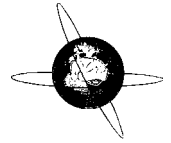




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Cognitive processes in disorders of consciousness as revealed by EEG time–frequency analyses

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HIGHLIGHTS

- Oscillatory analyses are suggested for testing cognition in patients with disorders of consciousness.
- Time–frequency analysis examines cognitive processes reflected by different oscillations.
- Actively counting a name induces strong event-related synchronization of theta oscillations.

ABSTRACT

Objective: Although behavioral evaluation of awareness in disorders of consciousness is difficult it remains the clinical standard. We believe that the refinement of EEG and analyses techniques would improve our characterization of those patients.

Methods: We focused on cognitive processing in a sample of 12 control subjects, eight vegetative-state patients, and 13 patients in the minimally consciousness state using EEG. We used an ‘active paradigm’ which asks subjects to follow instructions, specifically to actively count own or other names as compared to passively listening to them. EEG data was then analyzed using an advanced EEG analysis technique.

Results: Results revealed that all groups exhibit a stronger theta-synchronization to their own names when forced to count them. We also observed a delay in theta power in response to targets relative to non-targets when participants were instructed to count their own name.

Conclusion: Active paradigms are able to induce a different oscillatory activity compared to passive paradigms. Differences between controls and the pathologic groups are prominent in the theta- and alpha-band.

Significance: Time–frequency analyses allow to focus on distinct cognitive processes in patients with disorders of consciousness and thereby contribute to a refined understanding of severely brain-injured patients.

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1. Introduction

Progress of medicine in general and of intensive care in particular has increased the number of patients who survive severe acute brain injury. Some of these patients recover from their coma within the first days after an insult others will take more time and go through different stages before fully or partially recovering aware-

ness or before permanently losing all brain function (i.e., brain death).

While coma is characterized by the absence of arousal and thus also of consciousness the vegetative state (VS) is characterized by ‘wakeful unawareness’. Patients in a vegetative state show spontaneous eye opening, breathing and occasionally move their limbs in meaningless ways. Any evidence of communication, including a consistent response to command, or any purposeful movement indicates recovery of (minimally) consciousness. The minimally conscious state (MCS; Giacino et al., 2002) is used to describe patients who are unable to reliably follow instructions or communicate but who, nevertheless, demonstrate reproducible –

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but fluctuating – behavioral evidence of awareness of self or the environment.

Unfortunately, evidence for MCS can easily be missed, especially in patients whose senses and motor capacities are severely impaired and in whom a blink of an eye or the subtle movement of a finger may provide the only evidence of awareness (Laureys et al., 2005). Although behavioral assessment of disorders of consciousness (DOC) is susceptible to misdiagnosis mainly because of the use of inadequate scales or insufficient practical instruction (Gill-Thwaites, 2006) it remains the only standard procedure in clinical daily routine. In order to improve the specificity and sensitivity of diagnostic assessment, recently, an additional application of neurophysiologic methods was suggested (Demertzi et al., 2008; Giacino et al., 2009). For the same reason and because bedside EEG is a simple way to measure brain activity in response to external stimuli, several studies during the last years focused on preserved event-related potentials in DOC patients, in particular on the N100, MMN, P300 and N400 (Kotchoubey et al., 2005; Vanhauzenhuysse et al., 2008). Progress in this line of research has led to attempts to use ERPs as a potential tool for predicting the clinical outcome (Daltrozzo et al., 2007).

In the past it has been argued that “passive paradigms” (i.e., without the need for wilful intervention by the patient) as adopted in former event-related potential (ERP) and neuroimaging studies might merely identify neural activation which reflects automatic processing rather than demonstrating preserved awareness. For example, it could be demonstrated that with respect to auditory designs using stimuli with semantic content, speech processing must not be strictly related to successful semantic comprehension but can simply reflect perception (Davis et al., 2007). Some more critical evidence against standard procedures using passive stimulus presentation is that even in sleep reliable responses are observable to salient stimuli, like the subject’s own name (Perrin et al., 1999).

In response to this, we modified our classical auditory ERP paradigm (i.e., passive listening to own and other names; cf. (Perrin et al., 2006) and adopted an alternative “active” approach which explicitly asks subjects to follow instructions, specifically to actively count own or other names as compared to passively listening to them. Instruction following in “active paradigms” (Monti et al., 2009; Owen et al., 2006; Schnakers et al., 2008) allows to identify awareness in the complete absence of motor behavior (including eye movements). Evidence that such ‘active’ approaches can reveal some important insights in the actual condition of a specific patient was brought by Schnakers et al. (2009). In this single-case study a 21 year old woman suffering from total locked-in syndrome was confronted with an active own name paradigm. In fact, the patient showed an enhanced P300 to her own names when she was told to count compared to passive listening to it; critically – 14 days later she showed reliable behavioral signs of consciousness.

