Causal Linear and Non-linear Assessment of Central-Cardiorespiratory Network Pathways in Healthy Subjects in Comparison to a Neurological Disorder under Resting Conditions

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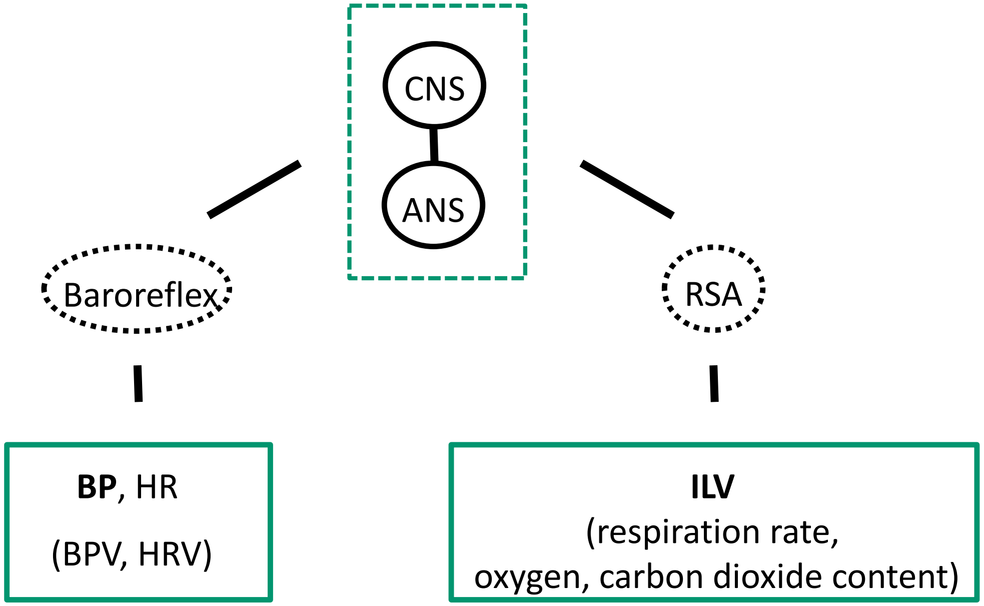
Basics

Physiologic background - cardiorespiratory control



Cardiorespiratory system – simplified basic control mechanisms

CNS - central nervous system, ANS – autonomic nervous system, RSA – respiratory sinus arrhythmia, BP – blood pressure, HR – heart rate, BPV –blood pressure variability, HRV – heart rate variability, ILV – instantaneous lung volume

Baroreflex

- Negative feedback mechanism
- Stretch receptors in aortic arch and carotid sinus
- Increase of arterial BP→ stronger firing signals to medulla oblongate (brain stem)
  Vagal activity ↑ sypathetic activity ↓ leading to heart rate ↓
- Low arterial BP→ reduced baroreceptos activity → reverse effects
- Noninvasive measurement: e.g. sequence method

Respiratory sinus arrhythmia (RSA)

- Important closed-loop within the cardiorespiratory system
- HRV in synchrony with the phases of respiration (Inspiration: RR ↓, Expiration RR ↑)
- RSA frequency changes with respiration rate → shift in the phase differences respiration-HR and change of HRV amplitude (max. at 6 Hz – cardiorespiratory system resonance)
- Functions as enhancement of pulmonary gas exchange efficiency, minimising cardiac work, buffering systemic blood flow oscillations???
- Baroreflex and/or central respiratory ceners generate predominantly RSA???
- Genesis of RSA involves a network of central, peripheral and mechanical elements (interacting biderectionally, influencing the HRV)
- Generation of an intrinsic cardiorespiratory rhythm within the nucleus tractus solitarius (NTS) and nucleus ambiguus regulating HR via parasympathic and sympathetic nerves (respiratory gate?)
- Believed to be a direct measure of vagal tone
- Noninvasive measurement: e.g. peak-valley method

Anatomic/ Physiologic background - central autonomic network

Cortex – subcortical forebrain – midbrain – medulla (brain stem)

Midcingulate Cortex

Thalamus (medial– dorsal nucleus, pulvinar), Superior colliculus/ periaqueductal gray

