Spectral Analysis of Resting State Magnetoencephalogram Activity in Patients with Bipolar Disorder

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***Abstract*–We analyzed the frequency spectrum of magnetoencephalogram (MEG) background activity in 16 bipolar disorder (BD) patients and 24 age-matched healthy control. Median frequency (*MF*), spectral entropy (*SpEn*), and relative power in delta (*RP*δ), theta (*RP*θ), alpha (*RP*α), beta (*RP*β), and gamma (*RP*γ) bands were computed for all 148 MEG channels. Significant differences between the two groups were found in the average level of *MF*, *RP*δ, and *RP*θ in the posterior region of the scalp. Moreover, the *MF*, *SpEn*, *RP*δ, and *RP*β values of BD patients had a different dependence on age as compared with the results of control subjects, which may suggest that BD affects how the brain activity develops with age. We conclude that the spectral analysis of the background MEG in BD patients may give insights into how this condition affects the brain activity.**

I. Introduction

BIPOLAR disorder (BD) affects approximately 5.7 million adult Americans, or about 2.6% of the U.S. population age 18 and older every year, according to the statistics of National Institute of Mental Health (NIMH) [1], [2]. This disease may cause striking shifts in energy, mood, and activity levels, which will affect the ability of the person to perform daily tasks [2].

The median age of onset of BD is 25 years but it may start in early childhood or as late as the 5th or 6th decade of life. The disease affects equally males and females in all ages and races [1], [2]. It may take years to recognize the disease. However, most patients are diagnosed before the age of 30 [3]. According to the World Health Organization, BD is regarded as one of the six largest causes of disability in the world. Furthermore, one in five patients diagnosed with BD may commit suicide according to the NIMH [1], which reflects the danger and seriousness of the BD on the patient. An early diagnosis of BD would help to start the treatment of the condition as soon as possible, thus facilitating disease management. Moreover, it is important to understand how BD affects the patient's brain activity to facilitate disease monitoring.

The magnetoencephalogram (MEG) measures the magnetic fields generated by the neurons directly and non-invasively with high temporal resolution. It provides an excellent opportunity to study brain function in health and disease [4]. However, few studies have been conducted analyses of MEG recordings in BD.

Lee *et al.* [5] tried to differentiate between BD and major depressive disorder (MDD), as patients with different affective disorders may have distinct patterns of oscillatory cortical activities in response to negative emotional stimuli. Based on the analysis of MEG signals of 20 controls, 20 BD and 20 MDD patients, they found that γ oscillation decreased in the frontal regions of both BD and MDD patients, and γ activity increased in the bilateral temporal regions of MDD, while α-β rhythms increased in only BD patients[5].

In a different study which investigated the change of neural dynamics in BD [6], a nonlinear measurement – "similarity index" – was used to analyze the MEG recordings of ten BD patients and ten controls to test the hypothesis that there are synchronization changes within different frequency bands in the frontal cortex of the patients. The synchronization level in δ, θ, α and β bands were calculated for each subject for only eleven frontal channels of MEG resting state data. The authors found significant dynamic changes in BD patients: decreased synchronization of fast frequencies (β) and increased synchronization of slow oscillations (δ).

Researchers also tried to investigate if there is any change in the electroencephalography (EEG) frequency band analysis for the BD patients. Howells *et al.* [7] analyzed the EEG in frequency bands for twelve BD patients and nine controls during resting states (eyes open, eyes closed) and also during the completion of a continuous performance task. They found an increase in β band power, a decrease in θ band power, and a decrease in the ratio of θ/β during the resting state, eyes closed, for frontal and cingulate cortices. In another study, resting state EEG power and coherence were investigated for 76 BD patients, 132 schizophrenia (SZ) patients, and 136 non-psychiatric controls to differentiate the groups from one another [8]. The group differences within seven frequency bands across several brain regions were examined. BD showed significantly greater power relative to SZ at higher frequencies including β and θ across all regions. In addition, both SZ and BD showed higher coherence in α1 and α2 bands in terms of intra-hemispheric coherence. On the contrary, BD and CON showed higher coherence within hemispheres compared

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to SZ in the β1 band. Finally, BD exhibited increased high frequency power with few disruptions in neural synchronization in terms of inter-hemispheric coherence.

