Analysis of the Non-stationarity of Neural Activity during an Auditory Oddball Task in Schizophrenia

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***Abstract*— The aim of this study was to characterize brain dynamics during an auditory oddball task. For this purpose, a measure of the non-stationarity of a given time-frequency representation (TFR) was applied to electroencephalographic (EEG) signals. EEG activity was acquired from 20 schizophrenic (SCH) patients and 20 healthy controls while they underwent a three-stimulus auditory oddball task. The Degree of Stationarity (DS), a measure of the non-stationarity of the TFR, was computed using the continuous wavelet transform. DS was calculated for both the baseline [-300 0] ms and active task [150 550] ms windows of a P300 auditory oddball task. Results showed a statistically significant increase (p<0.05) in non-stationarity for controls during the cognitive task in the central region, while less widespread statistically significant differences were obtained for SCH patients, especially in the beta-2 and gamma bands. Our findings support the relevance of DS as a means to study cerebral processing in SCH. Furthermore, the lack of statistically significant changes in DS for SCH patients suggests an abnormal reorganization of neural dynamics during an oddball task.**

I. Introduction

Schizophrenia (SCH) is a psychiatric disorder characterized by a cluster of symptoms and signs that vary between subjects. These symptoms include hallucinations, reduced motivation and delusions, among others [1], frequently accompanied by impairment in cognitive processing. SCH onset often appears during early adulthood [2]. It has an estimated prevalence of 0.5-1% [2]. It has been suggested that SCH is associated with abnormal neural synchronization and cognitive dysfunctions [3].

Electroencephalographic (EEG) recordings have been used in many studies to study alterations in cognitive processing in SCH patients through the analysis of event-related potentials (ERPs) such as the P300 wave [4]. In this regard, several P300 abnormalities were observed in comparison to healthy subjects, such as a decrease in P3b (i.e., a subcomponent of P300, a positive going-amplitude that peaks around 300 ms after a relevant stimulus) [5].

Time-frequency analyses overcome several limitations of traditional ERP analyses, such as the lack of simultaneous time and spectral information. Time- frequency analyses comprise a variety of methods that capture different aspects of magnitude and phase of EEG oscillations and provide information about neural activity [4]. Several classical methods, such as Spectral Entropy (SE) and Median Frequency (MF) have been used to analyze transient dynamics in neural activity [5], [6]. These studies showed differences between SCH patients and healthy controls regarding the response to relevant stimuli during an auditory oddball task. Specifically, compared to controls, SCH patients displayed a reduction of SE changes between response and baseline for both target and distractor tones. In the case of MF, it was similar for both patients and controls in the baseline window, whereas patients showed a significantly smaller MF change than controls during the active task window [5], [6].

In this study, we applied a recent measure to characterize the non-stationarity of a time-frequency representation (TFR): the Degree of Stationarity (DS). It was introduced by Huang *et al.* [7] and particularized for TFRs by Tong *et al.* [8]. In contrast to classical methods, such as SE or MF, DS is a frequency-dependent measure that is able to quantify the fluctuations in a TFR. Furthermore, a previous study suggested that an increased amount of noise power (NP) is associated with cognitive deficit in SCH [9]. Additionally, significant NP interference in the modulation of EEG activity during a cognitive task was found. This study also suggested that an increased amount of NP in the gamma band was associated with a decrease in SE change [9]. As DS measures the non-stationarity of a TFR, it could be useful in order to characterize the noise level at different frequency bands during the baseline and response windows, as well as assessing possible differences between SCH patients and controls.

The aim of this study was to analyze whether DS could be useful to study neural fluctuations and reorganization during an auditory oddball task. Furthermore, we also explored whether neural dynamics in SCH could be characterized by specific patterns of non-stationarity.

II. Materials

A. Subjects

The participants in the study were 20 SCH patients and 20 healthy controls. The SCH group was formed by 20 patients (age 32.78±9.49 years, mean ± standard deviation,

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SD). Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) [2]. The control group was formed by 20 healthy volunteers (age 33.40±10.55 years, mean ± SD). Patients and controls were matched according to age and sex.

