

Shared and separate patterns in brain morphometry across transdiagnostic dimensions

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ABSTRACT

Determining similarities and differences in brain structure across psychiatric disorders is important to determine if psychiatric taxonomy is reflected in distinct brain structural changes. Previous neuroimaging meta-analyses have typically focused on a single disorder, precluding transdiagnostic comparisons, we therefore aimed to quantify patterns of similarity and differences between psychiatric disorders in terms of regional brain volumes.

Here we show, in network and pairwise meta-analyses of 498 studies (51,227 individuals, 17 psychiatric disorders, 17 brain regions), that psychiatric disorders show both distinct and overlapping patterns of brain volume gain and loss. A principal components analysis demonstrated the first principal component could account for 48 percent of variance and corresponded to a pattern of increased basal ganglia and decreased hippocampal and amygdala volumes. This component loaded most strongly for disorders on the psychosis spectrum, and most weakly for affective disorders. Our findings illustrated that while similar volumetric alterations are frequently shared between disorders, neuroanatomical patterns also appear related to clinically meaningful categories.

PROSPERO Registration number: CRD42020221143

Main Text

A wide range of psychiatric disorders have been associated with alterations in regional brain volumes.¹⁻³ Understanding similarities and differences in brain structure between disorders has major relevance for understanding if there are transdiagnostic or distinct pathophysiological processes in psychiatric disorders.

Meta-analysis has been frequently used to synthesise findings from the large number of psychiatric structural neuroimaging studies. These meta-analyses, however, typically only examine a single disorder.^{2,3} Where there have been transdiagnostic meta-analyses, these have reported some shared patterns of structural abnormalities across disorders, but have studied a relatively restricted range of disorders.^{1,4-6} As such, it remains unclear whether regional patterns of structural abnormalities differ between disorders or represent a more general transdiagnostic process.

Meta-analyses of neuroimaging studies can use a coordinate based approach which allows an assessment of the spatial distribution of group differences.⁷ This approach, however, does not allow for analysis of the magnitude of group differences. An examination of the magnitude of differences can be undertaken via pairwise meta-analysis following the calculation of effect sizes from data reporting predefined regions of interest (ROIs). A pairwise approach allows for the examination of patient-control differences, but is not well suited to comparing multiple disorders.

Network meta-analysis is an approach originally used for the comparison of multiple health interventions,⁸ and allows comparisons to be made between interventions that have not been directly tested against one another. This approach has not previously been applied to neuroimaging studies. In addition to being a succinct approach to analysing data from multiple disorders, it has further advantages over a pairwise approach in that it allows for the inclusion of studies that have compared different disorders as well as those solely report patient-control differences. It has the potential to advance understanding by coherently synthesising structural imaging studies across multiple disorders, even in cases where these disorders have not been directly compared.

In the current paper we describe a network meta-analysis of structural MRI studies including individuals from seventeen separate diagnostic categories. The protocol was registered on PROSPERO on 18th November 2020 (CRD42020221143) and published in a peer-reviewed journal <https://ebmh.bmj.com/content/24/3/111>.⁹ Our primary objective was to quantify patterns of similarity and differences in regional brain volumes between disorders. We did this by estimating differences in volume between disorders for 17 brain regions, and then investigating similarities and differences between disorders in terms of their spatial distribution of volumetric gain or loss. This provided the means to derive a coherent understanding of brain abnormalities across psychiatric disorders.

Of the 10,861 citations retrieved, 498 studies met the inclusion criteria (See Figure 1 for PRISMA flow diagram). The overall sample included 51,227 participants. The mean age of participants was 39.3 years, and participants were 54.8% male (demographics by disorder are displayed in Table 1). While age and sex were matched for all direct comparisons, the mean values differed across disorders in the sample as a whole.

Sufficient studies were found to conduct analyses for the following regions: total gray matter, total white matter, lateral ventricles, cerebellum, corpus callosum, frontal lobe, anterior cingulate cortex, insula, temporal lobe, parahippocampal gyrus, hippocampus, amygdala, accumbens, caudate, putamen, pallidum, and thalamus. There were insufficient studies for the parietal and occipital lobes to undertake meaningful cross-disorder analyses.

Pairwise meta-analysis

117 pairwise meta-analyses were performed using a random effects model for all potential combinations of regions and disorders where there were at least 3 eligible studies. The full results of these meta-analyses, including forest plots, assessment of between-study heterogeneity, small study effects and publication bias are presented in the supplementary materials. We also calculated the percentage of heterogeneity that can be attributed to chance using the I^2 statistic, and performed meta-regressions of age and sex to determine if this contributed to any observed heterogeneity. Overall

we found indications of large heterogeneity in several meta-analyses. The mean I^2 across all pairwise analyses was 39%, and 15% of the pairwise analyses displayed high heterogeneity of over 75%. For the 49 analyses where metaregressions were performed 5 showed I^2 of over 75%. In 7 of the 49 cases age or sex significantly moderated the result, and in 2 of the 5 cases the addition of age and sex to the meta-analytic model reduced residual heterogeneity to below 75%. There was some evidence of publication bias or small study effects as indicated by the Egger's test, with 5 meta-analyses (out of a total of 32 analyses with 10 studies or more) giving a p -value <0.05 .

Network meta-analysis

For each brain region we fit a random-effects frequentist network meta-analysis using netmeta (version 1.0-5). The geometries of the various networks are shown in Figure 2. Forest plots for the estimated differences in volume for psychiatric disorders compared to healthy controls are shown in Figure 3, and league tables comparing disorders against one another for each brain region are shown eFigure1. For all brain regions there was frequently strong evidence of important differences between the volume of the control group and that of multiple other disorders, but evidence of a difference between disorders was less common. Details regarding measures of heterogeneity and inconsistency are displayed in eTable 2 and CINeMA confidence ratings are also shown in the supplementary materials.

