The event-related potentials Mismatch Negativity, P300, and N400: Effects of attentional modulation and application in patients with disorders of consciousness

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1 Graphical Abstract

Can event-related potentials complement the clinical assessment of patients with disorders of consciousness (DOC) and which stimulus features and task instructions can deliver the most reliable results?

Study 1:

Which opinions and expectations do practitioners working with DOC patients have concerning the complementation of clinical assessment of these patients through ERP-based measures?

N=9 neurologists

Guided interviews on current diagnostic procedures and requirements for a new diagnostic system

→ Practitioners are generally aware of the weaknesses of current procedures.

→ A new ERP-based system must be reliable and valid and provide prognostic results.

Study 2:

Can ERPs be elicited in patients diagnosed with the unresponsive wakefulness syndrome? Does task instruction make a difference regarding the elicited ERPs?

N=19 DOC patients

EEG measurements with four paradigms aiming at the elicitation of MMN, P300, and N400

→ ERPs can be elicited in patients with unresponsive wakefulness syndrome.

→ An instruction focusing attention on the relevant stimuli leads to a higher number of ERPs compared to a passive one.

Study 3:

To what extent are Mismatch Negativity and N400 affected by task instruction modulating attention on the relevant stimuli?

N=18 healthy participants

EEG measurements with three paradigms aiming at the elicitation of MMN and N400 under three different tasks

→ N400 is heavily effected by attention.

→ MMN is slightly affected by attention.

→ An instruction focusing attention on the relevant stimuli seems most appropriate.

Study 4:

To what extent is MMN affected by task instruction modulating attention? Does this effect depend on stimulus features like the amount of deviants and the magnitude of deviance?

N=32 healthy participants

EEG measurements with four paradigms aiming at the elicitation of MMN and P300 under three different tasks

→ P300 is heavily effected by attention.

→ MMN is slightly affected by attention.

→ Multifeature paradigms with highly different deviants seem most appropriate.

ERPs are a valuable tool to complement the clinical assessment of DOC patients. In healthy participants, focused instructions were most beneficial for N400 and P300. For MMN, multifeature paradigms with highly different deviants delivered the most prominent ERPs.

2 Abstract

The present work comprises four studies dealing with the investigation of the auditory event-related potentials (ERP) Mismatch Negativity (MMN), P300, and N400 under different attentional instructions, and with their application in patients with disorders of consciousness (DOC) to assess residual cognitive functioning. In guided interviews (study 1), practitioners working with DOC patients stated their general interest in and an objective need for the complementation of current diagnostic procedures by reliable and valid ERP-based methods. Subsequently, in study 2, simple oddball and semantic paradigms were applied to 19 behaviorally non-responsive DOC patients revealing the presence of at least one ERP in eight patients investigated. In the third and fourth study, specific attentional effects on ERPs were investigated in healthy participants to define optimal instructions and stimulus parameters. In study 3, MMN and N400 amplitudes were assessed in 18 participants, and in study 4, MMN and P300 amplitudes were assessed in 32 participants. Both studies included an ignore task (attention on simultaneous visual stimuli), a passive task, and a focused task and revealed distinct attentional effects on P300 and N400 with largest amplitudes in the focused task, smaller ones in the passive task and no ERP in the ignore task. An MMN was elicited in all tasks, but still, amplitudes differed as a function of task. In addition, study 4 included oddball paradigms comprising several deviants in different dimensions. Higher amplitudes were found in this multifeature paradigm compared to traditional oddball paradigms and larger amplitudes were elicited by deviants highly different from standards. It is concluded that ERPs represent a promising tool to complement clinical assessment of DOC patients. Application of ERP paradigms should include focused instructions, especially when using semantic material. Furthermore, multifeature paradigms have been proven especially useful eliciting large amplitudes and allowing for the investigation of several dimensions of deviants at the same time.

