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A Transdiagnostic Network for Psychiatric Illness Derived from Atrophy and Lesions

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Author Contributions

Conception and design of study: JJT, DT, SHS, and MDF. **Design of analytical procedures**: JJT, FS, MAF, SHS, MDF. **Preprocessing and preparation of data for analyses:** JJT, CL, DT, MAF, FLWVJS, JJ, MG, JG, AE, SHS, MDF. **Neuroimaging analyses and statistical analyses**: JJT, CL, MAF, FLWVJS, JJ, SHS, MDF. **Contribution of data**: MG, JG, AE, SHS, MDF. **Interpretation of analyses and writing of manuscript:** JJT, SHS, and MDF with input from all authors.

Competing Interests

JJT: none. CL: none, DT: none. MAF: none. FLWVJS: none. JJ: none. MG: none. JG: none. AE: salary and equity from Alto Neuroscience, and equity from Mindstrong Health and Akili Interactive. SS: Owner of intellectual property involving the use of brain connectivity to target TMS, scientific consultant for Magnus Medical, investigator-initiated research funding from Neuronetics and Brainsway, speaking fees from Brainsway and Otsuka (for PsychU.org), shareholder in Brainsway (publicly traded) and Magnus Medical (not publicly traded). None of these entities were directly involved in the present work. MDF: Scientific consultant for Magnus Medical, owns independent intellectual property involving the use of functional connectivity to target TMS. This intellectual property was not used in the present manuscript.

Code Availability

GingerALE is publicly available. The custom Matlab and Python code used in this study is available: https://github.com/nimlab/NHB_Taylor2023.

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Abstract

Psychiatric disorders share neurobiology and frequently co-occur. This neurobiological and clinical overlap highlights opportunities for transdiagnostic treatments. In this study, we used coordinate and lesion network mapping to test for a shared brain network across psychiatric disorders. In our meta-analysis of 193 studies, atrophy coordinates across six psychiatric disorders mapped to a common brain network defined by positive connectivity to anterior cingulate and insula, and by negative connectivity to posterior parietal and lateral occipital cortex. This network was robust to leave-one-diagnosis-out cross-validation and specific to atrophy coordinates from psychiatric versus neurodegenerative disorders (72 studies). In 194 patients with penetrating head trauma, lesion damage to this network correlated with the number of post-lesion psychiatric diagnoses. Neurosurgical ablation targets for psychiatric illness (four targets) also aligned with the network. This convergent brain network for psychiatric illness may partially explain high rates of psychiatric comorbidity and could highlight neuromodulation targets for patients with more than one psychiatric disorder.

Introduction

Psychiatric disorders are often studied individually[1]. However, up to half of patients who meet criteria for one psychiatric disorder also meet criteria for another[2–7]. These patients are difficult to diagnose and treat[6,8–13]. Relative to those with one disorder, patients with two or more have worse treatment outcomes, more functional impairment, and a greater risk of premature death[9,13–21].

High rates of psychiatric comorbidity are often attributed to symptom heterogeneity within diagnoses and symptom overlap between diagnoses [22,23]. The “p factor” intends to capture this shared variation across diagnoses, accounting for comorbidity and severity of psychopathology[5,24–27]. Genomic[28–34] and epidemiological[35,36] evidence further suggest that psychiatric comorbidity reflect a shared risk architecture. For example, any psychiatric disorder significantly increases the absolute risk of developing later psychiatric disorders[35,36]. In this context, it is unsurprising that many psychotherapies and medications reduce symptoms of various psychiatric disorders[37–40].

Psychiatric comorbidity is an important consideration for neuromodulation treatments like transcranial magnetic stimulation (TMS) that often target one psychiatric disorder at a time.

Targeting methods are increasingly focused on specific symptoms within a diagnosis[41–44], a strategy that may be difficult to scale and optimize in the setting of high psychiatric comorbidity. By contrast, neurosurgical ablation of single treatment targets has shown effectiveness across psychiatric disorders[45–47], suggesting that transdiagnostic targets are feasible.

Neuroimaging has revealed important insights into the neurobiological basis of psychiatric illness [48–57]. However, prior work has critical limitations that we seek to address. First, studies often attempt to map abnormalities to common brain regions[50,58] rather than to a common brain network. Natural heterogeneity and noise prevent some abnormalities from consistently mapping to the same brain region across studies. However, these same abnormalities map to different brain regions within the same brain network. Network-level analyses account for such a possibility, thereby increasing the statistical power to detect commonalities across studies[56,57,59]. Second, prior studies rarely test specificity by comparing psychiatric disorders to other brain disorders. Finally, the causal interpretation of neuroimaging findings is ambiguous when studies focus on correlates of illness. Neuroimaging correlates might cause, compensate for, or be coincidentally related to psychiatric disorders. The correct interpretation of these correlates is essential for developing effective neuromodulation targets[60,61].

In this study, we used morphometric and brain lesion datasets coupled with a wiring diagram of the human brain to derive a convergent brain network for psychiatric illness.

