Lagged Transfer Entropy Analysis to Investigate Cardiorespiratory Regulation in Newborns during Sleep

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Abstract: The autonomic nervous system (ANS) acts modulating the cardiac and respiratory systems by means of the sympathetic and parasympathetic branches. In this work, we propose to employ Transfer Entropy (TE) with the aim of disambiguating the contributions of the two branches over cardiorespiratory regulation in newborns during sleep. Specifically, we computed TE on the original time series representative of the two subsystems, namely Heart Rate Variability (HRV) and Respiration (RESP). Furthermore, we employed a lagged version of the two original signals to derive a TE estimation capable of providing and insight on the short-term memory between the two systems. Results show the information transfer quantified by $TE_{RESP \rightarrow RR}$ decaying rapidly as the shift between the two time series increases. On the other hand, $TE_{RR \rightarrow RESP}$ exhibits a slower but prolonged interaction, which lasts over numerous lags. The novel approach presented in this work affords the potential to assess infants' ANS development in terms of the quantification of cardiorespiratory control functioning.

1 INTRODUCTION

Sleep is a central activity in humans across all ages. The maturation of sleep is one of the most important physiological processes occurring during the first year of life and is particularly rapid during the first six months after birth. A human infant shows prolonged and characteristic epochs of stable behavior, called behavioral states. Many physiological variables are inter-related and mutually influencing during the state cycles and change their properties at the transition (Prechtl, 1974).

During sleep, autonomic nervous system (ANS) acts to modulate heart rate variability (HRV) and respiration, accordingly to sleep states (SS).

In the last few decades, knowledge about the mechanisms underlying cardiorespiratory interactions as a function of sleep states has grown (Berntson et al., 1993; Loewy and Spyer, 1990) underlying the complex linear and nonlinear interplay between the cardiac and respiratory systems. Nonetheless, a full characterization of such interaction is still pending and the investigation of sympatho-vagal interaction and its role in cardiorespiratory regulation needs further elucidation.

Cardiorespiratory interaction investigation relies on a joint analysis of HRV and respiration signals.

HRV is a non-invasive, indirect, but reliable measure of ANS functioning. It is ideally suited for

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tracking changes in cardiovascular autonomic control in subjects at rest as well as during physiological challenges (Schipke et al., 1999). Many studies have demonstrated the ability of HRV measures and derived parameters to characterize autonomic profiles and perform risk stratification (Farrell et al., 1991; Huikuri and Stein, 2013). In the perinatal field HRV has been particularly successful in the assessment of newborn infants for whom standard protocols designed for adults requiring cooperation are unfeasible (Galland et al., 2000; Harper et al., 1976; Lucchini et al., 2016b).

In order to integrate the respiratory signal for a bivariate approach, many signal processing approaches have been proposed, using either linear (e.g., cross-spectral analysis) or non-linear methods (e.g., mutual information) to model the interrelationship between HR and respiration signal (Frasch et al., 2007; Kluge et al., 1988; Lucchini et al., 2016a). Nonetheless, all the aforementioned techniques are lacking the capability of providing information on the directionality of such relationships.

Transfer Entropy (TE) was developed to precisely address this issue. The main focus of this methodology is on tracking the information flow between two given systems. Specifically, TE can enhance the quantification of the directional coupling between HRV and respiration providing insight on the relative contribution of the sympathetic and parasympathetic regulatory influences (Schreiber, 2000). In the context of biological time series, TE has been utilized to test the effect of age and gender on cardiorespiratory interaction complexity (Nemati et al., 2013), characterize tilt response (Faes et al., 2012; Porta et al., 2015), and highlight the importance of information storage, transfer and modification in interacting dynamical systems (Cațaron and Andonie, 2018; Faes et al., 2013a; Valenza et al., 2018).

In this paper we propose to employ TE methodology to characterize cardiorespiratory interaction during sleep in newborn infants. The novelty we introduce in this work is the computation of TE on time series shifted at various lags, to assess the short-term memory of one system with respect to the other. This approach provides further information on the relationship between the cardiac and respiratory systems at different time lags and thus better characterization of the different role of the sympathetic and parasympathetic branches of ANS, which are known to operate on different time frames and scales. We are searching for indices that could ultimately be used as early markers of regulatory alterations or malfunctions in the cardiorespiratory mechanisms, potentially leading to infant distress.

