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Changes in the MEG background activity in patients with positive symptoms of schizophrenia: spectral analysis and impact of age

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Abstract

The frequency spectrum of the magnetoencephalogram (MEG) background activity was analysed in 15 schizophrenia (SCH) patients with predominant positive symptoms and 17 age-matched healthy control subjects using the following variables: median frequency (*MF*), spectral entropy (*SpecEn*) and relative power in delta ($RP\delta$), theta ($RP\theta$), lower alpha ($RP\alpha 1$), upper alpha ($RP\alpha 2$), beta ($RP\beta$) and gamma ($RP\gamma$) bands. We found significant differences between the two subject groups in the average level of *MF* and $RP\gamma$ in some regions of the scalp. Additionally, the *MF*, *SpecEn*, $RP\beta$ and $RP\gamma$ values of SCH patients with positive symptoms had a different dependence on age as compared with the results of control subjects, suggesting that SCH affects the way in which the brain activity evolves with age. Moreover, we also classified the MEG signals by means of a cross-validated feature selection process followed by a logistic regression. The subjects were classified with 71.3% accuracy and an area under the ROC curve of 0.741. Thus, the spectral

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and classification analysis of the MEG in SCH may provide insights into how this condition affects the brain activity and may help in its early detection.

Keywords: classification, early diagnosis, magnetoencephalogram, positive symptoms, schizophrenia, spectral analysis

(Some figures may appear in colour only in the online journal)

1. Introduction

The electroencephalogram (EEG) and the magnetoencephalogram (MEG) measure the electrical and magnetic fields generated by the neurons, respectively (Rossini *et al* 2007, Sanei and Chambers 2007). These non-invasive techniques have been used to investigate several diseases, including Alzheimer's disease (Rossini *et al* 2007), attention-deficit/hyperactivity disorder (Fernández *et al* 2009), depression (Méndez *et al* 2012) and schizophrenia (SCH) (Hinkley *et al* 2010, Fernández *et al* n.d.). In contrast to other functional neuroimaging techniques (e.g., positron emission tomography or functional magnetic resonance imaging), the EEG and MEG have much higher temporal resolution and they record the neural activity directly without the need to interpret it in terms of proxy measures such as glucose consumption (Hinkley *et al* 2010, Rossini *et al* 2007, Sanei and Chambers 2007). Additionally, the MEG offers some advantages over the EEG because the magnetic recordings are reference-free and less affected by extra-cerebral tissues than the EEG (Rossini *et al* 2007). On the other hand, the accessibility to MEG equipment is more limited than to EEG devices (Sanei and Chambers 2007).

SCH is a serious psychiatric disorder characterized by a range of 'positive' and 'negative' symptoms (Picchioni and Murray 2007). The former include hallucinations, delusions and paranoia; while the latter comprise cognitive impairment, social withdrawal, self-neglect and loss of motivation and initiative (Picchioni and Murray 2007). Worldwide, SCH represents 1.1% of the total disability adjusted life years and 2.8% of the years lived with disability (Picchioni and Murray 2007). The prevalence of SCH is relatively high because it usually starts in late adolescence or early adulthood and then becomes a chronic condition (Picchioni and Murray 2007). This disease affects the patient's functioning at multiple levels: neurochemical, neurophysiological, neuroanatomical, emotional, cognitive, social and familial (Fernández *et al* n.d.). A prodromal stage of increasingly severe symptoms, which may last for months or years, usually occurs before the first psychotic episode arises. The longer the period of untreated psychosis, the worse the outcome (Picchioni and Murray 2007). Therefore, patients with SCH should be identified and treated as early as possible (Picchioni and Murray 2007).

A number of studies have analysed the EEG and MEG in SCH, reporting some abnormalities in the brain signals of SCH patients in comparison with control subjects (Itil 1977, Galderisi *et al* 2009, Hinkley *et al* 2010, Uhlhaas and Singer 2010, Shin *et al* 2011). Increases in the δ (and, to a lesser extent, θ) activity in SCH patients are often found (Itil 1977, Boutros *et al* 2008, Galderisi *et al* 2009, Hinkley *et al* 2010). Evidence for changes in other spectral bands is less consistent (Elbert *et al* 1992, Boutros *et al* 2008, Li *et al* 2008).

A few studies described spectral changes in the opposite direction of that reported by most articles (Galderisi *et al* 2009). Contradictory results have also been reported when applying nonlinear techniques to EEG and MEG recordings of SCH patients. Early studies showed higher complexity in the brain signals of SCH patients (Fernández *et al* n.d.). However,

subsequent analyses found both increased (Li *et al* 2008, Fernández *et al* 2011) and decreased (Raghavendra *et al* 2009, Sabeti *et al* 2009) levels of complexity in SCH patients' brain activity. These contradictory findings probably reflect the heterogeneity of SCH (Boutros *et al* 2008) and they may have been caused by not taking into account some cofactors (Raghavendra *et al* 2009). For instance, the chronicity of the disease might affect the power in δ and θ bands, leading to larger increases in the slow activity of chronic as compared with first-episode patients (Galderisi *et al* 2009). This potential effect of chronicity in the results was also highlighted in signal complexity studies (Lee *et al* 2008, Fernández *et al* n.d.). The presence of positive or negative symptoms may be important as well. The EEGs of SCH patients with positive symptoms were reported to have values of fractal dimension similar or even higher than those of control (CON) subjects on bilateral temporo-occipital regions, but such localized increases were not found in patients with negative symptoms (Raghavendra *et al* 2009). Positive symptoms have also been correlated with increased amplitude and synchronization of evoked and induced localized high frequency activity, but this was not the case in patients with negative symptoms (Uhlhaas and Singer 2010).

