

Distinct brain and body signatures characterize mood and energy symptoms of depression

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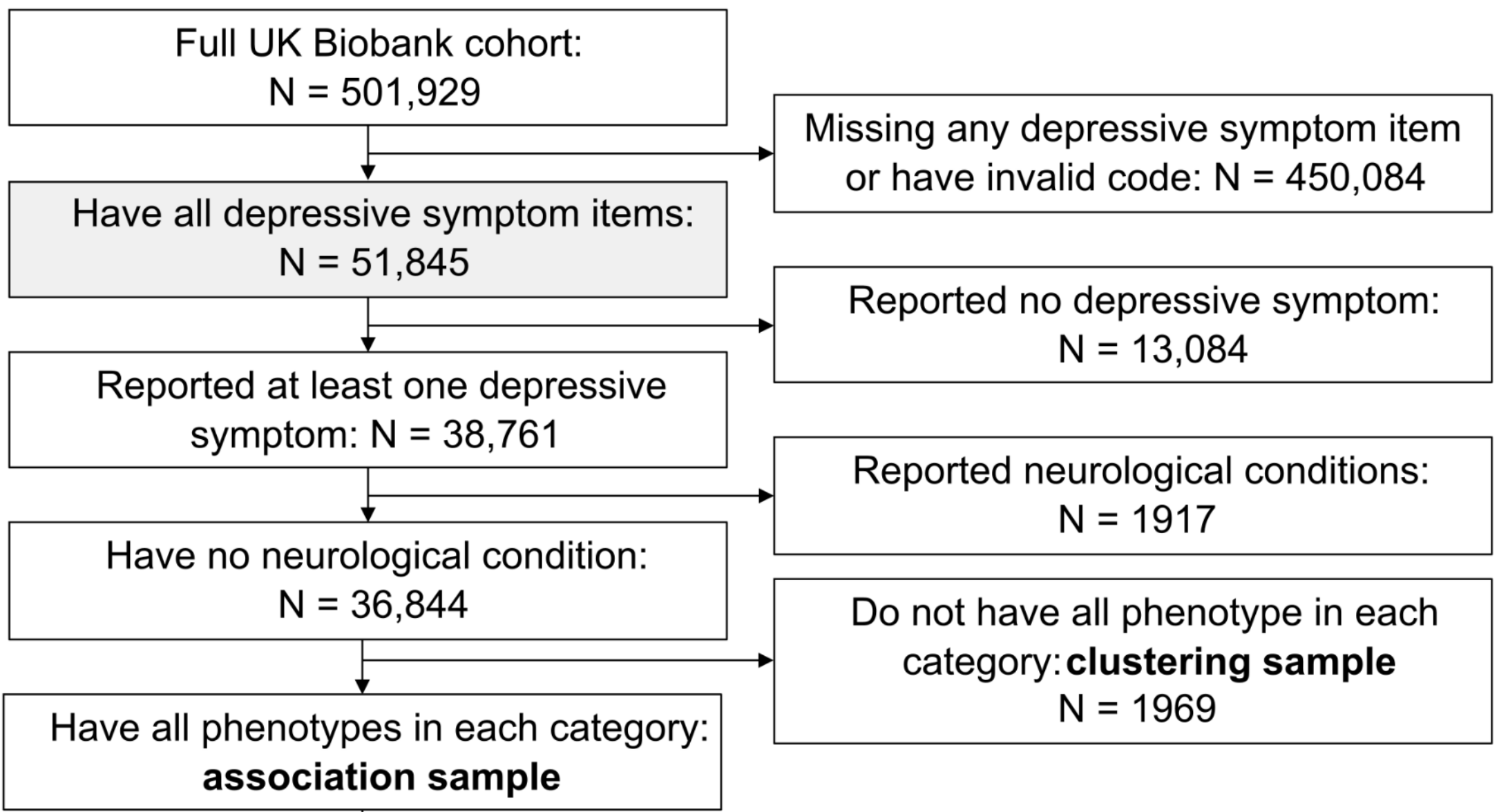
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Introduction