In the following we want to present bedside EEG data using an active paradigm and specifically an advanced EEG analysis technique (event-related desynchronisation, ERD (Pfurtscheller and Aranibar, 1977)) which might allow identifying otherwise hidden signs of conscious awareness in DOC. Moreover, the applied methods reveal the reactivity of ongoing oscillatory activity (i.e., the amplitude-size) in response to an event, which is not exactly time-locked (like event-related potentials). The contribution of ongoing activity, especially in the lower frequency range (i.e., theta and alpha) to cognitive processes related to memory and attention demands are well established (Klimesch, 1999). Therefore, task-related systematic changes in the oscillatory activity of DOC patients could substantiate specific residual cognitive abilities or efforts in DOC patients.

2. Methods

2.1. Subjects

A sample of 33 subjects, consisting of a control group and two types of disorders of consciousness (DOC) participated in the present study. The control group comprised 12 subjects (8 males, 4 females; mean age: 54 years). Furthermore, two DOC groups were distinguished, one diagnosed as minimally consciousness conscious state (MCS; $n = 13$; 10 males, 3 females; mean age: 47 years) and another as vegetative state (VS; $n = 8$; 6 males, 2 females; mean age: 47 years). Diagnosis was based on internationally established criteria (cf., The Multi-Society Task Force on PVS and (Giacino et al., 2002)). Only patients who did not receive (i) centrally acting drugs, (ii) neuromuscular function blockers and (iii) sedating drugs within 24 h preceding the experiment were included. All patients had periods of eye opening, indicating preserved sleep–wake cycles. Table 1 provides individual demographic data for all patients included in the sample.

2.2. Experimental procedure

The experiment comprised an auditory selective attention paradigm (introduced by Schnakers et al. (2008)). The stimuli were eight first names, the subject’s own name (SON) plus seven other unfamiliar names (UN’s). Stimuli were presented acoustically in nine different sequences. Each sequence consisted of 120 stimuli, obtained by 15 random repetitions of the eight names. UN’s were common French names with no emotional background to the subjects (this was evaluated by an interview with the relatives). Names were recorded with a female voice (neutral intonation plus digitized) and presented binaurally at a maximum of 90 dB. The ISI was 1500 ms.

The experimental design consisted of three different conditions, one passive listening condition and two active counting tasks in which subjects had either to count their own name (‘count SON’condition) or a specific unfamiliar target name (‘count UN’condition). The experiment always started with the passive listening condition, where subjects had only to listen to the presented names without responding to them. The order of the two active conditions was randomized between subjects. In the ‘count SON’-condition subjects were instructed to count the appearance of the SON, whereas in the ‘count UN’-condition subjects were asked to count a specified UN. Thus, the two active conditions differed with respect to the target that had to be counted. Before the presentation of each of the nine stimulus sequences, the patients were briefly stimulated (e.g. by deep pressure stimulation which is a kind of intense ‘massage’ of extremities) in order to ensure a sufficient arousal level. Between each task condition there was a five minute break. All tasks were performed during states with open eyes.

2.3. Data acquisition

EEG was recorded bedside with a NuAmp EEG amplifier (NeuroSoft, Sterling, VA). The sampling rate was set at 500 Hz. An analog bandpass filter from 0.1 to 200 Hz was used. The setup included three electrodes (Fz, Cz, Pz), a reference at the nose and a ground electrode near Fz. Additionally, EOG (two electrodes placed diagonally above and below the right eye) and EMG (two electrodes at the chin) were recorded. Impedances were kept below 5 k Ω and stimuli were presented binaurally via earphones.

Table 1
Demographic data for all patients (frequency-proportions inclusive).

