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Diverse pathophysiological processes converge on network disruption in mania

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Abstract

Background: Neuroimaging of psychiatric disease is challenged by the difficulty of establishing the causal role of neuroimaging abnormalities. Lesions that cause mania present a unique opportunity to understand how brain network disruption may cause mania in both lesions and in bipolar disorder.

Methods: A literature search revealed 23 case reports with imaged lesions that caused mania in patients without history of bipolar disorder. We traced these lesions and examined resting-state functional Magnetic Resonance Imaging (rsfMRI) connectivity to these lesions and control lesions to find networks that would be disrupted specifically by mania-causing lesions. The results were then used as regions-of-interest to examine rsfMRI connectivity in patients with bipolar disorder (n=16) who underwent imaging longitudinally across states of both mania and euthymia alongside a cohort of healthy participants scanned longitudinally. We then sought to replicate these results in independent cohorts of manic (n=26) and euthymic (n=21) participants with bipolar disorder.

Results: Mania-inducing lesions overlap significantly in network connectivity. Mania-causing lesions selectively disrupt networks that include orbitofrontal cortex, dorsolateral prefrontal cortex, and temporal lobes. In bipolar disorder, the manic state was reflected in strong, significant, and specific disruption in network communication between these regions and regions implicated in bipolar pathophysiology: the amygdala and ventro-lateral prefrontal cortex.

Limitations: There was heterogeneity in the clinical characterization of mania causing lesions.

Conclusions: Lesions causing mania demonstrate shared and specific network disruptions. These disruptions are also observed in bipolar mania and suggest a convergence of multiple disorders on shared circuit dysfunction to cause mania.

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Keywords

fMRI; lesion; mania; network; bipolar; disorder

1. Introduction

Bipolar disorders are common and severe but their pathophysiology is poorly understood and existing treatments are only partially effective and provoke significant side effects (Chen and Dilsaver, 1996; Kessler et al., 1999; Leverich et al., 2003; Perlis et al., 2006; Slama et al., 2004). Many previous studies have used functional magnetic resonance imaging (fMRI) in humans to understand bipolar pathophysiology at the network and circuit level. Fewer studies, however, have compared bipolar participants across different symptomatic states. In the clinic, treatment goals focus on shifting individuals from a pathologic, symptomatic state (e.g. mania or depression) to an asymptomatic, euthymic state. Without a biological mechanism that accounts for these different states, it is both unclear what process to target during therapeutic development and evaluation of therapeutics, and which animal models accurately recapitulate bipolar disease pathophysiology.

Our group and others have utilized fMRI to investigate how different bipolar mood states are reflected in brain network activity and connectivity. Previous studies utilized task-based fMRI to model how bipolar mood state is reflected in brain activation during emotion processing and regulation (Almeida et al., 2010; Cerullo et al., 2012; Chen et al., 2006; Chen et al., 2010; Hummer et al., 2013; Liu et al., 2012; Perlman et al., 2012; Rive et al., 2015; Strakowski et al., 2016; Van der Schot et al., 2010; Versace et al., 2010). Complementary experiments have used task-free ('resting-state', rsfMRI) imaging to generate connectome-wide maps of altered brain communication in different mood states, albeit without specific correlates to cognitive processes (Altinay et al., 2016; Anand et al., 2009; Brady et al., 2016; Brady et al., 2017b; Li et al., 2015; Spielberg et al., 2016).

These studies have provided a greater understanding of how mood state is reflected in brain activity and connectivity. A challenge to the interpretation of most neuroimaging studies (including our own), however, is the difficulty in establishing causal relationships between fMRI signals and psychopathology (Etkin, 2018). Significant differences in brain activation and connectivity exist between bipolar mood states, but these findings may reflect disease process, or a compensatory response, or may be epiphenomena.

Limiting our neuroimaging hypotheses to those with preexisting evidence of causality addresses this problem. Specifically, existing literature supports the idea that acute disruption of brain activity in circumscribed regions can cause mania. If these injuries impinge on a shared brain substrate, we can generate a model of how brain pathophysiology causes mania. This model could then be tested in bipolar disorder to determine if bipolar mania demonstrates the same relationship between behavior and pathophysiology.