A summary of these results is shown in Figure 4A where color intensity represents the magnitude of effect size: red indicates that relative to controls the disorder is associated with reduced volume of the region in question. Correlating disorder:control effect sizes between disorders (i.e. across brain regions) generated the heatmap shown in Figure 4B, where a positive correlation between disorders indicates a similar pattern of disorder:control brain differences. A high degree of similarity is observed between PTSD and controls exposed to trauma ($r=0.70$). Bipolar disorder with psychosis showed a similarity to other psychotic disorders (schizophrenia $r=0.71$, schizoaffective disorder $r=0.82$, unspecified psychosis $r=0.71$), which was not observed for bipolar disorder without psychosis (schizophrenia $r=0.13$, schizoaffective disorder $r=-0.02$, unspecified psychosis $r=0.11$). Psychotic depression meanwhile

showed greater similarity with depression ($r=0.82$) than with other psychotic disorders (schizophrenia $r=0.30$, schizoaffective disorder $r=0.39$, unspecified psychosis $r=0.20$). Borderline personality disorder, meanwhile, showed similarities with both affective and psychotic disorders (depression $r=0.74$, bipolar disorder with psychosis $r=0.50$, bipolar disorder without psychosis specified $r=0.56$, schizophrenia $r=0.43$, schizoaffective disorder $r=0.97$, unspecified psychosis $r=0.52$).

The inclusion or exclusion of studies reporting ENIGMA consortium results did not notably alter results (see supplementary materials).

Principal Components Analysis

In order to aid interpretation we next condensed the data by performing a principal components analysis in which disorders were treated as variables, and the effect sizes for the various brain regions as observations. Four components explained 93% of the variance (Figure 5A). The loading for each diagnosis is shown in Figure 5B and the scores for the various brain regions are illustrated in Figure 5C. For the first component, which explained 48 % of the variance one can see from Figure 5B that there is a high loading for disorders on the psychosis spectrum and a low loading for affective disorders. This component corresponds to relatively larger volumes of the pallidum, accumbens, and caudate and reduced volumes of the corpus callosum, parahippocampal gyrus, amygdala and hippocampus.

The second component accounted for 29% of the variance. This component shows the highest loading for anxiety disorders and trauma exposed controls, and low loadings for schizoaffective disorder, psychotic depression, and bipolar disorder with psychotic features. This component corresponds to relatively larger volumes for the anterior cingulate cortex and frontal lobe.

Discussion

We synthesised data from over 50,000 MRI scans and 17 different disorders to present a transdiagnostic analysis of structural brain abnormalities across psychiatric disorders.

We found, with some exceptions, that compared to control populations psychiatric disorders are associated with lower brain volumes across a wide range of brain regions. One exception relating to the direction of effect relates to schizophrenia, unspecified psychosis, bipolar disorder with psychosis and schizoaffective disorder which all showed relative increases in the basal ganglia volumes. This may be a medication-related phenomenon as previous studies have demonstrated an association between the use of dopamine receptor antagonists and volume increases in this region.^{10,11} Another finding of potentially increased volumes was seen with trauma exposed controls in which the direction of effect was positive for total white matter, frontal and temporal lobes, and anterior cingulate volumes. In this case these changes may potentially be a marker of resilience given the individuals had not developed a mental disorder despite exposure to significant trauma.

There is notable overlap between disorders, and statistically significant differences between disorders were much rarer than differences with control populations. When correlating the magnitude of differences across the brain certain disorders showed patterns of volume gain and loss that were very similar to other disorders. Examples include the high degree of similarity between PTSD and controls exposed to trauma, which may relate to the similar environmental exposures experienced by both groups. Bipolar disorder with psychosis showed a similarity to other psychotic disorders, which was not observed for bipolar disorder without psychosis. This is in keeping with recent findings of an analogous pattern of similarities at a neurochemical level.¹² Psychotic depression showed greater similarity with depression than with other psychotic disorders. The similarities between borderline personality disorder and both affective and psychotic disorders is in keeping with the occurrence of both affective and psychotic symptoms in the disorder.¹³

These findings are partially consistent with prior work investigating cross-disorder genetic correlations.¹⁴ This work had found positive correlations between ADHD,

bipolar disorder, autism spectrum disorder, schizophrenia, OCD, PTSD and anxiety disorders.¹⁴ Many of these correlations were similarly seen in the present work although there are also clear areas of distinction, with the current work observing negative correlations from PTSD and anxiety to a range of disorders. Further analyses examining whether the differences may be driven by environmental factors, including differing use of psychotropic medication between disorders is indicated.

It is also clear that while there is extensive overlap between disorders, there are some differences. Some of these differences may map to the clinical phenotype. This was illustrated by the principal components analysis that found a pattern of increased volume in the basal ganglia and reduced volume in hippocampal regions and the amygdala explained a large proportion of the overall variance. This pattern was primarily observed in disorders that can be understood as lying on the psychosis spectrum (schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, unspecified psychosis, and interestingly borderline personality disorder). As mentioned above, the basal ganglia association is likely to some extent reflect the medications most frequently used in this cohort.

Examining brain anatomy to better understand the pathophysiology of psychiatric disorders has a long history,¹⁵ and the number of studies investigating this in vivo has increased dramatically following the advent of MRI. While previous meta-analyses of individual disorders have helped to condense this large body of research, a coherent transdiagnostic synthesis is challenging. Previous large scale transdiagnostic meta-analyses are relatively few in number. A prior study of six disorders collated voxel-based morphometry studies.¹ This allowed for a more precise approach to spatial localisation, but as discussed above a coordinate based approach does not allow for comparison of the magnitude of abnormalities between disorders.