Patient ID	Age	Sex	Time since onset (month)	Etiology	CRS-R diagnose	CRS-R total	CRS-R audit. F.	EEG-frequency-proportions (%)				
								Delta	Theta	Alpha	Beta-1	Beta-2
1. HV	79	m	0.4 month	Trauma	VS	4	1	53	31	9	4	3
2. SM	49	m	31 month	Anoxia	VS	6	1	28	30	15	12	15
3. TJ	53	m	2 month	Heme. stroke	VS	4	1	54	20	10	8	8
4. NI	36	f	30 month	Anoxia	VS	7	1	39	16	12	15	18
5. ME	25	m	1.7 month	Trauma	VS	4	0	41	25	14	11	9
6. MD	42	f	5.8 month	Anoxia	VS	5	1	43	23	12	11	11
7. CD	36	m	91.2 month	Trauma	VS	6	1	65	18	7	5	5
8. LA	55	m	1.8 month	Meningo-encephalopathy	VS	4	1	42	34	14	6	4
9. FS	35	m	285.8 month	Trauma	MCS	10	2	38	25	14	11	12
10. PP	47	f	7.1 month	Hemorrhages	MCS	8	0	44	26	12	9	9
11. HJ	63	f	3.6 month	Trauma	MCS	17	3	43	27	15	8	7
12. GG	56	m	1.1 month	Anoxia	MCS	16	3	45	25	12	9	9
13. DJG	26	m	37.3 month	Anoxia	MCS	9	1	47	17	12	12	12
14. PD	59	m	8.8 month	Trauma	MCS	9	2	56	24	9	5	6
15. GM	36	f	268.3 month	Trauma	MCS	13	3	31	27	19	13	10
16. TJC	55	m	0.7 month	Anoxia	MCS	8	3	39	26	17	10	8
17. MJ	54	m	0.7 month	Trauma	MCS	7	1	55	26	11	5	3
18. FA	74	m	1.1 month	Trauma	MCS	14	3	37	28	18	9	8
19. VP	27	m	37.42 month	Cranial Trauma	MCS	16	4	46	26	13	9	6
20. RH	48	m	300 month	Cranial Trauma	MCS	11	3	33	26	15	12	14
21. CB	35	m	30 month	Cardiac Arrest	MCS	11	1	44	24	14	10	8

2.4. Data analyses

All data were bandpass-filtered between 1 and 30 Hz and an automatic ocular correction were applied to the raw data. Afterwards, data were segmented into epochs ranging from -200 to $+1300$ ms relative to stimulus-onset. In order to get an almost equal amount of segments (for targets and non-targets) in the two active conditions, only those non-targets were chosen which preceded a target. In order to avoid artificial priming effects in the second active condition, we did not analyse names that already appeared as targets in the first active condition. All of the available epochs were visually checked for artefacts and only artefact-free trials were used for further analyses. As can be seen in Fig. 1 (and in Table 1 for every subject individually) the EEG of patients was characterized by a surplus of slow frequencies (delta) and a reduced amount of activity in the higher frequency-range (alpha and beta-1) – a observation that is well in line with previous findings (Claassen et al., 2004; Nagata et al., 1989).

2.4.1. ERD/ERS

For time-frequency spectral analyses, complex Morlet wavelet transformations as implemented in BrainVision Analyser 1.05 (Brain Products, Munich) were applied. We calculated wavelet coefficients for frequencies between 1 and 30 Hz using a wavelet parameter of $c = 8$ with 1 Hz frequency steps for every trial. Subsequently the wavelets were averaged across trials. For further analysis we selected two frequency bands of interests: theta (ranging from 3.58 to 5.52 Hz) and alpha (ranging from 7.17 to 13.25 Hz). Given that only the theta frequency band (at electrode site Fz) and the alpha frequency band (at site Pz) showed systematic and reliable effects we will subsequently focus on these. Other frequency bands and electrode sites did not provide additional information and so they are not further reported.

With the obtained wavelet coefficients we calculated event-related de-/synchronization (ERD/ERS), reflecting the percentage change in test power with respect to a reference interval (Pfurtscheller and Aranibar, 1977) according to the formula: $ERD\% = [(reference - test power)/reference power] * 100$. As reference, the average between -100 and 0 ms relative to the stimuli was used. ERD/ERS was calculated for every sample-point and

averaged for statistical analysis. Note that contrary to the original formula ERS is expressed as positive and ERD as negative values.

2.4.2. Theta-power latency

In order to analyse the time course of ERD/ERS, we evaluated the time-point when subjects showed the greatest difference in band power between targets vs. non-targets. For this purpose we calculated the differences between the two stimuli sets and searched for the local maxima in a post-stimulus interval ranging from $+200$ to $+1000$ ms.

3. Statistical analysis

3.1. ERD/ERS

Four different repeated measures ANOVA's with theta and alpha ERS/ERD as dependent variables were calculated. ANOVA1 focuses on the effects of SON, stimulus type and time course of brain activation. It comprises the following four factors: CONDITION (count SON vs. count UN), TIME (t_1 , t_2 , t_3 ; $t_1 = 300-500$ ms, $t_2 = 500-700$ ms, $t_3 = 700-900$ ms poststimulus), STIMULUS (target vs. non-target) and GROUP (controls, MCS, VS) was calculated. Greenhouse-Geisser correction was applied where necessary. For post hoc analyses t -tests (for dependent samples) between targets and non-targets were computed for every time-interval, condition and group separately. A correction for multiple comparisons with the false discovery rate (FDR) according to (Benjamini and Hochberg, 2000) was used.