3 Zusammenfassung

Die vorliegende Arbeit beinhaltet vier Studien, die die auditorischen ereigniskorrelierten Potentiale (EKP) Mismatch Negativität (MMN), P300, und N400 unter verschiedenen Instruktionen untersuchen, und deren Anwendung bei Patienten mit Bewusstseinsstörungen darstellen. In Studie 1 äußerten neurologische Fachärzte in Leitfadeninterviews ein generelles Interesse und eine objektive Notwendigkeit der Ergänzung bisheriger diagnostischer Vorgehensweisen durch EKP-basierte Methoden. In Studie 2 wurden 19 motorisch nicht-responsiven Patienten verschiedene Stimuli in Form einfacher Oddball-Paradigmen und semantischen Materials dargeboten und es konnte in acht Patienten mindestens ein EKP nachgewiesen werden. Studie 3 und 4 dienten der Untersuchung spezifischer Aufmerksamkeitseffekte auf EKPs in Gesunden, um optimale Instruktionen und Stimulusparameter zu definieren. Es wurden jeweils MMN und N400 in 18 Teilnehmern und MMN und P300 in 32 Teilnehmern untersucht. Beide Studien enthielten eine Ablenkungsaufgabe (simultane visuelle Reize), eine passive und eine fokussierte Aufgabe und zeigten deutliche Aufgabeneffekte auf P300 und N400. Die höchsten Amplituden wurden in der fokussierten Aufgabe ausgelöst, kleinere in der passiven und kein EKP in der Ablenkungsaufgabe. Eine MMN wurde in allen Aufgaben ausgelöst, aber auch hier unterschieden sich die Amplituden in Abhängigkeit der Aufgabe. Studie 4 enthielt außerdem ein Oddball mit mehreren abweichenden Tönen in vier Dimensionen. Dieses erzielte höhere Amplituden als das klassische Oddball mit nur einem abweichenden Ton. Höhere Amplituden wurden von abweichenden Tönen ausgelöst, welche sich stark vom Standardton unterschieden. EKPs stellen ein vielversprechendes Instrument zur Ergänzung klinischer Diagnosen bewusstseinsgestörter Patienten dar. Es sollte auf eindeutig zu differenzierende abweichende Reize und bei semantischen Material auf fokussierte Instruktionen zurückgegriffen werden. Paradigmen mit verschiedenen abweichenden Tönen können aufgrund höherer Amplituden und eines umfassenden Reizverarbeitungsprofils besonders nützlich sein.

4 Introduction

The ability to attend to and focus on certain events in the environment forms the basis of all cognitive functions and mental processes. Thus, the concept of attention has been of great interest in investigating not only healthy individuals but also patients with cognitive impairment, for example after stroke, traumatic brain injury or incidents causing hypoxia. In this regard, electrophysiological imaging technologies represent an important tool in the study of attentional processes in general and as a complement to clinical assessment for detecting cognitive functions associated with attention. One of the most important techniques is the recording of event-related potentials (ERP), specific brain reactions following distinct endogenous or exogenous events (Kotchoubey et al., 2005). The allocation of attention to relevant or concurrent stimuli can easily be modulated by a specific instruction and subsequently affect the arising ERPs. Thus, amplitude, latency, and even the mere presence or absence of ERPs do not only depend on the stimulus material implemented but also on the instruction used to present it. However, at least in recordings with patients with severe disorders of consciousness (DOC), this aspect has rarely been considered and the instructions given are often passive or unspecific. Only recently, there have been specific calls for the use of active instructions (Kotchoubey & Lotze, 2013; Kübler & Kotchoubey, 2007).

Patients with severe DOC are often low or non-responsive in terms of behavioral reactions, but can exhibit various levels of consciousness. Thus, it is especially problematic to estimate their level of arousal or the ability to understand and follow instructions based on motor movements. In clinical assessments, ERPs can provide additional information about the current cognitive state of a DOC patient but at the moment, are not included in the standard diagnostic process because of their current lack of standardization. In fact, only positive ERP results can be interpreted. Negative results can be caused by various factors, such as varying states of arousal, focus of attention, and language understanding. Thus, to maximize the chance of positive ERP results, it is crucial to apply optimal stimulus material under the best conditions possible. In this context, stimulus parameters and recording instructions should be adjusted to elicit ERPs as reliable as possible. The extent to which attention allocation is modulated in active versus passive tasks is particularly relevant because it directly affects the arising ERPs.

4.1 The concept of attention

In psychology research, the concept of attention has been in the focus of many scientists over decades, but it is still difficult to define (Styles, 2006). James first differentiated sensorial from intellectual attention (1890). While sensorial attention is directed to objects that are perceived with senses, intellectual attention is paid to ideal, physically not present objects. Further, he distinguished between immediate and derived attention, depending on whether attention is paid to a stimulus being interesting itself or to a stimulus that is associated with something interesting. In the 1950s, the idea of attention capacity being limited by a *bottleneck* emerged (Welford, 1952). This assumption was derived from experiments on the psychological refractory period fostering the conclusion that processing of one stimulus has to be completed before processing of a second one can begin. Only few years later, Broadbent suggested a first structural model of attention (1958): According to the *filter theory*, processing capacity is limited and thus, relevant information are picked from incoming stimuli through a selective filter before proceeding to conscious processing. This assumption was later refined by a model postulating a mechanism attenuating irrelevant stimuli instead of filtering them (Treisman, 1969).

