Oscillatory brain activity in vegetative and minimally conscious state during a sentence comprehension task

Manuel Schabus, PhD[a]
Christoph Pelikan[a]
Nicole Chwala-Schlegel, MSc[a]
Katharina Weilhart, MSc[a]
Dietmar Roehm, PhD[b]
Johann Donis, MD[c]
Gabriele Michitsch, MD[c]
Gerald Pichler, MD[d]
Wolfgang Klimesch, PhD[a]

[a] Laboratory for Sleep and Consciousness Research, Division of Physiological Psychology, University of Salzburg, Austria
[b] Department of Linguistics, University of Salzburg, Austria
[c] Apallic Care Unit, Neurological Division, Geriatriezentrum am Wienerwald, Vienna, Austria
[d] Apallic Care Unit, Neurological Division, Albert-Schweitzer-Klinik, Graz, Austria

Corresponding author: Manuel Schabus
University of Salzburg
Department of Psychology
Laboratory for Sleep and Consciousness Research
Hellbrunnerstr. 34
5020 Salzburg, Austria
E-mail: Manuel.Schabus@sbg.ac.at

Summary

Patients with altered states of consciousness continue to constitute a major challenge in terms of clinical assessment, treatment and daily management. Furthermore, the exploration of brain function in severely brain-damaged patients represents a unique lesional approach to the scientific study of consciousness. Electroencephalography is one means of identifying covert behaviour in the absence of motor activity in these critically ill patients. Here we focus on a language processing task which assesses whether vegetative (n=10) and minimally conscious state patients (n=4) (vs control subjects, n=14) understand semantic information on a sentence level (*"The opposite of black is... white/yellow/nice"*). Results indicate that only MCS but not VS patients show differential processing of unrelated ("nice") and antonym ("white") words in the form of parietal alpha (10-12Hz) event-related synchronization and desynchronization (ERS/ERD), respectively. Controls show a more typical pattern, characterized by alpha ERD in response to unrelated words and alpha ERS in response to antonyms.

KEY WORDS: disorders of consciousness, electroencephalography, event-related synchronization/desynchronization, minimally conscious state, sentence processing, vegetative state

Introduction

Clinical practice shows how difficult it is to recognize unambiguous signs of conscious perception of the environment and of the self in vegetative (VS) and minimally conscious state (MCS) patients (1). This difficulty is reflected in frequent misdiagnoses of locked-in syndrome, coma, MCS and VS (2). Consciousness as a whole is best conceptualized using two major components: the level of consciousness (i.e., arousal/wakefulness) and the content of consciousness (i.e., awareness of the environment and of the self) (3). Yet damage to the peripheral motor system may preclude correct assessment if neuroimaging or electroencephalography is not used as complementary tool in order to identify residual cognitive functioning in patients assumed to be in VS (4). One crucial challenge is to establish whether and to what degree patients with severe disorders of consciousness understand speech. Activation paradigms such as alternating graphemic and lexical decision tasks demonstrate cortical activation associated with clear lateralization to the left hemisphere and might therefore be suitable for studying language processing in VS and MCS patients. (5) There are indeed data from several studies which indicate that at least some of these patients can process language stimuli on the "meaning level" [e.g., patients in persistent VS (6), MCS (7), and coma (8)]. However, there are also data showing that semantic processing or priming can be elicited by unconsciously perceived words (9,10) or during reduced levels of awareness in anaesthesia (11), raising the question of whether the processing of meaning can, in general, be treated as a clear sign of conscious experience (12,13). Event related potentials (ERPs) have been readily used since the '80s in order to assess comatose patients. Thus, previous studies using early "exogenous" ERP components – which are tightly time-locked to the presentation of an external stimulus and depend on the physical properties of the sensory stimuli used to elicit them (e.g., brainstem auditory evoked potentials) – suggest a relative preservation of primary sensory processing in comatose patients. Furthermore, these components have been found to be predictors of good functional outcome (14) or awakening (15,16) from coma. Late-latency ERP components, which depend more on the nature of the subject's interaction with the stimulus (e.g., attention, task relevance), have been related more to the (conscious or non-conscious) cognitive processing of information. In particular the N400 component has been taken as an indicator of semantic processing and has been used to explore language comprehension at the patient's bedside.

