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ORIGINAL ARTICLE

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Lithium monotherapy associated longitudinal effects on resting state brain networks in clinical treatment of bipolar disorder

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Abstract

Objectives: Lithium is one of the most effective and specific treatments for bipolar disorder (BP), but the neural mechanisms by which lithium impacts symptoms remain unclear. Past research has been limited by a reliance on cross-sectional designs, which does not allow for identification of within-person changes due to lithium and has not examined communication between brain regions (ie, networks). In the present study, we prospectively investigated the lithium monotherapy associated effects in vivo on the brain connectome in medication-free BP patients. In particular, we examined the within-person impact of lithium treatment on connectome indices previously linked to mania and depression in bipolar disorder.

Methods: Thirty-nine medication-free subjects – 26 BP (13 (hypo)manic and 13 depressed) and 13 closely matched healthy controls (HC) – were included. fMRI data were obtained at 3 timepoints: baseline, after 2 weeks, and after 8 weeks (total of 117 scans: 78 BP and 39 HC scans). BP subjects were clinically treated with lithium for 8 weeks while HC were scanned at the same time points but not treated. Graph theory metrics and repeated measures GLM were used to analyze lithium treatment associated effects.

Results: Consistent with hypotheses, lithium treatment was associated with a normalizing effect on mania-related connectome indices. Furthermore, shifts in both mania- and depression-related connectome indices were proportional to symptom change. Finally, lithium treatment-associated impact on amygdala function differed depending on baseline mood.

Conclusions: Present findings provide deeper insight into the therapeutic neural mechanisms associated with lithium treatment.

KEYWORDS
bipolar, brain networks, depression, graph theory, lithium, mania

1 | INTRODUCTION

Lithium remains one of the most effective and specific treatments for bipolar disorder (BP),[1,2] and is used for both the manic and depressive phases of BP.[3] Furthermore, lithium is an effective prophylactic treatment for preventing future manic and depressed episodes[4,5] and has consistently been shown to decrease suicides and overall mortality.[6] However, despite decades of use, the neural mechanisms by which lithium impacts symptoms remain unclear. Lithium administration has been associated with effects on biological systems at various levels – from molecular effects on gene expression and signal transduction to neurotrophic effects on brain structure.[7-11] However, lithium-associated longitudinal effects on functional brain networks has not been investigated to date. In the present study, for

the first time, we prospectively investigated lithium monotherapy-associated effects in vivo on the brain connectome in medication-free hypomanic/manic and depressed patients.

A large body of BP research implicates dysfunction in both regional activation and brain networks supporting emotion regulation.[12,13] Meta-analyses of regional activation indicate that structures involved in top-down control (eg, prefrontal cortex) may be *hypo*active, whereas structures crucial for bottom-up affective salience (eg, amygdala) may be *hyper*active.[14-16] In turn, imbalance between systems could lead to (hypo)mania and depression.

Mounting evidence also supports the existence of BP-related disturbances in functional networks (mapped via resting-state fMRI).[17] Recently, we used a functional connectomic approach in a sample of both hypomanic/manic and depressed BP patients to identify brain network disturbances associated with BP.[18] Employing graph-theory techniques, we identified unique connectome disturbances associated with each BP mood state. The use of graph theory methods was important, as these techniques take into account the role of a node or connection within the greater network, unlike typical methods which usually focus on pairwise connections. In particular, graph methods examine the *functional organization* of networks, which in turn provides insight into emergent properties (eg, communication efficiency) of both the global network and specific regions. In Spielberg et al,[18] higher levels of mania symptoms, as measured by the Young Mania Rating Scale (YMRS),[19] were associated with worse global network communication efficiency (Global Efficiency), suggesting that overall information flow across the brain appeared to be less effective at higher levels of YMRS. We also found that higher YMRS was associated with (a) higher interconnectivity in the local network surrounding right amygdala (Clustering Coefficient) and (b) higher connectivity within a sub-network centered on amygdala.[18] Given that this sub-network included a number of connections between amygdala and sensory association regions, we suggested that hyperconnectivity between amygdala and such regions may reflect a form of hyper-salience in which "affective significance is inappropriately overlaid on perception" (p. 3021).[18]

Spielberg et al[18] also found that higher levels of depression, as measured by the Hamilton Depression Rating Scale (HAMD),[20] were associated with less resilience against disruption in the global network (Assortativity), suggesting that network processing was less stable at higher levels of HAMD. Similarly, we found that higher levels of HAMD were associated with (a) higher interconnectivity in the local network surrounding left orbitofrontal cortex (OFC) (Clustering Coefficient), and (b) higher connectivity within a network centered on OFC.[18] Given the role of OFC in maintaining the motivational value of stimuli,[21] and that biases in affective value are often observed in depression,[22] we interpreted these last two effects as potentially indicating that depressed individuals may be engaging in more intense/frequent value-related processing, potentially because they are less able to discriminate value and attempt to compensate by overengaging OFC.[18] Given the effectiveness of lithium for all states of BP, it is reasonable to expect that lithium therapy will be associated with significant effects on the functional connectome across mood states. Surprisingly, lithium therapy associated changes in the functional connectome, and how it relates to behavioral change, have not been investigated to date.