Studies combining results of single-disorder ENIGMA meta-analyses were able to take a more fine-grained approach to cortical regions, but examined only six disorders, meaning they were not able to comment on disorders including PTSD, anxiety disorders, psychotic depression, schizoaffective disorder, or borderline personality disorder.^{4,6,16} In keeping with the current findings these prior studies found shared patterns of gray matter loss across disorders, with more severe cortical loss and

enlargement of the pallidum in schizophrenia. These studies were able to more precisely study spatial patterns of change given the use of a single parcellation scheme, this had the benefit of allowing links with patterns of gene expression to be identified, showing that regions with greater expression of pyramidal cell related genes tended to show the greatest case-control differences.¹⁷ The current sample, while providing less precise spatial localisation, covers a considerably wider range of disorders, allowing for a more comprehensively transdiagnostic view.

Limitations

While all direct comparisons were matched for age and sex, these variables do differ across disorders. Our analysis does not account for the fact that the magnitude of patient-control effect sizes may vary depending on age or sex. For example, given that the mean age of individuals with depression is different to that of CHR individuals the finding that individuals with depression have a larger amygdala than CHR individuals, could be explained if the magnitude of patient-control differences in either disorder changes markedly with age. Concerns about the magnitude of this impact may be tempered by the fact that meta-regressions rarely found a significant modifying effect of either age or sex.

As with previous single disorder meta-analyses, the current analyses are limited in terms of spatial resolution by the data reported in the primary studies. While activation likelihood meta-analyses may be able to provide great spatial precision, these can only provide an estimation of the spatial extent of any potential between group differences, thereby precluding comparisons between disorders in terms of magnitude of difference. Moreover, as many of the primary studies included patients taking psychotropic treatment, it is not possible to disambiguate volumetric changes associated with disorders from those associated with the drugs used to treat these disorders. Although a large number of participants were included in the study, certain comparisons for certain regions were based on relatively few studies, and some correlations between disorders calculated for the cluster analysis were based on a relatively small number of regions (see table 1, eTable 1, and supplementary forest plots). Also as seen in single disorder meta-analyses there was large heterogeneity observed for several regions,^{3,18} which may relate to differences in patient populations and methodology between studies.

Implications and future work

The finding that patterns of volumetric change heavily overlap across psychiatric disorders suggests that a general transdiagnostic dimension of psychopathology observed at the symptomatic level may be reflected in neurobiology.¹⁹ Transdiagnostic work looking at the influence of symptom severity on the magnitude of gray matter loss would help to refine this hypothesis. While some differences between disorders were observed, there was substantial between-disorder overlap and it would be of interest if other methods of psychiatric categorisation could lead to greater between category distinction.²⁰ Future work involving greater spatial precision, and examination of underrepresented disorders and regions would also be of benefit.

Conclusion

The current analysis shows that based on patterns of brain morphometry psychiatric disorders show many transdiagnostic features with between disorder differences less frequently being of statistical significance compared to disorder-control differences. Despite these similarities across disorders there are also areas of distinction, with disorders on the psychosis spectrum showing a different pattern of gain and loss compared to other diagnoses.

METHODS

Study Selection and data extraction

We searched MEDLINE, EMBASE, and PsychINFO databases from inception to March 1, 2022. We included the majority of psychiatric disorders in terms of lifetime prevalence.²¹ Eligible studies included individuals over the age of 18 that reported measures of regional brain volumes in at least two of the following seventeen groups: attention deficit hyperactivity disorder (ADHD), mixed anxiety and depression, anxiety disorders (including generalised anxiety disorder, social phobia, and panic disorder), autism spectrum disorder, bipolar disorder with psychosis, bipolar disorder without psychosis specified, borderline personality disorder, clinical high risk for psychosis (CHR), healthy controls, major depressive disorder, obsessive compulsive disorder (OCD), psychotic depression, psychosis otherwise unspecified, post-traumatic stress disorder (PTSD), schizophrenia, schizoaffective disorder, and trauma exposed controls that had not developed PTSD. We used this relatively fine grained classification of the psychosis spectrum because there is evidence of highly heterogeneous neurobiological correlates, and certain biological correlates have clear transdiagnostic relevance.^{12,22,23} The use of more precise categories (e.g. bipolar disorder with and without psychosis) allows differences within a broader category to be observed if they exist, and we felt that this outweighs the drawback of reduced category sample size.

We included only studies in which volumes of predefined regions (including total gray and white matter) were reported. We did not include studies reporting solely volumes of voxel based morphometry statistically defined clusters, given that these produce biased estimates as the cluster is defined as the area of maximum group difference. We included only studies in which participants' mean age was over 18 years and, given the well-established influence of age and sex on brain volumes, we only included studies in which groups were matched so that no group differed from another by more than ten years in term of mean age, or by 10% in terms of sex composition.²⁴

For each study and for each group, we extracted the mean and standard deviation of volumetric or thickness measurements for the following seventeen regions: total gray matter, total white matter, lateral ventricles, cerebellum, corpus callosum, frontal lobe,

anterior cingulate cortex, insula, temporal lobe, parahippocampal gyrus, hippocampus, amygdala, nucleus accumbens, caudate, putamen, pallidum, and thalamus. As with previous meta-analyses,^{2,22} relatively broad cortical areas were employed in order to allow for synthesis across studies. In addition, we extracted participant numbers, age, sex, and diagnosis. Using the group-level data from each study, we estimated the standardised mean difference (Hedges' g) for the volumetric difference between the groups and corresponding standard errors.