It is also important to assess the potential of the processing of the electromagnetic brain activity to help in the detection of SCH. To this end, diverse signal processing and classification techniques have been tested, achieving accuracies of about 80% to 90% (Boostani *et al* 2009, Sabeti *et al* 2009, 2011). Despite the relevance of this topic, these analyses have been carried out only on EEG data (Boostani *et al* 2009, Sabeti *et al* 2009, 2011). Thus, the potential of the MEG to aid in the detection of SCH has yet to be evaluated. Furthermore, the impact of other covariates (such as age or the presence of positive or negative symptoms) on the analyses of the brain activity has not been fully inspected (Boostani *et al* 2009, Sabeti *et al* 2009, 2011). In general, the application of advanced signal processing techniques to electromagnetic recordings is scarcer in SCH than in other pathologies (Sanei and Chambers 2007).

To sum up, there is evidence about the importance of cofactors (e.g., the presence of positive or negative symptoms) in the analysis of electromagnetic brain activity in SCH (Sabeti *et al* 2009, Fernández *et al* 2011, 2012, n.d.). In fact, recent results have highlighted the role that age could play in the brain activity of patients with this and other conditions (Rossini *et al* 2007, Fernández *et al* 2011). Additionally, there has been relatively little research on the potential of the processing and classification of MEG signals to contribute to the diagnosis of individual patients with SCH (Boostani *et al* 2009, Sabeti *et al* 2009, 2011). In order to shed light on these issues, we tackle the following research questions:

(1) Are spectral features able to reveal the potential abnormalities in the MEG activity due to SCH with predominant positive symptoms?
(2) Does the MEG activity of SCH patients with positive symptoms show an abnormal dependency on age in comparison with subjects?
(3) Do spectral features from the MEG activity contain relevant information to assist in the separation of SCH patients versus healthy subjects?

2. Materials and methods

2.1. Subjects

The dataset analysed in this study is composed of 15 SCH patients and 17 CON subjects. All participants provided informed consent for the research study, which was approved by the ethics committee of the San Carlos University Hospital, Madrid, Spain.

All SCH patients were receiving care at the San Carlos University Hospital Institute of Psychiatry and Mental Health and met the DSM-IV diagnostic criteria for SCH. Diagnosis

Table 1. Characteristics of the SCH and CON groups (given as counts for "Gender" and as mean ± standard deviation, SD, elsewhere).

	SCH	CON
Gender	11 Male / 4 Female	12 Male / 5 Female
Age (years)	31.93 ± 6.61	32.29 ± 6.12
Length of illness (years)	5.58 ± 3.20	Not applicable
Haloperidol equivalent dose (mg)	33.00 ± 19.02	Not applicable
Lorazepam equivalent dose (mg)	1.74 ± 1.70	Not applicable
Total SAPS score	89.75 ± 14.26	Not applicable

was made with the Spanish version of the SCID-I (First *et al* 1997). In order to obtain a homogeneous sample, only patients showing a high degree of positive psychotic symptoms were included. The scale for the assessment of positive symptoms (SAPS) (Andreasen 1984) was used to evaluate positive symptoms of SCH. Following previous studies (López-Ibor *et al* 2008, Fernández *et al* 2011), a minimum score of 70 (maximum: 165) and a minimal score of 29 (maximum: 65) in the delusional activity subscale were required to enter the study. At the time of the MEG acquisition, all SCH patients were using atypical antipsychotic medication and two were on the typical antipsychotic haloperidol.

The control group was composed by age-matched subjects with no history of psychiatric disorder. Subjects with a history of neurological diseases, head trauma or drug abuse were excluded from the study.

Table 1 summarizes the main characteristics of both subject groups, which have been partially described elsewhere (López-Ibor *et al* 2008, Fernández *et al* 2011).

2.2. MEG recording

The MEG recordings were acquired with a 148-channel whole-head magnetometer (MAGNES 2500 WH®,4D Neuroimaging) in a magnetically shielded room at the 'Centro de Magnetoencefalografía Dr Pérez-Modrego', Madrid, Spain. The MEG activity was recorded while the participants lay on a hospital bed in a relaxed state, awake with eyes closed, and under supervision. They were asked to avoid movements of eyes and head. For each subject, at least 5 min of MEG background activity were recorded at 678.19 Hz with a 0.1–200 Hz hardware band-pass filter. The MEG equipment decimated each dataset by a factor of four using a second-order Butterworth IIR anti-aliasing filter with cut-off frequency at 76.30 Hz (45% of the final sample rate: 169.55 Hz). This filter was applied to the signals in both forward and reverse directions to avoid net phase shift. Epochs of 10 s (1695 samples) with minimal ocular activity were visually selected for analysis by an expert unaware of the subjects' clinical condition with the aid of an amplitude thresholding method (Hornero *et al* 2008). On average, 28.38 ± 2.26 and 30.75 ± 7.94 (mean ± standard deviation, SD) epochs per CON and SCH subject, respectively, were copied to a computer as ASCII files for further analyses. They were filtered between 1.5 and 40 Hz using a 560th order FIR filter designed with a Hamming window. Such spectral band allowed us to analysing the relevant content of the MEG background activity, from δ to γ bands, while reducing the presence of ocular and muscular artefacts and power line noise.

