

Isolating the Norepinephrine Pathway Comparing Lithium in Bipolar Patients to SSRIs in Depressive Patients

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Abstract

Introduction: The purpose of this investigatory neuroimaging analysis was done to better understand the pharmacodynamics of Lithium by isolating the norepinephrine pathway in the brain. To accomplish this, we compared patients with Bipolar Disorder treated with Lithium to patients diagnosed with Major Depression or Depressive Disorder who are treated with Selective Serotonin Reuptake Inhibitors (SSRIs).

Methodology: We used Standardized Low Resolution Brain Electrotomography to calculate the whole brain, voxel-by-voxel, unpaired t-tests Statistical non-Parametric Maps. For our first electrophysiological neuroimaging investigation, we compared 46 patients (average age = 34 ± 16.5) diagnosed with Bipolar Affective Disorder to three patient groups all diagnosed with Major Depression or Depressive Episode. The first is with 48 patients diagnosed with Major Depression or Depressive Episode (average age = 49 ± 12.9), the second to 16 male depressive patients (average age = 45 ± 15.1), and the final comparison to 32 depressive females (average age = 50 ± 11.7).

Results: The results of sLORETA three-dimensional statistical non-parametric maps illustrated that Lithium influenced an increase in neurotransmission in the right Superior Temporal Gyrus ($t=1.403$, $p=0.00780$), Fusiform Gyrus ($t=1.26$), and Parahippocampal Gyrus ($t=1.29$). Moreover, an increased in neuronal function was found was also identified at the Cingulate Gyrus ($t=1.06$, $p=0.01200$).

Conclusion: We are proposing a translational clinical biological marker for patients diagnosed with Bipolar Disorder to guide physicians during the course of Lithium therapy and have identified neuroanatomical structures influenced by norepinephrine.

Keywords: bipolar disorder; neuroimaging; biomarker; lithium; SSRI; Lithium pharmacodynamics

1. Introduction

The purpose of this investigatory neuroimaging analysis was done to better understand the pharmacodynamics of Lithium by isolating the norepinephrine pathway in the brain. This was accomplished by conducting whole brain, voxel-wise, analysis comparing patients diagnosed with Bipolar Disorder and treated with the gold-standard mood stabilizer, Lithium, to patients diagnosed with Major Depression or Depressive episode medicated with Selective Serotonin Reuptake Inhibitors (SSRIs).

For clinicians, treating patients who suffer from the ‘moving target’ of mania and depression is often a very difficult task and is a daunting responsibility for the patient’s family as well. It is almost a given, that patients treated for Bipolar disorder will be prescribed Lithium and being able to provide a “picture” of how the drug is working over the course of their treatment may aid in patient compliance, as well as aid in identifying future target-engagement points for during receptor-ligand points during drug discovery, and as in our paper, provide a better understanding of the mechanisms of Lithium’s action in the brain.

Lithium is described to alter cation transport across cell membrane in nerve and muscle cells and influences reuptake of serotonin and/or norepinephrine; second messenger systems involving the phosphatidylinositol cycle to be inhibited (Ward et al., 1994). Research work carried out at the molecular, cellular, and in vivo levels, from the Pasteur Institute in Paris France, demonstrated that Lithium targets 5-HT_{1B} receptors at the molecular target (Massot et al., 1999). The classic textbook on pharmacology and therapeutics explains that upon ingestion of lithium, the drug becomes widely distributed in the central nervous system and interacts with a number of neurotransmitters and receptors, decreasing norepinephrine release and increasing serotonin synthesis (Brunton et al., 2011). So, to isolate the norepinephrine pathways, we conducted an unpaired t-tests with patients treated with SSRIs to increase serotonin in the brain. We hypothesized that Lithium’s norepinephrine neuronal activity would “light-up” key neuroanatomical structures associated with Bipolar Disorder. The resulting serotonin neurotransmitter neuronal effects from Lithium and the serotonin increase from the SSRIs would negate themselves through the whole brain unpaired t-tests via Statistical non-Parametric Mapping.

