

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.

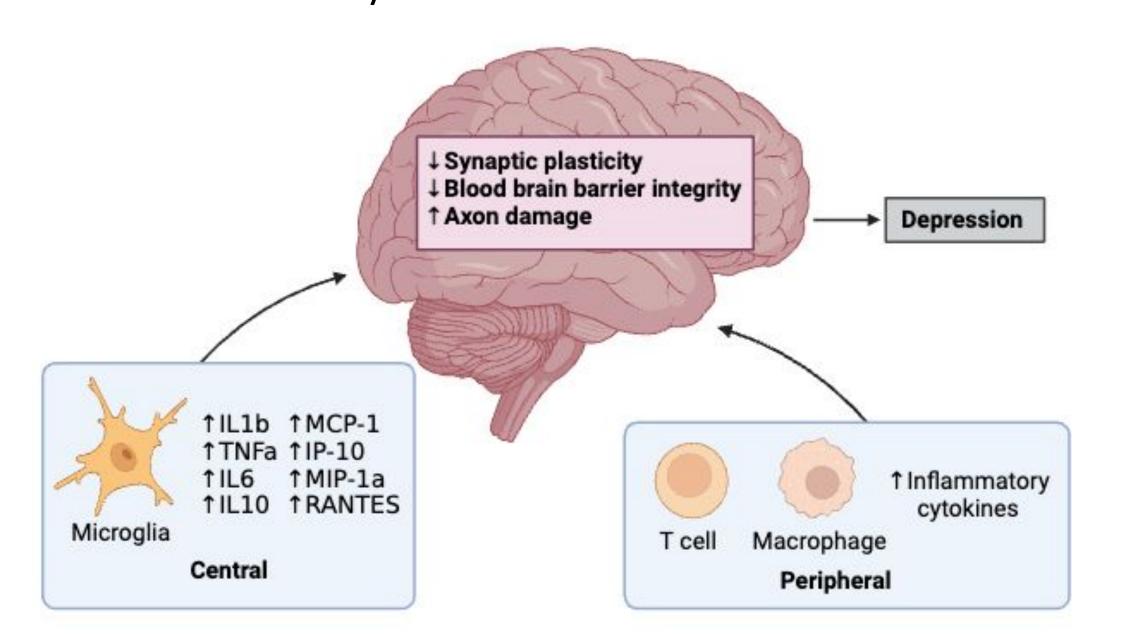


Figure 1. Mechanisms of Neuroinflammation [1]

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.

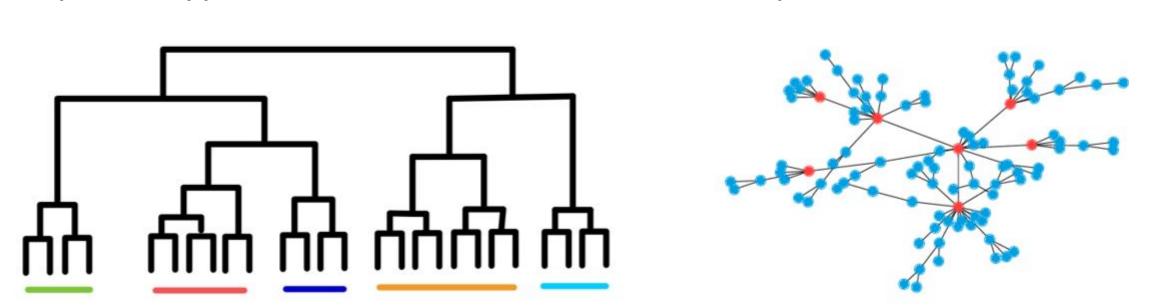


Figure 2. Hierarchical clustering for scale free networks [2-3]