The theories of filtering and attenuation were later replaced by broader views on attention incorporating different kinds of attentional performance. Posner and Petersen postulated three subsystems of attention that they later affirmed and refined (Petersen & Posner, 2012; Posner & Petersen, 1990): a) orienting, b) executive control (formerly called target detection), and c) alerting. The orienting network prioritizes sensory input through the selection of a modality or location. Executive control describes the ability to monitor and resolve conflict in the presence of competing information. Alerting enables the person to prepare and maintain alertness to process signals of high priority. Building up on this classification, Coull proposed four primary sources of attentional modulation (1998): a) attentional orienting, b) selective attention, c) divided attention, and d) sustained attention (vigilance) and arousal. Attentional orienting focuses attention in a certain direction (spatial) or on temporal cues. Selective attention is more specific and refers to a certain location of stimuli while other features are ignored. Divided attention takes place when simultaneous stimuli are processed in parallel and sustained attention describes the maintenance of attention over a prolonged period of time. The terms of these attentional generators were taken on by various other researchers and are still up-to-date (Leclercq, 2002; Sturm, 2007).

Thus, in current research, attention is not regarded as a system based on a *bottleneck* or *filter*. Instead, it is regarded as a process (Anderson, 2005) or system (Petersen & Posner, 2012) that enables us to concentrate selectively on certain events or features. However, the concept of limited processing capacities as it was already mentioned in the 1950s (Broadbent, 1958; Treisman, 1969) is still part of current definitions and it is assumed that attention allocates these limited resources to the entities most relevant in a specific situation (Anderson, 2005).

The concepts presented so far, are all derived from research with healthy participants who are consciously aware. However, attention gains special importance when it comes to patients with impaired consciousness. For DOC patients, the question whether or not they are able to attend to certain stimuli may be of large diagnostic and therapeutic value with very strong implications on the patients’ therapeutic treatment. In healthy participants, the processes of paying attention and being consciously aware of certain events can be considered two distinct entities (Koch & Tsuchiya, 2007). Likewise, in DOC patients, the presence of attention must not automatically imply the presence of consciousness. However, certain reactions of patients that can be achieved with or without attention, may serve as an important indicator of future development (see chapter 4.4.1).

4.2 Electroencephalography and event-related potentials

Electroencephalography (EEG) records electrical activity of the brain through electrodes placed on the scalp. These oscillations recorded on the scalp are assumed to be generated by the summation of excitatory and inhibitory post-synaptic potentials in cortical pyramidal neurons (Pizzagalli, 2007). EEG recordings provide a high temporal resolution and activity changes in the range of milliseconds can be observed. Thus, EEG can map certain frequencies (i.e. Delta, Theta, Alpha) as well as very fast electrical responses to certain stimuli. The studies presented in this work are based on the recording of ERPs which are time-locked electrical potentials. ERPs represent specific brain activity occurring in preparation or in response to certain events that can be of internal or external nature (Fabiani, Gratton, & Federmaier, 2007). They reflect the synchronous activity of various populations of neurons. ERPs are usually named according to their polarity and latency. The letter *P* or *N* indicate a positive or negative deflection and is followed by the rough latency of the potential. In the following chapter, the ERPs Mismatch Negativity (MMN), P300, and N400 are characterized.

4.2.1 The Mismatch Negativity (MMN)

The MMN belongs to a group of ERPs referred to as N200, which was first recorded in 1965 (Sutton, Braren, Zubin, & John, 1965). The N200 can be further subdivided into the N2a or MMN, N2b, and N2c subcomponents, depending on the stimuli used, scalp distribution, and allocation of attention (Pritchard, Shappell, & Brandt, 1991): MMN is associated with automatic processing irrespective of attention while N2b and N2c require attention and represent conscious perception and the classification of stimuli. An MMN is typically elicited in an oddball paradigm comprising one stimulus which occurs frequently (standard), and one that differs from this standard and occurs rarely and unpredictably (deviant). In the auditory domain, an MMN appears in response to deviants that vary in one or more stimulus features such as frequency, intensity, duration, or location (for a review, see Näätänen, 1992). The MMN is usually recorded in tasks where participants pay attention to some other irrelevant stimuli, because an N2b might be elicited alongside when stimuli are attended (Sams, Paavilainen, Alho, & Näätänen, 1985).

According to the memory-mismatch or trace-mismatch hypothesis, an MMN is elicited when an incoming stimulus differs from the memory representation formed by the preceding stimulus sequence (Näätänen, 1990). This concept was later challenged by the regulation violation hypothesis, assuming that not only static information but also dynamic information, like a regularity among repetitive stimuli, are encoded into a memory representation (Winkler, 2007). An MMN can also be elicited by the deviation from a certain regularity within a longer sequence of stimuli. However, the trace-mismatch and regulation violation hypotheses are not mutually exclusive but may exist and explain elicitation of an MMN effect alongside (Kimura, Schröger, Czigler, & Ohira, 2010).