The motivation for this effort is to aid in identifying neurotransmitter pathways for differentiating specific targets, neuroanatomical locations, to serve as biological markers for identifying the patients treated with lithium and identify gender differences with serotonin. To accomplish this task we retrospective study of patient electroencephalograms and conduct electrophysiological neuroimaging technique in 3 separate patient comparisons.

2. Methods

2.1 Patients

For this investigation, all patient data was obtained from a large database of electroencephalograms from the Department of Psychiatry’s Neurophysiology Study Laboratory of the Medical University of Lublin in Poland. All EEG recordings were performed according to the recommendations of the International Federation of Clinical Neurophysiology (“Recommendations for the practice of clinical neurophysiology: guidelines of the International Federation of Clinical Neurophysiology,” 1999). All patients were diagnosed by a board-certified Psychiatrist using the diagnostic criteria from the World Health Organization’s International Statistical Classification of Diseases and Related Health Problems (ICD-10) section on Mental, Behavioral, and Neurodevelopmental Disorders.

For our first electrophysiological neuroimaging investigation, we compared 46 patients (average age = 34 ± 16.5) diagnosed with Bipolar Affective Disorder and 48 patients diagnosed with Major Depression or Depressive Episode (average age = 49 ± 12.9). The gender distribution details for the 46 bipolar patients included 20-males (average age = 31 ± 12.9) and 26-females

(average age = 37 ± 18.6). The gender distribution details for the 48 depressive patients included 16-males (average age = 45 ± 15.1) and 32-females (average age = 50 ± 11.7).

For our second investigation, we compared the same 46 bipolar patients (average age = 34 ± 16.5), as in the above comparison, to the 16 male depressive patients (average age = 45 ± 15.1). For the third and final comparison, we analyzed the same original 46 bipolar patients (average age = 34 ± 16.5) to the 32 depressive females (average age = 50 ± 11.7).

Patient EEG recordings were then classified and categorized by both gender and the ICD-10 diagnosis. Similarly, each patient's birth-month was recorded in an effort to identify any associations of seasonality of birth psychiatric illness based on gender. Pharmacologically, all of the bipolar patients were medicated with Lithium, (dosage was 900 to 1,800 mg daily in 3 to 4 divided doses) and all of the depressive patients were medicated with Sertraline (50mg/day to 200mg/day maximum dose) or Citalopram (20mg/day to 40mg/day maximum dose). The investigation was approved by the Bioethical Commission of the Medical University of Lublin.

2.2 EEG Recording

All patients were comfortably seated at a semi-recumbent position in a sound and lighted attenuated and electrically shielded room, while 20-minutes or more of routine eye-open and eyes-closed resting EEG data were recorded using the 19-channel EEG Analysis Station (ELMIKO Medical, Poland) and Ag/AgCl electrodes. Patients EEG recordings were in accordance to the international 10/20 system with electrodes placed at Fp2, F8, T8/T4, P8/T6, O2, F4, C4, P4, Fp1, F7, T7/T3, P7/T5, O1, F3, C3, P3, Fz, Cz, and Pz. Electrodes were referenced to linked earlobes and impedances were kept below 5 k Ω . The data sampling rate was 250 Hz, and the acquired signals were filtered with a band-pass filter of 0.15–70 Hz after sampling. Prior to data analysis, artifact detection was performed, visually, to exclude eye-movements, head-movements, muscle-movements, and segments of decreased alertness. EEG recordings were then exported using ELMIKO's EEG DigiTrak Analysis Software to the ASCII format for later processing.

2.3 Neuroimaging – LORETA

Following the export of the ASCII formatted data from the ELMIKO EEG acquisition system, 30-seconds of eyes-open EEG signals were recomputed to the average reference. Subsequently, spectral analysis was performed for the same 30-seconds of artifact-free data of each ICD-10 diagnostic group. The cross-spectra were averaged across the 50% overlapping windows, which yielded 7 EEG frequency bands: delta (1.5–6 Hz), theta (6.5–8 Hz), alpha-1 (8.5–10 Hz), alpha-2 (10.5–12 Hz), beta-1 (12.5–18 Hz), beta-2 (18.5–21 Hz) and beta-3 (21.5–30 Hz) (Kubicki *et al.*, 1979). Lastly, LORETA was used to estimate the 3-dimensional statistical non-parametric maps of neuronal activity (Pascual-Marqui, 2002; Pascual-Marqui *et al.*, 1994).