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

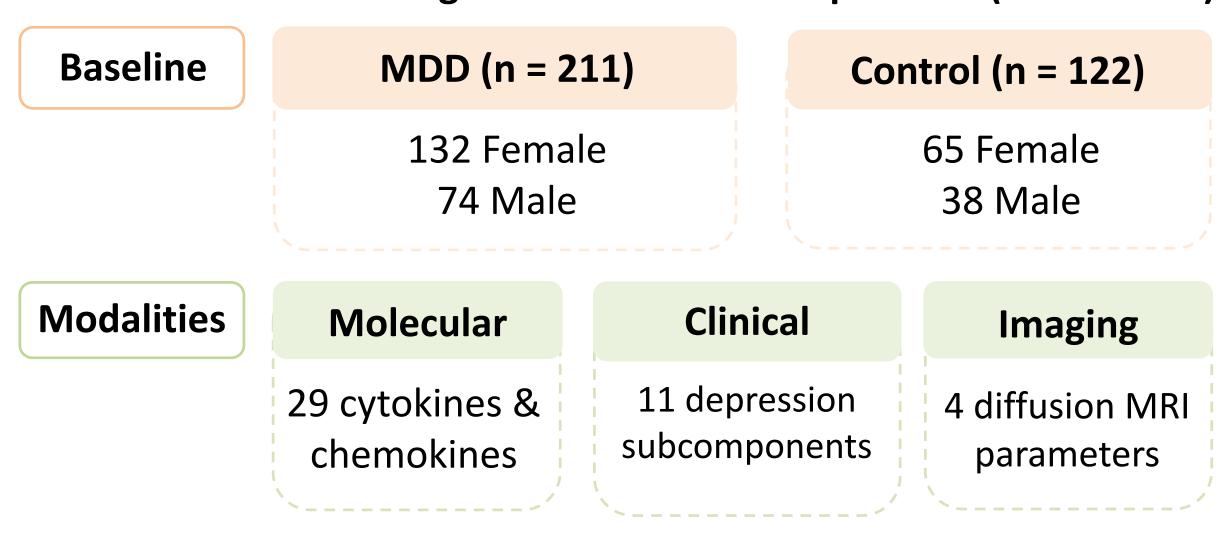
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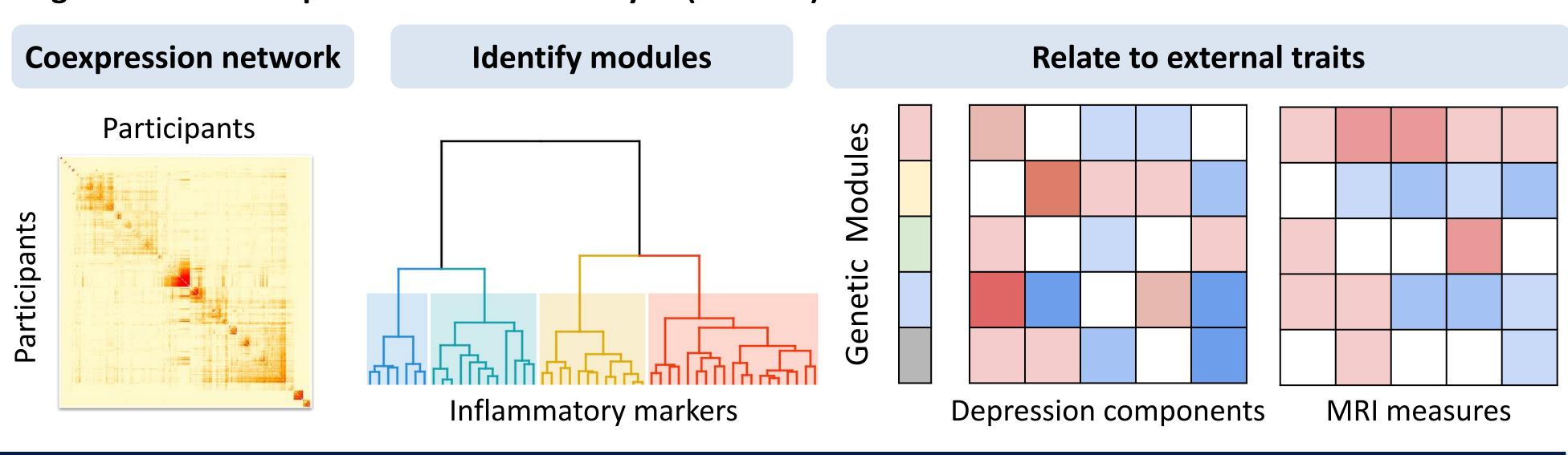
PIPELINE

RESULTS

Canadian Biomarker Integration Network in Depression (CANBIND-1) Weighted Gene Co-ex



Weighted Gene Co-expression Network Analysis (WGCNA)