Results

Significant, Sensitive, and Specific Transdiagnostic Network

Traditional ALE meta-analysis of psychiatric coordinates (Dataset 1) identified gray matter decreases in bilateral anterior insula, dorsal anterior cingulate cortex, dorsomedial prefrontal cortex, thalamus, amygdala, hippocampus, superior temporal gyrus, and parietal operculum, consistent with prior work[50] (Figure 1A). These regions survived cluster-wise multiple comparisons correction (Figure 1A Significant Results). However, fewer than 35% of studies contributed to any one cluster (Figure 1A Sensitivity), and no cluster was specific to psychiatric (Dataset 1) versus neurodegenerative coordinates (Dataset 2) (Figure 1A Specificity, two-sample t-test, nothing survives multiple comparisons correction).

Coordinate network mapping identified results that were more statistically robust than those from the ALE meta-analysis (Figure 1B Significant Results, one-sample t-test, voxels survive multiple comparisons correction). Psychiatric atrophy coordinates from 85% of studies were functionally connected to the same network of brain regions (Figure 1B Sensitivity). This network was defined by positive connectivity to bilateral insula, anterior cingulate cortex, posterior cingulate, and left frontal pole, and by negative connectivity to right inferior temporal gyrus, posterior parietal cortex, bilateral lateral occipital cortex (superior division), brainstem, and cerebellum (Supplementary Figure 1, Supplementary Table 1). The topography of this transdiagnostic network was independent of statistical threshold (Supplementary Figure 2) and specific to psychiatric (Dataset 1) versus neurodegenerative disorders (Dataset 2)(Figure 1B Specificity, two-sample t-test, voxels

survive multiple comparisons correction). The strongest peak of this transdiagnostic network was in the posterior parietal cortex (Brodmann Area 7) near the intraparietal sulcus (MNI Coordinates: −22, −70, 64).

All Psychiatric Diagnoses Independently Contribute

Leave-one-diagnosis-out analyses (Dataset 1) assessed whether any single diagnosis was disproportionately influencing our results. With ALE meta-analysis, dropping one diagnosis repeatedly changed the map topography, resulting in low spatial correlations with the comprehensive ALE map from all diagnoses (spatial r = 0.344–0.453, Supplemental Table 2). In contrast, coordinate network mapping results were robust to leave-one-out analyses (spatial r = 0.980–0.998) and significantly more robust than the ALE maps ($p<0.001$). These results did not change when we excluded negatively correlated regions from the coordinate network mapping results (Supplementary Table 2).

Network Damage Correlates with Psychiatric Comorbidity

We overlayed lesions from an independent dataset (Dataset 3; Figure 2A) onto the ALE map and the transdiagnostic network in order to evaluate whether damage to either map correlated with the number of post-lesion psychiatric diagnoses (i.e., psychiatric comorbidity). Each lesion was associated with a post-lesion SCID score (i.e., number of psychiatric diagnoses).

We found no evidence of a correlation between psychiatric comorbidity and damage to the ALE map (Pearson $r=0.02$, $p=0.766$; Figure 2B). By contrast, there was a statistically significant correlation between psychiatric comorbidity and lesion damage to the transdiagnostic network (Figure 2B and Figure 2C; Pearson $r=-0.21$, $p=0.01$), which was independent of statistical threshold (Supplemental Figure 3). A multiple regression model showed that the transdiagnostic network, but not the ALE map, independently predicted the number of post-lesion psychiatric diagnoses ($p = 0.003$ versus 0.1, respectively).

Replication in an Independent Lesion Dataset

The same lesion dataset (Dataset 3) was used to generate a data-driven lesion network showing connections that co-vary with the number of psychiatric diagnoses (Figure 3A and Figure 3B). The topography of this lesion network was similar when we controlled for lesion size (spatial $r=0.96$). Despite being derived from an independent dataset, the topography of this lesion network was similar to the coordinate-based transdiagnostic network ($r=0.65$) and more similar than expected by chance ($p=0.02$ with 10,000 permutations: Supplemental Figure 4). The lesion network was also significantly more similar to the transdiagnostic network than it was to the ALE map ($r=0.65$ versus $r=0.11$, $p=0.02$).

Neurosurgical Ablation Targets the Network

All four published neurosurgical ablative targets for psychiatric disorders (Dataset 4) intersected the transdiagnostic network (Figure 4). One-sample t-tests showed anterior capsulotomy ($p<0.001$), anterior cingulotomy ($p<0.001$), subcaudate tractotomy ($p<0.001$), and limbic leucotomy ($p<0.001$) damage the regions positively connected to psychiatric coordinates. Two-sample t-tests showed that these findings were all specific to psychiatric

versus neurodegenerative coordinates (anterior capsulotomy p=0.044, anterior cingulotomy p=0.007, subcaudate tractotomy p = 0.002, and limbic leucotomy p<0.001).

Spatial Correlation with Canonical Brain Networks

Canonical brain networks most similar to our transdiagnostic network were the visual (spatial r= 0.48), dorsal attention (spatial r=0.32), and default mode (spatial r=−0.34) networks (Supplemental Table 3). However, none of these canonical networks aligned with our transdiagnostic network as well as our data-driven lesion network for psychiatric comorbidity (spatial r=0.65).

Discussion

Psychiatric disorders are typically studied individually despite sharing neurobiology and frequently co-occurring. This neurobiological and clinical overlap highlights opportunities for transdiagnostic treatments that target a shared brain network. In this study, we used morphometric and brain lesion datasets coupled with a wiring diagram of the human brain to derive this convergent brain network for psychiatric illness.

