**Data Access Statement:** The raw data are available at https://nda.nih.gov/ccf/lifespan-studies (HCP-A) and at https://nda.nih.gov/ccf/disease-studies (PDC, HCP-EP) upon completion of the relevant data use agreements. The data used in this report came from the Lifespan Human Connectome Project-Aging Annual Release 2.0 (NDA Collection ID 2847), DOI: 10.15154/1520707. The HCP-EP (NDA Collection ID 2914) 1.1 Release data used in this report came from DOI: 10.15154/1522899. The PDC data (NDA Collection ID 2844) used in this report came from Data Release 1.0, DOI: https://doi.org/10.15154/1528673.

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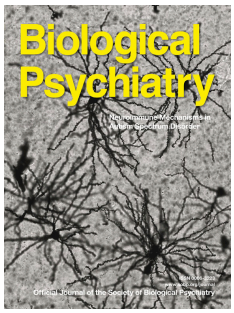


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Running head: CARDIOMETABOLIC AGING, BRAIN FLEXIBILITY, AND PSYCHOPATHOLOGY

# Sex-differential markers of psychiatric risk and treatment response based on premature aging of functional brain network dynamics and peripheral physiology

Raluca Petrican[1], Sidhant Chopra[2,3,4], Christopher Murgatroyd[5], & Alex Fornito[6]

[1]Institute of Population Health, Department of Psychology, University of Liverpool, Bedford Street South, Liverpool, L69 7ZA, UK. [2]Department of Psychology, Yale University, New Haven, USA. [3]Department of Psychiatry, Brain Health Institute, Rutgers University, Piscataway, USA. [4]Orygen, Parkville, Australia. [5]Department of Life Sciences, Manchester Metropolitan University, Manchester, UK.[6]The Turner Institute for Brain and Mental Health, School of Psychological Sciences, and Monash Biomedical Imaging, Monash University, Melbourne, VIC, Australia. Corresponding author email address: raluca.petrican@liverpool.ac.uk (R.P.).

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## Abstract

### Background

Aging is a multilevel process of gradual decline that predicts morbidity and mortality. Independent investigations have implicated senescence of brain and peripheral physiology in psychiatric risk, but it is unclear whether these effects stem from unique or shared mechanisms.

### Methods

To address this question, we analyzed clinical, blood chemistry and resting state functional neuroimaging data in a healthy aging cohort (N= 427; age 36-100 years) and two disorder-specific samples encompassing patients with early psychosis (100 patients, 16-35 years) and major depressive disorder (MDD) (104 patients, 20-76 years).

### Results

We identified sex-dependent coupling between blood chemistry markers of metabolic senescence (i.e., homeostatic dysregulation), functional brain network aging, and psychiatric risk. In females, premature aging of frontoparietal and somatomotor networks was linked to greater homeostatic dysregulation. It also predicted the severity and treatment resistance of mood symptoms (depression/anxiety [all three samples], anhedonia [MDD]) and social withdrawal/behavioral inhibition (avoidant personality disorder [healthy aging]; negative symptoms [early psychosis]). In males, premature aging of the default mode, cingulo-opercular, and visual networks was linked to reduced homeostatic dysregulation and predicted severity and treatment resistance of symptoms relevant to hostility/aggression (antisocial personality disorder [healthy aging]; mania/positive symptoms [early psychosis]), impaired thought processes (early psychosis, MDD) and somatic problems (healthy aging, MDD).

### Conclusions

Our findings identify sexually dimorphic relationships between brain dynamics, peripheral physiology, and risk for psychiatric illness, suggesting that the specificity of putative risk biomarkers and precision therapeutics may be improved by considering sex and other relevant personal characteristics.

*Keywords*: cardiometabolic aging; functional brain network flexibility; sex differences; psychosis; major depressive disorder.

Aging is an intricate biological process of gradual decline that unfolds across multiple interconnected levels within a living organism (1, 2). Biological senescence can thus be measured at multiple scales, from cellular indices of altered gene expression to organism-level biomarkers of cardiometabolic functioning (1, 3, 4). Although biological senescence tracks with chronological age, trajectories of decay show considerable inter-individual variability as a function of time since birth, with more advanced biological, relative to chronological, age emerging as a critical predictor of morbidity and mortality (4-6).

A rapidly growing literature underscores the relevance of biological senescence to both physical and psychological health outcomes across the lifespan. For instance, genetic risk for metabolic dysfunction is linked to poorer cognitive performance in childhood (7), while lifestyle factors supportive of cardiometabolic health (e.g., exercise) alleviate cognitive and brain decline in older adulthood (7-10). The interdependence of these and other systems means that the combined use of physiological and brain indicators of aging yields the most accurate prediction of cognitive functioning from midlife onwards (5, 11-13).

Differences in cardiometabolic and brain aging between neurotypical and psychiatric populations are gaining increasing attention as a potential gateway to understanding and treating mental ill-health. Extant evidence implicates premature cardiometabolic and structural brain aging in the pathophysiology of anxiety (14-17), major depressive disorder (MDD) (15, 16, 18) and psychosis spectrum disorders (19-23). Conversely, greater structural brain similarity to MDD and psychosis among healthy individuals is related to poorer cardiometabolic health and mental processing (24).

The evidence reviewed above comes mainly from independent investigations of premature structural brain aging and cardiometabolic senescence. This work has linked brain aging to diagnoses of anxiety, MDD, and psychosis (16, 22), with cardiometabolic aging only linked to specific symptoms, such as anxious fatigue and blunted reward responsiveness in

MDD (25-28) or negative symptoms in psychosis (29). It is therefore unclear whether premature brain and cardiometabolic senescence have unique or shared connections with mental health, at the disorder and/or symptom level, and whether any such connections show continuity across the subclinical-to-clinical spectrum. It is also unclear whether the robustly documented sex differences in vulnerability to psychopathology (30-38) may (partially) stem from distinct patterns of overlap between sex-specific and cardiometabolic senescence-related brain patterns (30-38). The answers to these questions have critical implications for the design of personalized psychiatry interventions targeting sub-optimal aging trajectories in a multilevel (i.e., psychological and physical health), domain-specific, and/or sex-differential manner.

The present study focused on brain aging patterns correlated with cardiometabolic senescence and probed their relevance to mental well-being across the subclinical-to-clinical spectrum, including their power to explain sex differences in psychiatric risk (see Figure 1 for a schematic representation of our model). To this end, we analysed data from a healthy aging cohort (i.e., Human Connectome Project-Aging [HCP-A]) and two disorder-specific samples, encompassing early psychosis (i.e., HCP-EP) and MDD (i.e., Perturbation of the Depression Connectome [PDC]) patients. Our objectives were two-fold. First, among the HCP-A participants, we sought to identify how sexually dimorphic patterns of yoked cardiometabolic and brain aging are linked to subclinical variations in psychiatric symptoms. Given prior literature (25-28), we expected that premature brain and cardiometabolic senescence would be related to symptoms associated with internalizing disorders. Second, within each of our two psychiatric diagnosis-specific samples, we examined whether the neural aging patterns linked to cardiometabolic senescence and subclinical variations in disorder-specific symptoms in the HCP- A cohort predicted symptom severity and/or treatment-resistance in psychosis and/or MDD (25-29).