Mounting evidence suggests a neurotrophic effect of lithium,[23] and such effects could restore the integrity of the corticolimbic circuits involved in mood regulation, via greater neuronal plasticity.[24-26] While meta-analyses[27,28] and data from an international consortium[29] have provided evidence of neural changes associated with lithium, a number of studies have also reported no change.[23] One major methodological issue is that the majority of studies are cross-sectional, comparing patients on lithium (and for a variable period of time) to those not currently on lithium. This does not allow for identification of within-person changes due to lithium, which is crucial for identifying the precise neural mechanisms at play. In many of these studies, participants were also taking other medications, which confounds identification of specific lithium-associated effects.

To address these issues, we longitudinally examined lithium monotherapy-associated effects on the functional connectome in patients who were medication-free at baseline (and only receiving lithium at follow-up). Importantly, all patients were currently either hypomanic, manic, or depressed at baseline. Using an overlapping sample with this study, Altinay et al[30] examined the impact of lithium on connectivity between amygdala and ventral and medial PFC. Overall, they found that connectivity between amygdala and medial OFC/subgenual anterior cingulate cortex (ACC) increased in BP patients (but not healthy controls) after lithium treatment, and this pattern also emerged when examining hypomanic and depressed BP patients separately. In addition, increased connectivity between amygdala and OFC/ACC was associated with greater global improvement.

Although interesting, these findings do not provide insight into restructuring of the *functional organization* of networks. For example, is lithium associated with improvements in the communication efficiency of the network? As mentioned above, such questions can be tested using graph theory techniques, and thus these methods can be used to delineate the functional mechanisms by which lithium contributes to altered network structure and behavioral changes in BP.

Given that we previously identified baseline associations between graph metrics and mania and depression in BP,[18] we wanted to determine whether these differences were normalized by lithium treatment (see Table 1 for a summary of each property examined). Thus, the present study examined change over time in (a) Global Efficiency, (b) right amygdala Clustering Coefficient, and (c) mean connectivity in an amygdala-centered network (all previously associated with YMRS), along with change over time in (d) Assortativity, (e) left OFC Clustering Coefficient, and (f) mean connectivity in an OFC-centered network (all previously associated with HAMD) to determine whether the metrics found in Spielberg et al[18] showed normalization after lithium treatment. Data for the present study were collected in 3 waves: baseline, 2 and 8 weeks. We predicted that lithium would normalize network disturbances observed in our previous work.

TABLE 1 Graph theory network metrics

Metric category	Metric
Resilience: Vulnerability of network to disruption	*Assortativity*: Extent to which network has "backup" hubs in case main communication hubs become disrupted
Segregation: Optimization of network for specialized processing	*Clustering Coefficient*: Communication efficiency in local sub-network
Integration: How well network combines information across distributed regions	*Global Efficiency*: Extent to which global network is able to communicate efficiently

2 | MATERIALS AND METHODS

This research was conducted with the approval of the Indiana University Hospital Investigational Review Board. Informed consent was obtained from all participants prior to beginning any study procedures.

2.1 | Participants

Participants (ages = 18-60) were recruited via the Indiana University Hospital outpatient psychiatry clinic and community advertisement. Patients were included if they satisfied DSM-IV-TR criteria for BP and were willing to be treated with lithium monotherapy (both BP I and II included). Diagnoses were determined via Mini International Neuropsychiatric Interview[31] and a clinical interview by a psychiatrist (AA). Patients were rated on the Hamilton Depression Rating Scale (HAMD) and Young Mania Rating Scale (YMRS) during screening and all three scanning days. Healthy controls (HC) were also scanned at all three timepoints but did not receive lithium.

All participants were medication-free at baseline (including "rescue" medications, eg, benzodiazepines) for ≥2 weeks prior to study inclusion and many for much longer. Participants were medication-free at baseline, because they (a) had never been diagnosed, (b) could not afford medication, and/or (c) did not want to take medication (eg, they had been euthymic until recently, and did not want to take medication while euthymic). Importantly, all enrolled participants were already medication-free at the initial screening, and thus were never encouraged to cease medication in order to take part. Scanning was arranged to be as soon as possible after screening, usually within a week.

Patients were largely moderately depressed or hypomanic. Although participants were medication-free at baseline, they reported having had multiple hypomanic/manic and/or depressive episodes for many years, consistent with epidemiological studies which note high rates of BP in community samples and a large proportion not receiving treatment.[32]

Exclusion criteria were: schizophrenia/schizoaffective, current primary anxiety disorder, fluoxetine use over past 4 weeks, acute suicidal/homicidal ideation/behavior, recent/current inpatient hospitalization, past year substance dependence (except nicotine), positive toxicology screening, recent (<1 week) alcohol use, serious medical/neurological illness, current pregnancy/breast feeding, metallic implants or other contraindications to MRI. Exclusion criteria for HC also included personal/family history of psychiatric illness.

2.2 | Lithium treatment

Immediately after the baseline scan, BP subjects began lithium treatment: 300 mg p.o. BID. Levels were checked after one week, and when necessary lithium was increased to achieve trough levels between 0.5-1.0 mEq/L, depending on efficacy and tolerance. Lithium levels were also checked near the time of the second and third scans. Patients were educated in detail about the side effects of lithium, ways to avoid these side effects, and how to contact the research team in case of uncomfortable side effects.

