Published in final edited form as:

Synapse. 2018 February ; 72(2): . doi:10.1002/syn.22015.

Diffusion Entropy: A Potential Neuroimaging Biomarker of Bipolar Disorder in the Temporal Pole

Karl Spuhler^a, Elizabeth Bartlett^a, Jie Ding^a, Christine DeLorenzo^{a,b}, Ramin Parsey^b, and Chuan Huang^{a,b,c,*}

^aDepartment of Biomedical Engineering, Stony Brook University. Biomedical Engineering, Stony Brook, NY, USA 11794

^bDepartment of Psychiatry, Stony Brook Medicine. 101 Nicolls Rd, Stony Brook, NY, USA 11794

^cDepartment of Radiology, Stony Brook Medicine. 101 Nicolls Rd, Stony Brook, NY, USA 11794

Abstract

Despite much research, bipolar depression remains poorly understood, with no clinically useful biomarkers for its diagnosis. The paralimbic system has become a target for biomarker research, with paralimbic structural connectivity commonly reported to distinguish bipolar patients from controls in tractography-based diffusion MRI studies, despite inconsistent findings in voxel-based studies. The purpose of this analysis was to validate existing findings with traditional diffusion MRI metrics and investigate the utility of a novel diffusion MRI metric, entropy of diffusion, in the search for bipolar depression biomarkers. We performed group-level analysis on 9 un-medicated (6 medication-naïve; 3 medication-free for at least 33 days) bipolar patients in a major depressive episode and 9 matched healthy controls to compare: (1) average mean diffusivity (MD) and fractional anisotropy (FA) and; (2) MD and FA histogram entropy—a statistical measure of distribution homogeneity—in the amygdala, hippocampus, orbitofrontal cortex and temporal pole. We also conducted classification analyses with leave-one-out and separate testing dataset (N=11) approaches. We did not observe statistically significant differences in average MD or FA between the groups in any region. However, in the temporal pole, we observed significantly lower MD entropy in bipolar patients; this finding suggests a regional difference in MD distributions in the absence of an average difference. This metric allowed us to accurately characterize bipolar patients from controls in leave-one-out (accuracy=83%) and prediction (accuracy=73%) analyses. This novel application of diffusion MRI yielded not only an interesting separation between bipolar patients and healthy controls, but also accurately classified bipolar patients from controls.

Keywords

Bipolar depression; diffusion; temporal pole; diffusion MRI

*Corresponding author: Chuan Huang, PhD, Stony Brook MedicineHSC-L4-120, Stony Brook, NY 11794, USA, TEL: +1-631-638-1536, chuan.huang@stonybrookmedicine.edu.

1. Introduction

Bipolar disorder (**BD**) is a debilitating illness characterized by recurrent major depressive and manic episodes. BD incurs high costs to society (Fajutrao et al., 2009), particularly due to the fact that patients with the disease tend to exhibit reduced societal and occupational functioning, even when compared to peers with other mood disorders (Pini et al., 2005). The intense burden of this disease is compounded by its high lifetime prevalence, which is estimated to be 1.3% (Kleinman et al., 2003). Globally, BD has been ranked 6th in terms of disability-adjusted life years among all mental disorders (Whiteford et al., 2013).

The prevalence and chronicity of BD are further exacerbated by complications and challenges in its treatment. Despite the disease's severity, its pathophysiology and etiology remain poorly understood, leading to relatively poor clinical outcomes. In particular, insufficient understanding of the neurobiological underpinnings of BD has not only prevented significant drug development over the past several decades, but has also hindered the discovery and translation of clinically useful biomarkers for optimal treatment selection, diagnosis of BD, or differentiation from related psychiatric diseases (Phillips and Kupfer, 2013; Tamminga et al., 2017). In the latter sense, discovering sensitive and specific biomarkers of BD stands to benefit a wide range of non-BD mood disorder patients, most notably those with major depressive disorder, as differentiation between BD and similar disorders is a clinically non-trivial task, and misdiagnosis frequently delays efficacious treatment (Houenou et al., 2011; Vöhringer and Perlis, 2016).