## Methods and Materials

### Participants

Our analyses leveraged three publicly available datasets, the Human Connectome Project-Aging (HCP-A) (N = 427, 233 females, age range 36-100 years), Human Connectome Project-Early Psychosis (HCP-EP) (N = 77 non-affective [21 females] and 23 affective [16 females] psychosis patients, age range 16-35 years) and Perturbation of the Depression Connectome (PDC) (N = 104 [59 females] severely depressed patients, age range 20-76 years). All participants contributed complete data on all the scrutinised variables. Inclusion of data in the analyses was guided by the recommendations of the respective study teams. All three samples were predominantly White and right-handed (see Supplemental Information ([SI] A.1 for details).

### Cardiometabolic Aging

In the BioAge R software package (https://github.com/dayoonkwon/BioAge), aging-related decline in cardiometabolic function within the HCP-A sample was quantified with three well-accepted and validated algorithms, Klemera-Doubal method (KDM, (39)), homeostatic dysregulation(3), and PhenoAge (40), whose outputs predict mortality, morbidity and healthspan in younger and older adults (3-6, 39, 40). The KDM algorithm uses linear regression to predict chronological age from a set of biomarkers within a reference group. An individual's KDM biological age prediction corresponds to the chronological age at which their physiology would be normal in the reference group. The homeostatic dysregulation (thereafter dubbed "dyshomeostasis") algorithm applies Mahalanobis distance to a biomarker set to estimate the dissimilarity between an individual's physiology and the physiology of a healthy young adult (20-30 years) group. The PhenoAge algorithm uses an exponential function to predict mortality from a set of biomarkers in a reference group. An individual's PhenoAge biological age prediction corresponds to the chronological age at

which their mortality risk would be normal in the reference group. To quantify premature aging, we computed the difference between an individual's estimated age from each of KDM and PhenoAge algorithms and their chronological age (4, 41). Positive and negative values reflect premature and delayed cardiometabolic senescence, respectively. Due to the skewness of the raw dyshomeostasis score distribution, log-transformed scores outputted by the BioAge R package were used in all analyses. SI A.2 contains further details on the age prediction algorithms and the inputted biomarker set.

**Psychological Functioning**

In the HCP-A sample, psychological functioning was assessed via participants' responses on the DSM-oriented scales (Depression, Anxiety, Attention Deficit Hyperactivity Disorder [ADHD], Avoidant Personality, Antisocial Personality, Somatic Symptom Disorder) from the Achenbach Adult Self-Report (ASR) instrument for ages 18–59 (42). In the HCP-EP sample, positive, negative and cognitive psychotic symptoms were estimated based on Marder's (43) five-factor taxonomy of the Positive and Negative Symptom Scale (PANSS, (44)), while depressive and manic symptoms were measured using the Montgomery-Asberg Depression Rating Scale (MADRS, (45)) and the Young Mania Rating Scale (YMRS, (46)), respectively. Among the PDC patients, pre- and post-treatment depressive symptom severity was assessed with the Hamilton Depression Rating Scale (HDRS) (47) with a focus on the following HDRS subscales: Depressed Mood, Psychic Anxiety, Somatic Anxiety, Feelings of Guilt, Hypochondrias, Loss of Appetite, Weight Loss, Retardation, Agitation, Work and Activities, Libido, and Suicidal Tendencies. Changes in symptom severity were operationalized as the difference between standardized post-treatment (electroconvulsive therapy [ECT]: post-full series completion; ketamine treatment [KET]: 24 hours post-last infusion; total sleep deprivation [TSD]: immediately after the overnight session) and standardized pre-treatment scores on the same HDRS subscale (see SI A.3 and

Table S2).

**Dynamic Functional Brain Architecture Related to Premature Cardiometabolic Aging**

**Functional connectivity and network-level analyses**. We analyzed resting state data already preprocessed using nearly identical pipelines by the HCP-A, HCP-EP and PDC study teams, respectively (cf. (48, 49), SI A 4.2). The concatenated preprocessed resting state runs were broken down into 30-s (i.e., 38 volumes) long non-overlapping windows. Across the three samples, network analyses were conducted on the same number of windows (N = 25) matching the duration of the sample with the least available data (PDC) (cf. (50-52), SI A 4.3-4.4). Pairwise Pearson correlations between regional time series extracted from the Schaefer 300 parcel/17-network functional atlas (53-55) within each window were computed separately in Matlab (version 2022a) and expressed as Fisher's z-transformed scores. Negative scores were set to zero (cf. (56, 57), SI A 4.4). All the reported results were replicated with the Gordon atlas (58) (SI B).

The network-level metrics were computed with the Network Community Toolbox ((59)) (SI A 4.5). Window-specific community organisation was estimated with a multilayer generalized Louvain-like community detection algorithm (57, 60, 61). ROI-level variability in functional organisation was quantified using the "flexibility" function in the Network Community Toolbox as the number of times a given ROI changed functional communities between two consecutive windows. For each participant, the network analyses yielded a vector of 300 regional values indexing functional brain network flexibility (BNF).

***Disorder and symptom-related brain network flexibility (BNF) maps.***

All the partial correlation analyses described below controlled for age, average relative scan-to-scan displacement, gender, site, race, handedness, antipsychotic medication dosage (HCP-EP only), as well as treatment group and delay [in days] between the pre- and post-treatment assessments (PDC only) (SI A.5, 7).

*HCP-A.* BNF maps linked to psychiatric disorder scores were computed via partial Spearman's correlations between ROI-specific BNF scores and scores on each of the six DSM-oriented scales from the ASR.

*HCP-EP.* Symptom-specific BNF maps were estimated via Spearman's partial correlation of ROI-specific network flexibility indices with the PANSS (positive, negative and cognitive) factors, YMRS mania and the MADRS depression scores across all participants.

*PDC.* To characterise the BNF correlates of overall MDD symptom severity at each time point, as well as depressive symptom change, partial Spearman's correlations were computed between the ROI-specific network flexibility and the HDRS scores at baseline/post-treatment, as well as the HDRS difference scores (post-treatment – pre-treatment).