The purpose of the present study was to explore, at the bedside, the possible preservation of sentence comprehension in coma survivors in order to better differentiate patients diagnosed with VS or MCS by means of an objective electrophysiological measurement (using oscillations). In contrast to previous studies, we used a design which allowed us to distinguish between two different aspects of language processing: i) semantic relatedness/priming, which could be due to passive (unconscious) semantic activation, and ii) prediction (or top-down attention), which could reflect the presence of active (conscious) language processing on a sentence level. Previous research has shown that sentences of the form *"The opposite of X is Y"* are linguistically maximally restricted with respect to "*Y*", in the sense that in the presence of "X" there is only one possible insertion for "Y" which renders the sentence well-formed. Hence, the sentence context (*"The opposite of black is..."*) strongly induces prediction of the (unique) sentence-final antonym (*"white"*), whereas semantically highly related words (*"yellow"*) violate the sentence-level interpretation despite their strong semantic relatedness. The present paradigm tries to replicate previous findings that predicted antonyms lead to graded, reduced N400 in comparison with related and unrelated non-antonyms (17,18). It is important to stress that this N400 effect can be expected only when participants are able to comprehend sentence-level information. The present study thus set out to examine the described N400 effect in the time-frequency domain, using healthy control subjects, as well as VS and MCS patients.

Materials and methods

The EEG was recorded using a 32-channel BrainAmp (Brain Products, Gilching, Germany) amplifier. Eighteen Ag/AgCl electrodes were placed on the participant's scalp according to the International 10-20 System (Fz, F3, F4, F7, F8, FC5, FC6, Cz, C3, C4, T3, T4, Pz, P3, P4, PO7, PO8, Oz) and the ground electrode was positioned between FPz and Fz. Recordings were referenced to FCz (as is usual for long-term recordings) but re-referenced to linked mastoids (A1, A2) post-hoc. The electrooculogram (EOG) was monitored by means of electrodes placed at the outer canthus of each eye for horizontal eye movements and above and below the left eye for later correction of vertical eye movements. Electrode impedances were kept below 10 kOhm. All channels were recorded with a digitization rate of 500 Hz and amplified using a BrainAmp amplifier (0.10 Hz high-pass filter; 70 Hz low-pass filter; 50 Hz notch filter). For EEG analysis we carefully pre-processed data using Independent Component Analysis (ICA)-based EOG correction and manual correction for residual artifacts. Subsequently we segmented (-1500 to 1500ms), wavelet-transformed and averaged the data. To establish an adequate time-frequency resolution for lower frequencies a 10-cycle complex Morlet wavelet was utilized.

Subjects

Fourteen patients with a disorder of consciousness [10 VS (mean age =44.10 years, SD=12.32) and 4 MCS (mean age =52.25 years, SD=17.8 patients)], recruited from two "apallic care centres" (Graz and Vienna, Austria), were tested on two separate occasions (Table I). Each session included several EEG paradigms with breaks between tasks. These breaks were extended if arousal could not be recovered using the Coma Recovery Scale-Revised (CRS-R) arousal facilitation protocol. A second EEG recording of identical tasks was conducted within 14 days. Patients were off sedative medication for at least 24 hours before each session. Behavioural assessment was conducted by two independent scorers using the CRS-R (19) before and after each session. In addition a sample of 14 age- and sex-matched controls (mean age=43.86 years, SD=13.43) was tested on the linguistic sentence paradigm in a controlled setting (EEG laboratory at the Dept of Psychology, University of Salzburg, Austria). No age differences between the three experimental groups were observed.