2.3. Spectral analysis

Every MEG channel was characterized with a set of spectral features: median frequency (*MF*), spectral entropy (*SpecEn*) and the relative power (*RP*) in δ (1.5–4 Hz; $RP\delta$), θ (4–8 Hz; $RP\theta$), lower α (8–10.5 Hz; $RP\alpha 1$), upper α (10.5–13 Hz; $RP\alpha 2$), β (13–30 Hz; $RP\beta$) and

γ (30–40 Hz; $RP\gamma$) bands. These features provided a holistic view of the frequency spectrum of the signal.

2.3.1. Power spectral density (PSD). To assess the spectral content of the MEG recordings, we computed the power spectral density (PSD) of each signal as the Fourier transform of its autocorrelation function (Hornero *et al* 2008). The PSDs obtained from all artefact-free epochs of each channel and subject were averaged to compute the mean PSD corresponding to that channel and subject.

Afterwards, the range from 1.5 to 40 Hz (pass-band of the filter applied to the signals) was selected and the PSD was normalized by the total power in this band. This led to a normalized PSD (PSD_n):

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

so that

$$\sum_{f=1.5\,\mathrm{Hz}}^{40\,\mathrm{Hz}} \mathrm{PSD}_n(f) = 1. \tag{2}$$

The PSD_n simplified the computation of the features considered in this study.

2.3.2. Median frequency (MF). The *MF* summarizes the signal spectrum of the MEG background activity by providing information about the relative strength of low- and high-frequency oscillations. The *MF* was defined as the frequency value that separated the frequency range of the PSD_n in two bands so that each of them contained half the PSD_n power (Hornero *et al* 2008):

$$\sum_{f=1.5\,\mathrm{Hz}}^{\mathrm{MF}} \mathrm{PSD}_n(f) = {}^{1}\!/_{2}. \tag{3}$$

2.3.3. Spectral entropy (SpecEn). The PSD_n can be seen as a probability density function in order to characterize it with features derived from information theory. One of such features is Shannon's entropy, which measures the uncertainty of information in terms of diversity of a probability distribution. When applied to the PSD_n, it is known as spectral entropy (*SpecEn*) and it assesses the flatness of the signal spectrum (Sleigh *et al* 2004, Hornero *et al* 2008, Sabeti *et al* 2009). A broad and flat spectrum results in high *SpecEn* values, whereas a predictable signal with narrow spectral content has low *SpecEn* (Sleigh *et al* 2004). *SpecEn* was computed as

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

where N denotes the number of frequency bins and the factor ${}^{-1}\!/_{\log(N)}$ normalizes *SpecEn* to the [0,1] range (Sleigh *et al* 2004, Hornero *et al* 2008, Sabeti *et al* 2009).

2.3.4. Relative power in bands. Finally, the relative power (*RP*) of the MEG background activity was computed in the δ (1.5–4 Hz), θ (4–8 Hz), $\alpha 1$ (8–10.5 Hz; $RP\alpha 1$), $\alpha 2$ (10.5–13 Hz; $RP\alpha 2$), β (13–30 Hz) and γ (30–40 Hz) bands (Sanei and Chambers 2007, Sabeti *et al* 2011).

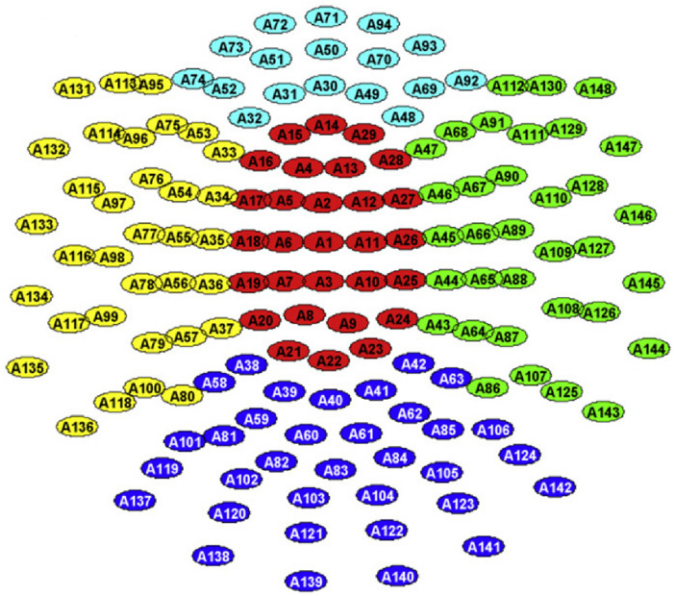

Figure 1. Representation of the channels included in each region: anterior (cyan), central (red), left (yellow), right (green) and posterior (blue).

Let f_{low} and f_{high} be the low and high cut-off frequencies of each band (e.g., $f_{\text{low}} = 1.5$ Hz and $f_{\text{high}} = 4$ Hz for δ). The *RP* of a band was computed from the PSD_n as follows:

$$RP = \sum_{f=f_{\text{low}}}^{f_{\text{high}}} \text{PSD}_n(f). \tag{5}$$

2.4. Statistical and classification analysis

For each feature and subject, there were 148 values available for further statistical and classification analysis (one per MEG channel). In order to reduce the dimensionality and the likelihood of spurious p-values due to multiple statistical comparisons, the 148 channels were grouped into five regions (Anterior, Central, Left, Right and Posterior) as depicted in figure 1. Then, the average value of each feature was computed for each region. This approach had been successfully applied elsewhere (Fernández *et al* 2009, 2011, 2012, Méndez *et al* 2012).