There are five main findings. First, atrophy coordinates across psychiatric disorders mapped better to a common brain network than they did to common brain regions. This transdiagnostic network included positive connectivity to insula, anterior cingulate, posterior cingulate, and left frontal pole as well as negative connectivity to posterior parietal cortex, lateral occipital cortex, brainstem, and dorsal attention regions of the cerebellum[62]. Second, this network was robust to leave-one-diagnosis out analyses. Third, this network was specific to psychiatric versus neurodegenerative disorders. Fourth, lesion-induced damage to the network correlated with the number of post-lesion psychiatric diagnoses. Finally, this network aligned with neurosurgical ablation targets for psychiatric disorders, suggesting possible therapeutic relevance and generating testable hypotheses for neuromodulation studies.

Our study builds on prior work leveraging neuroimaging, genetic, and phenotypic data to identify commonalities across psychiatric diagnoses[6,26,50,51,63–72]. An example of this prior work is the ALE meta-analysis by Goodkind et al.[50] showing convergent gray matter loss in bilateral insula and anterior cingulate. We reproduced these ALE results, but we also found limitations in terms of sensitivity, specificity, robustness, and correlation with lesion-induced effects. We addressed these limitations by analyzing the same dataset with coordinate network mapping and by leveraging additional datasets. Our findings are consistent with recent work suggesting that coordinate network mapping can identify convergent findings across neuroimaging studies in ways that complement ALE meta-analyses[53,54,57]. More broadly, our findings suggest that atrophy coordinates across psychiatric diagnoses map better to a brain network than they do to an individual brain region.

Our transdiagnostic network includes positive peaks in the bilateral insula, anterior cingulate, posterior cingulate, and left frontal pole. As expected, many of these positive peaks are consistent with Goodkind et al. and with an ENGIMA consortium study that examined structural variance across six major psychiatric disorders[48,49]. Our positive peaks

are commonly associated with psychiatric illnesses, with hypothesized roles in salience detection, emotion regulation, self-referential processes, and executive function[48–50,73–76].

Our transdiagnostic network also includes negative peaks in the posterior parietal cortex, occipital cortex, brainstem, and dorsal attention regions of the cerebellum[62]. In fact, the strongest overall peak in our network was a negative peak near the intraparietal sulcus in Brodmann Area 7. Our negative peaks are not traditionally associated with psychiatric illnesses. Instead, they are associated with non-specific processes such as visual processing and multisensory integration[77–86]. However, data-driven transdiagnostic research has increasingly highlighted occipitoparietal regions as well as cerebellum[63,72,80–83,87]. For example, a data-driven analysis of connectome-wide functional connectivity found an association between higher "p factor" scores and connectivity abnormalities between visual association cortex and frontoparietal networks implicated in executive control and self-referential processes [63]. Similarly, an integrated analysis of structural connectomes and single nucleotide polymorphisms highlighted occipital cortex and its links to default mode and cognitive control networks in a "vulnerability network" for psychiatric illness[64]. There is also evidence from data-driven multimodal neuroimaging that higher "p factor" scores are associated with structural changes within cerebello-thalamo-cortical circuit as well as visual association cortex, although the reproducibility of the cerebellum finding has been slightly less consistent [71,72,87].

Taken together, the positive and negative peaks that emerged from our analyses represent a transdiagnostic network that might be implicated in selective attention and multisensory processing, both of which are important for cognitive control [63,72,80–83,87]. This transdiagnostic network cuts across canonical brain networks. There is precedent for looking beyond single canonical brain networks to explain transdiagnostic psychopathology[64]. For example, the triple network model proposes that general psychopathology is associated with an imbalance between multiple networks (i.e., CEN, DMN, and salience network)[88]. Similarly, the "vulnerability network" for psychiatric illness mentioned above overlapped with but was not fully encapsulated by canonical networks[64]. In our study, no single canonical network showed more spatial similarity to our transdiagnostic network than the network generated from an independent lesion dataset (Dataset 3).

In the end, our study answers important questions about if and where psychiatric neuroimaging findings converge, but it does not address why or how these locations contribute to psychiatric illness.

Our transdiagnostic network was derived from gray matter atrophy across psychiatric disorders. Gray matter atrophy is challenging to interpret, especially in psychiatric disorders for which there are few sources of causal information. Even studies that show reversal of gray matter atrophy with successful treatment provide limited causal insights, as morphometric changes could still be correlates or epiphenomena of illness or treatment [57,89–91]. An important strength of our study is that we tested correlative findings from a morphometric dataset with brain lesions associated with psychiatric illness in an independent dataset (dataset 3). These tests examined the correlation between lesion location and the number of post-lesion psychiatric diagnoses quantified via SCID. It is possible

that some participants had psychiatric illnesses that preceded the brain lesion or the SCID. Similarly, some participants may have had psychiatric illnesses that were causally unrelated to the brain lesions. However, such cases would bias us against the present findings[59,92]. Our lesion location results were statistically significant despite these sources of noise, highlighting the possibility that the true effect size is larger than what we observed.