2.3 | MRI acquisition

Scans were performed using a Siemens 3 T Tim Trio. Resting-state scans were T2*-weighted gradient EPIs (TR/TE 2250/29 ms, 2.5 × 2.5 × 3.5 mm voxels, GRAPPA factor = 2) 5:33 min in length (sufficient for connectivity estimates to stabilize[33]). Participants were instructed to lie awake with eyes closed and to not think about anything in particular. They were asked post-scan whether they remained awake. Scanning procedures were identical across waves.

2.4 | MRI preprocessing

The images were corrected for physiological noise[34-36] using signals obtained with PESTICA (Physiologic Estimation by Temporal ICA).[37] Motion correction was performed using SLice-Oriented MOtion Correction,[34] which partials out physiologic noise in parallel (estimated via temporal ICA).[37] Timeseries obtained from eroded

white matter/ventricular masks were partialled,[38] and bandpass filtered (0.008-0.08 Hz) via 3dBandpass.[39] Participants with ≥15 motion-corrupted (>2 mm displacement) volumes were excluded from analysis.[36]

We used the same ROI atlas as in our previous study: a 195-ROI atlas created via spatially constrained spectral clustering of resting-state fMRI.[40] A resting-fMRI-based atlas was used, because such atlases are thought to better reflect the organization of the brain into functionally homogenous units. ROI timeseries were extracted (first principal component across timeseries for all ROI voxels) and used to compute a Pearson correlation matrix per participant, per timepoint.

2.5 | Dependent variables

Dependent variables were calculated separately at each timepoint. Dependent variables were those found in Spielberg et al[18] to be associated with YMRS and HAMD scores in BP. Specifically, that study identified a network in which interconnectivity was positively correlated with YMRS (Figure 1A). In the present work, a single value (per time point) for this network was computed by averaging connectivity across links in the network. Similarly, that study identified a network in which interconnectivity was positively correlated with HAMD, and a single mean value (per time point) for this network was computed for the present study. Note that a mean value (across links) was computed for these networks (vs examining each link individually) in order to be able to examine change in the overall network, which should be more reliable than individual links. Thus, correction for multiple comparisons across links was not needed in the present work.

In addition to these networks, Spielberg et al[18] identified several graph properties that were correlated with YMRS or HAMD. In particular, YMRS was negatively correlated with Global Efficiency and positively correlated with right amygdala Clustering Coefficient. HAMD was negatively correlated with Assortativity and positively correlated with right