Mania after an acute onset, localized brain lesion is rare, but well-documented in many case reports (reviewed in (Santos et al., 2011; Satzer and Bond, 2016)). Starkstein and Robinson

used brain imaging to localize lesions in patients experiencing mania associated with a brain lesion (Robinson et al., 1988; Starkstein et al., 1988; Starkstein et al., 1990; Starkstein et al., 1987). They found these lesions were anatomically distributed, which raises an intriguing possibility: perhaps rather than sharing a unitary anatomical vulnerability to mania, these lesions all *disrupted a shared brain network*. Starkstein et al. postulated such a model (Starkstein et al., 1988) but neuroimaging at the time did not allow visualization of network communication between regions. Relevance of these lesion-induced manic syndromes to bipolar mania remained undetermined.

The hypothesis that disparate lesions may cause a common phenotype via disruption of a shared brain network is well validated (Carrera and Tononi, 2014; Feeney and Baron, 1986; He et al., 2007; Honey and Sporns, 2008). Broader application of this understanding has been limited by two challenges 1) performing imaging in acutely ill clinical populations and 2) accumulating a sufficient number of cases to make valid and generalizable inferences. “Lesion network mapping” is designed to circumvent these challenges (Boes et al., 2015). This imaging analysis method utilizes published cases of lesions associated with a particular behavioral phenotype and, using brain connectivity data from healthy participants, demonstrates which network(s) the lesions would be expected to disrupt. Compiled records of these cases that document both behavioral phenotype and imaging data allows for sufficient sample size to discern behavior-specific patterns of network disruption in a variety of phenotypes. This approach has already been used to analyze a variety of phenotypes such as criminality (Darby et al., 2018), hallucinations (Boes et al., 2015), movement disorders (Fasano et al., 2017; Laganieri et al., 2016), and delusions (Darby et al., 2017).

We used lesion network analysis to determine if anatomically distinct lesions that cause mania converge on a common brain network(s). We then tested the generalizability of the relationship between network disruption and the mania phenotype by determining if networks disrupted in lesion-induced mania were also disrupted in patients with bipolar disorder mania. Our hypothesis was that diverse pathophysiological processes (e.g. ischemic strokes vs. bipolar disorder) can give rise to a shared manic behavioral phenotype by disrupting the same brain network.

2. Materials and Methods

2.1 Methods Overview

In the first step of the analysis, we used lesion network mapping to determine whether lesions that cause mania converge on a shared network. We then tested the hypothesis that different pathophysiological causes of mania disrupt the same brain network by asking whether the disruption we observed in our lesion network mapping experiment was also present in bipolar disorder mania. This test was performed in a cohort of participants with bipolar disorder imaged longitudinally in both a manic and euthymic state to isolate state related changes in brain connectivity. Finally, we tested this network in a replication dataset of an additional cohort of bipolar participants.

2.2.1 Lesion Network Mapping Overview.—Lesion network mapping was performed using methods similar to Boes et al. (Boes et al., 2015). In brief, this involves three steps: 1)

A literature search for case reports of brain lesions causing mania. 2) Lesions from MRI or CT scans are hand traced onto a standardized template brain. Each traced lesion is used as a region of interest (ROI) in a rsfMRI analysis using data from 40 healthy control participants. 3) The connectivity maps of lesions causing mania are compared to maps of connectivity to randomly selected, publicly available brain lesion tracings (Liew et al., 2018). Brain regions that were significantly more likely to be functionally connected to mania-inducing lesions are then reported.

2.2.2 Case Reports of Lesion-induced Mania with Neuroimaging.—We conducted a literature review to find cases of lesion-induced mania using a PubMed search with terms such as ‘mania AND lesion’ followed by searches of other literature referenced in those publications. Inclusion criteria were: 1) Cases had to describe a temporally linked onset of neurological symptoms and mania, suggesting a causal relationship between brain injury and manic symptoms. 2) Cases had to include published imaging (e.g. MRI or CT scan) that allowed tracing. 3) Patients could not have a pre-existing bipolar or psychotic disorder. 23 cases met these criteria, including many found in a recent review of stroke related mania (Santos et al., 2011). Case reports and references to original literature are included in Appendix Table 1. MRI and CT images included with these published case reports were used as guides to hand trace lesions onto a standardized Montreal Neurological Institute 152 (MNI152) template brain using FSL (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) and 3D Slicer (<https://www.slicer.org/>). (Figure 1) Lesion tracing fidelity to the published image was confirmed by consensus agreement between I.L. and R.B. To ensure inter-rater reliability, and another study member traced the lesions entirely independently (U.N.).

