A Transfer Entropy-based methodology to analyze information flow under eyes-open and eyes-closed conditions with a clinical perspective

A Preprint

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Abstract

The study of brain dynamics under normal or pathological conditions has proven to be a difficult task, there is no unified consensus on how it should be studied. In this article we present a methodology based on Transfer Entropy to characterize the information flow between different brain hemispheres in eyes-open (EO) and eyes-closed (EC) resting states in healthy subjects, with an experimental setup that resembles the technical conditions found in a clinical setting. We have estimated the Transfer Entropy between the Hilbert phases of bandpass filtered EEG channels. We have designed a methodology to analyze the interhemispheric and intrahemispheric information flow in both conditions. Our results suggest an increased information transfer in the EC condition for the alpha, beta1 and beta2 frequency bands. Furthermore, we do not observe a preferred direction of interhemispheric information movement in both conditions. In conclusion, there is evidence of a significant difference in the brain's information transfer dynamics between EO and EC resting states.

Keywords Information flow, Transfer Entropy, Eyes-open and Eyes-closed, Brain Dynamics, EEG

The activity recorded by electroencephalography (EEG) comes usually from the encephalic cortex (Brain and Cerebrum). Once the inputs from the thalamus reach the fourth layer of the cerebral cortex, local microcircuits are responsible for amplifying and computing these signals. However, 75% of the cerebral cortex is composed of association areas that receive multiple multimodal inputs even under conditions of wakefulness, eyes closed or open [1]. This generates an activity known in clinical practice as basal activity. These dynamics are studied for diagnostic purposes. The strength of EEG lies in the electrophysiological dynamics in relation to time in the order of seconds-minutes-hours, unlike evoked potentials (order of milliseconds). One of its limitations is its low spatial resolution (in the order of centimetres) compared to the precision achieved with a functional Magnetic Resonance Imaging (fMRI). Even so, it is possible to describe local behaviour in the order of centimetres -this can be seen in focal dysfunctions in epilepsy, mostly those with clinically observable partial seizures.

For the study of EEG dynamics, it is important to understand the collective behavior of the signals. In other words, the interrelationship that exists between the different channels. From this arises the concept of "functional connectivity" (FC), which can be defined as the statistical relationship between specific physiological signals over time. Beyond the existence of FC between two brain areas, there is no direct structural correlation observable by tractography that can demonstrate that these two brain areas are connected. It is possible to think that this FC would describe the shared dynamics between areas (similar functioning or shared information). This is the basis of the amplification and computation of neuronal signals, in the tangential component of axons connecting the cerebral cortex of the association areas - layers 1, 2 and 3. This microconnectivity cannot be studied by brain tractography (MRI) so far, as it describes predominantly the behavior of projection fibers. For this reason, the study of FC is one of the most important areas to be studied in neuroscience. However, the possibility of knowing how much information two EEG signals share has always been a challenge. Currently there are several metrics to study the correlation between EEG signals, such as Spectral Coherence [2], Magnitude Squared Coherence [3], Amplitude Envelope Correlation [4], Synchronization Probability [5], Phase Lag Index [6], Symbolic Weighed Mutual Information [7], however these measures do not give information about the direction of the information flow i.e. which channel is the source and which is the target. To address this problem, other metrics that measures the directionality of information have been developed, e.g., Granger Causality [8] or Transfer Entropy (TE) [9].

Transfer Entropy is a measure of information transport based on Shannon entropy [9]. This measure is able to quantify the strength and direction of the coupling between simultaneously observed systems [10]. Moreover, it have attracted general interest because it can be used to study complex interaction phenomena found in several disciplines [10]. In particular, we can mention some of the application of TE in different areas of neuroscience such as seizure quantification [11, 12], degenerative decease [13], Hyperactivity Disorder [14] or Schizophrenia [15].

Previous studies showed a reduction in the FC during the eyes-closed condition compared to the eyes-open condition, this phenomenon is termed "alpha desynchronization" [16, 17]. Geller and colleagues found that closing the eyes causes generalized low-frequency power increase and focal gamma attenuation in the human electrocorticogram [18]. Barry et al. found topographical and spectral-power differences, in EEG recordings, between the eyes-closed and eyes-open resting states. Other work using the Lagged Linear Coherence algorithm, as a measure of functional connectivity, found that the difference between closed and open eyes can be observed mainly in the alpha band, being larger in closed eyes, while the opposite is true for the beta1 and beta2 bands, which are larger in open eyes. A recent study, conducted on intracranial EEG data, found that phase-based connectivity is sensitive to the transition from eyes-closed to eyes-open condition, only in interhemispheric and frontal electrodes [19]. Other studies in EEG using symbolic analysis showed that this technique can distinguish between the two conditions [20]. In a statistical mechanic approach over the connectivity study, Guevara et al. gave evidence that in baseline state entropy increases during eyes-open condition compared to the eyes-closed condition [21].

