Supplementary Materials

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STROBE Statement: checklist of items that should be included in reports of observational studies

Item	No	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Title and abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	

		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

Supplementary Methods: UKB Participants Selection Criteria for Current Depressive Symptoms

Within the UK Biobank (UKB) general population cohort, a subset of individuals with current depression was identified using the following two UKB data fields.

Based on the UKB data fields:

- 2050: "frequency of depressed mood over the past two weeks"
- 2060: "frequency of unenthusiasm or disinterest over the past two weeks":

The potential ratings were:

1. ' Not at all'
2. 'Several days'
3. 'More than half the days'
4. 'Nearly every day'

Inclusion criteria were participants who endorsed responses of either "3: More than half the days" or "4: Nearly every day" were selected.

Exclusion criteria were comorbid psychiatric, neurological, or medical disorders identified through ICD-10 diagnostic codes (data field: 41202). A total of 21 participants were excluded based on these criteria. Comorbid psychiatric disorders were: F200, "paranoid schizophrenia", 3 participants; F209, "unspecified schizophrenia", 3 participants; F239, "acute and transient psychotic disorders", 1 participant; F250, "schizoaffective disorders", 1 participant; F319, "unspecified bipolar affective disorder", 6 participants; F21, "schizotypal disorder", 0 participants; F30, "manic episodes", 0 participants; F42, "obsessive-compulsive disorder", 0 participants; and F43, "reaction to severe stress or post-Adverse life eventstic stress disorder", 1 participant. Neurological disorders were Parkinson's disease (G20, "Parkinson's disease", 2 participants), Huntington's disease (G10, "Huntington's disease", 0 participants), Alzheimer's disease (G30, "Alzheimer's disease", 0 participants), and epilepsy (G40, "epilepsy", 0 participants). Medical disorders were primary hypertension (I10, "primary hypertension", 20 participants); insulin-dependent diabetes mellitus (E10, "insulin-dependent diabetes mellitus", 0 participants), gestational diabetes (O240, "gestational diabetes", 0 participants).

Supplementary Methods: External validation of pre-trained HYDRA model to UKB general population (Junhao et al., 2022)

Once the HYDRA model was trained on the COORDMDD dataset, the optimal polytope distinguishing the diagnosis group across k dimensions was identified and saved. This polytope was defined in high-dimensional space using the weight (w_i) and bias (b_i) parameters, where i represents the i -th linear SVM.

For each subtype (k), the corresponding pre-trained SVM model is retrieved, containing the weights and biases that define the hyperplane for that dimension. The expression score (E) for each participant is then calculated as the dot product of the feature matrix (X) with the weight vector (w_i), adjusted by the bias (b_i).

Mathematically, the expression score (E) is calculated based on the distance from the respective SVM hyperplanes:

$$E = X \cdot w_i^T + b_i$$

where X represents the feature matrix (consisting of 207 ROI volumes) for the UKBB participants. A higher score suggests a greater alignment with the anatomical profile of the specific subtype, whereas a lower score indicates a profile more similar to control-like anatomy. The dimension membership D for each individual can be determined using hard-coded thresholds or criteria derived from the SVM outputs.

Supplementary Methods: Brain Volumetric Differences Across Dimension Membership Groups

To investigate differences in brain volumetric measures associated with dimension membership, a detailed post-hoc analysis was performed on MUSE features. This analysis aimed to evaluate group-level differences in volumetric measures across four predefined groups: Dimension 1 (D1), Dimension 2 (D2), a combined group representing membership in both D1 and D2, and a group representing neither D1 nor D2.

One-way analysis of variance (ANOVA) was conducted for each MUSE feature to determine whether significant differences existed among the groups. The groups were treated as independent categorical variables, and volumetric measures for each feature were used as dependent variables. To account for the potential inflation of Type I error due to the large number of comparisons performed across all MUSE features, the False Discovery Rate (FDR) correction was applied. The threshold for statistical significance was set at an FDR-adjusted p-value of < 0.05. Additionally, for each significant feature, the proportion of variance explained by group differences was calculated using eta-squared (η^2), a measure of effect size. Features with higher η^2 values were interpreted as having stronger associations with dimension membership, highlighting their neuroanatomical relevance.

To supplement the statistical analysis, heatmaps were generated to provide a visual summary of group means for all significant MUSE features. To ensure that the heatmaps clearly represented group-level differences without being dominated by variability across features, the data for each feature were normalized. For each feature, the mean volumetric value across all four groups was subtracted from the mean for each group. This step centered the values around zero, removing baseline differences between features. The mean-centered values were divided by the standard deviation of the feature across the four groups. This step standardized the variability across groups, placing all features on a consistent scale where the mean was 0 and the standard deviation was 1.

This normalization ensured that the focus of the heatmaps was on relative differences across groups, rather than absolute volumetric variations between features. Normalized heatmaps used a consistent color scale to visually highlight the magnitude and direction of group-level differences, making patterns more interpretable. In addition to the heatmaps, a summary table was prepared, listing all features with significant group differences, their corresponding FDR-adjusted p-values, and η^2 values.

Supplementary Methods: UKB Items for Cognitive Measures

Following Qureshi et al. (2024), cognitive traits were evaluated through standardized tests, each designed to measure distinct domains of cognitive function. These tests, administered during the Imaging visit (2014+), provided reliable and detailed data on participants' executive function, memory, reasoning, and processing speed. The following section provides a detailed breakdown of these measures and their corresponding UKB codes. 1. Executive Function: Executive function was assessed using the Trail Making Test: Trail A (Data-Field 6348): Participants were required to complete a numeric path, with the duration (in deciseconds) to complete this task reflecting their processing speed and cognitive flexibility. Trail B (Data-Field 6350): This test involved completing an alphanumeric path, providing a more complex measure of executive function. Both tasks are highly sensitive to changes in cognitive flexibility and efficiency. 2. Verbal and Numerical Reasoning: Verbal and numerical reasoning was evaluated using the Fluid Intelligence Test (Data-Field 20016). Participants answered as many questions as possible within a two-minute time limit, providing a measure of reasoning ability and cognitive problem-solving. 3. Working Memory: Working memory was assessed using the Backward Digit Span Task (Data-Field 4282), where participants were asked to recall digits in reverse order. The maximum number of digits correctly remembered reflects short-term memory capacity and cognitive control. 4. Processing Speed: Processing speed was measured through the Symbol Digit Substitution Test (Data-Field 23324). This test required participants to match symbols with corresponding digits within 60 seconds, providing a quantitative measure of complex processing speed. 5. Verbal Declarative Memory: Verbal memory was evaluated using the Paired Associate Learning Test (Data-Field 20197). Participants were tasked with recalling word pairs, with the total number of correct associations reflecting their ability to encode and retrieve verbal information. 6. Non-Verbal Reasoning: Non-verbal reasoning was measured using the Matrix Pattern Completion Test (Data-Field 6373). Participants were required to solve a series of visual puzzles within a three-minute time limit. The number of puzzles correctly solved reflected their ability to process and reason with abstract visual information, independent of language-based skills.

Supplementary Table 1. Cognitive test measures and UK Biobank codes

Domain	UKB Category	Field ID	UKB Description	UKB notes
Executive function	Trail Making	6348	Duration (in deciseconds) to complete numeric path (trail #1)	Duration to complete numeric path (trail #1)
	Trail Making	6350	Duration (in deciseconds) to complete alphanumeric path (trail #2)	Duration to complete numeric path (trail #2)
Verbal and numerical reasoning	Cognitive function summary	20016	Fluid intelligence score (based on # of questions answered correctly in two minutes)	This is a simple unweighted sum of the number of correct answers given to the 13 fluid intelligence questions. Participants who did not answer all of the questions within the allotted 2-minute limit are scored as zero for each of the unattempted questions.
Working memory	Numeric memory	4282	Maximum digits remembered correctly	Longest number correctly recalled during the numeric memory test.
Complex processing speed	Symbol Digit Substitution	23324	Number of symbol digit matches made correctly in 60 seconds	This is the number of symbols correctly matched to digits by the participant.
Verbal memory	Paired Associate Learning	20197	Number of word pairs correctly associated	This is the number of word pairs correctly associated out of ten attempts.
Non-verbal memory	Matrix Pattern Completion	6373	Number of puzzles correctly solved in 3 minutes	This is the number of puzzles for which the participant gave the correct solution.

Supplementary Methods: UKB Items for Depressive Symptoms

Following Davis et al. (2020) and Howard et al., (2020), lifetime depressive symptoms traits were identified by selecting participants who reported a core symptom of depression persisting for two weeks or more, specifically persistent sadness (Data-Field: 20446) or loss of interest (Data-Field: 20441). A "Yes" response to either Field 20446 or Field 20441 prompted a set of questions evaluating the severity and impact of symptoms during the participant's worst depressive episode. The evaluation of depressive symptoms was based on the Composite International Diagnostic Interview Short Form (CIDI-SF) (Kessler et al., 1998) and was administered in the UK Biobank (UKB) through an online mental health questionnaire completed by 109,049 participants. The answer array for the weight change is “0 Stayed about the same or was on a diet”, “1 Gained weight”, “2 Lost weight” “3 Both gained and lost some weight during the episode”, here the answer of 1, 2 and 3 was re-coded as 1 indicating “Yes”.
Based on Thorp et al. (2021), depressive symptoms were extracted using questions derived from the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001) depressive symptom fields to evaluate specific aspects of depression in greater detail.

The symptoms were categorized as Yes (1) to indicate the presence of the symptom, or No (0) to denote its absence. The response options for the PHQ-9 questions were: 1, Not at all; 2, Several days; 3, More than half the days; 4, Nearly every day. A response of 1 was recoded as 0, indicating that the symptom was not present, while responses of 2, 3, or 4 were recoded as 1 to indicate the presence of anxiety-related symptoms. These data fields were recorded for consistency in the analysis, ensuring a robust examination of depressive symptoms across core and non-core dimensions, as well as the additional PHQ-9 indicators.

The table below summarizes the depressive symptoms and their corresponding UKB data fields, highlighting their categorization into core symptoms, non-core symptoms, and PHQ-9 depressive symptoms. These traits were assessed with the mental well-being questionnaire that was sent to participants to complete in 2017.

Supplementary Table 2. Depressive Symptoms Measures and UK Biobank codes

Trait	Field ID	UKB Description	Mental well-being online questionnaire question (2017)
Ever had Core Depressive Symptoms	20446	Persistent sadness	Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row?
	20441	Loss of interest	Have you ever had a time in your life lasting two weeks or more when you lost interest in most things like hobbies, work, or activities that usually give you pleasure?
Depressive Symptoms During worst period of depression	20449	Feelings of tiredness during worst episode of depression	Did you feel more tired out or low on energy than is usual for you?
	20532	Changes in sleep patterns	Did your sleep change?
	20435	Difficulty concentrating during worst depression	Did you have a lot more trouble concentrating than usual?
	20450	Feelings of worthlessness during worst period of depression	People sometimes feel down on themselves, no good, worthless. Did you feel this way?
	20437	Thoughts of death during worst depression	Did you think a lot about death - either your own, someone else's or death in general?
	20536	Weight change during worst depression	Did you gain or lose weight without trying, or did you stay about the same weight?
Patient Health Questionnaire-9 (PHQ-9)			*Over the last 2 weeks, how often have you been bothered by any of the following problems?*
	20514	Recent lack of interest or pleasure in doing things	Little interest or pleasure in doing things
	20511	Recent poor appetite or overeating	Poor appetite or overeating
	20508	Recent trouble concentrating on things	Trouble concentrating on things, such as reading the newspaper or watching television
	20510	Recent feelings of depression	Feeling down, depressed, or hopeless

20519	Recent feelings of tiredness or low energy	Feeling tired or having little energy
20507	Recent feelings of inadequacy	Feeling bad about yourself or that you are a failure or have let yourself or your family down
20518	Recent changes in speed/amount of moving or speaking	Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual
20517	Trouble falling or staying asleep, or sleeping too much	Trouble falling or staying asleep, or sleeping too much
20513	Recent thoughts of suicide or self-harm	Thoughts that you would be better off dead or of hurting yourself in some way

Supplementary Methods: UKB Items for Anxiety-Related Traits

Following Thorp et al. (2021), anxiety-related traits were selected based on the Generalized Anxiety Disorder-7 (GAD-7) scale (Spitzer et al., 2006), using UKB data fields. The responses for these traits were: 1, Not at all; 2, Several days; 3, More than half the days; 4, Nearly every day. A response of 1 was recoded as 0, indicating that the symptom was not present, while responses of 2, 3, or 4 were recoded as 1 to indicate the presence of anxiety-related symptoms.