The three-dimensional intracerebral neuronal source activity, illustrating statistical non-parametric maps of neuronal activity, are derived from the 19-channel electrodes were assessed using Low Resolution Brain Electrotomography (LORETA) (Pascual-Marqui, 2002). When considering the available methodologies of detecting intracerebral activity, it is important to note that of all available published three-dimensional, discrete, distributed, linear EEG/Magnetoencephalography (MEG) tomography methods for solving the classic EEG inverse problem, LORETA has been identified to report the lowest localization error (to within 1 voxel resolution on average) (Pascual-Marqui, 2002). The source localization results from LORETA, even without utilizing an individual patient's MRI anatomical scans, has demonstrated that with as many as 16-electrodes, and using the approximate three-shell head model registered to the Talairach human brain (Talairach and Tournoux, 1988), localization accuracy of EEG is 10 mm, for worst cases (Cohen *et al.*, 1990). By adding the expected localization error, as a result of the head model, the average error is not expected to exceed 2 to 3 cm in the final LORETA source localization results. LORETA inverse solutions are a model of the 3D distribution of electric neuronal activity, represented by adjacent voxels, has maximum synchrony relative to the orientation and strength

between neighboring neuronal populations (Pascual-Marqui, 2002). LORETA inverse solutions are restricted to 2394 voxels (spatial resolution=7mm) within cortical gray matter and hippocampi, as determined by the digitized Talairach and probability atlases of the Brain Imaging Centre, Montreal Neurological Institute (MNI305).

EEG electrode coordinates are derived from cross-registrations between spherical and head geometry (Towle *et al.*, 1993). Concerning the validity of the neuronal activation results, currently, LORETA has received robust theoretical and cross-modal validation from localization studies combining this method with both structural and functional Magnetic Resonance Imaging, Positron Emission Tomography (PET), visual and auditory event-related potentials, and well as intracranial recordings (Pascual-Marqui, 2002).

In our investigation, of neurotransmission pattern differences of the bipolar disorder patients compared to depressive patients, Standardized LORETA (sLORETA) (Pascual-Marqui, 2002) was used. The sLORETA inverse solutions are constrained to the MNI152 (Mazziotta *et al.*, 2001) template composed of 6239 cortical gray matter voxels at 5mm spatial resolution.

The sLORETA software package was used as a new improvement relative to LORETA. With sLORETA, realistic scalp electrode coordinates are adapted to a 10/5 electrode system (Oostenveld and Praamstra, 2001) and are registered to the Montreal Neurological Institute's MNI152 (Mazziotta *et al.*, 2001) scalp, with a 12-parameter transformation followed by a spline solution that projects the electrodes onto the scalp with minimal distortion (Jurcak *et al.*, 2007). By transforming the electrode system, sLORETA provides a much more realistic head-surface based coordinate system. Moreover, the sLORETA transformation matrix for the inverse solution uses the electric potential lead field computed within the boundary element method applied to the MNI152 digitized structural MRI template (Fuchs *et al.*, 2002). Further, the identified sLORETA inverse solutions are reported on MNI152 template which is composed of 6239 cortical gray matter voxels at 5 mm with anatomical labels as Brodmann areas are also reported using MNI space, with correction to Talairach space (Brett *et al.*, 2002).

2.4 Statistical Analysis

The localization of the differences in activity between the bipolar and depressive patients was assessed by whole brain, voxel-by-voxel, unpaired t-tests of the LORETA images, based on the log-transformed power of the estimated electric current density, which resulted in t-statistic 3-dimensional images (Mientus *et al.*, 2002). In these images, cortical voxels of statistically significant differences were displayed as statistical parametric maps (SPMs) using a randomization strategy that determined the critical probability threshold values for the actually observed statistic with corrections for multiple testing (Holmes *et al.*, 1996).