2.2.3 Normative resting-state fMRI data for lesion mapping—rsfMRI data was acquired from a cohort of 40 healthy control (HC) participants (20 female, 20 male. Age: mean 29.4, SD $\pm$ 10.7). Details of their assessment are included in Supplemental Methods. All MRI data was acquired on a 3T Siemens Trio-TIM scanner using a standard 12-channel head coil. No scanner upgrade occurred during the duration of data collection. Scanner sequences and subsequent imaging data preprocessing steps were the same as performed in previous studies and are detailed in Supplemental Methods (Brady et al., 2017a; Brady et al., 2016; Brady et al., 2017b). Preprocessing methods were chosen to minimize motion artifacts.

2.2.6 Connectivity Maps to Mania-inducing Lesions—The time course of voxels in each traced lesion ROI was extracted and Pearson correlation coefficients between this time course and those of all other voxels in all HC participants were calculated using DPABI (Yan et al., 2016). These values were transformed to Fisher’s z scores to generate FC maps of regions functionally connected to mania-inducing lesion ROIs. One-sample t-tests of these maps from all 40 participants were generated using SPM. Resulting connectivity maps were thresholded at a p value $<.0001$. The resulting maps of functionally connected areas were binarized using FSL (Figure 2).

2.2.7 Comparison with Random Control Brain Lesions—Mania after a brain lesion is a rare outcome. In order for disruption of network connectivity to be a plausible

explanation for this behavioral phenotype, these lesions must disrupt connectivity in networks that are not typically disrupted in brain lesions. To control for lesion specificity, we made use of a publicly available database of hand traced stroke lesions (Liew et al., 2018). We randomly selected 23 lesions from the database and completed the same process described above under ‘Connectivity Maps to Mania-inducing Lesions’ to generate maps of connectivity to control brain lesions. As in prior lesion network mapping studies, we compared the connectivity maps of mania-inducing lesions to maps generated from control lesions using a voxel-wise Lieberman test (Rorden et al., 2007). This test generates a map of voxels that are more likely to be connected to mania-inducing lesions than control lesions. Multiple comparison correction in the Lieberman test occurs via False Discovery Rate (FDR) correction.

2.2.8 Comparison with Size Matched Control Brain Lesions—As an additional control for the network specificity of our mania-causing lesions, we compared the 23 mania-causing lesions to another set of 23 distinct control brain lesions, chosen based upon size matching to the mania-causing lesions. Connectivity maps to this second set of lesions were again compared to the networks derived from mania-causing lesions using the Lieberman test described above.

2.2.9 Comparison with Single-Plane Traced Control Brain Lesions—In lesion network analysis, lesions are traced in a single plane by virtue of data presented (i.e. single plane images in case report figures). Prior studies that directly compared representative single-plane and 3-D tracings saw high concordance (spatial correlation coefficient of 0.96) in the resultant network connectivity maps (Boes et al., 2015). While this method has been accepted in all prior lesion network mapping studies, we took a conservative approach by comparing connectivity maps from the single-plane mania-causing lesion tracings to a set of 23 control lesions that were re-traced in a single plane (i.e. a direct comparison of mania-causing lesions traced in a single plane to control lesions traced in a single plane). Resultant connectivity maps were again compared using the Lieberman test.

2.3 Comparison to Bipolar Disorder Mania Overview

We sought to compare the results of our mapping analysis from lesion-induced mania to patients with bipolar disorder mania. We hypothesized that mania caused by both neurological lesions and by bipolar disorder result from a shared pattern of network disruption. To test this, we collected rsfMRI data from a cohort of participants (n=16) with bipolar disorder type I scanned longitudinally, with one scan during a manic state and the other during a euthymic state. The results of the lesion mapping analysis above were then used as ROIs to determine whether disruptions in similar networks were observed in bipolar mania (as opposed to euthymia). We then sought to replicate this analysis in an independent historical cohort of participants with bipolar disorder in a cross-sectional comparison of participants with bipolar disorder type I imaged while manic (n=26) to those imaged while euthymic (n=21).

2.3.1 Bipolar & Healthy Comparison Longitudinal Participants—Study recruitment was performed as in our previous studies and as detailed in Supplemental

Methods (Brady et al., 2017a; Brady et al., 2016; Brady et al., 2017b). Longitudinal participants with bipolar disorder type I were all recruited, characterized, and imaged while in a manic state. Participants were then contacted subsequently for imaging and clinical characterization while euthymic. Of the cohort of bipolar participants with usable scan data at both time points, almost all (15/16) of were initially scanned while manic and hospitalized on an inpatient unit. All euthymic scans took place during outpatient treatment.