Although, these studies provide a deeper understanding of eyes-open/closed dynamics, none of them address the problem of how the information moves or flows from one area to other. On the other hand, Olejarczyk et al. used Transfer Entropy, Multivariate TE (Partial Transfer Entropy) and other measures to analyze effective connectivity in resting state EEG data [22]. They observed that the biggest difference in TE between eyes conditions was given in the alpha band. Nevertheless, their experimental setup is difficult to implement in a clinical environment characterized for using short-time and low-density EEG recordings, with a low rate.

In this work we analyze 15 EEG recordings from different subjects during eyes-closed and eyes-open resting state following a Transfer Entropy framework but with a clinical perspective. The characterization of the information flow between cortical areas in resting conditions is fundamental for describing patterns observed in control subjects. This would give us a baseline to study connectivity changes in pathological scenarios.

1 Methods

1.1 Participant recruitment

This study has a comparative, observational, prospective design between two electrophysiological conditions (open and closed eyes) in the same control group during resting state. The 15 subjects were selected using the following inclusion criteria: a) Women and men aged between 20 and 50 years old. b) Individuals holding 7 or more years of complete formal education. c) Individuals without neurological and psychiatric medical history and normal values on the Beck Depression Inventory [23] and State-Trait Anxiety Inventory, form X and Y [24]. d) Individuals with a normal EEG report according to St. Louis EK and Frey LC's [25] criteria

of normality. e) Not to consume psychotropic drugs or drugs with effects on the Central Nervous System. f) Not to present an abusive consumption of psychoactive substances such as cocaine, marijuana, alcohol or others. g) Not to have had a moderate or minimum consumption of alcohol in the 48 hours prior to the Full Investigation Evaluation. h) Individuals that have accepted and signed the informed consent. This research protocol was accepted and approved by the ethics committee of the Hospital Córdoba (Córdoba-Argentina) and registered in the ministry of health of the Córdoba Province on 20-03-2017 under number 3170.

1.2 EEG recordings and prepossessing

The EEG data were measured according to the standards of the International Federation of Clinical Neurophysiology [26], following the international 10-20 system. The recordings have monopolar montages, with a bimastoid reference. Twenty channels (F1-F3-C3-P3-O1-F7-T3-T5-Fz-Cz-Pz-Oz-T6-T4-F8-O2-P4-C4-F4-F2) were recorded with a 24 channels polysomnograph (Neutronic, model ME-2400) at 65 Hz sampling frequency.

EEG channels were average referenced and filtered in the following frequency bands: $[4, 8)$ Hz (theta) , $[8, 12)$ Hz (alpha), $[13, 19)$ Hz (beta1), $[19, 25)$ Hz (beta2) and $[25, 31]$ Hz (beta3) [27]. The instantaneous phase of each EEG channel was estimated through the Hilbert transform [22].

1.3 Transfer entropy estimation

Transfer entropy [9] between all pairs of EEG electrode phases, was calculated (in both directions) with the k-nearest-neighbor (KNN) methodology proposed in [28][1]. Phase signals where embedded using an embedding-dimension equal to 4 and an embedding-lag that changes in accordance with the frequency band ($\tau = 10$ for theta band, $\tau = 8$ for alpha band, $\tau = 7$ for beta1 band; and $\tau = 6$ for beta2 and beta3 bands). Each value of τ was obtained as the first zero of the correlation function between the filtered phases of the F1 and F3 channels (very close and correlated channels). For the KNN-algorithm, the number of the nearest neighbors was set to 8.

A conventional surrogate test was chosen to evaluate the statistical significance of the transfer entropy estimations [29]. Here, the null hypothesis is that there is no relation between the target and the source signals, i.e. $T_{xy} = T_{yx} = 0$. Two different surrogate distributions were calculated for each TE estimator. The first surrogates were estimated from circular-shifted versions of the original phases. A random index was sampled from a uniform distribution and both signals (target and source) were shifted with the same index. These surrogates preserve all the characteristics of the original phases, as well as the time connection between the target and the source. However, the estimation of transfer entropy differs from the original data, because the embedding scheme used by the KNN-algorithm. The estimations from these surrogates generate a distribution grouped around the value calculated from the original phases and accounts for the variability of the algorithm. The second surrogates seek to break any possible link between source and target signals, but keeping each one inner correlation. A surrogate realization of the source was obtained using the inverse Fourier transform of the product between the amplitude spectrum of the signal and the Fourier phase of random normal noise [30]. Then, a surrogate estimation of TE is calculated from the target signal and the surrogate source.

