Ictal and interictal respiratory changes in temporal lobe and absence epilepsy in childhood.

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Abstract

Background

Autonomic dysfunctions occur during but also in between seizures. During seizures, the direct involvement of central autonomic control centers cause specific changes in heart rate and respiration. The pathophysiology of autonomic dysfunctions that are observed in the interictal period is more difficult to explain. These alterations are most likely due to changes in the epileptic network and/or to a lesser extent due to direct interictal spike activity disturbing central autonomic centers.

The aim of our study is to investigate whether ictal and interictal respiratory changes do occur in temporal lobe and absence epilepsy in children. We hypothesize that the interictal autonomic changes are due to changes in the neuronal network, by studying epilepsy patients with normal interictal background EEG.

Methods

Ictal and interictal single-lead ECG signals were extracted from 24 hour video-EEG recordings in 10 children with refractory temporal lobe seizures, in 10 children with absence seizures with occasional interictal discharges and 10 control subjects. RR interval time series were calculated and respiration parameters were derived from the ECG signal. ECG-derived respiration (EDR) signals were computed and time and frequency domain parameters were extracted to characterize the respiratory function.

Results

In the ictal registrations we observed bradypnea in 10 out of the 12 recorded seizures from the temporal lobe. In absence seizures, we observed a variable ictal effect on respiratory rate. In the analysis of the interictal data, the most remarkable finding was the higher power in the low frequency band and lower power in the high frequency band of the EDR signals in patients with absence seizures compared to control subjects, indicating a shift of respiratory rate to the lower frequencies.

Conclusion

In conclusion we found a uniform pattern in ictal respiratory changes in temporal lobe seizures, due to direct involvement of central respiratory centers. In absence epilepsy, we found a disturbed respiratory control in between seizures. These changes were not present in the patients with temporal lobe epilepsy. The observed interictal changes in respiration in absence epilepsy are most likely due to epileptogenetic changes in the thalamocortical network, involved in absence epilepsy and could not be explained by interictal spike activity.

Highlights:

° Ictal bradypnea is present in temporal lobe epilepsy in children.

° Absence seizures have a various effect on respiratory rate.

° Interictally, respiratory rate is altered in absence epilepsy but not in temporal lobe epilepsy.

Key words: epilepsy, respiration, autonomic, childhood, seizures

Introduction

Autonomic dysfunction during and in between seizures are frequently reported in patients with epilepsy (Baumgartner et al. 2001; Fogarasi et al. 2006; Chroni et al.2008; Jansen and Lagae 2010).

During seizures, spike activity influencing autonomic control centers of the central autonomic nervous system can cause changes in heart rate or respiration. Ictal autonomic symptoms occur as epileptic discharges propagate to the central autonomic network and disturb normal autonomic control of vital functions (Schernthaner et al. 1999; Leutmezer et al. 2003; Di Gennaro et al. 2004; Singh et al. 2013).

The autonomic changes that are observed in patients with epilepsy in between seizures are more difficult to explain (Sathyaprahba et al. 2006;Sevcezu et al. 2010). The exact pathophysiology remains difficult to disentangle. Patients with seizures develop changes in their neuronal network. The evolution from a normal neuronal network to a hyperexcitability state is referred to as epileptogenesis (De Curtis et al. 2001). Similar changes to the central autonomic neuronal network during this process of epileptogenesis can be an explanation for altered autonomic control in patients with epilepsy. However, patients with epilepsy often have excessive interictal spike activity in the brain. In this process, the presence of interictal spikes are considered a biomarker of the epileptogenetic process itself (Staley et al. 2005). The presence of interictal epileptic discharges could influence cardiovascular and respiratory control centers, comparable with the findings during seizures. In this case, changes in autonomic control could only be observed in the presence of excessive spike activity (Seri et al. 2012).

In childhood epilepsy, data about autonomic changes during and in between seizures are sparse, especially on respiratory changes. Seyal and Bateman showed that contralateral spread of seizure activity is linked with the onset of apnea, possibly because of bilateral downstream influences on the respiratory centers (Seyal and Bateman 2009). Besides apnea, an increase in end-tidal CO2 has been demonstrated with seizures, possibly due to transient neurogenic edema or pulmonary shunting during seizures (Seyal et al. 2010; Seyal et al. 2012).