**Statistical Analysis**

A discovery partial least squares (PLS) correlation analysis (62) with 10-fold cross-validation (SI A 6.1) identified BNF patterns related to sex and cardiometabolic senescence in the HCP-A sample. In this analysis, a robust correlation between the extracted BNF latent variable and sex/cardiometabolic senescence suggests that the former differs between males and females/depends on physiological aging measures. Conversely, the lack of a robust correlation implies that the BNF profile is common to males and females/unrelated to physiological aging measures. A robust correlation of the BNF latent variable with both sex and cardiometabolic senescence would indicate overlap between sex-specific and cardiometabolic senescence-related BNF patterns. The discovery PLS analysis was conducted on non-residualized data. However, the cross-validation partial correlation analyses linking the predicted values of the brain latent variable to sex, cardiometabolic senescence (Figure 2-B) or ROI-specific BNF scores (Figure 2-D) controlled for

chronological age in addition to site, race, handedness, and average relative scan-to-scan displacement (SI A.7). Because advancing age predicts greater cardiometabolic senescence (3, 4, 41) and BNF (63-66), a positive correlation between the cross-validated BNF latent variable and cardiometabolic senescence would imply that premature brain aging is linked to premature cardiometabolic senescence, whereas a negative correlation would imply that premature brain aging is linked to delayed cardiometabolic senescence (and vice versa).

Canonical correlation analyses (CCA) (67) probed the relationship between the partial correlation BNF maps linked to sex-cardiometabolic senescence in the HCP-A (Figure 2-D) and the BNF maps tracking psychiatric disorder scores in the same HCP-A sample (CCA 1), symptom severity in early psychosis (CCA 2) or MDD (CCA 3), respectively.

## Results

### Associations between Dyshomeostasis and Brain Network Flexibility are Sex-Specific

The discovery PLS analysis conducted in the full HCP-A sample revealed a single latent variable pair ($p$ = .0002, shared variance of 73.75%). The cross-validated latent variable pair ($r$ = .30, permutation-based $p = 10^{-5}$) identified sexually dimorphic associations between BNF and dyshomeostasis, but not KDM/PhenoAge (Figure 2-A). Thus, greater dyshomeostasis, particularly among females, was related to greater Control and SM network flexibility, whereas reduced dyshomeostasis, particularly among males, was yoked to greater DMN, SAL, VIS and DAN network flexibility (Figure 2-A, B). The unique, additive contributions of sex and dyshomeostasis to the extracted brain latent variable (Figure 2-B) were confirmed through a linear regression analysis predicting the cross-validated BNF latent variable scores from sex, dyshomeostasis and the confounders listed in SI A.7 (*b*s of 2.08, 95% CI = [1.25; 2.91] and .70, 95% CI = [.27; 1.16] for sex and dyshomeostasis, respectively).

In the following analyses, we examine the relevance of the cross-validated

dyshomeostasis-BNF profile (Figure 2-D) to BNF patterns tracking psychiatric symptoms in healthy aging, early psychosis and MDD. We predicted that the dyshomeostasis-BNF profile will correlate positively with symptoms mainly detected among females showing greater physiological aging (e.g., mood problems, anhedonia) (15, 20, 30, 33) and correlate negatively with symptoms primarily observed among physiologically "young" males (3) (e.g., aggressive behavior) (68).

**Sexually Dimorphic Associations Between Brain Network Flexibility and Subclinical Internalizing and Externalizing**

A cross-validated CCA revealed a single statistically significant mode ($r$ = .72, permutation-based $p = 10^{-5}$, Figure 3-C) reflecting a positive association between BNF patterns linked to female dyshomeostasis and those tracking higher anxiety, avoidant personality, and depressive disorder scores across sexes (Figure 3-A, B) Conversely, there was a positive correlation between BNF patterns linked to reduced male dyshomeostasis and those related to higher antisocial and somatic personality disorder scores across sexes (Figure 3-A, B).

**Dyshomeostasis-BNF Patterns are Related to Symptom Severity in Psychosis**

We next used CCA to investigate whether the dyshomeostasis-BNF profile from the HCP-A sample would relate to depressive and negative psychotic symptom severity in the HCP-EP patient data (25, 27, 29). The resultant cross-validated CCA variate pair ($r$ = .56, permutation-based $p = 10^{-5}$, Figure 4-C) unveiled a positive relationship between BNF patterns linked to female dyshomeostasis and those linked to depressive as well as negative symptoms in the HCP-EP sample (Figure 4-A, B). The extracted CCA mode also revealed that BNF patterns associated with reduced male dyshomeostasis overlapped with those

tracking manic and positive symptom severity in the HCP-EP (Figure 4-B).

**Dyshomeostasis-BNF Patterns Are Related to Treatment-Resistant Anxiety and Anhedonia**

Finally, we probed the relationship between the dyshomeostasis-BNF profile from HCP-A and BNF patterns correlated with overall MDD severity at each time point (longitudinal *r* of .18]), as well as MDD symptom resistance following treatment. The discovery CCAs unveiled a sole CCA variate pair, which was cross-validated across all 10 test folds ($r$ = .82, permutation-based $p = 10^{-5}$, Figure 5-C). The identified mode positively linked BNF patterns associated with female dyshomeostasis to those associated with greater overall MDD severity after treatment, as well as treatment-resistant anhedonia (i.e., engagement with work and personal interests, libido), suicidal tendencies, agitation and psychic anxiety (Figure 5-B). A positive association also emerged between BNF patterns correlated with reduced male dyshomeostasis and those tracking treatment resistance in appetite and retardation (i.e., mental and physical slowness) (Figure 5-B).

## Discussion

Prior research linked cardiometabolic aging to specific psychiatric symptoms and brain aging to specific diagnoses (16, 22, 25-29). The present study indicates that sex-differential patterns of functional brain dynamics linked to metabolic senescence, specifically, dyshomeostasis (3), predict vulnerability to psychopathology in healthy aging, as well as the occurrence and treatment resistance of individual symptoms in two clinical groups. The identified neural profiles, suggestive of premature vs delayed functional aging (i.e., greater vs lower BNF, (63-66)) spanned networks implicated in psychopathology broadly (69), as well as those related specifically to the two disorders under scrutiny (70-77). The unique association between BNF patterns and dyshomeostasis, but not KDM or PhenoAge, indices

of premature aging suggests that sex-dependent psychiatric vulnerability is related to absolute distance from the optimal "young adult" cardiometabolic profile rather than rate of decline relative to peers of the same chronological age. Whether the null effects observed for KDM and PhenoAge stem from the greater heterogeneity of the associated functional brain profiles is a question worth probing in the future.