The following statistical and classification analyses were applied to the features grouped in regions.

The test of Kolmogorov–Smirnov with the Lilliefors significance correction was used to check whether the distributions of the results are Gaussian. The Levene test was applied to assess the homogeneity of the variances of the spectral features between SCH and CON groups. Then, the relationships between the same spectral features computed from different regions were inspected using correlation coefficients. Additionally, we also assessed the correlation between the spectral features and the clinical covariates included in table 1. Afterwards, an analysis of variance with the Holm–Bonferroni multiple-comparison correction and age as a covariate was used to evaluate the differences in the spectral features between the two groups (CON and SCH). In the cases of the features and regions for which, at least, a tendency towards

an interaction between age and diagnosis was found (tendency defined as the corresponding p-value being <0.10), further analyses were carried out by calculating the correlation coefficient between age and the results of the spectral feature separately for each subject group.

Moreover, we performed a classification analysis to measure the ability of the spectral features to aid in the detection of individual SCH patients. To avoid any over-fitting, these classification results were computed over ten complete runs of a stratified five-fold cross-validation (Witten *et al* 2011). This means that, in each one of the ten runs, the dataset was randomly divided into five folds. Four of these folds were used to develop the classifier, which was then used to classify the subjects in the left-out fold as CON or SCH. The results were aggregated over all folds.

Due to the potential redundancy between features (Balli and Palaniappan 2010), we measured the classification performance in two situations: with and without a feature selection step. The feature selection was based on evaluating the predictive ability of each feature on its own and the degree of redundancy among them, looking for sets of attributes that are highly correlated with the diagnosis but with low inter-correlation (Witten *et al* 2011). In order do so, we used the *CfsSubsetEval* method from Weka (Witten *et al* 2011). As search method for combinations of features, we employed a bidirectional greedy hill climb with backtracking (Witten *et al* 2011). As classifier, we used logistic regression (LR), a classical and widespread technique (Witten *et al* 2011). LR builds a decision rule based on a linear model of a transformed target variable. This target variable represents the probability that the case being classified corresponds to a patient (Witten *et al* 2011).

The classification performance was measured in terms of the mean $\pm$ SD of the accuracy, sensitivity, specificity and area under the ROC curve (AUC) computed across all ten runs of the cross-validation process. Accuracy denotes the total fraction of subjects well recognized. Specificity is defined as the percentage of healthy subjects correctly detected and sensitivity represents the proportion of all SCH patients for whom the test was positive (Sabeti *et al* 2011, Witten *et al* 2011). The AUC is a summary of the separation between groups. It can be interpreted as the probability that a randomly selected SCH patient is ranked higher by the LR than a randomly chosen CON subject (Hornero *et al* 2008, Witten *et al* 2011).

3. Results

As all features considered in this study were derived from the PSD_n, figure 2 depicts the average PSD_n for the subject group in each of the five regions considered in this study.

The distributions of the results were Gaussian and homoscedastic. The results of the spectral features in each region for CON and SCH subjects are summarized in table 2. The distributions of the clinical variables summarized in table 1 for the SCH patients were also Gaussian. Thus, the Pearson's correlation coefficient (ρ) was computed between the values of the same spectral feature obtained from different scalp regions (e.g., $MF_{\mathrm{Posterior}}$–MF_{Right}, $MF_{\mathrm{Posterior}}$–MF_{Left}, and so on). For all features, the pair of regions with the smallest correlation was 'Anterior–Posterior'. Except for the correlation between the *SpecEn* values computed in the Anterior and Posterior areas ($\rho = 0.177$, p-value $= 0.332$), all other pairs of correlations computed for the same feature were significant (p-value $= 0.011$ or smaller in all cases). As for the correlations of the spectral features with the clinical variables contained in table 1 (age, length of illness, haloperidol equivalent dose, lorazepam equivalent dose and SAPS score), most of them were not significant. Of all possible pairs, only the following ones barely reached significance: $SpecEn_{\mathrm{Anterior}}$—total SAPS score ($\rho = -0.655$), $SpecEn_{\mathrm{Posterior}}$—length of illness

Table 2. Results (given as mean ± SD) of the spectral features for each subject group and region.