The first aim of our study was to investigate if ictal epileptic activity changes respiration in two different models of epilepsy. The second aim of our study was to investigate if there were interictal differences on respiratory control in temporal lobe epilepsy and absence epilepsy. We designed a study where we analyzed respiration parameters during and in between seizures in 2 different models of epilepsy, focal seizures originating in the temporal lobe and absence seizures, and compare them with age-matched control subjects. In our study we use data of patients with

uncontrolled seizures but only occasional interictal spikes to exclude the influence of excessive interictal spikes. We used a model of focal and generalized epilepsy to make a difference between two forms of epilepsy network involvement.

Methods

Single lead ECG signals were obtained from 24 hour video EEG recordings in children with temporal lobe epilepsy, children with absence epilepsy and control subjects. All children with epilepsy were referred to the epilepsy clinic for 24 hour EEG to monitor the effect of treatment. Control subjects were referred with a suspicion of epilepsy but EEG evaluation remained normal. The 3 cohorts were age matched to take into account age-dependent differences. None of the children was known with a cardiac or respiratory problem. All EEG data were reviewed by 2 independent EEG specialists and the start and end of all seizures were annotated. Lead II ECG recordings were collected with a sampling frequency of 250 Hz.

After preprocessing the ECG signals, the signals were segmented into epochs of one minute. Minutes containing ictal EEG were analyzed separately from those without ictal changes. In total, 3 hours of interictal ECG were analyzed per patient. All interictal data were recorded in the morning during an awake and resting state. R-peaks were detected using the Pan-Tompkins algorithm. A search back procedure identified misdetected and ectopic beats, while ECG segments containing artefacts were detected using the methodology presented in Varon et al (Varon et al. 2012). The epochs containing artefacts and ectopic beats were removed from the study.

Next, the RR interval time series and 2 different ECG derived respiratory (EDR) signals were computed by means of linear principal component analysis (PCA) and kernel principal component analysis kPCA, based on the mechanical interaction of the respiration with the ECG (Widjaja et al. 2012). Respiration alters the ECG signal due to a mechanical interaction. The volume changes in the lungs during respiration alter the electrical impedance. The changing position of the electrodes with respect to the heart change the morphology of the heart beats in the ECG signal. Due to these interactions, it is feasible to derive a respiratory signal from the ECG, termed ECG-derived respiration (EDR). A wide range of EDR methods have already been developed. The early algorithms are based on the amplitude of the R-peak or the area under the QRS-complex. The method based on principal component analysis takes into account the morphological beat-to beat variations. Using the kPCA, non-linear components are added to the algorithm and improve correlation and coherence values.

For this study, we first measured respiration with conventional respiration belts in 2 index cases and compared the signal with ECG-derived respiration signal. Figure 1. The mean of the coherence

between the respiration measured by respiration belts and EDR was 0.7. Correlation between the two respiratory signals was calculated and showed a coefficient of 0.45 with a p-value <0.001, confirming a close approximation of the ECG-derived signal to the conventional measured respiratory signal.

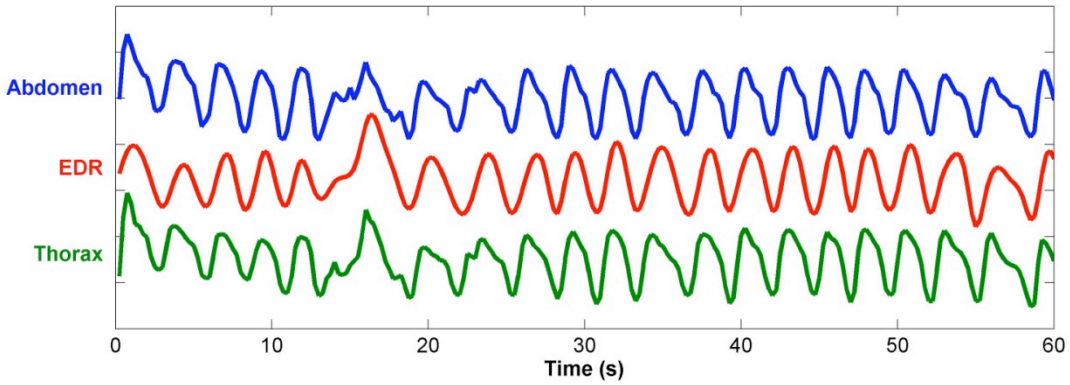


Figure 1: comparison of conventional measured respiratory signal using respiratory belts on thorax and abdomen and the ECG-derived respiratory signal (EDR) in case 13.