Recent studies have begun to unravel the sex-dependent molecular and functional brain pathways underpinning global psychopathology risk (37), and differential risk for externalizing vs internalizing problems (34). Complementing this work, we document the divergent, sex-dependent relationship of metabolic senescence and associated BNF patterns with risk for internalizing vs externalizing psychopathology in typical aging. Specifically, among the healthy adults from HCP-A, BNF patterns related to female dyshomeostasis (i.e., higher Control and SM, but lower DMN, SAL, DAN and VIS, BNF) overlapped those tracking depression, anxiety and avoidant personality disorder symptoms across sexes (see Figure 3-B). Complementarily, BNF patters linked to reduced male dyshomeostasis (i.e., greater DMN, SAL, DAN and VIS, but lower Control and SM BNF) overlapped those tracking antisocial personality and somatic disorder symptoms. Broadly, our results fit well with extant evidence and evolutionary theory connecting internalizing psychopathology to "diseased"-like states associated with high inflammation (78-80) and connecting externalizing behaviours to physical attributes and neuroendocrine responses that tend to typify younger males in good health (68). The sex-dependent association between premature metabolic senescence and depression/anxiety disorders further aligns with evidence that females show more intense and prolonged responses to stressors compared to males (30, 33, 36).

Premature female and delayed male senescence were linked to opposite patterns of DMN-SM functional stability (i.e., lower BNF), which accords with prior reports linking

older (relative to younger) adulthood to more dwell time in brain states dominated by internal mentation rather than sensory and SM networks (81). The link between depression/anxiety disorder scores and greater DMN (rather than Control or SM) stability is consonant with extant evidence that the severity of internalizing psychopathology tracks with relative DMN (over Control and SM) functional dominance (i.e., comparatively greater connectivity strength, as well as higher frequency and more time spent in DMN-dominated states) (82, 83).

The association between externalizing risk and lower functional stability in DMN and VIS, two networks involved in perceiving and creating mental representations of contextual information (84-86), resonates with recent proposals implicating deficient processing of contextual information in the pathology of antisocial personality disorders (87). Likewise, the correlation between predisposition towards externalizing disorders and greater BNF in SAL, a network linked to transdiagnostic deficits in cognitive control (69), is in line with extant theory and evidence on the importance of inhibitory resources in antisocial personality disorders (88, 89).

Beyond disorder-level associations with internalizing vs externalizing risk, the sex-dependent BNF profile linked to metabolic senescence also showed symptom-specific relationships. Thus, the brain patterns yoked to age-premature female dyshomeostasis, as well as depression, anxiety and avoidant personality disorders in HCP-A, were associated with BNF patterns tracking severity and treatment resistance of symptoms related to mood (depression [HCP-EP, PDC], anxiety [PDC], anhedonia [PDC]) and social withdrawal/behavioral inhibition (negative psychotic symptoms [HCP-EP]) (42, 43). These findings extend prior research linking cardiometabolic dysfunction and inflammation to negative and depressive symptoms in psychosis (29, 90), as well as anxious fatigue (28) and anhedonia (25) in MDD. Our results also could also advance existing efforts to differentiate

psychosis spectrum pathologies and predict responsiveness to treatment based on cellular senescence, as well as structural and functional brain indices associated with specific symptom types (91-93). The involvement of the BNF profile linked to female dyshomeostasis in negative symptoms dovetails nicely with reports of greater cellular senescence among females diagnosed with psychosis spectrum disorders (38). Its relevance to the post-treatment persistence of anhedonia further resonates with evidence on sex differences in the normative development of reward processing skills (31) and as observed in MDD (35).

The BNF patterns linked to reduced male dyshomeostasis (i.e., greater DMN, SAL, DAN and VIS, but lower Control and SM, BNF), as well as antisocial personality and somatic problems in healthy aging, correlated positively with the severity of mania and positive psychotic symptoms, in which externalizing features, such as hostility and aggressive behaviour, are prominent (43, 46). This finding echoes prior reports linking familial risk for psychosis to delayed cellular senescence (94), as well as evidence implicating greater DMN (over SM) BNF (95) and atypical VIS network connectivity and processing in the pathology of psychosis disorders (96-98). The relationship between mania severity and BNF patterns linked to reduced male dyshomeostasis sheds further light on the proposed role of metabolic overdrive in the pathophysiology of manic episodes (99). Specifically, in younger patient samples such as the HCP-EP, the higher metabolic rate conducive to systemic dysregulation in the long run may lend the appearance of greater physiological youth, either directly or via associated behaviours, such as heightened physical activity levels (99).

The brain patterns related to delayed male metabolic senescence further overlapped with those tracking treatment resistance for appetite and impaired/slowed thought processes in MDD. This association with appetite resonates with the relevance of the male homeostasis-BNF profile to somatic symptoms in the HCP-A sample. Given the transdiagnostic relevance of impaired thought processes, likely linked to deficient cognitive control (69), the findings

involving the reduced male dyshomeostasis-BNF patterns in HCP-EP and PDC are consistent with reports that individuals at clinical risk for psychosis have multiple comorbidities (100), which is reflected in the substantial number of deficient brain pathways shared between psychosis and multiple psychiatric and neurological disorders (101).

**Limitations and Future Directions**

Aging is a multilevel process (1) and investigations combining markers of cellular (e.g., DNAm, (102) and organism-level cardiometabolic senescence as those used here could improve measurement sensitivity and accuracy (14, 103-108). Moreover, structural and functional brain aging show distinguishable trajectories, which, in turn, are differentially associated with mood and psychotic pathology (18, 109-113). Future cross-species studies incorporating pharmacological and/or experimental manipulations of mood and psychotic symptoms while collecting (quasi-)contemporaneous assessments of multiple structural (e.g., neurogenesis rate, gray matter volume, white matter microstructure) and functional indices of brain aging, including behavioural and neural responses to clinically relevant task contexts (e.g., linked to impulsivity or reward sensitivity) could help provide a more comprehensive characterization of the effects herein reported. Such investigations could further shed light on the specific neurotransmitter systems and neuronal (inhibitory, excitatory) vs non-neuronal (e.g., astrocytes), cell types likely to bridge mental health, as well as cardiometabolic and brain senescence (21, 29, 104, 114, 115). Cellular and organism-level senescence can be accelerated by environmental adversity (107, 116-120) and maladaptive lifestyle choices (e.g., lack of regular exercise (9, 20), poor diet (121, 122)). Cross-species research which manipulates exposure to environmental adversity and lifestyle factors, such as aerobic exercise and diet, could help elucidate the “driver” behind the inter-relationships among sex-differential patterns of cellular and organism-level senescence, structural/functional brain aging and vulnerability to internalizing/externalizing psychopathology.

Our analyses focused on blood-chemistry-derived measures of physiological aging as these are highly predictive of cardiometabolic outcomes (123). However, the development of DNA methylation (DNAm) aging algorithms, termed “clocks”, has much potential. While first-generation DNAm clocks were developed to predict chronological age and were less sensitive to cardiometabolic aging compared to blood-chemistry–derived measures (124), newer DNAm clocks, developed to predict mortality, could be fine-tuned to dissect multimorbidity within cardiometabolic diseases and the impact of different lifestyle factors.