Region	Group	*MF* (Hz)	*SpecEn*	*RPδ*	*RPθ*	*RPα*1	*RPα*2	*RPβ*	*RPγ*
Anterior	SCH	14.35 ± 4.39	0.943 ± 0.047	0.152 ± 0.100	0.166 ± 0.054	0.092 ± 0.043	0.071 ± 0.028	0.450 ± 0.126	0.069 ± 0.019
	CON	9.87 ± 2.32	0.923 ± 0.073	0.229 ± 0.129	0.208 ± 0.041	0.096 ± 0.030	0.093 ± 0.026	0.324 ± 0.092	0.051 ± 0.018
Central	SCH	15.15 ± 4.02	0.959 ± 0.018	0.107 ± 0.060	0.144 ± 0.039	0.115 ± 0.057	0.085 ± 0.033	0.461 ± 0.108	0.087 ± 0.024
	CON	11.39 ± 1.41	0.942 ± 0.019	0.134 ± 0.039	0.185 ± 0.037	0.127 ± 0.046	0.139 ± 0.055	0.358 ± 0.065	0.057 ± 0.012
Left	SCH	12.31 ± 3.18	0.931 ± 0.026	0.129 ± 0.051	0.164 ± 0.050	0.173 ± 0.086	0.097 ± 0.040	0.385 ± 0.117	0.052 ± 0.017
	CON	9.99 ± 1.40	0.918 ± 0.023	0.177 ± 0.059	0.195 ± 0.055	0.138 ± 0.056	0.155 ± 0.077	0.297 ± 0.062	0.037 ± 0.008
Right	SCH	12.40 ± 3.19	0.931 ± 0.040	0.148 ± 0.077	0.153 ± 0.042	0.165 ± 0.083	0.091 ± 0.032	0.391 ± 0.116	0.053 ± 0.018
	CON	10.10 ± 1.58	0.917 ± 0.019	0.194 ± 0.065	0.179 ± 0.041	0.131 ± 0.051	0.148 ± 0.071	0.308 ± 0.067	0.039 ± 0.008
Posterior	SCH	12.05 ± 2.96	0.926 ± 0.027	0.119 ± 0.071	0.150 ± 0.034	0.192 ± 0.102	0.110 ± 0.046	0.381 ± 0.111	0.048 ± 0.016
	CON	10.70 ± 1.28	0.915 ± 0.027	0.122 ± 0.042	0.185 ± 0.066	0.151 ± 0.066	0.187 ± 0.096	0.318 ± 0.070	0.037 ± 0.010

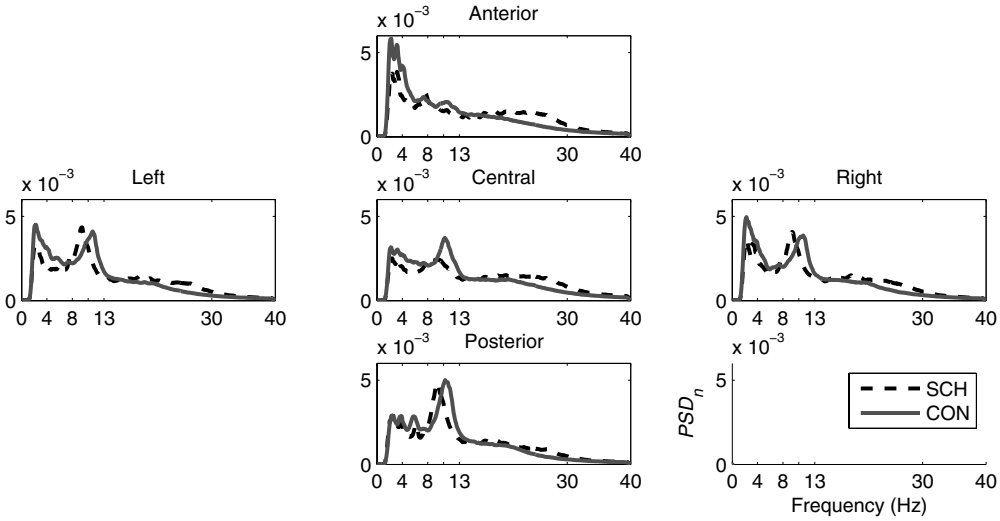

Figure 2. Mean PSD_n for SCH (black dashed line) and CON (grey solid line) subjects in each region.

($\rho = -0.595$,) and $RP\alpha 2_{\text{Posterior}}$—length of illness ($\rho = -0.653$), with $0.01 < p\text{-value} < 0.05$ in all cases.

An analysis of variance with age as a covariate was applied to evaluate the potential differences between SCH and CON subjects for each spectral feature and region. Table 3 summarizes these results in terms of the Holm–Bonferroni-corrected p-value for the differences between both groups ('Diagnosis') and the p-value for the interaction of diagnosis and age ('Diag $\times$ Age'). *MF*, $RP\beta$ and $RP\gamma$ had the largest group differences. The differences were significant (p-value < 0.05) for $RP\gamma_{\text{Central}}$, MF_{Anterior} and MF_{Central} and there was a tendency (p-value < 0.10) for $RP\gamma_{\text{Left}}$, $RP\beta_{\text{Central}}$, $RP\beta_{\text{Anterior}}$ and $RP\alpha 2_{\text{Central}}$. As for the evolution of the spectral features with age, the p-values in table 3 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*, *SpecEn*, RPβ and RPγ.

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 3, table 4 contains the Pearson's correlation coefficients (ρ), and the corresponding p-values, computed separately for each subject group, between age and the spectral features. It can be seen that the spectral features of the SCH patients showed a stronger dependency on age, and that this dependency tended to be the opposite to that of CON subjects. The relationship between each spectral feature and age is represented in figure 3 for *MF* and figure 4 for *SpecEn*. These figures contain the scatter plot of the spectral features for each group of subjects and region and the corresponding linear regression between the spectral results of each group and age. The scatter plots and behaviours of the regressions for $RP\beta$ and $RP\gamma$ were similar to those of *MF*.