As the respiratory signal is a slow signal and seizures had a very variable and often short duration, ictal changes were calculated in every one minute epoch where ictal discharges occurred. In order to define pre- or post-ictal respiratory changes, respiratory rate was assessed in the minute before onset and the minute after onset of ictal activity. Changes in respiratory rate were defined as follows: bradypnea 10% decrease in respiratory rate from the interictal baseline, tachypnea 10% increase from the interictal baseline, following the definition of O'Regan and Brown (O'Regan and Brown 2005). In power spectrum density analysis, spectral components were defined as low frequency (LF) between 0.04 - 0.15 Hz and high frequency (HF) between 0.15 – 0.4 Hz components. The components in the LF band are indicative for slower breathing frequencies and apneic events, whereas the components in the HF band include the normal respiratory rate for age and the faster breathing frequencies. Finally, the respiration parameters for the three different groups of subjects were compared using Kruskal-Wallis analysis to find differences between pairs of groups. This statistical test was used because the distributions were not normal. To determine if the mean ranks of the groups were significantly different, a multiple comparison test based on the Tukey's honestly significant difference criterion was used, where $p<0.05$ is considered statistically significant.

Results

Ten patients with focal seizures originating from the temporal lobe and 10 patients with typical absence seizures were included and compared with 10 age matched control subjects. All subjects with epilepsy suffered from uncontrolled seizures. Mean age was 10,4 years (range 7-16) in the cohort of focal seizures, 10 years (range 8-14) in the cohort of generalized absence seizures and 10,8 years (range 6-15) in the control group. Mean duration of epilepsy was 24,3 months in the cohort of temporal lobe epilepsy and 27,4 months in the cohort of absence epilepsy. A total of 36 seizures could be analyzed, 12 focal seizures originating from the temporal lobe and 24 absence seizures. Mean duration of the temporal lobe seizures was 40 seconds, mean duration of absence seizures was 8 seconds. In patients with temporal lobe epilepsy, 1 seizure per patients was included in 8 subjects and 2 seizures in 2 subjects. For temporal lobe seizures, the same pattern of apnea was noted in every seizures. In patients with absence seizures, 1-6 seizures were included per patients with a median of 2. All seizures were recorded during an awake state.

3 hours of interictal data were analysed per patient. All interictal EEG data showed only occasional interictal spikes, defined as less than 1% of the time. Patient characteristics and anti-epileptic drug treatment are shown in the table.

Subject	Age at EEG evaluation	Sex Male(m) Female(f)	Type of epilepsy	Duration of epilepsy in months (m) Years (y)	AED	Seizure frequency in number /day
1	11	m	TLE/left	1 y	none	7
2	8	m	TLE/left	4 m	levetiracetam	8
3	13	m	TLE/right	9m	carbamazepine, sulthiame	2
4	16	m	TLE/left	9y	lamotrigine, levetiracetam	7
5	9	f	TLE/right	4m	oxcarbazepine, sulthiame	>10
6	11	f	TLE/right	6m	valproate, carbamazepine	2
7	7	m	TLE/right	2m	valproate	8
8	7	f	TLE/right	11m	Topiramate, carbamazepine	2
9	10	m	TLE/left	7y	carbamazepine, sulthiame	2
10	11	f	TLE/left	3m	levetiracetam	3
11	8	f	AE	3m	Valproate	>10
12	12	f	AE	6m	None	>10
13	9	f	AE	4y	ethosuximide	>10

14	8	m	AE	2y	Levetiracetam, lamotrigine	5
15	10	m	AE	5y	Lamotrigine	>10
16	10	m	AE	4y	Ethosuximide	>10
17	14	f	AE	1y	Valproate	7
18	11	m	AE	1m	None	>10
19	8	m	AE	5y	ethosuximide	>10
20	10	m	AE	1y	none	>10

TLE temporal lobe epilepsy/AE absence epilepsy

Table: patient characteristics

A Ictal analysis

In a first analysis we looked at the spectral density of the ictal segments. In this analysis we observe a higher power in the LF band en lower power in the HF band of respiratory signal in patients with temporal lobe seizures. There is a shift of respiratory rate towards the lower frequencies in patients with temporal lobe seizures compared to control subjects as can be seen in figure 2. These findings indicate that temporal lobe seizures are often accompanied by slower breathing frequencies. This phenomenon was not present in the patients with absence seizures.