Written informed consent was obtained from SCH patients, as well as from healthy controls, after providing full written information. The research board of the Valladolid University Hospital endorsed the study according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

B. Electroencephalographic Recordings

EEG recordings were acquired with a BrainVision® (Brain Products GmbH; Munich, Germany) system, consisting of 32 sensors mounted in an electrode cap (Electro-Cap International, Inc.; Eaton, Ohio, USA) and placed according to the International 10/20 System. Thirteen minute-length recordings were acquired at a sampling rate of 500 Hz. Participants underwent a three-stimulus auditory oddball task. The tones (duration 50 ms, rise and fall time 5 ms, and intensity 90 dB) were presented to participants in random 600 tone series consisting of target (500 Hz tone), distractor (1000 Hz tone), and standard (2000 Hz tone), with probabilities of 0.20, 0.20, and 0.60 respectively. Participants were asked to press a button whenever they heard a target tone. Unattended target tones were discarded, that is, only target tones followed by a button press were taken into account.

The recordings were referenced over Cz electrode and re-referenced to the average activity of all active sensors [10], yielding a total of 33 channels. Electrode impedance was kept under 5 kΩ. Then, each ERP recording was filtered with a 1-70 Hz finite impulse response (FIR) filter and a 50 Hz notch filter. Channels TP9 and TP10 were subsequently discarded due to abundant muscle artifacts throughout most recordings, reducing the channel count to 31. Afterwards, a two-step artifact rejection procedure was conducted. Firstly, an independent component analysis (ICA) was carried out to decompose ERPs into 31 components; then, after a visual inspection, ICA components associated with artifacts such as eye blinks were discarded. Secondly, EEG recordings were segmented into 1000 ms epochs (-300 ms to 700 ms with respect to the stimulus onset, 500 samples per epoch). Finally, data were reconstructed and artifacts were automatically rejected by means of an adaptive thresholding method in order to remove ERP trials displaying amplitudes that exceeded a statistically based local threshold [11].

III. Methods

A. Continuous Wavelet Transform

EEG time-frequency analysis can provide additional information that is not apparent in the ongoing EEG. It has been revealed that there are event-related changes in the magnitude and phase of EEG oscillations at certain frequencies [4]. In this study, the method used to compute time-frequency maps was the Continuous Wavelet Transform (CWT).

The CWT is a TFR conceptually related to the windowed short-term Fourier transform (STFT) [12]. A wavelet is zero-mean, limited duration waveform that is characterized by being relatively localized in both time and frequency. They also have large fluctuating amplitudes during a restricted time period and very low amplitude outside of that time range [13]. In order to accurately characterize a biological signal, such as EEG, it must provide a biologically plausible fit to the modeled signal. One such waveform is the Morlet wavelet, a Gaussian-windowed sinusoidal wave [3].

The CWT is defined as the convolution of $x(t)$ with a scaled and translated version of the 'mother wavelet'

$$CWT_x(\tau,a)=\frac{1}{\sqrt{a}}\int x(t)h^*\left(\frac{t-\tau}{a}\right)dt, \quad (1)$$

where a is the scale factor, τ is the time interval and $h(t)$ is the 'mother wavelet' [12]. The scale factor was set to include frequencies from 1 to 70 Hz in intervals of 0.5 Hz [11].

B. Degree of Stationarity

DS characterizes the non-stationarity of a TFR at each frequency. Therefore, it is useful to quantify the fluctuations of the neural dynamics in ERPs. It is defined in equation (2), through the marginal frequency distribution, $tfr(\omega_i)$, described in equation (3) [8]

$$DS(w_i)=\frac{1}{N}\sum_{n=1}^{n=N}\left(1-\frac{tfr(\omega_i,n\Delta t)}{tfr(\omega_i)}\right)^2 \quad (2)$$

$$tfr(\omega_i)=\frac{1}{N}\sum_{n=1}^{n=N}tfr(\omega_i,n\Delta t), \quad (3)$$

where $tfr(\omega_i,n\Delta t)$ is constant for stationary signals at each ω_i, that is, $tfr(\omega_i)= tfr(\omega_i,n\Delta t)$. In such a case, $DS(\omega_i)$ is equal to zero. $DS(\omega_i)$ increases as the signal becomes less stationary at a given frequency ω_i.

In this study, DS values were computed using the wavelet scalogram (WS) as an estimation of the TFR. The WS is calculated as the squared modulus of the CWT coefficients

$$WS_x(\tau,a)=|CWT_x(\tau,a)|^2. \quad (4)$$

One second-length target trials were decomposed into the baseline, defined as the [-300 0] ms window (where 0 marks the stimulus onset), and the response [150 550] ms window. DS values were computed separately for each of these windows and averaged in five frequency bands: theta (θ, 4-8 Hz), alpha (α, 8-13), beta-1 (β1, 13-19 Hz), beta-2 (β2, 19-30 Hz) and gamma (γ, 30-70 Hz). Of note, the delta band was excluded from the analysis, as its associated wavelet duration is longer than hundreds of milliseconds. It requires a window length longer than the baseline and response intervals to be correctly analyzed [14].