Pairwise meta-analysis

For each brain region where between-disorder pairwise comparisons were informed by three or more studies, we synthesised data in a meta-analysis using a random effects model. We estimated the standard deviation of random effects (τ) with the restricted maximum likelihood estimator,²⁵ and the corresponding 95% Confidence Interval using the Q-profile approach.²⁶ We also calculated the percentage of heterogeneity that can be attributed to chance using the I^2 statistic, and performed meta-regressions of age and sex to determine if this contributed to any observed heterogeneity.²⁷ These meta-regressions were only performed on a pairwise basis as current frequentist network meta-analysis packages do not allow for the inclusion of covariates. We created forest plots to illustrate all meta-analyses. Where there were at least ten studies, we assessed the existence of small-study effects or publication bias by visually inspecting contour-enhanced funnel plots and also via Egger's test.²⁸ We performed all analyses using the metafor package (version 3.0–2)²⁹ in R (version .6.1).

Network meta-analysis

For each brain region we fit a random-effects frequentist network meta-analysis for each pairwise effect size and its variance, and assuming a common heterogeneity parameter across the whole network. We produced league tables to illustrate indirect and direct comparisons between diagnoses, and created forest-plots showing the estimated relative effects vs. healthy controls. These analyses were performed using netmeta (version 1.0-5).³⁰

Assessments of heterogeneity and inconsistency

We assessed network heterogeneity by monitoring τ and the I^2 statistic. Consistency of each network (i.e. the agreement between direct and indirect evidence) was evaluated using a global method (“design-by-treatment”) as well as a local method (back-calculation).^{31,32}

Risk of bias

Risk of bias for individual studies was assessed using a modified version of the Newcastle-Ottawa scale for observational studies.³³ We incorporated the results of this into the Confidence in Network Meta-Analysis (CINeMA) application, to assess credibility of each network meta-analysis.³⁴

Sensitivity analyses

Following the protocol,⁹ we performed a prespecified sensitivity analysis where we included studies from the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium. These were excluded from analyses presented in the main paper given the large number of participants included in these studies, and the fact that it is not always clear if subjects included in ENIGMA analyses have also been reported on in previously published work.

Principal components analysis

We performed a principal components analysis in which disorders were treated as variables, and the effect sizes for the various brain regions treated as observations. Probabilistic principal components analysis was implemented using the `pcaMethods` package (version 1.89.0).³⁵ We illustrated the results of this analysis using the R package `ggseg` (version 1.6.4).³⁶

Data availability

All data obtained from publicly available research accessed via Medline, EMBASE and PSYCHINFO databases.

Code availability

All code available at https://github.com/rob-mccutcheon/volumetric_network_meta

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Contribution statement

RAM and TP participated in the conception, drafting, revising and final approval of this manuscript. GW, LV, CC, XG, TAH, MG, OE, AC and ODH participated in the revising and final approval of this manuscript

Competing interests statement

RAM has received honoraria from Otsuka and Janssen for educational talks. AC has received research and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), CARIPLO Foundation and Angelini Pharma, outside the submitted work. TP has participated in speaker meetings organised by Sunovion, Lundbeck, Janssen and Otsuka. ODH is a part-time employee of H. Lundbeck A/S and has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organized by Angellini, Autifony, Biogen, Boehringer-Ingelheim, Eli Lilly, Heptares, Global Medical Education, In-vicro, Janssen, Lundbeck, Neurocrine, Otsuka, Sunovion, Rand, Recordati, Roche and Viatris/Mylan. The remaining authors declare no competing interests.

Tables

Diagnosis	Number of Studies	Number of Participants	Mean Age (Years)	Sex (Percent Male)
CON	481	26246	41.8	53.0
SCZ	169	6909	31.1	67.0
MDD	117	6451	49.1	46.6
PTSD	53	1412	40.0	70.3
BPAD.NP	46	1811	39.6	44.8
OCD	39	2081	30.0	56.1
TCON	29	845	43.6	71.9
PSY	25	1491	27.2	63.6
ASD	22	1120	29.4	55.3
BPAD.P	16	466	31.9	55.5
BPD	13	302	29.7	16.5
ANX	12	277	35.3	57.0
CHR	10	955	21.5	56.5
ADHD	7	441	35.1	43.5
PDEP	7	121	44.7	47.8
SZAF	5	211	36.9	50.4
A&D	1	88	37.3	33.0

Table 1: Details of included studies

A&D: Mixed Anxiety and Depression, ADHD: Attention Deficit Hyperactivity Disorder, ANX: Anxiety Disorder, ASD: Autism Spectrum Disorder, BPAD.P: Bipolar Disorder with Psychosis, BP.NP: Bipolar Disorder without Psychosis Specified, BPD: Borderline Personality Disorder, CHR: Clinical High Risk for Psychosis, CON: Controls, MDD: Major Depressive Disorder, OCD: Obsessive Compulsive Disorder, PDEP: Psychotic Depression, PSY: Unspecified Psychosis, PTSD: Post Traumatic Stress Disorder, SCZ: Schizophrenia, SZAF: Schizoaffective Disorder, TCON: Trauma Exposed Controls

Figure Captions

Figure 1: PRISMA flow chart

Figure 2: Network graphs for brain regions examined

Disorders with direct comparisons are linked with a line. The thickness of connecting lines corresponds to the number of studies evaluating the comparison.

A&D: Mixed Anxiety and Depression, ADHD: Attention Deficit Hyperactivity Disorder, ANX: Anxiety Disorder, ASD: Autism Spectrum Disorder, BPAD.P: Bipolar Disorder with Psychosis, BP.NP: Bipolar Disorder without Psychosis Specified, BPD: Borderline Personality Disorder, CHR: Clinical High Risk for Psychosis, CON: Controls, MDD: Major Depressive Disorder, OCD: Obsessive Compulsive Disorder, PDEP: Psychotic Depression, PSY: Unspecified Psychosis, PTSD: Post Traumatic Stress Disorder, SCZ: Schizophrenia, SZAF: Schizoaffective Disorder, TCON: Trauma Exposed Controls

Figure 3: Forest plots for standardised mean differences of individual disorders compared with healthy controls

The x-axis represents Hedges' g , with a negative number indicating the observed volume for the disorder is smaller than that observed for healthy controls. The width of the lines extending from the center point represent the 95% confidence interval.

