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Some quantitative EEG features in default mode resting state network under general anaesthesia

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Abstract

OBJECTIVES: The default mode resting state network (DMRSN) constitutes a circuit which is active in conditions when the subject is at rest. We tested the hypothesis that its function will be altered during unconsciousness.
METHODS: Changes in the mean squared coherences in five conventional frequency bands (delta to gamma) in DMRSN during general anaesthesia (GA) were investigated in 39 patients. They were compared with the normal EEG of 86 alert subjects, severely abnormal EEG of 112 patients with dementia and/or encephalopathy, and the mathematical model of brain death.
RESULTS. Anaesthetised patients showed significant decrease in the gamma coherence in the posterior area of the DMRSN compared to both the control group and the patients with dementia and/or encephalopathy. Among the anaesthetized patients 21 had a clear burst suppression pattern with prolonged epochs of suppression in EEG. In suppressed EEG segment the differences between the connections of the anterior to posterior parts and connections between the posterior parts of the DMRSN were almost lost. However, they still showed highly significant differences in most items when compared with coherences in the mathematical model of brain death.
CONCLUSION: The functional connectivity in the DMRSN could be a reliable and robust method for assessing the depth of anaesthesia and maybe also disorders of consciousness in general. The mean squared coherences in the gamma frequency band indicated the highest sensitivity for the depth of unconsciousness. The measure is not dependent on the diffused slowing in dementia or encephalopathy patients as long as they remain in a full consciousness.

O R I G I N A L A R T I C L E

INTRODUCTION

The default mode resting state network (DMRSN) (Bassett & Bullmore 2009) constitutes a set of brain areas which are active in conditions when the subject is at rest, typically with eyes closed. In this condition the mental contents are delivered from the internal contents, i.e. the subject's memory. They are subjected to the imaginary process, when attitudes are formed and future plans are created. The main areas that constitute this network are the following: the ventral medial prefrontal cortex, dorsal medial prefrontal cortex, posterior cingulate/retrosplenial cortex and the inferior parietal lobule (Buckner *et al.* 2008). The co-working between these spatially separated regions of the brain can be studied using methods which analyze the indices of connectivity in the EEG signals of spatially separated regions (Lehembre *et al.* 2012; Greenblatt *et al.* 2012; Sakkalis 2011). One such method of analysis is cross spectrum analysis and one of its products, squared coherence, can reflect the functional connectivity. Squared coherence is the squared correlation coefficient between the cyclical components in the two series at the respective frequency. It is the product of the cross-amplitude values by squaring them and dividing by the product of the spectrum density estimating for each series (Bowyer 2016). It is well known that the squared coherence value decreases with increasing distances between the electrodes. The coherences can also show some variability over time, i.e. by changing the analysis epoch duration (Bullock *et al.* 1995). The function of the DMRSN is altered in several pathological states (Buckner *et al.* 2008). Moreover, disorders of the consciousness should also interfere with the proper functioning of the DMRSN (Guldenmund, *et al.* 2012). It has been shown that general anaesthesia (GA) is associated with decrease in the coherences in several frequency bands (Cavinato *et al.* 2015; John *et al.* 2001). Some decrease in coherences is also present in patients with dementia and encephalopathy. According to our hypothesis, different levels of consciousness loss should be reflected in different levels of DMRSN functional derangements. Derangement of the DMRSN function should be more profound in unconscious subjects than in patients with dementia and/or encephalopathy, despite the comparable levels of EEG background abnormality. GA can serve as a model of consciousness loss (Alkire *et al.* 1998).

For this reason we studied subjects with dementia and/or encephalopathy together with markedly abnormal EEG, and patients in GA during thorax lung surgery.

MATERIALS AND METHODS

Studies on patients or volunteers require ethics committee approval and informed consent, which should be documented in the paper.