The predominantly cross-sectional design of our study limits causal inferences. The sample's demographic composition, being predominantly White and right-handed, may affect the generalizability of the findings. Longitudinal investigations with more diverse populations are needed to better understand the temporal dynamics and universality of brain-metabolic aging associations. For instance, examination of cardiometabolic senescence in socioeconomically diverse samples of children and adolescents could be instrumental in identifying and facilitating early amelioration of suboptimal brain maturation trajectories likely to enhance vulnerability to psychopathology. Such work is well-justified considering evidence that the functional impact of modifiable risk factors (e.g., exercise, diet) is stronger in earlier life (125). Similarly, future research could extend our analyses on the independent additive contributions of sex and cardiometabolic senescence to brain network flexibility by directly testing for or using genetic strategies (e.g., Mendelian randomization, (126)) to parse causal interactions between these variables.

We did not have sufficient statistical power to probe treatment-specific effects on the brain patterns associated with cardiometabolic senescence. Such research is worth pursuing since different treatments impact distinct physiological systems (127-132) and patterns of neuroplasticity (133, 134), which, in turn, are likely to show distinguishable associations with cellular and organism-level markers of senescence. The potential modulatory effects of

ongoing and lifetime psychotropic medication use on treatment response also warrant further study.

We used three publicly available datasets (HCP-A, HCP-EP and PDC) to reveal convergent patterns of association between BNF profiles linked to physiological aging and psychiatric symptoms. While corresponding measures showed substantial conceptual overlap, further efforts should be made to harmonize data collection methods to improve the consistency and comparability of findings.

**Conclusions**

We identified a multimodal marker of metabolic and functional brain network senescence predictive of psychiatric disorder- and symptom-level vulnerability. By characterizing complementary, sex-dependent patterns of neurobiological aging that predict mental health outcomes, our investigation can act as a springboard for future research into the mechanisms underpinning sex differences in risk for internalizing vs externalizing disorders, as well as those accounting for sex differences in the burden of psychotic and depressive symptoms.

**Materials & Correspondence.** Correspondence and material requests should be addressed to R.P. (raluca.petrican@liverpool.ac.uk).

**Data statement.** The raw data are available at https://nda.nih.gov/ccf/lifespan-studies (HCP-A) and at https://nda.nih.gov/ccf/disease-studies (PDC, HCP-EP) upon completion of the relevant data use agreements. The data used in this report came from the Lifespan Human Connectome Project-Aging Annual Release 2.0 (NDA Collection ID 2847), DOI: 10.15154/1520707. The HCP-EP (NDA Collection ID 2914) 1.1 Release data used in this report came from DOI: 10.15154/1522899. The PDC data (NDA Collection ID 2844) used in this report came from Data Release 1.0, DOI: http://dx.doi.org/10.15154/1528673.

**Code availability.** We used already existing code, as specified in the main text with links for free download.

**Supplement Description:**

Supplemental Methods, Results, Tables S1-S2, and Figures S1-S6

Figure Captions

*Figure 1*. Schematic representation of our framework. Panel A: The KDM algorithm uses linear regression to predict chronological age from a set of biomarkers within a reference group. An individual's KDM biological age prediction corresponds to the chronological age at which their physiology would be normal in the reference group. The PhenoAge algorithm uses an exponential function to predict mortality from a set of biomarkers in a reference group. An individual's PhenoAge biological age prediction corresponds to the chronological age at which their mortality risk would be normal in the reference group. Indices of premature aging are computed by subtracting from an individual's age estimate as outputted by the KDM and PhenoAge algorithms, respectively, from an individual's chronological age. Positive and negative indices reflect premature and delayed cardiometabolic senescence, respectively. Panel (B): The homeostatic dysregulation algorithm applies Mahalanobis distance to a biomarker set in order to estimate the dissimilarity between an individual's physiology and the physiology of a healthy (overall physically fit) young adult (20-30 years) group. Individuals with reduced homeostatic dysregulation (represented by the gray circle) have a physiological profile relatively *more similar* to that of the young adult reference group, whereas those with greater homeostatic dysregulation (represented by the red circle) have a physiological profile relatively *more dissimilar* to that of the young adult reference group**.** Panel (C): BNF was computed for each ROI in the Schaefer300-17 Networks atlas as the number of times it changed functional community affiliation (shown as differently coloured shades) between two consecutive non-overlapping time windows. For ease of interpretation, BNF scores are described in reference to the ROI's network affiliation in the Schaefer atlas. The subnetworks from the Schaefer 17-network atlas (e.g., Control A/B/C) have been combined into one to increase comparability with the Gordon atlas. In panels (D)-(F), disorders or symptoms expected to correlate with cardiometabolic and brain aging are in

black font, whereas those scrutinised on an exploratory basis and to establish the specificity of any observed effects are in grey font. Panel (F): Correlated patterns of change in BNF and clinical symptoms assessed before and after treatment with ECT, ketamine or sleep deprivation in a sample of MDD patients. Premature cardiometabolic aging, estimated in reference to one's chronological age (A) or a healthy young adult sample (B) was posited to predict, in a sex-differential manner, patterns of functional brain network aging (i.e., BNF) (C). The latter were hypothesized to explain sex-differential subclinical variations internalizing vs externalizing disorder symptoms in healthy aging (D), as well as severity and treatment-resistance of specific symptoms along the internalizing/negative to positive symptom spectrum in early psychosis (E) and MDD (F), respectively. BNF = brain network flexibility. ROI = region-of-interest. ECT = electroconvulsive therapy. MDD = major depressive disorder. Schaefer networks: TP= temporo-parietal. SAL-VAN = salience/ventral attention. LB = limbic. DMN = default mode. DAN = dorsal attention. SM-A =somatomotor-A. SM-B =somatomotor-B. VIS = visual.