These traits were assessed with the mental well-being questionnaire that was sent to participants to complete in 2017. The table below provides a summary of the anxiety traits and their associated UKB data field ID:

Supplementary Table 3. Anxiety-related Measures and UK Biobank codes

Field ID	UKB Description	Mental well-being online questionnaire question (2017)
		Over the last 2 weeks, how often have you been bothered by any of the following problems?
20506	Recent feelings or nervousness or anxiety	Feeling nervous, anxious or on edge
20512	Recent feelings of foreboding	Feeling afraid as if something awful might happen
20505	Recent easy annoyance or irritability	Becoming easily annoyed or irritable
20516	Recent restlessness	Being so restless that it is hard to sit still
20515	Recent trouble relaxing	Trouble relaxing
20520	Recent worrying too much about different things	Worrying too much about different things
20509	Recent inability to stop or control worrying	Not being able to stop or control worrying

Supplementary Methods: UKB Items for Neuroticism-Related Traits

Traits related to neuroticism and depressive symptoms, as categorized by the UK Biobank (UKB). Neuroticism-related items were derived from the Eysenck Personality Inventory framework (Eysenck & Eysenck, 1975) and assigned individual codes within the UKB dataset. These traits align with the approach outlined in the study by Okbay et al. (2016). The table below summarizes the neuroticism traits, their UKB field ID, UKB description and the corresponding questions. Response options were “No”, coded and 0, and “yes”, coded as 1. Responses were collected at the initial imaging visit (instance 2) from 2014 onwards.

Supplementary Table 4. Neuroticism Measures and UK Biobank codes

Field ID	UKB Description	ACE touchscreen question
1920	Mood swings	Does your mood often go up and down?
1930	Miserableness	Do you ever feel 'just miserable' for no reason?
1940	Irritability	Are you an irritable person?
1950	Sensitivity / hurt feelings	Are your feelings easily hurt?
1960	Fed-up feelings	Do you often feel 'fed-up'?
1970	Nervous feelings	Would you call yourself a nervous person?
1980	Worrier / anxious feelings	Are you a worrier?
1990	Tense / 'highly strung'	Would you call yourself tense or 'highly strung'?
2000	Worry too long after embarrassment	Do you worry too long after an embarrassing experience?
2010	Suffer from 'nerves'	Do you suffer from 'nerves'?
2020	Loneliness, isolation	Do you often feel lonely?
2030	Guilt Feelings	Are you often troubled by feelings of guilt?

Supplementary Methods: UKB Items for adverse life events

The adverse life event traits included in this analysis are based on UK Biobank (UKB) data fields following Holmes et al (2016), covering experiences of violence, abuse, and neglect across different stages of life. These traits are identified by specific UKB codes. For instance, participants were asked if they had experienced a violent or sexual assault (UKB Code: 29086) with response options including "No, never," "Yes, but not in the last 12 months," or "Yes, within the last 12 months". Both "Yes, but not in the last 12 months" and "Yes, within the last 12 months" were coded as 1 to indicate the presence of history of Adverse life events or abuse. Other traits assessed included physical violence, sexual interference, or lack of consent involving a partner or ex-partner, as well as experiences of being stopped from seeing friends or family. Childhood adverse life events was also evaluated, including feeling hated by a family member (UKB Code: 29078), being physically abused by family (UKB Code: 29077), or sexually molested as a child (UKB Code: 29079). Childhood adverse life events were had response options including “never”, coded and 0, and “rarely true”, “sometimes true”, “often true” and “very often true” which were recoded as 1 to indicate the presence of historic events. Adverse life events questionnaires were recorded using the Mental Wellbeing Questionnaire that was emailed to all UKB participants in 2023. These traits capture a broad spectrum of Adverse life events-related experiences and provide insights into participants' life events.

Supplementary Table 5. Adverse Life Events measures and UK Biobank codes

Field ID	UKB Description	Mental well-being online questionnaire question (2023)
29086	Experienced a violent or sexual assault	Since you were sixteen, have you experienced: a violent or sexual assault?
29083	Physical violence by partner or ex-partner as an adult	Since you were sixteen, has a partner or ex-partner (by partner we mean any boyfriend or girlfriend as well as a husband, wife or civil partner): pushed you, held or pinned you down, slapped you, kicked, bitten or hit you (with a fist or something else), or thrown something at you that hurt you?
29081	Stopped from seeing friends or family by partner or ex-partner as an adult	Since you were sixteen, has a partner or ex-partner (by partner we mean any boyfriend or girlfriend as well as a husband, wife or civil partner): stopped you from seeing friends and relatives?
29085	Sexual intercourse by partner or ex-partner without consent as an adult	Since you were sixteen, has a partner or ex-partner (by partner we mean any boyfriend or girlfriend as well as a husband, wife or civil partner): engaged in sexual intercourse with you without your consent?
29084	Sexual interference by partner or ex-partner without consent as an adult	Since you were sixteen, has a partner or ex-partner (by partner we mean any boyfriend or girlfriend as well as a husband, wife or civil partner): touched you, or got you to touch them, in a sexual way without your consent?
29078	Felt hated by family member as a child	When I was growing up: I felt that someone in my family hated me
29079	Sexually molested as a child	When I was growing up: Someone molested me (sexually).
29077	Physically abused by family as a child	When I was growing up: People in my family hit me so hard that it left me with bruises or marks.

Supplementary Methods: UKB Items for Self-Harm

Self-harm traits were analysed using data from the UKB following Zhang et al. (2024). This included the evaluation of self-harm and suicide attempts, captured under two distinct UKB data fields: 20480 (Ever self-harmed) and 29116 (Ever attempted suicide). Participants' responses were categorised as "Yes" (1) to indicate the presence of self-harm or suicide attempts, and "No" (0) to denote their absence.

The table below summaries the self-harm traits and their corresponding UKB data fields:

Supplementary Table 6. Self-harm behaviors measures and UK Biobank codes

Field ID	UKB Description	**Mental well-being online questionnaire question**	**Assessment timepoint**
20480	Ever self-harmed	Have you deliberately harmed yourself, whether or not you meant to end your life?	2017
29116	Ever attempted suicide	Have you harmed yourself with the intention of ending your life?	2023

Supplementary Methods: UKB Items for lifestyle factors

The analysis incorporated several lifestyle factors recorded in the UK Biobank (UKB) that were significantly associated with suicide attempts in Zhang et al. (2024), covering behaviors and habits related to sexual activity, smoking, alcohol consumption, diet, and sleep. The assessments for these traits were conducted during the Imaging visit (2014+). Participant responses were categorized based on predefined answer arrays where applicable. Below is a summary of the traits and their corresponding data fields:

Supplementary Table 7. Lifestyle factors measures and UK Biobank codes

Field ID	UKB Description	ACE touchscreen question	Answer Arrays
2139	Age first had sexual intercourse	What was your age when you first had sexual intercourse? (Sexual intercourse includes vaginal, oral or anal intercourse)	Enter number. Special responses: -2 = "Never had sex", -3 = "Prefer not to answer", -1 = "Do not know"
20160	Ever smoked	Do you smoke tobacco now? In the past, how often have you smoked tobacco?	Individual classed as Ever smoker (1) if Current tobacco smoking = most days (1) or occasionally (2) OR Past tobacco smoking = most days (1) or occasionally (2) or tried once or twice (3). Individual were classed as Never smoker (0) if Current tobacco smoking = no (0) AND Past tobacco smoking = never (4)
1239	Current tobacco smoking	Do you smoke tobacco now?	1, Yes, on most or all days; 2, Only occasionally 0, No
1618	Alcohol usually taken with meals	When you drink alcohol, is it usually with meals?	Yes (1) / No (0)
2149	Lifetime number of sexual partners	About how many sexual partners have you had in your lifetime?	Enter number. Special responses: -1 = "Do not know", -3 = "Prefer not to answer"
1200	Sleeplessness / insomnia	Do you have trouble falling asleep at night or do you wake up in the middle of the night?	1, Never/rarely; 2, Sometimes; 3, Usually Prefer not to answer
20116	Smoking status	This field summarises the current/past smoking status of the participant.	1, Never; 2, Previous; 3, Current Prefer not to answer
1190	Nap during the day	Do you have a nap during the day?	1, Never/rarely; 2, Sometimes; 3, Usually Prefer not to answer
1478	Salt added to food	Do you add salt to your food? (Do not include salt used in cooking)	1, Never/rarely; 2, Sometimes; 3, Usually; 4, Always Prefer not to answer
1458	Cereal intake	How many bowls of cereal do you eat a WEEK?	Enter number. -10 = "Less than one", -1 = "Do not know", -3 = "Prefer not to answer"
1279	Exposure to tobacco smoke outside home	Outside of your home, about how many hours per WEEK are you exposed to other people's tobacco smoke?	Enter number. -1 = "Do not know", -3 = "Prefer not to answer"

Supplementary Methods: UKB Items for Metabolic Measures

Following significant findings from Amin et al. (2023) and Mao et al. (2024) the analysis included various metabolites measured in the UK Biobank (UKB) dataset, reflecting metabolic processes, lipid profiles, blood cell counts, and other health indicators. These traits provide insights into key biological markers relevant to respiratory health, cardiovascular measures, lipid metabolism, and inflammation. These traits were assessed during the UKB's Initial assessment visit (2006-2010).