- Major depressive disorder (MDD) is a complex condition with heterogenous aetiology and symptomatic profiles.
- Growing evidence points towards at least two partially separable symptom dimensions, an atypical “energy-related” dimension and an affective dimension [1][2][3].
- Understanding the biological signatures of the different depressive dimensions is crucial towards understanding their impacts on pathophysiology and treatment responses.
- However, comprehensive characterisation of these dimensions, based on data-driven evidence and the biological underpinnings at a population scale, remains lacking.
- We aim to identify naturally occurring depressive dimensions across the full subclinical-to-clinical spectrum, and map their biological correlates across neuroimaging, immuno-metabolic, and body composition markers in a large population sample, separated by biological sex.

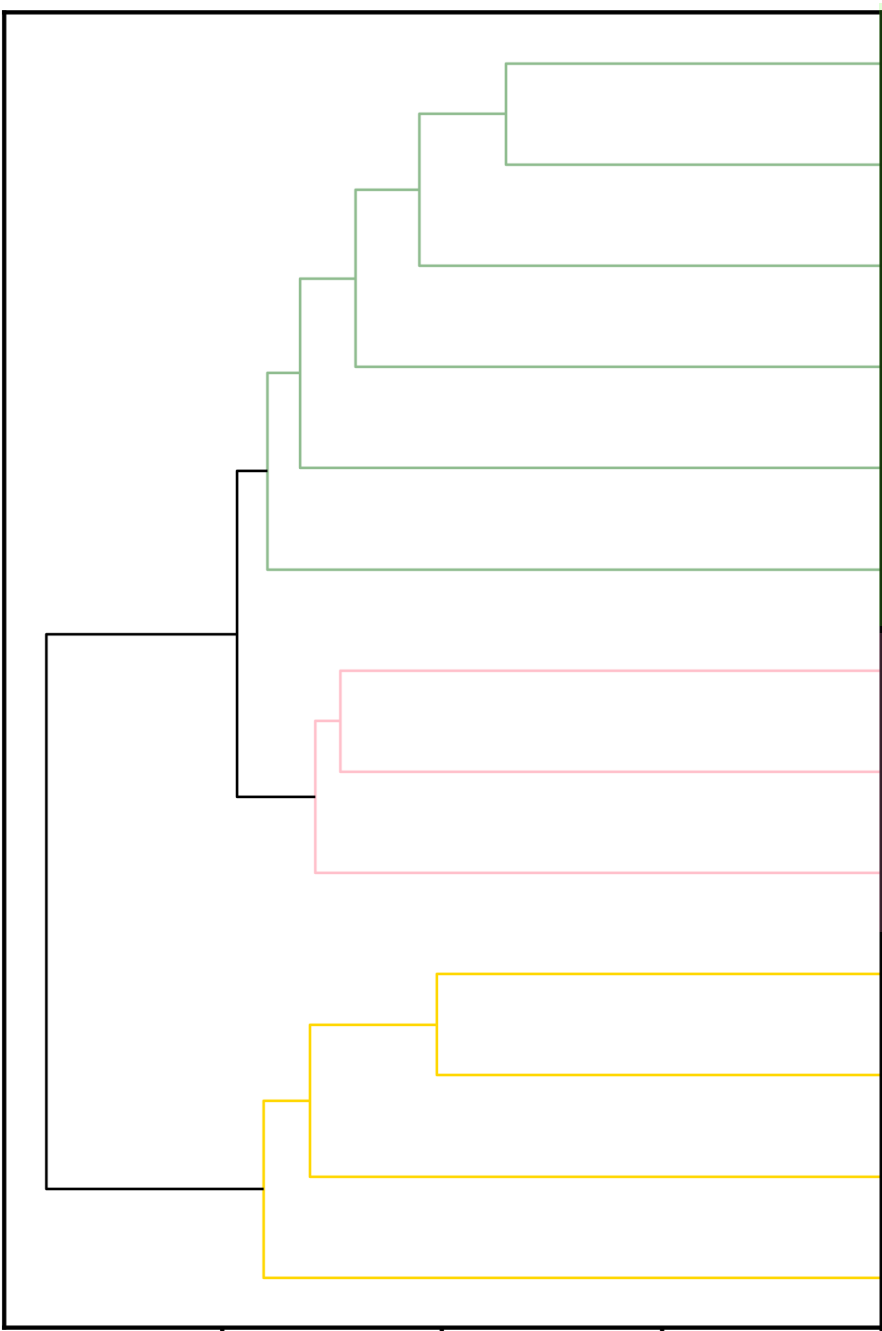
Study cohort



Body fat		Blood cell count		Blood metabolic markers		Brain GMV		Brain DTI & NODDI		
Total N = 16,079		Total N = 2575		Total N = 23,583		Total N = 16,414		Total N = 29,047		