The MMN occurs in a latency range of 100-250 ms after deviant onset and in analyses is obtained by subtracting the ERP response elicited by the standards from that elicited by the deviants (Duncan et al., 2009). Furthermore, MMN amplitudes typically reverse polarity at the mastoid electrodes when referenced to the nose and this reversal can be used to differentiate the MMN from other potentials like N2b (Näätänen, Paavilainen, Rinne, & Alho, 2007). According to the two-component model of MMN, one sensory-specific component, generated in auditory cortices, and one frontal component contribute to the MMN effect (Näätänen & Michie, 1979). Giard and colleagues confirmed this classification and reported one contralaterally larger component over the temporal scalp and one frontal-central component that is larger over the right than the left hemisphere, irrespective of the ear of stimulation (Giard, Perrin, Pernier, & Bouchet, 1990). It is assumed that amplitudes recorded at the mastoids represent an estimate of the mere supratemporal component without an overlap of N2b (Näätänen, 1992).

4.2.1.1 MMN and attention

The MMN is often regarded as a response generated by an automatic change detection mechanism that occurs without conscious perception and independently of the attention of the listener (Folstein & van Petten, 2007; Muller-Gass, Stelmack, & Campbell, 2005; Näätänen, 1990). However, other findings indicated that under some conditions, the MMN amplitude can be either enhanced by directing attention toward a discrimination task (Oades & Dittmann-Balcar, 1995; Woods, Alho, & Algazi, 1992), or attenuated by strongly focusing attention toward some other (irrelevant) stimuli (Woldorff, Hackley, & Hillyard, 1991; Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998). Näätänen later criticized Woldorffs study from 1991 assuming that the effects were mainly due to N2b overlap (Näätänen, 1992), but conceded a potential effect on intensity MMN when attention is withdrawn (Näätänen, Paavilainen, Titinen, Jiang, & Alho, 1993). Furthermore, it is suggested that two divisions of neurons contribute to the MMN effect, computational and amplifying ones (Näätänen, 1991). Following this assumption, computational neurons are not affected by the focus of attention while amplifying ones are.

To resolve the debate on the attentional effect, Sussman (2007) proposed that two steps are necessary to elicit an MMN: standard formation and deviance detection. She argues that only the first process, the formation of a standard memory trace, is directly affected by attention. An acoustic stimulus becomes a standard through repetition and is then maintained in the auditory memory. This process establishes the basis of the second process, detection of the deviant, which fully relies on the representations formed by the standard and is fairly indifferent to attention. Thus, the MMN is not a pre-attentive process but a part of a larger system of auditory scene analysis consisting of interacting sub-processes, which can be modulated by attention (Sussman, 2007).

4.2.1.2 Measurement of MMN

The MMN is a relatively small component and thus, a high number of deviant stimuli is necessary to achieve an appropriate signal-to-noise ratio (Duncan et al., 2009). However, an MMN can be elicited even at very short inter-stimulus intervals (ISI). It is considered to be stable with ISIs ranging from about 300 to 1000 ms, but a reliable MMN is even still elicited with an ISI as short as 26 ms (for a review, see Schröger, 1998). Thus, paradigms can still be short in time, even if a high number of repetitions is needed. Amplitudes of the MMN are usually determined in a relatively short time interval of 20 to 50 ms around the maximum negative peak because it often overlaps N1 and N2b. Choosing a short interval in the latency range of the polarity reversal at the mastoid minimizes the danger of confounding effects with other potentials. For analyses, the electrodes Fz, C3, Cz, and C4 are recommended (Duncan et al., 2009).

4.2.2 The P300

The P300 occurs as a positive deflection about 300 ms after a rare stimulus in an oddball paradigm containing one irrelevant stimulus that is presented very often and one target stimulus that is presented only rarely (Fabiani, Gratton, & Federmaier, 2007; Sutton, Braren, Zubin, & John, 1965). The P300 comprises the two sub-components P3a and P3b (Comerchero & Polich, 1999; for a review, see Polich, 2007): Both arise in response to rare events in oddball tasks. The P3b is elicited in the usual oddball task comprising one frequent and one rare stimulus. The P3a also comprises a novelty P300 and a no-go P300. These variants of the same ERP are elicited by a non-attended target (P3a), an unknown infrequent distracter stimulus inserted in an oddball paradigm (novelty P300) or by a known distracter stimulus in a three-stimulus oddball paradigm (no-go P300) (Polich, 2007). While the P3b reaches its maximum over parietal areas, the P3a exhibits highest amplitudes over frontal and central areas (Polich, 2007).