A&D: Mixed Anxiety and Depression, ADHD: Attention Deficit Hyperactivity Disorder, ANX: Anxiety Disorder, ASD: Autism Spectrum Disorder, BPAD.P: Bipolar Disorder with Psychosis, BP.NP: Bipolar Disorder without Psychosis Specified, BPD: Borderline Personality Disorder, CHR: Clinical High Risk for Psychosis, CON: Controls, MDD: Major Depressive Disorder, OCD: Obsessive Compulsive Disorder, PDEP: Psychotic Depression, PSY: Unspecified Psychosis, PTSD: Post Traumatic Stress Disorder, SCZ: Schizophrenia, SZAF: Schizoaffective Disorder, TCON: Trauma Exposed Controls

Figure 4: Summary of regional volume differences

3a: Heat map of disorders ranked according to regional brain volumes

Color intensity represents the magnitude of effect size: red indicates that relative to controls the disorder is associated with reduced volume of the region in question (with the exception of the lateral ventricle for which the reverse is true). Grey squares indicate that data were not available.

3b: Disorder correlations based on brain volume differences

Heatmap illustrates between-disorder effect size correlations where green equates to a positive, and red to a negative correlation.

A&D: Mixed Anxiety and Depression, ADHD: Attention Deficit Hyperactivity Disorder, ANX: Anxiety Disorder, ASD: Autism Spectrum Disorder, BPAD.P: Bipolar Disorder with Psychosis, BP.NP: Bipolar Disorder without Psychosis Specified, BPD: Borderline Personality Disorder, CHR: Clinical High Risk for Psychosis, CON: Controls, MDD: Major Depressive Disorder, OCD: Obsessive Compulsive Disorder, PDEP: Psychotic Depression, PSY: Unspecified Psychosis, PTSD: Post Traumatic Stress Disorder, SCZ: Schizophrenia, SZAF: Schizoaffective Disorder, TCON: Trauma Exposed Controls

Figure 5: Principal Components Analysis

4a: Cumulative variance explained

The first two components account for > 75% of total variance.

4b: PCA loadings for first two components

Loading of principal components onto disorders. Green indicates a positive, and red a

negative loading. Psychosis spectrum disorders have a high loading for component 1, which as can be seen in 3C equates to relatively larger pallidum, accumbens and putamen, and relatively smaller corpus callosum, parahippocampal gyrus and amygdala.

4c: PCA scores for first two components

Green indicates a component is associated with a relatively larger volume of the region in question, and red a smaller volume (with the exception of the lateral ventricle in which the direction is reversed).

A&D: Mixed Anxiety and Depression, ADHD: Attention Deficit Hyperactivity Disorder, ANX: Anxiety Disorder, ASD: Autism Spectrum Disorder, BPAD.P: Bipolar Disorder with Psychosis, BP.NP: Bipolar Disorder without Psychosis Specified, BPD: Borderline Personality Disorder, CHR: Clinical High Risk for Psychosis, CON: Controls, MDD: Major Depressive Disorder, OCD: Obsessive Compulsive Disorder, PDEP: Psychotic Depression, PSY: Unspecified Psychosis, PTSD: Post Traumatic Stress Disorder, SCZ: Schizophrenia, SZAF: Schizoaffective Disorder, TCON: Trauma Exposed Controls