In recent years, neuroimaging studies have emerged as one of the most promising techniques for biomarker-oriented mood disorder research (Frey et al., 2013). Particularly, Magnetic Resonance Imaging (**MRI**) has become a preeminent tool in neurobiological research of mood disorders, including BD. Technological improvements have been extremely impactful in the field of diffusion tensor imaging (**DTI**) MRI—which uses multiple magnetic field gradients to image water diffusion in the brain—where whole brain images with high spatial resolution and, in particular, angular resolution, can now be acquired in clinically-relevant timespans.

Paralimbic structures represent perhaps the most frequently studied and experimentally implicated regions in neurobiological research of BD. Paralimbic regions include temporal lobe structures such as the amygdala and hippocampus, along with prefrontal regions with which they share strong connection, most notably the orbitofrontal cortex. White matter abnormalities in these areas have been a central focus of MRI studies of BD pathophysiology, particularly within and between paralimbic structures (Hibar et al., 2014; Rajkowska et al., 2001; Wise et al., 2016). While tractography-based white matter analyses have yielded some of the most consistently reported pathophysiological findings in BD research, voxel-based studies have generally reported inconsistent findings, with no average differences in diffusivity throughout the regions implicated in tractographic and volumetric studies (Vederine et al., 2011).

Given the historical lack of consistency in regional diffusivity findings among paralimbic structures, we sought to investigate the homogeneity of diffusion in these areas: namely the

bilateral amygdalae, hippocampi, orbitofrontal cortices and temporal poles. A motivating consideration of this work was that differences in the homogeneity of diffusivity values could exist in the absence of significant average differences. We hypothesized that such changes would be reflected by the information theoretic notion of entropy. In particular, this statistic generalizes the notion of information provided by a random variable, in this instance diffusivity values, by calculating the homogeneity of its distribution. Although this application of entropy to DTI data is novel, similar metrics have been used in the analysis of functional brain networks (Carhart-Harris et al., 2014). Significant differences in such a metric would reflect differences in the homogeneity of diffusivity values in the region being considered, suggesting possible alterations in its organization, function or integrity. We first report group-wise average values for the mean diffusivity (**MD**) and fractional anisotropy (**FA**) in these regions among BD patients suffering a depressive episode and age- and sex-matched healthy controls. This analysis will corroborate our measurements with the historical lack of significant local diffusivity differences. Next, we report the MD and FA distribution entropy for the *a priori* regions of interest amongst the BD and healthy control groups. Lastly, we report the group-wise classification accuracy of MD and FA diffusion entropy using a leave-one-out and a separate testing dataset approach.

2. Materials and Methods

2.1 Participants

This study made use of MRI scans conducted for a study investigating the effects of treatment in bipolar depression (Clinical trial ID: NCT0188095). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. IRB approval was acquired through Stony Brook University Medical Center, and data were acquired subject to the approved protocol. Informed consent was obtained from all subjects prior to their participation. Individuals incapable of providing informed consent were excluded. Patients and healthy controls were recruited through radio and newspaper advertisement, along with fliers on local campuses. Participants underwent metal screening to ensure MRI-compatibility. All individuals were right handed.

Patients were evaluated using the Structured Clinical Interview for DSM IV to confirm diagnosis of BD and current mood state. Patients with both bipolar I and II disorder were eligible for inclusion. Exclusion criteria included: a history of schizophrenia, schizoaffective disorder, recent drug or alcohol dependence, having a first degree family history of schizophrenia were excluded from the study, significant active illness, pregnancy, lactation, plans to conceive, abortion in the past two months, dementia, neurological disease or a previous head injury involving loss of consciousness or motor deficits, suicidal ideation, history of nonresponsiveness to both lithium and lamotrigine, and treatment with ECT in the last 2 years. For patients with BD and a current major depressive episode, assessed by SCID I, inclusion criteria included a score of at least 15 on the 17-item Hamilton Depression Rating Scale (HDRS) or a score of 10–14 on the 17-item HDRS in conjunction with a score of at least 29 on the Beck Depression Inventory (BDI). Patients receiving ineffective antidepressant treatment underwent a 3-week medication washout.