To analyze the statistical significance of the TE estimation between a pair of channels' phases, we used the following methodology: we compute the difference $T =< T_{xy} - T_{yx} >$ where the median value is estimated along the first surrogate realizations (included the one with the original data). Then, we obtain the distribution of the difference between Fourier surrogates $Ts_i = \mathrm{T}^{(i)}_{xy} - \mathrm{T}^{(i)}_{yx}$, where $\mathrm{T}^{(i)}_{xy}$ is the i-th Fourier surrogate of T_{xy}. Finally, we perform a two sided statistically significant test, using the difference Ts_i as surrogate distribution and T as test statistics. The significance level was set to $\alpha = 0.05$ and we compute 512 realizations of each surrogates. If the probability of test statistic is greater or equal to $1 - \alpha/2$, we consider that the difference $T_{xy} - T_{yx}$ is statistically greater than zero and $T_{xy} > T_{yx}$. On the other hand, if the probability of T is below or equal to $\alpha/2$, we conclude that $T_{xy} < T_{yx}$. Other wise we consider that $T_{xy} - T_{yx} = 0$.

Following the above mentioned procedure, we construct two matrices named Transfer Entropy matrix (Tent matrix) and information Flow matrix (figure 1). For a single subject and a given frequency band, the Transfer Entropy matrix (figure 1a) shows the difference $T_{xy} - T_{yx}$ between EEG channels. A positive value ($T_{xy} > T_{yx}$) indicates that information is greater in the $X \to Y$ direction than in the opposite. For example,

[1]The code is located at https://bitbucket.org/jrinckoar/knn-information-measures/src/master/

the red-shaded value in the 2nd-row and 7th-column says that the information flows from $F3$ channel to $T3$ channel. The flow matrix (figure 1b) can be read in the same way, however it contains only three values $[-1, 0, 1]$ given by $\text{sgn}(T_{xy} - T_{yx})$. In this sense, the flow matrix gives us information about which connections, between EEG channels, are active; whereas the transfer entropy matrix tells us the amount of information shared through that connection. Note these matrices are upper triangular since $T_{xy} - T_{yx} = -(T_{yx} - T_{xy})$. Finally, we divided the area of these matrices into smaller subareas (figure 1c), each of them representing a group of connections between EEG channels. For example, the matrix subarea G_3 contains the connections between the channels placed over the left-hemisphere and the channels placed over the right-hemisphere.