Elicitation of P300 is explained in the context-updating theory: P300 is assumed to origin from brain activities involved in the revision of mental representations of incoming stimuli (Donchin, 1981). Incoming events are held in working memory and after initial sensory processing, an attention-based comparison process evaluates the representation of previous stimuli. If a new stimulus is detected, stimulus representation is updated and a P300 is elicited (Polich, 2007).

4.2.2.1 P300 and attention

Elicitation and physiology of a P300 depend on the levels of attention and arousal the person engages (Polich & Kok, 1995), as well as working memory capacity (Linden, 2005). In general, elicitation of a P300 requires a minimum of attention to the stimuli and is not elicited when a demanding secondary task is given (Johnson, 1984). Thus, its amplitude is increased when the person focuses on the specific task or stimuli in comparison to rather passive task with no requirement to focus on the stimuli (i.e. Bennington & Polich, 1999; Polich, 1986; Spencer & Polich, 1999; Wickens, Kramer, Vanasse, & Donchin, 1983). In experiments where both, passive and active tasks, are studied, passive tasks are usually presented before active tasks to avoid the participants to consciously or subconsciously transfer instructions from the active task to the passive task and thus, provoking larger ERP responses (Bennington & Polich, 1999; Polich, 1987).

4.2.2.2 Measurement of P300

Compared to MMN, recording a reliable P300 requires a lower number of trials. (Duncan et al., 2009) recommended at least 36 artifact-free trials, while (Cohen & Polich, 1997) stated that even 20 trials are enough. In P300 recordings, ISI is often chosen to be in the range of seconds, however, research on brain-computer interfaces (BCI) has proven that a reliable P300 can even be recorded at ISIs of 175 ms. Thus, it is well possible to keep P300 paradigms short and still record reliable components although this increases the risk of overlapping ERPs. Since the P300 effect comprises P3a and P3b with different scalp distributions, it is recommended to include the electrodes Fz, Cz, and Pz in the analyses of the potential (Duncan et al., 2009).

4.2.3 The N400

The N400 was first recorded in 1980 (Kutas & Hillyard, 1980a). It occurs as slow monophasic negativity between 200 and 600 ms and is mainly regarded as a specific response to violations of semantic expectations (Kutas & Hillyard, 1980b). It occurs in response to congruent versus incongruent sentence endings (Kutas, 1987; Kutas & Hillyard, 1984), and related versus unrelated word-pairs (Bentin, McCarthy, & Wood, 1985; Hagoort, Brown, & Swaab, 1996), as well as to line drawings completing a sentence (Ganis, Kutas, & Sereno, 1996), incongruent endings of picture stories (West & Holcomb, 2002), and inappropriate objects in video films (Sitnikova, Kuperberg, & Holcomb, 2003). However, the N400 has also been observed in response to pseudowords with no relation to real words (Deacon, Dynowska, Ritter, & Grose-Fifer, 2004), which implies that specific semantic meaning is not a necessary condition for its elicitation.

The N400 is not regarded as a neural entity with undifferentiable and localizable features. Instead, the name is used in a heuristic manner to describe brain activity that arises 200-

600 ms after stimulus onset with a characteristic morphology and functionality (Kutas & Federmeier, 2011).

4.2.3.1 N400 and attention

The N400 could represent an automatic or controlled mechanism of semantic processing. Attenuation of the N400 in response to unattended targets varies considerably (Kutas & Federmeier, 2011; McCarthy & Nobre, 1993). The masking of prime words, which makes them less perceptible and reportable, did attenuate the N400 in a word priming paradigm; however, masking did not eliminate it (Holcomb & Grainger, 2009). In contrast, just a moderate masking completely suppressed the N400 in a sentence paradigm (Daltrozzo, Wioland, & Kotchoubey, 2012; Kutas & Federmeier, 2011). It seems likely that the N400 comprises characteristics of both, automatic and controlled processing. Since the role of attention in eliciting the N400 is not yet completely understood, it is particularly important to be able to estimate attentional effects on the N400 component, especially if the presence or absence of this kind of ERP component is to be used to assess cognitive functioning of DOC patients.

4.2.3.2 Measurement of N400

The N400 arises as a broad potential and thus, relatively long time intervals of a few hundred milliseconds are chosen to determine mean amplitudes and it is recommended to analyze interactions between experimental conditions and scalp sites, such as frontal, central, and parietal ones when studying N400 (Duncan et al., 2009). To record a reliable N400, 40-120 trials are recommended (Duncan et al., 2009). Since the N400 does not need to be negative in absolute terms, the amplitude is calculated as the difference between responses to congruent and incongruent stimuli (Kutas & Federmeier, 2011).