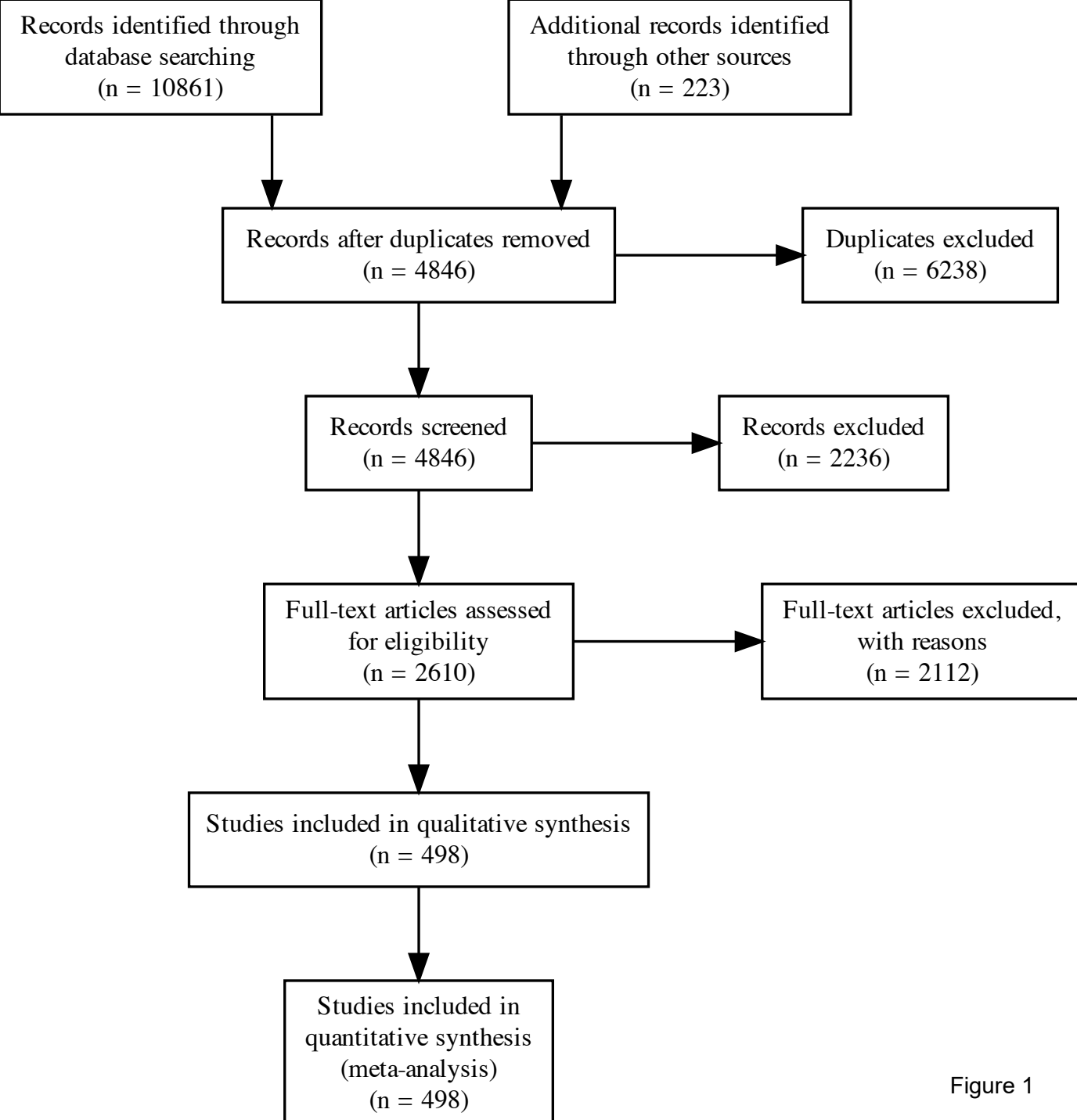


Figure 1

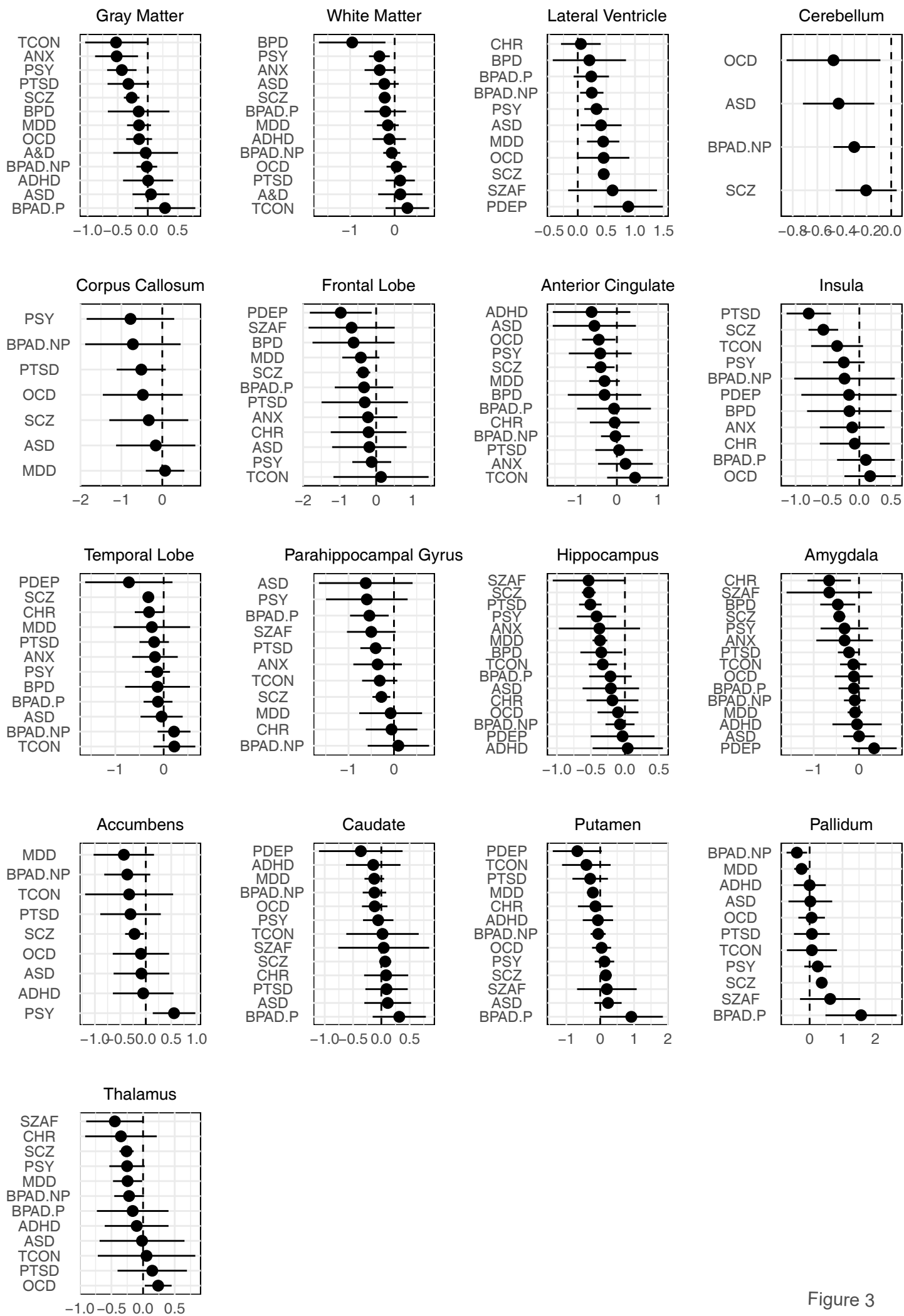