We also recruited a cohort of sex and age matched healthy control participants to scan longitudinally at a similar interval to the bipolar cohort, in order to control for non-specific effects such as scanner drift.

2.3.2 Bipolar Replication Dataset Participants: For the replication dataset, participants with bipolar disorder type I had been previously recruited, characterized, and imaged a single time each during either a manic state (n=26) or a euthymic state (n=21). Recruitment and characterization was otherwise performed identically to the longitudinal participants described above.

2.3.3 MRI data Acquisition & fMRI data processing—Data acquisition for bipolar longitudinal imaging was collected on the same scanner using the same sequence as above. fMRI data processing was performed exactly as described above. No scanner upgrades occurred during the duration of the study.

2.3.4 Bipolar Mania versus Euthymia Resting-State Longitudinal Connectivity Analysis—Regions identified in the lesion mapping study were used as ROIs to examine whole-brain connectivity differences using a within-subject design. The time course of voxels in each ROI was extracted and Pearson correlation coefficients between this timecourse and those of all other voxels were calculated using DPABI (Yan et al., 2016). These values were transformed to Fisher's z scores to generate FC maps of regions functionally connected to these ROIs. Maps were then entered into a second level design in SPM using a paired t-test to compare the manic state and euthymic state within-subjects. Given concerns about false positives resulting from more permissive voxel thresholds (Eklund et al., 2016), and concerns about the reproducibility of spatially constricted, highly thresholded imaging signals (Duncan et al., 2009), we required that the resulting maps of mood state differences meet two different standards for statistical significance: 1) thresholding at the voxelwise level of $p < .001$ with an extent threshold of $k = 28$ voxels for $p < .016$ clusterwise significance ($\alpha < .05$ corrected for three comparisons). 2) a voxelwise threshold of $p < .005$, $k = 59$ voxels for $p < .016$ clusterwise significance. The threshold for cluster level significance was determined using Monte Carlo simulation as implemented in DPABI (Yan et al., 2016).

Regions of significant difference between bipolar mood states were used to generate ROI to ROI z-transformed functional connectivity values in the bipolar participants and in a cohort of healthy comparison (HC) participants imaged longitudinally. To control for non-specific effects (e.g. scanner drift), these results were entered into a two-way mixed ANOVA to determine the effect of time/mood state on diagnosis (bipolar vs. HC).

To control for within-subject differences in medication regimen we performed a linear mixed model analysis using SPSS statistical software (SPSS Inc., Chicago, IL, USA) to examine the effect of mood state with medications as time-varying covariates.

2.3.5 Bipolar Mania versus Euthymia Resting-State Replication Cohort

Connectivity Analysis—Regions identified in the lesion mapping study were used as ROIs to examine functional connectivity differences using a between-group design. The time course of voxels in each ROI was extracted and Pearson correlation coefficients between this timecourse and those of all other voxels were calculated using DPABI (Yan et al., 2016). These values were transformed to Fisher's z scores to generate FC maps of regions functionally connected to these ROIs. Maps were then entered into a second level design in SPM using an independent sample t-test comparing the manic group to the euthymic group. Covariates included age, sex, and prescribed antipsychotic dosage (CPZE). Between-group connectivity analyses were confined to regions that were identified in the longitudinal bipolar cohort. Within these regions, voxelwise significance was thresholded at $p < .05$ and cluster extent thresholded significance set at $p < .025$ clusterwise significance ($\alpha < .05$ corrected for two comparisons).

3. Results

3.1.1 Lesions temporally associated with mania are spatially heterogeneous:

We found 23 cases of lesion-induced mania with imaging data (Appendix Table 1). In all cases these patients had no prior history of bipolar or psychotic disorder and only became manic following lesion development. The 23 lesions were spatially diverse (Figure 1). When overlaid, the highest area of overlap was between 3 lesions in the thalamus.

3.1.2 Lesions that cause mania show substantial overlap in functional connectivity

Although there was heterogeneity in the location of mania-causing lesions, we observed substantial overlap in their functional connectivity. More specifically, overlap was observed in the salience network broadly (Dosenbach et al., 2008; Seeley et al., 2007) and most prominently in the right amygdala (20/23 lesions), which is unsurprising given that the amygdala is a broadly connected network 'hub' (van den Heuvel and Sporns, 2013). Indeed, lesions in the set of 23 randomly selected control stroke tracings were commonly functionally connected to the bilateral amygdala (15/23 lesions).