Finally, we assessed the ability of the spectral features, in combination with the age and gender of the participants, to separate SCH from CON subjects using LR as classifier with and without a feature selection step. The results of this classification task, averaged over ten runs of the five-fold cross-validation process, appear in table 5. When the feature selection was applied, on average, 7.52 ± 1.33 features were selected for classification (out of a total number of

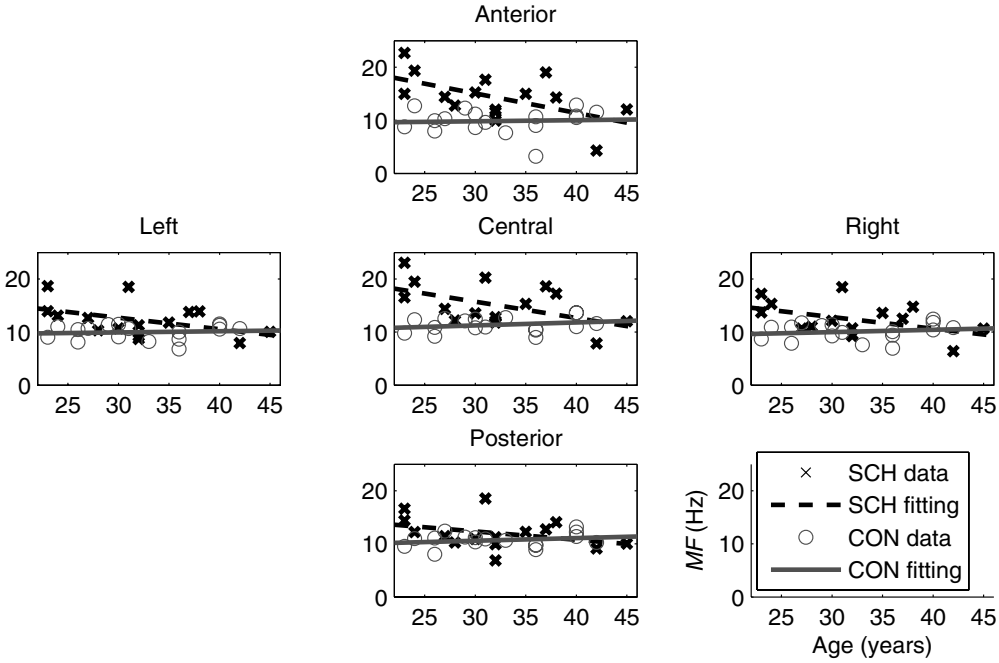

Figure 3. Linear regression of the *MF* results (*y* axis) versus age (*x* axis) in the five regions for SCH (black dashed line and black crosses) and CON (grey full line and grey circumferences) subjects. Patients with SCH show a tendency towards having smaller *MF* values as age increases.

Table 3. *p*-values for the difference between SCH and CON subject groups (labelled as 'Diagnosis' and with the multiple-comparisons correction of Holm–Bonferroni) and for the interaction of age and diagnosis (labelled as 'Diag × Age') for each combination of spectral feature and region.

		Region				
Feature	*p*-value for	Anterior	Central	Left	Right	Posterior
MF	Diagnosis	0.017	0.019	>0.10	>0.10	>0.10
	Diag × Age	0.038	0.025	0.078	0.061	>0.10
SpecEn	Diagnosis	>0.10	>0.10	>0.10	>0.10	>0.10
	Diag × Age	>0.10	0.026	0.052	0.032	0.021
RPδ	Diagnosis	>0.10	>0.10	>0.10	>0.10	>0.10
	Diag × Age	>0.10	>0.10	>0.10	>0.10	>0.10
RPθ	Diagnosis	>0.10	>0.10	>0.10	>0.10	>0.10
	Diag × Age	>0.10	>0.10	>0.10	>0.10	>0.10
*RPα*1	Diagnosis	>0.10	>0.10	>0.10	>0.10	>0.10
	Diag × Age	>0.10	>0.10	>0.10	>0.10	>0.10
*RPα*2	Diagnosis	>0.10	0.095	>0.10	>0.10	>0.10
	Diag × Age	>0.10	>0.10	>0.10	>0.10	>0.10
RPβ	Diagnosis	0.070	0.054	>0.10	>0.10	>0.10
	Diag × Age	>0.10	0.040	0.091	0.093	0.076
RPγ	Diagnosis	>0.10	0.002	0.052	>0.10	>0.10
	Diag × Age	0.038	0.017	0.023	0.007	0.011

42 possible features: eight spectral parameters measured in five regions plus age and gender). Because of the cross-validation process, not the same features were selected in all folds. For illustration purposes, the variables that would have been chosen by the feature selection process