To visualize the global distributions of the t-test differences, for each band we computed the location of the average center of gravity of all voxels with positive and negative t-values. To correct for multiple comparisons, a nonparametric single-threshold test was applied on the basis of the theory of randomization and on permutation tests (Holmes *et al.*, 1996). The omnibus null hypothesis of no activation anywhere in the brain was rejected if at least 1 t-value (i.e. voxel, t-max) was above the critical threshold for $p = 0.05$, determined by 5,000 randomizations (Horacek *et al.*, 2007).

3. Results

3.1. Results of 46 Bipolar Patients compared to 48 Depressive Patients

The whole brain, voxel-wise analysis comparing the 46 bipolar patients to the 48 depressive patients did not yield statistically significant sLORETA neuroimaging results. The results of the one tailed t-tests yielded a trending value ($p=0.06880$) for the 46 bipolar patients and a non-statistically significant ($p=0.53300$) finding for a one-tailed t-test for the 48 depressive patients.

3.2. Results of 46 Bipolar Patients compared to 16 Depressive Males

Our whole brain statistical non-Parametric Mapping comparing the 46 bipolar patients with the 16 depressive males identified a statistically significant increase in neuronal activity for the 46 bipolar patients. The results illustrated that Lithium influenced an increase in neurotransmission in the *theta frequency band* (6.5Hz-8Hz) at the *right Superior Temporal Gyrus* ($t=1.403$, $p=0.00780$, BA 41, MNI X=45, Y= -35, Z=10), *Fusiform Gyrus* ($t=1.26$, BA 20, MNI X= 45, Y= -35, Z=10), and *Parahippocampal Gyrus* ($t=1.29$, BA 36, MNI X=45 , Y= -35 , Z=10). Moreover, an increased in neuronal function was found was also identified at the *Cingulate Gyrus* ($t=1.06$, $p=0.01200$, BA 32, MNI X=45, Y= -35, Z=10) at the *alpha-1 frequency band* (8.5Hz-10Hz).

Table 1: Patient group results of sLORETA analysis between the 46 Bipolar Patients vs. 16 Depressive Males

sLORETA Brain Mapping Results			
Patient Group with the Statistically Significant Neuronal Synchronization	46 Bipolar Patients		
	Location 1	Location 2	Location 3
Whole Brain Voxel-wise t-test Result	t=1.403	t=1.26	t=1.29
p-Value	p=0.00780	p<0.01	p<0.01
Frequency Band	Delta (6.5Hz – 8Hz)	Delta (6.5Hz – 8Hz)	Delta (6.5Hz – 8Hz)
Neuroanatomical Locations(s)	Right Superior Temporal Gyrus	Right Fusiform Gyrus	Right Parahippocampal Gyrus
Lobe	Temporal Lobe	Limbic Lobe	Temporal Lobe
Brodman Area	BA 41	BA 20	BA 36
Montreal Neurological Institute Coordinates	X=45, Y= -35, Z=10	X=42 , Y= -35 , Z= -25	X=29, Y= -35, Z= -16