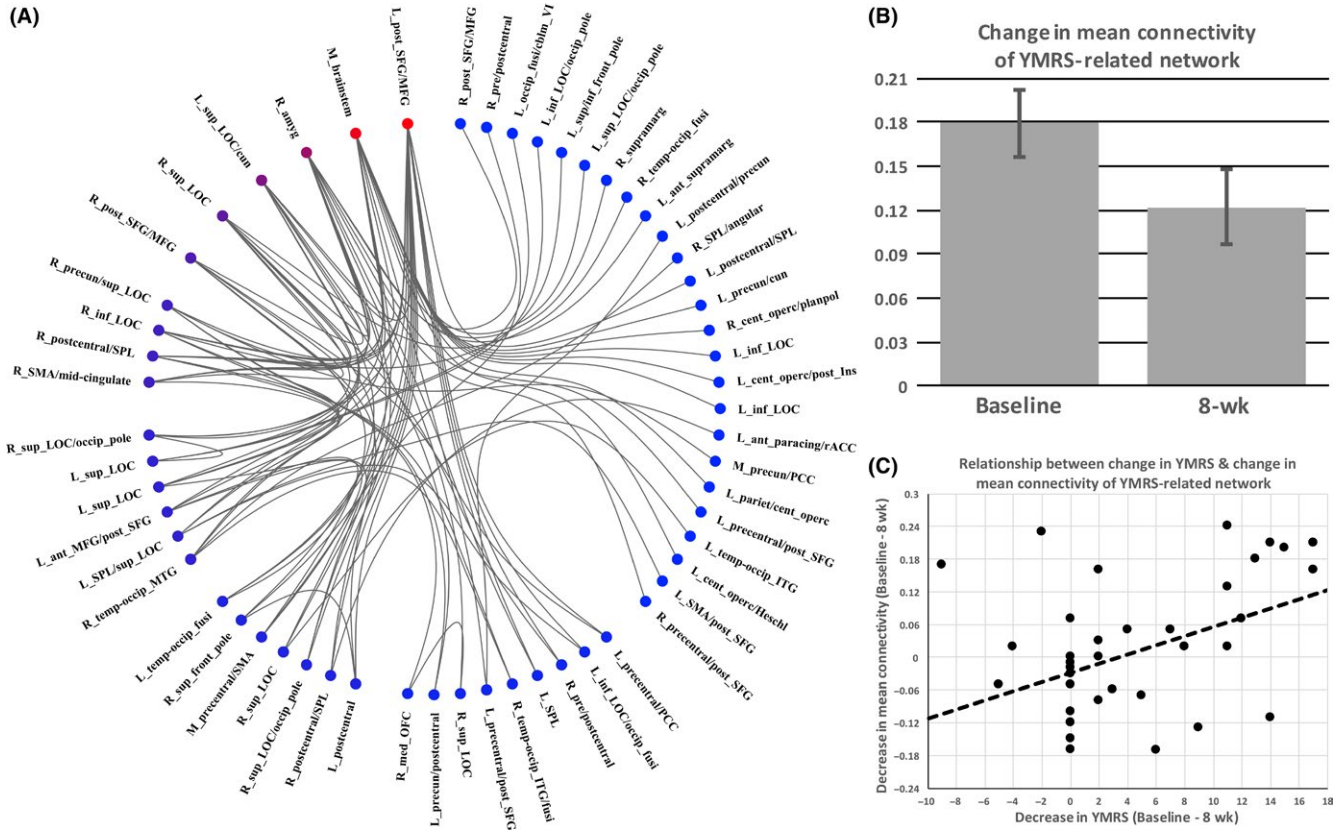

FIGURE 1 Impact of lithium on network previously linked to manic symptoms. (A) Connectivity diagram for the network previously found[18] to have stronger interconnectivity with higher values on the Young Mania Rating Scale (YMRS). Note that this diagram does not itself reflect a finding from the present study. This diagram was included because change over time in the mean link weight for this network was examined in the present study. (B) Lithium-related decreases from baseline to 8-weeks in mean connectivity of the network pictured in 1A (averaged across all BP patients). Error bars reflect the standard error. (C) Positive relationship between change over time in YMRS symptoms (*x*-axis) and change in mean connectivity (*y*-axis). R, right; L, left; M, midline; ant, anterior; post, posterior; sup, superior; inf, inferior; med, medial; cent, central; temp, temporal; pariet, parietal; occip, occipital; fusi, fusiform; cblm, cerebellum; amyg, amygdala; cun, cuneus; Ins, insula; ITG, inferior temporal gyrus; LOC, lateral occipital cortex; MFG, middle frontal gyrus; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; operc, opercular cortex; paracing, paracingulate gyrus; PCC, posterior cingulate cortex; planpol, planum polares; precun, precuneus; rACC, rostral anterior cingulate cortex; SFG, superior frontal gyrus; SMA, supplementary motor area; supramarg, supramarginal gyrus; SPL, superior parietal lobule

posterior-middle orbitofrontal gyrus Clustering Coefficient. Global Efficiency is a property of the global network and indexes overall integration. Higher values indicate greater efficiency of overall network communication, with efficiency measured as the extent to which each pair of nodes is connected via the fewest possible paths. Clustering Coefficient is a property of each node and indexes local network segregation. Higher values indicate greater clustering around a node, and clustering is the extent to which neighbors of a node are also connected to each other. Assortativity is a property of the global network and indexes overall network resilience. Higher values indicate greater resilience to disruption, with resilience measured as the extent to which highly-connected nodes are linked to other highly-connected nodes (ie, extent to which there is redundancy in key communication hubs).

To compute graph properties, connectivity matrices were entered into the Graph Theory GLM (GTG) toolbox v.44,[41,42] which uses the Brain Connectivity Toolbox.[43] Each matrix was first thresholded to include only positive connections. Unlike some studies which use higher (and often multiple) density thresholds and which binarize networks, we used only one threshold (zero) and retained link weights. This was done, because other strategies remove important information[44] and were employed historically because methods were not available for weighted networks. A zero threshold was used, because positive and negative weights are typically analyzed separately.[44]

2.6 | Statistical analyses

Permutation-based repeated-measures GLMs (5000 permutations) were conducted in GTG. Time was the repeated measure, with the initial comparison being baseline vs 8 weeks. When this comparison was significant, we examined the two constituent comparisons (ie, baseline vs 2 weeks, 2 vs 8 weeks) to better isolate when change occurred.

The main effect of time was examined to identify changes associated with lithium across BP patients only (healthy controls were not included initially, as they did not receive lithium). For all significant effects, the analysis was redone in all participants using change in HC as a comparison, thus ensuring that all observed changes were not due to simple variation over time. Specifically, a BP vs HC variable was entered as a predictor, with time as the repeated measure. In these analyses, a predictor modeling BP groups was entered as a covariate of no interest.

Next, we tested whether the main effect of time differed between the hypomanic/manic and depressed groups, in order to test whether the impact of lithium varies with baseline mood. Specifically, a hypomanic/manic vs depressed variable was entered as a predictor, with time as the repeated measure (only BP patients included in this analysis).

Finally, we examined the correlation between change in symptoms (YMRS, HAMD) and change in networks/properties. Specifically, symptom change scores were computed (eg, HAMD = HAMD at baseline–HAMD at 8 weeks) and entered as predictors, with time as the repeated measure. Thus, these analyses tested whether lithium-related change in symptoms (ie, YMRS, HAMD) predicted change in network interconnectivity/graph properties. Both YMRS and HAMD were entered simultaneously as continuous predictors, isolating unique variance associated with each set of symptoms. Bipolar subtype and mean and quadratic DVARS for both time points were covariates of no interest for all analyses (as done in Ref. [18]). DVARS[45] estimates the spatial standard deviation of successive difference images, and this measure is sensitive to motion-related shifts in signal. Thus, including DVARS helps to reduce the impact of motion-related variance. For these analyses, HC were included (along with BP patients) to provide a comparison to control for repeated effects, to effectively separate variance unique to YMRS and HAMD, and to ensure an appropriate multivariate distribution.