Amygdala, hypothalamus, ventral tegmental area, hippocampal formation

Anterior insula

Medulla

Ventromedial prefrontal cortex, subgenual anterior cingulate cortex

Pregenual anterior cingulate cortex

lingual gyrus

Frontoinsular cortex

Posterior insula

Angular gyrus, supramarginal gyrus

Ventral posterior cingulate cortex, precuneous cortex

Beissner et al., J. Neurosci. 2013

Silvani et al., PTRSA 2016

Schizophrenia – a neurologic disease

- **Schizophrenia is one of the most serious mental illnesses in the world** with a lifetime prevalence rate of approximately 1% (US: 2.2 million people, Germany: 800,000)

- Patients suffering from schizophrenia
  - Relative risk for cardiovascular diseases (CVD) up to **three-times higher**
  - **Life expectancy 15-20 years shorter** in comparison to general population

  (Hennekens et al., 2005).

- Causal factors for the increased mortality rates are under debate

Schizophrenia – a neurologic disease

Structural Magnetic Resonance Imaging studies indicate that schizophrenia is associated with volumetric reductions in a network of frontal, temporal, limbic, striatal, and thalamic regions.

Cortex orbitofrontalis

Orbitofrontal Cortex
Medial prefrontal cortex (PFC)
Dorsolateral PFC
Ventrolateral PFC
Anterior Cingulate Cortex
Posterior Cingulate Cortex
Temporal lobe Hippocampus
Caudate nucleus
Thalamus
Fornix
Amygdala
Striatum

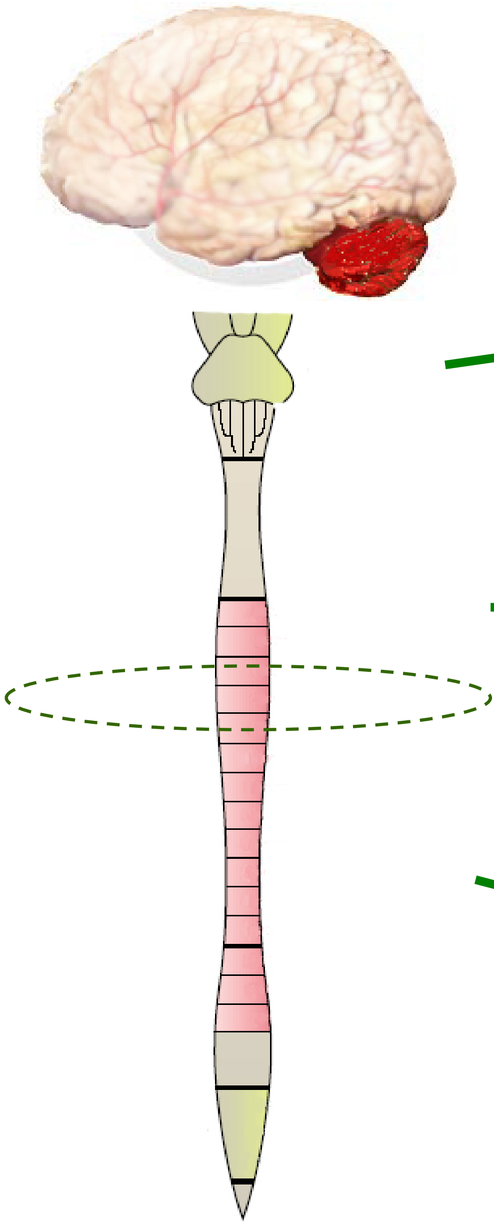
Locus coeruleus (?)

Modified from http://www.gehirn-atlas.de/schizophrenie.html

I. Introduction

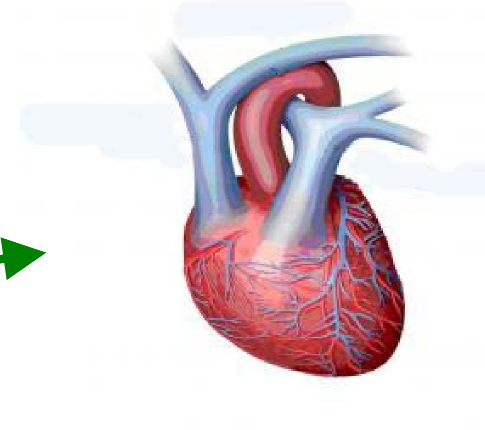
- **Dynamical interplays** between the **brain** and the **heart** ensure **fundamental homeostasis** and **mediate a number of physiological functions** as well as **disease-related alterations**
- Quantitatively characterization of complex **brain-cardiovascular and cardiorespiratory interactions** allow the **improved understanding of (patho)physiological** structural, dynamical and regulatory processes
- **Interaction** between **central nervous system (CNS)** and **autonomic nervous system (ANS) → central-autonomic-network (CAN)**
- **CNS-ANS interactions:**
  - Interplay of several regulatory mechanisms (**linear** and **non-linear**)
  - **Feedback-feedforward** network
- **ANS dysfunctions** in schizophrenia have been demonstrated