We examined next groups of patients:

1. *The control group of waking subjects with normal EEG*
   EEG read-outs of 9 adolescents and 77 adults, (57 women and 29 men; mean age 41.15; SD 18.39; range 12–77 years) were visually assessed. EEGs of 42 adults and 2 adolescents, roughly age-matched subjects (23 women and 21 men; mean age 41.57; SD 17.55; range 14–77 years) were analysed. The data were retrospectively selected from our EEG database (Zvolen Hospital, Department of Neurology). The data constituted a 19-channel EEG recording in accordance with the international 10–20 system, referenced to the FAz electrode, sampled at 128 Hz and band-pass filtered at 0.5–45 Hz. The criteria for inclusion were the following: normal EEG features on visual inspection by two independent examiners and normal indices of quantitative background analysis of the EEG sample (i.e. an epoch with duration of 8 seconds), which represented the typical features of the subject's waking artefact-free EEG record. Only records of subjects who were not taking psychotropic medication were included in the study.

2. *EEG of waking patients with abnormal EEG with diffused slowing group*
   These data were also retrospectively selected from our EEG database (Zvolen Hospital, Department of Neurology) and were recorded, sampled and band-pass filtered in the same manner as described above. They constituted EEG records of 112 patients with dementia and/or encephalopathy of various cause (63 women and 49 men; mean age 65.57; SD 14.65; range 11–96 years) – so called **slowing group**.

3. *EEG of patients during GA*
   The EEG data were recorded using the Neuron Spectrum-AM. EEG evaluating by means of classic visual assessment and cross spectral analysis (CSA) with one of the three commonly used derivatives of the CSA – mean squared coherencies (MSC) in DMRSN as a measure of functional connectivity of the network controlling features of consciousness during GA .
   EEGs were recorded of 39 adult subjects in GA during **surgery for lung resection** (17 women; 22 men; mean age 61.94; SD 11.16 years; University Hospital in Martin, Department of Anaesthesiology). These data constituted a 19-channel EEG recording in accordance with the international 10–20 system, referenced to the Cz electrode, sampled at 500 Hz and band-pass filtered at 0.5–45 Hz.
   In each of the 36 subjects one (8 s) EEG epoch was selected for further analysis.

All these selected epochs were recorded during the key phase of the surgery, when the lung resection was done (Figures 1 and 2). This step of the surgery was

Fig. 1. EEG in light anaesthesia during OLV. The raw EEG in this anaesthetised patient showed only slight deviation from normal waking EEG, pattern with spreading of the alpha rhythm to the frontal areas.