In order to limit the number of comparisons, YMRS was only examined as a predictor for network/graph properties found to be associated with YMRS in Spielberg et al[18] and similarly for HAMD. The main effect of time (ie, lithium) and BP group comparison were examined for all networks/properties. Only significant effects are reported.

2.7 | Post-hoc power analysis

Given the relatively small within-group sample sizes, we conducted a post-hoc power analysis to estimate the smallest effect size that was detectable. Specifically, we used G*Power ($\alpha = 0.05$, $\beta = 0.80$) to determine the effect size needed for a significant within-subject effect or within-between interaction in a repeated-measures ANOVA. The required Cohen's f effect size was $f = 0.29$ for both 26 and 39 participants, which correspond to "medium" effects. It is important to note that, because we used a repeated-measures design, we were able to detect smaller effects than would be possible with a solely between-subject design.

3 | RESULTS

3.1 | Participants

A total of 29 patients completed 8 weeks of treatment, and data from 3 were excluded because of poor data quality, missing scan, or excessive motion. No patients reported falling asleep during any scans. Close gender/age match was achieved across 13 bipolar hypomanic/manic, 13 bipolar depressed, and 13 healthy controls (see Table 2 and Supporting Information, for demographics, illness characteristics, and other participant information). Two of the BP participants included in this analysis reported a change in their mood state from screening to scan day. HAMD and YMRS ratings indicated that one was predominantly manic (17-item HAMD = 6; YMRS = 13) on scan

day, and this participant was included in the hypomanic/manic group in the BP group-wise analysis. The second patient was predominantly depressed (HAMD = 19; YMRS = 5) and was included in the depressed group. In the hypomanic/manic group, one participant was in a manic episode at baseline, and the others were in hypomanic episodes. No groups significantly differed in age, gender, ethnicity, or BP subtype.

3.2 | Longitudinal analyses

In order to ensure that we were examining lithium-related change in indices that were disturbed in BP at baseline, we only analyzed effects from Spielberg et al[18] that replicated in the present sample (see Supporting Information for further detail). For all effects, the N used in that particular analysis is noted below for clarity: n = 26 indicates that all BP patients were included, n = 39 indicates that BP patients and healthy controls were included. No analyses used a sample smaller than 26. See Table 3 for a summary of all effects.

3.3 | Lithium treatment-associated changes over time in BP

3.3.1 | Baseline vs 8 weeks

Both YMRS (t_{25} = 4.58, P < 0.001, n = 26) and HAMD (t_{25} = 2.31, P = 0.029, n = 26) evidenced decreases over time (see Table S1 for means and standard deviations). The network pictured in Figure 1A showed decreased mean connectivity over time (Figure 1B; $F_{(1,25)}$ = 5.51, P = 0.023, n = 26). In Spielberg et al,[18] this network evidenced hyperconnectivity at higher levels of YMRS. Decreased connectivity in this network in BP participants was also significant when connectivity in HC was used as a comparison ($F_{(1,37)}$ = 13.78, P < 0.001, n = 39).

3.3.2 | Baseline vs 2 weeks

Both YMRS (t_{25} = 5.42, P < 0.001, n = 26) and HAMD (t_{25} = 3.26, P = 0.003, n = 26) evidenced decreases over time.

TABLE 2 Demographics & illness characteristics

	BP (n = 26)	BP-M (n = 13)	BP-D (n = 13)	HC (n = 13)
Age	34.5 (12.0)	32.5 (12.4)	36.6 (11.8)	32.8 (9.4)
Female	14 (53.8%)	9 (69.2%)	5 (38.4%)	8 (61.5%)
African American	1 (7.7%)	1 (7.7%)	1 (7.7%)	2 (15.4%)
BP subtype I	12 (46.2%)	8 (61.5%)	4 (30.8%)	—
Age at first episode (based on retrospective report)	13.2 (4.5)	12.1 (4.1)	14.3 (4.7)	—
Months off medication prior to scan	33 (35)	31 (39)	36 (33)	—
# of prior depressed episodes	>20	>20	>20	—
# of prior (Hypo)manic episodes	>20	>20	>20	—
Weeks in current episode	4 (4)	2 (2)	7 (5)	—

Cell entries represent either means, with standard deviations in parentheses, or frequencies with percentage in parentheses.
BP, bipolar patients; BP-M, patients in hypomanic/manic episode at baseline; BP-D, patients in depressed episode at baseline.

TABLE 3 Relationships with change in network metrics from baseline to 8 weeks

	Previously related to YMRS in Spielberg et al[18]		Previously related to HAMD in Spielberg et al[18]	
	Connectivity in Amygdala-centered network	Right Amygdala clustering coefficient	Connectivity in OFC-centered network	Global assortativity
Change over time in BP (n = 26/39[a])	↓	ns	ns	ns
Differential change over time in BP-M vs BP-D (n = 26)	ns	↓ for BP-M ↑ for BP-D	ns	ns
Correlation with change over time in YMRS (n = 39)[b]	↓ YMRS related to ↓ Connect.	ns	n/a	n/a
Correlation with change over time in HAMD (n = 39)	n/a	n/a	ns	↓ HAMD related to ↑ Assort.