Despite its limitations, mapping brain lesions is an important strategy for beginning to address the causality gap in psychiatric neuroimaging[60,61,93]. Our results highlight the importance of causal sources, as lesion-induced effects on our transdiagnostic network were opposite of what one may have predicted if atrophy was causally linked with greater psychiatric illness or higher psychiatric comorbidity. In our study, atrophy in anterior cingulate and bilateral insula (as well as regions positively connected to them) correlated with transdiagnostic psychiatric illness. This finding alone provides limited insight into how such atrophy should be interpreted. However, brain lesions that intersect anterior cingulate and bilateral insula (as well as regions positively connected to them) correlated with lower psychiatric comorbidity, aligning with neurosurgical ablation targets for psychiatric disorders. Taken together, our results suggest that transdiagnostic gray matter atrophy in anterior cingulate and bilateral insula are not causally related to psychiatric illness. Instead, this atrophy may be a consequence of or a compensation for psychiatric illness. This interpretation is difficult to contextualize because no prior studies leveraged brain lesions to assess transdiagnostic circuitry or comorbidity. The field of epilepsy offers some precedent for interpreting volumetric changes as an effect of a disorder rather than a cause of it. In patients with epilepsy, gray matter atrophy and cortical thinning may be prevented or diminished with resective surgery[94–96]. Similar models have been proposed for psychiatric disorders, but more data are needed[97–99].

Our preliminary results may have therapeutic relevance for neuromodulation. Historically, lesion-based treatments have often targeted the same brain region for different psychiatric diagnoses[45–47]. Our transdiagnostic network aligns with these lesion-based targets and identifies testable targets for future trials that consider psychiatric comorbidity. For example, our peak near the intraparietal sulcus could be targeted with excitatory TMS in patients with multiple psychiatric disorders. This trial would be justified by mounting evidence that brain lesions can provide the causal insights necessary for treatment target derivation[100–102]. Our results may also have relevance for medications and psychotherapies that are effective for multiple psychiatric illnesses, but it is challenging to measure their focal effects on brain networks.

There are several limitations to consider. First, this study was retrospective rather than prospective. We intentionally used data from published meta-analyses to minimize selection bias, so future studies are needed to prospectively test our findings. Second, our morphometric dataset (Dataset 1) had no accompanying metadata on demographics, illness severity or duration, medication use, or biopsychosocial variables that might vary across studies and influence morphometric changes. However, these variables should increase the probability of a false negative. Our transdiagnostic network survived multiple statistical tests across multiple datasets despite these sources of noise, highlighting the possibility that the true effect size may be larger than what we observed. Third, we only had access to

a single lesion dataset that quantified the number of post-lesion psychiatric diagnoses at a single timepoint (Dataset 3). It is possible that some participants had psychiatric illnesses that preceded the brain lesion or was unrelated to the brain lesion. However, such cases would bias us against the present findings. Future work replicating our findings in additional independent lesion datasets is needed. Fourth, coordinate and lesion network mapping were performed with a normative connectome. Prior work suggests that disorder-specific connectomes do not change results[43,103], but future studies could explore this possibility further. Fifth, our study highlights similarities across psychiatric diagnoses, but it does not address differences between them.

In summary, atrophy coordinates across psychiatric disorders mapped to common brain network that was sensitive, specific, robust, and aligned with lesion-induced effects. This network may help explain high rates of psychiatric comorbidity and could highlight neuromodulation targets for patients with psychiatric comorbidities.

Methods

Dataset Overview

We analyzed four independent published datasets in full to minimize selection bias. In each dataset, participants provided informed consent to data collection or the institutional review board approved retrospective analysis of symptom and imaging data.

Dataset 1 was sourced from a published activation likelihood estimation (ALE) meta-analysis of whole-brain voxel-based morphometry studies comparing patients with psychiatric disorders to healthy controls[50]. The authors excluded neurodevelopmental disorders, personality disorders, patients with neurological comorbidities, and disorders assessed in fewer than 10 studies. These criteria yielded a sample size of 15892 individuals from 193 studies[50] covering six diagnostic categories (i.e., schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety). Each of the 193 studies reported MNI coordinates at which patients with psychiatric disorders had more atrophy than controls.

Dataset 2 was sourced from published neuroimaging studies in patients with Alzheimer's disease, behavioral variant frontotemporal dementia, corticobasal syndrome, and progressive non-fluent aphasia[54]. Each of the 72 studies reported a series of coordinates at which patients with neurodegenerative disorders had more atrophy than controls.

Dataset 3 was sourced from the Vietnam Head Injury Study, a multi-decade prospective follow-up study of veterans with and without penetrating head injuries[104,105] . Data from 194 veterans who had completed the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID) after a penetrating head injury were analyzed. For each participant, penetrating lesions were localized using head CT and post-lesion psychiatric diagnoses were quantified via SCID. The lesion masks used in this study were identical to those used in prior studies[106,107]. These lesion masks were created by manual segmentation, spatial normalization to Montreal Neurological Institute (MNI) 152

atlas space, and binarization such that voxels inside the lesion were assigned a value of "1" and voxels outside the lesion were assigned a value of "0"[107].

Dataset 4 was sourced from published neurosurgical ablation coordinates for depression, all of which have also been used for multiple psychiatric disorders[46].