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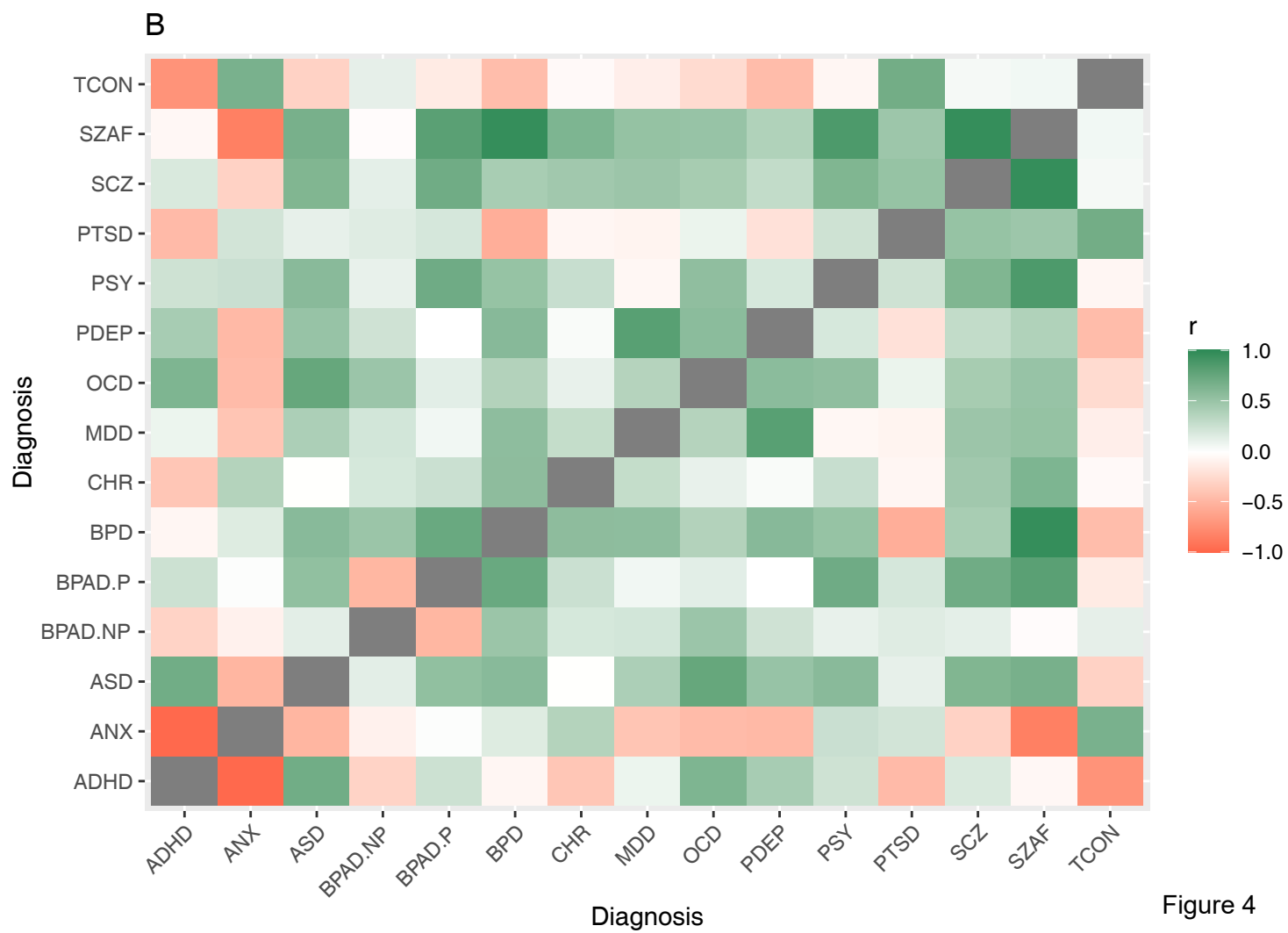
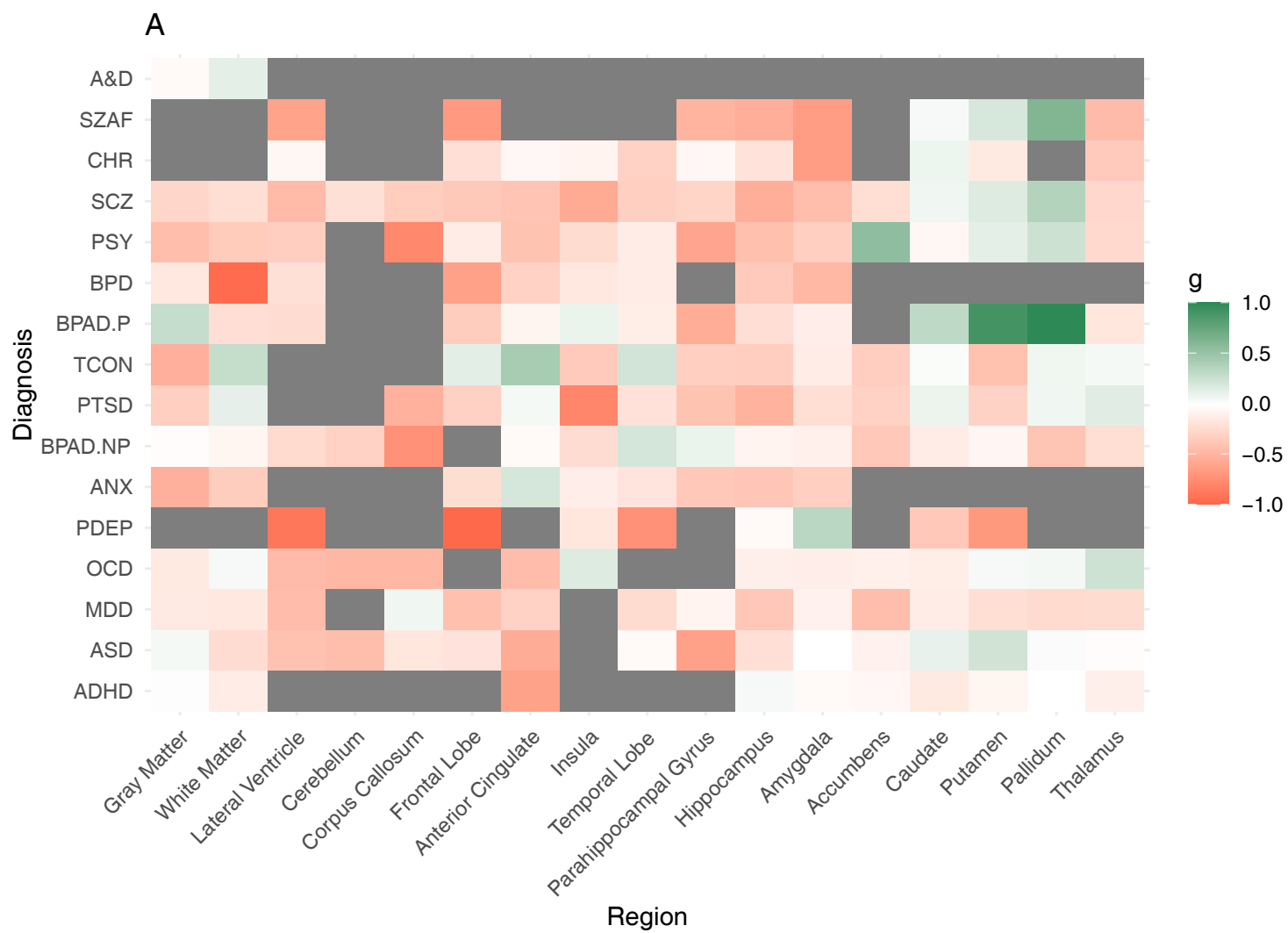