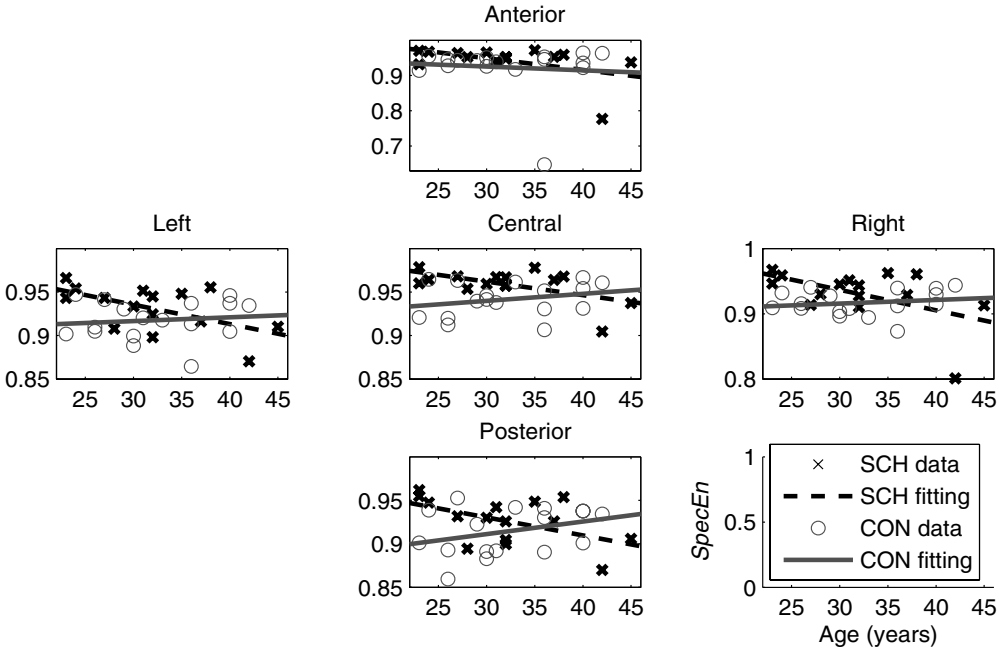

Figure 4. Linear regression of the *SpecEn* results (*y* axis) versus age (*x* axis) in the five regions for SCH (black dashed line and black crosses) and CON (grey full line and grey circumferences) subjects. Patients with SCH show a tendency towards having smaller *SpecEn* values as age increases.

if no cross-validation had been applied were: MF_{Anterior}, $SpecEn_{\text{Central}}$, $RP\delta_{\text{Anterior}}$, $RP\delta_{\text{Central}}$, $RP\delta_{\text{Right}}$, $RP\theta_{\text{Central}}$, $RP\alpha 2_{\text{Anterior}}$, $RP\alpha 2_{\text{Posterior}}$, $RP\gamma_{\text{Central}}$, $RP\gamma_{\text{Left}}$ and $RP\gamma_{\text{Right}}$.

4. Discussion

We analysed MEG recordings from 15 CON subjects and 17 SCH patients with a high degree of positive psychotic symptoms (mainly delusional activity) according to the SAPS score (Andreasen 1984) because patients with different kinds of symptomatology may have different changes in their brain activity (Lee *et al* 2008, Raghavendra *et al* 2009, Fernández *et al* 2012, n.d.). We employed a set of spectral features—*MF* (Hornero *et al* 2008), *SpecEn* (Sleigh *et al* 2004), and the *RP* in δ, θ, $\alpha 1$, $\alpha 2$, β and γ bands (Sabeti *et al* 2011)—to provide a holistic view of the frequency spectrum of the MEG recordings. The analysis of this kind of activity was motivated by the fact that the MEG measures the brain activity directly and it is less distorted by head structures than the EEG (Rossini *et al* 2007). Furthermore, if this techniques are transferred to clinical practice, the acquisition of background activity is easier to perform by clinicians and easier to tolerate by patients than other alternatives (Boutros *et al* 2008). We addressed three research questions. First, we inspected whether some of the aforementioned spectral features were able to show differences between both subject groups. Second, we studied the role of age in the brain activity of SCH patients with positive symptoms, as previous studies highlighted the relevance of this cofactor (Fernández *et al* 2006, 2011, 2009, 2012, Rossini *et al* 2007, Méndez *et al* 2012). Third, we assessed the potential of

Table 4. 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 3 are considered here.

SCH group						
		Region				
Feature		Anterior	Central	Left	Right	Posterior
MF	ρ	−0.555	−0.504	−0.450	−0.453	–
	p-value	0.032	0.055	0.092	0.090	–
SpecEn	ρ	–	−0.570	−0.563	−0.512	−0.517
	p-value	–	0.027	0.029	0.051	0.048
RPβ	ρ	–	−0.440	−0.463	−0.441	−0.418
	p-value	–	0.100	0.082	0.100	0.121
RPγ	ρ	−0.590	−0.473	−0.527	−0.552	−0.524
	p-value	0.020	0.075	0.044	0.033	0.045
CON group						
		Region				
Feature		Anterior	Central	Left	Right	Posterior
MF	ρ	0.056	0.246	0.097	0.167	–
	p-value	0.831	0.342	0.710	0.521	–
SpecEn	ρ	–	0.258	0.119	0.178	0.326
	p-value	–	0.317	0.650	0.495	0.202
RPβ	ρ	–	0.293	0.053	0.110	0.202
	p-value	–	0.254	0.840	0.674	0.437
RPγ	ρ	0.160	0.403	0.211	0.396	0.367
	p-value	0.540	0.109	0.415	0.115	0.149

Table 5. Classification results (in terms of accuracy, sensitivity, specificity and AUC) for the separation of SCH versus CON subjects with and without feature selection with an LR classifier. Ten runs of a five-fold cross-validation were computed and the results are given as mean ± SD.

	Accuracy	Sensitivity	Specificity	AUC
Without feature selection	67.7 ± 16.1%	65.3 ± 29.3%	69.5 ± 24.3%	0.698 ± 0.200
With feature selection	71.3 ± 16.9%	68.0 ± 32.2%	74.2 ± 22.2%	0.741 ± 0.205

the spectral features and LR as classification techniques to help in the recognition of individual SCH patients.

Only three pairs of correlations between spectral features and clinical variables barely reached significance. We infer that the information conveyed by the spectral features is mostly complementary to that of the clinical variables. On the other hand, for every spectral feature, the results calculated in different regions tended to be highly correlated. Nonetheless, the feature selection process tended to include in the LR classifier spectral features computed in more than one region. This suggests that, in spite of those high correlations, grouping the results into regions kept relevant information for diagnostic purposes. Similar approaches have been used in previous studies (Fernández *et al* 2009, 2011, 2012, Méndez *et al* 2012).