Supplementary Table 8. Metabolic Measures and UK Biobank codes

Field ID	UKB Description	UKB Note
3063	Forced expiratory volume in 1-second (FEV1)	FEV1 value calculated from blow
4080	Systolic blood pressure, automated reading	Blood pressure, automated reading, systolic. Two measures of blood pressure were taken a few moments apart.
30750	Glycated haemoglobin (HbA1c)	Measured by HPLC analysis on a Bio-Rad VARIANT II Turbo
30690	TC, total cholesterol	Measured by CHO-POD analysis on a Beckman Coulter AU5800
30000	White blood cell (leukocyte) count	White blood count is the number of leukocytes.
30270	Mean cell volume (MCV)	Mean Sphered Cells Volume
30180	Lymphocyte ratio	White blood count is the number of leukocytes.
30740	Glucose	Measured by hexokinase analysis on a Beckman Coulter AU5800
30600	Albumin	Measured by BCG analysis on a Beckman Coulter AU5800
30610	Alkaline phosphatase (ALP)	Measured by AMP(IFCC) analysis on a Beckman Coulter AU5800
30710	C-reactive protein (CRP)	Measured by immunoturbidimetric - high sensitivity analysis on a Beckman Coulter AU5800
23447	Monounsaturated Fatty Acids	Monounsaturated Fatty Acids from Nightingale Health data. Biomarker group: Fatty acids
23452	Omega-6 Fatty Acids to Total Fatty Acids percentage	Percentage of Omega-6 Fatty Acids to Total Fatty Acids from Nightingale Health data. Biomarker group: Fatty acids, Biomarker sub-group: Fatty acid ratios
23453	Polyunsaturated Fatty Acids to Total Fatty Acids percentage	Percentage of Polyunsaturated Fatty Acids to Total Fatty Acids from Nightingale Health data. Biomarker group: Fatty acids, Biomarker sub-group: Fatty acid ratios
23454	Monounsaturated Fatty Acids to Total Fatty Acids percentage	Percentage of Polyunsaturated Fatty Acids to Total Fatty Acids from Nightingale Health data. Biomarker group: Fatty acids, Biomarker sub-group: Fatty acid ratios
23456	Linoleic Acid to Total Fatty Acids percentage	Percentage of Linoleic Acid to Total Fatty Acids from Nightingale Health data. Biomarker group: Fatty acids, Biomarker sub-group: Fatty acid ratios
23481	Concentration of Chylomicrons and Extremely Large VLDL Particles	Biomarker subgroup: Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards)
23482	Total Lipids in Chylomicrons and Extremely Large VLDL	Biomarker subgroup: Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards)

23483	Phospholipids in Chylomicrons and Extremely Large VLDL	Biomarker subgroup: Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards)
23484	Cholesterol in Chylomicrons and Extremely Large VLDL	Biomarker subgroup: Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards)
23485	Cholesteryl Esters in Chylomicrons and Extremely Large VLDL	Biomarker subgroup: Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards)
23486	Free Cholesterol in Chylomicrons and Extremely Large VLDL	Biomarker subgroup: Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards)
23487	Triglycerides in Chylomicrons and Extremely Large VLDL	Biomarker subgroup: Chylomicrons and extremely large VLDL (particle diameters from 75 nm upwards)
23488	Concentration of Very Large VLDL Particles	Biomarker subgroup: Very large VLDL (average diameter 64 nm)
23489	Total Lipids in Very Large VLDL	Biomarker subgroup: Very large VLDL (average diameter 64 nm)
23490	Phospholipids in Very Large VLDL	Biomarker subgroup: Very large VLDL (average diameter 64 nm)
23491	Cholesterol in Very Large VLDL	Biomarker subgroup: Very large VLDL (average diameter 64 nm)
23492	Cholesteryl Esters in Very Large VLDL	Biomarker subgroup: Very large VLDL (average diameter 64 nm)
23493	Free Cholesterol in Very Large VLDL	Biomarker subgroup: Very large VLDL (average diameter 64 nm)
23494	Triglycerides in Very Large VLDL	Biomarker subgroup: Very large VLDL (average diameter 64 nm)
23495	Concentration of Large VLDL Particles	Biomarker subgroup: Large VLDL (average diameter 53.6 nm)
23496	Total Lipids in Large VLDL	Biomarker subgroup: Large VLDL (average diameter 53.6 nm)
23497	Phospholipids in Large VLDL	Biomarker subgroup: Large VLDL (average diameter 53.6 nm)
23498	Cholesterol in Large VLDL	Biomarker subgroup: Large VLDL (average diameter 53.6 nm)
23499	Cholesteryl Esters in Large VLDL	Biomarker subgroup: Large VLDL (average diameter 53.6 nm)
23500	Free Cholesterol in Large VLDL	Biomarker subgroup: Large VLDL (average diameter 53.6 nm)
23501	Triglycerides in Large VLDL	Biomarker subgroup: Large VLDL (average diameter 53.6 nm)
23503	Total Lipids in Medium VLDL	Biomarker subgroup: Medium VLDL (average diameter 44.5 nm)
23508	Triglycerides in Medium VLDL	Biomarker subgroup: Medium VLDL (average diameter 44.5 nm)
23509	Concentration of Small VLDL Particles	Biomarker subgroup: Small VLDL (average diameter 36.8 nm)
23510	Total Lipids in Small VLDL	Biomarker subgroup: Small VLDL (average diameter 36.8 nm)
23515	Triglycerides in Small VLDL	Biomarker subgroup: Small VLDL (average diameter 36.8 nm)
23522	Triglycerides in Very Small VLDL	Biomarker subgroup: Very small VLDL (average diameter 31.3 nm)
23524	Total Lipids in IDL	Biomarker subgroup: IDL (average diameter 28.6 nm)
23526	Cholesterol in IDL	Biomarker subgroup: IDL (average diameter 28.6 nm)
23527	Cholesteryl Esters in IDL	Biomarker subgroup: IDL (average diameter 28.6 nm)
23528	Free Cholesterol in IDL	Biomarker subgroup: IDL (average diameter 28.6 nm)
23529	Triglycerides in IDL	Biomarker subgroup: IDL (average diameter 28.6 nm)
23551	Concentration of Very Large HDL Particles	Biomarker subgroup: Very large HDL (average diameter 14.3 nm)
23552	Total Lipids in Very Large HDL	Biomarker subgroup: Very large HDL (average diameter 14.3 nm)
23553	Phospholipids in Very Large HDL	Biomarker subgroup: Very large HDL (average diameter 14.3 nm)
23554	Cholesterol in Very Large HDL	Biomarker subgroup: Very large HDL (average diameter 14.3 nm)

23555	Cholesteryl Esters in Very Large HDL	Biomarker subgroup: Very large HDL (average diameter 14.3 nm)
23556	Free Cholesterol in Very Large HDL	Biomarker subgroup: Very large HDL (average diameter 14.3 nm)
23558	Concentration of Large HDL Particles	Biomarker subgroup: Large HDL (average diameter 12.1 nm)
23559	Total Lipids in Large HDL	Biomarker subgroup: Large HDL (average diameter 12.1 nm)
23560	Phospholipids in Large HDL	Biomarker subgroup: Large HDL (average diameter 12.1 nm)
23561	Cholesterol in Large HDL	Biomarker subgroup: Large HDL (average diameter 12.1 nm)
23562	Cholesteryl Esters in Large HDL	Biomarker subgroup: Large HDL (average diameter 12.1 nm)
23563	Free Cholesterol in Large HDL	Biomarker subgroup: Large HDL (average diameter 12.1 nm)
23565	Concentration of Medium HDL Particles	Biomarker subgroup: Medium HDL (average diameter 10.9 nm)
23568	Cholesterol in Medium HDL	Biomarker subgroup: Medium HDL (average diameter 10.9 nm)
23569	Cholesteryl Esters in Medium HDL	Biomarker subgroup: Medium HDL (average diameter 10.9 nm)
23570	Free Cholesterol in Medium HDL	Biomarker subgroup: Medium HDL (average diameter 10.9 nm)
23571	Triglycerides in Medium HDL	Biomarker subgroup: Medium HDL (average diameter 10.9 nm)
23578	Triglycerides in Small HDL	Biomarker group: Lipoprotein subclasses, Biomarker subgroup: Small HDL (average diameter 8.7 nm)
23472	Pyruvate	Biomarker group: Glycolysis related metabolites
23473	Citrate	Biomarker group: Glycolysis related metabolites

Supplementary Methods: UKB Items for Physical Measures

Following significant results from Zhang et al. (2024) this analysis includes a variety of physical measures obtained from the UK Biobank (UKB) dataset, providing detailed insights into body composition, strength, and fat distribution across different regions of the body. These traits were assessed during the Imaging visit (2014+).

The table below summarizes the physical measures and their corresponding UKB data fields:

Supplementary Table 9. Physical Measures and UK Biobank codes

Field ID	UKB Description	UKB Note
23111	Leg fat percentage (right)	Body composition estimation by impedance measurement. Right leg fat percentages
23115	Leg fat percentage (left)	Body composition estimation by impedance measurement. Left leg fat percentage
23104	Body mass index (BMI)	Body composition estimation by impedance measurement. Body Mass Index.
47	Hand grip strength (right)	Right grip strength.
23099	Body fat percentage	Body composition estimation by impedance measurement. Body fat percentage
23123	Arm fat percentage (left)	Body composition estimation by impedance measurement. Left arm fat percentage
46	Hand grip strength (left)	Left grip strength.
23127	Trunk fat percentage	Body composition estimation by impedance measurement. Trunk fat percentages
23112	Leg fat mass (right)	Body composition estimation by impedance measurement. Right leg fat mass (Kg)
23119	Arm fat percentage (right)	Body composition estimation by impedance measurement. Right arm fat percentage
23120	Arm fat mass (right)	Body composition estimation by impedance measurement. Right arm fat mass (Kg)
23129	Trunk fat-free mass	Body composition estimation by impedance measurement. Trunk fat free mass (Kg)
23124	Arm fat mass (left)	Body composition estimation by impedance measurement. Left arm fat mass (Kg)
23130	Trunk predicted mass	Body composition estimation by impedance measurement. Trunk predicted mass (Kg)
23116	Leg fat mass (left)	Body composition estimation by impedance measurement. Left leg fat mass (kg)

Supplementary Methods: Genetic analysis

Genetic preprocessing protocol (Hwang et al., 2023)

Participants with second-degree familial relationships were identified and excluded using KING software for relationship inference (Manichaikul et al., 2010). Additionally, individuals with mismatched genetically identified sex and self-reported sex, as well as those with chromosome aneuploidy, were removed from the dataset. Duplicate variants were excluded, along with variants exhibiting a minor allele frequency (MAF) below 1%, a missing genotype rate above 3%, or failing the Hardy-Weinberg equilibrium test. Participants with more than 3% missing genotypes were also excluded to maintain high data quality.

To address population stratification, the first 40 principal components (PCs) were calculated using PLINK 2 (v2.0.0) (Purcell et al., 2007). After completing these quality control steps, the final dataset comprised 30,376 samples and 6,288,959 variants from UK Biobank participants of European ancestry, which were used for genome-wide association studies (GWAS).

Categorization of Genetic Variants in FUMA (Hwang et al., 2023)

FUMA (Functional Mapping and Annotation) categorizes genetic variants into independent significant SNVs, lead SNVs, candidate SNVs, and genomic risk loci, streamlining post-GWAS annotation processes by integrating data from various biological resources (Watanabe et al., 2017). Independent significant SNVs are defined as variants with a p-value $\leq 5\times10^{-8}$, independent at a user-defined r^2 threshold (e.g., 0.6). Candidate SNVs are those in linkage disequilibrium (LD) with these significant SNVs, and FUMA uses the GWAS Catalog to identify clinical traits associated with them.

Lead SNVs, in contrast, are independent significant SNVs uncorrelated at $r^2 < 0.1$. Among correlated variants ($r^2 \geq 0.1$), the lead SNV is determined by the lowest p-value. FUMA recommends setting an r^2 threshold of 0.6 or higher for more precise differentiation. Variants without prior clinical associations are classified as novel lead SNVs.

Genomic risk loci encompass clusters of independent signals within a defined distance (e.g., 250 kilobases). These loci consolidate variants correlated at $r^2 \geq 0.1$ and are represented by the variant with the lowest p-value. FUMA's integrative approach allows researchers to identify and priorities functional variants using positional, expression quantitative trait loci (eQTL), and chromatin interaction mapping, with optional filtering based on functional scores such as CADD or RegulomeDB.