	non-MDD	MDD	non-MDD	MDD	non-MDD	MDD	non-MDD	MDD	non-MDD	MDD
female	8635	412	1340	77	12,330	542	8870	425	15,685	695
male	6816	216	1117	41	10,407	304	6906	213	12,333	334

Depressive symptoms

- Recent Depressive Symptoms (RDS-4) & Patient Health Questionnaire (PHQ-9)
- Agglomerative hierarchical clustering



Mood

- PHQ-9 Recent lack of interest or pleasure in doing things
- PHQ-9 Recent feelings of depression
- PHQ-9 Recent feelings of inadequacy
- PHQ-9 Recent trouble concentrating on things
- PHQ-9 Recent thoughts of suicide or self-harm
- PHQ-9 Recent changes in speed/amount of moving or speaking

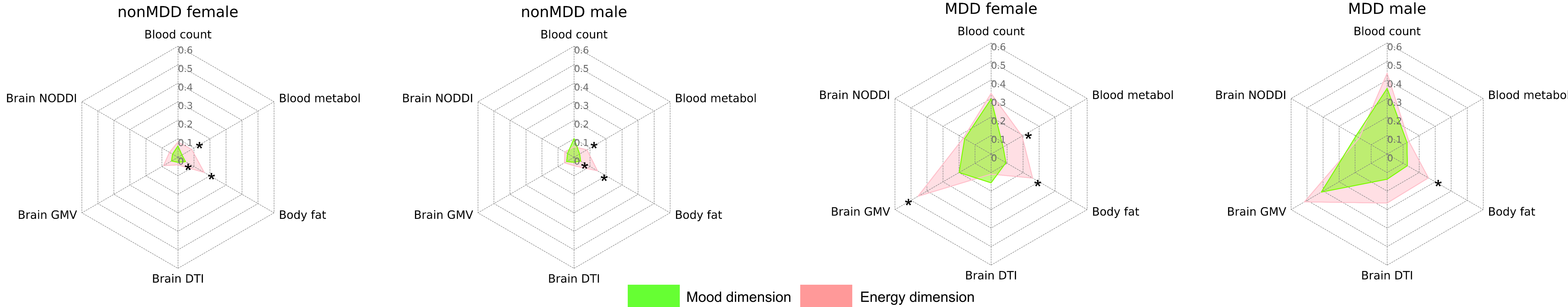
Energy

- PHQ-9 Recent feelings of tiredness or low energy
- PHQ-9 Recent poor appetite or overeating
- PHQ-9 Trouble falling or staying asleep, or sleeping too much
- RDS-4 Frequency of unenthusiasm / disinterest in last 2 weeks
- RDS-4 Frequency of depressed mood in last 2 weeks
- RDS-4 Frequency of tenseness / restlessness in last 2 weeks
- RDS-4 Frequency of tiredness / lethargy in last 2 weeks

- Mood and energy sum score are regressed out from each other to remove common variance