4.3 Disorders of consciousness

Disorders of consciousness (DOC) describe medical conditions in which conscious awareness of the self and the environment is impaired or presumably absent. DOC encompass the minimally conscious state (MCS), the unresponsive wakefulness syndrome (UWS, Laureys et al., 2010), coma, and brain death (Bernat, 2006). Patients are diagnosed as comatose when no eye-opening can be observed and no signs of awareness can be achieved by external stimulation (Plum & Posner, 1982). After several weeks, most patients proceed into UWS (Bernat, 2006). UWS is defined as wakefulness without awareness meaning that these patients show signs of wakefulness like sleep-wake-cycles including phases of eye-opening but are still assumed to be unaware of themselves and their environment (Jennett & Plum, 1972). UWS patients exhibit reflex movements to touch, pain, bright light, or noise. However, no reproducible reactions following commands can be observed (Laureys et al., 2010). In contrast, MCS patients do show signs of awareness such as reproducible reactions, gaze following, or yes/no gestures (Bernat, 2006). However, these behaviors are inconsistent and may occur on some days, but not on others. Thus, diagnosis of MCS is especially difficult and largely depends on the current status of the patient.

A medical condition that can easily be confused with DOC is the locked-in state (LIS). Like patients in UWS or coma, LIS patients are unable to move or speak, but are consciously aware of themselves and their environment (Smith & Delargy, 2005). LIS patients can be completely locked-in with no means of communication but full awareness, or incompletely locked-in with preserved movements, such as eye gaze or single fingers (Smith & Delargy, 2005). Thus, LIS patients can easily be misdiagnosed as UWS or MCS or even comatose if only judged on behalf of their behavioral responses.

However, the differentiation between LIS and UWS, MCS, and coma is not the only difficulty, but numerous studies have provided evidence for different degrees of awareness also in UWS and coma (i.e. Daltrozzo, 2006; Kotchoubey et al., 2005; Menon et al., 1998;

Owen et al., 2006). The patients assessed in these studies showed preserved cognitive functioning in response to auditory stimulation that could, in some cases, also indicate preserved consciousness. Thus, patients diagnosed with these DOC are not automatically completely unaware of their environment. Alongside with that, high rates of misdiagnosis of patients in UWS have been published repeatedly (i.e. Andrews, Murphy, Munday, & Littlewood, 1996; Schnakers et al., 2009). In addition, DOC patients do not remain in a certain state of consciousness for an unlimited time but experience eminent fluctuation of vigilance (Kübler & Kotchoubey, 2007). Thus, patients may be able to follow commands on one day, but not on the other, complicating a correct diagnosis.

As a consequence, numerous authors suggested a continuum of states of consciousness rather than a simple classification (i.e. Laureys, Owen, & Schiff, 2004; Schnakers, Giacino, & Laureys, 2010). The continuum comprises the dimensions awareness and arousal (Figure 1).