Supplementary Methods: Presentation of statistics (Junhao et al., 2022)

We summarize the statistics used in the paper:

1. The HYDRA model was used to identify two neuroanatomical dimensions (D1, D2) in

first-episode and recurrent MDD based on z-scored brain ROIs, with k=2 selected as the optimal number of clusters using the Adjusted Rand Index (ARI). Dimension scores and memberships for the UK Biobank cohort were computed based on thresholds for expression scores (E1, E2), defining D1, D2, combined, and neither groups.

To evaluate brain volumetric differences, one-way ANOVA were conducted across the groups, with significance determined by FDR correction ($p < 0.05$), and group means along with explained variance for each MUSE feature were reported.

2. For group comparisons in cognitive assessments, general linear models adjusted for age, sex, and dimension membership (D1, D2) were applied to standardised scores, with effect sizes represented as beta coefficients. False Discovery Rate (FDR) correction was applied to set a significance threshold of $p < 0.05$. For group comparisons in emotional, psychological, and behavioural traits, Chi-Square tests were used to compare binary variables between dimensions, with effect sizes (Cramér's V) and response patterns (standardised residuals) summarised. For group comparisons in metabolomic data, standardised measures were analysed using beta coefficients to reflect group differences, with positive coefficients indicating higher scores in D2 and negative coefficients indicating higher scores in D1.

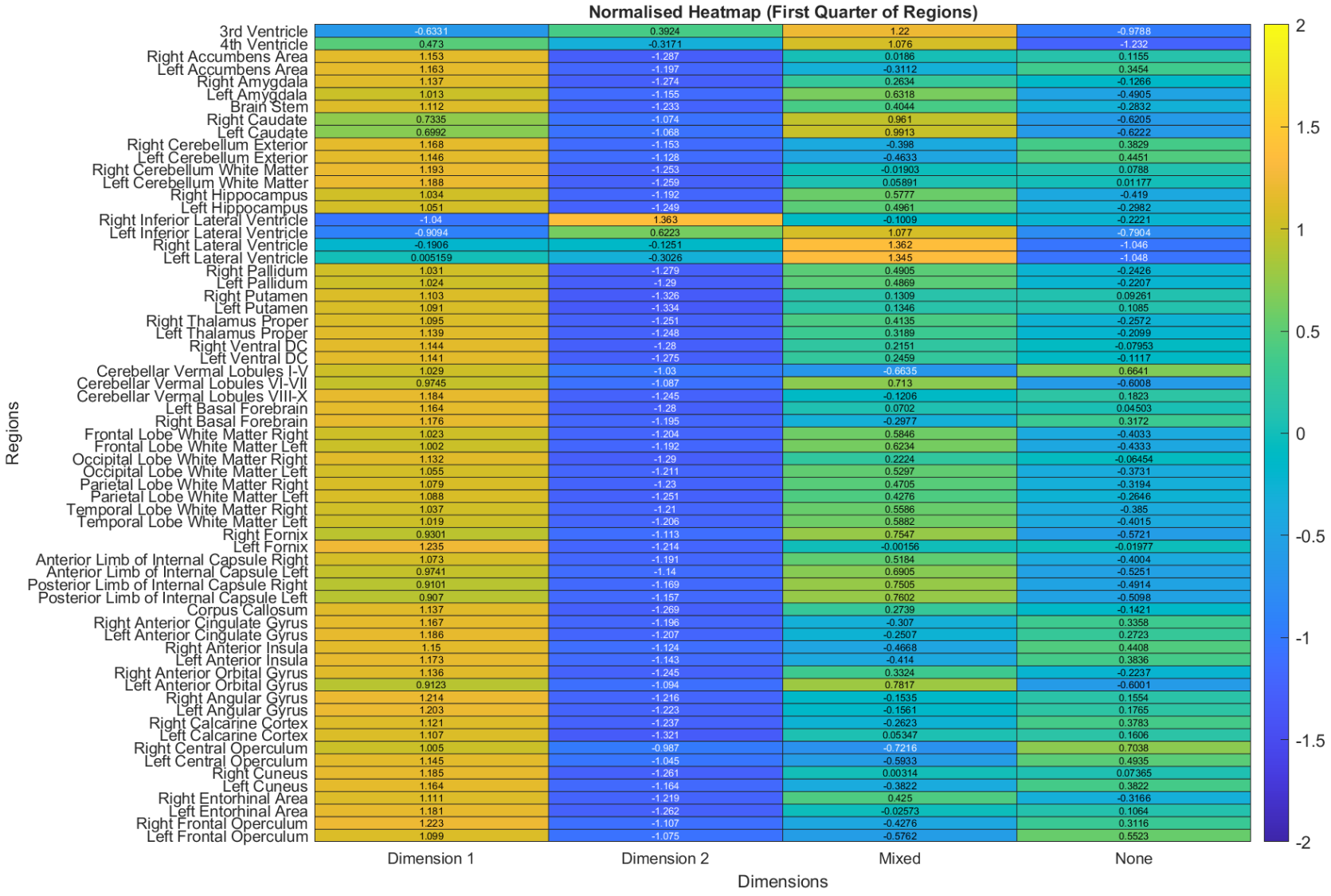
3. For GWAS analysis, we set the P-value threshold to be 5×10^{-8}, which is a strict threshold in genome-wide analyses.

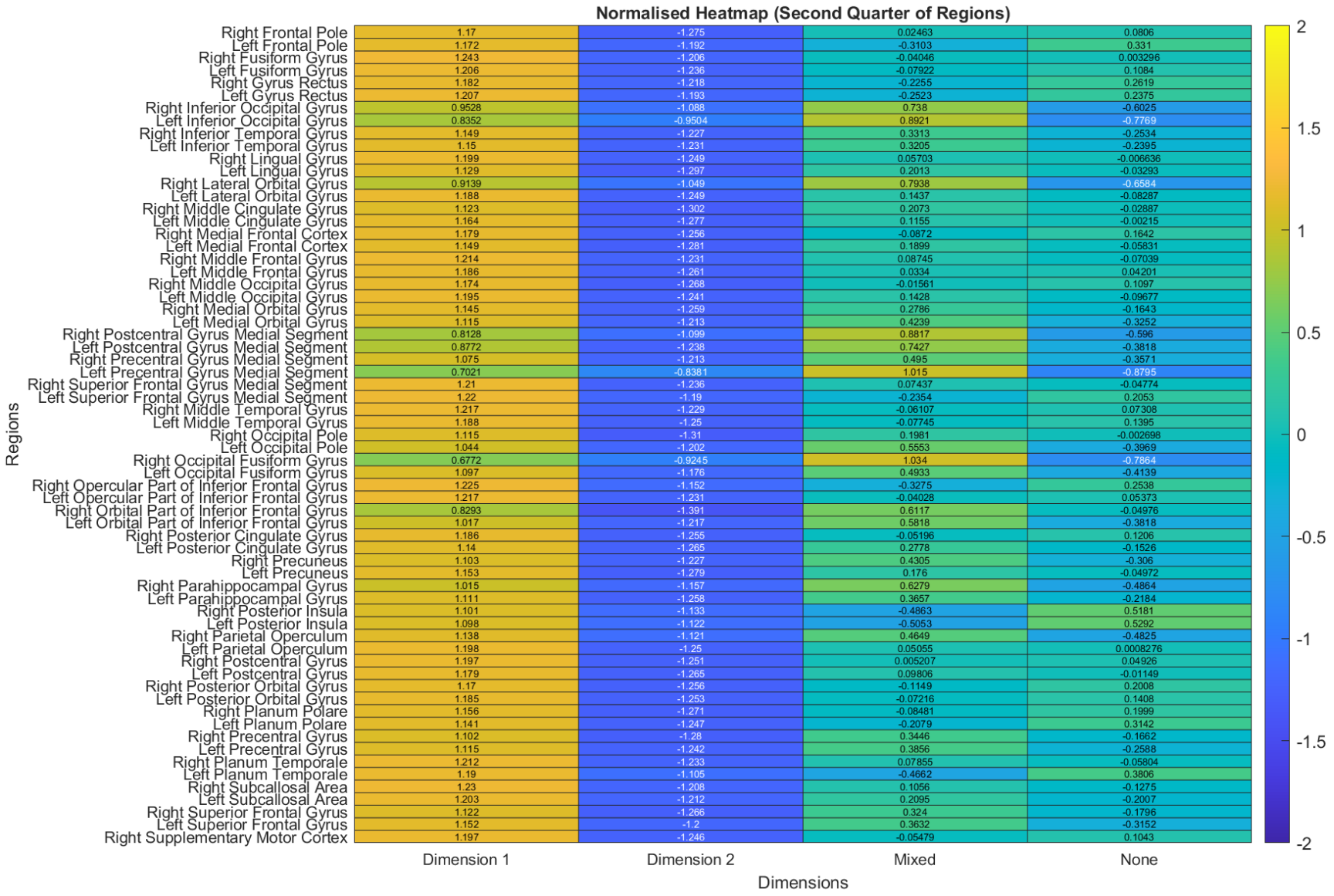
Supplementary Table 10. Research Domain Criteria (RDoC) assessment items and criteria thresholds

RDoC/phenotype		HAMD	MADRS
Citrome et al. (2022)			
Negative Valance Systems	Items	#1 depressed mood #10 anxiety psychic #11 anxiety somatic #15 hypochondriasis	#1 apparent sadness #2 reported sadness #3 inner tension #10 suicidal thoughts
	Maximum total score	16	24
Positive Valance Systems	Items	#7 Work and activities #14 genital symptoms	#8 inability to feel
	Maximum total score	6	6
Cognitive Systems	Items	#2 feelings of guilt	#6 concentration difficulties
	Maximum total score	4	6
Arousal/Regulatory Systems	Items	#4 insomnia early night #5 insomnia middle night #6 insomnia early morning #9 agitation #15 hypochondriasis #16 loss of weight	#4 reduced sleep #5 reduced appetite
	Maximum total score	22	12
Sensorimotor Systems	Items	#8 retardation #15 hypochondriasis	#7 lassitude
	Maximum total score	8	6
Ahmed et al. (2018)			
Core Depression	Items	#1 depressed mood #7 work and activities	#1 apparent sadness #2 reported sadness #8 inability to feel
	Maximum total score	8	18
	Phenotype criteria	Score of 3 or 4 on both items	Score of 2 or more on item #1 and a score of 4 or more on items #2 and #8
Anxiety	Items	#9 agitation #10 anxiety psychic #11 anxiety somatic #15 hypochondriasis	#3 inner tension
	Maximum total score	16	6
	Phenotype criteria	A score of 6 or more across all items	a score of 4 or more on item #.3
Neurovegetative symptoms of melancholia	Items	#6 insomnia early morning #12 somatic gastrointestinal	#4 reduced sleep #5 reduced appetite
	Maximum total score	6	12
	Phenotype criteria	Score of 1 or more on both items.	Score of 3 or more on both items.

RDoC, Research Domain Criteria; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale. HAMD item 17 (insight) was excluded from cognitive systems due to score of 0 for 98% of participants.

Supplementary Figure 1. Heatmaps of group means for all significant MUSE features. Normalized heatmaps used a consistent color scale to visually highlight the magnitude and direction of group-level differences, making patterns more interpretable.