Healthy controls were screened for mental and physical health. Inclusion and exclusion criteria were the same as patients except that they did not meet SCID criteria for current or past psychiatric diagnosis, and had no first degree relatives with a history of affective disorder or schizophrenia.

A total of 34 DTI datasets were available for this study. A total of 5 studies were excluded due left handedness. The 18-individual matched dataset was constructed from all pairs of right-handed patients and controls with matching age and sex. A remaining 11 datasets (4 BD, 7 control) could not be age- and sex-matched due to demographic differences. These individuals were separated into an external testing dataset in order to assess the predictive value of findings in the matched dataset.

2.2 MRI acquisition: Anatomical Imaging

All MRI scans were performed on a Siemens 3T Trio MRI scanner with a Siemens 12 channel head matrix coil. Anatomical T1-weighted images were acquired using a 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence. (TR=2300 ms, TE=2.98 ms, TI=900 ms, acquisition matrix: 256×240×160 coronal slices, field of view: 240×256×160 mm³, flip angle=9°, acquisition time=5 min 10 sec).

MPRAGE images were used for region of interest segmentation (see MRI image processing). Regions of interest included the bilateral amygdalae, hippocampi, orbitofrontal cortices, and temporal poles. White and gray matter segmentations in the orbitofrontal cortices and temporal poles were pooled together into combined regions of interest.

2.3 MRI acquisition: Diffusion-tensor Imaging

Diffusion images were acquired using a multi-directional diffusion weighting sequence with 64 diffusion encoding directions and fat saturation. (Slices acquired parallel to AC-PC line, slice thickness=2.5 mm, TR=8300 ms, TE=95 ms, flip angle=90°, acquisition matrix: 96 × 96, 60 slices, slice spacing=0, field of view: 240×240×150 mm³, b=1000, acquisition time=9 min).

2.4 MRI image processing

MPRAGE images were visually inspected for motion artifacts and automated segmentation was performed using FreeSurfer 5.3.0 (surfer.nmr.mgh.harvard.edu) along with the Desikan-Killiany atlas (Desikan et al., 2006). Trained technicians, blinded to diagnosis, inspected MPRAGE images and FreeSurfer segmentations with a previously validated quality-control procedure shown to improve accuracy and reliability, as detailed in (Isan et al., 2015).

Diffusion images were inspected for artifacts due to motion, signal interference or system imperfection, using a published quality control pipeline (Liu et al., 2010). Eddy current correction was performed using the eddy correction routine in FSL (FMRIB software library). Diffusion tensor fitting was then applied on the corrected images using Camino (Cook et al., 2006; DeLorenzo et al., 2013). MD and FA values were then calculated for each voxel.

2.5 Entropy Calculation

Statistical entropy, as determined by histogram analysis was the primary metric utilized in this work. In each region of interest, MD and FA data were extracted for each individual using masks generated from the FreeSurfer segmentation. This data was then histogrammed and normalized to represent the relative likelihood of a voxel in the region of interest taking on a particular MD or FA value; histograms for MD and FA data consisted of 5 equally sized bins. FA data were grouped into bins centered between 0 and 1, with a distance of 0.25 between them; MD data were grouped into bins centered between 0 and 20×10^{-4} , with a spacing of 5×10^{-4} between them. The histogrammed data were then used for entropy calculation, where entropy was calculated as:

$$H = - \sum_{i=1}^N P(x_i) \log P(x_i),$$

where x_i is the center of a given histogram bin, $P(x_i)$ is the number of voxels belonging to that bin and $\log$ denotes the natural logarithm. When computed using the natural logarithm, the conventional unit for entropy is the “nat,” which shall be the unit all raw entropy values are reported in.