ANOVA2 was performed to test specifically for effects of instruction related top-down modulations. The question of interest is, whether there is an increase in theta ERS for the subject's own name (SON) between the count SON and passive listening condition. For this purpose we investigated the differences in averaged theta-ERS for the interval ranging from $+300$ to $+900$ ms. The following three factors were used: ACTVPASS (consisting of the levels: count SON vs. passive listening condition), NAME (SON vs. UN) and GROUP (controls, MCS, VS). Post hoc t -tests were computed for SON and UN between the two conditions for every group separately.

ANOVA3 and 4 are structurally identical to ANOVA1 and 2 but used alpha rather than theta-ERS/ERD as dependent variable.

3.2. Theta-power latency

As variances were not homogeneous (according to Leven's tests) the non-parametric Kruskal-Wallis test was used to compare the latencies between groups and Mann-Whitney tests were performed for post hoc comparisons.

4. Results

4.1. ANOVA1, theta-ERS: effects of SON, stimulus type and time course of brain activation

The respective findings, as summarized in Fig. 2a, show that theta ERS is largest for targets under the SON condition. This observation is reflected by the main effect for STIMULUS ($F_{1/30} = 30.72$,

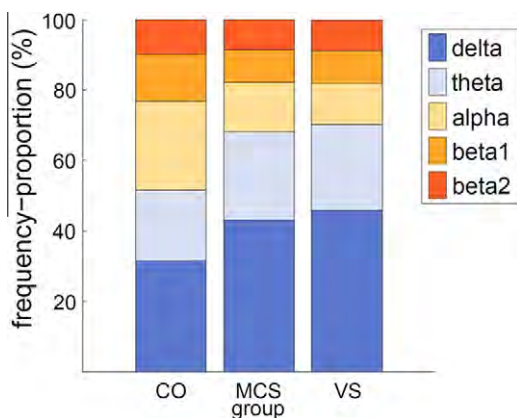


Fig. 1. EEG frequency-proportions across groups. The bar-graphs depict the respective frequency-proportions for controls, MCS and VS patients averaged for all conditions (mean center-frequencies: delta = 2 Hz, theta = 5.5 Hz, alpha = 10 Hz, beta-1 = 16 Hz, beta-2 = 22.5 Hz). In general, a slowing of the EEG-signal can be observed for patients (clear delta/theta dominance) together with a lack of higher-frequency oscillations (alpha and beta-1).

$p < .001$ and the interaction COND \times STIMULUS ($F_{1/30} = 13.13$, $p < .001$). Furthermore, ERS is generally larger for control subjects as compared to patients, and exhibits a differences in time as the main effects for GROUP ($F_{2/30} = 24.58$, $p < .001$), and TIME ($F_{2/60} = 23.29$, $p < .001$) indicate. Furthermore, these differences are more pronounced for target-stimuli and also show a different time course between stimulus type and groups as the 3-way interaction TIME \times STIMULUS \times GROUP, $F_{4/60} = 12.06$, $p < .001$, and the following 2-way interactions, TIME \times STIMULUS, ($F_{2/60} = 5.52$, $p < .05$) and TIME \times GROUP ($F_{4/60} = 13.25$, $p < .001$) STIMULUS \times GROUP ($F_{2/30} = 10.97$, $p < .001$) indicate.

Post-hoc *t*-tests, carried out to test for differences between targets and non-targets revealed that in the SON condition, significant effects were obtained in all of the three groups of subjects; controls: t1 ($t_{11} = 6.11$, $p = .000$), t2 ($t_{11} = 5.99$, $p < .001$), t3 ($t_{11} = 3.57$, $p < .01$); MCS: t1 ($t_{12} = 2.63$, $p < .05$), t2 ($t_{12} = 3.20$, $p < .01$); VS: t2 ($t_7 = 2.68$, $p = .032$), t3 ($t_7 = 2.88$, $p < .05$). In sharp contrast, in the UN condition (cf. the asterisks in Fig. 2a) no significant differences were observed in the two groups of patients; controls: t1 ($t_{11} = 3.37$, $p < .01$), t2 ($t_{11} = 3.10$, $p < .05$).

4.2. ANOVA2, theta-ERS: instruction related top-down modulation

The differences between the two conditions, actively counting SON and passive listening are embedded in the 3-way interaction ACTIVPASS \times NAME \times GROUP ($F_{2/30} = 3.77$, $p < .05$) which indicates that a higher extent of ERS to SON (as compared to UN) can be observed in the active condition only and is largest for control subjects (cf. Fig. 2b). This pattern of results is also reflected by the 2-way interactions. Additionally, the interactions ACTIVPASS \times GROUP ($F_{2/30} = 6.52$, $p < .01$), and ACTIVPASS \times NAME ($F_{1/30} = 27.55$, $p < .001$) as well as the main effects for NAME ($F_{1/30} = 12.63$, $p < .001$) and GROUP ($F_{2/30} = 16.34$, $p < .001$). The main effect for ACTIVPASS closely missed the 5%-significance level ($F_{1/30} = 3.99$, $p = .055$). Post hoc tests for targets (i.e., SON) between the active and passive condition revealed significant group effects for control subjects ($p < .001$) and the MCS group ($p < .05$). No post