C. Statistical Analysis

Initially, an exploratory analysis was performed to analyze data distribution. Normality was tested with a Kolmogorov-Smirnov test and homoscedasticity with a Levene test. These analyses revealed that the data did not meet parametric test assumptions. Therefore, in order to analyze the within-group statistical differences between the values of DS in the baseline and response windows, the Wilcoxon signed rank test was used. A false discovery rate

(FDR) correction was applied to the *p*-values in order to minimize type I error [15].

IV. Results and Discussion

DS was computed in the baseline and response windows for the five frequency bands previously defined. For every subject, DS was initially obtained at every electrode. Then, DS values were averaged across all trials for each frequency band. The Wilcoxon signed rank test results for healthy controls and patients, as well as the average DS of all subjects, are shown in Fig. 1. The control group shows a statistically significant increase ($p<0.05$) of DS values between the baseline and response windows at several electrodes in the central region. This is especially significant in the beta-1 and beta-2 bands, which also exhibit the lowest degree of stationarity during the baseline window. This result is in agreement with previous studies that found a significant reorganization of neural dynamics from baseline to active window during an auditory oddball task using SE and MF [6], as well as Wavelet Entropy [16]. Interestingly, a similar pattern of statistical differences appears in all frequency bands, which may be partly due to the definition of DS.

On the other hand, in the SCH group the areas of statistically significant change between baseline and response values are less widespread, especially in the beta-2 and gamma bands. This finding suggests that healthy subjects exhibit a greater reconfiguration of brain activity than SCH patients during the cognitive task. Indeed, this result can be linked to the abnormal neural network reorganization previously found in SCH patients during an oddball task [5]. In addition, SCH patients show higher DS values during the baseline window than healthy controls in the beta-2 band. This result indicates a higher non-stationarity in brain function during resting state and could be related with the cortical hyper-activation previously found in SCH [9].

As previously stated, DS is a frequency-dependent measure, which is helpful to quantify TFR fluctuations across a frequency range. In this regard, Fig. 2 shows DS values for all SCH patients and controls at electrode Pz across the frequency range under study. This property could prove useful in order to characterize the evolution of certain non-stationarity patterns and study their behavior in different frequency bands. This would allow a detailed examination of which frequencies change the most (or least) in stationarity during neural fluctuations and reorganization after an auditory oddball task. It would also help evaluate whether there are significant differences in change from the baseline to the active task window between SCH patients and controls, as well as which group exhibits more stationarity before and after the task.

There are some limitations in this study. Firstly, the sample size should be increased. Secondly, it would be interesting to include other measures of non-stationarity such