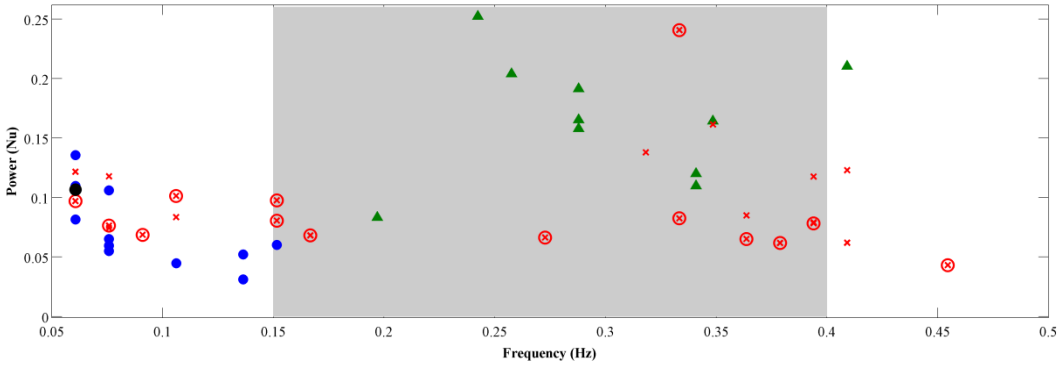


Figure 2 representation of temporal lobe seizures (blue dots), absence seizures (red crosses) and controls (green triangle) at their respiratory frequency. Shaded area indicates normal respiratory frequency of our control data. The black dot represents the temporal lobe seizure of the subject without anti-epileptic medication. The red crosses with circles indicate the absence seizures of the subjects without anti-epileptic medication.

Looking at the seizure data in more detail, we found ictal bradypnea during seizures in 11/12 of the temporal lobe seizures. There were no pre or post-ictal changes in respiratory rate in the temporal lobe seizures. There was no difference in left or right sided seizures. During absence seizures, no

consistent change in respiration rate was noted but a very different effect on respiration can occur. In 8 seizures bradypnea was detected as illustrated in figure 3. In 3 seizures tachypnea was observed and in the others breathing frequency was within normal limits. Pre-ictally there was no change in respiration. In the ictal data it remained difficult to determine if respiratory rate changes only during ictal activity or also post-ictally.

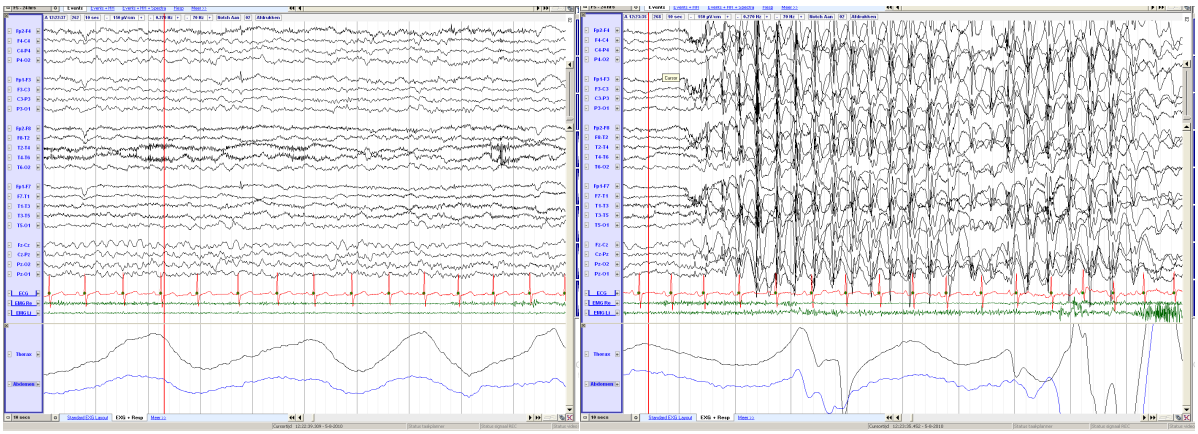
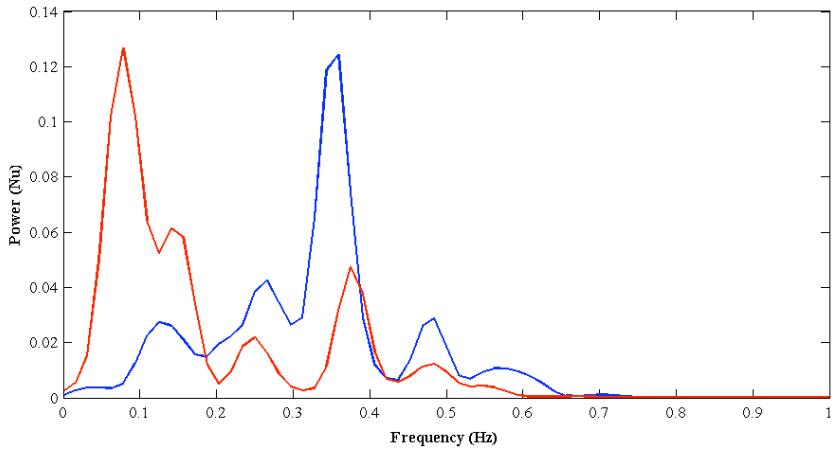