Sentence comprehension task

To test sentence comprehension we used an antonym sentence paradigm (17) including three critical conditions: antonym pairs (e.g. *black – white*), pairs of related words (e.g. *black – yellow*) and pairs of unrelated words (e.g. *black – nice*). These critical stimuli were embedded in a fixed sentence context of the form *The opposite of X is Y*, with X and Y instantiating the manipulation of interest. Stimuli were taken from Roehm et al. (17). Twenty sets (triplets) of the three conditions (antonyms, related, unrelated) were created, thus resulting in a total of 60 critical stimuli. All sentences were presented in randomized order in a (passive) auditory listening task. Sentences were spoken by a male trained speaker who was instructed to read the sentences as naturally as possible. All sentences were recorded on tape in order to be digitized afterwards (44.1 kHz, 16-bit sample rate). The onset of the critical second word (Y) was determined offline by means of acoustic analysis software and triggered for subsequent EEG analyses. (Minimal sentence duration = 2156 ms; maximal sentence duration = 3210 ms; critical stimulus duration varied between 340 to 819 ms, mean = 582 ms). Between sentences there was a fixed break of 2000 ms.

Statistical analysis

For statistical analysis we used repeated measures ANOVA. Specifically, we calculated ANOVA values using the within-subject factors TYPE (unrelated, antonyms) and TIME (0-200, 200-400, 400-600, 600-800 and 800-1000ms post-stimulus), and the between-subject factor GROUP (representing the VS and MCS patients, as well as a control sample). ANOVAs calculated with the factor TYPE with three levels (unrelated, related, antonyms) did not add any information and were therefore not included in the following analysis. The interactions of interest included, at least, the factors TYPE and GROUP (i.e., TYPE x GROUP as well as three-way interactions TYPE x TIME x GROUP). Analyses were done separately for three electrode sites (Fz, Cz, Pz) and for five frequency bands of interest (4-6Hz, 6-8Hz, 8-10Hz, 10-12Hz, 12-14Hz). The dependent variable was ERS/ERD (mean of the two sessions), which in our case is a measure (in percent) relative to a baseline recorded before sentence onset [i.e., 1500 to 1300ms before the critical (*unrelated/related/anonym*) second word was presented]. Because of the preliminary nature of the current study sample (4 MCS and 10 VS patients)

Table 1 - Demographic data of vegetative state and minimally conscious state patients

Patient ID	Age (years)	Sex	Aetiology	Time since injury	Clinical assessment	CRS-R total score	CRS-R auditory score
AT	37	F	Trauma; calvaria fracture right, right frontal haemorrhage, contusion	11 years 2 months	VS	5	2
EL	33	M	Trauma after car accident	5 years 5 months	VS	8	2
HS	56	F	Hypoxic brain injury	7 years 10 months	MCS	12	3
HW	73	M	Intracerebral haemorrhage	8 months	MCS	17	3
SR	50	F	Trauma, subdural haemorrhage following a violent attack	9 years 5 months	MCS	14	4
WL	30	M	Trauma	9 years 3 months	MCS	13	3
AR	20	M	SSPE (van Bogaert encephalitis)	3 years	VS	3	1
DS	48	M	Hypoxic brain injury	9 years 3 months	VS	5	0
KG	58	F	Subarachnoid haemorrhage; ruptured aneurysm of anterior artery communis	2 years 4 months	VS	4	0
GP	52	M	Trauma; subdural haemorrhage right, fronto-temporo-parietal osteoclastic trephination right (day of injury)	12 years 3 months	VS	8	2
JP	53	M	Trauma	1 years 10 months	VS	4	0
RF	62	M	Hypoxic brain injury after cardiopulmonary resuscitation	2 years 8 months	VS	4	2
SH	41	F	Trauma, subarachnoid haemorrhage	12 years 8 months	VS	7	2
US	51	F	Ruptured aneurysm of anterior artery communis	4 years 10 months	VS	4	0

Abbreviations: SSPE:subacute sclerosing panencephalitis; VS=vegetative state, MCS=minimally conscious state.

we refrained from applying correction for multiple comparisons. Note that in order to increase the validity of the data we re-recorded the same paradigm within two weeks in all patients. The two sessions were thereby not treated independently but averaged for each patient.