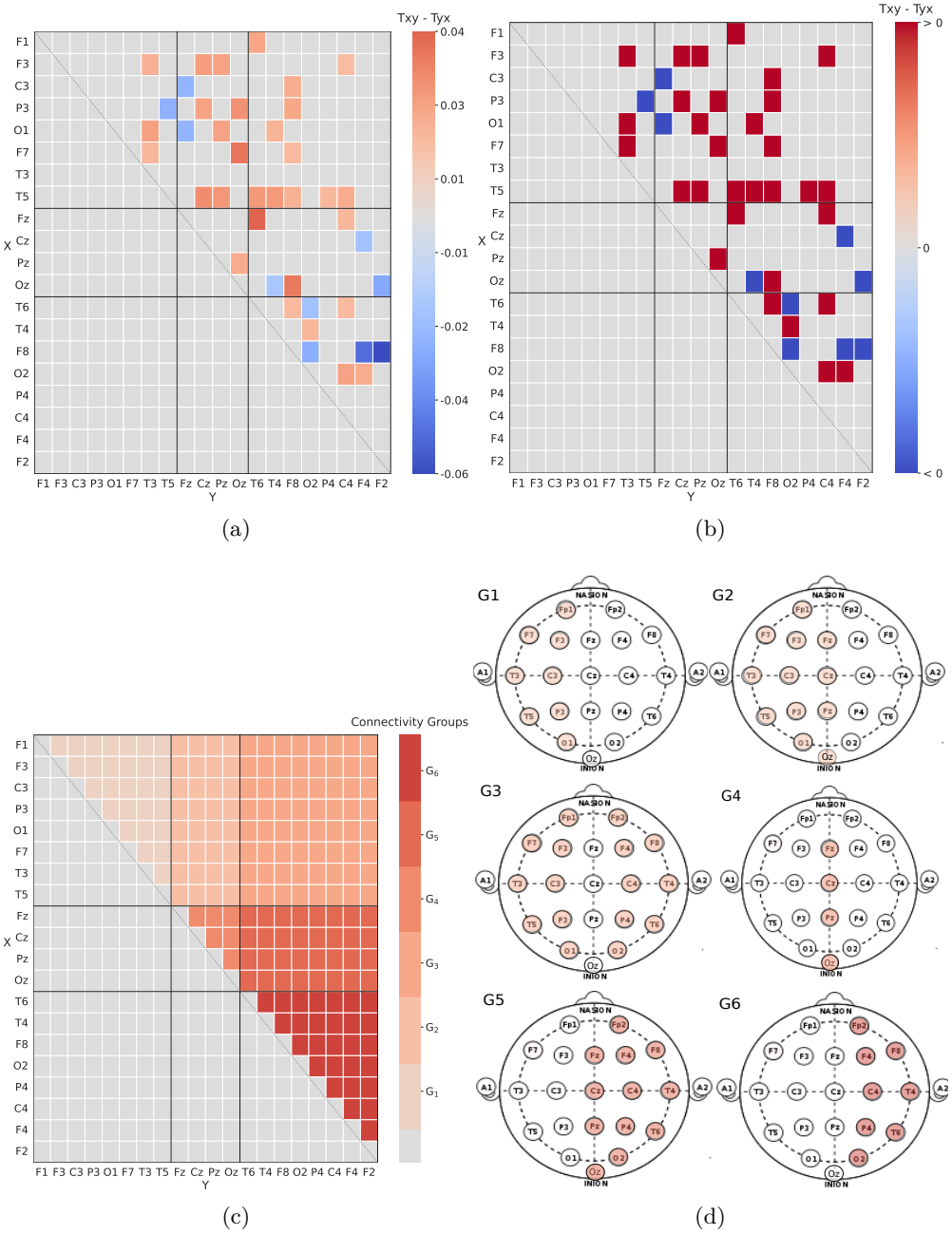


Figure 1: Information flow matrices of a single subject in alpha band: (a) Transfer entropy matrix (Tent matrix). (b) Flow matrix. (c-d) Connectivity groups.

From the information provided by these matrices we define a set of measures over each subject (table 1): The Total Activity is calculated, from the information flow matrix, as the sum of all active connections between channels over all possible pairwise (190), it is an estimation of the amount of interactive channels. The Total Tent (total transfer entropy) is the sum of transfer entropy values over the active connections and it accounts for the magnitude of the information transferred between active channels. The Local Activity measures the amount of interactive channels in each connectivity group, is computed as the number of active channels over all possible connections inside that group. Please note each group, showed in figure 1c, has a different number of possible connections. Finally, the Directed Activity measures the proportion of activity that goes in a particular direction ($X \rightarrow Y$ or $Y \rightarrow X$), is calculated as the sum of active connections in that direction over the total number of active connections.

Table 1: Measures definition over flow and transfer entropy matrices

Measure	Definition [a]	Description
Total Activity	$\text{TA} = \frac{\sum (F_{xy} + \lvert F_{yx} \rvert)}{T_c}$	(Flow matrix) Number of active connections over all possible connection.
Total Tent	$\text{Tent} = \frac{\sum (T_{xy} + \lvert T_{yx} \rvert)}{\sum (F_{xy} + \lvert F_{yx} \rvert)}$	(Tent and Flow matrices) Total magnitude of Tent over number of active connections.
Local Activity	$\text{LA} = \frac{\sum_G (F_{xy} + \lvert F_{yx} \rvert)}{T_G}$	(Flow matrix) Number of active connections over all possible connections in the group G.
Directed Activity	$A_{X \rightarrow Y} = \frac{\sum F_{xy}}{\sum (F_{xy} + \lvert F_{yx} \rvert)}$ $A_{Y \rightarrow X} = \frac{\sum \lvert F_{yx} \rvert}{\sum (F_{xy} + \lvert F_{yx} \rvert)}$	(G_3 of Flow matrix) Number of positive/negative connections over the number of active connections.