  (heart rate and respiratory variability; e.g. Bär K.J, 2015; Schulz et al., 2015)



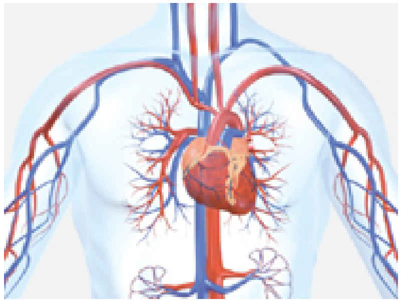
Heart rate variability

HR↑, variability & complexity↓



Blood pressure variability

unchanged



Respiration

BF↑, inspiration- and expiration time↓, RSA↓, shallow breathing, correlation with psychopathology

known

Objective

- **Linear and non-linear** couplings between the ANS (**heart rate**, **respiration**) and CNS (**EEG activity**) are not addressed

The aim of this study was to investigate the central-cardiorespiratory network (CCRN) in patients suffering from paranoid schizophrenia in comparison to healthy subjects.

II. Materials and methods - study population

Subjects	Healthy subjects (**CON**)	Schizophrenic patients (**SZ**)
Number of participants	17	17
Gender (male/female)	15/2	13/4
Age (mean ± sd in years)	37.5 ± 10.4	37.7 ± 13.1

- SZ had been treated with depot antipsychotic medication.
- All participants (SZ and CON) provided their written informed consent to a protocol approved by the local ethics committee of the Jena University Hospital. This study complies with the Declaration of Helsinki.

II. Materials and methods - data recording and pre-processing

Biosignal recordings

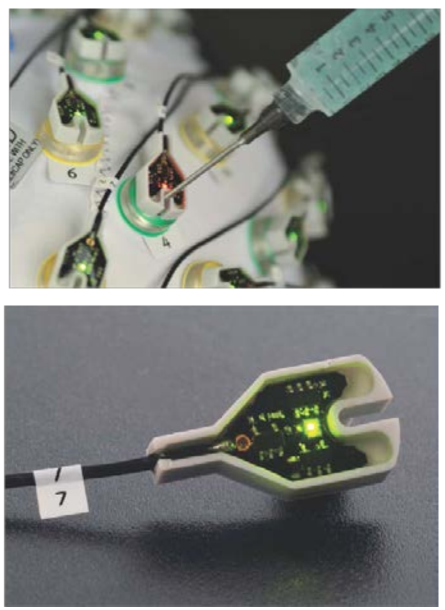
- 3-channel ECG (500Hz), 64 channel EEG
- Synchronized calibrated respiratory inductive plethysmography signal (LifeShirt®, Vivometrics, Inc., Ventura, CA, USA)
- Recording between 2 and 6 p.m. in a quiet room; comfortably warm (22–24˚C)
- Supine position, starting with 10 min rest
- Afterwards recording biosignals for 15 min under resting conditions (seated, closed eyes)