Normalised Heatmap (Second Quarter of Regions)
Regions
Right Frontal Pole 1.17 -1.275 0.02463 0.0806
Left Frontal Pole 1.172 -1.192 -0.3103 0.331
Right Fusiform Gyrus 1.243 -1.206 -0.04046 0.003296
Left Fusiform Gyrus 1.206 -1.236 -0.07922 0.1084
Right Gyrus Rectus 1.182 -1.218 -0.2255 0.2619
Left Gyrus Rectus 1.207 -1.193 -0.2523 0.2375
Right Inferior Occipital Gyrus 0.9528 -1.088 0.738 -0.6025
Left Inferior Occipital Gyrus 0.8352 -0.9504 0.8921 -0.7769
Right Inferior Temporal Gyrus 1.149 -1.227 0.3313 -0.2534
Left Inferior Temporal Gyrus 1.15 -1.231 0.3205 -0.2395
Right Lingual Gyrus 1.199 -1.249 0.05703 -0.006636
Left Lingual Gyrus 1.129 -1.297 0.2013 -0.03293
Right Lateral Orbital Gyrus 0.9139 -1.049 0.7938 -0.6584
Left Lateral Orbital Gyrus 1.188 -1.249 0.1437 -0.08287
Right Middle Cingulate Gyrus 1.123 -1.302 0.2073 -0.02887
Left Middle Cingulate Gyrus 1.164 -1.277 0.1155 -0.00215
Right Medial Frontal Cortex 1.179 -1.256 -0.0872 0.1642
Left Medial Frontal Cortex 1.149 -1.281 0.1899 -0.05831
Right Middle Frontal Gyrus 1.214 -1.231 0.08745 -0.07039
Left Middle Frontal Gyrus 1.186 -1.261 0.0334 0.04201
Right Middle Occipital Gyrus 1.174 -1.268 -0.01561 0.1097
Left Middle Occipital Gyrus 1.195 -1.241 0.1428 -0.09677
Right Medial Orbital Gyrus 1.145 -1.259 0.2786 -0.1643
Left Medial Orbital Gyrus 1.115 -1.213 0.4239 -0.3252
Right Postcentral Gyrus Medial Segment 0.8128 -1.099 0.8817 -0.596
Left Postcentral Gyrus Medial Segment 0.8772 -1.238 0.7427 -0.3818
Right Precentral Gyrus Medial Segment 1.075 -1.213 0.495 -0.3571
Left Precentral Gyrus Medial Segment 0.7021 -0.8381 1.015 -0.8795
Right Superior Frontal Gyrus Medial Segment 1.21 -1.236 0.07437 -0.04774
Left Superior Frontal Gyrus Medial Segment 1.22 -1.19 -0.2354 0.2053
Right Middle Temporal Gyrus 1.217 -1.229 -0.06107 0.07308
Left Middle Temporal Gyrus 1.188 -1.25 -0.07745 0.1395
Right Occipital Pole 1.115 -1.31 0.1981 -0.002698
Left Occipital Pole 1.044 -1.202 0.5553 -0.3969
Right Occipital Fusiform Gyrus 0.6772 -0.9245 1.034 -0.7864
Left Occipital Fusiform Gyrus 1.097 -1.176 0.4933 -0.4139
Right Opercular Part of Inferior Frontal Gyrus 1.225 -1.152 -0.3275 0.2538
Left Opercular Part of Inferior Frontal Gyrus 1.217 -1.231 -0.04028 0.05373
Right Orbital Part of Inferior Frontal Gyrus 0.8293 -1.391 0.6117 -0.04976
Left Orbital Part of Inferior Frontal Gyrus 1.017 -1.217 0.5818 -0.3818
Right Posterior Cingulate Gyrus 1.186 -1.255 -0.05196 0.1206
Left Posterior Cingulate Gyrus 1.14 -1.265 0.2778 -0.1526
Right Precuneus 1.103 -1.227 0.4305 -0.306
Left Precuneus 1.153 -1.279 0.176 -0.04972
Right Parahippocampal Gyrus 1.015 -1.157 0.6279 -0.4864
Left Parahippocampal Gyrus 1.111 -1.258 0.3657 -0.2184
Right Posterior Insula 1.101 -1.133 -0.4863 0.5181
Left Posterior Insula 1.098 -1.122 -0.5053 0.5292
Right Parietal Operculum 1.138 -1.121 0.4649 -0.4825
Left Parietal Operculum 1.198 -1.25 0.05055 0.0008276
Right Postcentral Gyrus 1.197 -1.251 0.005207 0.04926
Left Postcentral Gyrus 1.179 -1.265 0.09806 -0.01149
Right Posterior Orbital Gyrus 1.17 -1.256 -0.1149 0.2008
Left Posterior Orbital Gyrus 1.185 -1.253 -0.07216 0.1408
Right Planum Polare 1.156 -1.271 -0.08481 0.1999
Left Planum Polare 1.141 -1.247 -0.2079 0.3142
Right Precentral Gyrus 1.102 -1.28 0.3446 -0.1662
Left Precentral Gyrus 1.115 -1.242 0.3856 -0.2588
Right Planum Temporale 1.212 -1.233 0.07855 -0.05804
Left Planum Temporale 1.19 -1.105 -0.4662 0.3806
Right Subcallosal Area 1.23 -1.208 0.1056 -0.1275
Left Subcallosal Area 1.203 -1.212 0.2095 -0.2007
Right Superior Frontal Gyrus 1.122 -1.266 0.324 -0.1796
Left Superior Frontal Gyrus 1.152 -1.2 0.3632 -0.3152
Right Supplementary Motor Cortex 1.197 -1.246 -0.05479 0.1043
Dimension 1
Dimension 2
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Dimensions
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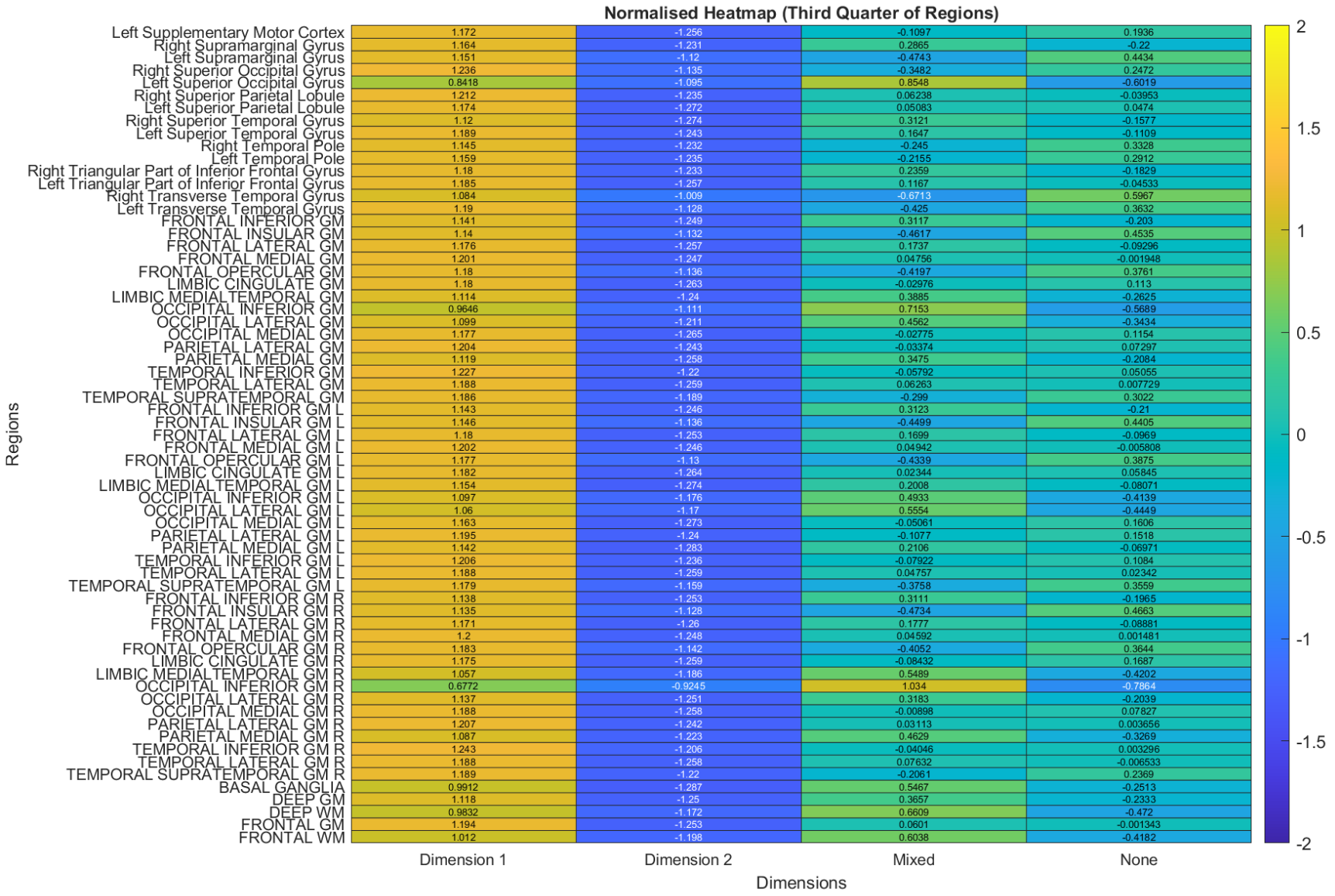
0.5
0
-0.5
-1
-1.5
-2