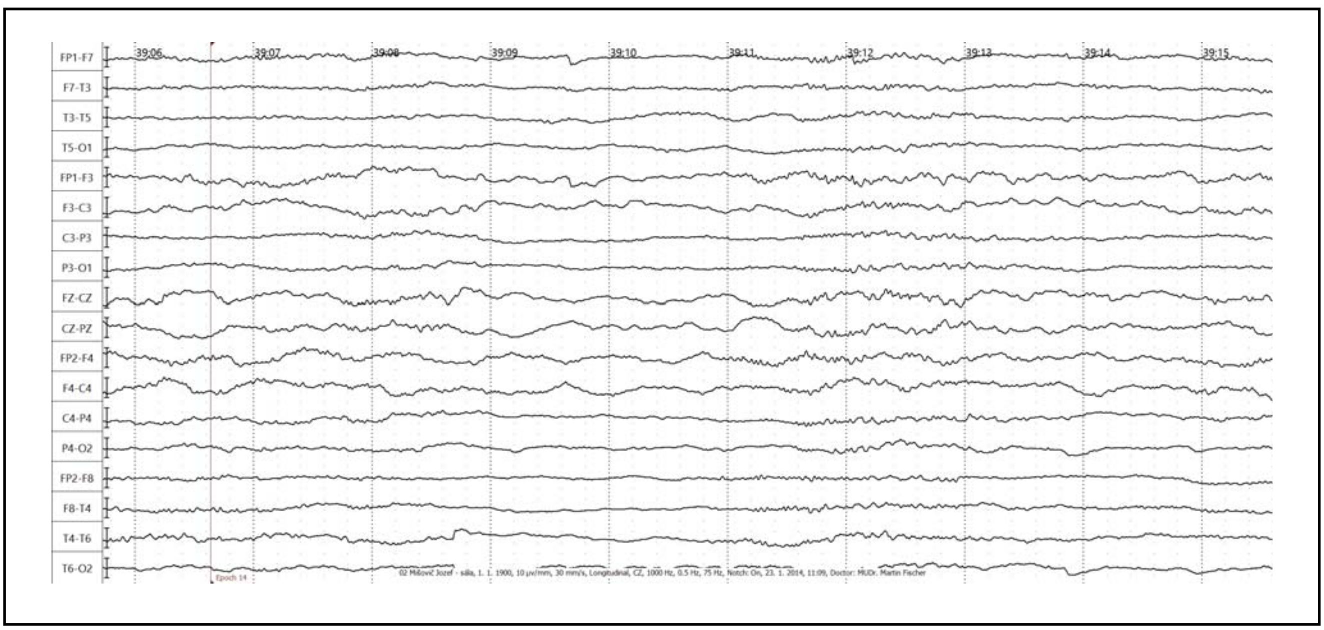

Fig. 2. EEG in Deep anaesthesia during OLV, showing a mixture of the diffused slowing with some patches of low voltage fast activity, and flat traces.

always associated with **one lung ventilation (OLV).** We assumed that in this step of the surgery the depth of the anaesthesia was most appropriate and roughly comparable across the subjects. Moreover, in most of the anaesthetized subjects a clear burst-suppression pattern was present which was induced by intravenous application of propofol at the beginning of the GA (Purdon,2012).

In 21 subjects the suppression length of the flat EEG (Flat) was long enough (i.e. not interrupted by episodes of the burst) to allow analysis as an 8 s long epoch. Thus two different EEG patterns were subjected to analysis in the anaesthetized group: the OLV (36) and **the Flat epochs (21).**

In summary, four EEG groups were subjected to analysis and comparison: the Control group (86); Slowing group (112); OLV (36); Flat (21). In order to make the EEG data of each group comparable, the data from the Control group and the Slowing group were re-referenced to Cz (Thatcher 2012; Vatta *et al.*

Tab. 1. Indexes of the diffused background slowing in the studied group (0.5–45 Hz; refers to diffused background slowing in the 0.5–45 Hz band-pass; 2–25 Hz; refers to diffused background slowing in the 0.5–25 Hz band-pass; AQ apg; refers to quantitative antero-posterior gradient of the alpha rhythm).

		Q EEG features		
		0.5–45 Hz	**2–25 Hz**	**AQ apg**
Upper normal limits		<0.82	<0.60	<0.31
Control	Mean	0.567	0.382	0.133
	SD	0.131	0.113	0.074
Slowing	Mean	0.907	0.829	0.419
	SD	0.056	0.074	0.131
OLV	Mean	0.868	0.727	0.617
	SD	0.139	0.166	0.124
Flat	Mean	0.991	0.945	0.408
	SD	0.006	0.029	0.163

Tab. 2. Between-group differences in the Indexes of the diffused background slowing.

Diffused slowing in the range 0.5–45 Hz				
	Control	Slow	OLV	Flat
Control		**0.000**	**0.000**	**0.000**
Slow			ns	**0.000**
OLV				**0.000**
Flat				
Diffused slowing in the range 2–25 Hz				
	Control	Slow	OLV	Flat
Control		**0.000**	**0.000**	**0.000**
Slow			ns	**0.001**
OLV				**0.000**
Flat				
Quantitative apg of the alpha rhythm				
	Control	Slow	OLV	Flat
Control		**0.000**	**0.000**	**0.000**
Slow			**0.00**	ns
OLV				**0.004**
Flat				

Results of the Kruskal-Wallis ANOVA. The highly significant differences are displayed in bold

2005), and the data of the patients recorded during the GA were down-sampled to 128 Hz. Epochs with duration of 8 seconds after DC shift and trend removal were subjected to Hann weighted analysis using FFT. The FFT results of the whole scalp 19 electrode array were then used to obtain some derivatives of the quantitative EEG power-spectral analysis. These derivatives included the following indexes: diffused slowing in the band-pass 0.5–45 Hz, and in the band-pass 2–25 Hz and the anterior-posterior gradient of the alpha rhythm (Gotman *et al.* 1973; Lodder &Van Putten 2013). Moreover, six electrode position pairs which represent the DMRSN assembly (Fz–Pz; Fz–P3; Fz–P4; Pz–P3; Pz–P4 and P3–P4) were subjected to Hamming weighted FFT and cross-spectrum analysis with $\Delta\phi$ at 0.125 sec. The complete epochs with duration of 8 seconds were processed separately using the cross-spectrum analysis method. Mean squared coherences were calculated in the following spectral bands; delta 0.5–3.9; theta 4–7.9; alpha 8–12.9; beta 13–29.9 and gamma 30–45 Hz. The between-group differences in the quantitative EEG indexes of the background were assessed with Kruskal-Wallis ANOVA. The between-group differences in the coherences were estimated with Mann-Whitney U test. The statistical significance level was set to $p<0.05$.