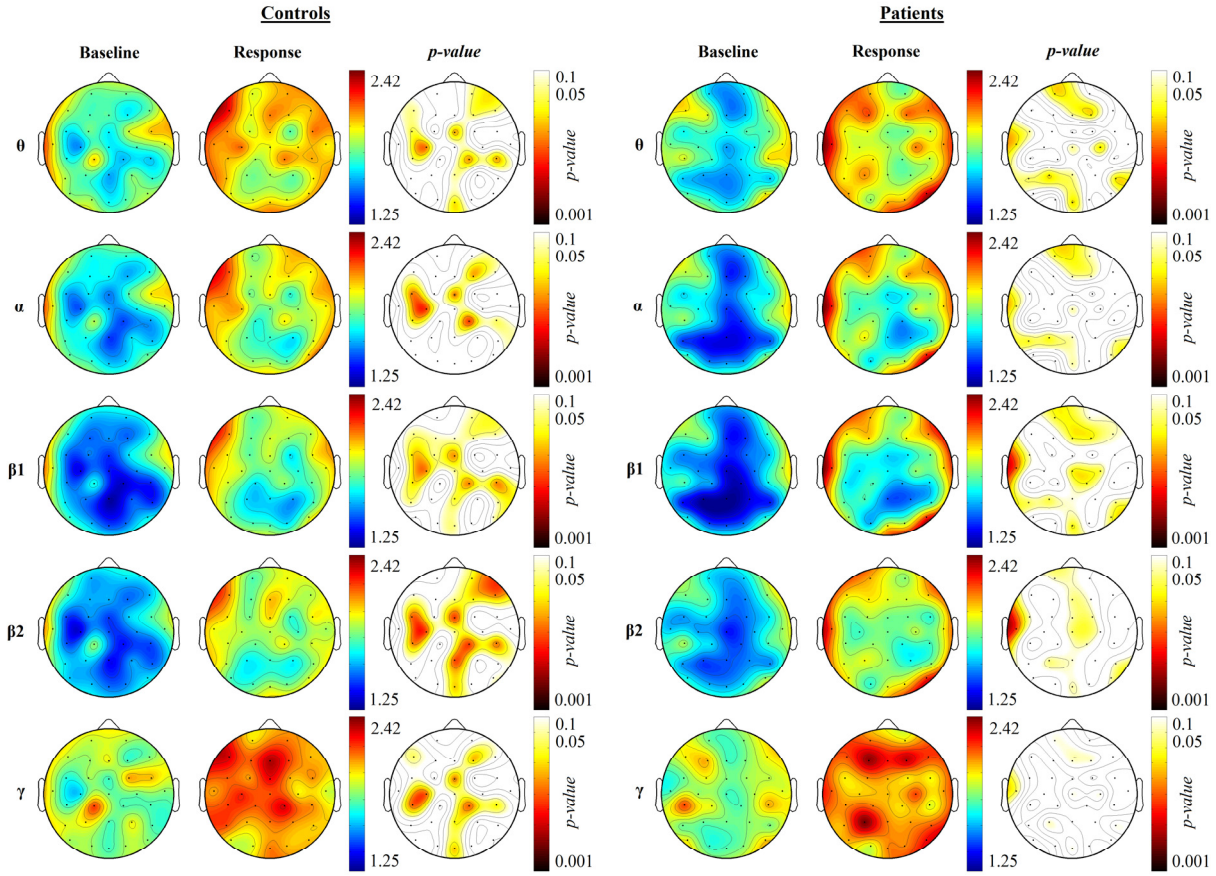

Figure 1. Sensor-level DS maps at baseline and active window for controls and SCH patients at each frequency band under study (*p*-values of the within group differences are shown in the right column).

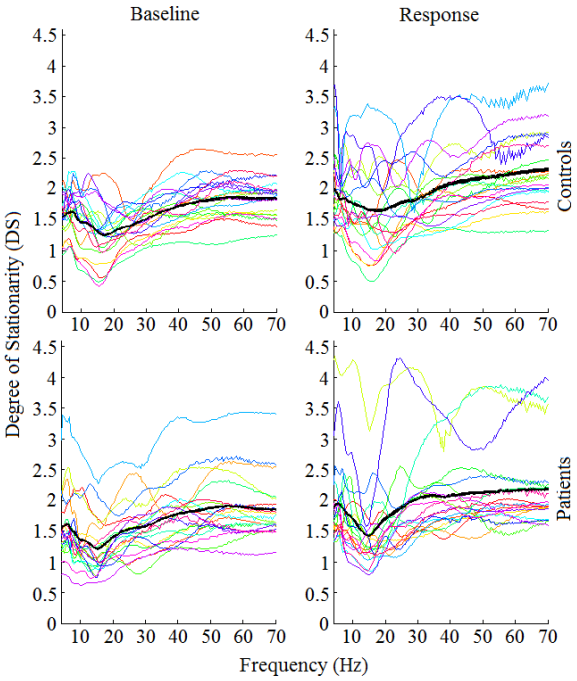

Figure 2. DS values for controls and SCH patients at electrode Pz. The thick black line represents the average values.

as Kullback-Leibler Distance (KLD) [6]. Previous studies have found a reduction of the evoked response in the delta band [17], so this frequency band could be included in future research. Finally, there are other TFRs that could be used as well, such as the Hilbert-Huang Transform (HHT) [7] or STFT instead of CWT.

V. Conclusion

To summarize, in this study we applied a novel measure that quantifies the non-stationarity of a TFR. Our findings suggested that it may prove useful in order to characterize neural dynamics during an auditory oddball task. We have found non-stationarity changes in the central and lateral regions in controls that are less pronounced in patients, which may characterize differences in neural dynamics between controls and SCH patients. Furthermore, the differences in non-stationarity changes between SCH patients and controls lead us to suggest that SCH is accompanied by abnormal neural network reorganization during an auditory oddball task. In conclusion, we have found that DS could prove to be a useful tool for characterizing brain dynamics during an auditory oddball task by measuring changes in non-stationarity across a wide frequency band.

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