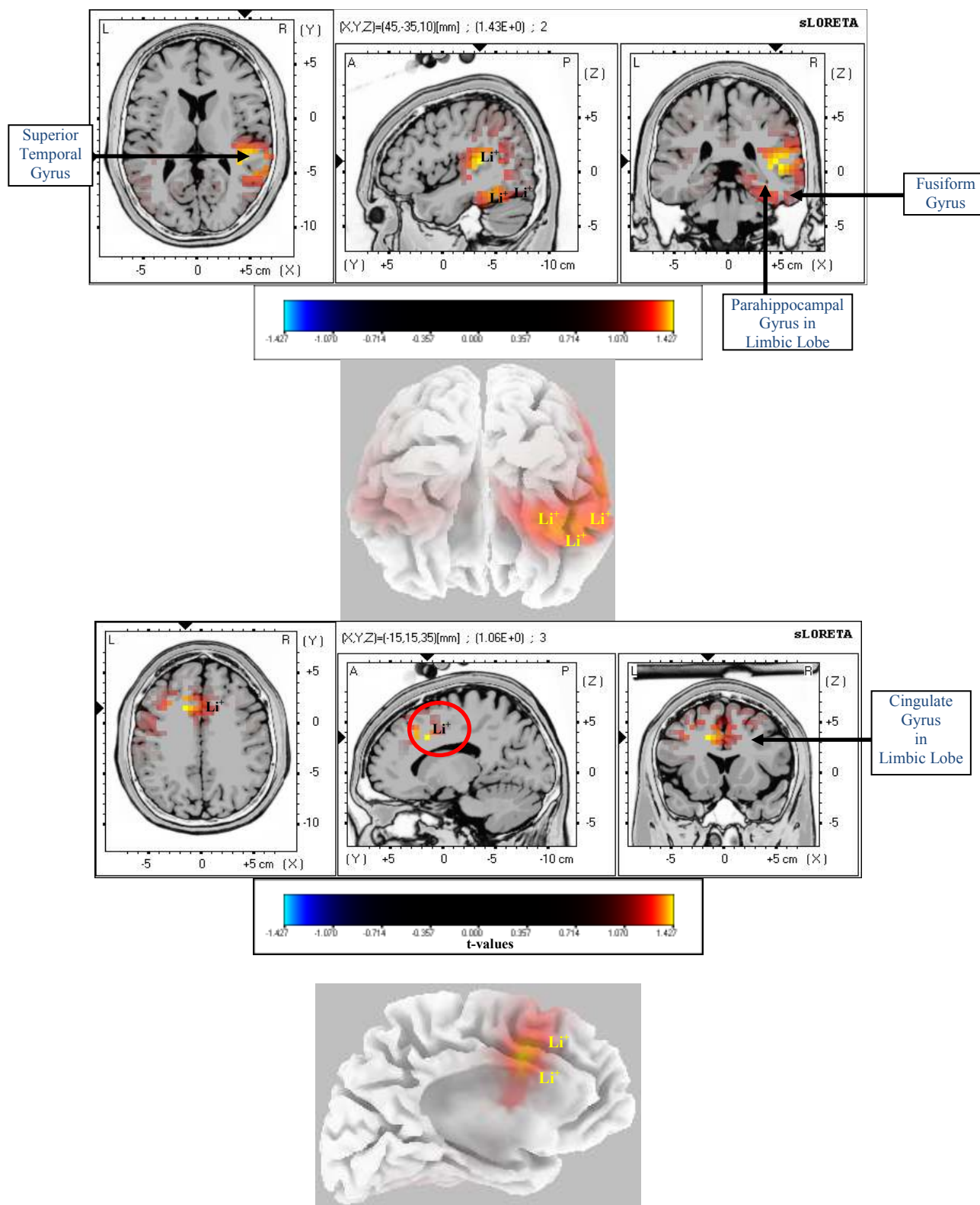


Figure 1. Resting state neuroimaging findings illustrating the action of Lithium following whole brain, voxel-by-voxel, unpaired statistical non-parametric maps (SnPM) of sLORETA images

The axial, sagittal, and coronal MRI activation maps illustrate neuronal activity of 46 patients diagnosed with Bipolar Affective Disorder compared to 16 male patients diagnosed with Major Depressive Disorder of Depressive Episode. The Yellow/Orange shades indicate increased neuronal activity in the *right Superior Temporal Gyrus* ($t=1.403$, $p=0.00780$, BA 41, MNI X=45, Y= -35, Z=10) with activation also in the *Fusiform Gyrus* ($t=1.26$, BA 20, MNI X= 45, Y= -35, Z=10), the *Parahippocampal Gyrus* ($t=1.29$, BA 36, MNI X=45, Y= -35, Z=10). (b) Increased neuronal activity in the *Cingulate Gyrus* ($t=1.06$, BA 32, MNI X=45, Y= -35, Z=10). Structural anatomy is shown in grey scale (A – anterior; S – superior; P – posterior; L – left; R – right).