Normalised Heatmap (Third Quarter of Regions)
Regions
Left Supplementary Motor Cortex 1.172 -1.256 -0.1097 0.1936
Right Supramarginal Gyrus 1.164 -1.231 0.2865 -0.22
Left Supramarginal Gyrus 1.151 -1.12 -0.4743 0.4434
Right Superior Occipital Gyrus 1.236 -1.135 -0.3482 0.2472
Left Superior Occipital Gyrus 0.8418 -1.095 0.8548 -0.6019
Right Superior Parietal Lobule 1.212 -1.235 0.06238 -0.03953
Left Superior Parietal Lobule 1.174 -1.272 0.05083 0.0474
Right Superior Temporal Gyrus 1.12 -1.274 0.3121 -0.1577
Left Superior Temporal Gyrus 1.189 -1.243 0.1647 -0.1109
Right Temporal Pole 1.145 -1.232 -0.245 0.3328
Left Temporal Pole 1.159 -1.235 -0.2155 0.2912
Right Triangular Part of Inferior Frontal Gyrus 1.18 -1.233 0.2359 -0.1829
Left Triangular Part of Inferior Frontal Gyrus 1.185 -1.257 0.1167 -0.04533
Right Transverse Temporal Gyrus 1.084 -1.009 -0.6713 0.5967
Left Transverse Temporal Gyrus 1.19 -1.128 -0.425 0.3632
FRONTAL INFERIOR GM 1.141 -1.249 0.3117 -0.203
FRONTAL INSULAR GM 1.14 -1.132 -0.4617 0.4535
FRONTAL LATERAL GM 1.176 -1.257 0.1737 -0.09296
FRONTAL MEDIAL GM 1.201 -1.247 0.04756 -0.001948
FRONTAL OPERCULAR GM 1.18 -1.136 -0.4197 0.3761
LIMBIC CINGULATE GM 1.18 -1.263 -0.02976 0.113
LIMBIC MEDIALTEMPORAL GM 1.114 -1.24 0.3885 -0.2625
OCCIPITAL INFERIOR GM 0.9646 -1.111 0.7153 -0.5689
OCCIPITAL LATERAL GM 1.099 -1.211 0.4562 -0.3434
OCCIPITAL MEDIAL GM 1.177 -1.265 -0.02775 0.1154
PARIETAL LATERAL GM 1.204 -1.243 -0.03374 0.07297
PARIETAL MEDIAL GM 1.119 -1.258 0.3475 -0.2084
TEMPORAL INFERIOR GM 1.227 -1.22 -0.05792 0.05055
TEMPORAL LATERAL GM 1.188 -1.259 0.06263 0.007729
TEMPORAL SUPRATEMPORAL GM 1.186 -1.189 -0.299 0.3022
FRONTAL INFERIOR GM L 1.143 -1.246 0.3123 -0.21
FRONTAL INSULAR GM L 1.146 -1.136 -0.4499 0.4405
FRONTAL LATERAL GM L 1.18 -1.253 0.1699 -0.0969
FRONTAL MEDIAL GM L 1.202 -1.246 0.04942 -0.005808
FRONTAL OPERCULAR GM L 1.177 -1.13 -0.4339 0.3875
LIMBIC CINGULATE GM L 1.182 -1.264 0.02344 0.05845
LIMBIC MEDIALTEMPORAL GM L 1.154 -1.274 0.2008 -0.08071
OCCIPITAL INFERIOR GM L 1.097 -1.176 0.4933 -0.4139
OCCIPITAL LATERAL GM L 1.06 -1.17 0.5554 -0.4449
OCCIPITAL MEDIAL GM L 1.163 -1.273 -0.05061 0.1606
PARIETAL LATERAL GM L 1.195 -1.24 -0.1077 0.1518
PARIETAL MEDIAL GM L 1.142 -1.283 0.2106 -0.06971
TEMPORAL INFERIOR GM L 1.206 -1.236 -0.07922 0.1084
TEMPORAL LATERAL GM L 1.188 -1.259 0.04757 0.02342
TEMPORAL SUPRATEMPORAL GM L 1.179 -1.159 -0.3758 0.3559
FRONTAL INFERIOR GM R 1.138 -1.253 0.3111 -0.1965
FRONTAL INSULAR GM R 1.135 -1.128 -0.4734 0.4663
FRONTAL LATERAL GM R 1.171 -1.26 0.1777 -0.08881
FRONTAL MEDIAL GM R 1.2 -1.248 0.04592 0.001481
FRONTAL OPERCULAR GM R 1.183 -1.142 -0.4052 0.3644
LIMBIC CINGULATE GM R 1.175 -1.259 -0.08432 0.1687
LIMBIC MEDIALTEMPORAL GM R 1.057 -1.186 0.5489 -0.4202
OCCIPITAL INFERIOR GM R 0.6772 -0.9245 1.034 -0.7864
OCCIPITAL LATERAL GM R 1.137 -1.251 0.3183 -0.2039
OCCIPITAL MEDIAL GM R 1.188 -1.258 -0.00898 0.07827
PARIETAL LATERAL GM R 1.207 -1.242 0.03113 0.003656
PARIETAL MEDIAL GM R 1.087 -1.223 0.4629 -0.3269
TEMPORAL INFERIOR GM R 1.243 -1.206 -0.04046 0.003296
TEMPORAL LATERAL GM R 1.188 -1.258 0.07632 -0.006533
TEMPORAL SUPRATEMPORAL GM R 1.189 -1.22 -0.2061 0.2369
BASAL GANGLIA 0.9912 -1.287 0.5467 -0.2513
DEEP GM 1.118 -1.25 0.3657 -0.2333
DEEP WM 0.9832 -1.172 0.6609 -0.472
FRONTAL GM 1.194 -1.253 0.0601 -0.001343
FRONTAL WM 1.012 -1.198 0.6038 -0.4182
Dimension 1
Dimension 2
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Dimensions
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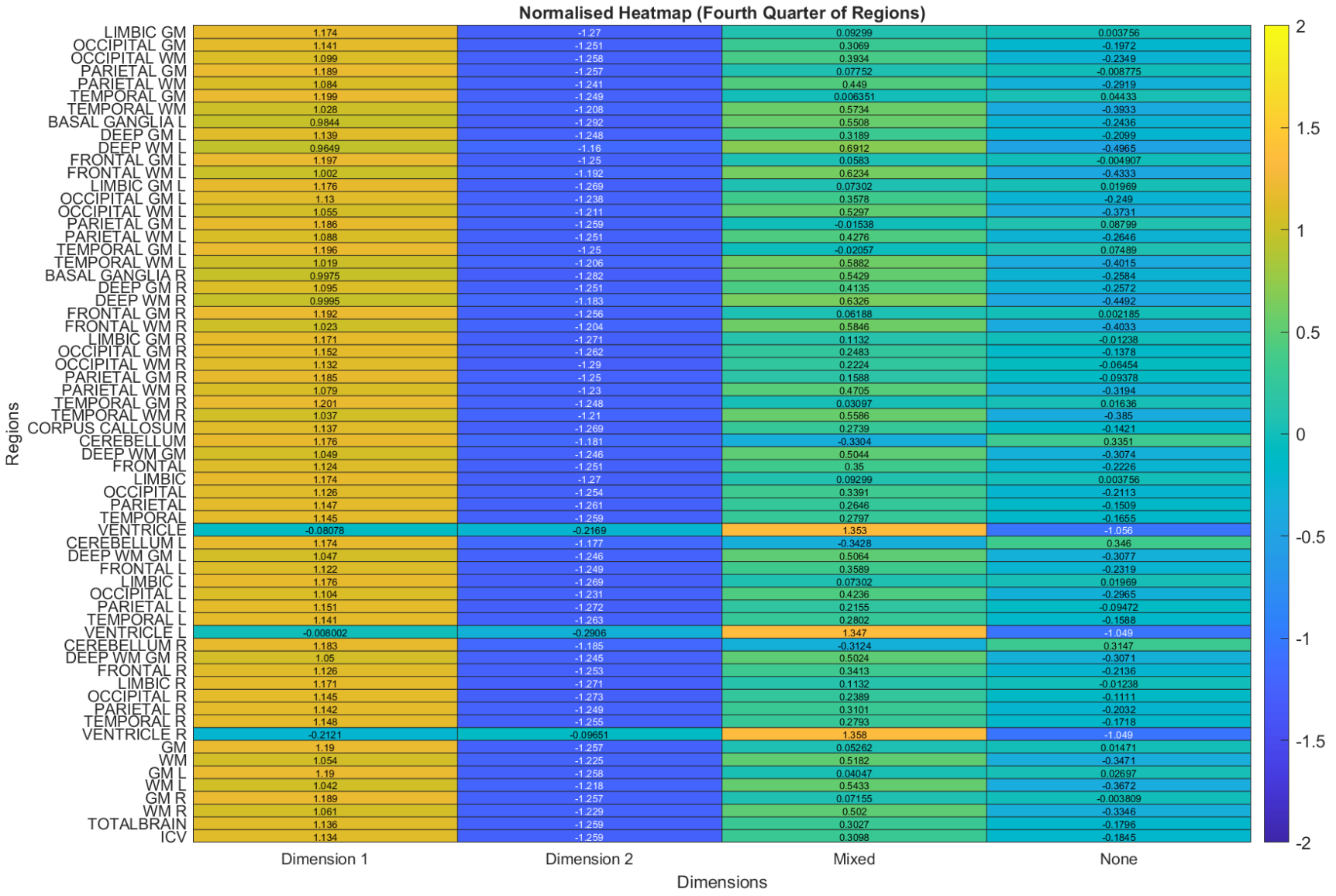
-2