2 MATERIALS AND METHODS

2.1 Subjects and Data Collection

The results presented in this paper are based on the analysis of a dataset of 157 newborns, whose gestational age at birth varies from 38 to 40 weeks (mean±std: 39.03±0.80).

None of the enrolled infants had been admitted to the Neonatal Intensive Care Unit nor had any major illness, congenital abnormalities or known genetic disorders. Mothers were at least 18 years of age and displayed no evidence of major illness or psychiatric disorders during the pregnancy.

Data collection was performed at Columbia University Medical Center, upon mothers' consent and approval of the Institutional Review Board of the New York State Psychiatric Institute and of the Columbia University Medical Center. Electrocardiography (ECG) and respiration signals were recorded non-invasively at a sampling rate of 500 Hz and 200 Hz respectively, by means of three leads on the chest in standard positions (RA, RL, LL, DATAQ Instruments) and by a respiratory inductance belt around the infant abdomen (Ambulatory Monitoring Inc., Ardsley, NY, USA).

During the study, infants were sleeping supine and sleep states were classified into active sleep (AS) and quiet sleep (QS) by an automated algorithm (Isler et al., 2016) and further validated by expert clinicians (Stefanski et al., 1984).

2.2 Signal Pre-Processing

R wave peaks were detected on the ECG employing the Pan-Tompkins algorithm (Pan and Tompkins, 1985). An adaptive filter was then applied to remove ectopic beats or artifacts, preserving the beat-to beat sequence. Respiration signals were band-pass filtered in the interval 0.05-3.5 Hz and were then resampled at the time of occurrence of R peaks. The RR series was then defined so that RR(n), is time interval between the n-th R peak and the successive one at time ($n+1$)-th. Similarly, the n-th sample of resampled respiration series RESP(n) is obtained by resampling the original respiration series at the onset of the n-th R peak which coincides with the time previously defined for RR(n) as schematically shown in Figure 1.

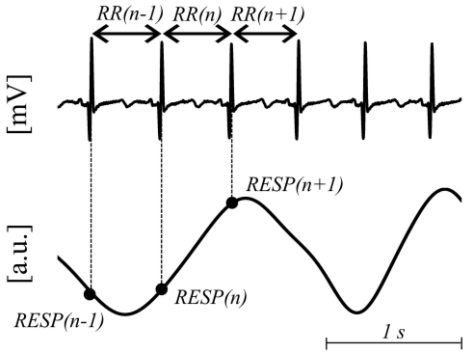

Figure 1: Schematic representation of RR and RESP series extraction starting from ECG and respiration signals.

Within the same sleep state, segments of 300 consecutive RR intervals (RR) and 300 respiration samples (RESP) were identified. The resulting series, RR(n) and RESP(n) with n=1,…,300, were normalized to zero mean and unit variance to be employed for further analysis. The segments length was chosen based on previous studies, reporting 300 samples series as appropriate for a reliable Transfer Entropy (TE) estimation (Faes et al., 2014, 2011; Lucchini et al., 2017). Each subject had at least one segment in either AS or QS and 17 of them presented both states during the study. The total number of analyzed segments was 174, 79 in AS and 77 in QS.

2.3 Transfer Entropy

Since its definition by Schreiber (Schreiber, 2000), TE has been vastly described as a powerful tool to unveil information transfer between subsystems (Faes et al., 2013b; Vicente et al., 2011). The method incorporates the notion of directional and causal information exchange in a model-free framework, bridging its applicability towards short and experimental datasets as in this context.

The traditional formulation for TE considers a set of M interacting dynamical systems and aims at quantifying the information flow from a source system X to a target system Y, conditioned to the remaining M-2 systems. In the context of this work, the number M of subsystems is equal to 2, namely the cardiac and respiratory systems, represented by the time series RR and RESP respectively.

Denoting x_n, y_n as the stochastic variables representing the states of the processes X and Y at time t, and $x_{1:n}$, $y_{1:n}$ the vectors of their respective past states, TE is defined as reported in Equation 1:

$$TE_{X\to Y} = \sum p(y_{1:n}, x_{1:n-1}) log \frac{p(y_n|x_{1:n-1}, y_{1:n-1})}{p(y_n|y_{1:n-1})} \quad (1)$$

where the sum incorporates all states visited by the subsystems.