2.6 Statistical analysis

Three primary data analyses were conducted. The age- and sex-matched BD patients and healthy controls were compared at the group-level for differences in average FA and MD across all regions of interest in order to examine our hypothesis that the groups should not generally differ along these lines; we subsequently sought to determine whether entropy of FA and MD was significantly different between bipolar patients and matched controls.

Following this primary analysis, the potential utility of these metrics in the temporal pole as diagnostic biomarkers was assessed using both leave-one-out validation and diagnostic classification in the external 11-subject testing dataset. Data analysis and visualization was performed in MATLAB.

For all analyses, significance was predefined as a p-value of less than 0.05. Two sample t-tests were used for all group-wise comparisons. Statistically significant findings were corrected for multiple comparisons using the Bonferroni method. Multiple comparison corrections were performed separately for the mean-level data, wherein we sought to validate our measurements against the cumulative literature suggesting that BD and healthy controls should not significantly differ along these lines, and the entropy analysis, wherein we sought to validate that this statistic would engender statistically significant separations. Entropy differences were categorically constrained to the bilateral temporal poles, encouraging us to further analyze the region as a distinct group in the leave-one-out and prediction analyses. Both mean and entropy comparisons between bipolar individuals and healthy controls were corrected for the 16 individual comparisons made in their respective analyses (both FA and MD comparisons made for 8 regions of interest).

2.7 Group-wise analysis

Student's t-tests were used to ensure that the healthy control group was well matched and reflective of the age and sex of the BD patient population analyzed.

The histogram of voxel-wise diffusivity data was determined and the statistical entropy of these distributions was calculated as a metric of the organizational differences regions of interest. A t-test was again used to determine the differences in these data.

2.8 Leave-one-out analysis

We assessed the potential for temporal pole MD and FA entropy to serve as diagnostic biomarkers of BD using leave-one-out validation. Each individual in the matched dataset was iteratively removed, and an optimal threshold between the remaining BD and healthy populations was determined by maximizing the Youden j-index. The removed individual was then assigned to either group based off of this optimal threshold. Reported metrics are the sensitivity, specificity and total diagnostic accuracy of each metric.

2.9 Training-Testing

We gathered data for an additional 11 right-handed individuals who could not be age- and sex-matched and used these individuals to assess the generalizability of findings from the matched dataset. This testing dataset consisted of 4 bipolar individuals—one of whose diagnosis was bipolar II—and 7 healthy controls. Individuals were classified by strict thresholding, as in the leave-one-out analysis. The optimal threshold was determined in the training dataset, as described above, this threshold was used to predict the diagnostic status of all individuals in the testing dataset. Lastly, in order to assess the performance of a range of thresholds, and the consistency thereof between the training and testing datasets, we calculated the area under the receiver operating characteristic (**ROC**) curve (**AUC**) for the training and testing datasets, as well as a combined dataset which incorporated all 29 individuals in both datasets.

3. Results

Demographics for all participants are shown in Table 1.

3.1 Matched Participants

Nine patients were included in the matched dataset along with age- and sex-matched controls. Participants in this dataset ranged from 24–58 years old. The average ages of the patients and controls were 39.0 (± 11.1) years and 39.4 (± 11.3) years. In both groups, there are 5 males and 4 females. Using an unpaired Student's t-test, the p-values for the age and sex of the two groups are 0.93 and 1, respectively, demonstrating that the groups are well matched.

3.2 Group-wise analysis

3.2.1 Mean MD and FA analysis—We began our analysis by investigating the hypothesis that both bipolar patients and healthy controls would exhibit similar average MD and FA in the 16 regions of interest. Concordant with the current literature, we did not

observe statistically significant differences in average FA or MD in any region of interest analyzed in this study.