BP, bipolar patients; BP-M, patients who were hypomanic/manic at baseline; BP-D, patients who were depressed at baseline; YMRS, Young Mania Rating Scale; HAMD, Hamilton Depression Rating Scale; Connect., mean network connectivity; Assort., global Assortativity; ns, not significant.
[a]Also significant when compared against healthy controls.
[b]Also significant for baseline vs 2 weeks pairwise comparison.

3.3.3 | 2 weeks vs 8 weeks

No significant findings.

3.4 | Differential effects associated with lithium treatment over time in hypomanic vs depressed patients

3.4.1 | Baseline vs 8 weeks

Patients who were hypomanic (at baseline) significantly differed from depressed patients in change over time of right amygdala Clustering Coefficient ($F_{(1,24)} = 4.77$, $P = 0.032$, n = 26), which was previously found to be elevated at higher levels of manic symptoms.[18] In particular, the present study found that right amygdala Clustering Coefficient decreased over time in the hypomanic group, whereas increases were noted in the depressed group (Figure 2). Neither of these shifts over time were significant when examined within each group.

3.4.2 | Baseline vs 2 weeks

No significant findings.

3.4.3 | 2 weeks vs 8 weeks

No significant findings.

3.5 | Network shifts associated with change in YMRS over time

3.5.1 | Baseline vs 8 weeks

YMRS decreases over time were related to decreases in mean connectivity of the Figure 1A network (Figure 1C; $F_{(1,31)} = 7.12$, $P = 0.014$, n = 39).

3.5.2 | Baseline vs 2 weeks

YMRS decreases over time were related to decreases in mean connectivity of the Figure 1A network ($F_{(1,31)} = 5.08$, $P = 0.025$, n = 39).

3.5.3 | 2 weeks vs 8 weeks

No significant findings.

3.6 | Network shifts associated with change in HAMD over time

3.6.1 | Baseline vs 8 weeks

Decreases in HAMD over time were related to increases in Assortativity (Figure 3; $F_{(1,31)} = 8.98$, $P = 0.010$, n = 39), which was previously found to be negatively related to HAMD.[18]

3.6.2 | Baseline vs 2 weeks

No significant findings.

3.6.3 | 2 weeks vs 8 weeks

No significant findings.

4 | DISCUSSION

The present study provides an initial window into the neural mechanisms by which lithium impacts symptoms of bipolar disorder. Using a sample comprised of medication-free hypomanic/manic or depressed BP patients, we prospectively investigated changes associated with lithium monotherapy in vivo on indices of the functional brain connectome that were previously linked to manic and depressive symptoms.[18] Consistent with our hypotheses, lithium clinical treatment was associated with a normalizing effect on mania-related connectome indices over an 8-week period. Importantly, shifts in both mania- and depression-related connectome indices were proportional to symptom change, more directly supporting the idea that connectome indices reflect key pieces of the neural mechanisms by which lithium impacts symptoms.

4.1 | Normalizing lithium monotherapy-associated effects on connectome indices

As evident in Figure 1B, lithium was linked to decreases in mean connectivity in a network (pictured in Figure 1A) previously found to be

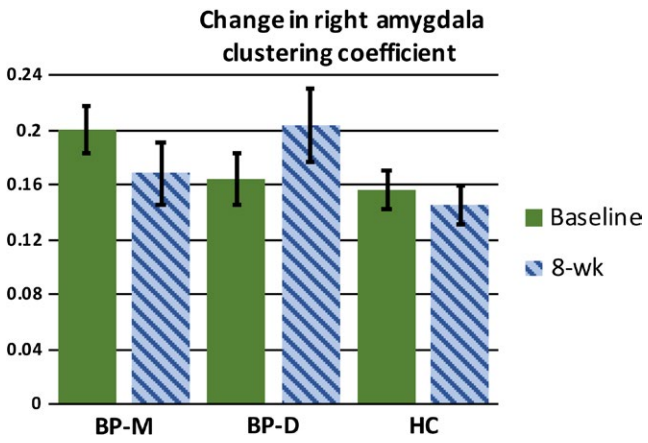

FIGURE 2 Impact of lithium on right amygdala clustering coefficient for baseline hypomanic/manic and depressed patients. Lithium-related change from baseline to 8-weeks in right amygdala clustering coefficient. Solid green columns represent values for patients who were hypomanic/manic at baseline (BP-M), and blue striped columns represent values for patients who were depressed at baseline (BP-D). As shown, right amygdala clustering coefficient decreases over time in BP-M patients, whereas an increase in observed for BP-D patients. Error bars reflect the standard error. Although not included in analyses, levels for healthy controls (HC) are also shown for comparison