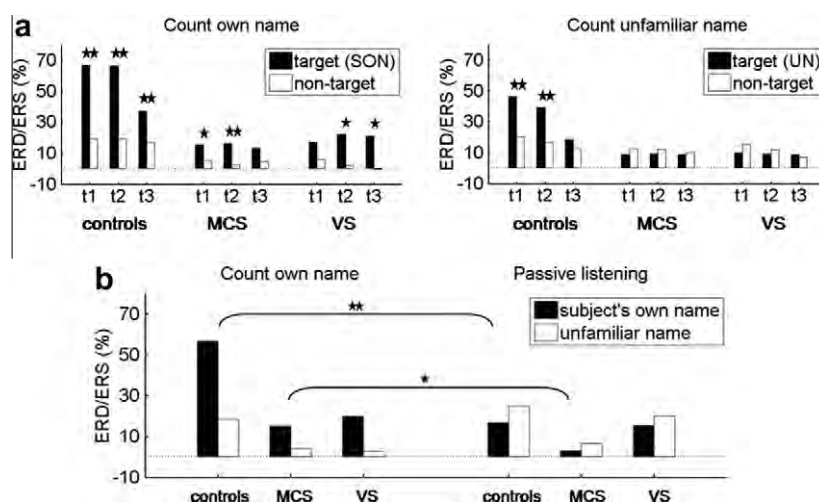


Fig. 2. Frontal theta ERS (Fz). (a) The graphic depicts the mean for targets and non-targets for the two active conditions (count SON and count UN), the three groups of subjects and three time-intervals post-stimulus. Post hoc analyses revealed that in the count SON condition every group shows higher frontal theta-ERS for the target name, whereas in the count UN condition only healthy controls showed a target effect. The asterisks indicate the significance-level for post hoc *t*-tests (** $p < .01$, * $p < .05$), which are corrected for multiple comparison according to FDR (adjusted false discovery rate, see Benjamini & Hochberg, 2000). Also note that the theta ERS response in VS appears delayed as compared to controls and even MC patients. (b) Frontal theta-ERS in the active (count SON) and passive listening condition. Controls and MCS show higher frontal theta-ERS (from +300 to +900 ms) for their respective own names when they were told to count them ('count own name'-condition) compared to the 'passive listening'-condition. The higher theta-ERS when actively counting SON in MCS patients could reflect a top-down biased bottom-up driven response that is induced by the instruction to focus on the subjects own name. Alternatively, it has to be noted that priming effects (i.e., passive conditions always precede active counting conditions) or simple baseline fluctuations can account for the result.