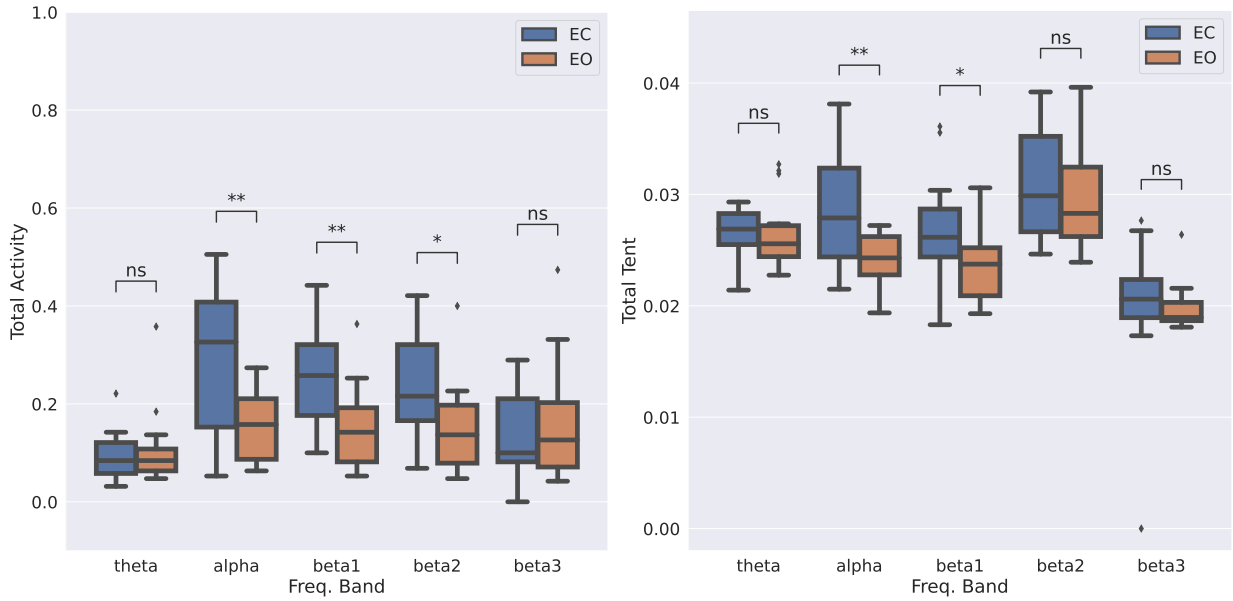
[a] Throughout the table,

- F_{xy}: Positive Flow matrix's cell .
- F_{yx}: Negative Flow matrix's cell.
- T_{xy}: Positive Tent matrix's cell.
- T_{yx}: Negative Tent matrix's cell.
- T_c: Total number of cells in Flow matrix above the main diagonal (190).
- T_G: Total number of cells in Flow matrix that belong to the G connectivity group.
- $\sum_G$: Sum over the connectivity group G.
- $\sum$: Sum over the entire matrix.
- $\lvert \cdot \rvert$: Absolute value.

2 Results

In order to analyze the Total Activity between different eyes conditions, we have applied a Wilcoxon test for each frequency band (figure 2a). More over, we have used a Conover-Iman test with a Holm-Bonferroni correction and a H_0 rejection threshold of 0.05 to verify if there are differences for each eye's condition between the frequency bands (see table 2).

The magnitude of the information transferred for different frequency bands and eyes conditions can be evaluated through the Total Tent estimator. As well as in the above analysis, we have made a Wilcoxon test for each frequency band to evaluate differences between the two eyes conditions (figure 2a), and a Conover-Iman test for differences across the frequency bands (see table 3).



(a) (b)

Figure 2: (a) Total Activity. (b) Total Tent. Wilcoxon rank test p-values range: ns: $p \leq 1$, $*$: $0.01 < p \leq 0.05$, $**$:$0.001 < p \leq 0.01$.

Table 2: Total Activity Conover–Iman test p-value for different frequency bands and same eyes condition.

		EC					EO				
		theta	alpha	beta1	beta2	beta3	theta	alpha	beta1	beta2	beta3
EC	theta		**1.12e-05**	**6.61e-05**	**2.01e-04**	1.00e+00					
	alpha			1.00e+00	1.00e+00	**1.90e-03**					
	beta1				1.00e+00	**8.66e-03**					
	beta2					**2.18e-02**					
	beta3										
EO	theta							2.64e-01	7.94e-01	8.37e-01	1.00e+00
	alpha								1.00e+00	1.00e+00	1.00e+00
	beta1									1.00e+00	1.00e+00
	beta2										1.00e+00
	beta3										

Table 3: Total Tent Conover–Iman test p-value for different frequency bands and same eyes condition