Normalised Heatmap (Fourth Quarter of Regions)
Regions
Dimensions
Dimension 1
Dimension 2
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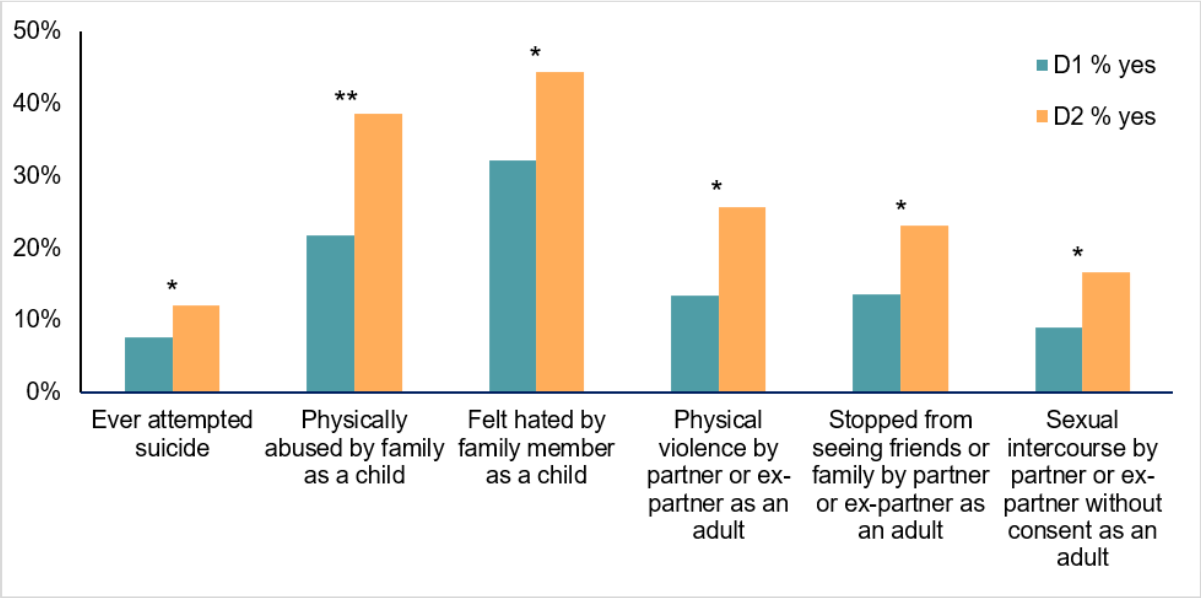
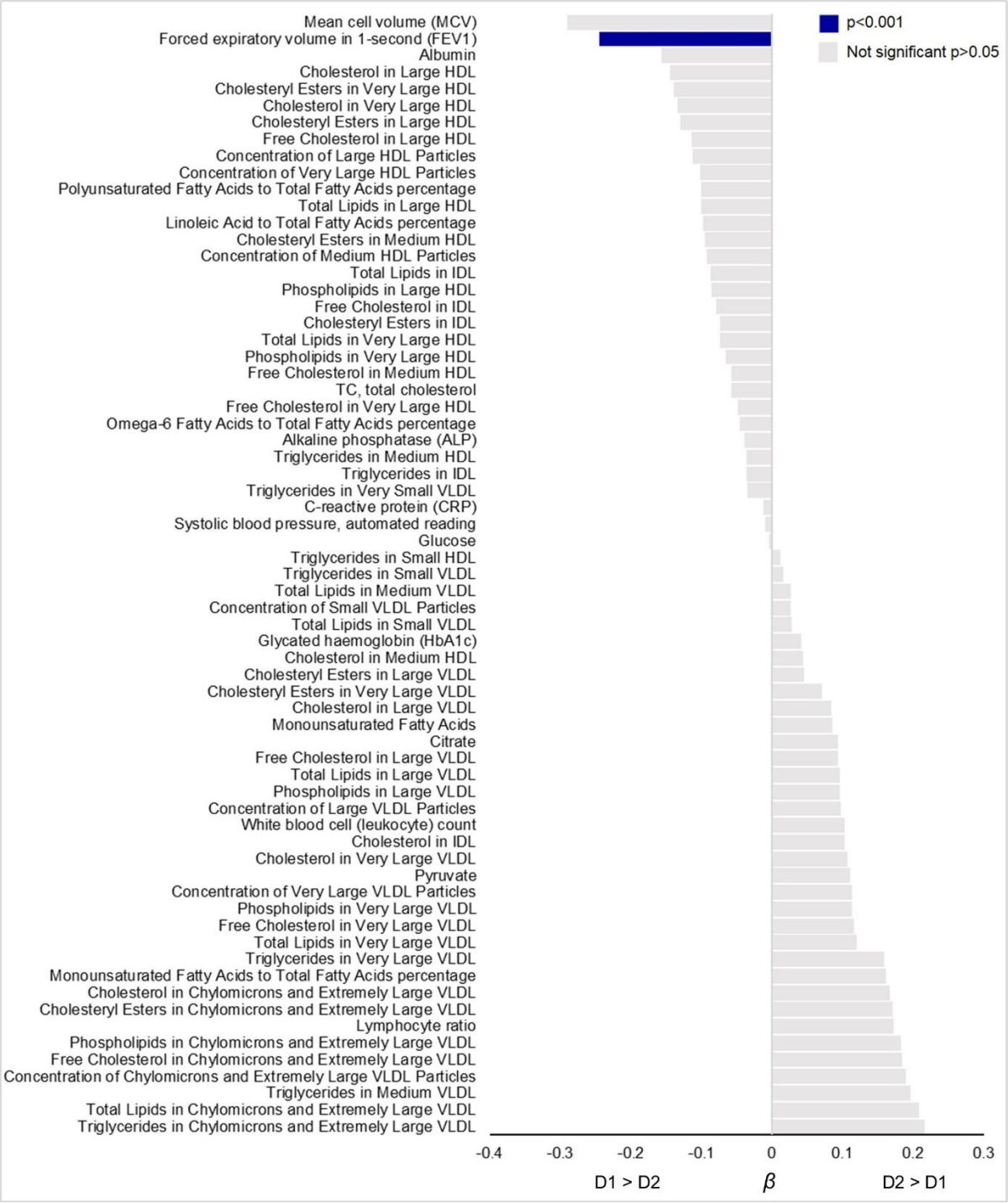
OCCIPITAL GM 1.141 -1.251 0.3069 -0.1972
OCCIPITAL WM 1.099 -1.258 0.3934 -0.2349
PARIETAL GM 1.189 -1.257 0.07752 -0.008775
PARIETAL WM 1.084 -1.241 0.449 -0.2919
TEMPORAL GM 1.199 -1.249 0.006351 0.04433
TEMPORAL WM 1.028 -1.208 0.5734 -0.3933
BASAL GANGLIA L 0.9844 -1.292 0.5508 -0.2436
DEEP GM L 1.139 -1.248 0.3189 -0.2099
DEEP WM L 0.9649 -1.16 0.6912 -0.4965
FRONTAL GM L 1.197 -1.25 0.0583 -0.004907
FRONTAL WM L 1.002 -1.192 0.6234 -0.4333
LIMBIC GM L 1.176 -1.269 0.07302 0.01969
OCCIPITAL GM L 1.13 -1.238 0.3578 -0.249
OCCIPITAL WM L 1.055 -1.211 0.5297 -0.3731
PARIETAL GM L 1.186 -1.259 -0.01538 0.08799
PARIETAL WM L 1.088 -1.251 0.4276 -0.2646
TEMPORAL GM L 1.196 -1.25 -0.02057 0.07489
TEMPORAL WM L 1.019 -1.206 0.5882 -0.4015
BASAL GANGLIA R 0.9975 -1.282 0.5429 -0.2584
DEEP GM R 1.095 -1.251 0.4135 -0.2572
DEEP WM R 0.9995 -1.183 0.6326 -0.4492
FRONTAL GM R 1.192 -1.256 0.06188 0.002185
FRONTAL WM R 1.023 -1.204 0.5846 -0.4033
LIMBIC GM R 1.171 -1.271 0.1132 -0.01238
OCCIPITAL GM R 1.152 -1.262 0.2483 -0.1378
OCCIPITAL WM R 1.132 -1.29 0.2224 -0.06454
PARIETAL GM R 1.185 -1.25 0.1588 -0.09378
PARIETAL WM R 1.079 -1.23 0.4705 -0.3194
TEMPORAL GM R 1.201 -1.248 0.03097 0.01636
TEMPORAL WM R 1.037 -1.21 0.5586 -0.385
CORPUS CALLOSUM 1.137 -1.269 0.2739 -0.1421
CEREBELLUM 1.176 -1.181 -0.3304 0.3351
DEEP WM GM 1.049 -1.246 0.5044 -0.3074
FRONTAL 1.124 -1.251 0.35 -0.2226
LIMBIC 1.174 -1.27 0.09299 0.003756
OCCIPITAL 1.126 -1.254 0.3391 -0.2113
PARIETAL 1.147 -1.261 0.2646 -0.1509
TEMPORAL 1.145 -1.259 0.2797 -0.1655
VENTRICLE -0.08078 -0.2169 1.353 -1.056
CEREBELLUM L 1.174 -1.177 -0.3428 0.346
DEEP WM GM L 1.047 -1.246 0.5064 -0.3077
FRONTAL L 1.122 -1.249 0.3589 -0.2319
LIMBIC L 1.176 -1.269 0.07302 0.01969
OCCIPITAL L 1.104 -1.231 0.4236 -0.2965
PARIETAL L 1.151 -1.272 0.2155 -0.09472
TEMPORAL L 1.141 -1.263 0.2802 -0.1588
VENTRICLE L -0.008002 -0.2906 1.347 -1.049
CEREBELLUM R 1.183 -1.185 -0.3124 0.3147
DEEP WM GM R 1.05 -1.245 0.5024 -0.3071
FRONTAL R 1.126 -1.253 0.3413 -0.2136
LIMBIC R 1.171 -1.271 0.1132 -0.01238
OCCIPITAL R 1.145 -1.273 0.2389 -0.1111
PARIETAL R 1.142 -1.249 0.3101 -0.2032
TEMPORAL R 1.148 -1.255 0.2793 -0.1718
VENTRICLE R -0.2121 -0.09651 1.358 -1.049
GM 1.19 -1.257 0.05262 0.01471
WM 1.054 -1.225 0.5182 -0.3471
GM L 1.19 -1.258 0.04047 0.02697
WM L 1.042 -1.218 0.5433 -0.3672
GM R 1.189 -1.257 0.07155 -0.003809
WM R 1.061 -1.229 0.502 -0.3346
TOTALBRAIN 1.136 -1.259 0.3027 -0.1796
ICV 1.134 -1.259 0.3098 -0.1845
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2

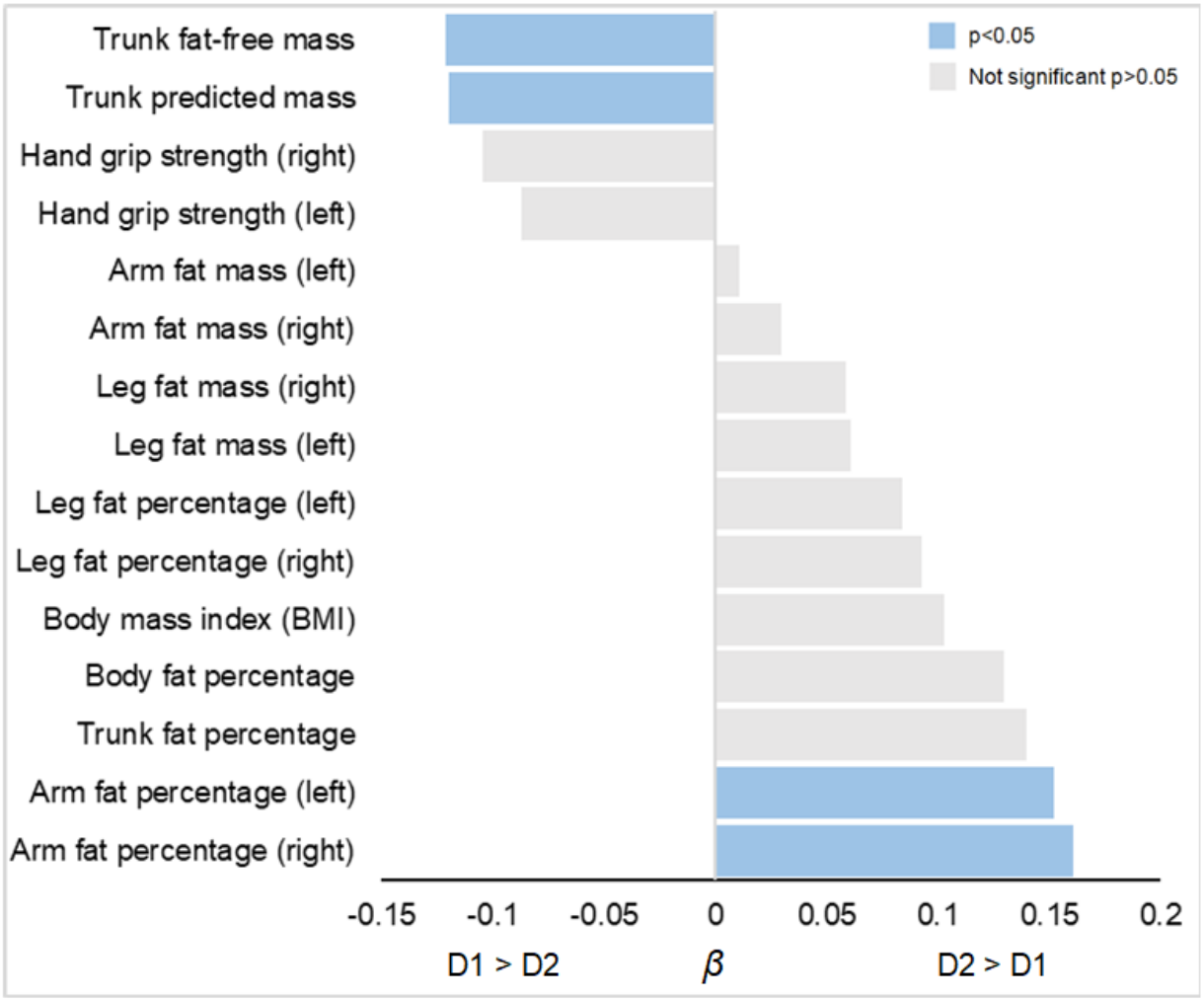
Supplementary Figure 2. UK Biobank currently depressed subsample significant differences in Adverse Life Events and Self Harm variables between D1 and D2.
Participants in the D2 group said “yes” to having attempted suicide and to having experienced adverse life events in significantly higher proportions than participants in the D1 group. Significance was determined using two-sided Chi-Square test. . * = p<0.05, ** = p<0.005.



Supplementary Figure 3. UK Biobank currently depressed subsample metabolomic comparisons between D1 and D2. The x-axis represents the beta value with a negative value indicating that D1 has higher levels than D2 for the metabolite, and a positive beta value indicates that D2 has greater levels than D1. Significant results are presented in blue and non-significant differences are presented in grey.



Supplementary Figure 4. UK Biobank currently depressed subsample physical measures between D1 and D2. The x-axis represents the beta value with a negative value indicating that D1 has higher levels than D2 for the physical measure, and a positive beta value indicates that D2 has greater levels than D1. Significant results are presented in blue and non-significant differences are presented in grey.