II. Materials and methods - data recording and pre-processing

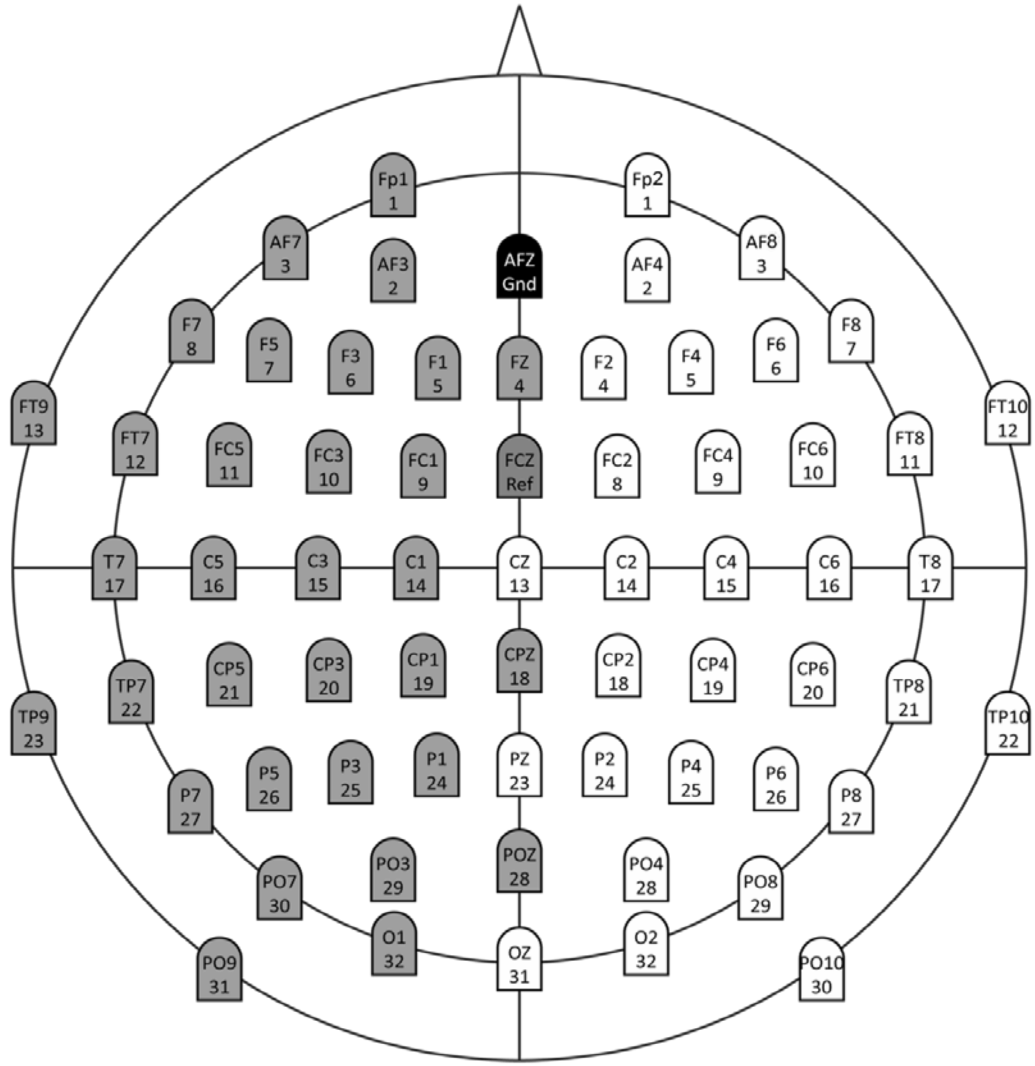
EEG

- 64 active Ag/AgCl electrodes
  (BrainAmp Amplifier, Brain Products, Germany (500Hz))
- AFZ: ground, FCZ: reference
- Extended 10–20 system using an electrode cap
- Impedance levels (<25kΩ)
- Band-pass filtered (0.05–60Hz, Butterworth filter, order=3)
- Artefact-free time series
  (visual inspection and automatic classification using the Brain Products software ANALYZER v. 2.0)