Table 2: Patient group results of sLORETA analysis between the 46 Bipolar Patients vs. 16 Depressive Males

sLORETA Brain Mapping Results	
Patient Group with the Statistically Significant Neuronal Synchronization	46 Bipolar Patients
Whole Brain Voxel-wise t-test Result	t=1.06
p-Value	p=0.01200
Frequency Band	Alpha-1 Frequency Band (8.5Hz-10Hz)
Neuroanatomical Locations(s)	Cingulate Gyrus
Lobe	Limbic Lobe
Brodmann Area	32
Montreal Neurological Institute Coordinates	X= -15, Y=15, Z=35

3.3. Results of 46 Bipolar Patients compared to 32 Depressive Females

Our neuroimaging results identified a statistically significant increased neuronal activity in the 46 bipolar patients. The results illustrated that Lithium influenced an increase in neurotransmission in the *delta frequency band* (1.5Hz-6Hz) at the *right Superior Frontal Gyrus* (t=0.920, p=0.05060, BA 6, MNI X=20, Y=0, Z=70) and in the *right Cingulate Gyrus* (t=0.0846, BA 24, MNI X= 5, Y=0, Z=51).

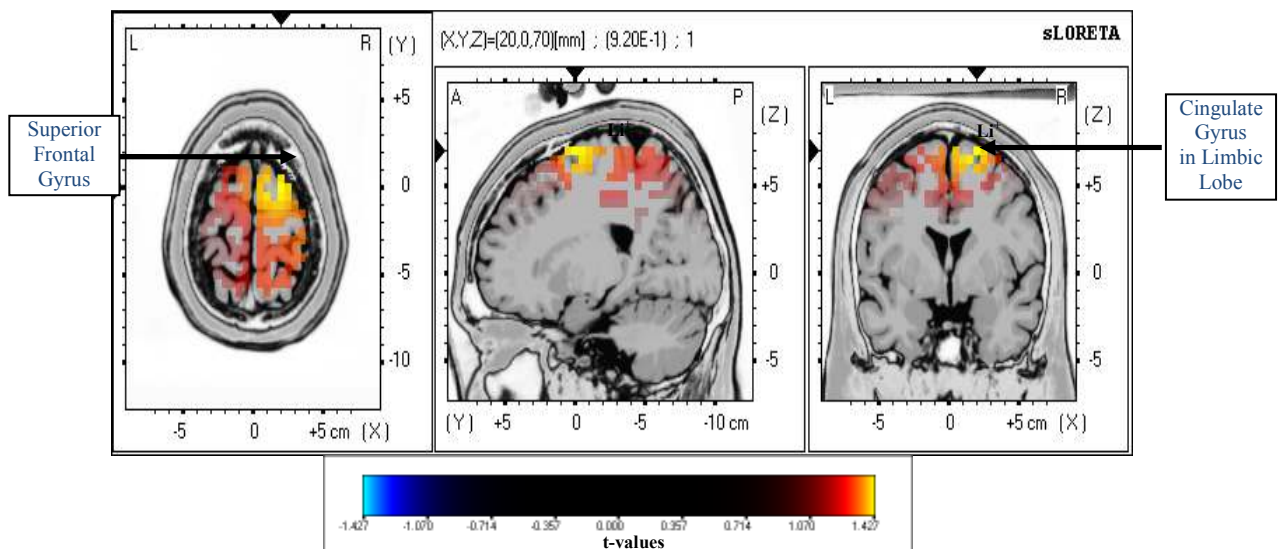


Figure 2. Resting state neuroimaging findings illustrating the action of Lithium following whole brain, voxel-by-voxel, unpaired statistical non-parametric maps (SnPM) of sLORETA images

The axial, sagittal, and coronal MRI activation maps illustrate increased delta frequency band neuronal activity in the 46 patients diagnosed with Bipolar Affective Disorder compared to 32 female patients diagnosed with Major Depressive Disorder of Depressive Episode. The Yellow/Orange shades indicate increased neuronal activity in the right Superior Frontal Gyrus (t=0.920, p=0.05060, BA 6, MNI X=20, Y=0, Z=70) and in the right Cingulate Gyrus (t=0.0846, BA 24, MNI X= 5, Y=0, Z=51). Structural anatomy is shown in grey scale (A – anterior; S – superior; P – posterior; L – left; R – right).

