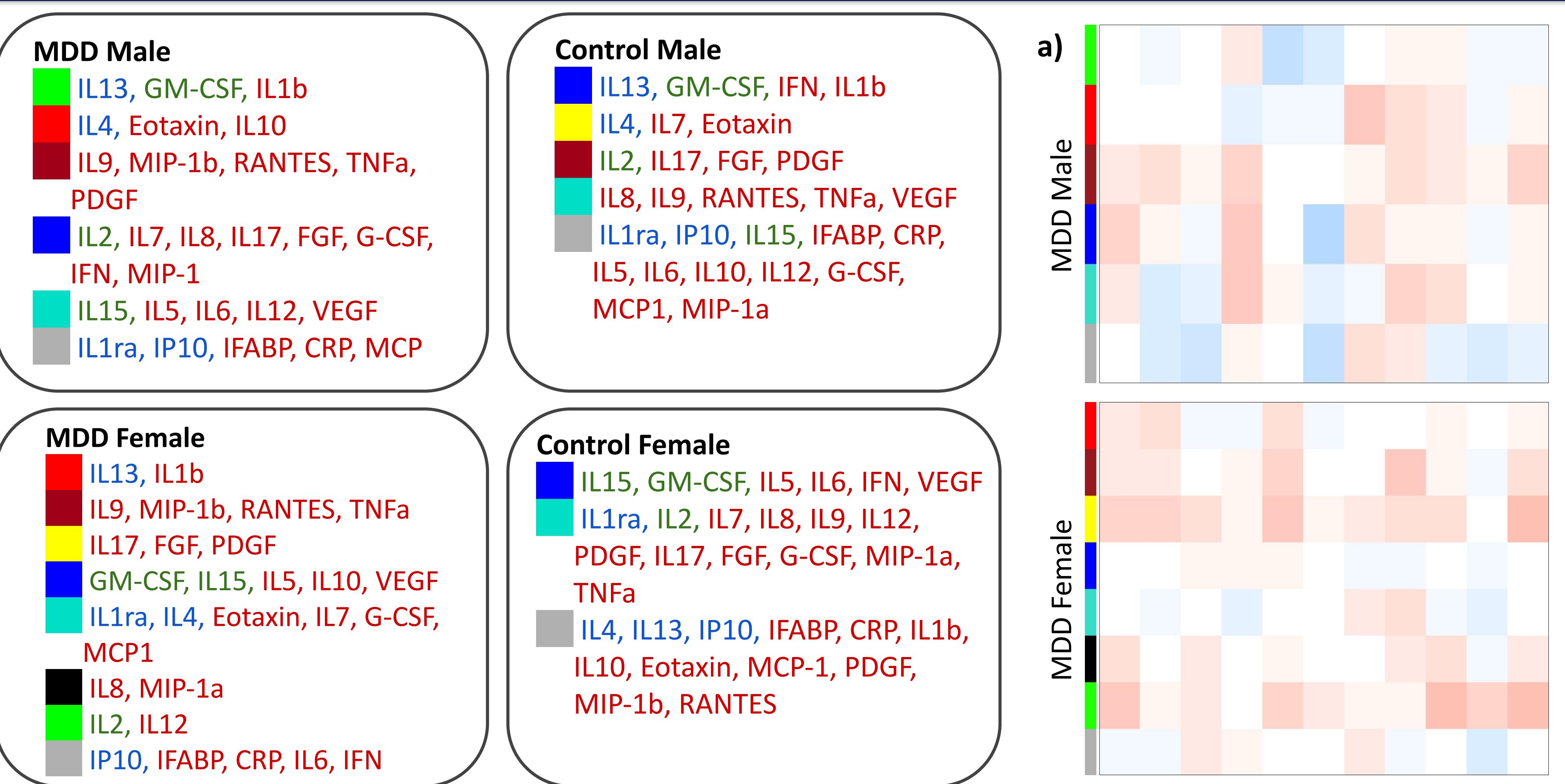


Figure 1. Inflammatory modules detected by WGCNA. Red: pro-inflammatory. Blue: anti-inflammatory. Green: both pro- and anti-inflammatory.