It appears clear that the formulation of TE can be also written in terms of difference between two Conditional Entropy (CE) terms, as expressed in Equation 2:

$$TE_{X\to Y} = H(y_n|y_{1:n-1}) - H(y_n|x_{1:n-1}, y_{1:n-1}) \quad (2)$$

It becomes evident that, regardless the formulation, TE quantifies the information provided by the past of the process X about the present of the process Y, that is not already provided by the past of Y.

An open issue regarding TE estimation is the quantification and disambiguation of instantaneous effects, namely addressing the information flow $x_n \to y_n$. Instantaneous causality has been reported to have impact on TE computation and various approaches to address it have been proposed in literature. In this work, compensated Transfer Entropy (cTE) as formulated by Faes et al. (Faes et al., 2013) has been computed. The method assimilates instantaneous effects with the past states ($x_{1:n}$ becomes x_n) if causally meaningful. On the other hand, in case of non causal meaningful interaction, instantaneous effects are considered as a conditioning factor (x_n plays a role analogous to $y_{1:n-1}$). In the latter case, the present state of the source is compensated to have instantaneous causality removed from TE computation.

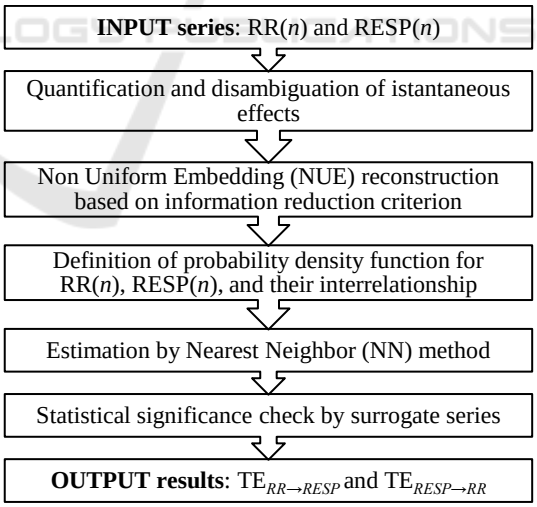

Figure 2: Schematic workflow of the steps for TE estimation starting from the RR series and resampled respiration signal.

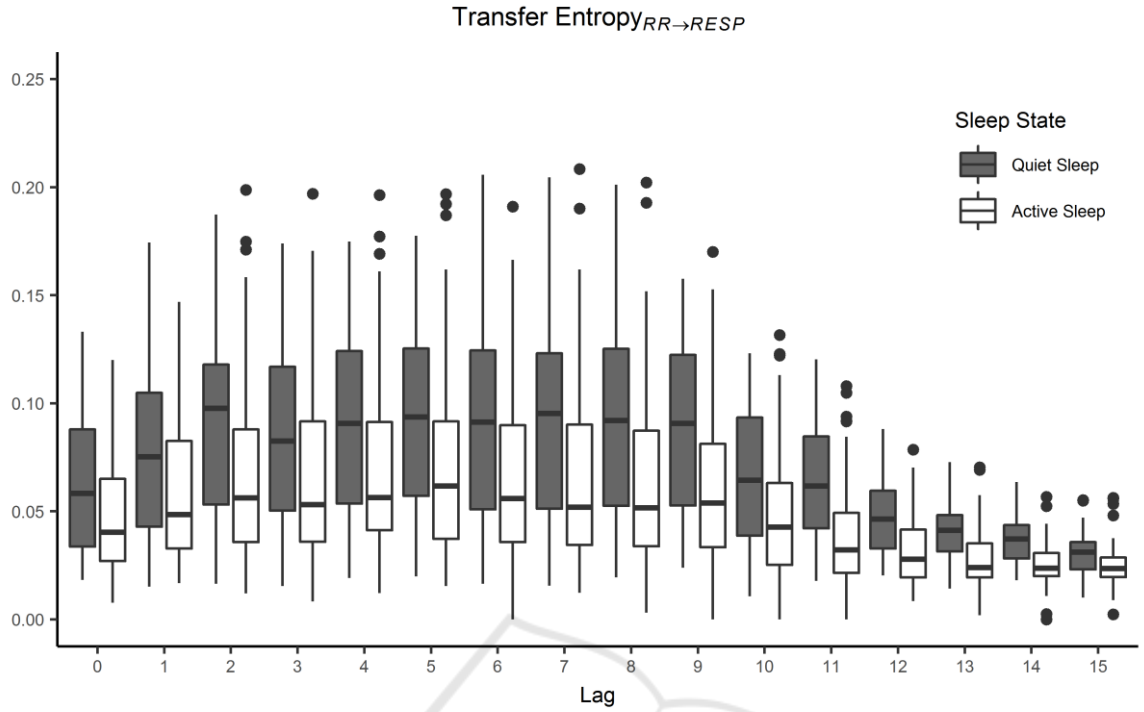

Figure 3: TE$_{RR\rightarrow RESP}$ distributions as a function of lag and grouped based on sleep state. TE increases from lag equal to 0 and remains stable to higher values for intermediate lags. From lag 9 on, TE decreases due to a vanishing mutual influence between the two series.