*Figure 2*. The brain latent variable from the behavioral-PLS analysis linking sex and cardiometabolic aging to BNF in the HCP-A sample. Panel (A) shows the correlations of the sex and cardiometabolic aging variables with the brain latent variable scores in the discovery PLS analysis. Panel (B) shows the correlations of the sex and homeostatic dysregulation variables with the predicted brain latent variable scores (based on the 10-fold cross-validation procedure). Error bars are the 95% bootstrapped confidence intervals (described in SI A 6.1), as conducted in the discovery (panel A) and cross-validation (panel B) PLS analyses. Confidence intervals that do not include zero reflect robust correlations between the respective behavioral variable and the discovery (panel A) or predicted (panel B) brain latent variable score across all participants. Panel (C) depicts the ROI-specific weights/loadings on the brain latent variable identified with the discovery PLS analysis with a bootstrap ratio

greater than 2 in absolute value (cf. (135, 136)). These weights reflect the within-sample unique association between an ROI and the extracted brain latent variable after controlling for the association of the brain latent variable with all the other ROIs from the Schaefer atlas. Panel (D) depicts the Schaefer ROIs robustly correlated (based on cross-validated 99.9% confidence intervals, as described in SI A 6.1) with the predicted value of the brain latent variable from the cross-validation procedure. These are partial correlations controlling for chronological age, race, testing site, handedness and average motion per participant, as described in the main text under "Statistical Analysis" (PLS analysis section). These partial correlation coefficients between an ROI and the predicted value of the brain latent variable do not control for the correlation between the brain latent variable and the remaining Schaefer ROIs entered in the analysis. To facilitate interpretation, panels (E) and (F) present Schaefer network-based distributions of PLS weights (panel E) or partial correlations (panel F) summarizing the ROI-specific results from panels (C) and (D), respectively. The subnetworks from the Schaefer 17-network atlas (e.g., Control A/B/C) have been combined into one to increase comparability with the Gordon atlas. Error bars represent standard deviations. KDM = Klemera-Doubal Method. PLS = partial least squares. BNF = brain network flexibility. ROI = region-of-interest. Schaefer networks: TP= temporo-parietal. SAL-VAN = salience/ventral attention. LB = limbic. DMN = default mode. DAN = dorsal attention. SM-A =somatomotor-A. SM-B =somatomotor-B. VIS = visual.

*Figure 3*. Psychiatric disorder-specific BNF patterns linked by CCA to the homeostatic dysregulation-BNF profile identified in the same HCP-A sample (cf. Figure 2). Panel (A) depicts the cross-validated BNF patterns associated with sex and homeostatic dysregulation in the PLS analysis (cf. Figure 2-B, D). Unlike the brain maps in Figure 2-D, which are thresholded based on cross-validated 99.9% confidence intervals, the brain maps in panel (A), same as the disorder-BNF maps, are not thresholded. The CCA's were run on

unthresholded brain maps in order to avoid any bias introduced by applying (somewhat) arbitrary statistical thresholds. The circular graph in panel (B) contains the correlation coefficients describing the relationship between the observed disorder-specific BNF scores and the predicted value of their corresponding canonical variate across all test CCAs. The shaded areas correspond to robust correlations observed in cross-validated CCAs featuring both Schaefer and Gordon atlas-based homeostatic dysregulation-BNF scores (see SI A 6.2 for details on the 99.9% bootstrapped confidence intervals). Panel (C) contains the scatter plot describing the linear relationship between the predicted values of the homeostatic dysregulation-BNF profile from the PLS analysis (Figure 2) and the predicted psychiatric disorder-BNF profile from the cross-validation of the CCA 1 results. BNF = brain network flexibility. ROI = region-of-interest. Depress = Depression. ADHD = attention deficit hyperactivity disorder. Antisoc = antisocial personality disorder. Avoid = Avoidant personality disorder. Som = Somatic Disorder.

*Figure 4*. Early psychosis symptom-specific BNF patterns linked by CCA to the homeostatic dysregulation-BNF profile identified in the HCP-A sample (cf. Figure 2). Panel (A) depicts the cross-validated BNF patterns associated with sex and homeostatic dysregulation in the PLS analysis (cf. Figure 2-B, D). Unlike the brain maps in Figure 2-D, which are thresholded based on cross-validated 99.9% confidence intervals, the brain maps in panel (A), same as the symptom-BNF maps, are not thresholded. The CCA's were run on unthresholded brain maps in order to avoid any bias introduced by applying (somewhat) arbitrary statistical thresholds. The circular graph in panel (B) contains the correlation coefficients describing the relationship between the observed symptom-specific BNF scores and the predicted value of their corresponding canonical variate across all test CCAs. The shaded areas correspond to robust correlations observed in cross-validated CCAs based on both the Schaefer and Gordon atlas data (based on the bootstrapping-derived 99.9% confidence intervals). The shaded areas

on the brain images reflect the strength of the partial correlation between the BNF scores and psychotic symptoms (see the Method for the confounders controlled for in the partial correlation). Panel (C) contains the scatter plot describing the linear relationship between the predicted values of the homeostatic dysregulation-BNF profile from the PLS analysis (Figure 2) and the predicted psychosis symptom-BNF profile from the cross-validation of the CCA 2 results. PLS = partial least squares. CCA = canonical correlation analysis. BNF = brain network flexibility. ROI = region-of-interest.

*Figure 5*. BNF change patterns corresponding to treatment-related symptom change in MDD linked by CCA to the homeostatic dysregulation-BNF profile identified in the HCP-A sample (cf. Figure 2). Panel (A) depicts the cross-validated BNF patterns associated with sex and homeostatic dysregulation in the PLS analysis (cf. Figure 2-B, D). Unlike the brain maps in Figure 2-D, which are thresholded based on cross-validated 99.9% confidence intervals, the brain maps in panel (A), same as the symptom-BNF maps, are not thresholded. The CCA's were run on unthresholded brain maps in order to avoid any bias introduced by applying (somewhat) arbitrary statistical thresholds. The circular graph in panel (B) contains the correlation coefficients describing the relationship between the observed symptom-specific BNF (change) scores and the predicted value of their corresponding canonical variate across all test CCAs. The shaded areas correspond to robust correlations observed in cross-validated CCAs based on both the Schaefer and Gordon atlas data (based on the bootstrapping-derived 99.9% confidence intervals). The shaded areas on the brain images reflect the strength of the partial correlation between pre-to-post treatment change in BNF and MDD symptoms (see the Method for the confounders controlled for in the partial correlation). Panel (C) contains the scatter plot describing the linear relationship between the predicted values of homeostatic dysregulation-BNF profile from the PLS analysis (Figure 2) and the MDD symptom (change)-BNF profile. PLS = partial least squares. CCA = canonical correlation analysis.

BNF = brain network flexibility. ROI = region-of-interest. Depress_1 = total HDRS score (as described in the text) before treatment. Depress_2 = total HDRS score (as described in the text) after treatment. Agit = agitation. Anx = psychic anxiety. Sadness = depressed mood. Hypoch= hypochondriasis. Slowed = retardation (thought-related/motor). Som = somatic anxiety. Work/Int = work/interests. HDRS = Hamilton Depression Rating Scale. MDD = Major Depressive Disorder.