To shed light on the changes that BD induces on the resting state MEG activity and how this activity may depend on age, we propose to evaluate spectral features of MEG for CON subjects and BD patients.

II. Materials

A. Subjects

The MEG sample analyzed in this pilot study includes 16 type 1 [9] BD patients and 24 CON subjects. The research study was approved by the ethics committee of the Hospital Gregorio Marañón, Madrid, Spain. All participants gave their informed consent.

The average age of the BD group was 46.4±18.7 years (mean ± standard deviation, SD) and it was composed of eight males and eight females. The control subjects (12 males and 12 females) were volunteers with no history of psychiatric disorder. Subjects with a history of neurological diseases, head trauma or drug abuse were excluded from the study. The average age of the controls was 41.25±12.3 years (mean ± SD). The difference in age between both groups was not significant (p-value=0.303, Student's t-test).

B. MEG acquisition

The MEG recordings were acquired using a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) located in a magnetically shielded room at the "Centro de Magnetoencefalografía Dr. Pérez-Modrego," Spain. The resting state brain activity was recorded while each volunteer was laying on a patient bed, awake and with eyes closed. For each subject, 5 minutes of MEG signals were recorded with a final sampling rate of 169.54 Hz and they were transferred to a computer as ASCII files. No movement compensation was applied to the MEG signals.

MEG epochs of 10s with reduced ocular activity were selected for further analysis blindly to the subject's diagnosis by means of a visual inspection assisted with an amplitude thresholding method [10]. Finally, the MEG epochs were digitally filtered between 1.5Hz and 40Hz using a 560th order FIR filter designed with a Hamming window to reduce the impact of ocular, muscular and mains artefacts in the analyses. The ECG signal was not removed from the MEG recordings in this pilot study.

III. Methods

A. Spectral analysis

We perform a detailed spectral analysis of the MEG signals. Each MEG channel is characterized with its power spectral density (*PSD*) and the following features will be computed from the corresponding *PSD*s: median frequency (*MF*), spectral entropy (*SpEn*) and relative power (*RP*) in δ (1.5Hz–4Hz; *RP*δ), θ (4Hz– Hz; *RP*θ), α (8Hz–13Hz; *RP*α), β (13Hz–30Hz; *RP*β) and γ (30Hz–40Hz; *RP*γ) bands.

For each MEG epoch, channel and subject, the *PSD* is computed as the Fourier transform of the corresponding autocorrelation function [10]. The *PSD*s are then averaged to calculate a mean *PSD* per channel and subject.

To simplify subsequent analyses and minimize the effect of potential co-founding factors, the *PSD* is normalized by the power in the filter's pass-band (1.5Hz–40Hz), leading to a normalized *PSD* (PSD_n):

$$PSD_n(f) = \frac{PSD(f)}{\sum_{f=1.5\,\mathrm{Hz}}^{40\,\mathrm{Hz}} PSD(f)}, \quad (1)$$

with

$$\sum_{f=1.5\,\mathrm{Hz}}^{40\,\mathrm{Hz}} PSD_n(f) = 1. \quad (2)$$

The first feature is *MF*, which is a summary of the relative strength of low- and high-frequency oscillations in the frequency spectrum. *MF* is defined as the frequency value that splits the band-pass of the PSD_n in two bands with half the PSD_n power[10]:

$$\sum_{f=1.5\mathrm{Hz}}^{MF} PSD_n(f) = 1/2. \quad (3)$$

Considering that PSD_n can be seen as a probability density function, it is possible to use Shannon's entropy to characterize its shape. This feature is known as *SpEn*. It assesses the flatness of the signal spectrum [10]. A broad and flat spectrum leads to high *SpEn*, whereas a predictable signal with narrow spectrum has low *SpEn* [11]. *SpEn* is calculated as follows:

$$SpecEn = \frac{-1}{\log(N)} \sum_{f=1.5\,\mathrm{Hz}}^{40\,\mathrm{Hz}} PSD_n(f) \log[PSD_n(f)], \quad (4)$$

where N is the number of frequency bins.