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

Control

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

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

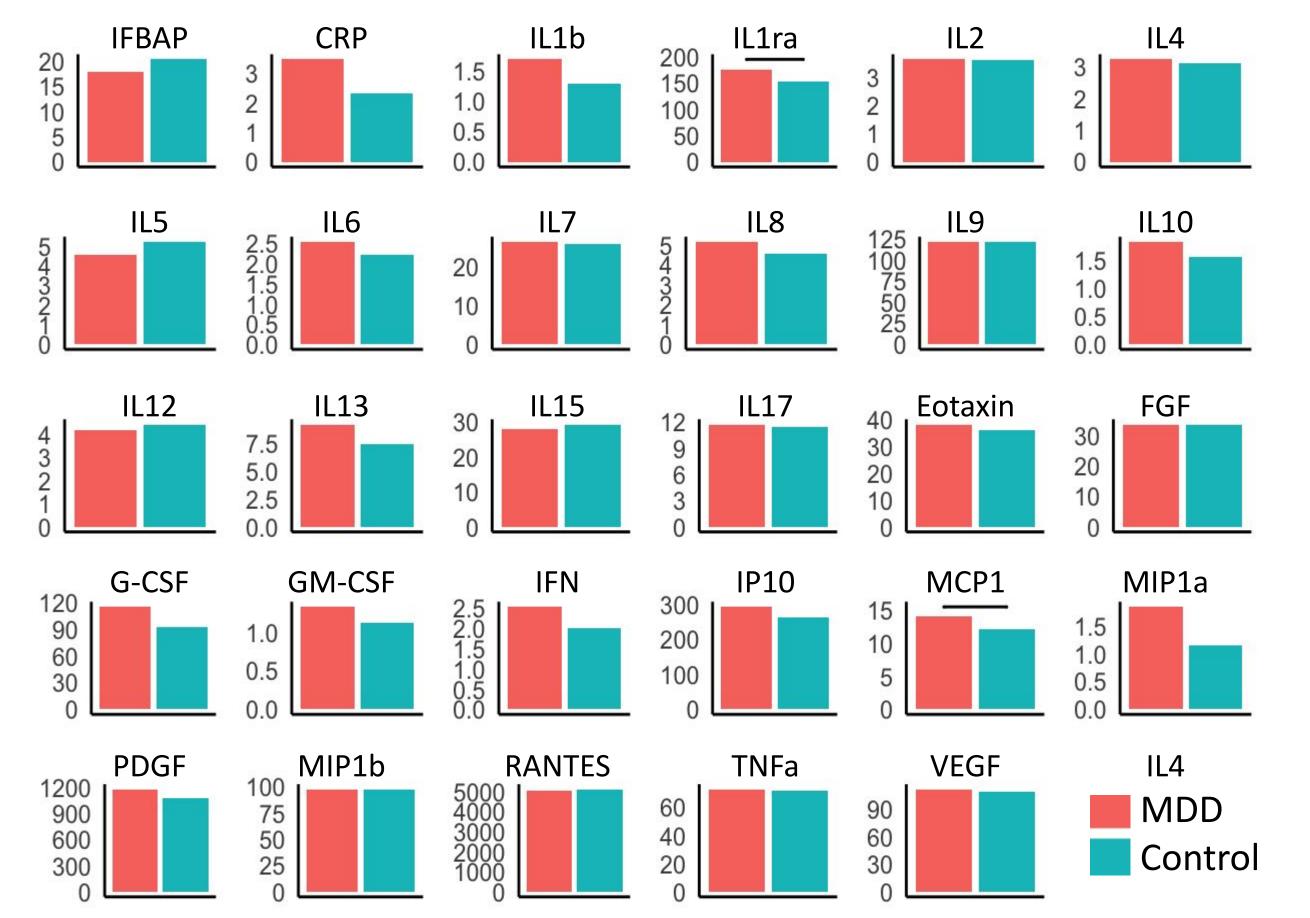
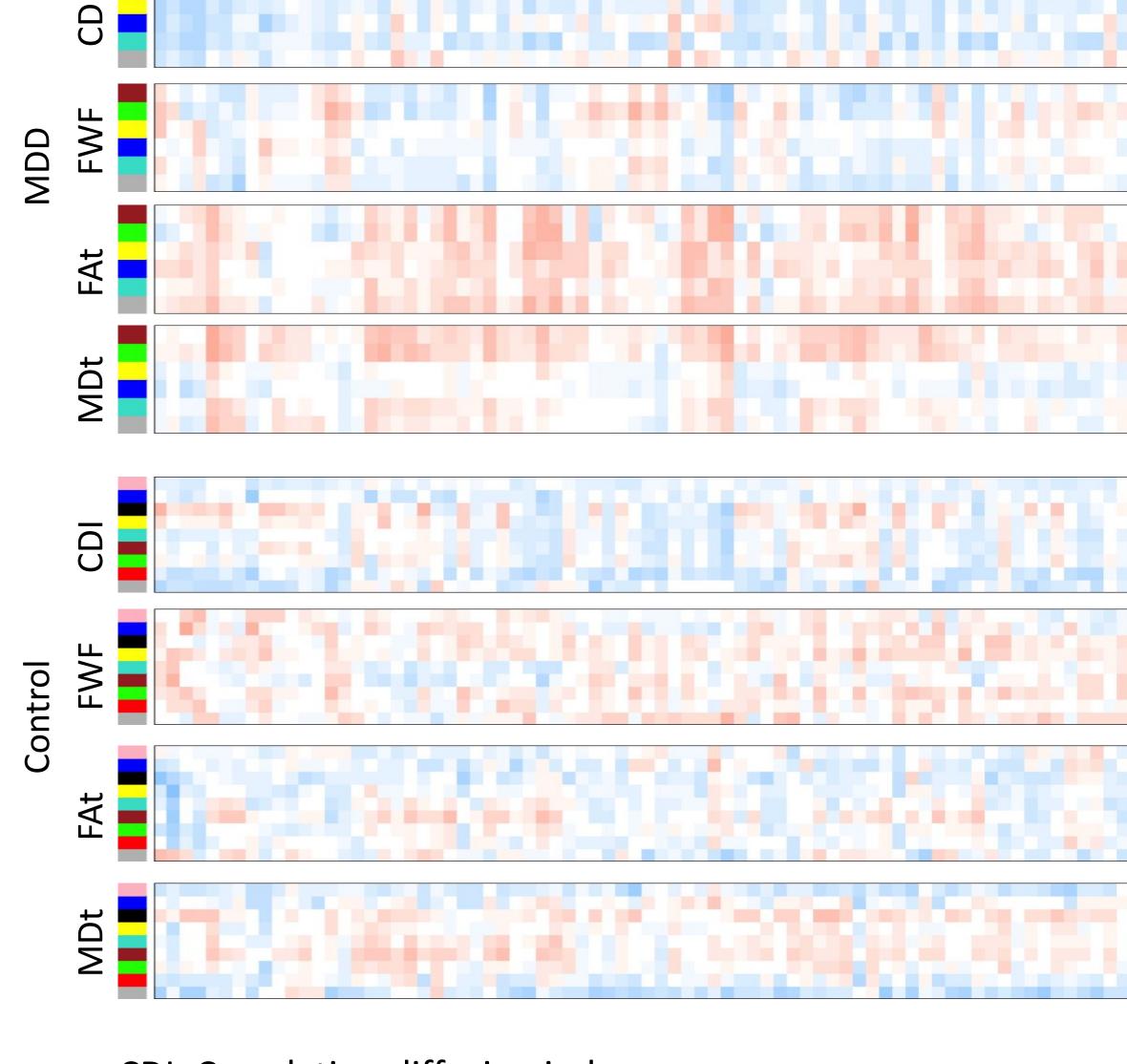


