Cardiovascular Diseases Inhibit the Activation of Cardio-Cerebral Coupling During Arousals

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Abstract

Arousals are spontaneous activations of the central nervous system (CNS) that cause a reaction in the autonomic nervous system (ANS). We investigated transfer entropy (TE) between CNS and ANS to characterize cardio-cerebral coupling in patients with cardiovascular diseases (CVDs) and healthy subjects. 2,154 recordings from the Sleep Heart Healthy Study were investigated to find differences between both groups. CNS activity was measured by EEG band power parameters, while activity in the ANS was measured by various heart rate and QT interval variability parameters. To determinate the effect ρ of arousals, TE was calculated before and after an arousal. Information transfer from the CNS to parasympathetic dominated parameters was stronger influenced due to arousal ($\rho = 1.126$) compared to information transfer from CNS to sympathetic dominated parameters ($\rho = 1.118$). Our results indicate, that arousals lead to an activation of the parasympathetic nervous system but also an increase in the sympathetic response is necessary to return to homeostasis. The increase in information transfer due to an arousal was significantly lower ($p < 0.05$) in patients with CVD compared to healthy subjects, suggesting that CVD inhibits the cardio-cerebral regulatory system. Our finding may contribute to understand the pathophysiological effects of CVD beyond the autonomic regulatory function.

1. Introduction

The human body is characterized by its adaptability to various extrinsic and intrinsic stimuli, which is achieved by multiple regulatory mechanisms. Regulatory actions are necessary to cope the stimuli and return the organism back to homeostasis. Arousals are a spontaneous central nervous activation leading to a change in the frequency of the electroencephalogram (EEG). Thus, arousals are non-invasive measurable during polysomnography (PSG). Moreover, the EEG also affect the autonomic nervous system (ANS), resulting in a higher respiration rate, heart rate and blood pressure. [1]

In the context of an information theoretic approach, the central nervous system (CNS), as the source of an arousal, is coupled to the ANS and therefore part of the cardio-cerebral coupling [2]. To measure this coupling, an information transfer between both systems is feasible. Several methods are known to model coupling between physiological systems. However, recent research has shown promising results using transfer entropy (TE) as a metric of information transfer [3–5]. Cardiovascular diseases (CVDs) cause changes in the ANS activity [6] and lead to increased amount of arousals [1]. This raises the question of whether CVDs also affect the information transfer between ANS and CNS, and what the role of cardio-cerebral coupling plays during arousals. To investigate the cardio-cerebral coupling during an arousal, EEG and electrocardiography (ECG) data from PSG records were investigated. To compare the information transfer of healthy subjects and patients with CVD, we considered a time window before and after an arousal. Thus, our work aims to contribute to the understanding of the role of sympathetic-parasympathetic interplay and the information transfer to the CNS as part of the regulatory response induced by arousals.

2. Methods

2.1. Data Material

The Sleep Heart Health Study follow-up (SHHS2) [7] contains PSGs from 2,154 sleep recordings of 1,734 healthy subjects and 420 patients with CVD, according to the definition of CVD in the SHHS guidelines. In this work EEG channel 1 (C4-A1), ECG (correspondents to Einthoven lead II) and the sleep event records of the participants from the SHHS2 dataset were used. Overall, the sleep events record contains 32,767 arousals.

2.2. Signal Processing

EEG and ECG signals were notch filtered at 60 Hz. Additionally, artifacts from cardiac electrical activity reflections were removed from EEG. Subsequently, we derived the power of the α, β, γ, δ and θ bands as well as

the Shannon entropy H_S from EEG. To extract beat-to-beat changes in RR and QT intervals, we used the two-dimensional signal warping (2DSW) algorithm [8,9]. Furthermore, we extracted 14 heart rate variability (HRV) and 6 QT-interval variability (QTV) parameters from ECG using sliding windows at a size of 100 seconds and 99 % overlap. During parameter extraction, records with more than 50 % of abnormal QT or RR intervals were excluded. HRV and QTV parameters were selected according to their relation to the sympathetic (SNS) and parasympathetic nervous system (PNS), both describing the activity of the ANS.

For the calculation of TE at least 300 samples per variable are recommended for interaction analysis [10]. Since our work focuses on the influence of arousal, we considered a 300 s window before and after the arousal. The sampling frequency of all parameter time series was 1 Hz. Only arousals were taken into account, were no other arousal occurs within these windows plus additional 100 s window (HRV and QTV sliding window). Thus, we ensured, that no information of previous or information from the investigated arousal itself is contained within the HRV, QTV or EEG time series. Also the subject must been in stable sleep condition during both time spans according to the SHHS definition. The distribution of age, gender and CVD diagnosis was in line with the whole dataset.