3.1.3 Mania-causing lesions are functionally connected to regions that are not connected to control lesions

Connectivity maps to mania lesions were compared to maps from control lesions. Three brain regions were significantly more likely to be functionally connected to mania-causing lesions than control lesions: 1) The bilateral temporal lobe, most prominently in the temporal poles but extending to the hippocampus, 2) The medial orbitofrontal cortex (OFC), and 3) Brodmann's area 46 (Dorso-Lateral Prefrontal Cortex, DLPFC) (Figure 3). The temporal regions and OFC were correlated with mania-causing lesions and the BA46 region was anti-correlated with mania-causing lesions. Notably, the areas of significant differences were *only* functionally connected to mania-inducing regions - none of the 23 random control

lesions were functionally connected to these regions. We observed the same pattern of differential connectivity to mania-causing lesions under multiple control comparisons i.e. when compared to random ischemic lesions, a distinct set of size matched ischemic lesions, and ischemic lesions traced in a single plane (Supplemental Figures 1, and 2). We also observed the same pattern of connectivity to mania-causing lesions when using a set of lesions that had been traced entirely independently by another study member (Supplementary Figure 3).

As an exploratory analysis, we asked if these network connectivity relationships could explain *all* cases of lesion-induced mania. 12 of 17 non-thalamic lesions were fully in locations functionally connected to the regions described above (i.e. regions that were not connected to *any* of the random control lesions). The 6 thalamic lesions that caused mania were all located in the right hemisphere and were functionally connected to the salience network.

We also performed a post-hoc analysis to reduce heterogeneity among the pathological mechanisms involved in mania-causing lesions. When we confined our lesions of interest to those resulting from an infarct (n=13) and compared these network maps to the 23 control lesions. We continued to observe the same mania lesion specific connectivity in the temporal lobes and orbito-frontal cortex, but the previously observed region of anti-correlation to mania-causing lesions in BA46 was no longer statistically significant (Supplemental Figure 4).

3.2 Extension of Lesion-induced Mania Studies to Bipolar Disorder Mania

3.2.1 Bipolar Disorder Longitudinally Scanned Participants—Bipolar participants were significantly more symptomatic on all measures (YMRS, MADRS, PANSS, PANSS positive sub-score) during the manic state than during the euthymic state (Supplemental Table 2). Increased MADRS scores in manic subjects were typically the result of high scores on the reduced sleep, concentration difficulties, and inner tension items. Symptom scales were not available for one participant who was euthymic on SCID. Medication regimens did not differ significantly between these two time points.

3.2.2 Networks Disrupted in Lesion-induced Mania are Disrupted in Bipolar Disorder Mania—We compared within-subject differences in functional connectivity between bipolar mania and euthymia in the three regions (temporal poles, OFC, and BA46) identified in lesion-induced mania above. Consistent with our original hypothesis, we observed significant and specific disruptions in connectivity (Figure 4): The temporal lobes ROI demonstrated decreased connectivity to the bilateral ventro-lateral prefrontal cortex (VLPFC) in mania compared to euthymia. No significant increases in connectivity to the temporal poles ROI in mania were observed. The BA46 ROI demonstrated increased connectivity to the left amygdala and dorso-medial prefrontal cortex in mania compared to euthymia. No significant decreases in connectivity to the BA46 ROI in mania were observed. Of note, BA46 is normally anti-correlated to the amygdala- this result along with decreased connectivity between temporal poles and VLPFC are consistent with a disruption of coordinated (i.e. either correlated or anti-correlated) activity in mania compared to

euthymia. The orbitofrontal ROI did not demonstrate significant differences in functional connectivity when comparing mania to euthymia.

The BA46-Left Amygdala ROIs connectivity showed a strong effect of mood state ($T(1,15)=6.236$, $p=.000016$, Cohen's $d=1.56$) with these regions effectively disconnected in mania (mean $zFC = -.022$) compared to euthymia (mean $zFC = -.252$). Temporal lobe- VLPFC connectivity also showed a strong effect of mood state ($T(1,15)=5.659$, $p=.000045$, Cohen's $d=1.42$) with these regions also effectively disconnected in mania (mean $zFC = -.003$) compared to euthymia (mean $zFC = .277$). See Supplemental Figure 5 for individual plots of connectivity in each participant in both time points.