In the context of TE computed upon series of short length, as for physiological time series, the reconstruction of the vector of past states and the estimation of probability density functions are crucial. Regarding the reconstruction of vector of the past states, the basic idea is to optimize the time-delay embedding based on a sequential procedure capable of selecting a reduced subset of components which better describe the destination process, allowing the inclusion of the present state. It is important to underline that the presented selection procedure is based on information reduction given the assumption that joint probabilities are insensitive to temporal ordering of components. This procedure, called non uniform embedding procedure is explained in details in (Faes et al., 2013). In this word, the maximum number of candidates L is set to 10 and the resulting embedding vector is denoted as V_k.

The final step towards TE estimation relies on the definition of probability density functions to approximate the interrelationship between X and Y from a single realization of the two processes. The estimation of terms in Equation 1 is based on previously defined embedding vectors (V_k) only and it employs a Nearest Neighbor (NN) estimator. Considering NN estimator, it is possible to rewrite Equation 2 as follows:

$$TE_{X\rightarrow Y} = H(y_n, V_k^Y) - H(V_k^Y) - H(y_n, V_k) + H(V_k) \quad (3)$$

where is V^Y denotes the relevant visited states by the subsystem Y only. Terms in Equation 3 are estimated based on the formulation reported in (Montalto et al., 2014).

The combination of non uniform embedding and NN estimator (NN NUE) has been reported to be optimal for the selection of candidates in the context of TE estimation (Kugiumtzis, 2013).

Furthermore, the statistical significance of computed TE is assessed using surrogate data implemented by time shift procedure. In this work, the number of employed surrogate series is equal to 100 and the maximum allowed time shift is set to 20 samples. The threshold employed for the definition of a significant TE value is set above the 95th percentile of surrogate series distribution.

Figure 2 reports the workflow of TE computation starting from the original time series RR(n) and RESP(n) to obtain both TE$_{RR\rightarrow RESP}$ and TE$_{RESP\rightarrow RR}$.

2.4 Lagged Transfer Entropy

In this work, a novel approach to quantify the short-term memory effect of two interacting systems starting from the notion of TE is proposed. The new

approach lies its foundations on the previously described TE implementation, yet it considers several lagged versions of the original series. Supposing to quantify $TE_{X\rightarrow Y}$ at lag value equal to one, the target series is shifted forward of a quantity equal to one sample so that x(*n*) is now aligned with y(*n-1*).

The lagged version of TE proposed in this work aims at quantifying the information provided by the past of *X* on the shifted portion of the process *Y*, that is not already provided by the past of *Y*.

The underlying idea is the quantification of the source series effects on the target and the quantification of the short memory effect between the two. In this work, the maximum allowed value for the lag between RR and RESP series is set to 15, which corresponds to 15 beats. The choice of maximum lag equal to 15 beats is related to the physiological imping effect of sympathetic and parasympathetic systems on cardiac and respiratory systems, as well as the operational cardiac and breathing frequencies in newborns (Frasch et al., 2007).

2.5 Statistical Analysis

The significance of TE measures was assessed by performing a two-way ANOVA testing separately the two directionalities, namely $TE_{RR\rightarrow RESP}$ and $TE_{RESP\rightarrow RR}$ and as fixed factor the sleep state (AS vs QS) and lag values ranging from 0 to 15. The covariates included in the model were infant's sex (Sex), mode of delivery (MoD) and hours of life (HoL) from delivery to time of the study assessment. Significance is reported for main effects as well as interactions between independent variables. Post-hoc tests were performed to assess significant differences between pairs of lags and to disambiguate interaction effects among fixed factors.

3 RESULTS

3.1 TE Directionality from RR to RESP

The analysis of TE in the directionality RR→RESP reports a significant between-subjects effect for both fixed factors, SS and lag ($p<0.001$ and $p<0.001$), but no interaction effect between the two. Moreover, covariates included in the model are no significant in explaining the behavior of TE with exception for HoL ($p<0.001$).