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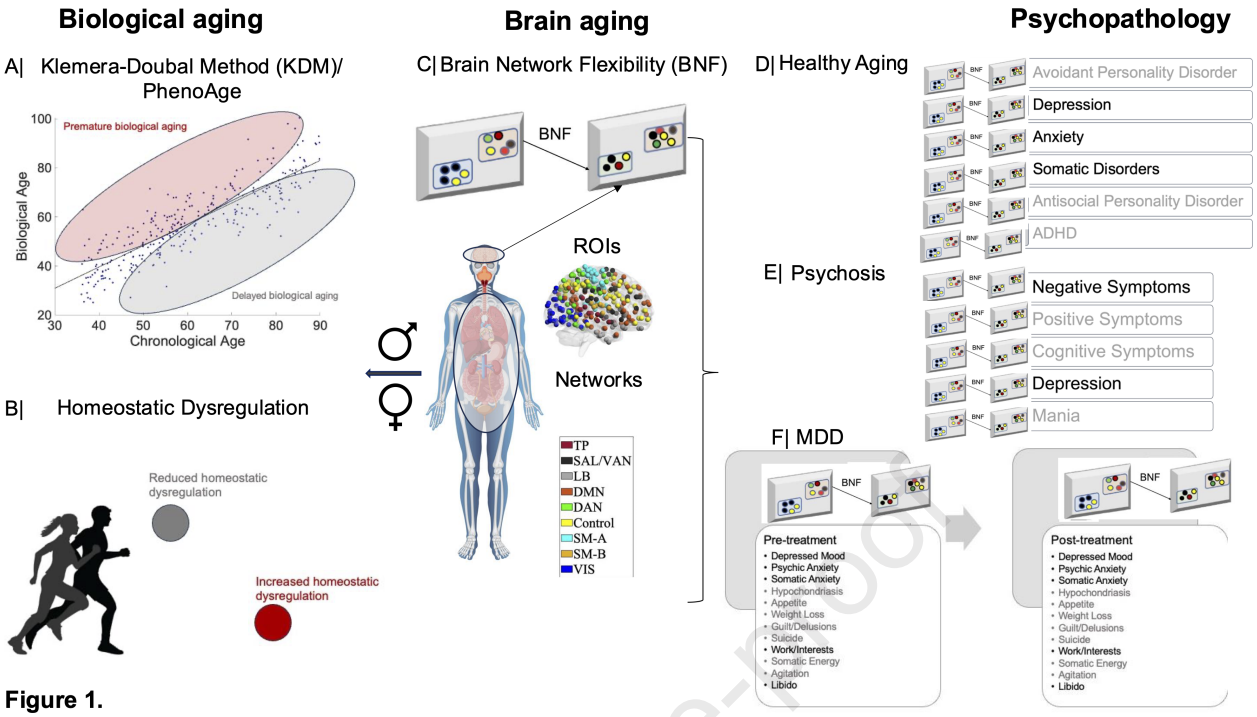