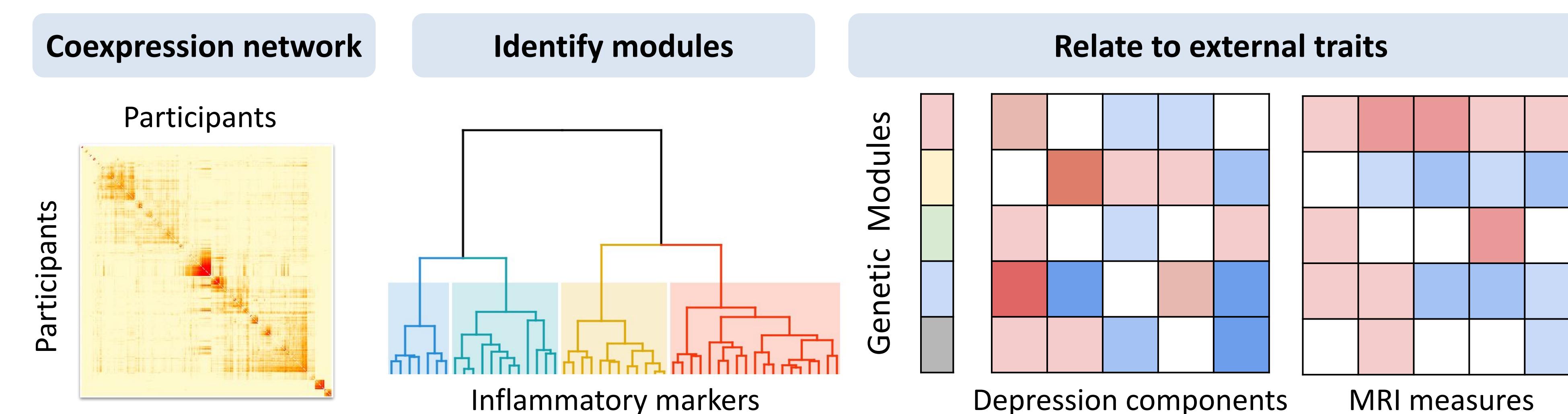
Figure 2. Average marker levels (mg/L) in MDD (left) and control (right).