		EC					EO				
		theta	alpha	beta1	beta2	beta3	theta	alpha	beta1	beta2	beta3
EC	theta		1.00e+00	1.00e+00	3.75e-01	**5.76e-04**					
	alpha			1.00e+00	1.00e+00	**7.28e-05**					
	beta1				9.58e-02	**3.73e-03**					
	beta2					**1.50e-07**					
	beta3										
EO	theta							6.54e-01	5.93e-02	3.04e-01	**1.30e-07**
	alpha								1.00e+00	**1.17e-03**	**2.08e-04**
	beta1									**3.39e-05**	**5.92e-03**
	beta2										**1.17e-11**
	beta3										

Figure 2a shows the Total Activity values of the EO and EC conditions for the different electrophysiological bands analyzed. The Wilcoxon test shows greater activity for the EO condition in alpha, beta1 and beta2 bands. Moreover, figure 2b presents the Total Tent values for the different conditions and bands. As it can be seen, only alpha and beta1 bands shows significantly higher values for EC than for EO condition.

We performed a Conover–Iman test to analyze if there are differences in Total Activity (table 2) and Total Tent (table 3) across frequency bands for each condition. From table 2 we do not observe any difference in

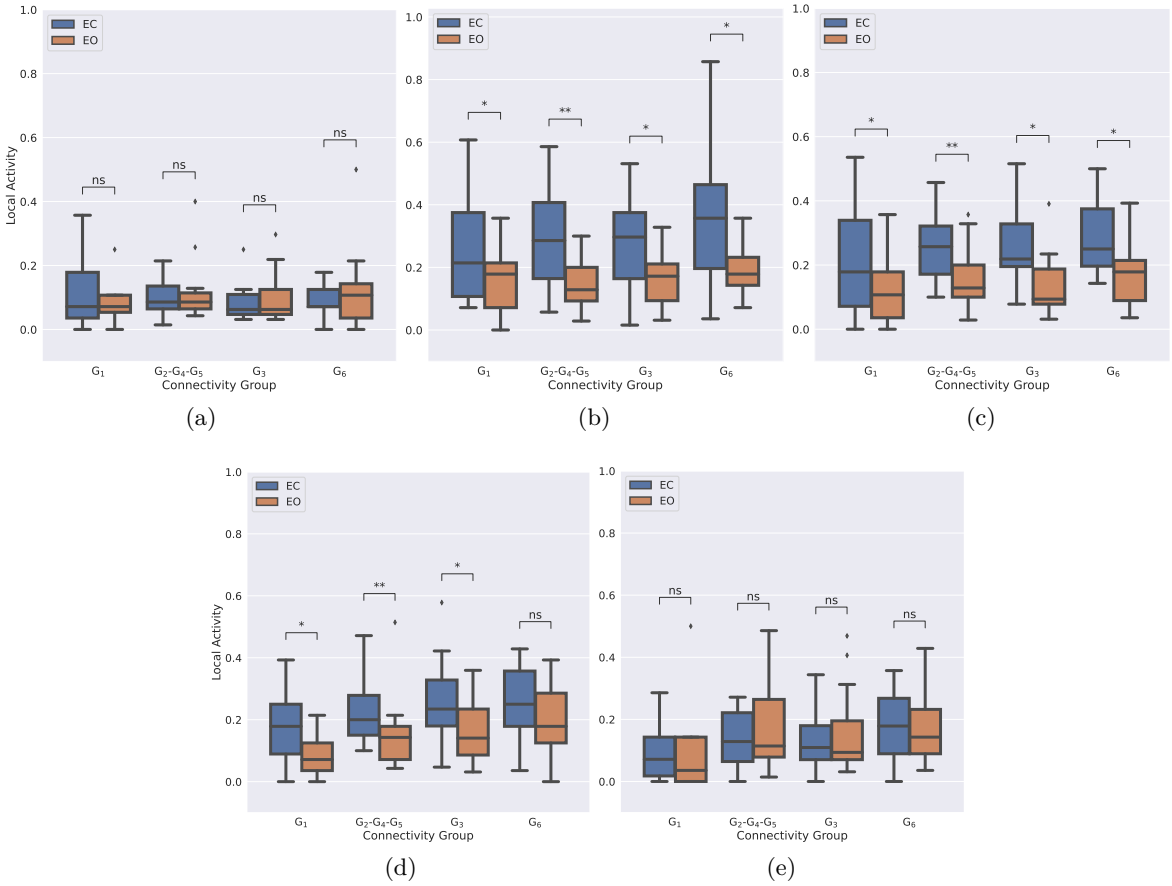


Figure 3: Activity by regions: (a) theta band. (b) alpha band. (c) beta1 band. (d) beta2 band. (e) beta3 band. Wilcoxon rank test p-values range: ns: $p \leq 1$, $*$: $0.01 < p \leq 0.05$, $**$:$0.001 < p \leq 0.01$.

the number of active connections for the EO condition, but for the EC condition, there is less activity in the theta and beta3 bands. Table 3 shows that beta3 band has less amount of transferred information in both eyes conditions.