3.2.2 Group-Level Entropy Analysis—Figure 1 shows group-wise histograms of MD in the left, right and combined bilateral temporal poles. Histogram differences, in the absence of mean-level differences, between bipolar patients and healthy controls were a noteworthy feature of the temporal pole regions, wherein we observed a qualitatively larger peaks in the BD population MD distributions, suggesting a greater homogeneity of MD values; this was observed in both the left and right temporal pole (see Figure 1, left and middle). In accordance with this observation, mean MD entropies were significantly lower in both the left and right temporal pole in BD patients than in healthy controls. Such an effect was not observed for FA. The histograms shown account for all individuals in the age- and sex-matched dataset, although entropies for each individual were extracted for later separation and thresholding calculations.

Entropy differences between BD patients and healthy controls were found to be an exclusive feature of temporal pole MD, where this effect was observed bilaterally. We observed significantly lower entropy of MD in the left ($p_{\text{Left}}=0.0085$, uncorrected) and right ($p_{\text{Right}}=0.0081$, uncorrected) temporal pole in the bipolar group relative to the age- and sex-matched controls. We observed a significantly lower entropy of FA in the right temporal pole ($p_{\text{Right}}=0.003$, uncorrected), and no difference in entropy of FA in the left temporal pole ($p_{\text{Left}}=0.42$, uncorrected)

Entropy findings did not survive correction for the 16 comparisons made across all ROIs. Pooling both the left and right temporal pole voxels into a combined, bilateral ROI, we observed significantly lower MD entropy in the BD group ($p_{\text{combined}}=0.0027$), alongside significantly lower FA entropy ($p_{\text{combined}}=0.015$). Inclusive of these two additional comparisons, only the MD finding in the combined ROI maintained its significance ($p_{\text{mc}}=0.0486$, p_{mc} representing multiple comparison corrected p-value).

Entropy comparisons between the BD and control groups in the temporal pole are summarized in Figure 2.

3.3 Leave-One-Out Analysis

The utility of bilateral temporal pole MD entropy as a biomarker for bipolar disorder was investigated. We began this analysis by investigating the generalizability of our findings in the bilateral temporal pole region of interest using a leave-one-out analysis in the matched dataset. Bilateral temporal pole MD entropy was seen to be highly sensitive to bipolar condition, correctly classifying 8 out of the 9 BD patients (sensitivity=89%), while also correctly classifying 7 out of the 9 healthy controls (specificity=78%). The total diagnostic accuracy across all individuals in the matched dataset was 83%, with 15 out of 18 individuals correctly classified as either BD or healthy control.

3.4 Training-Testing Analysis

To validate the performance of the diagnostic accuracy of the proposed metric, we tested it using a separate testing data set. The testing dataset consisted of all right handed individuals

who were not previously included in the matched dataset: 4 BD patients and 7 healthy controls. Their inability to be matched against one another is reflected in their demographics: the bipolar group had a mean age of 20.8 (± 3.4) years, while the control group had a mean age of 51.7 (± 5.1) years. Moreover, the 4 patients in this group were all male, while the 6 of 7 controls were female. It is noteworthy to point out that the threshold used in this analysis was determined using the independent training set.

As with the leave-one-out analysis bilateral temporal pole MD entropy was highly sensitive to BD, correctly predicting the status of all 4 patients in the testing dataset. At the same time, 4 out of the 7 healthy controls' statuses were correctly predicted; total diagnostic accuracy across these 11 individuals in the testing dataset was 73%.

Entropy of MD ROC analysis in the bilateral temporal pole of the training and testing datasets, and the combination thereof, yielded consistent results, the AUC for the training, testing and combined datasets were all 0.90. (Figure 3).

4 Discussion

This study's outcome measure, the entropy of diffusivity values, showed a strong separation between healthy controls and the un-medicated bipolar patients enrolled. This work is not only methodologically novel for analyzing the entropy of diffusivity, but is also the first to report differences in diffusivity throughout the temporal pole in BD. Our primary finding was the entropy of mean diffusivity is diminished in the temporal poles of individuals with bipolar depression. This effect was seen at the group level, and held for 8 out of the 9 pairs of individuals in the matched dataset. Entropy of MD was seen to generalize very well when evaluated as a diagnostic biomarker of BD: leave-one-out and training-testing analysis achieved total accuracies of 83% and 73%, respectively. It is important to note that these prediction results, particularly in the case of the leave-one-out validation, should be interpreted cautiously in light of the small sample size employed.