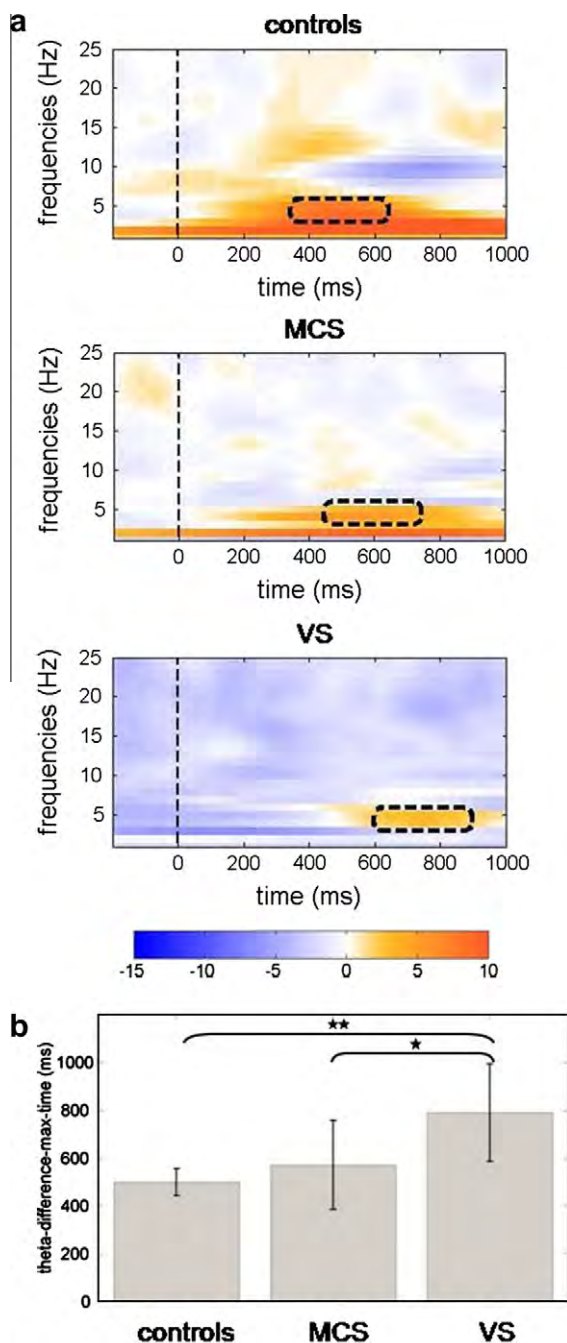


Fig. 3. Theta-power latency. (a) Time–frequency difference-plots [targets (SON) – non-targets] for the ‘count own name’-condition at the frontal electrode Fz. The dashed lines mark the presentation of the stimuli (names) and the rectangles the area with the highest difference in the theta-range. Note the increasing processing delay in theta power over groups. (b) To validate the prolonged latencies for the theta-effect in DOC groups, this graph shows the mean time-points when subjects exhibited the strongest difference between targets and non-targets in total power. In addition to prolonged theta peak latencies also the variance between groups increase with DOC severity probably reflecting less exact timing of stimulus processing (errorbars depict the standard deviations, asterisks indicate the respective significance-level: ** < .01, * < .05).

hoc tests between the two conditions were significant for non-targets (i.e., UN). This finding rules out a simple block effect.

4.3. Theta-power latency

As the findings for ANOVA1 have shown, the time course of theta ERS is different between the patients and the control group.

Visual exploration of the (wavelet) power plots (expressed as differences between targets and non-targets), as depicted in Fig. 3a, suggests that the time point of maximal theta power differences is considerably later for patients as compared to controls. Statistical analyses confirmed that the groups differed in the time-point where they reached maximal difference in theta power (for targets as compared to non-targets; $\chi^2 = 10.53$, $p = .005$; see Fig. 3b). Post-hoc tests revealed that this is true for controls vs. VS ($U_{(n1=12, n2=8)} = 7.00$, $p < .01$) and MCS vs. VS ($U_{(n1=13, n2=8)} = 23.50$, $p < .05$) and that the variances increase for the DOC groups (Levene’s tests: controls vs. MCS, $p < .01$; controls vs. VS, $p < .01$) indicating an increasing time jitter in stimulus processing in DOC.

4.4. ANOVA3, alpha-ERD

The findings are summarized in Fig. 4a and show that alpha ERD is largest for control subjects and for SON. This result is reflected by the main effects for GROUP ($F_{2/30} = 10.79$, $p < .001$), and for STIMULUS ($F_{1/30} = 15.23$, $p < .001$), and the interaction STIMULUS \times GROUP ($F_{2/30} = 18.84$, $p < .001$). These differences are interactively nested with TIME as the following interactions demonstrate: COND \times TIME \times GROUP ($F_{4/60} = 3.64$, $p < .05$), TIME \times STIMULUS ($F_{2/60} = 10.11$, $p < .001$), TIME \times GROUP ($F_{4/60} = 4.96$, $p < .01$), TIME \times STIMULUS \times GROUP ($F_{4/60} = 15.61$, $p < .001$), COND \times TIME \times STIMULUS ($F_{2/60} = 6.17$, $p < .01$). They show that the sharp increase in ERD over time (from t1 to t3) is more pronounced for (i) control subjects, (ii) SON and (iii) the count SON condition.

Post-hoc t -tests, carried out to test for differences between targets and non-targets revealed that in the count SON condition, significant effects were obtained for control subjects and two time intervals t2 and t3 only (t2: $t_{11} = -5.78$, $p < .001$; t3: $t_{11} = -8.33$, $p < .001$), as Fig. 4a shows. In the count UN condition significant differences were obtained for controls (t1: $t_{11} = -3.49$, $p < .01$; t2: $t_{11} = -4.79$, $p < .001$; t3: $t_{11} = -4.31$, $p < .001$), but most interestingly also for the MCS patient group (t: $t_{12} = -3.25$, $p < .01$; t2: $t_{12} = -2.55$, $p < .05$).

4.5. ANOVA4, alpha-ERD: count own name (active) vs. passive listening

The effects between the two conditions, actively counting SON and passive listening are also embedded in the 3-way interaction ACTIVPASS \times STIMULUS \times GROUP ($F_{2/30} = 3.62$, $p < .05$) which means that a higher ERD to SON (as compared to UN) is evident in the active condition for control subjects (cf. Fig. 4b). This line of results is also reflected by the 2-way interaction ACTIVPASS \times GROUP ($F_{2/30} = 4.38$, $p < .05$) as well as the main effects for STIMULUS ($F_{1/30} = 9.76$, $p < .01$) and GROUP ($F_{2/30} = 6.47$, $p < .01$). Post hoc tests for SON between the active and passive condition revealed a significant effect for control subjects only ($p < .01$).