Supplementary Table 11. RDoC Domains Distributions Across Dimension 1 and 2 Groups in COORD-MDD

	Dimension 1	Dimension 2	P value
Phenotypes			
Core Depression	0.594 ± 0.165	0.556 ± 0.154	0.037*
Anxiety	0.324 ± 0.171	0.355 ± 0.177	0.122
Neurovegetative symptoms of melancholia	0.276 ± 0.207	0.307 ± 0.203	0.155
RDoC domain			
Sensorimotor systems	0.233 ± 0.241	0.315 ± 0.245	0.005*
Negative Valance Systems	0.395 ± 0.111	0.423 ± 0.116	0.052
Positive Valance Systems	0.601 ± 0.176	0.603 ± 0.174	0.937
Arousal/Regulatory systems	0.257 ± 0.159	0.285 ± 0.272	0.142
Cognitive systems	0.485 ± 0.160	0.474 ± 0.191	0.611

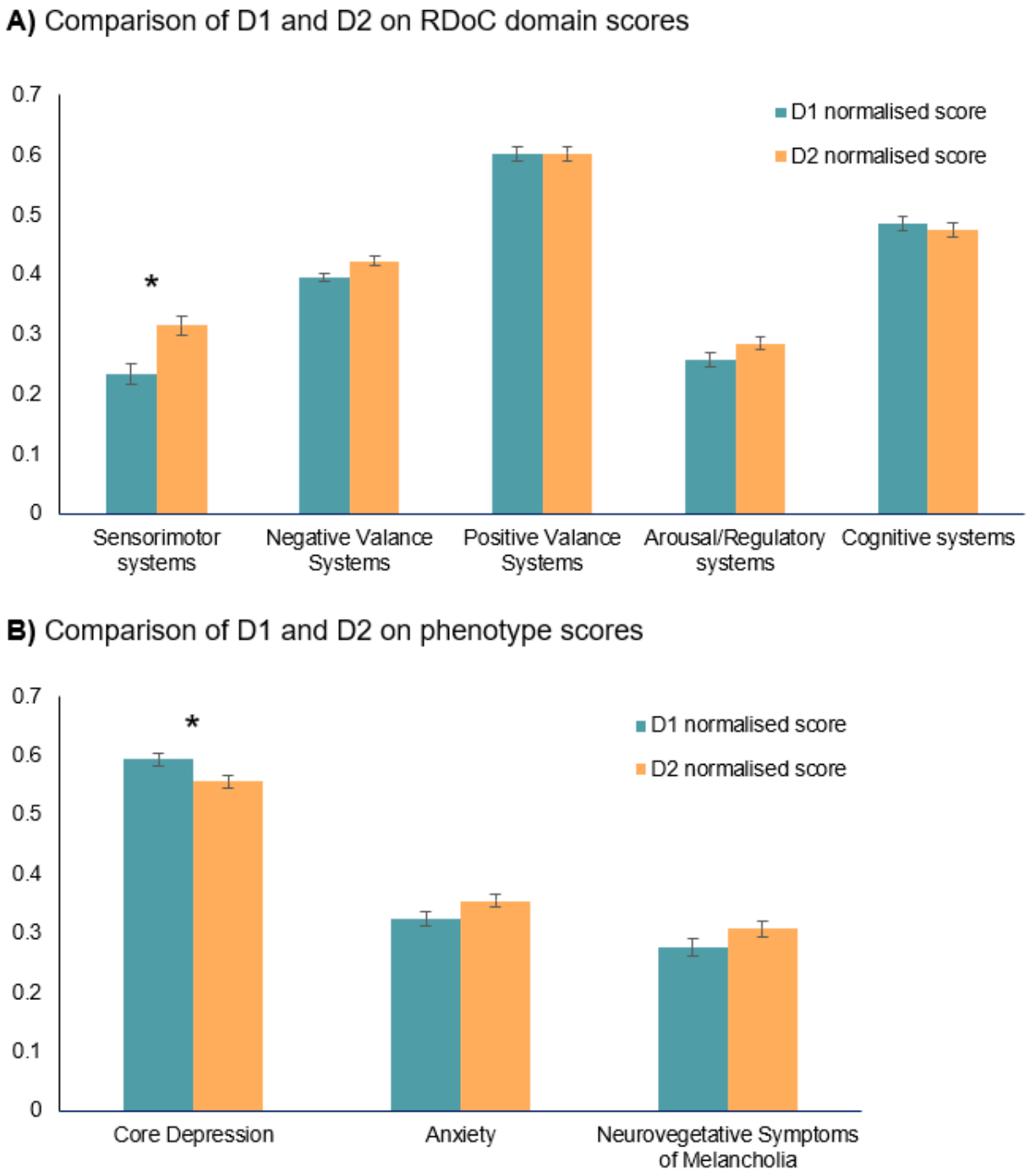
Values are normalized total scores expressed as a mean percentage of the total possible score for all assessment items within each category with ± standard deviation. RDoC, Research Domain Criteria. P-values calculated with ANOVA and corrected using FDR. * = $p < 0.05$.

Supplementary Table 12. Comparison of Phenotype Distributions Across Dimension 1 and 2 Groups in COORD-MDD

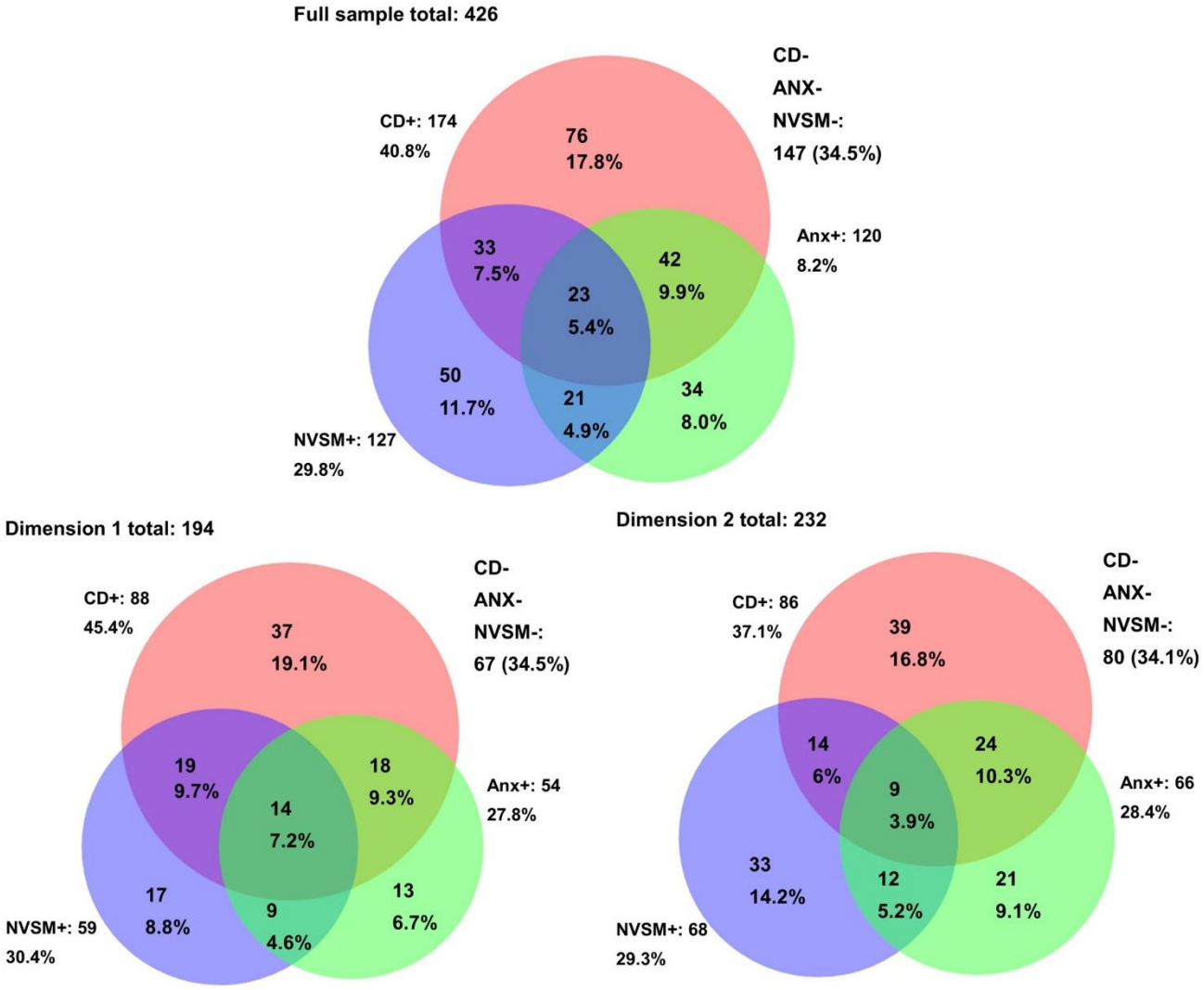
CD	Dimension 1	Dimension 2	P value
Phenotype +	88 (45.3)	86 (37.1)	0.249
Phenotype -	106 (54.6)	146 (62.9)	
ANX	Dimension 1	Dimension 2	P value
Phenotype +	54 (27.8)	66 (28.5)	0.999
Phenotype -	140 (72.4)	166 (71.5)	
NVSM	Dimension 1	Dimension 2	P value
Phenotype +	59 (30.4)	68 (29.3)	0.889
Phenotype -	135 (69.6)	164 (70.7)	

Values presented are number of participants with percentage in parenthesis. CD, core depression; ANX, anxiety; NVSM, neurovegetative symptoms of melancholia. P values calculated with Chi-square test and corrected using FDR.

Supplementary Figure 5. Comparison of D1 and D2 total score on clinical assessment items used to measure RDoC domains (Citrome et al., 2022) and phenotypes (Amin et al., 2018). A) Normalised total scores expressed as a mean percentage of the total possible score for all assessment items within each category with error bars representing standard error, shown for D1 and D2 for each RDoC domain, B) and for each phenotype. * P<0.05.



Supplementary Figure 6. Overlap between phenotype positive participants (Core Depression (CD), Anxiety (ANX) and Neurovegetative Symptoms of Melancholia (NVSM)) in the COORD-MDD full sample, Dimension 1 and Dimension 2. Circles represent each phenotype positive group, and the overlapping circles represent participants who were positive for more than one phenotype.



Supplementary Table 13. Demographic information for UKB subsample of participants with bipolar disorder for total sample and classification groups

	Number	Female%	Age
Bipolar disorder			
Total sample	92 (100%)	47.8	62.18 ± 7.07
Dimension 1	13 (14.1%)	30.8	62.76 ± 7.12
Dimension 2	30 (32.6%)	43.3	63.69 ± 6.56
Combined D1 and D2	3 (3.3%)	33.3	70.33 ± 7.26
Neither D1 nor D2	30 (32.6%)	60.0	59.73 ± 6.90
Margin	16 (17.4%)	50.0	61.96 ± 7.06

The mean age of participants is presented with ± standard deviation. Percentages shown in parentheses indicate proportions relative to the total sample. Bipolar disorder participants are participants from general population sample with MRI data who have a diagnosis of bipolar disorder, UK Biobank Field ID: 20126 (bipolar and major depression status); response options, Bipolar I disorder and Bipolar II Disorder.

Supplementary Table 14. Demographic information for UKB general population subgroups for sensitivity analysis.

	Number	Female%	Age
Age 45-55			
Dimension 1	1172	49.6	52.88 ± 2.15
Dimension 2	1940	59.4	52.56 ± 2.24
Ages 56-65			
Dimension 1	2715	52.7	61.46 ± 2.87
Dimension 2	3808	55.4	61.25 ± 2.84

Number of participants in the sample is presented. The mean age of participants is presented in years with ± standard deviation.

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