Results

Repeated measures ANOVAs showed a significant TYPE x GROUP interaction ($F_{2,25}$=6.697, p=.005) and a significant TYPE x TIME x GROUP interaction ($F_{8,100}$=2.44, p=.019) for the upper alpha band (10-12 Hz) at electrode site Pz. This effect indicates that i) whereas control subjects show a small upper alpha ERD response to unrelated words (0-800 ms post-stimulus) and a significant upper alpha ERS response to antonyms, ii) MCS patients exhibit an upper alpha ERS response to unrelated words and a strong upper alpha ERD response to antonyms (0-600 ms post-stimulus). Post-hoc t-tests revealed significant differences between the antonym and unrelated word conditions in control subjects (0-200 ms: t_{13}=3.095, p=.009; 200-400 ms: t_{13}= 4.519, p=.001; 400-600 ms: t_{13}=2.719, p=.018; and a trend towards significance at 600-800 ms: t_{13}=1.835, p=.089), as well as trends towards significance in the small group of MCS patients (0-200 ms: t_3=-2.847, p=.065; 200-400 ms: t_3=-2.853, p=.065) (Fig. 1). In VS, no significant difference was found between conditions (unrelated vs. antonym sentence endings).

Time-frequency plots depict the event-related synchronization/desynchronization (ERS/ERD) difference (unrelated [red line] minus antonym [black line]) in response to critical words at parietal site Pz. ERS/ERD is shown 500 pre- to 1000ms post-stimulus (baseline: 1500 to 1300ms before critical word onset). Note that MCS patients showed upper-alpha (10-12Hz) ERD (0-400ms) after the presentation of the antonym (e.g., "The opposite of black is *white*"). Control subjects, on the other hand, even revealed significant upper-alpha ERS (0-600ms) in response to critical antonyms, as well as a small alpha ERD in response to unrelated words (left panel). Note that in the case of acoustically presented words, processing can already start at the initial word onset, explaining early ERS/ERD effects. Statistical differences between conditions (**, p<.05) and statistical trends (*, p<.10) are marked with dashed rectangles.

Discussion

Preliminary results of a novel sentence processing paradigm revealed significant differences between healthy controls, VS and MCS patients. Specifically,