5. Discussion

The findings of the present study indicate that both groups of patients (MCS and VS) are capable of responding neuronally with an increase in theta ERS to their own name (SON) when instructed to focus on and count their own name. No brain response to targets in the theta frequency was observed for patients when they were instructed to focus on a specific unfamiliar name (i.e., UN target vs. Other UN non-targets) or if they were passively listening to their own name (cf. Fig. 2a and b). These findings suggest that patients recovering from their disorder of consciousness were able to respond to the instruction (at least in essential parts) and try to establish some kind of top-down processing stage. We also could show that the theta response in the count SON condition (mea-

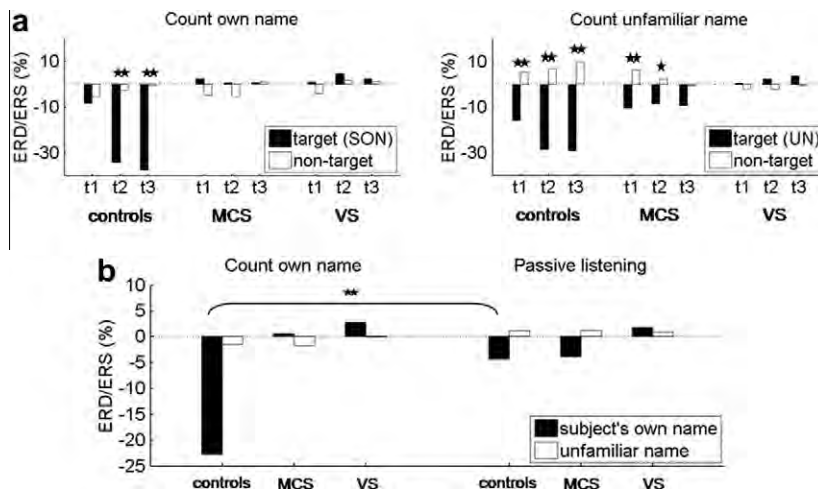


Fig. 4. Posterior alpha-ERD (Pz). (a) Note that alpha ERD is higher in controls when focusing on target stimuli (SON, or target UN according to condition) probably reflecting successful LTM access. MCS patients show a small but significant alpha ERD when counting UN as compared to other UN. (b) Significant alpha ERD differences between actively counting and passively listening to the SON are only evident in controls.

sured as the maximal power differences between targets and non-targets) was delayed in a graded manner from controls to MCS to VS (cf. Fig. 3).

Strictly speaking one basic question has to be addressed before interpreting the results, namely the question whether patients will accomplish the active task instruction (to count a name) or in other words if negative findings necessarily indicate absence of cognitive processing. We believe that the most important issue is indeed impaired sensory gating. In our case stimuli were presented auditory and therefore we provide the respective CRS-R auditory function values for each single patient. We also do not claim that a negative finding means that a patient is definitely in VS, yet positive findings should be taken as clear indication that patients understood the instruction and therefore have residual cognitive processing. Refusing to do a task is probably also less of a problem as one would assume that patients are trying hard to show their residual capacities when they are allowed to do so.

One important issue for interpreting the functional meaning of the obtained findings relates to the question which type of brain process is reflected by theta ERS. Previous research allows to distinguish at least three types of theta responses (Klimesch, 1999) which reflect (i) the maintenance of information in short-term memory (STM), (ii) sustained attention, and (iii) episodic encoding/retrieval. Studies focusing on the maintenance of information in STM have shown consistently that with increasing load, theta power or theta ERS increases (Fingelkurts et al., 2002; Gevins and Smith, 2000; Gevins et al., 1998, 1997; Grunwald et al., 1999; Jensen and Tesche, 2002; Mecklinger et al., 1992; Raghavachari et al., 2001). These results suggest that the active maintenance of information in STM (e.g. by rehearsal or other executive functions) is reflected by a sustained increase in theta power particularly at frontal sites. A second type of theta response can be observed in tasks requiring prolonged sustained attention. Under these conditions, a power increase over frontal midline sites (also termed 'frontal midline theta' or 'Fm θ ') can be observed (Aftanas and Golocheikine, 2001; Asada et al., 1999; Ishihara and Yoshii, 1972; Ishii et al., 1999; Kubota et al., 2001). In contrast to these prolonged increases of theta (occurring over a period of several seconds and minutes), a third type of theta response is characterized by a brief, transient, event-related increase in theta power that can best be measured in terms of theta ERS. This third type of theta response can be observed consistently during episodic encoding and retrieval (Burgess and Gruzelier, 1997, 2000; Klimesch et al., 1997a,b, 2000, 2001a,b, 1994). This conclusion

can be illustrated by the theta old-new effect which shows that during recognition ERS for old words is larger than for new words (Klimesch et al., 1997b, 2000). It is also supported by the theta subsequent memory effect which is characterized by a brief increase in ERS (around 100–400 ms) during the encoding of items that can later successfully be recognized.