Finally, the *RP* of the resting state MEG activity is calculated in traditional bands: δ, θ, α, β, and γ [12], [13]. This computation is straightforward from the PSD_n. Denoting with f_{low} and f_{high} the low and high cut-off frequencies of each band, the corresponding *RP* is:

$$RP = \sum_{f=f_{low}}^{f_{high}} PSD_n(f). \quad (5)$$

B. Statistical analysis

The spectral features are computed for each subject and channel. To reduce the dimensionality of the results, the 148 MEG channels were grouped into five regions (Anterior, Central, Left, Right, and Posterior). Then, the mean value of each feature was computed for each region following successful previous approaches [14]–[16].

In order to evaluate the differences in the spectral features between the two groups (CON and BD), an analysis of variance with age as a covariate (ANCOVA) was used. Further analyses were carried out by calculating the correlation coefficient between age and the results of the spectral feature separately for each subject group in the cases of the features and regions for which, at least, a tendency towards an interaction between age and diagnosis was identified (corresponding p-value <0.10).

TABLE 1. MEAN VALUE OF THE SPECTRAL FEATURES FOR THE BIPOLAR DISEASE (BD) AND THE CONTROL (CON) GROUP FOR EACH REGION.

Region	Group	*MF (Hz)*	*SpEn*	*RP*δ	*RP*θ	*RP*α	*RP*β	*RP*γ
Ant.	BD	11.13	0.92	0.23	0.19	0.17	0.35	0.06
	CON	10.99	0.93	0.20	0.19	0.19	0.36	0.06
Cent.	BD	12.37	0.94	0.15	0.18	0.22	0.38	0.07
	CON	12.54	0.95	0.11	0.16	0.26	0.40	0.06
Left	BD	10.40	0.91	0.19	0.21	0.26	0.30	0.04
	CON	10.86	0.92	0.15	0.18	0.29	0.33	0.04
Right	BD	10.17	0.91	0.22	0.19	0.24	0.30	0.04
	CON	10.97	0.92	0.16	0.16	0.29	0.34	0.04
Post.	BD	9.92	0.91	0.17	0.23	0.27	0.29	0.04
	CON	11.21	0.92	0.11	0.18	0.33	0.34	0.04

IV. RESULTS

The test of Kolmogorov–Smirnov with the Lilliefors significance correction showed that the distributions of the results were Gaussian. The results of the spectral features in each region for CON and BD subjects are summarized in Table 1.

Table 2 summarizes these results of the analysis of variance with age as a covariate in terms of *p*-value for the differences between both groups ('Diag.') and the *p*-value for the interaction of diagnosis and age ('D. × A.'). (*RPγ* did not provide any significant results or tendency and, thus, it is not included in Table 2). The spectral features that have the largest group differences were *MF*, *RPδ*, and *RPθ*. The differences were significant (*p*-value < 0.05) for $MF_{\text{Posterior}}$, $RP\delta_{\text{Posterior}}$ and $RP\theta_{\text{Posterior}}$. It is noteworthy that these significant differences appeared in the posterior region. As for the evolution of the spectral features with age, the *p*-values in Table 2 for the interaction of age and diagnosis indicated that there was a tendency towards interaction between the age of the subjects and their diagnosis for *MF*, *SpEn*, *RPδ* and *RPβ*. *RPθ, RP*α, and *RPγ* did not provide any significant differences or tendencies and, therefore, they were removed from subsequent analyses.