Activation Likelihood Estimation

First, we mapped atrophy coordinates to common brain regions by replicating the Goodkind et. al.[50] results using Dataset 1 and GingerALE[108] (10,000 permutations, cluster-forming threshold at voxel-level $p < 0.005$, cluster-level I-corrected threshold $p < 0.05$). We assessed sensitivity by quantifying the number of studies contributing to each significant cluster. Next, we assessed specificity by comparing ALE maps for psychiatric disorders (Dataset 1) versus neurodegenerative disorders (Dataset 2) using the Contrast Analysis function in GingerALE (10,000 permutations), which searches for statistically significant differences in convergence between two datasets. We also generated an unthresholded ALE map for analyses requiring whole-brain coverage.

Coordinate Network Mapping

Next, we mapped atrophy coordinates to a common brain network. This network was identified in accordance with previously published methods using custom Python code[54]. Study-level atrophy maps were created with spherical seeds (4mm radius) centered at each coordinate associated with greater atrophy in patients with psychiatric disorders versus controls. A normative connectome of healthy controls (n=1000)[109] was used to generate resting-state functional connectivity maps for each study-level atrophy map (Figure 1B). Resting-state functional connectivity data were processed in accordance with prior work[109]. A composite t-map was generated from these study-level maps using a voxel-wise one-sample t-test, with Bonferroni correction resulting in a threshold t-value of 5.66 ($p<0.05/285{,}903$ voxels $= 1.76\times10^{-7}$). Sensitivity was assessed by combining thresholded ($t>5$) study-level maps into a composite map depicting the percentage of studies overlapping at each brain voxel. We will refer to this coordinate network overlap map as the "*transdiagnostic network*."

To ensure the transdiagnostic network was not dependent on our threshold choice, we repeated our analysis at higher thresholds as in prior work ($t>7$, $t>10$)[54]. We assessed specificity by comparing the resting state functional connectivity maps from psychiatric coordinates (Dataset 1) to similar maps from neurodegenerative coordinates (Dataset 2) using a voxel-wise two-sample t-test and Permutation Analysis of Linear Models (PALM) in FSL[110,111], correcting for multiple comparisons using threshold-free cluster enhancement with a voxel-based FWE-corrected $p<0.05$. Note that this specificity map was generated using unthresholded functional connectivity maps, and thus is independent of the statistical threshold used to generate the overlap map.

Leave-One-Diagnosis-Out Analyses

We assessed the impact of each psychiatric diagnosis on our results by repeating ALE and coordinate network mapping in serial fashion, each time with one psychiatric diagnosis

omitted (Dataset 1). Spatial correlation was used to compare each leave-one-diagnosis-out map to the comprehensive ALE map and transdiagnostic network[101,107]. Two-sample t-tests were used to determine whether coordinate network mapping was more robust than ALE meta-analysis for leave-one-diagnosis out analyses ($p < 0.05$).

Lesion Network Mapping

We used an independent lesion dataset (Dataset 3) to inform the causal interpretation of the ALE map and our transdiagnostic network (Dataset 1). First, we hypothesized that damage to our transdiagnostic network, but not the ALE map, would correlate with psychiatric comorbidity. To test this hypothesis, we overlayed each lesion onto the ALE map and the transdiagnostic network. The sum of lesion-circumscribed voxel values is considered the "damage score" [107,112]. We assessed the correlation between damage score and the number of post-lesion psychiatric diagnoses while controlling for lesion size, GAF, and outliers.

Second, we hypothesized that a network derived from lesions associated with psychiatric disorders (Dataset 3) would align better with the transdiagnostic network than it did with the ALE map (Dataset 1). To test this hypothesis, we computed the whole-brain connectivity of each lesion using a normative connectome. Connections that co-varied with the number of psychiatric diagnoses were identified, generating a lesion network for psychiatric comorbidity. We used permutation testing[101] with custom Matlab code to assess the similarity between this lesion network and the ALE map and the transdiagnostic network. Briefly, we recomputed the lesion network 10,000 times by randomly assigning SCID scores to connectivity profiles. Each randomly generated map was compared to the ALE map and the transdiagnostic network via spatial correlation. Significance was defined as greater spatial correlation between real versus randomly permuted maps in at least 95% of instances ($p<0.05$).

Neurosurgical Ablation Alignment

We tested whether neurosurgical ablation targets for psychiatric disorders aligned better with the transdiagnostic network than they did with the ALE map. We placed 10mm spheres at published target coordinates for anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy, and limbic leucotomy [46]. For each sphere, we calculated the "damage score" by summing the lesion-circumscribed voxel values on the ALE map and the transdiagnostic network [107,112]. Significance ($p < 0.05$) was assessed in Excel by comparing this damage score versus zero (via one-sample t-test). We also compared the damage score of each simulated lesion versus the damage score on the neurodegenerative network (via two-sample t-test).

Canonical Network Comparison

We compared the transdiagnostic network to canonical Yeo networks via spatial correlation. This exploratory analysis, run using custom Python code, tested the extent to which the transdiagnostic network was distinct from existing canonical networks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

This paper used de-identified data from multiple datasets collected by different investigators at different institutions. Datasets 1 (doi: 10.1001/jamapsychiatry.2014.2206), 2 (doi:10.1093/brain/awy292), and 4 (doi:10.1038/npp.2010.132) are publicly available peer-reviewed publications. Inquiries regarding the Vietnam Head Injury Study (Dataset 3) can be directed to Jordan Grafman, Ph.D. (jgrafman@northwestern.edu). The one-sample t-test transdiagnostic network is available: https://github.com/nimlab/NHB_Taylor2023.