Energy-related symptoms show stronger associations with systemic markers

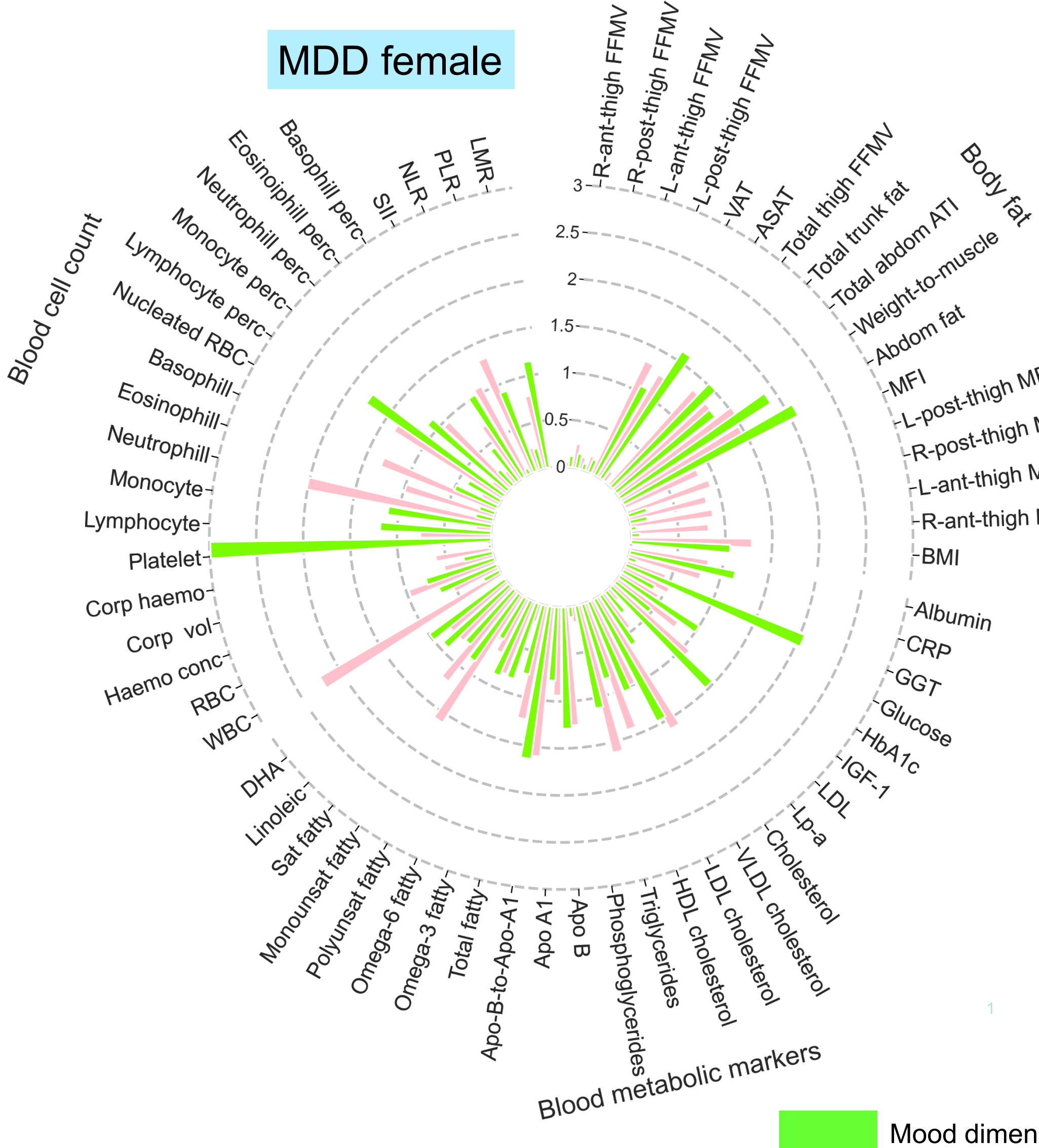
- PLS regression between each depressive sum score and category of biomarkers
- Top component is correlated with the depressive sum score