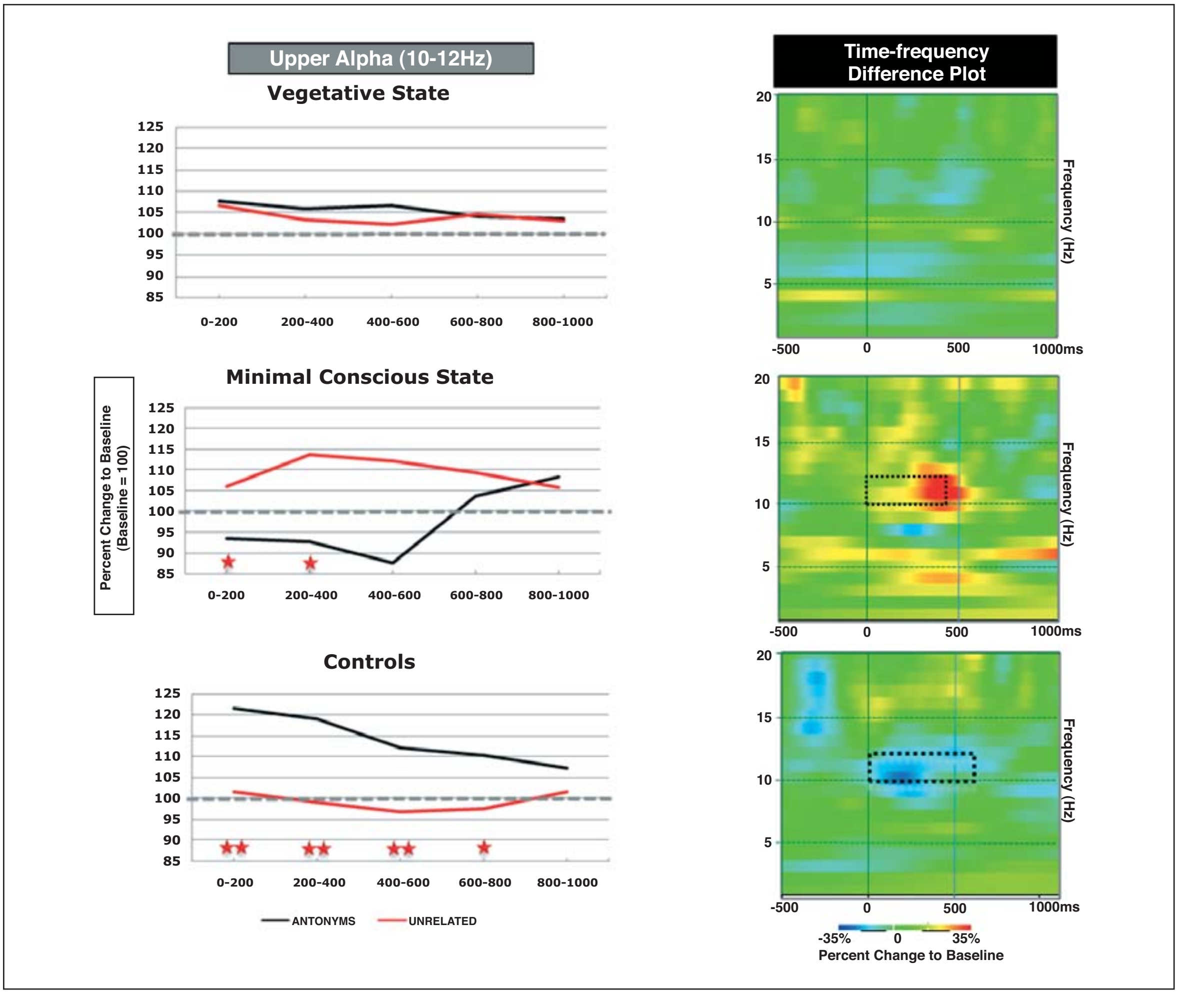

Figure I - Time-frequency difference plots between antonym and unrelated sentence endings.
Time-frequency plots depict the event-related synchronization/desynchronization (ERS/ERD) difference (unrelated [red line] minus antonym [black line]) in response to critical words at parietal site Pz. ERS/ERD is shown 500 pre- to 1000ms post-stimulus (baseline: 1500 to 1300ms before critical word onset). Note that MCS patients showed upper-alpha (10-12Hz) ERD (0-400ms) after the presentation of the antonym (e.g., "The opposite of black is *white*"). Control subjects, on the other hand, even revealed significant upper-alpha ERS (0-600ms) in response to critical antonyms, as well as a small alpha ERD in response to unrelated words (left panel). Note that in the case of acoustically presented words, processing can already start at the initial word onset, explaining early ERS/ERD effects. Statistical differences between conditions (**, p<.05) and statistical trends (*, p<.10) are marked with dashed rectangles.

analysis in the time-frequency domain revealed that the MCS but not the VS patients showed specific upper alpha (10-12Hz) ERS and ERD responses to unrelated words ("The opposite of black is… *nice*") and antonyms ("The opposite of black is… *white*"), respectively. This result – higher alpha ERD for antonyms than unrelated words – was unexpected as higher alpha ERD is usually observed in response to the stronger semantic violation ("nice") in the specific (highly restricted) sentence context ("The opposite of black is…). Our interpretation of this finding is that MCS patients do not use "predictive processing" but only post-stimulus relational processing (17), in other words, the semantic integration is carried out post-hoc in a bottom-up manner. By this, we mean that MCS patients are able to start lexical processing only upon presentation of the final word in the sentence. Controls, on the other hand, can preprocess the final word in the sentence, when it is semantically appropriate (antonym), as soon as the first word (of the antonym word pair) has been presented. If these assumptions are true it should be neuronally more "effortful" (i.e., semantic processing of the antonym relation and long-term memory access) for MCS patients to respond to matching (antonyms) than non-matching (unrelated) words as reflected in alpha ERD (20). Alternatively, and given that VS and MCS patients usually show a considerable slowing of the EEG, it could be that the reversed "upper alpha" effect seen in the MCS patients is actually a classical "beta" ERS effect. If one considers this possibility and visually shifts the MCS plot in (Fig. 1) two to three Hz upwards a stronger alpha ERD for unrelated than antonyms (between 200-400ms) becomes apparent. It is to be noted that VS patients did not show either ERS or ERD in any analyzed frequency band, or any between-condition differences; in short, they showed no signs of residual cognitive processing or even awareness.