In order to further explore the potentially abnormal dependence between MEG activity and age in the patients for the cases where at least a tendency (*p*-value < 0.10) appeared in Table 2, Table 3 contains the Pearson's correlation coefficients (ρ), and the *p*-values, computed separately for each subject group, between age and the spectral features. It can be seen that the spectral features of the BD patients tended to show no correlation with age whereas the features of CON subjects had a significant dependency on age in most cases.

TABLE 2. P-VALUES FOR THE DIFFERENCES BETWEEN BD AND CON SUBJECT GROUPS (LABELLED AS 'DIAG.') AND FOR THE INTERACTION OF AGE AND DIAGNOSIS (LABELLED AS 'D.×A.') FOR EACH COMBINATION OF SPECTRAL FEATURE AND REGION.

		Region				
Feature	***p*-value**	***Ant.***	***Cent.***	***Left***	***Right***	***Post.***
MF (Hz)	Diag.	0.894	0.827	0.551	0.392	0.047
	D. × A.	0.011	0.018	0.048	0.013	0.179
SpEn	Diag.	0.566	0.488	0.266	0.256	0.251
	D. × A.	0.199	0.045	0.115	0.013	0.430
*RP*δ	Diag.	0.383	0.053	0.182	0.104	0.006
	D. × A.	0.027	0.015	0.029	0.011	0.071
*RP*θ	Diag.	0.959	0.322	0.127	0.087	0.021
	D. × A.	0.193	0.064	0.392	0.112	0.906
*RP*β	Diag.	0.813	0.446	0.266	0.276	0.067
	D. × A.	0.014	0.013	0.054	0.022	0.150

TABLE 3. PEARSON'S CORRELATION COEFFICIENTS (ρ) AND THE CORRESPONDING P-VALUES FOR THE RELATIONSHIP BETWEEN SPECTRAL FEATURES AND AGE IN EACH REGION COMPUTED SEPARATELY FOR EACH SUBJECT GROUP. ONLY COMBINATIONS OF FEATURES AND REGIONS THAT SHOWED AT LEAST A TENDENCY (P-VALUE <0.10) FOR THE INTERACTION BETWEEN AGE AND DIAGNOSIS IN TABLE 2 ARE CONSIDERED.

BD group						
		Region				
Feat.	**Correlation**	***Ant.***	***Cent.***	***Left***	***Right***	***Post.***
MF (Hz)	ρ	-0.364	-0.264	-0.175	-0.347	-0.068
	p-value	0.166	0.324	0.516	0.188	0.802
SpEn	ρ	-0.316	-0.373	-0.265	-0.495	-0.057
	p-value	0.233	0.155	0.321	0.051	0.833
RPδ	ρ	0.381	0.318	0.256	0.349	0.284
	p-value	0.145	0.230	0.339	0.185	0.286
RPβ	ρ	-0.376	-0.189	-0.108	-0.307	-0.026
	p-value	0.152	0.484	0.692	0.248	0.923
CON group						
		Region				
Feat.	**Correlation**	***Ant.***	***Cent.***	***Left***	***Right***	***Post.***
MF (Hz)	ρ	0.475	0.533	0.537	0.484	0.446
	p-value	0.019	0.007	0.007	0.017	0.029
SpEn	ρ	0.143	0.281	0.287	0.268	0.207
	p-value	0.504	0.184	0.174	0.205	0.333
RPδ	ρ	-0.339	-0.529	-0.538	-0.531	-0.347
	p-value	0.105	0.008	0.007	0.008	0.096
RPβ	ρ	0.412	0.550	0.522	0.428	0.429
	p-value	0.045	0.005	0.009	0.037	0.036

Fig.1 displays the scatter plot of *MF* for each group of subjects and region and the corresponding linear regression between the spectral feature of each group and age, as an example of the different dependency of the spectral features on age for both subject groups.