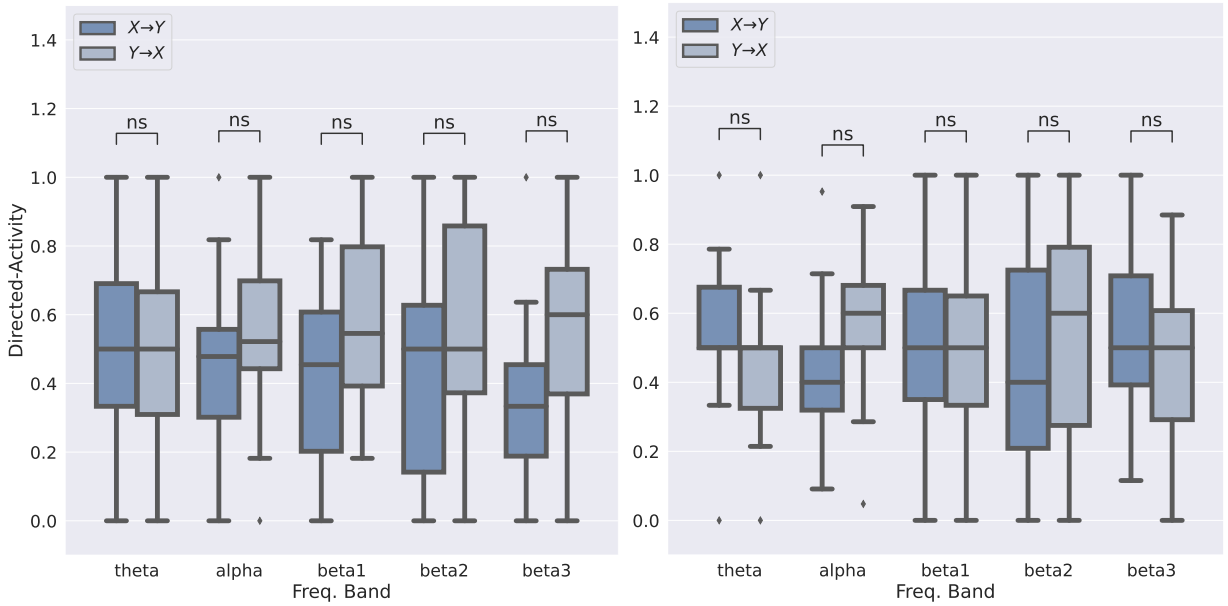
The Local Activity for different connectivity regions[2] in the analyzed frequency bands can be seen in figure 3 . For the theta and beta3 bands (figures 3a and 3e) we do not detect any difference between eyes conditions. On the other hand, we observe a greater number of active connections in the EC condition for the alpha, beta1 and beta2 bands in almost all connectivity groups (see Figures 3b, 3c and 3d). This result is under the Total Activity values.

Since the $G3$ region represents the interhemispheric information flow, we studied the direction of the flow in the different conditions and bands. Figure 4 shows the Directed Activity for EC and EO. For both conditions, none of the bands present significant values, suggesting that there is not a preferred direction but a bi-directionality of the information flow.

3 Discussion

The purpose of this study is to characterize the information flow during EO and EC conditions in healthy subjects. In this sense, we seek to evaluate some of its aspects, such us, the number of active connections, the magnitude of the information transferred through those connections, and the flow direction. Moreover,

[2]Regions $G2$, $G4$ and $G5$ were grouped together because they represent the activity in the middle-line EEG channels.



(a) (b)

Figure 4: Connectivity group G3 Directed Activity: (a) Flow direction EC. (b) Flow direction EO. Here X and Y represents the left and right hemispheres, respectively. Wilcoxon rank test p-values range: ns: $p \leq 1$, $*$: $0.01 < p \leq 0.05$, $**$:$0.001 < p \leq 0.01$

the difference in these quantities by frequency bands and the contribution of each connectivity group to the global information flow.