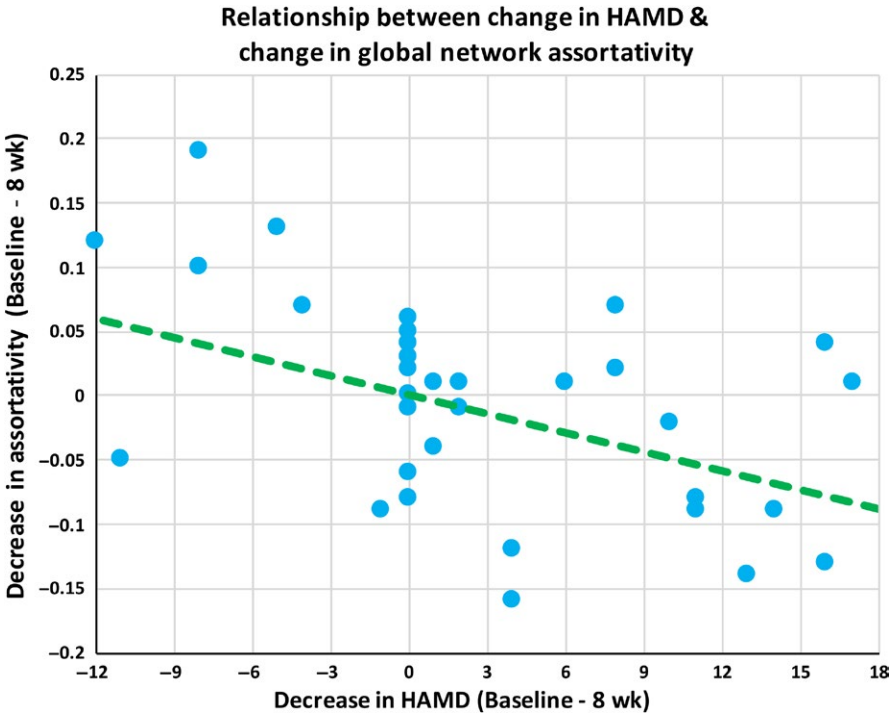

FIGURE 3 Relationship between changes over time in depression & assortativity. Negative relationship between change over time in Hamilton Depression Rating Scale (HAMD) symptoms (*x*-axis) and change in global network Assortativity (*y*-axis). As shown, increases over time in network resilience (Assortativity) were observed in patients who experienced reductions in depression

hyper-connected in patients with higher levels of manic symptoms.[18] Thus, decreased connectivity after lithium monotherapy suggests that treatment has a normalizing effect. Importantly, this effect was significant both when examining only BP patients (n = 26) and when compared to connectivity changes in this network in healthy controls (n = 39), ensuring that this effect was not due simply to change over time.

As evident in Figure 1A, this network was centered around right amygdala, midbrain, and left superior frontal gyrus, and a large percentage of connections in this network were between these hubs and regions in association cortex. Thus, lithium-related decoupling in this network may lead to reductions in the influence of these hubs on sensory-integrative processing. For example, Spielberg et al[18] suggested that hyperconnectivity between amygdala and sensory regions in this network may reflect a form of hyper-salience in which "affective significance is inappropriately overlaid on perception" (p. 3021). Thus, one mechanism by which lithium may impact BP symptoms is to attenuate the influence of amygdala-mediated affective responses on perceptual processing. In turn, this may help to reduce disturbances in emotional regulation observed in mania/hypomania, given that bottom-up amygdala-driven influences are thought to underlie these regulation difficulties. In other words, sensory properties for stimuli deemed by amygdala to be salient are typically elaborated upon to a greater extent by networks linked to amygdala than non-salient stimuli. Thus, more frequent or intense identification of salience by amygdala, as may be the case in mania/hypomania, will have a direct impact on sensorial experience. Consequently, if lithium normalizes the connectivity of amygdala-linked networks, as suggested by present findings, this may provide a mechanism by which lithium impacts the sensory experience of patients.

4.2 | Lithium monotherapy-associated impact on connectome indices differs by baseline mood

As evident in Figure 2, the impact of lithium on right amygdala clustering coefficient (CC) differed by the mood experienced by patients at baseline (analysis n = 26). Specifically, patients who had been hypomanic/manic at baseline evidenced decreases over time in right amygdala CC, whereas the opposite was observed for those who had been depressed at baseline. Given that greater right amygdala CC was previously found in patients with higher levels of manic symptoms,[18] decreases in CC over time in the hypomanic/manic group appear to reflect normalization due to lithium, as hypothesized.

However, increases over time observed in the baseline depressed group were unexpected and potentially provocative. Clustering coefficient indexes the amount of interconnectivity in the local network surrounding a node. Given the prominent role of amygdala in affective salience,[46] increases over time in amygdala CC may indicate more complex and elaborated processing of affectively salient stimuli. Thus, these neural changes may reflect the activating component of depression reduction (eg, as done in behavioral activation treatment).

Although interesting, these findings are not directly informative as to whether network changes actually relate to changes in BP symptoms. Thus, we directly tested the relationship between change in connectome indices and change in BP symptoms in a third set of analyses.

4.3 | Relationship between lithium-related connectome shifts & changes in manic symptoms

We observed a significant relationship between change over time in manic symptoms and change in mean connectivity in the

network (pictured in Figure 1A; analysis n = 39) found previously to be hyper-connected at higher levels of manic symptoms. As evident in Figure 1C, lithium-related decreases in connectivity in this network were linked to decreases in manic symptoms. Thus, as network hyper-connectivity normalized with lithium treatment, so did manic symptoms. This underscores the relationship between this network and manic symptoms and suggests that connectivity in this network plays a role in the neural mechanisms by which lithium influences such symptoms. Interestingly, not only was this relationship observed when examining change over the entire length of the study (ie, baseline vs 8-week follow-up), but also when examining change occurring by the 2-week follow-up (baseline vs 2-week follow-up). However, this was not true when comparing the two follow-up periods (2- vs 8-week follow-up), suggesting that symptom change related to this network occurs primarily during very early treatment.