This study was approved by the Ethic Committee in Jessenius Medical Faculty in Martin.

RESULTS

Quantitative EEG features

All three global indices, i.e. diffused slowing in the range 0.5–45 Hz; diffused slowing in the range 2.0–25 Hz; and the quantitative anterior-posterior gradient of the alpha rhythm, were abnormal in all three patient groups. The degree of the abnormality in diffused slowing showed an increase from the OLV through the Slowing to the Flat group. The quantitative anterior-posterior gradient of the alpha rhythm was the most abnormal in the OLV group. The between-group differences in all indices were significant, with the exception of diffused slowing in the range 0.5–45 and 2–25 Hz between the Slowing and the OLV groups, and the quantitative anterior-posterior gradient (AQ apg) of the alpha rhythm between the Slowing and the Flat groups (Tables 1 and 2).

General findings in linear regressions

The coherences showed a decrease with increasing electrode pair distance. This decrease in the coherences in the Control, the Slowing and the OLV groups was roughly proportional to the increasing distance between the electrodes. The Pz–P3 and the Pz–P4 pairs showed the highest coherences in contrast to the Fz–P3 and the Fz–P4 pairs, which did the lowest figures. Exceptions were the alpha frequency band in the Control group and the gamma frequency band in the OLV group. The former showed significantly higher coherences in the anterior-posterior connections in comparison to the rest of the investigated groups. The latter showed significantly lower coherences in the posterior connections (Pz–P3 and Pz–P4 pairs) compared to the Control and the Slowing groups. Thus in the graphical presentation these figures created a pattern, i.e. some kind of "structure" in the DMRSN. This feature was lost