The idea of "functional connectivity" raises some controversy because of the relationship between its conceptual imprecision and the multiplicity of meanings assigned to it in the literature, as a result of the observation of multiple physical phenomena. Sometimes it is used to account for temporal changes in brain perfusion observed by fMRI, sometimes it is related to the measure of coherence or correlation between EEG and/or MEG signals describing voltage variation over time. Recent studies attempt to establish some kind of correlation between the two approaches, referring to Functional Neuroimaging studies, those that describe the functional organization of the brain independently of the observation instrument [31].

Even if one studies a phenomenon through a single observation instrument, e.g. EEG, this does not guarantee that there is a single definition of functional connectivity. In our case, the idea of functional connectivity is given by the information that is shared or transferred between 2 EEG signals, defined by the Bivariate Transfer Entropy. From this measure, we calculate two matrices, one accounts for the active connections (Flow matrix) and the other accounts for the magnitude of the information flowing by those connections (Transfer Entropy matrix); then over these matrices, we calculate four information quantifiers (Total Activity, Total Tent, Local Activity and Directed Activity) which allow us to extract different and complementary information from each one. It is worth mentioning that, because our data set did not meet the criterion of independence between observations (EEG records or EEG bands), we could not use the ANOVA statistical test. Because of that, we opted for the Wilcoxon test to evaluate interhemispheric connectivity, and the Conover-Iman test for the analysis of frequency bands and clinical conditions.

In this work, we observe that the Total Activity (number of active connections) is greater during the EC condition compare to the EO condition in alpha and beta1 and beta2 bands. In addition, the more significant differences are shown in the alpha and beta1 bands (see figure 2). This result is in accordance with the one reported in [22], where the authors observed that the biggest difference in TE between eyes conditions was given in the alpha band. We should remark that our results are obtained from a less complex protocol setup (less EEG channels and reduced sampling frequency). From table 2 we see there is no statistical difference between frequency bands alpha and beta1 within the same physiological condition. This suggest that the number of active connections is independent of these frequency bands. The questions about why these frequency bands are predominant? Why there are more active connections in EC condition? and what

are the intrinsic neurophysiological mechanisms that produce this response? Can not be answered by the present experimental setup.

Using Transfer Entropy versus the use of Partial Transfer Entropy (Multivariate Entropy) to study the brain dynamics is a subject of wide discussion. In [22] the authors compare both information transfer measures, concluding the transfer entropy is susceptible to false positive connections. The Partial Transfer Entropy is a measure employed to avoid indirect information transfer. For example, suppose, there are 3 random processes with the following causation chain: $X \rightarrow Y \rightarrow Z$; here, the Transfer Entropy will confirm that Y causes Z but will also say that X causes Z, which is a false link since X is not connected directly with Z. The Partial Transfer Entropy was designed to avoid this king of false positive connections. However, increasing the number of variables entails a bigger increase in the data needed for its valid calculation. This condition is very difficult to satisfy in clinical context where the time of signal acquisition is limited. In our experimental setup, we choose to calculate the Transfer Entropy in conditions that are met in clinic, such us: 20 to 32 EEG channel setup, 65 Hz of sampling frequency and 30 second signal length.

Among the limitations of the work, we can point it out that the number of patients are limited and the sampling rate of the equipment is low. However, as mentioned before, in daily clinical practice, the sampling rate of the equipment is not as high as in research equipment. Additionally, we are obtaining similar results to those obtained by studies with a more complex setup.

For future works remains to: i) Demonstrate the differences between the two conditions are maintained in different data sets. ii) Evaluate in experimental designs with repeated measures, whether information transfer is consistent within the same electrophysiological condition. iii) Study entropy transfer in other electrophysiological conditions such as hyperventilation and Opto-stimulation conditions. iv) Explore the information flow in resting vs. activity conditions, e.g., Wakefulness Open Eyes in Resting state vs Active state (intellectual activity assessed in a standardized way, e.g. “neurocognitive assessment”).

4 Conclusions

In this work, we have proposed a simple method to analyze information flow between EEG channels during the open eyes and closed eyes conditions in healthy subjects. This approach is based on Transfer Entropy quantifiers but simplified to be computed on general clinical consults. Our results suggest that more information is transferred (greater number of active connection and increased magnitude) throughout the closed eyes condition, in the alpha and beta1 frequency bands, compared to the open eyes condition. The transfer entropy approach is presented as a very useful tools to study different electrophysiological conditions in the clinical practice.

5 Aknowledgements

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