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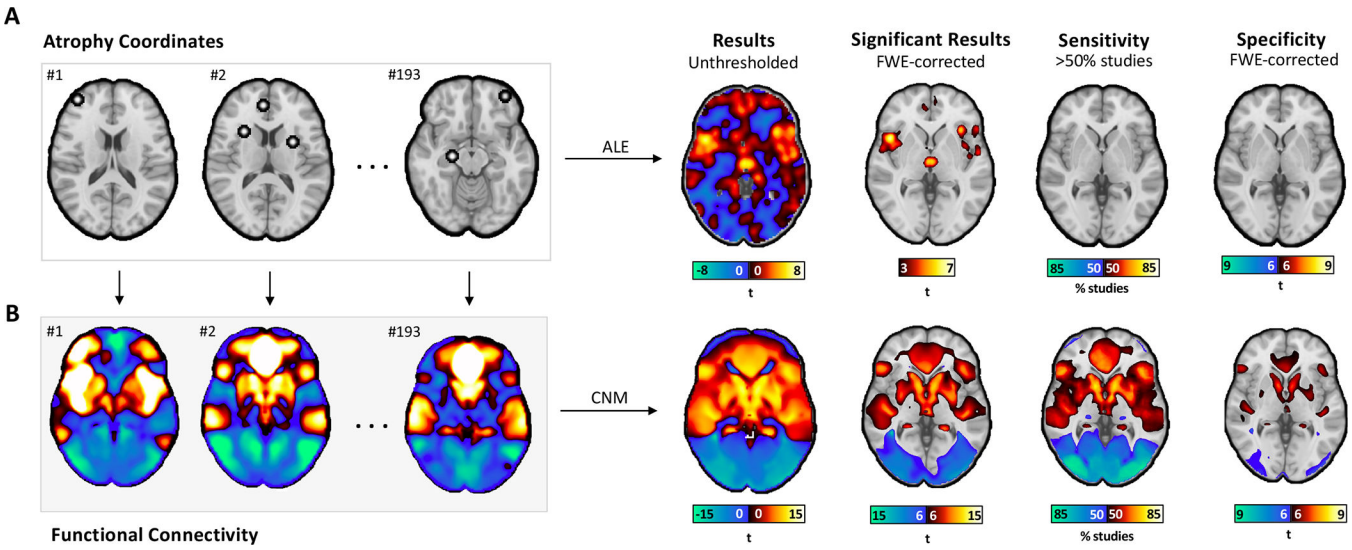

Figure 1.

Mapping atrophy coordinates in psychiatric illness to networks rather than regions. (A) Atrophy coordinates from 15892 individuals in 193 VBM studies were analyzed via ALE. The results of this regional analysis aligned with those published previously (Significant Results). However, none of the ALE clusters had more than half of studies contributing to them (Sensitivity), and none of the ALE clusters were specific to psychiatric disorders versus neurodegenerative disorders (Specificity, two-sample t-test, no voxels survived multiple comparisons correction). (B) The same atrophy coordinates were analyzed via coordinate network mapping (CNM), a network-based analysis. Functional connectivity between atrophy coordinates in each study and the rest of the brain was computed using a normative connectome (n=1000). Positive functional connectivity is shown in warm colors, and negative functional connectivity (i.e., anticorrelations) are shown in cool colors. Relative to ALE results, CNM results were statistically stronger (Significant Results, one-sample t-test, voxels displayed survived multiple comparisons correction), explained more variance (Sensitivity), and survived comparison to neurodegenerative disorders (Specificity, two-sample t-test, voxels displayed survived multiple comparisons correction).