2.3. Interaction Analysis

To study the interactions between the CNS and ANS, TE [14] was chosen to quantify the amount of information transferred between both systems. We therefore used the JIDT toolbox [15] to calculate TE from a source to a destination variable, where source and destination variables are permuted over each investigated parameter. As TE to the variable itself is not defined, this calculation was not performed. The embedding for the TE calculation was chosen based on an maximum TE optimization approach. Therefore, a grid search for the optimal lag and history for source and destination parameters was performed with physiological related borders from 1 to 30 s. To achieve a better comparability between the interactions, a grid search was performed over all source and destination approaches for random set of 100 arousals out of the 8,136 arousals of the dataset, where 6,841 arousal come from healthy subjects and 1,295 arousal from patients with CVD. Then, the mean TE over all variable combinations and arousal was calculated for each embedding. Additionally, a surrogate test, implemented in the JIDT toolbox was performed on a random test split of 100 arousals with 100 different permutations for each variable combination. The embedding of source and destination was chosen to be equal, so the information in both variables represent the same time span. Further, we introduce the concept of influence factor ρ, which is the quotient of TE before and after the arousal, see equation 1. Where ρ becomes greater one if TE after the arousal is higher compared to TE before the arousal and vice versa.

$$\rho = \frac{TE_{after}}{TE_{before}} \tag{1}$$

For the evaluation only parameters were used, that show a significant ($p < 0.05$, Bonferoni-Holm corrected) change in ρ between healthy subjects and CVD patients. A ρ of 1 means, that there is no significant difference between TE after the arousal compared to TE before the arousal.

3. Results

To visualize the influence of arousals on the interactions between ANS and CNS, the above defined influence factor ρ was used. Figure 1 shows ρ between selected HRV, QTV and EEG parameters for the optimal embedding with the highest mean TE with a lag of five samples and a history of three samples. Source parameters are shown as rows and destination parameters are shown in columns. Table 1 contains parameters, that did show significant changes in TE due to arousals, thus six HRV, four QTV and six EEG-parameters remain for evaluation and all parameters were assigned to SNS, PNS or CNS activity. The mean of ρ over all parameter combinations was 1.110 ± 0.111. Interactions from SNS to CNS showed a ρ of 1.098 ± 0.100 compared to interactions from PNS to CNS with a ρ of 1.059 ± 0.078. Interaction sourced in the CNS are slightly higher influenced to the PNS by arousals resulting in a ρ of 1.126 ± 0.146 compared to interactions to SNS by ρ of 1.118 ± 0.113. EEG γ-Power showed higher values of ρ compared to other CNS parameters, as source and destination variable. The average ρ for interactions with the γ-Power parameter was 1.270 ± 0.149. The highest value of $\rho = 1.470$ was found between QT variability index (QTVi) and HRV parameter SD2.

Table 2 shows the influence of CVD on the influence factor ρ, indicating the change of TE before and after the arousal differs between healthy subjects and patients with CVD. All analyzed interactions showed a lower value ρ in the CVD patients compared to healthy subjects. The largest difference between both groups occurred for interactions from parameters influenced by CNS to parameters influenced by both, SNS and PNS, with a change of ρ by -0.033. The lowest difference was measured in the opposite direction from SNS+PNS parameters to CNS parameters by -0.007.

Table 1. Parameters selected for investigation and their assignment to sympathetic (SNS), parasympathetic (PNS) and central nervous system (CNS).

Parameter class	Parameter	Description	Assignment
Heart rate variability	HR	Mean heart rate	SNS + PNS [11]
	HF	Absolute power of the high frequency band (0.15 ... 0.4 Hz)	PNS [12]
	LF	Absolute power of the low frequency band (0.04 ... 0.15 Hz)	SNS [12]
	LF-HF ratio	Ratio between LF and HF frequency bands	SNS + PNS [12]
	SD1	Standard deviation perpendicular from the identity line of the Poincare map	PNS [12]
	SD2	Standard deviation along the identity line of the Poincare map	SNS [12]
QT variability	QTVN	Normalized QT variance	SNS [13]
	QTVi	QT variability index	SNS [13]
	QTmean	Mean QT interval length	SNS [13]
	SDTQT	Standard deviation of QT intervals	SNS [13]
Cortical activity (EEG spectral power)	α-Power	8 ... 15 Hz frequency band	CNS
	β-Power	15 ... 30 Hz frequency band	CNS
	γ-Power	30 ... 60 Hz frequency band	CNS
	δ-Power	0 ... 4 Hz frequency band	CNS
	θ-Power	4 ... 8 Hz frequency band	CNS
	H_s	Shannon Entropy	CNS

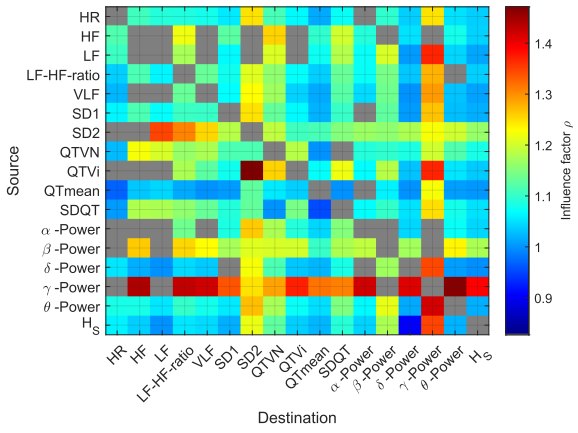

Figure 1. Influence factor ρ of all subjects. As transfer entropy is not defined to a variable itself no values of ρ are available on the main diagonal. Dark gray indicate interactions that are not significant ($p > 0.05$, Bonferoni-Holm corrected).