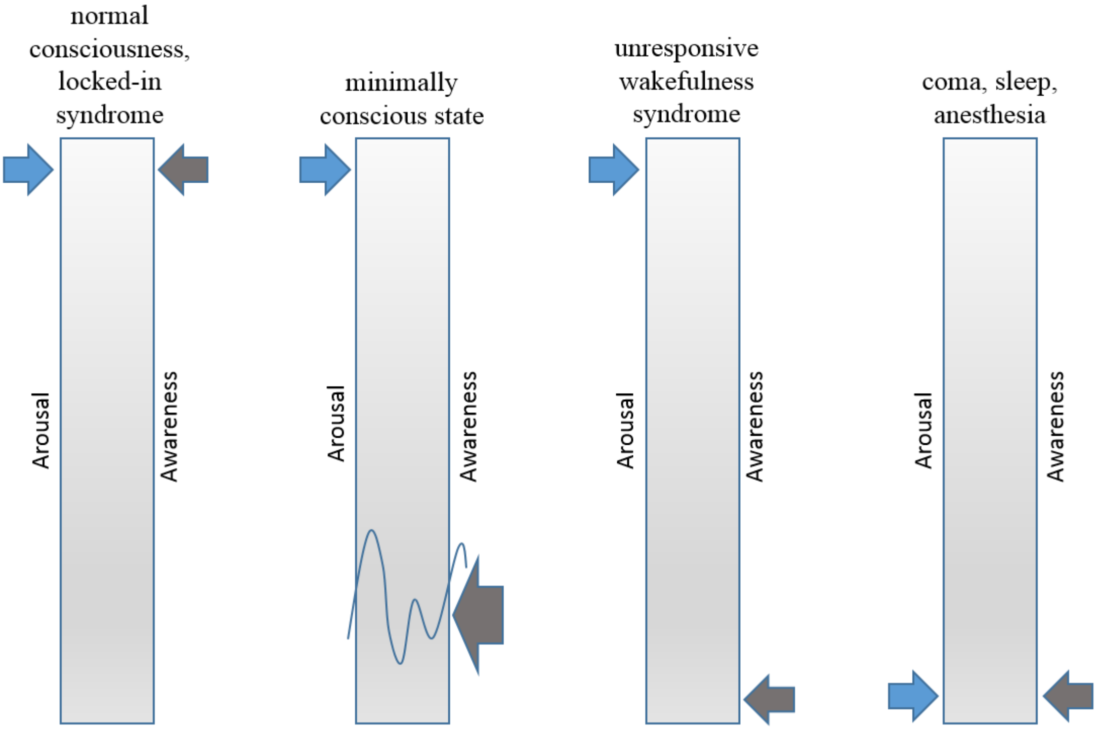

Figure 1: Comparison of different DOC in terms of arousal and awareness (adapted from Laureys et al., 2004). The four bars represent different states of consciousness while the blue and grey arrows represent the levels of arousal and awareness, respectively. An oscillating graph and a larger arrow represent fluctuating awareness in MCS patients. Arrows in the bottom area denote low and arrows at the top indicate high levels of arousal and awareness.

In persons with normal consciousness or in LIS, arousal and awareness are high while in coma, sleep and anesthesia, both are at a minimum. In MCS and UWS, arousal can be high since behaviors like spontaneous movements, eye-opening and reflexes can be observed. However, in UWS, awareness is at a minimum while in MCS, patients exhibit fluctuating awareness.

4.3.1 Hierarchical approach

ERPs have long been discussed for their benefit in the assessment of cognitive functioning in DOC patients, complementing a mere behavioral assessment. However, measurements in clinical environments are subject to several constraints, like limited attention span of the patient and limited time available for testing. Thus, a hierarchical approach for those investigations was proposed. According to this theory, the presence of simple processing mechanisms such as the N1-P2 complex is a prerequisite for more complex processes and later components like MMN and P300 as well as responses to semantic material such as N400 and P600 (Kotchoubey et al., 2005). Following this approach, recordings using complex paradigms can be skipped if no ERPs emerged in reaction to simple stimuli. Kübler and Kotchoubey (2007) designed a detailed theory including five steps: (1) recording of resting state EEG and auditory evoked potentials to rule out the possibility of hearing loss, (2) stimulation using passive paradigms aiming at the elicitation of MMN/P300 (oddball) and N400/P600 (semantic material), (3) stimulation with the same paradigms as in (2) with the additional task to specifically concentrate on certain stimuli, i.e. counting the odds, (4) volitional tasks, i.e. imagination of movements according to certain stimuli, and (5) decision making using BCI, i.e. answering yes/no questions.

A similar approach was presented for studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) in DOC patients (Owen et al., 2005). The first step includes paradigms to test basic acoustic processing to ensure normal or near-to-normal sensory processing. In a second step, perceptual processing in terms of the ability to discriminate between different categories of sound is explored. The third step uses semantic material to investigate phonological processing for which the authors recommend sentences of varying intelligibility. In the fourth step, semantic processing is studied by using sentences containing ambiguous words eliciting specific patterns of activation if they are consciously processed (words with two meanings, i.e. “bark”, or with the same pronunciation but different meaning, i.e. knight/night). However, the authors also note that even detectable responses to ambiguous sentences do not automatically evidence awareness because semantic processing can also take place without conscious awareness. Thus, additional tasks including the formation of intention and volition are necessary. Such tasks, as a last step in a hierarchical approach, may comprise the imagination of movement, i.e. playing tennis or moving around the house (Owen et al., 2006).

In essence, both approaches postulate a similar procedure starting with paradigms to ensure intact hearing, slowly proceeding to more complex stimulation and terminating with the attempt to establish communication through conscious decision between different options. Following such a hierarchical approach can save time and resources but presumes the absence of higher order information processing if no signs of simple discrimination abilities can be found.