Interestingly, the effects in the (age and sex-matched) healthy controls contrasted with the ERS/ERD pattern observed in MCS patients. Control subjects exhibited a small upper alpha ERD response to unrelated word pairs and a significant upper alpha ERS response to antonyms. Although post-hoc tests revealed clear differences between the two conditions, the amount of upper alpha ERD (to unrelated words) was surprisingly small. We believe that this effect might be due to a combination of fatigue and lack of intrinsic motivation as the present paradigm was always recorded in the evening in a series of low-level tasks. Indeed, these low-level cognitive tasks might have caused a serious lack of attention and even sleepiness, particularly in the healthy individuals. Nevertheless, the fact that healthy subjects showed upper alpha ERD in response to the semantic violation (unrelated critical word) is in line with earlier findings of a distinctly enhanced N400 response to unrelated non-antonyms versus sentence terminating antonyms (17,18). In contrast to MCS patients, control subjects therefore appear to process the complete sentence online, and react to the violation of their specific expectation ("white" in response to "black") with an upper-alpha ERD response; the expected antonym, on the other hand, is processed only in a stimulus unspecific way, as the word had already been predicted *before* onset of the final sentence word. Whether the reported results can be related to "conscious" processing is debatable. However, the paradigm depends on at least keeping track of a complete sentence structure, as the violation of an expectation – and therefore differences between the unrelated and antonym word condition – can only be expressed (and reflected on a brain oscillation level) if the final word is processed in the context of the complete sentence structure. It is unlikely that simply contrasting words such as "white" and "nice" would depict the characteristic ERS/ERD pattern observed in the MCS and control subjects (Fig. 1).

There may be several reasons why we did not find more widespread effects in the frequency domain, as well as across different EEG topographies or all stimulus types (i.e., additional related words). Indeed, we found differences only in a specific oscillatory band recording site and only between unrelated and antonym sentence endings. Besides the small sizes of the groups (MCS, n=4; VS, n=10), studies of this kind always have to reckon with the problem of highly varying etiology, site of lesion and age (Table I). Unfortunately, all these factors can lead to systematic changes in brain oscillations and, specifically, dominant peak frequency. In the future, therefore, special attention should be paid to the possibility of adjusting EEG frequencies individually (20). As the baseline in our ERS/ERD analysis was set to the time period immediately before sentence onset (1500 to 1300ms before the critical word) the unusual small upper alpha ERD observed in the control subjects could also be a side effect of the expectation of sentence onset. In other words, it is well known that, especially in paradigms using fixed interstimulus intervals, (alpha) ERD can appear before stimulus onset, thus masking "critical word" (antonyms or unrelated) ERD subsequently. Another problem of many EEG studies of patients with disorders of consciousness is the considerable amount of EEG artifacts and fluctuating arousal levels (21). In order to circumvent the resulting problem of insufficient clean trials per stimulus type we decided to conduct two independent recordings per individual, as suggested earlier (21).

To summarize, the use of bedside electroencephalography may help to improve the clinical characterization of vegetative and minimally conscious patients after severe brain damage, making it possible not only to redefine the diagnosis, but also to differentiate patients in terms of treatment, outcome and end-of-life decisions.

Acknowledgements

We also would like to thank Theresa Stemeseder who was involved in recording and testing subjects as well as Kerstin Hoedlmoser who assisted with comprehensive EEG expertise. Special thanks also to the support from the nursing staff of the "Apallic Care Unit" (Neurological Division, Geriatriezentrum am Wienerwald, Vienna) as well as the "Apallic Care Unit" (Neurological Division, Albert-Schweitzer-Klinik, Graz, Austria).

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