Examining connectivity in these ROIs in both bipolar participants and longitudinally imaged HC participants to control for non-specific (e.g. scanner) effect, we continue to observe a statistically significant interaction : Using a mixed ANOVA with time as within-subject factor and diagnosis (bipolar vs HC) as a between group factor we continue to observe a significant time*state interaction in both the BA46-amygdala ROIs ($F(1, 29) = 14.203$, $p = .0001$, partial $\eta^2 = .329$) as well as the temporal lobe-Right VLPFC ROIs ($F(1, 29) = 14.734$, $p = .001$, partial $\eta^2 = .337$).

We did not observe any significant within-subject changes in medication regimen in the bipolar participants. Nevertheless, we re-performed these connectivity analyses with medication status as a time-varying covariate. These results remained highly significant (Supplemental Results). We did not exclude bipolar participants on the basis of a substance use disorder so we repeated these analyses excluding any participant that met criteria for a substance use disorder at either time point. This analysis continued to demonstrate significant effects of mood with similar or stronger effect sizes (Supplemental Results).

3.2.2 Partial Replication of Bipolar Disorder Results in an Independent Cohort.—Reproducibility in clinical neuroimaging studies is a significant concern. We sought to replicate our longitudinal bipolar imaging analysis in an independent cohort. While we did not have access to another cohort of bipolar patients with longitudinal imaging across mood states, we were able to make a cross-sectional comparison of two groups of bipolar disorder type I participants: One group imaged in a manic state ($n=26$) and the other imaged in a euthymic state ($n=21$) (Clinical / demographic information in Supplemental Table 3). We examined functional connectivity between regions identified in the lesion network analysis and in the longitudinal bipolar cohort. We observed the same pattern of disconnectivity between the temporal lobe ROI and the right VLPFC in the bipolar mania cohort when compared to the bipolar euthymia cohort. (Figure 5). We did not observe the mood state dependent differences in BA46 connectivity that we observed in the longitudinal cohort.

4. Discussion

Here we observe that mania-causing lesions do not show significant anatomic co-localization but instead impinge upon shared brain networks. Two patterns of network localization are observed: For non-thalamic lesions, mania-causing lesions differed from

non-mania-causing lesions via a pattern of connectivity whose distribution includes territories (OFC, BA46, temporal poles) that were not connected to control lesion locations. All thalamic lesions that caused mania were functionally connected to the salience network, suggesting that disruption of the thalamic node of this network may have different behavioral consequences than disruption of other nodes in this network, consistent with recent discovery that the thalamus controls cortical functional connectivity (Schmitt et al., 2017).

Furthermore, fMRI data from bipolar participants scanned longitudinally across mood states demonstrated disruption in these same networks. Specifically, we observed disconnectivity in mania to structures previously implicated in the pathophysiology of bipolar disorder (i.e. amygdala and VLPFC) but heretofore not linked causally to mania (Blond et al., 2012; Chase and Phillips, 2016; de Zwarte et al., 2014; Womer et al., 2009)). Most imaging studies of bipolar disorder identify signals in these structures either by investigating these regions as *a priori* regions of interest or using paradigms known to activate these structures (e.g. emotion processing tasks). Here, we identify empirically that completely distinct pathophysiological processes converge on both a shared behavioral phenotype and shared network disruption, particularly in structures long implicated in bipolar disorder pathophysiology.

While this work draws upon a convergence of multiple pathological processes to identify a shared network basis for mania, all of these analyses rely on a single imaging modality (rsfMRI connectivity). Other imaging modalities, however, also implicate this network in bipolar disorder. Two recent studies examined structural connectivity and controllability (i.e. how neuronal activity propagates in local networks) in both bipolar participants and participants at genetic high risk for bipolar disorder (Jeganathan et al., 2018; Roberts et al., 2018). Structural (as opposed to functional) MRI data analysis identified structural dysconnectivity and control deficits in high risk participants in a right-lateralized network involving dorsomedial and ventrolateral prefrontal cortex, the superior temporal pole, putamen, and caudate nucleus, which all correspond to the territories identified in our analysis.