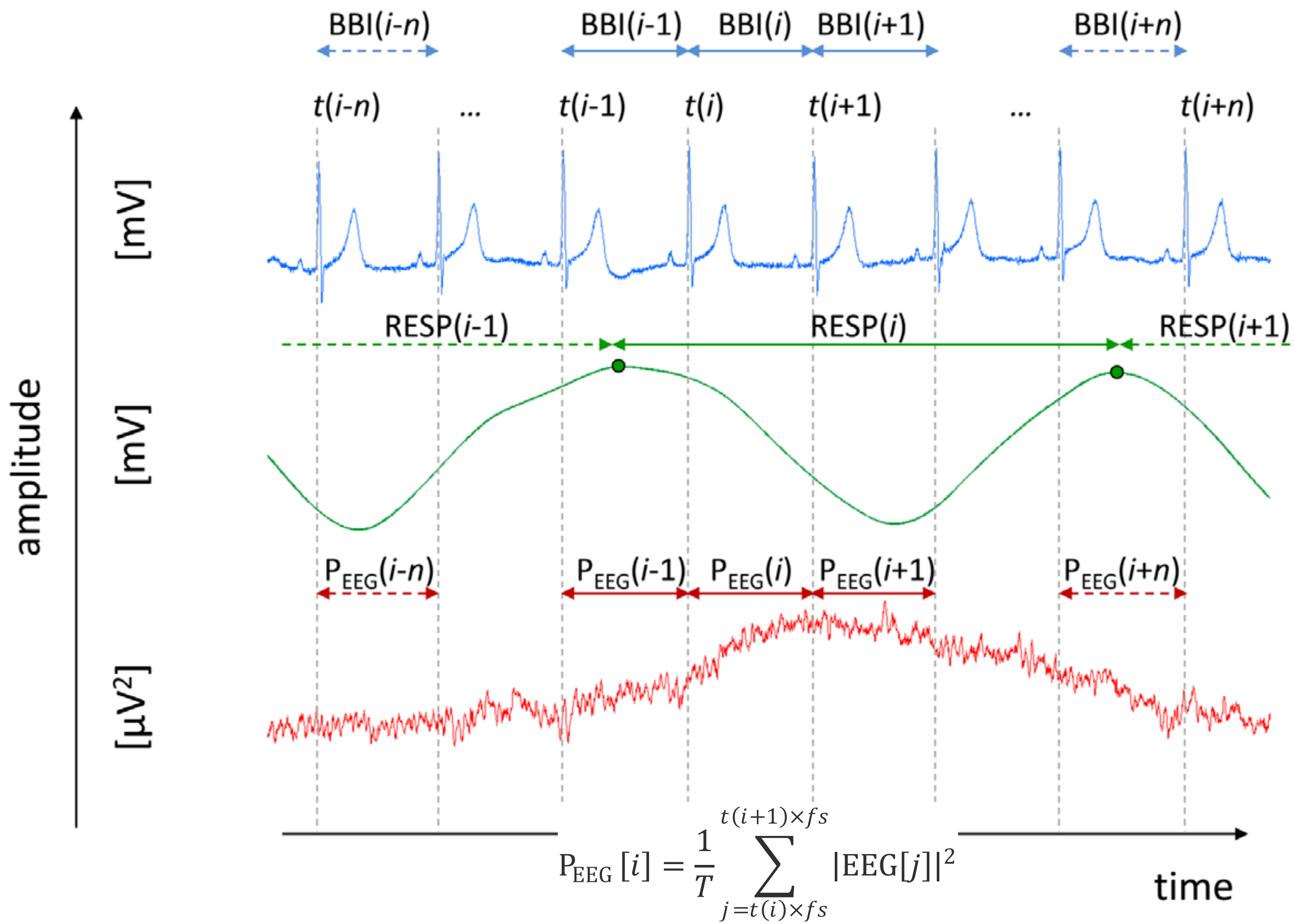
II. Materials and methods - data recording and pre-processing



Brain Products, actiCAP 64Ch



II. Materials and methods - data recording and pre-processing



$$P_{EEG}[i] = \frac{1}{T} \sum_{j=t(i)\times fs}^{t(i+1)\times fs} |EEG[j]|^2$$

II. Materials and methods - data recording and pre-processing

Time series

- Time series of **heart rate** (lead I) consisting of successive beat-to-beat intervals (**BBI**, tachogram, [ms])
- Time series of **respiratory frequency** as time intervals between consecutive breathing cycles (**RESP**, [s])
- Time series of the **mean power P_{EEG} from the EEG** (in relation to each RR-interval) (**P_{EEG}**, [μV^2]). Here, only the frontal lobe with the related EEG electrodes (AF3, AF4, AF7, AF8, Fp1, Fp2, F1, F2, F3, F4, F5, F6, F7, F8, Fz) were analysed
- Adaptive filtering: interpolation of artefacts and ventricular premature beats (Wessel et al., 2000)
- **Synchronization**: BBI, RESP and P_{EEG} (linear interpolation, f=2Hz)

II. Materials and methods - coupling approaches

Central-autonomic coupling approaches

- **Normalized short time partial directed coherence (NSTPDC)** (Adochiei et al., 2013)
  - **Multivariate transfer entropy (MuTE)** (Montalto et al., 2014)
    - Coupling direction and strength