Figure 4. Average inflammatory marker levels (mg/L) in MDD and control subjects. Horizontal bar depicts p<0.05.

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Montgomery-Åsberg Depression Rating Scale



CDI: Correlation diffusion index

FWF: Free water fraction

FAt: Free water corrected fractional anisotropy

MDt: free water corrected mean diffusivity

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

Diffusion MRI-based Brain Parcellation

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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Control (n = 122)

65 Female

Canadian Biomarker Integration Network in Depression (CANBIND-1)

Clinical

11 depression

subcomponents

MDD (n = 211)

132 Female

74 Male

Molecular

29 cytokines &

chemokines

OBJECTIVES

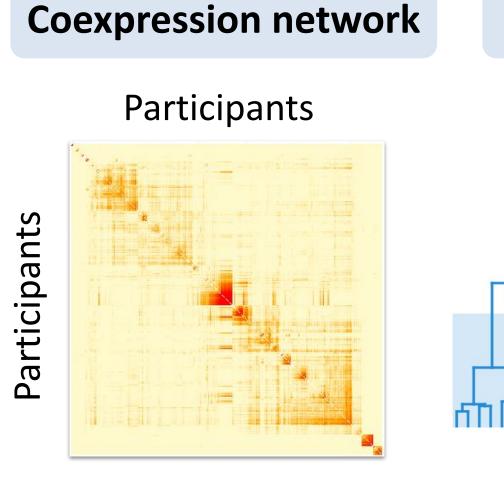
- Identify sex-dependent modules of co-expressed genes associated with inflammatory biomarkers in MDD patients and healthy controls, elucidating shared and distinct networks underlying inflammation in depression.
- Assess the correlation between inflammatory gene expression modules, clinical variables,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