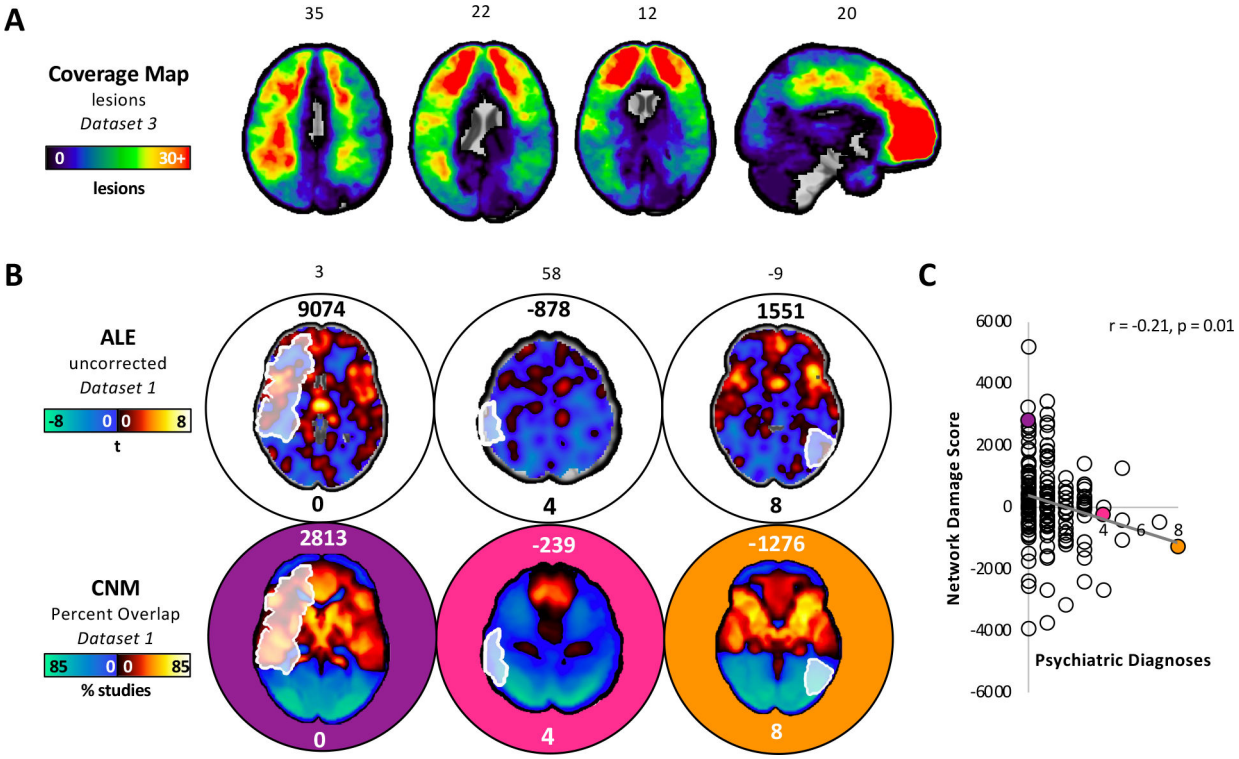

Figure 2.

Network mapping results align better with lesion-induced psychiatric diagnoses than traditional ALE. (A) A coverage map depicting the number of lesions in an independent dataset (dataset 3) that intersected each voxel in the brain. (B) The top panel shows three lesions overlayed onto the ALE map. The number above each brain slice represents the network damage score, or the sum of the voxel values circumscribed by each lesion. The number below each brain slice represents the number of psychiatric diagnoses associated with that lesion. We found no evidence of a correlation between network damage and the number of post-lesion psychiatric diagnoses (Pearson r=0.02, p=0.766). The bottom panel shows the same three lesions overlayed onto the transdiagnostic network from coordinate network mapping (CNM). (C) There was a correlation between network damage and the number of post-lesion psychiatric diagnoses (Pearson r=−0.21, p=0.01). Lesions with positive network damage scores on the transdiagnostic network were correlated with lower psychiatric comorbidity. By contrast, lesions with negative network damage scores on the transdiagnostic network were correlated with higher psychiatric comorbidity. A multiple regression model showed that the transdiagnostic network, but not the ALE map, independently predicted the number of post-lesion psychiatric diagnoses (p = 0.003 versus 0.1, respectively).

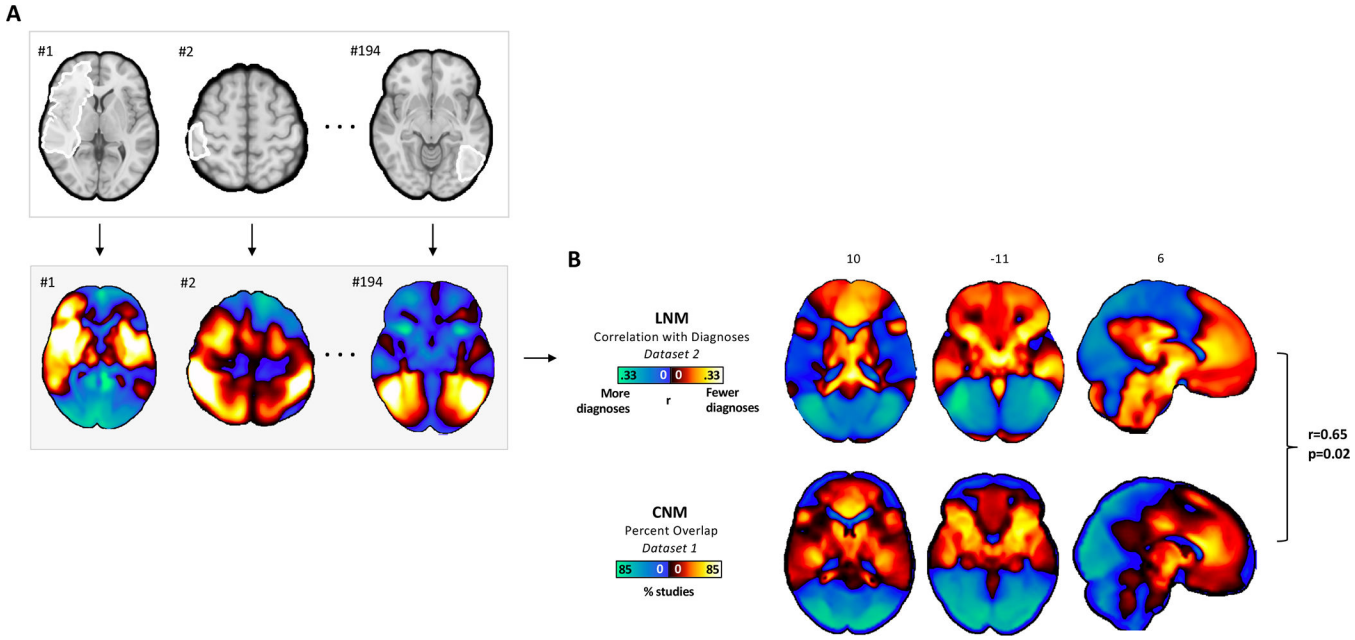

Figure 3.