Figure 3

A interictal EEG with normal respiratory rate and ictal tracing of the same patient showing generalized spike wave discharges (upper part) and slower respiratory rate (lower part).

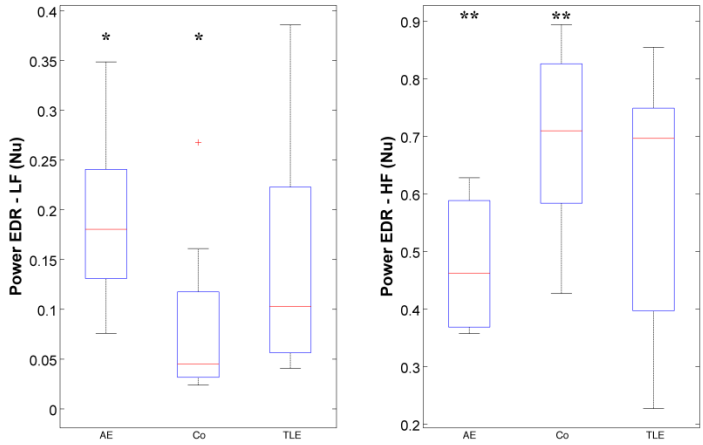


B respiratory frequency before (blue) onset and after (red) onset of generalized spike wave discharges on EEG in an absence seizure (patient 18) showing a shift towards a lower breathing frequency.

B Interictal analysis

The power spectrum analysis of the interictal data, the most remarkable finding is the higher power in the low frequency band (p=0.007) and lower power in the high frequency band (p=0.005) of the

EDR signal in patients with absence seizures compared to control subjects. This means that in between seizures in patients with absence epilepsy we see lower respiratory frequencies compared to control subjects and patients with focal epilepsy. Figure 4



	Absence epilepsy (AE)	Control (Co)	Temporal lobe epilepsy (TLE)
Power EDR-LF	0.1804 (0.1311,0.2406)*	0.0451 (0.0317,0.1175)*	0.1031 (0.0566,0.2228)
Power EDR-HF	0.4625 (0.3686,0.5884)**	0.7094 (0.5837,0.8260)**	0.6964 (0.3969,0.7490)

Figure 4

A Boxplots of the power of the interictal EDR signal in absence epilepsy (AE), control subjects (Co) and temporal lobe epilepsy (TLE). The low frequency (LF) and B high frequency (HF) bands expressed in normalized units (Nu).

B Table indicating statistical results: median(25th,75th).

* Indicates that there is a significant difference (p=0.007) between the control groups and patients suffering from absence seizures in the low frequency band. ** Indicates a significant difference between Control and AE group in the high frequency band (p=0.005)

Discussion

Respiratory control is located in the brainstem in the dorsal rostral pons, inferior ventral pons and lateral medulla. These centers receive afferent input from central and peripheral chemoreceptors and stretch receptors. Higher brain systems including the prefrontal cortex, amygdale and insula have a descending control on the respiratory centers. More recently connection of these centers with thalamic nuclei and gating to the cortex was highlighted using combined functional and structural MRI techniques. Studies using CO2 stimulation showed that brain stem centers as well as thalamus have an important role in regulation and control of respiration. Subsequently connectivity of the thalamus with higher cortical centers was demonstrated using DTI (Pattinson et al. 2009).

Acute respiratory compromise has already been documented during seizures and is due to direct involvement of respiratory centers in seizure activity. This can be involvement at a cortical level or discharges in the respiratory centers of the brainstem. It is also known that most of the cases of ictal apnea in focal seizures seem to originate from the temporal lobe (Watanabe et al. 1982). This has been confirmed in stimulation studies (Kaada and Jasper 1952) and has been described in various case reports where symptomatic seizures are due to temporal lobe pathology (Redline et al. 2008, Sirsi et al. 2007).