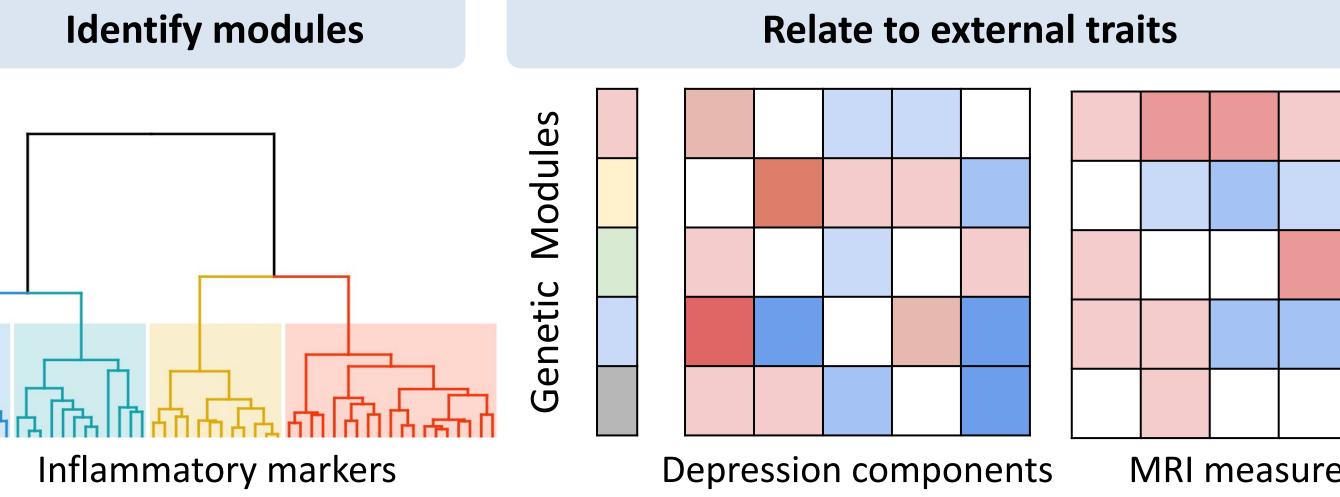




PIPELINE

Weighted Gene Co-expression Network Analysis (WGCNA)





38 Male **Imaging** 4 diffusion MRI parameters MRI measures

MDD Male

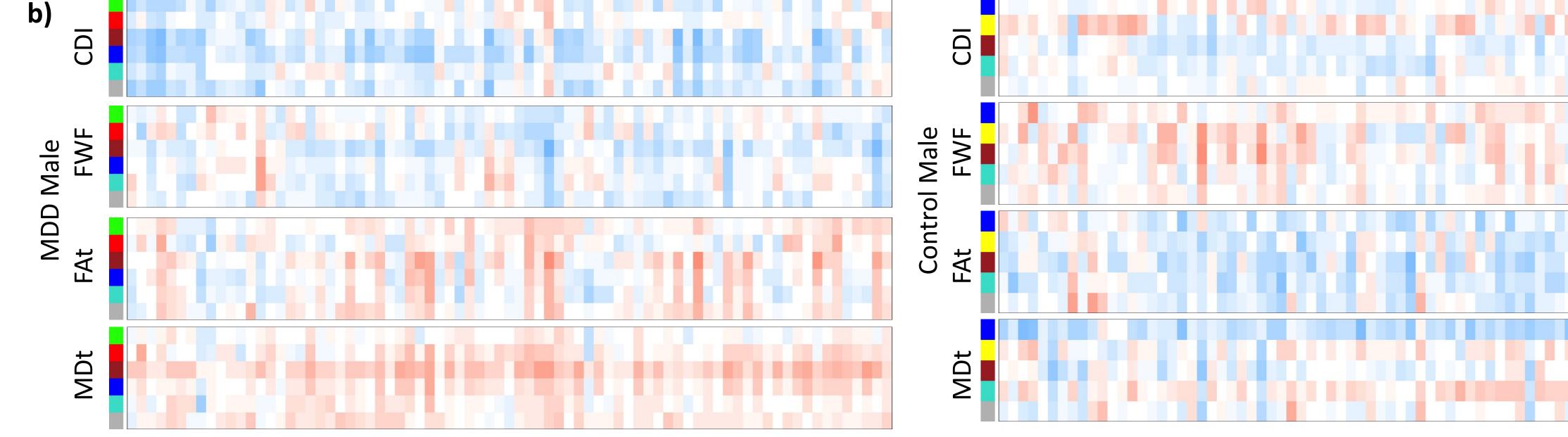
- **Blue**: IL2, IL7, IL8, IL17, FGF, G-CSF, IFN, MIP-1
- Red: IL4, Eotaxin, IL10
- Turquoise: IL5, IL15, IL6, IL12, VEGF
- Brown: IL9, MIP-1b, RANTES, TNFa, **PDGF**
- Green: IL1b, IL13, GM-CSF
- Grey: IFABP, CRP, IL1ra, IP10, MCP

Control Male

- Blue: IL1b, IL13, GM-CSF, IFN
- Brown: IL2, IL17, FGF, PDGF
- Yellow: IL4, IL7, Eotaxin
- Turquoise: IL8, IL9, RANTES, TNFa,
- Grey: IFABP, CRP, IL1ra, IL5, IL6, IL10, IL12, IL15, G-CSF, IP10, MCP1, MIP-1a