With respect to the theta frequency range our findings thus suggest that DOC patients were capable of using their working memory (WM) to establish an episodic memory trace for SON-targets. Most interestingly, they were not able to do so for UN-targets. This may indicate that episodic cues which are plentiful for SON but not for UN are helpful to tap WM-resources and/or to initiate a top-down processing mode in WM. Concerning the second argument we propose that own-names (SON) are more salient than other names (UN) and are therefore processed more strongly bottom-up which in turn allows top-down processing and attentional boost of attended SON stimuli.

Finally, as the non-significant differences for non-targets (and unfamiliar names, respectively) between the active SON and passive listening condition indicate, the obtained findings cannot simply be interpreted in terms of (task-) block or order effects (cf. Fig. 2b, white bars). Interestingly, there is some indication for a possible block effect for MCS relating to SON (cf. Fig. 2b, black bars). Only MCS but not VS show enhanced theta responses to own names when instructed to count as compared to passively listen to them. There are three obvious possibilities to interpret this finding. One is methodological and is related to fluctuations in baseline activities. Another interpretation may explain the increase in theta ERS during the later performed active counting condition to reflect a priming effect of SON being elicited subliminally already during passive listening. A third interpretation may be based on the extent of remaining processing capacities differentiating between MCS and VS. As previous findings indicate, remaining processing capacities are more reduced for VS than MCS, and as a consequence MCS show enhanced theta during active counting SON as compared to passive listening. In addition, a systematic theta power delay related to the perception of own names (relative to unfamiliar names) from controls, to MCS, to VS is seen when instructed to count their own names. This may indicate systematic processing decrements according to underlying structural brain damage.

The obtained results in the alpha frequency range replicate well known findings showing that alpha ERD is particularly sensitive to

retrieval of knowledge that is well integrated in long-term memory (LTM; Klimesch et al., 2007). The fact that control subjects exhibit a significantly larger ERD to SON as compared to UN (under all active conditions) underlines the validity of this interpretation. Most interestingly, no significant differences between SON and UN were found for patients, suggesting that retrieval of knowledge stored along with SON in LTM does not take place. The only significant effect for patients was observed in the count UN condition for MCS subjects. Here, patients exhibit a significantly larger ERD in response to the UN target as compared to non-targets. It can be speculated that this may indicate either that MCS patients became aware that the target was a name and/or that they were capable of establishing a LTM trace for the target item. A possible reason why there were no findings present for the own-name condition could be due to the strong systematic theta-effects in this condition that served as a confounding variable for systematic alpha-effects in DOC patients. Nonetheless it should be mentioned that due to the considerably reduced alpha-proportion in the EEG-spectrum of DOC patients those alpha effects have to be interpreted with caution.

In clinical practice some EEG-parameter related to ongoing activity have already been used, e.g. for the evolution of stroke. Some examples are the delta-alpha ratio (Claassen et al., 2004), the power Ratio Index (PRI, Nagata et al., 1989) and the mean Brain Symmetry Index (mBSI, van Putten, 2007). In general the relative 'slowing' of the power-spectrum is a stable phenomenon of many pathologic states (Kobylarz and Schiff, 2005). In contrast to the mentioned indices which solely rely on the task-unspecific activity during a 'resting' period a clinical approach grounded on active paradigms and concentrating on event-associated power changes would be able to reveal the reactivity of large, local neuronal assemblies entrained to a specific sub-band representing the activity of a specific cognitive system.

Altogether the data indicate that time-frequency analyses allow to focus on distinct cognitive processes and thereby contribute to a refined understanding of residual cognitive processing in DOC. A limitation of the present study is that the results are confined to the group-level. Nonetheless we believe that it is warranted to identify valid paradigms and EEG signatures in order to apply these to a single-subject level in a next step. Future studies should therefore include longitudinal designs in order to investigate reliable oscillatory markers at an individual level. We believe that the increasing use and refinement of EEG and advanced EEG analyses techniques has the potential to improve our clinical characterization of VS, and MCS patients, not only for re(de)fining their diagnosis, but also to better differentiate patients in terms of appropriate treatment (including administration of analgesics and access to neuro-rehabilitation programs), outcome and end-of-life decisions. While EEG as an ambulatory method carries the big advantage of being easily introduced to clinical DOC evaluation worldwide the presented analysis technique allows studying distinct cognitive processes by focusing on various brain oscillations which are simultaneously present at all times. With this paper we hope to provide a new perspective which might complement clinical diagnosis in the future.

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