Table 3: Patient group results of sLORETA analysis between the 46 Bipolar Patients vs. 32 Depressive Females

sLORETA Brain Mapping Results		
Patient Group with the Statistically Significant Neuronal Synchronization	46 Bipolar Patients	
	Location 1	Location 2
Whole Brain Voxel-wise t-test Result	t=0.920	t=0.0846
p-Value	p=0.05060	p<0.05
Frequency Band	Delta Frequency Band (1.5Hz-6Hz)	Delta Frequency Band (1.5Hz-6Hz)
Neuroanatomical Locations(s)	Right Superior Frontal Gyrus	Right Cingulate Gyrus
Lobe	Frontal Lobe	Limbic Lobe
Brodmann Area	BA 6	BA 24
Montreal Neurological Institute Coordinates	X=20, Y=0, Z=70	X=5, Y=0, Z=51

4. Discussion

Our results appeared were statistically significant, illustrating different neurophysiological and pharmacodynamic brain activations, in depressive female patients treated with SSRIs. Testing our original hypothesis that the activated norepinephrine brain structures involved in Bipolar Disorder would be activated after whole brain voxel-wise analysis, our results suggest that there were no statistically significant differences in serotonin neurotransmitter activity in depressive males relative to the coupled norephrine/serotonin neurotransmitter imbalance occurring in bipolar patients. Futher, this would suggest that there are gender differences in catecholamine neurotransmitters.

Current theories on limbic-cortical dysregulation state that dysfunction in the neural circuit linking the hippocampus, prefrontal cortex, and anterior cingulate cortex are tightly linked to the affective and cognitive abnormalities seen in mood disorders and depression (Mayberg, 1997). The Psychiatry Genetic Team at the University Paris Est-Créteil conducted 2 meta-analyses of 13 functional magnetic resonance imaging (fMRI) studies, involving 156 bipolar disorder patients and 164 mentally healthy controls and identified that patients with Bipolar Disorder had increased activity in ventral-limbic brain structures (the parahippocampal gyrus and the amygdala) compared with controls (Houenou *et al.*, 2011), as with our findings in this investigation.

Further, a cross-sectional, between-subjects study with 16 euthymic, medicated patients with bipolar disorder and 11 age-matched healthy controls measured resting glucose metabolism with 18FDG-PET found that patients with bipolar disorder, compared to healthy controls, showed that resting metabolic rates in bipolar patients were significantly greater than in controls in bilateral amygdalae, bilateral parahippocampal gyri, and right anterior temporal cortex (BA 20, 38)(Brooks *et al.*, 2009).

After corroborating our results with other studies, it appears that our findings with neuronal activations in the cingulate gyrus provided a unique biological marker. A group from the University

of Newcastle in the United Kingdom, identified that bipolar patients had a significant increase in immunoreactivity of intercellular adhesion molecule-1 (ICAM-1) in postmortem tissue analysis in the gray and white matter of the anterior cingulate cortex (ACC)(Thomas *et al.*, 2004). This electrophysiological neuroimaging finding may be significant due to ICAM-1 being identified as a marker of cerebral inflammation(van de Stolpe and van der Saag, 1996). Having said this, increased in neuronal activity in the patients taking Lithium may indicate the role that Lithium plays in regulating mood. Moreover, the elevation in ICAM-1 is said to be consistent with an inflammatory response in ACC and might be associated with dysregulation of the hypothalamic–pituitary–adrenal axis (Rybakowski and Twardowska). There may be a future work to couple therapeutics of lithium with anti-inflammatory drugs that are known to cross the blood-brain barrier for the treatment of patients with bipolar disorder.

5. Conclusions

Based on the results of this experimental neuroimaging investigation of therapeutics of lithium compared to SSRIs, we are not proposing a mechanism of action for Lithium; instead, we are proposing a translational clinical biological marker for patients diagnosed with Bipolar Disorder. Further, we are proposing specific neuroanatomical locations (*superior temporal gyri, the parahippocampal gyri, the amygdala, and the cingulate gyrus*) that may be identified using fMRI, PET, and/or EEG neuroimaging, as biological markers where Lithium interacts with receptors for both drug discovery and to guide physicians during therapeutic management of patients with bipolar disorder.

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7. Conflicts of Interest

The authors declare no conflict of interest.

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