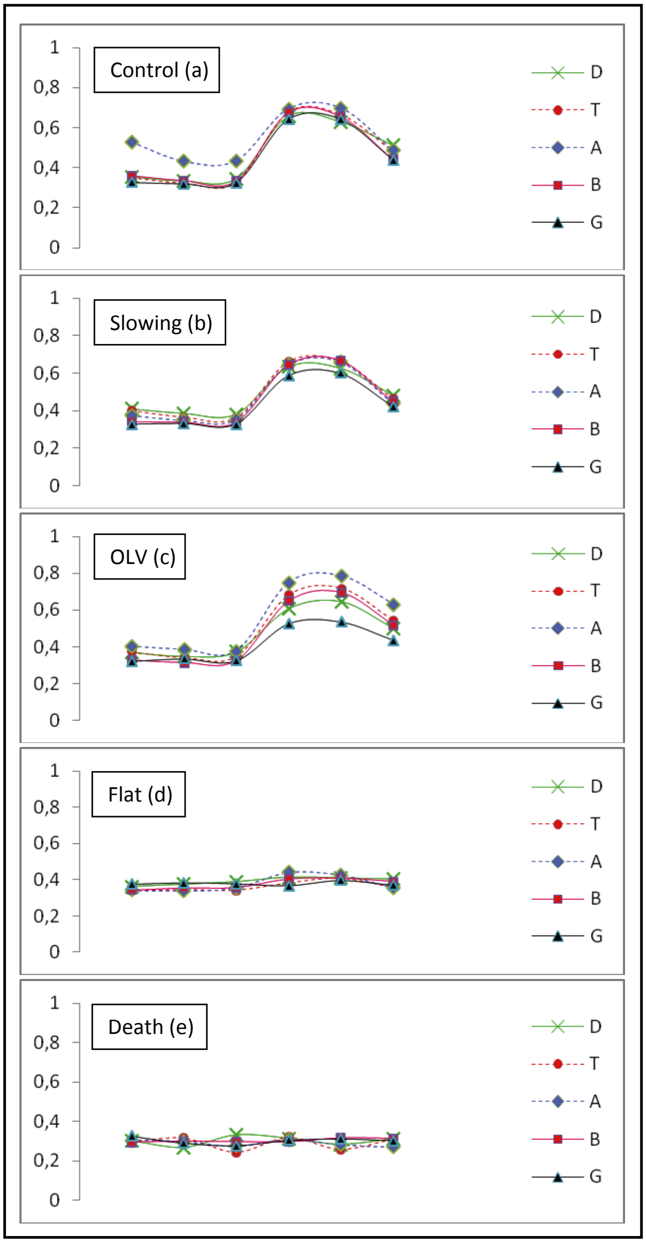

Fig. 3a–e. Coherences in the DMRSN; the five panels from top to bottom show the coherences in the normal – Control group (a); Slowing group (b); OLV group (c); Flat group (d) and in the Brain death model (e); the marks on the traces refer to Fz–Pz; Fz–P3; Fz–P4; Pz–P3; Pz–P4 and P3–P4 pairs; note that the decrease in the coherences in the gamma frequency band in the posterior areas of the network is the most sensitive indicator of the depth of unconsciousness; note also the loss of structure in the Flat group (D=delta 0.5–3.9; T=theta 4–7.9; A=alpha 8–12.9; B=beta 13–29.9; G=gamma 30–45 Hz).

in the Flat group. The separation of the different pairs tended to become almost negligible, and the "structure" collapsed, as will be described in more detail later (Figure 3).

Differences between the groups

The Control group vs. the Slowing and the OLV groups.

Alpha frequency band

The Control group showed significantly higher coherences in the alpha frequency band in all three anterior-posterior connections (Fz–Pz; Fz–P3; Fz–P4) compared to the Slowing and the OLV groups. On the other hand the coherence values in the posterior connections (Pz–P3; Pz–P4; P3–P4) and the alpha band coherences were significantly higher in the OLV group compared to both the Control and the Slowing groups. Finally, the Slowing group showed significantly lower coherence compared to the Control group in all six pairs.

Gamma frequency band

The coherences in the gamma frequency band in the Pz–P3 and Pz–P4 pairs were significantly higher in the Control group than in the Slowing and the OLV groups. However, the Slowing group also showed significantly higher coherences in these pairs than the OLV group (Figure 3; Tables 3 and 4).

Flat vs. OLV group

Differences with significantly lower coherences in the Flat group were consistently present for all frequency bands in pairs with the shortest distances, connecting the posterior parts of the DMRSN (Pz–P3; Pz–P4 and P3–P4 pairs). The differences were less consistent in the pairs with longer distances connecting the anterior to the posterior parts of the DMRSN. (Figure 3; Table 5).

Comparison of the Flat group with the mathematical model of brain death

The OLV and the Flat groups compared to the Control and the Slowing groups showed some features of progressively increasing entropy. The data of the Flat group were therefore compared with the coherences in the mathematical model of brain death. Brain death in this model was approximated using pseudo-random numbers. They were generated by the random number generator in Excel. The plots of the Flat group and the bran death model were very similar. However, the statistical analysis revealed significant differences in all frequency bands for all pairs connecting the posterior parts of the DMRSN, with lower coherences in the brain death model. This was also true for the majority of the frequency bands in pairs connecting the anterior to the posterior parts of the DMRSN (Figure 3).