5. Limitations

Methodological limitations of our study include: 1) Reliance on external reports of symptomatology and characterization by studying published case reports. Standardized reporting of symptom severity (e.g. Young Mania Rating Scales, SCID criteria for a manic episode) are not available in these cases or in any other syndromes analyzed using lesion network mapping (Boes et al., 2015; Darby et al., 2018; Darby et al., 2017; Fasano et al., 2017; Laganieri et al., 2016). Despite this limitation, the cases analyzed demonstrate a significant network co-localization that also distinguishes them from randomly selected brain lesions and supports the hypothesis that these cases share a common biological feature of network co-localization. 2) We are limited to discovering lesions that are survivable and allow a conscious patient to express the symptoms of mania. This likely limits the number of territories that can be afflicted. 3) We used HC rsfMRI data to estimate patterns of network connectivity that would be disrupted by lesions. The patients in the lesion-induced mania

studies were, on average, older than our HC dataset and therefore might have age-related differences in intrinsic connectivity from the HC dataset. We decided to use this HC dataset because it was collected on the same scanner, using the same scan sequence as the bipolar participant data. Prior reports comparing lesion network mapping rsfMRI data between young and elderly participants did not give divergent results (Boes et al., 2015). 4) The control lesions used for comparison to mania-causing lesions were taken from an open resource that did not detail patient post-stroke behavior. It is possible, though exceedingly unlikely, that these control lesions could have contained a lesion that caused mania. This would presumably cause a false negative result.

Limitations in imaging bipolar participants include: 1) Motion confounds of rsfMRI data are an obvious concern when imaging manic patients. We attempted to minimize motion confounds through a combination of procedures that have been shown effective in removing spurious motion effects (Power et al., 2014; Yan et al., 2013). 2) The participants of our study were taking medications at the time of imaging. Our hypothesis that a within-subjects design would minimize medication changes between scans was proven correct, as we found no significant differences in regimens between mood states. The preponderance of evidence in bipolar neuroimaging suggests that medications effects normalize differences rather than exacerbate them (Hafeman et al., 2012). From both an ethical and a pragmatic standpoint, imaging participants while hospitalized for mania, but un-medicated, and then re-imaging while in a euthymic, un-medicated state appears untenable and unfeasible. 3) The number of participants in our longitudinal bipolar cohort was limited (N=16). It should be noted that the study cohort was more than adequately powered to detect effects of the magnitude we describe here.

6. Conclusions

We hypothesize that both circumscribed anatomical lesions and bipolar disorder can give rise to the same manic phenotype via disruption of mediating brain networks. Specifically, these networks can be disrupted by either acute injury at critical nodes (e.g. temporal lobe stroke) or by an interaction between environmental stressors and heritable pathology (e.g. altered signal transduction (Tobe et al., 2017) or excitability (Mertens et al., 2015)) (Figure 6). The networks identified are consistent with existing models positing that mania results from a loss of ventral prefrontal modulation of limbic brain areas (Strakowski, 2012)

While our findings support a hypothesis that disruption of this network is causally related to mania, this study is observational in nature. That said, we constrained our testable hypotheses by analyzing cases where a brain injury appears causally linked to mania, and then tested these networks in bipolar disorder. Definitive testing of this hypothesis will require a non-human (e.g. primate) model system. One implication of our findings is that our approach may be generalizable to other symptoms and behaviors. Traditionally, animal models of psychiatric disorders are developed using perturbations of unclear relationships to disease pathology in humans (e.g. manipulation of candidate genes) followed by a search for plausible mouse behavioral analogues of human symptoms (e.g. motor activity). The convergence of genetically determined and lesion-based causes of psychiatric symptoms on a finite set of circuit targets, provides an opportunity for a conceptual advance. Our method

of circuit identification may allow scientifically-based prospective laboratory models based on pathophysiology rather than behavioral output.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Establishing causal links between fMRI findings and behavior is a challenge
- Brain lesions that cause mania present an opportunity to understand bipolar mania
- Mania causing lesions selectively disrupt specific brain networks
- These networks are also strongly and significantly disrupted in bipolar mania
- We present a model of how network disruption gives rise to the manic phenotype

Figure 1: Tracings of Lesions that Induced Mania

Lesion location of 23 cases of lesion-induced mania, traced onto a standard template brain.

Horizontal sections are oriented with the right side of the brain on the reader's left.

Figure 2: Network Mapping for Mania-inducing Lesions

23 mania-causing lesions were traced from published images in case reports onto a template brain (column A). Each lesion tracing was used as a ROI for mapping functional connectivity to this region in healthy control subjects (B), allowing visualization of the network disrupted by the lesion. Regions of positively correlated activity to the ROI are shown in hot colors and negatively correlated activity in cold colors. These lesion network maps were overlaid to identify convergent areas of network connectivity among mania-inducing lesions (C). Left Color Bar: T-statistic. Right Color Bar: Number of lesion maps converging on a given voxel.