4.4 | Relationship between lithium-related connectome shifts & changes in depressive symptoms

We observed a significant relationship between change over time in depressive symptoms and change in Assortativity of the global connectome (analysis n = 39). Assortativity assays the resilience of a network to disruption and we found previously that it was suppressed at higher levels of BP depression.[18] As evident in Figure 3, lithium-related *increases* in Assortativity were linked to *decreases* in depressive symptoms. Thus, lithium appears to have a normalizing impact, reducing susceptibility to disruption. Clinically, depression is associated with a vulnerability to disruption in goal-directed processing (eg, rumination, loss of concentration), which may be reflected in the resilience of the connectome to disruption. Thus, lithium-related increases in network resilience may protect against the factors that maintain depression, thereby serving to decrease pathology. In other words, one neural mechanism by which depression is maintained over time is that networks are more vulnerable to interruption by information non-relevant to current goals (eg, aversive memories). If lithium increases resilience to disruption, as suggested by present findings, this will both decrease the time spent recursively processing maladaptive information and increase the ability to achieve goals, both of which would be quite useful therapeutically.

4.5 | Strengths & limitations

The present study benefited from a number of strengths, including a longitudinal design with multiple follow-up assessments, a sample that was medication-free at baseline (and only receiving lithium at follow-ups), examination of hypomanic/manic and depressed BP patients simultaneously, the use of cutting-edge graph-theory methods, and the use of a priori connectome indices to examine lithium-related change. Several limitations must also be considered. First, as only open label lithium treatment was given in the BP group, it is not possible to tease out whether the observed changes were due to lithium treatment or to a placebo effect. To determine whether changes are due to lithium itself, studies which compare lithium treatment to placebo will need to be conducted. These studies are difficult to justify on an ethical basis and are unlikely to be conducted in a clinical population. However, results of this study do show connectivity changes associated with the open-label lithium treatment that is characteristic of real-world practice. The use of a healthy control group ensured that effects were not due simply to change over time, but it does not allow us to determine whether observed effects are due to lithium and/or reflect typical temporal fluctuation unique to BP patients. However, correlation with symptom changes provides face validity that the changes in connectivity measures were associated with lithium treatment-related clinical response. Keeping in mind this limitation, we have characterized the connectome changes observed as lithium-*associated* effects rather than lithium effects, per se. Second, the sample size is moderate (26 patients), due to the difficulty in recruiting medication-free patients who were willing to do a longitudinal study and retaining BP patients across 3 assessment waves. However, it should be noted that the use of repeated measures increases power appreciably, rendering this sample size reasonable for this type of study. In other words, although only 26 patients were examined, the actual number of patient scans was 78 (+39 healthy control scans = 117 scans total). A third limitation was that follow-up was limited to 8 weeks, and thus we cannot report on longer term changes related to lithium. For example, we did not observe significant changes in several of the connectome indices previously found to be associated with BP. This may be because change in these network properties occurs over a longer period of time. Thus, follow-up studies with larger samples and over longer periods of time are necessary. Fourth, given that only lithium was examined, it is not possible to determine what effects are specific to lithium and what effects would be found with other related medications. Fifth, the intensity of current manic symptoms was relatively mild, which limits the extent to which we can make inferences about the impact of lithium on patients with more severe current pathology. Finally, we did not examine molecular mechanisms of change, and as such cannot determine the manner in which lithium directly impacts the connectome. Thus, further research using molecular-level tools (eg, changes in gene expression) is needed to more fully elucidate the potential causal change.

4.6 | Summary & conclusions

We found a shift toward normalization in a network previously linked to manic symptoms, and this shift was proportional to reduction in manic symptoms, underscoring the importance of this potential link. Furthermore, lithium-related reduction in depression symptoms was linked to increases in an index of brain network resilience, which was found to be disturbed in BP depression in our previous work. Unexpectedly, lithium appeared to have contrasting effects in patients who were hypomanic/manic at baseline compared to those who were depressed. Specifically, hyperconnectivity in the network surrounding right amygdala was reduced in the hypomanic/manic group, whereas this network clustering increased over time in the depressed group.

Present findings provide deeper insights into the therapeutic neural mechanisms of lithium monotherapy, the frontline treatment for bipolar disorder. These insights may have key implications for the development and refinement of pharmaceutical interventions. Specifically, the observed network changes provide targets for the development of more precisely tailored interventions. In addition, examination of pre-treatment network status may provide insight into whom will benefit most from treatment. For example, individuals with worse pre-treatment brain network resilience may show the largest decrease in depressive symptomology. In summary, we offer an initial view into connectome-level changes associated with lithium monotherapy. Results move us closer to understanding the precise neural pathways by which lithium effects change manic and depressive symptoms in bipolar disorder.

DISCLOSURES

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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