The amount of significant TE estimates, based on surrogate testing, progressively decreases as a function of lag moving from the non-lagged version

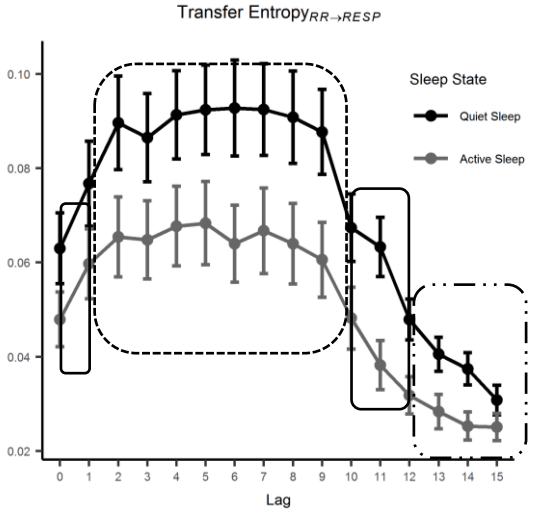

Figure 4: $TE_{RR\rightarrow RESP}$ distributions as a function of lag and grouped based on SS. Error bars represent 95% confidence interval (CI) of the derived distributions. TE increases from lag equal to 0 and remains stable to higher values for intermediate lags. From lag 9 on, TE decreases due to a vanishing mutual influence between the two series.

of the two signals to lag=15. The non-significant estimates are on average 15 over 174 in the lag interval 0-12 and they further increase up to an average of 62 from lag 12 to 15. The TE values for each lag and grouped based on SS are reported in Figure 3.

The results for the post-hoc test performed on the independent factor lag are graphically shown in Figure 4. Circles enclose groups of lags among which no significant differences are found. The influence of RR modulation over respiration is significantly increasing when comparing the instantaneous effect (lag = 0) with respect to the two signals lagged by one beat. This increase in $TE_{RR\rightarrow RESP}$ stays stable over 8 lags to then decrease and return to values similar to the result for lag equal to zero. Lags from 12 to 15 are statistically different from the previous ones, yet their distributions are obtained by a reduced poll of TE values due to lack of significant TE estimates after performing surrogate check. TE values are consistently lower for AS compared to QS and this is independent from the lags. Nevertheless, higher lags exhibit a flatter trend possibly as a consequence of more hampered and inconsistent TE estimates.

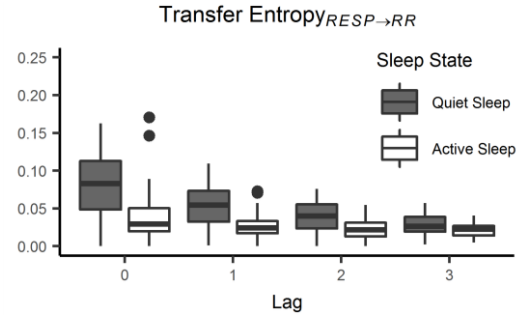

Figure 5: TE$_{RESP→RR}$ distributions as a function of lag and grouped based on SS for the proposed restricted model. TE progressively decreases from lag 0 to lag 3 with a more pronounced trend in QS.

3.2 TE Directionality from RESP to RR

In contrast to the behavior previously reported for the directionality RR→RESP, RESP→RR analysis shows a TE decrease as lags are progressively increasing from 0 to 15. In this context, significant between-subjects effects for both SS and lag are reported, $p<0.001$ and $p<0.001$ as well as an interaction effect of SS*Lag, $p<0.001$.

It is remarkable to notice that no differences in TE distributions are found comparing each pairs of lags from lag 3 to lag 15. It is possible to assimilate the described lag interval to a unique class towards the aim of avoid over-representing similar class distributions in the successive statistical analysis. Furthermore, surrogate testing procedure excludes an average of 66 TE values from lag 4 to lag 15 but only around 30 from 0 to 3. Given these considerations, the statistical results reported for TE$_{RESP→RR}$ are extracted by considering lags from 0 to 3 only, as reported in Figure 5. The ANOVA performed on this restricted number of lags is consistent with the results obtained considering all computed lags. Significant between-subjects effects for SS and lag are reported, $p<0.001$ and $p<0.001$ and SS*Lag $p<0.001$. No significance for covariates is found.