DISCUSSION

The trends in coherence decrease were roughly proportional to the distance between the electrodes. One of the reasons for this might be the volume conduction component. However, other factors might also contribute to the coherence differences between the anterior-posterior and the posterior connections of the DMRSN. They could reflect some differences in the mode of functioning of different parts of the network. The posterior areas are associated with the imaginary

Tab. 3. Coherence differences between the Pz–P3 and Pz–P4 pairs in the DMRSN of awake controls and patients with diffused slowing – dementia and/or encephalopathy.

delta		**M**	**SD**	***p*-value**	**delta**	**M**	**SD**	***p*-value**
Normal	Pz–P3	0.65662	0.14405		Pz–P4	0.62799	0.13193	
Slow	Pz–P3	0.63212	0.13952	ns	Pz–P4	0.62471	0.13872	ns
theta					theta			
Normal	Pz–P3	0.67927	0.10317		Pz–P4	0.66666	0.09865	
Slow	Pz–P3	0.65975	0.11801	ns	Pz–P4	0.66319	0.11648	ns
alpha					alpha			
Normal	Pz–P3	0.69393	0.0829		Pz–P4	0.6982	0.08321	
Slow	Pz–P3	0.64495	0.10706	**0.00156**	Pz–P4	0.65834	0.10667	**0.0036**
beta					beta			
Normal	Pz–P3	0.67594	0.0742		Pz–P4	0.65569	0.07438	
Slow	Pz–P3	0.64369	0.09248	**0.00718**	Pz–P4	0.66763	0.08959	ns
gamma					gamma			
Normal	Pz–P3	0.64145	0.09305		Pz–P4	0.64203	0.08299	
Slow	Pz–P3	0.58858	0.09655	**3.2E–05**	Pz–P4	0.59993	0.09648	**0.00111**

Tab. 4. Coherence differences between the Pz–P3 and Pz–P4 pairs in the DMRSN of awake controls and the anaesthetised patients.

delta		**M**	**SD**	***p*-value**	**delta**	**M**	**SD**	***p*-value**
Normal	Pz–P3	0.65662	0.14405		Pz–P4	0.62799	0.13193	
OLV	Pz–P3	0.60652	0.15434	ns	Pz–P4	0.64376	0.16731	ns
theta					theta			
Normal	Pz–P3	0.67927	0.10317		Pz–P4	0.66666	0.09865	
OLV	Pz–P3	0.68102	0.14421	ns	Pz–P4	0.71729	0.13779	***0.0014155***
alpha					alpha			
Normal	Pz–P3	0.69393	0.0829		Pz–P4	0.6982	0.08321	
OLV	Pz–P3	0.75001	0.14956	***0.0007992***	Pz–P4	0.78475	0.15237	***3.412E-07***
beta					beta			
Normal	Pz–P3	0.67594	0.0742		Pz–P4	0.65569	0.07438	
OLV	Pz–P3	0.64802	0.13118	ns	Pz–P4	0.69341	0.12166	***0.0030882***
gamma					gamma			
Normal	Pz–P3	0.64145	0.09305		Pz–P4	0.64203	0.08299	
OLV	Pz–P3	0.52716	0.12899	**4.607E-06**	Pz–P4	0.53533	0.13488	**2.083E-05**

The *p*-values refer to the significance levels of Mann-Whitney U test between the two groups. The significant differences are displayed in bold. The *p*-values which refer to significantly higher coherences in the OLV group are displayed in bold italics. M refer to mean of the coherence values. SD refer to standard deviation of the coherence values.

processes (Agnati *et al.* 2013; Zvyagnitsev *et al.* 2013). These processes are permanent and may show more stability regardless of the content which is imagined. On the other hand, the connection between the anterior and the posterior areas of the network could work in a pulse manner, i.e. sending and/or receiving some information and/or processing it in a much shorter time interval. It is probably dependent on the mesoscopic connections where are fundamentally manifested laws of microcosm, that is laws of quantum physics. Collectively, mesoscopic systems are called electron-conductive objects whose dimensions are less than coherent length, mean free path or Fermi wavelength of conductive electrons. However, we realize that these explanations are only speculative and further research will be needed here.