Figure 3: Anatomical Specificity of Lesion-induced Mania

Network connectivity to mania-causing lesions is compared to network connectivity in a set of control stroke lesions. A voxelwise Lieberman test reveals regions significantly (p -FDR $< .05$) more functionally connected to mania-causing lesions than controls lesions. Regions of positively correlated activity to the ROI are shown in hot colors and negatively correlated activity in cold colors. Three regions of significant differences in connectivity were observed: The Orbitofrontal Cortex (OFC), the bilateral temporal lobe, and the bilateral Dorso-Lateral Pre-Frontal Cortex (DLPFC, Brodmann Area 46). The OFC and temporal lobes were intrinsically correlated with areas of mania-causing lesions. BA46 was intrinsically anti-correlated with mania-causing lesions. None of the control lesions were connected to these areas. Color Bar: Z-stat.

Figure 4: Lesion-induced and Bipolar Mania Converge On Shared Network Dysconnectivity

We sought to determine if the networks identified in the lesion mapping analysis of mania were also disrupted in bipolar mania. Using the regions identified in lesion-induced mania as ROIs, we compared functional connectivity to these areas in participants with Bipolar Disorder type I imaged in a manic state and then in a euthymic state. A) Using the temporal pole ROIs from lesion network mapping (inset), we observe disconnection in mania to the bilateral Vento-Lateral Pre-Frontal Cortex (VLPFC) (Right: $k=47$, peak voxel T-stat 5.89 $p<.001$, $x+57$ $y+27$ $z0$; Left: $k=32$, peak voxel T-stat 5.39 $p<.001$, $x-54$, $y+21$, $z-3$). B) The BA46 ROIs from the lesion mapping analysis (inset) demonstrate increased connectivity in mania to the left amygdala ($k=29$, peak voxel T-stat 4.74, $p<.001$, $x-21$ $y0$ $z-24$). Here increased connectivity indicates dis-connectivity between normally anti-correlated structures. BA46 also demonstrated increased connectivity to the dorso-medial Pre-Frontal Cortex (dmPFC) ($k=32$, peak voxel T-stat 4.97, $p<.001$, $x-12$, $y+9$, $z+36$). A set of healthy comparison participants imaged longitudinally across these time points did not demonstrate any significant change in connectivity in these regions. Images are thresholded voxelwise $p<.001$, cluster-extent $p<.016$. Color Bar: T-stat.

Figure 5: Replication of Temporal-VLPFC Disconnectivity in Bipolar Mania Compared to Euthymia

We sought to determine if the networks identified in the lesion mapping analysis of mania also disrupted in bipolar mania. Using the regions identified in lesion-induced mania as ROIs, we compared functional connectivity to these areas in participants with Bipolar Disorder type I imaged in a manic state and then in a euthymic state. A) Using the temporal pole ROIs from lesion network mapping (inset), and examining the VLPFC regions identified in the longitudinal analysis (Figure 4), we again observe disconnectivity in mania to the bilateral Ventro-Lateral Pre-Frontal Cortex (VLPFC) (Right: $k=52$, peak voxel T-stat 3.78, $p<.001$, $x=45$ $y=30$ $z=-9$; Left: $k=23$, peak voxel T-stat 3.33 $p=.001$, $x=51$, $y=27$, $z=-9$). While the VLPFC of both hemispheres showed reduced connectivity to the temporal lobe ROIs in mania, only the right VLPFC met extent significance ($k=33$ for $p<.025$ corrected for multiple comparisons). Images are thresholded voxelwise $p<.05$. Color Bar: T-stat.

Figure 6: A Model of The Network Basis of Mania

We propose that multiple causes of mania converge on the same networks and that it is disruption of distributed brain networks that mediate the link between pathophysiology and behavioral phenotype. Specifically, this network can be disrupted by either acute lesioning of critical nodes of this network (e.g. temporal lobes, OFC) or may be due to a combination of genetic factors and environmental stressors that give rise to manic episodes in bipolar disorder. In either scenario, the disruption of communication across polysynaptic networks causes the manic phenotype. Within these networks, longitudinal imaging data supports disconnection between (A) Temporal poles and VLPFC and (B) Between amygdala and DLPFC (BA46) as causes of mania in bipolar disorder. Arrows here are not meant to denote a monosynaptic pathway.