Changes in information theoretic entropic states have potential applications for both local and global brain function. Mood disorders, increasingly, are coming to be understood as disorders in the interconnected network structure of the brain (Brady Jr et al., 2017; Korgaonkar et al., 2014). The integrity of such networks is dependent upon well-ordered anatomical connectivity and concurrent functional activations. The discovery of entropic changes in diffusion at the regional level, as presented here, strongly suggest deviation from the brain's typical network properties. Whereas global changes were not examined in this work, such phenomena have been examined in functional brain networks. Notably, hallucinogens have been widely demonstrated to engender entropy increases in global functional activation networks; these entropy-based changes in network state have been seen to predict persistent changes in personality (Lebedev et al., 2016).

There is a paucity of research regarding the temporal pole in BD. This constitutes a significant gap in the literature, not only in the context of our findings, but also given the region's proximity and strong structural connectivity to widely researched regions such as the amygdala and orbitofrontal cortex (Brooks III and Hoblyn, 2005; Duvernoy, 2012; Jorge

et al., 1993). The temporal pole was referred to as “enigmatic” in a 2007 review of findings centered upon the region (Olson et al., 2007), and indeed the region’s precise functions remain largely undiscovered. The temporal pole has been consistently reported to regulate processes such as discerning emotional states of facial expressions (Royet et al., 2000), subjectively assessing affect (Mathiak et al., 2011) and empathy (Damasio et al., 2000). In addition to our results, clinical evidence has suggested that temporal pole lesions can precipitate BD in previously healthy individuals (Brooks III and Hoblyn, 2005; Jorge et al., 1993; Murai and Fujimoto, 2003). In combination with our results, these findings demonstrate the need for further research into the temporal pole in BD.

This work suffers from a handful of limitations. Notably, the modest sample size limits statistical resolution, and precludes covariate analysis of such factors as medication history and symptom duration. The use of a single scanner for this study may limit its generalizability, as inter-scanner differences in DTI findings are common (Takao et al., 2012). Moreover, echo planar imaging pulse sequences used in diffusion MRI can exhibit significant distortion artifacts in regions with large variance in magnetic susceptibility, such as the inferior regions of the brain, where air and tissue are in close proximity to one another (Wan et al., 1997). These effects are a reasonable concern in DTI of the temporal pole, although there is no reason to assume off-resonance effects would skew results by being more common in either BD patients or healthy controls.

The possible confounding effect of previous medication history is also a concern. That said, the population utilized was largely medication-naïve (6 out of 9 patients), and all individuals had been medication-free for at least the 3-week washout period. In particular, 3 out of the 9 bipolar patients in this study had previously taken psychiatric medication of some sort. One individual had previously taken sertraline, which was ceased 33 days prior to baseline MRI; another individual had taken sertraline two years prior to participation, and more recently ceased lamictal (43 days prior to scan); this individual also was prescribed alprazolam on the scan date due to claustrophobia. The final previously medicated patient had taken both bupropion and venlafaxine, though both were ceased prior to two years before their participation in this study. In both the left and right temporal pole, the previously medicated subgroup of the bipolar population was seen to have lower MD entropies than their medication-naïve peers (Figure 4), although this was not significant in the left ($p=0.30$) or right ($p=0.24$) temporal pole.