The differences between the *Control*, the *Slowing*, and the *OLV* groups were subtle. In the *Control* and the

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Tab. 5. Coherences differences between the Pz-P3 and Pz-P4 pairs in the DMRSN of Anaesthetised patients during OLV and Flat conditions.

delta		**M**	**SD**	***p*-value**	**delta**	**M**	**SD**	***p*-value**
OLV	Pz–P3	0.60652	0.15434		Pz–P4	0.64376	0.16731	
Flat	Pz–P3	0.41265	0.10571	**8.31E-06**	Pz–P4	0.40852	0.09617	**5.72E-07**
theta					theta			
OLV	Pz–P3	0.68102	0.14421		Pz–P4	0.71729	0.13779	
Flat	Pz–P3	0.38402	0.09269	**2.96E-11**	Pz–P4	0.41072	0.09278	**3.57E-10**
alpha					alpha			
OLV	Pz–P3	0.75001	0.14956		Pz–P4	0.78475	0.15237	
Flat	Pz–P3	0.44047	0.12849	**2.64E-09**	Pz–P4	0.42643	0.09760	**7.57E-11**
beta					beta			
OLV	Pz–P3	0.64802	0.13118		Pz–P4	0.69341	0.12166	
Flat	Pz–P3	0.40200	0.06230	**6.79E-10**	Pz–P4	0.40738	0.07898	**3.59E-11**
gamma					gamma			
OLV	Pz–P3	0.52716	0.12899		Pz–P4	0.53533	0.13488	
Flat	Pz–P3	0.36722	0.06148	**7.80E-07**	Pz–P4	0.39855	0.07263	**0.000165**

The *p*-values refer to the significance levels of Mann-Whitney U test between the two groups. The significant differences are displayed in bold. M refer to mean of the coherence values. SD refer to standard deviation of the coherence values.

Slowing groups some extra-cerebral electrical activity could alter the coherences. In patients with dementia and/or encephalopathy the clearness of their consciousness can show great fluctuations even during short time intervals. Estimation of the consciousness level in these patients is rather difficult. Moreover the *Slowing group* comprised a heterogeneous group of patients, and many of them could have had some structural damage in the DMRSN itself. Finally, the level of consciousness loss during the main part of general anaesthesia was variable, and in 3 patients not very deep. However, a considerable proportion of the anaesthetised patients showed only slight deviation from normal waking EEG pattern (i.e. spreading of the alpha rhythm to the frontal areas, (Cascella 2016). Finally, the level of consciousness loss during the main part of general anaesthesia in some patients is not very deep. May be therefore there are reports showing that in many patients some memory retention is preserved (Sániová 1998, 2010; Ghoneim & Block 1992; McLeskey 1996; Wolters 1993).

The main findings of this study were the following. First, there was a decrease in the gamma coherence in the posterior part of the DMRSN in the OLV group. Despite the grave abnormality with profound diffused slowing in the EEGs of the patients with dementia and/or encephalopathy, they showed significantly higher gamma coherences in the above-mentioned area than the OLV group (Figure 3). Thus the coherence in the gamma band could be considered as one of the most sensitive indices of consciousness loss (John *et al.* 2001, Jombík *et al.* 2016). Moreover, this decrease was greatly pronounced and expanded to the rest of the frequency bands in the deepest stage of anaesthesia, when flat epochs of the burst-suppression pattern were taken for analysis. The differences between connections in the anterior to posterior areas and the connections between posterior areas of the DMRSN were almost lost. The graphical structure of the DMRSN collapsed and it took on an appearance which was similar to the brain death model, but statistically it was still significantly different from that model.

The results of the present study support recent findings suggesting that regional differences in coherence in DMRSN may have a crucial interpretation that higher coherence in comparison of the specific mental states may reflect their unique integrative functions in cognitive processing closely linked to basic neural correlates of consciousness such as synchronous gamma activity that plays a significant role in selective attention, perceptual processing, and recognition (Jensen *et al.* 2007; John *et al.* 2001). Nevertheless recent neuroscience did not find a distinct place in the brain, in which distributed information comes together (John *et al.* 2001; Crick & Koch 1992; Singer 1993). In addition there is evidence that this binding process plays a significant role in attentional and memory processing, and logical inference (Singer 1993; Jensen *et al.* 2007). These findings indicate that this information integration enables that the coherent cognitive processing may put together the information processed in various relatively specialized brain regions (John *et al.* 2001; Singer 1993).

The coherences in the gamma frequency band showed the highest sensitivity with regard to the depth of unconsciousness. Analysis of the EEG mean squared coherences of EEG signal in the DMRSN may constitute a robust method for quantitative assessment of the depth of unconsciousness. It is independent with regard to the diffused slowing caused by diseases of the brain as long as the patient remains in a conscious state.

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