Table 2. Influence factor ρ between sympathetic (SNS), parasympathetic (PNS) and central nervous system (CNS) and the difference in ρ due to cardiovascular disease (CVD). Analyzed parameters are averaged over their associated nervous system. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, n.s.: not significant.

Source	Destination	Healthy	CVD	Difference
SNS + PNS	CNS	1.119***	1.112***	-0.007**
PNS	SNS	1.090***	1.069***	-0.021**
	CNS	1.063***	1.042***	$-0.021^{\text{n.s.}}$
SNS	PNS	1.076***	1.047***	-0.029*
	CNS	1.100***	1.088***	-0.012*
CNS	PNS + SNS	1.152***	1.119***	-0.033***
	PNS	1.127***	1.117***	$-0.010^{\text{n.s.}}$
	SNS	1.120***	1.107***	-0.013**

4. Discussion

Our results indicate a significant difference in TE before and after arousals over the SHHS2 dataset, suggesting that arousals affect regulatory functions and alter information transfer between ANS and CNS. Arousals trigger an regulatory response, that requires more information transfer within the autonomic function, between SNS and PNS, but also between the ANS and CNS, showed by an influence factor ρ greater one, as the TE after the arousal is higher compared to before. Our results do not allow to distinguish if the CNS, representing the source of the arousal is also the source of the increased information transfer or if the overall increased TE resulting as feedback loop between CNS and ANS. Arousals also influence the TE from SNS to CNS stronger than the TE from PNS to CNS. Thus, we hypothesize that an arousal triggers a sympathetic response to cope the higher demand of cardiac output, while an increase in information transfer from PNS to CNS might result as a feedback loop to control the cardio-cerebral regulation. High values of ρ in the γ-Power may result from the high frequency spectrum, covered by the γ-Band. This allows a high bandwidth to transfer information. The highest ρ was found between SD2 and QTVi, both sympathetic associated parameters. Thus, they may have a crucial role in the SNS activity during arousal-caused regulatory response. Figure 1 contains values of ρ below one, resulting in a reduced information transfer after the arousal. As TE is sensitive to noise [16], we averaged ρ over parameters that are linked to the same nervous system, to ensure the representation of the system change due to the arousal. In-

fluence factor ρ is lower in patients with CVD compared to healthy subjects, showing that information transfer is affected by the presence of CVD. Luo et al. [17] found higher absolute values in TE between HRV LF and HF in patients with congestive heart failures compared to healthy subjects as significant impact of CVD on the information transfer. Our results show strong difference of ρ between healthy subjects and CVD patients occurs between SNS and PNS, with ρ from PNS to SNS -0.021 and SNS to PNS -0.029, see Table 2. This results conclude with the literature, as CVD distract the regulatory functions within the ANS during sleep [6]. Further, the information transfer between ANS and CNS is also distracted, resulting in lower ρ values in CVD patients compared to healthy subjects, see Table 2. Our results also show that CVD affects the information transfer between ANS and CNS. Analyzed effects on arousals came with limitations due to the signal processing and dataset. Short arousals below 8 s are underrepresented in the selected arousal dataset compared to the full SHHS2 dataset. Arousals, where the sleep 30 s before the arousal onset was labeled as NREM1 and NREM2 are also underrepresented in the arousal dataset compared to the full dataset, while NREM3/4 and REM sleep are over-represented. Additionally, arousals extracted for this calculation occur separated, meaning that in a window of 400 s before and after the arousal exists no other arousal. The dataset showed, that most of the arousals, 269,337 out of 277,473, are not suitable for this calculation. Further investigations need to be carried out to evaluate the statistical influence of the limitations on our results.

5. Conclusion

Arousals, as a spontaneous central nervous event, causing a change in the information transfer between CNS and ANS. Our results indicating, that information transfer, measured with TE, mainly increases after the arousal to cope the stimulus, which triggered the arousal. The primary path is from the CNS to the ANS, as ρ shows higher values for this direction but the information transfer from the ANS to CNS is also rising due to the arousal, leading to the assumption that the underlying regulatory mechanism activates a feedback loop from ANS to CNS. Furthermore, ρ is higher for CNS to PNS interactions compared to CNS to SNS interactions, assuming, that arousal leads to the activation of the PNS, while the SNS is activated to return the organism back to homeostasis. CVDs affect the information transfer between ANS and CNS, resulting in a lower influence of arousal on the information transfer between both nervous systems. Further investigations are necessary to comprehend the impact of CVDs influence on the information transfer between CNS and ANS, as well as to determine an appropriate therapy to address these conditions.

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