Convergent network topography across atrophy and brain lesions associated with psychiatric illness. (A) Brain lesions from an independent dataset (Dataset 3) were analyzed via lesion network mapping, a network-based analysis. Functional connectivity between each brain lesion and the rest of the brain was computed using a normative connectome. (B) The lesion network map shown reflects the correlation between each brain voxel and post-lesion psychiatric diagnoses. This lesion network map was compared to the coordinate network map (Dataset 2) via permutation testing. Briefly, the lesion network map was recomputed 10,000 times after random assignment of psychiatric diagnoses to functional connectivity profiles. Each of the 10,000 recomputed lesion network maps was compared to the coordinate network map via spatial correlation. The real lesion network map showed a higher spatial correlation to the coordinate network map than randomly permuted lesion network maps in greater than 98% of the instances (r=0.65, p=0.02). The lesion network was also significantly more similar to the transdiagnostic network than it was to the ALE map (r=0.65 versus r=0.11, p=0.02).

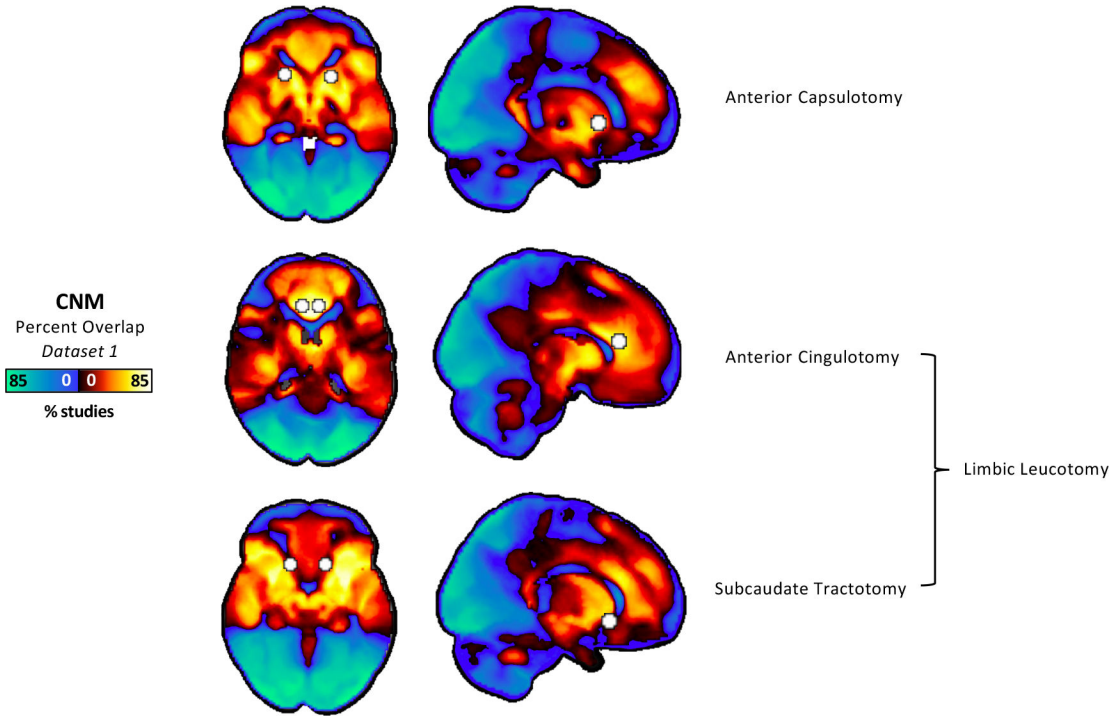

Figure 4.

Alignment between neurosurgical ablation targets for psychiatric disorders and our coordinate-based transdiagnostic network. Spheres were placed at published coordinates for anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy, and limbic leucotomy. These spheres were overlayed onto the transdiagnostic network from CNM. All targets hit the regions with positive connectivity to atrophy coordinates, which aligns with prior analyses showing that atrophy in these regions correlates with lower psychiatric comorbidity. One-sample t-tests showed anterior capsulotomy ($p<0.001$), anterior cingulotomy ($p<0.001$), subcaudate tractotomy ($p<0.001$), and limbic leucotomy ($p<0.001$) damage the regions positively connected to psychiatric coordinates. Two-sample t-tests showed that these findings were all specific to psychiatric versus neurodegenerative coordinates (anterior capsulotomy $p=0.044$, anterior cingulotomy $p=0.007$, subcaudate tractotomy $p = 0.002$, and limbic leucotomy $p<0.001$).