PIPELINE

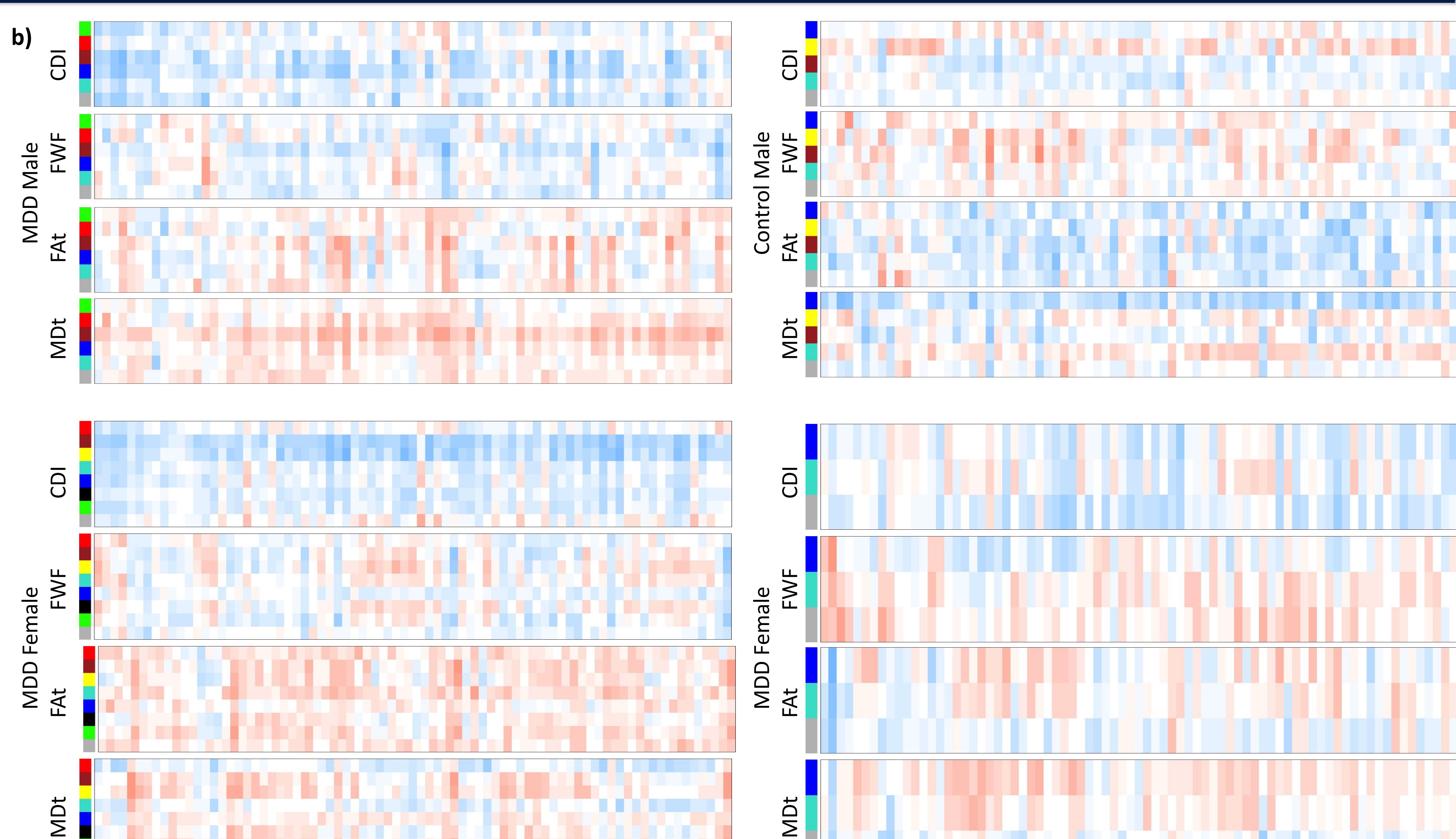
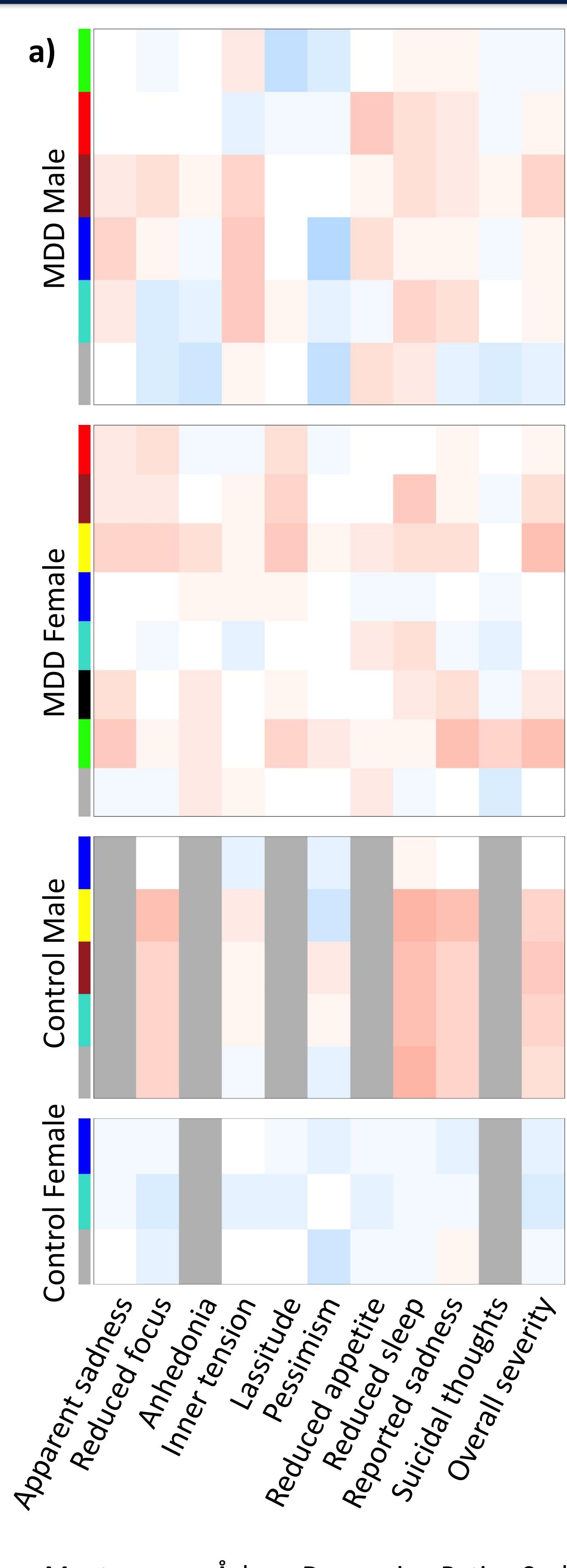
Canadian Biomarker Integration Network in Depression (CANBIND-1)