**Figure 1.**

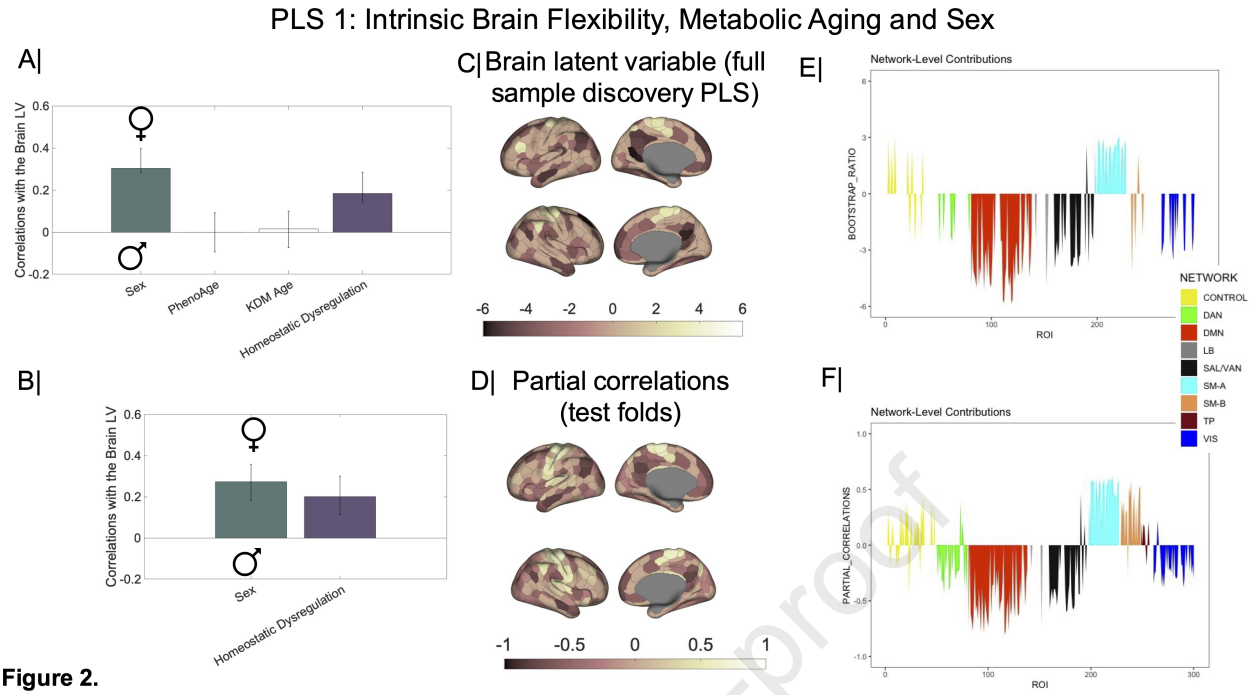


**Figure 2.**

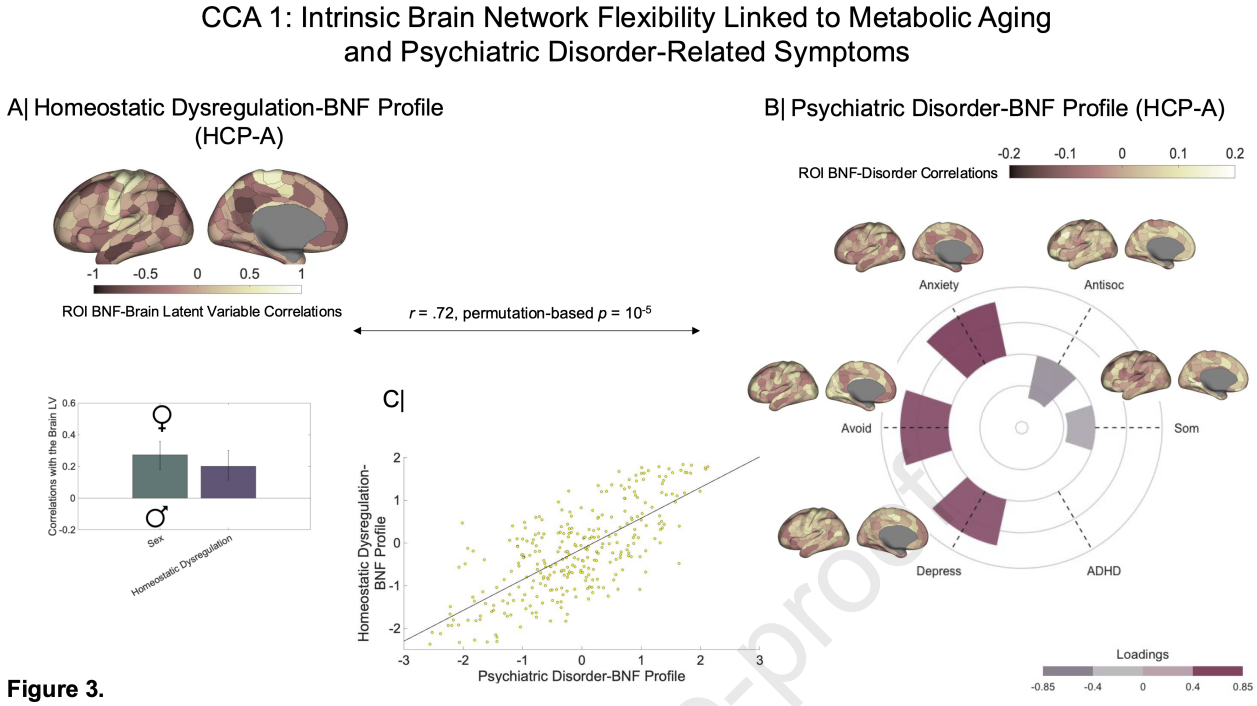


**Figure 3.**

CCA 2: Intrinsic Brain Network Flexibility Linked to Metabolic Aging and Psychotic Symptoms

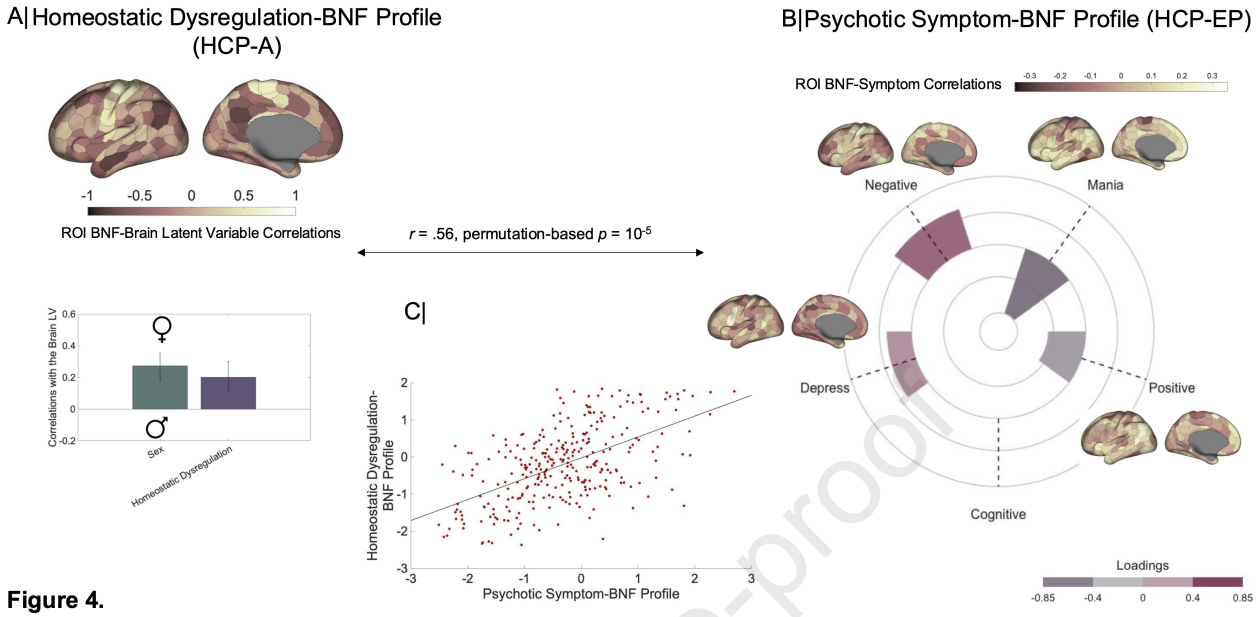


**Figure 4.**

CCA 3: Intrinsic Brain Network Flexibility Linked to Metabolic Aging and Treatment-Related Resistance in MDD

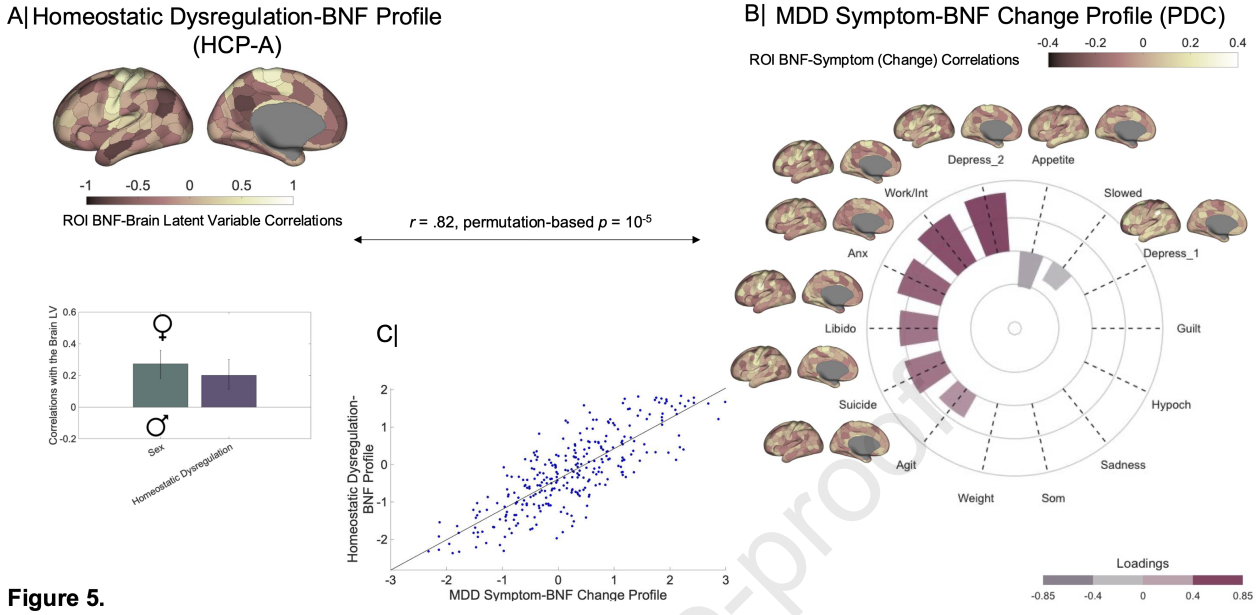


**Figure 5.**