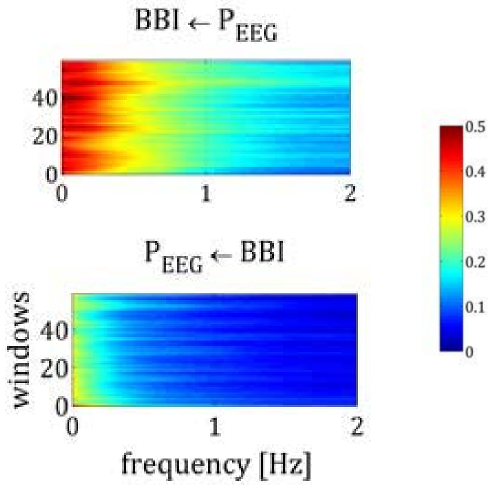
NSTPDC

- *m*-dimensional multivariate autoregressive model (**linear Granger causality** in the frequency domain)
- Time-variant partial directed coherence (tvPDC, $\pi_{xy}(f,n)$) (Milde et al., 2011) (f - frequency, n - the number of windows)

II. Materials and methods - coupling approaches

NSTPDC

- Stepwise least squares algorithm and the Schwarz's Bayesian Criterion (SBC) to calculate the optimal model order
- Window function (Hamming): lengths = 120 samples, shift = 30 samples (90 samples overlap between each window)
- Stationarity and scale-invariance
  Normalization (zero mean and unit variance) of BBI, RESP and P_{EEG}



Averaged NSTPDC plots of the central-cardiac coupling (healthy subjects).

II. Materials and methods - coupling approaches

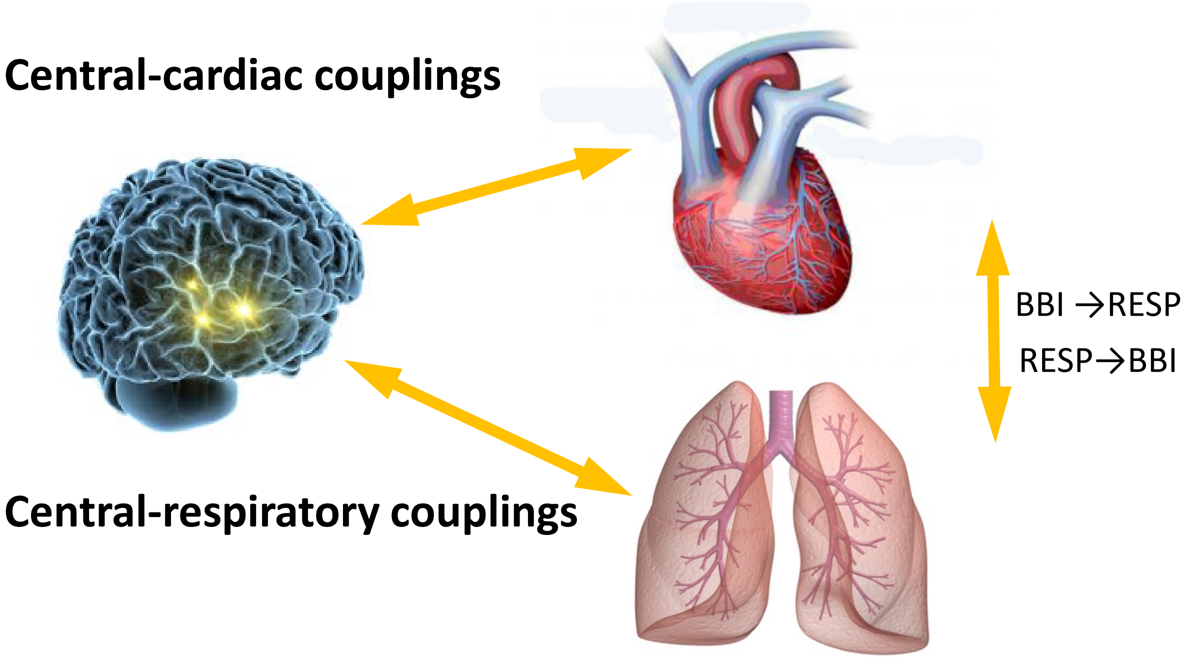
MuTE

- Transfer entropy (TE) (Schreiber, 2000)
- “model-free”
- **Nonlinear interactions** with interaction delays
- **Nearest neighbour** estimator and **non-uniform embedding (NN NUE)** (Montalto et al., 2014)

II. Materials and methods - coupling approaches/statistics

$P_{EEG} \rightarrow BBI$, $BBI \rightarrow P_{EEG}$

$P_{EEG} \rightarrow RESP$, $RESP \rightarrow P_{EEG}$



Statistics

- Nonparametric exact two-tailed Mann-Whitney U-Test (SPPS 21.0)
- Significance level:

  $p < 0.01$*

  $p < 0.00625$** (Bonferroni-Holm adjustment)

II. Materials and methods - coupling approaches

Surrogates

- **15 independent surrogates** from BBI, RESP and P_{EEG} for CON and SZ
- **Randomly permuting in temporal order** of the samples
- Different permutations to destroy any temporal structure
- Significance threshold:

  t_{su}=mean+2*SD

III. Results

Results of central-autonomic and autonomic coupling analyses (linear: NSTPDC, nonlinear: MuTE)

Coupling direction		p	Coupling strength CON mean ± sd	SZO mean ± sd
MuTE	BBI→P_{EEG}	*	0,014 ± 0,011	0,012 ± 0,011
	P_{EEG}→BBI	n.s.	0,016 ± 0,010	0,014 ± 0,010
	RESP→P_{EEG}	**	0,017 ± 0,010	0,014 ± 0,009
	P_{EEG}→RESP	**	0,015 ± 0,008	0,012 ± 0,009
	BBI→RESP	**	0,020 ± 0,013	0,015 ± 0.012
	RESP→BBI	**	0,033 ± 0,009	0,026 ± 0.012
NSTPDC	BBI→P_{EEG}	**	0,10 ± 0,05	0,12 ± 0,05
	P_{EEG}→BBI	*	0,19 ± 0,10	0,16 ± 0,10
	RESP→P_{EEG}	**	0,17 ± 0,07	0,23 ± 0,10
	P_{EEG}→RESP	**	0,07 ± 0,06	0,06 ± 0,05
	BBI→RESP	**	0,05 ± 0,02	0,04 ± 0.03
	RESP→BBI	n.s.	0,25 ± 0,08	0,27 ± 0,17

#

Nonlinear couplings

ANS→CNS

(BBI→P_{EEG}), RESP→P_{EEG}

CNS→ANS

P_{EEG}→RESP

ANS

BBI→RESP

RESP→ BBI

↓SZO

Linear couplings

ANS → CNS

RESP→P_{EEG}

BBI → P_{EEG}

↑SZO

CNS→ANS

P_{EEG}→RESP

(P_{EEG}→BBI)

↓SZO

ANS

BBI→RESP

↓SZO

III. Results

- **We found that the central-cardiorespiratory coupling was a bidirectional one, with reduced central driving mechanisms towards BBI (P_{EEG}→BBI) and respiration (P_{EEG}→RESP), and increased autonomic coupling towards central centers represented by the P_{EEG} (RESP→P_{EEG}, BBI→P_{EEG}) in SZ**
- **The coupling between RESP and BBI was reduced in SZ**

IV. Summary and Conclusion

Altered brain-heart couplings in SZ are expressed by a **weaker linear and non-linear central influence on the cardiac system**, and a **stronger linear respiratory influence on CNS** compared to CON

CNS →ANS (P_{EEG}→RESP, P_{EEG}→BBI) ↓

ANS→CNS (RESP→P_{EEG}, BBI→P_{EEG}) ↑

CNS controls the heart more than the breathing in CON compared to SZ

In SZ the reduced non-linear couplings express a more rigid coupling as a sign of a maladaptation in brain-heart and brain-respiratory interactions

Known significant heart rate changes are probably caused by the diminished closed-loop interactions (central-cardiac) in SZ

Decreased coupling between RESP and BBI is probably caused by the diminished RSA (confirmed by the peak-valley method)

The increased linear couplings of RESP and BBI towards the central regulation probably reflect the permanent attempt to normalize heart rate, heart rate variability and respiration

IV. Summary and Conclusion

Limitations

- SZ patients received antipsychotic treatment
- Only short term couplings were considered
- Only global (and averaged) and simplified sight on the regulatory processes

This study can only be seen as a small contribution to a more in-depth understanding of the interplay of neuronal and autonomic cardiorespiratory regulatory pathways in schizophrenia leading to a greater insight into the complex central-autonomic-network.

Outlook

- Time-variant analyses and topographical EEG cluster analyses
- Considering the more detailed local and frequency band resolution
- Performing fMRI data analyses in parallel

Thank you for your attention !

Acknowledgment

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More detailed information:

Schulz S, Haueisen J, Bär KJ, and Voss A.

Altered Causal Coupling Pathways within the Central-Autonomic-Network in Patients Suffering from Schizophrenia.

***Entropy* 2019, 21, 733.**