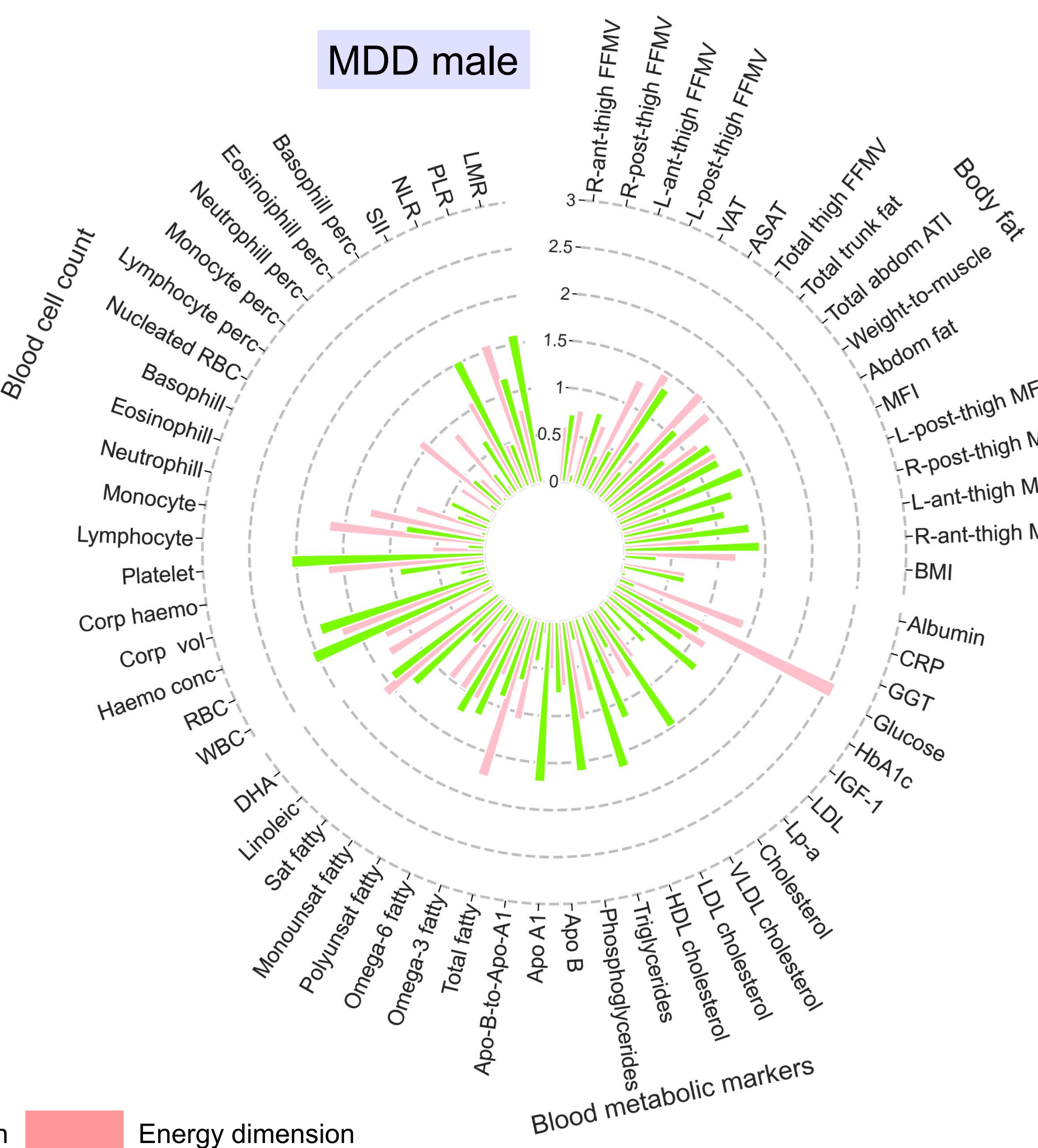
Patterns of importance of immuno-metabolic markers