As a general consideration, regardless SS, TE$_{RESP→RR}$ decreases as lags increase with a marked drop between lag 0 to lag 1. Post-hoc test on the factor lag reports significant differences when comparing pairs of lags with exception in the comparison of lag equal to 2 versus lag equal to 3. SS-related changes of TE are similar to what previous reported for TE$_{RR→RESP}$ even if such slope decrease is less marked and flatter when passing from TE in AS vs TE in QS. Given the reported interaction between fixed factors (SS*Lag), simple main effects were tested. The results indicate that differently from TE$_{RR→RESP}$, SS differences are mainly driven by lags.

4 DISCUSSION AND CONCLUSIONS

For healthy full-term newborns, as the cohort investigated in this work, sleep constitutes the predominant state, with an average prevalence of AS over QS. ANS modulation over either the cardiac and respiratory systems is strongly dependent upon sleep state dynamics, thus its regulation is indeed responsible for the generation and modulation of cardiorespiratory patterns. Investigation of the functional organization of these neurophysiological systems is extremely challenging, due to their intrinsic complexity and the necessity to access them by means of noninvasive recordings only. Fortunately, the analysis of HRV, breathing and their coupling provide an optimal set of noninvasive functional probes of the behavior of cardiorespiratory systems.

In this paper we deepened the investigation presented in Lucchini et al. (Lucchini et al., 2017). Our previous investigation focused on the traditional TE estimation and highlighted a predominant information transfer in QS vs AS regardless the sleep state, with a stronger TE gap when considering the directionality from RESP to RR (TE$_{RESP→RR}$).

In this present work, the use of the lagged series allowed us to gain insight on the temporal relationships between systems as a function of increasing lags providing a transferrable link to the beat scale. As a matter of fact, results show that the information transfer from RESP to RR (TE$_{RESP→RR}$) decays rapidly as the shift between the time series increases. The statistical significance of TE estimation progressively decreases for increasing lags, consolidating the hypothesis that the mutual influence of RR over RESP is rather transient and acts on a very short scale. On the other hand, considering the directionally from RR to RESP (TE$_{RR→RESP}$), the maximum information transfer between the subsystems requires an average of 2 beats to activate but it remains stable for a longer period of approximately 8 or 9 beats.

Findings considering the unlagged (lag=0) TE estimates reported in this work are in accordance with the TE results previously reported in Lucchini et al. (Lucchini et al., 2017) for the same cohort of newborns. TE values in QS are on average higher with respect to TE in AS, regardless the considered directionality and sleep state.

Coming to the findings obtained by employing the lagged version of TE, results might suggest that different information transfer directionality are in fact driven by one of the two autonomic branches of the

ANS (Hoyer et al., 2005) respectively. As a matter of fact, the sympathetic branch intervenes on a slower time scale, but its effect last longer in the target system, whereas the parasympathetic has a punctual yet rapidly vanishing action. Given these considerations, it is possible to speculate that that the vagal system is possibly more implicated in the directionality from RESP to RR while the sympathetic in the opposite directionality. The latter assumption is based on the behavior of $TE_{RR \rightarrow RESP}$ showing higher TE values for intermediate lags up to the point of reaching almost comparable values to the maximum information transfer for $TE_{RESP \rightarrow RR}$.

In sum, we have provided a noninvasive characterization of the sleep state effects on cardiorespiratory regulation in newborns, by employing a measure of TE capable of quantifying both linear and nonlinear aspect of the interrelationship between the cardiac and respiratory system. The novel approach of lagged TE was capable of highlighting interactions occurring on different time scales and possibly related to the activation of the two autonomic branches. The proposed interpretation of TE related findings is also consistent with previous works, modelling the interrelationship between the two branches of ANS and cardiorespiratory regulation (Ataee et al., 2012). In the specific context of this work, information flow between HR and respiration is increased in QS with respect to AS, indicating that in such sleep state more information is exchanged between the cardiac and the respiratory systems on average. This approach to the quantification of cardiorespiratory interactions affords the potential for early assessment of infant development of bidirectional control between physiological systems providing a more comprehensive framework of investigation rather than studying the two signals on their own.

Lastly, the proposed approach could facilitate early risk assessment for neurophysiological disorders such as Sudden Infant Death Syndrome (SIDS) by tracking adverse profile of information exchange between the two systems, thus exposing infants to greater risk for a variety of pathology involving the malfunction of cardiorespiratory controlling mechanism.

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