The analysis of variance with age as a covariate reported some significantly increased *MF* and *RP*γ values in SCH patients with positive symptoms in comparison with CON subjects. Additionally, a non-significant tendency for the patients to have higher *RP*β and *RP*γ and

lower $RP\alpha 2$ was found in a few regions. A previous study analysed a similar dataset with Lempel–Ziv complexity (Fernández *et al* 2011). Our findings of higher *MF*, $RP\gamma$ and, to a lesser extent, $RP\beta$ values in some regions of the SCH patients agree with the increased level of complexity found in the SCH patients' MEG recordings (Fernández *et al* 2011). Furthermore, some other studies have reported abnormalities in high frequency bands of the electromagnetic brain activity in SCH (Lee *et al* 2008, Uhlhaas and Singer 2010). It has been suggested that positive symptoms in SCH may be linked with specific increases in oscillatory activity showing the read-out of previous experiences, a hypothesis coherent with the role that fast activity plays in the generation of internal representations (Lee *et al* 2008, Uhlhaas and Singer 2010). In this sense, abnormalities in γ frequencies and impaired neural communication would lead to wrong processing of information in several cognitive functions causing the symptoms of SCH (Shin *et al* 2011). Regarding low frequency bands, some studies have reported increases in the δ and θ power in SCH patients (Itil 1977, Boutros *et al* 2008, Galderisi *et al* 2009, Hinkley *et al* 2010). However, our results were not significant for these bands. This might be due to the small sample size or to focusing on SCH patients with positive symptoms because patients with more negative symptoms have been characterized with increased low frequencies (Boutros *et al* 2008).

We considered age as a covariate due to previous results indicating that the MEG background activity change with age across the life-span (Rossini *et al* 2007, Fernández *et al* 2012) and that such evolution with age may be different in control subjects as compared with patients with several conditions (Fernández *et al* 2009, Méndez *et al* 2012), including SCH (Fernández *et al* 2011). We found interactions between age and diagnosis for *MF*, *SpecEn*, $RP\beta$ and $RP\gamma$. This agrees with the hypothesis that some neuropsychiatric diseases—including Alzheimer's disease, depression and attention deficit-hyperactivity disorder (Fernández *et al* 2006, 2009, Méndez *et al* 2012)—introduce a dependency of the brain activity with age that is different from that seen in healthy controls. The results of this paper corroborate that SCH may also be an example of this 'rupture' phenomenon (Fernández *et al* 2011). Of note is that age was not correlated with any of the clinical scores or with the drug equivalent doses ($|\rho| \leqslant 0.272$ with p-value $\geqslant 0.392$ in all cases).

Moreover, we evaluated the ability of the spectral features to distinguish SCH from CON subjects. Both feature selection and classifier training were embedded into a cross-validation process to avoid any over-fitting (Witten *et al* 2011). Despite the relative simplicity of the techniques used in this study—*CfsSubsetEval* and *Logistic* methods from Weka (Witten *et al* 2011)—the average accuracy and AUC of the classification were 71.3% and 0.741%, respectively, when feature selection was used. These results highlight the potential importance of the feature selection process, as it allowed us to reduce the redundancy in the pool the features and increase the performance of the classification slightly. Still, the classification performance is lower than that reported by Sabeti *et al* (Boostani *et al* 2009, Sabeti *et al* 2009, 2011) in the classification of EEG signals in SCH but the results cannot be directly compared due to the different datasets. Yet, our classification results are encouraging for two reasons. First, they confirm the potential of MEG signal processing to help in the classification of SCH patients. Second, it is expected that more advanced classification settings could improve the performance obtained with LR.

Some limitations of our study merit consideration. Firstly, the sample size is relatively small. Ideally, the effect of age in the spectral features would be better investigated in a longitudinal study. Secondly, the patients were on medication. There was no significant correlation between the spectral features and the equivalent doses. This suggests that the effect of medication in the results may be marginal, but it cannot be completely ruled out. Finally, while figure 2 suggests that there is a shift in the α band peak in the SCH patients, $RP\alpha 1$

and $RP\alpha 2$ did not show significant results. This might be due to these bands being too narrow or to the reduced sample size and it is possible that other spectral features would be better able to characterize this phenomenon. Future work will study this issue and will assess the ability of other signal characterization techniques, such as connectivity and nonlinear metrics (Rossini *et al* 2007, Hornero *et al* 2008, Balli and Palaniappan 2010), and more advanced classification schemes (Witten *et al* 2011) to detect the disease more accurately.

5. Conclusion

In summary, this study presented the results of a spectral and classification analysis of MEG background activity recorded from SCH patients with positive symptoms. Our objectives were to assess how age and SCH affect the frequency spectrum of the MEG and to evaluate the potential of the spectral analysis of the MEGs to separate the SCH patients from CON subjects. There were significant differences in the average level of *MF* and $RP\gamma$ and *MF*, *SpecEn*, $RP\beta$ and $RP\gamma$ showed a different evolution with age in the patients from controls. This suggests that the pathology causes a 'rupture' in the normal evolution of the electromagnetic brain activity with age. In addition, a methodology composed of LR as classifier and a feature selection step achieved a cross-validated accuracy of 71.3% with and AUC of 0.741. We infer that spectral analysis may provide useful insights into how SCH affects the MEG background activity and may assist in its diagnosis. The long-term objective is to enable the periodical evaluation of the SCH patients' electromagnetic brain activity to monitor the disease in a non-invasive way.

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