Variable Importance in Projection (VIP) scores

MDD female

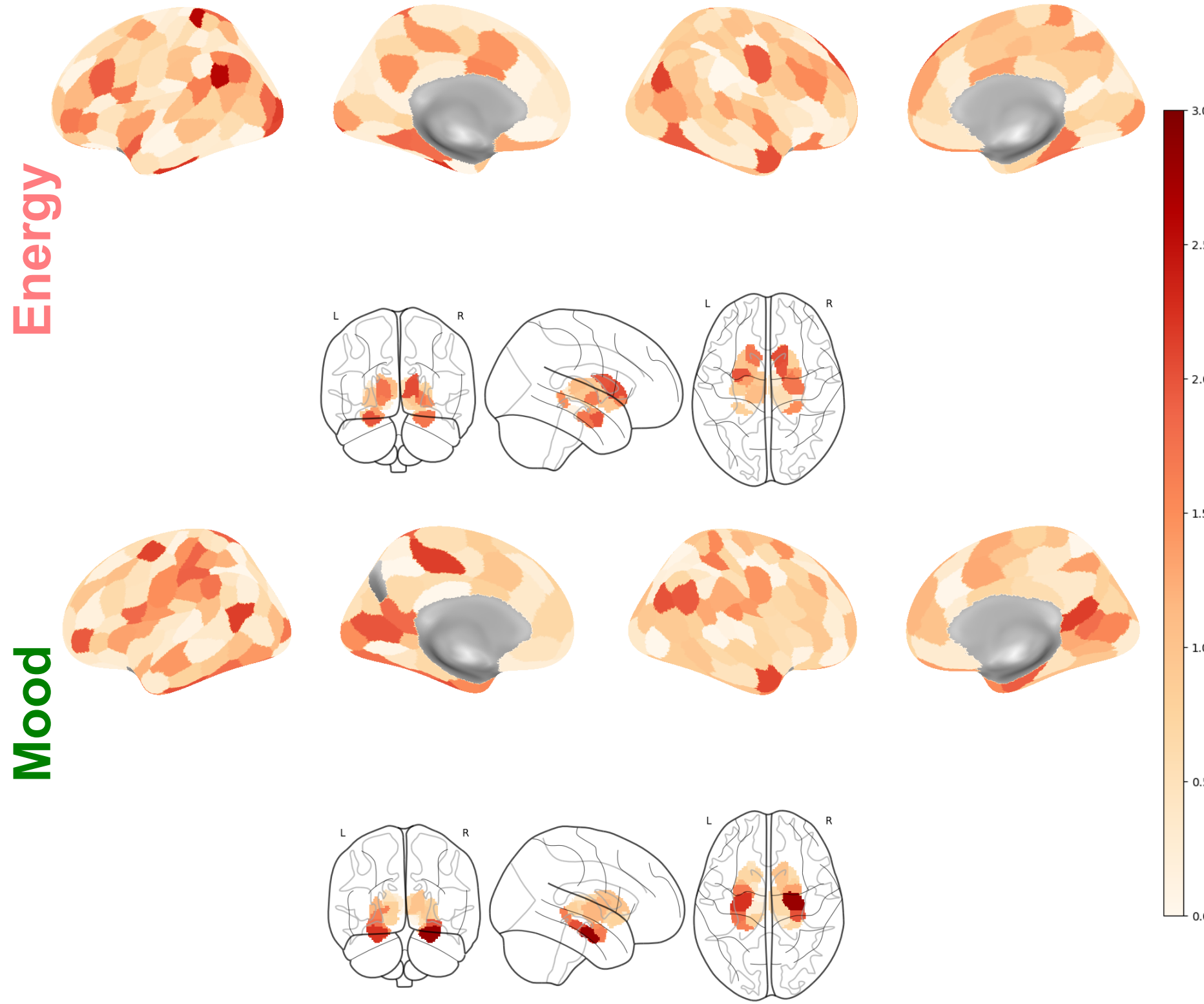


MDD male

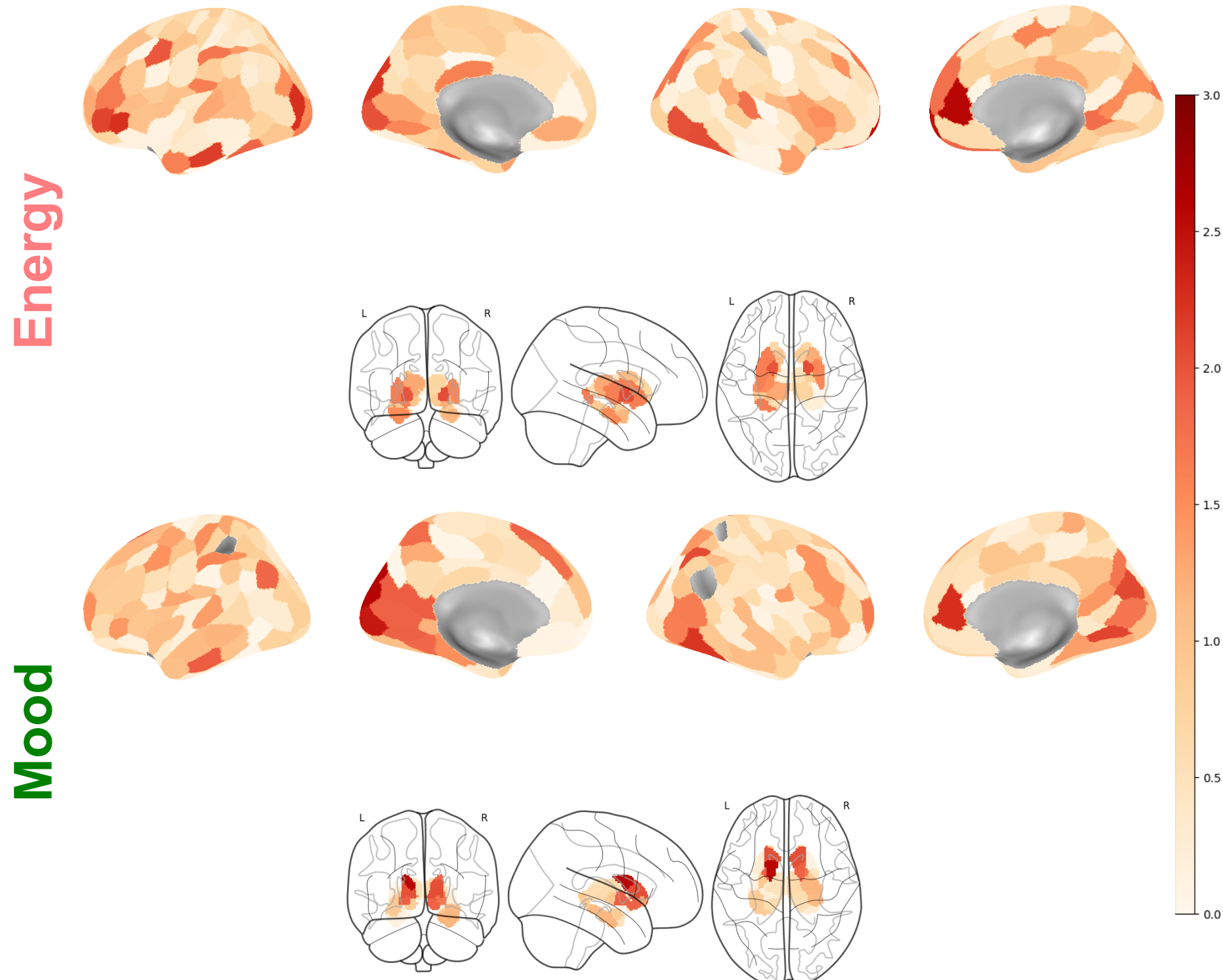


Brain GMV markers

MDD female



MDD male



Conclusion

Mood and energy-related symptoms show distinct systemic embedding. Energy-related symptoms are more robustly linked to body metabolic and inflammatory markers. However, these systemic embeddings may slightly differ across sexes.

References: [1] Wade B, et al. 2020. "Depressive symptom dimensions in treatment-resistant major depression and their modulation with electroconvulsive therapy". *The Journal of ECT*. [2] Franklin SI, et al. 2022. "Developing symptom clusters: linking inflammatory biomarkers to depressive symptom profiles". *Translational Psychiatry*. [3] van Loo HM, et al. 2022. "The structure of the symptoms of major depression: Factor analysis of a lifetime worst episode of depressive symptoms in a large general population sample". *Journal of Affective Disorders*. [4] Sudlow C, et al. 2015. "UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age". *PLoS Medicine*.

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