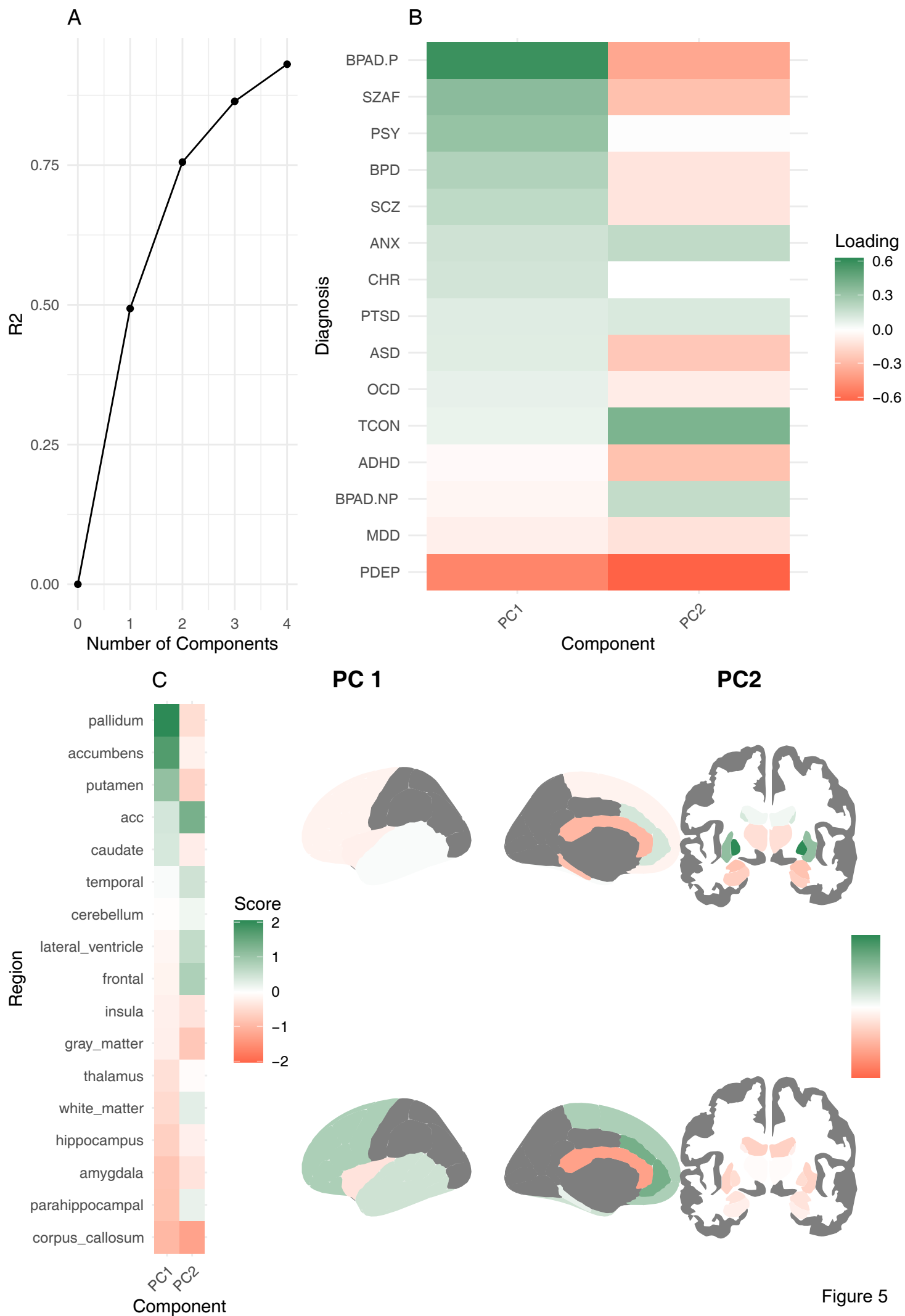


Figure 4



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