• Turquoise: IL1ra, IL7, IL8, IL9, IL12,

RESULTS

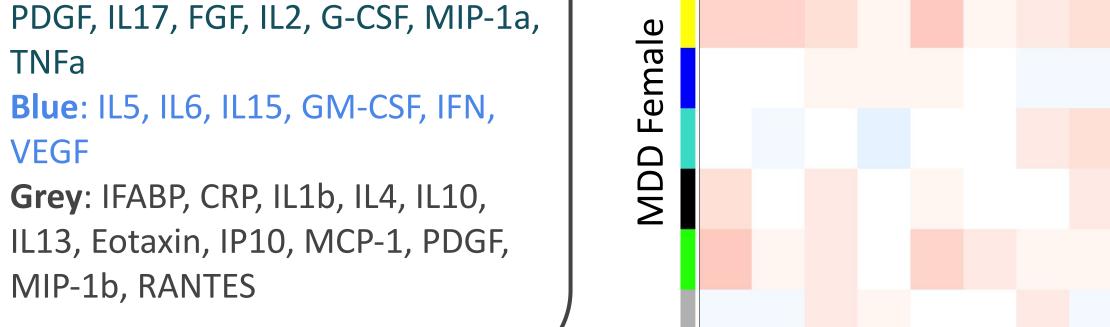


MDD Female

- **Red**: IL1b, IL13
- Turquoise: IL1ra, IL4, Eotaxin, IL7, G-CSF, MCP1
- **Green**: IL2, IL12
- Blue: IL5, IL15, IL10, GM-CSF, VEGF
- Black: IL8, MIP-1a
- Brown: IL9, MIP-1b, RANTES, TNFa
- Yellow: IL17, FGF, PDGF • Grey: IFABP, CRP, IL6, IFN, IP10
- **TNF**a • Blue: IL5, IL6, IL15, GM-CSF, IFN,
- **VEGF**

Control Female

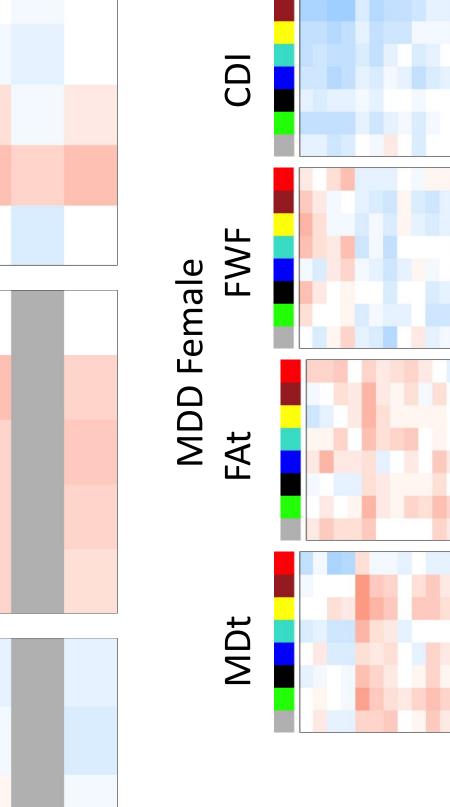
• Grey: IFABP, CRP, IL1b, IL4, IL10, IL13, Eotaxin, IP10, MCP-1, PDGF, MIP-1b, RANTES