V. DISCUSSION AND CONCLUSIONS

In this pilot study, MEG recordings from 16 BD patients and 24 CON subjects were analyzed with a set of spectral features including *MF*, *SpEn*, and the *RP* in δ, θ, α, β, and γ bands [10] in order to provide a comprehensive view of the frequency spectrum of the MEG activity. Our aim was to examine whether some of the aforementioned spectral features were able to reveal differences between both subject groups. In addition, we studied the role of age in the brain activity of BD patients. We found significant differences in the *MF*, *RPδ*, and *RP*θ between the two groups in the posterior region of the scalp. It is noteworthy that the differences in *RP*δ agree with the previous literature [6], although the nature of the signal feature and the region of the scalp are different and further research is needed to confirm this result. Despite the fact that there were no significant changes in higher bands (α, β, and γ), there was a significant differences for *MF*. This may suggest that *MF* can be used as an appropriate metric to characterize the diffused changes in the frequency spectrum due to BD.

We chose Age as a covariate because of previous work indicating that the background of MEG activity changes with age across the life-span [15] and that this dependency on age might be different in patients with different psychiatric conditions in comparison with CON subjects [14]. Interactions between age and diagnosis were found for the *MF*, *SpEn*, *RP*δ, and *RP*β. From the calculation of Pearson's correlation coefficients (*ρ*) and the corresponding *p*-values displayed in Table 3, it can be

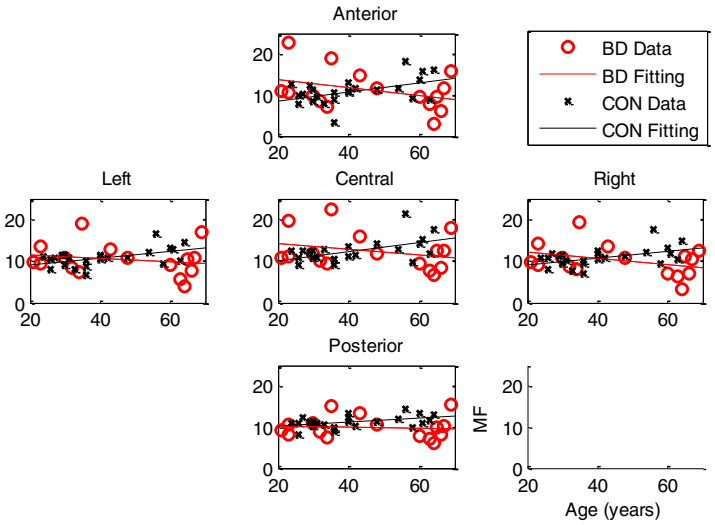

Fig. 1. Linear regression of the *MF* results (*y* axis) versus age (*x* axis) in the five regions for BD (red dashed line and red circles) and CON (black full line and black crosses) subjects. Patients with BD show a tendency towards having smaller *MF* values as age increases

noticed that there was a strong dependency on age for some spectral features (*MF*, *RP*δ, *RP*β) for the controls. However, this dependency appears to be diminished or disrupted for BD patients.

The study has some limitations. Firstly, it is limited by the reduced sample size. Moreover, differences in arousal between the two groups and the effect of medication (particularly antidepressants with anticholinergic action) were not investigated. Both the arousal state and anticholinergic drugs can shift the center of mass of the frequency spectrum (*MF*) which may affect the measurements since power was normalized to the full band. Future research lines will include the use of advanced classification techniques to separate the BD patients from CON subjects. We also will assess the usefulness of nonlinear features [17] to characterize the MEG background activity in BD.

In summary, we presented the results of a spectral analysis of MEG background activity recorded from BD patients. Our aim was to investigate how age and BD affect the MEG frequency spectrum. We found significant differences and a different evolution with age in the BD patients, in comparison with controls. In this sense, *MF* might be used to characterize the diffused changes in the frequency spectrum due to BD. These and future results might lead to the consideration that BD pathology changes the normal evolution of the electromagnetic brain activity with age. Our conclusion is that the spectral analysis of the MEG in BD patients may provide information on how this condition affects brain activity.

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