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



CDI: Correlation diffusion index

FWF: Free water fraction

FAt: Free water corrected fractional anisotropy

MDt: free water corrected mean diffusivity

Montgomery-Åsberg Depression Rating Scale

Diffusion MRI-based Brain Parcellation



git lucy-mhui

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.

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



Lucy Hui, Joanna Chen, Jean Chen

Rotman Research Institute, Baycrest Health Sciences, Toronto, Canada

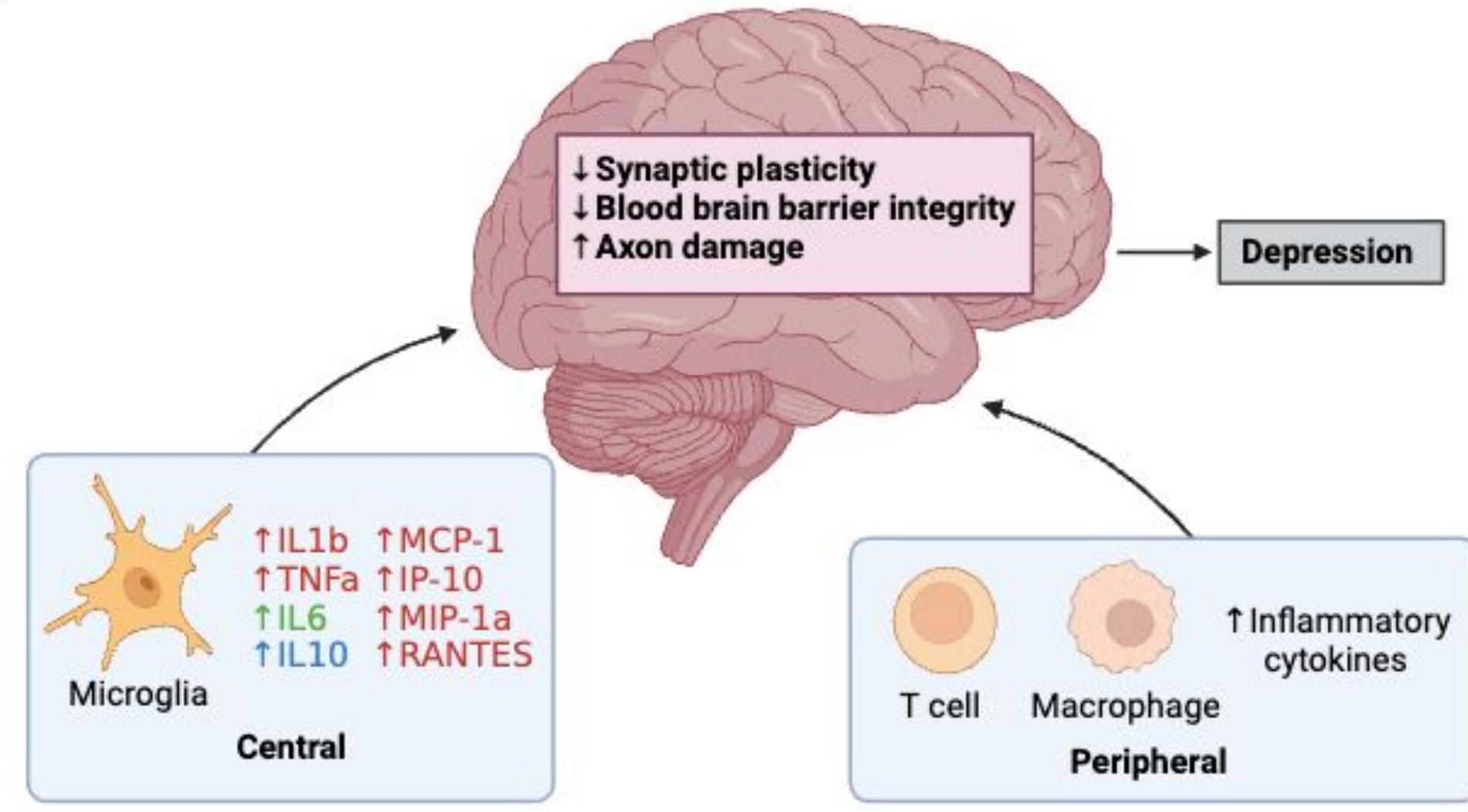


Figure 1. Mechanisms of Neuroinflammation [1]