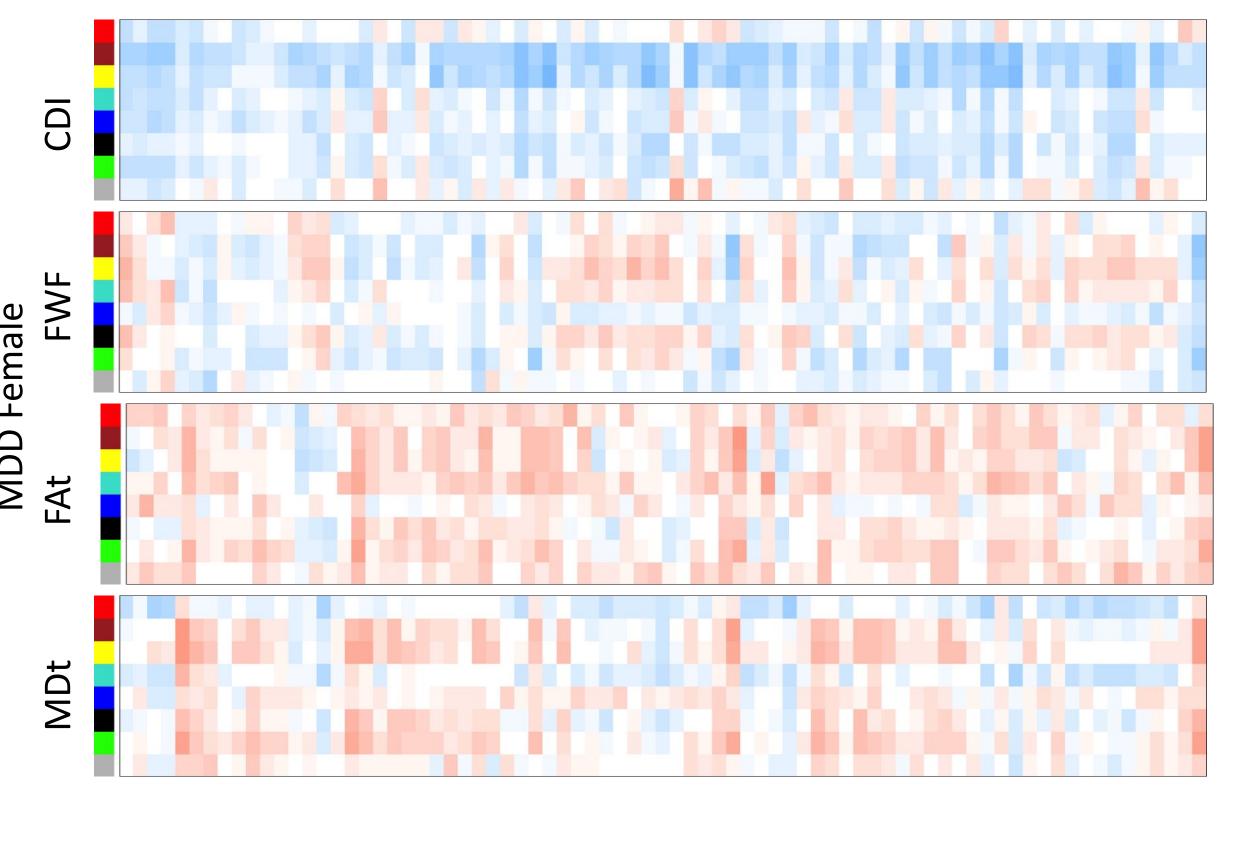


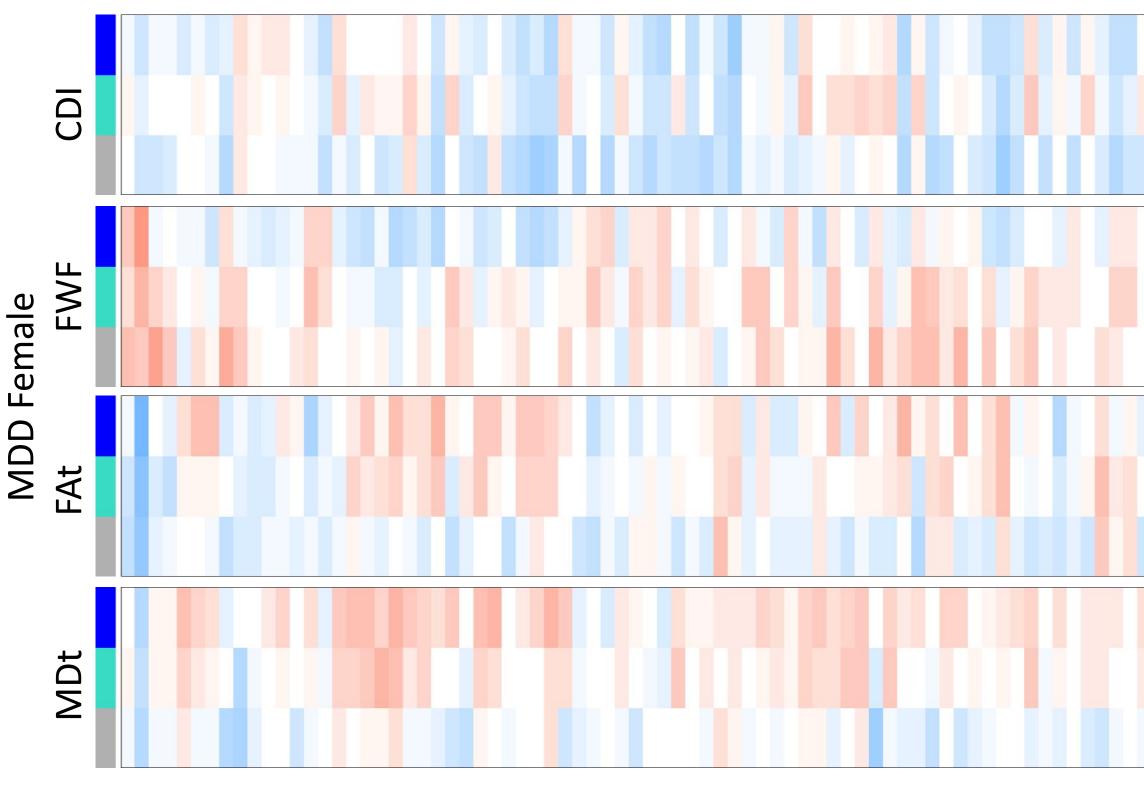
Baseline

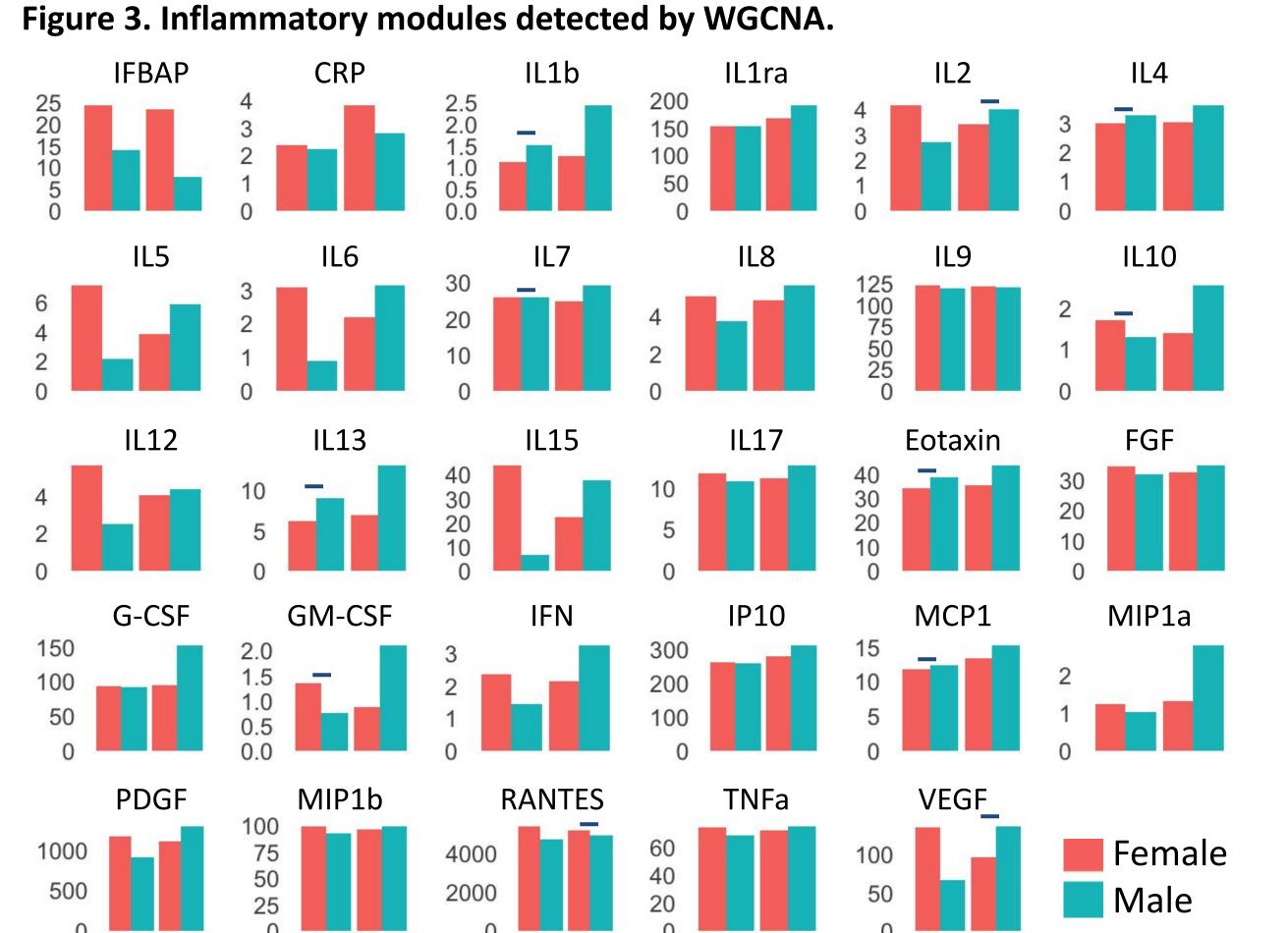
Modalities

a)









Montgomery-Åsberg Depression Rating Scale

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FAt: Free water corrected fractional anisotropy MDt: free water corrected mean diffusivity

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Figure 4. Average marker levels (mg/L) in MDD (left) and control (right).