Diagnostic status in the bipolar individualizes analyzed is a final complication of this work. In particular, 3 of the 9 individuals in the training dataset were bipolar II patients, while one individual in the testing dataset was bipolar II. Whereas our sample size obviates the possibility of directly controlling for this effect, we observed that the bipolar II individuals exhibited lower entropy of MD in the combined temporal pole, although not statistically significant. MD entropy data and clinical diagnosis for all individuals in both the training and testing datasets are provided in Table 1. Whereas the lack of covariate analysis is a limitation, the strong diagnostic performance of a model trained using a partially bipolar II population suggests generalizability to clinical practice. A further, fully powered analysis seeking to differentiate between bipolar subtypes based on the entropy metric shown in this manuscript would be an exciting avenue for future research. Whereas the prediction analyses

reported, in particular the application of MD entropy to an external dataset, show promise for generalizability to clinical populations, it should be noted that the stringent inclusion and exclusion criteria—related to these individuals' enrollment in a clinical trial—warrants a prospective study meant to validate these findings in a more general population.

Investigation into diagnostic and individualized treatment selection biomarkers is essential for improving patient outcomes and reducing the overall burden of psychiatric illness. With a growing body of literature detailing structural and functional properties of the paralimbic system as potential biomarkers for bipolar depression, this study sought to detail the paralimbic group-wise interactions between BD patients and healthy controls using the diffusion metrics FA and MD and the novel metric of diffusion entropy. We first provided further evidence of the absence of localized, group-wise effects of MD and FA in the paralimbic system at the mean level. Next, we identified the entropy of MD in the temporal pole as a potential diagnostic biomarker for BD in group-wise comparisons, as well as in classification analyses with an independent validation set of BD patients and controls. Entropy of MD provided strong separations between patients and controls in both paired and predictive analyses. Future investigation of this novel diffusion measurement in prospective BD neuroimaging studies would help to elucidate the diagnostic power of this potential biomarker.

Acknowledgments

This study was in part supported by NIH grant R01MH090276 (RP) and Stony Brook Bridge Funding Program (CH).

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Figure 1. Representative histograms of voxel-wise MD values in the left, right and combined bilateral temporal poles. Vertical lines indicate the mean value of their color-matching curve; p values refer to the significance of differences in average values across the two populations.

Figure 2. Box plots for left (left) and right (middle) temporal pole MD (top) and FA (bottom) along with the combined bilateral ROI (right). Red line = mean; red bar = 95% confidence interval; blue line = 1 standard deviation. P values are not multiple comparison corrected.

Figure 3.
ROC analysis in the matched training dataset, testing dataset, and combination thereof.
Diagonal line, in green, indicates 50–50 diagnostic performance.

Figure 4. Box plots demonstrating entropy findings in previously medicated and medication-naive patients. Red line = mean; red bar = 95% confidence interval; blue line = 1 standard deviation.

Table 1

Demographic information and diagnostic status for all individuals analyzed in the matched training dataset (top) and the testing dataset employed in prediction analysis (bottom)

Bipolar Training Data					Healthy Controls Training Data				
Subject	Age	Sex	Diagnosis	Combined TP MD Entropy	Subject	Age	Sex	Combined TP MD Entropy	
1	30	F	BD-I	0.842	1	30	F	1.16	
2	47	M	BD-II	1.02	2	29	M	0.956	
3	24	F	BD-II	0.837	3	25	F	1.20	
4	42	F	BD-I	0.860	4	40	F	1.16	
5	43	M	BD-I	1.07	5	44	M	1.43	
6	47	M	BD-I	1.15	6	47	M	1.21	
7	29	M	BD-I	0.868	7	52	M	1.39	
8	58	F	BD-I	1.05	8	57	F	1.16	
9	31	M	BD-II	0.942	9	31	M	1.01	

Bipolar Testing Data					Healthy Controls Testing Data				
Subject	Age	Sex	Diagnosis	Combined TP MD Entropy	Subject	Age	Sex	Combined TP MD Entropy	
1	22	M	BD-II	0.892	1	47	F	1.29	
2	18	M	BD-I	1.05	2	54	M	1.10	
3	25	M	BD-I	0.857	3	58	F	1.30	
4	18	M	BD-I	1.12	4	44	F	1.29	
					5	54	F	0.98	
					6	56	F	1.40	
					7	49	F	1.13	

* P values of the age and gender are 0.93 and 1, respectively (student t-test, unpaired)
Note: All units of entropy are listed in nats.