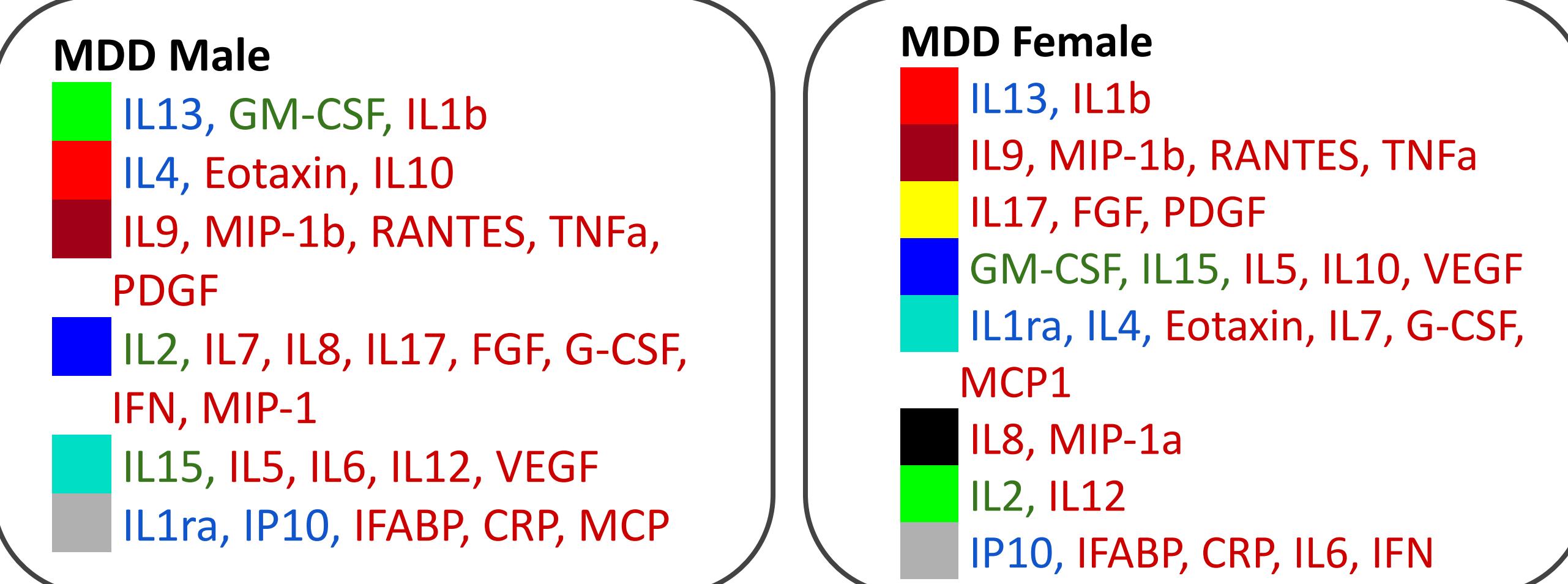
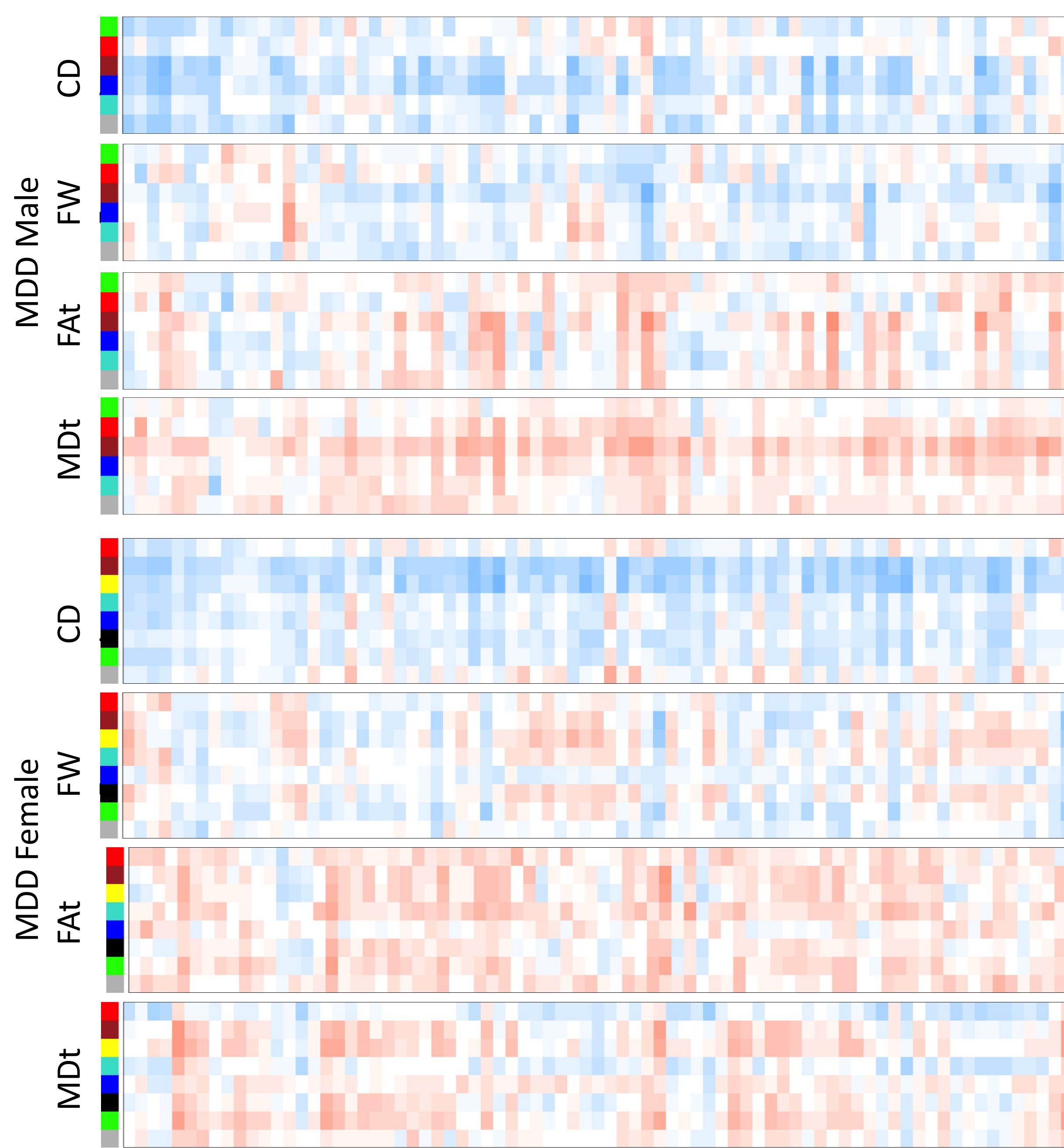


Figure 2. Inflammatory modules detected by WGCNA. Red: pro-inflammatory. Blue: anti-inflammatory. Green: both pro- and anti-inflammatory.



CDI: Correlation diffusion index

FWF: Free water fraction

FAt: Free water corrected fractional anisotropy

MDt: free water corrected mean diffusivity

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

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