The pathophysiology of interictal respiratory changes is more difficult. One hypothesis could be that the changes caused by seizures and by interictal epileptic discharges are similar. Another explanation could be that due to epilepsy, changes in the neuronal network occur that also affect the respiratory network. In absence epilepsy we know that the thalamocortical network has an important role in the generation of spike wave discharges (Danober et al. 1998). Part of the thalamus has a gating function between brain stem respiratory centers and the cortex.

The results of our study shows that respiration is influenced in temporal lobe epilepsy and absence epilepsy in childhood. However, both types of seizures have very different effects on respiratory control.

The previous findings of ictal bradypnea during temporal lobe seizures in adults were confirmed in our pediatric population (O' Regan and Brown 2005). In temporal lobe seizures, no interictal changes in respiratory control were found. This suggests that the presence of seizure activity has an influence on regulation of respiration but apparently there are no interictal changes after recurrent seizures in this population.

In absence seizures, no stable pattern of ictal respiratory changes was noted. In this type of epilepsy, seizure activity itself does not alter respiratory rate in a consistent way. Different changes in respiration could be observed including some patients with bradypnea or tachypnea. An

important difference between absence seizures and temporal lobe seizures is duration of spike wave discharges. Absence seizures are mostly shorter compared to temporal lobe seizures. We can speculate that the shorter duration of the seizures prevent longer and more consistent pattern of impairment of respiration as we see in temporal lobe seizures. Due to the short duration of absence seizures and the fact that respiration is a very slow signal it was not possible to define the exact moment of onset of the respiratory changes. Our "ictal" data in absence seizures therefore should be considered ictal/post-ictal.

On the other hand, interictally we see a shift towards lower respiratory frequencies compared to control subjects in absence epilepsy. As there are no frequent spikes in our interictal data, we believe the observed changes are more likely due to modifications of the neuronal network as a result of epilepsy. One hypothesis could be that involvement of the thalamocortical network in the epilepsy syndrome also causes interictal changes in respiratory control and that the respiratory network is more sensitive to neuronal network changes in generalized epilepsy syndromes due to its thalamocortical representation. Therefore we see the changes in absence epilepsy but not in temporal lobe epilepsy.

We did consider the influence of medication on respiratory control in our study population. None of the patients received drugs known to cause respiratory depression. We included 4 patients before use of anti-epileptic drugs and respiratory changes could be observed in this subgroup. There is also an important overlap in anti-epileptic drug use in both types of epilepsy and we found very different results in both cohorts.

Looking at the mean duration of epilepsy in our population, we see autonomic changes after a mean of 27.4 months of absence epilepsy. Compared to the duration of epilepsy in patients were chronic cardiac changes can be identified, this is very soon after the onset of epilepsy. Within the cohort of absence epilepsy, we performed an additional analysis of interictal respiratory changes in patients having absence epilepsy for one year or less (subject 11,12,17,19,20) and over one year (subject 13,14,15,16,18). The two cohorts showed no significant differences in power spectral analysis. As we see the changes very early in the course of the disease in absence epilepsy, we believe location of the epileptogenetic process if probably important. Whether the respiratory system is more vulnerable to neuronal network changes compared to the cardiovascular system needs further research.

Conclusion

In conclusion we found ictal bradypnea in temporal lobe epilepsy in children, most likely due to direct involvement of respiratory centers in epileptic activity. In absence epilepsy, we found a disturbed respiratory control in between seizures, with a shift of respiratory rate towards the lower frequencies. The observed changes in respiratory control in absence epilepsy are most likely due to epileptogenetic changes in the thalamocortical network.

Acknowledgements

This research was supported by: Research Council KUL: Research Council KUL: GOA MaNet, PFV/10/002 (OPTEC), IDO 08/013 Autism, several PhD/postdoc & fellow grants; Flemish Government: FWO: PhD/postdoc grants, projects: G.0427.10N (Integrated EEG-fMRI), G.0108.11 (Compressed Sensing) G.0869.12N (Tumor imaging) G.0A5513N (Deep brain stimulation); IWT: TBM070713-Accelero, TBM080658-MRI (EEG-fMRI), TBM110697-NeoGuard, PhD Grants; iMinds 2013; Flanders Care: Demonstratieproject Tele-Rehab III (2012-2014); Belgian Federal Science Policy Office: IUAP P719/ (DYSCO, `Dynamical systems, control and optimization', 2012-2017); ESA AO-PGPF-01, PRODEX (CardioControl) C4000103224; EU: RECAP 209G within INTERREG IVB NWE programme, EU HIP Trial FP7-HEALTH/ 2007-2013 (n° 260777), EU MC ITN Transact 2012 # 316679

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