4.4 Event-related potentials in patients with disorders of consciousness

4.4.1 Event-related potentials in diagnostic application

Attention processes measured by ERPs take on special practical importance when it comes to the diagnosis and treatment of patients with severe cognitive impairment following head injury, stroke, or anoxia (Ilvonen, 2003; Kotchoubey et al., 2005; Schnakers et al., 2008). Previous studies indicated that the presence of an MMN is a strong predictor for awakening from coma and UWS (Fischer, Luaute, Adeleine, & Morlet, 2004; Wijnen, van Boxtel, Eilander, & Gelder, 2007). Similarly, the P300 (Daltrozzo, Wioland, Mutschler, & Kotchoubey, 2007; Lew et al., 2003; Signorino, D'Acunto, Cercaci, Pietropaoli, & Angeleri, 1997) and N400 (Faran, Vatine, Lazary, Birbaumer, & Kotchoubey, 2006; Steppacher et al., 2013) have been proven to be a successful indicator of recovery or awakening from coma. N400 effects have been found to indicate preserved semantic processing in some DOC patients (Kotchoubey et al., 2005; Schoenle & Witzke, 2004). In addition, the N400 was identified as a correlate of quality of life and thus, successful coping in patients with amyotrophic lateral sclerosis (ALS) (Real et al., 2014).

In comparison to healthy participants, persons with closed head injuries have been found to have reduced N200 amplitudes, both visually and auditorily (Duncan, Kosmidis, & Mirsky, 2005). Other studies, however, found no differences in auditory N200 between healthy participants and patients with mild brain injuries (Potter, Bassett, Jory, & Barrett, 2001; Sivák et al., 2008). Auditory P300 amplitude was flattened in well-functioning healthy persons after mild traumatic brain injury (TBI) compared to persons without head injuries (Segalowitz, Bernstein, & Lawson, 2001). Differential effects on auditory and visual P300 were reported additionally (Duncan et al., 2005). Auditory ERPs appeared to be more susceptible to the effects of closed head injury, revealing more strongly reduced amplitudes and prolonged latencies. In contrast, other studies failed to find differences in auditory P300 between healthy participants and persons with mild head injury (Potter, Bassett, Jory, & Barrett, 2001; Sivák et al., 2008). However, these diverse results may stem from a heterogeneous sample of brain injuries whose effects on cognitive functioning largely depend on the location and the extent of the lesion. Elting and colleagues conducted separate analyses for P3a and P3b and concluded that only differences in P3a amplitudes account for reduced P300 amplitudes (Elting, Naalt, Weerden, Keyser, & Maurits, 2005). Some patients with head injuries did not show a P3a component at all and no difference in P3a amplitude between the groups was found when only patients with identifiable P3a were included. Thus, it might also be possible that specific parameters of the stimulus material lead to differential effects. Regarding the N400 in healthy persons and patients, smaller auditory N400 were found in patients with TBI as compared to healthy persons (Knuepffer, Murdoch, Lloyd, Lewis, & Hinchliffe, 2012). In addition, also Münte and Heinze (1994) reported diminished and delayed auditory N400 responses after closed head injury. In their study, a clear N400 component was only identifiable in response to sentences, but not to word-primes, thus indicating a potential benefit of sentence based stimulus material.

As a consequence, albeit playing an important role in the assessment of DOC patients, ERPs are often altered following injuries of the brain. Diminished amplitudes and prolonged latencies can complicate the identification of the relevant deflections, thus fostering the need for a comparison of ERPs within patients across various different paradigms.

4.4.2 Event-related potentials in communication applications

Once preserved consciousness is detected in a patient, the next logical step comprises the establishment of communication means using, for example, brain computer interfaces (BCI). In this context, the P300 is one of the most important brain signals for research in behaviorally non-responsive patients such as DOC, LIS, or ALS. ALS is a neurodegenerative disease affecting the motor system, leading to proceeding muscle weakness and atrophy (Kiernan et al., 2011). In its late stages ALS leaves the patients unable to move or breathe while being fully aware of themselves and the environment. This is an important difference between DOC and ALS or LIS patients. In ALS and LIS patients, consciousness might be altered but the person is generally aware of the environment and the self. In DOC patients, consciousness and awareness have still to be assessed. However, once signs of awareness have been detected, establishment of communication through the application of a BCI represents the next necessary step.

BCIs use brain signals and automatically convert them into an output replacing or restoring the natural output the patient is no longer able to perform, or enhancing the natural output of the central nervous system (Wolpaw & Wolpaw, 2012). Most BCIs based on ERPs utilize P300 responses elicited by visual stimuli in a matrix containing all letters of the alphabet that are flashed randomly. Since P300 is highly dependent on attention, users are able to write words and sentences on the computer screen by concentrating on specific letters (Farwell & Donchin, 1988; Kleih et al., 2011; Nijboer et al., 2008). In addition to those visually based systems, there has also been research to design auditory BCIs solely relying on sounds for users with impaired vision or eye gaze control (i.e. Kleih, Herweg, Kaufmann, & Kübler, 2014; Klobassa et al., 2009). In some patients, even the application of tactile BCIs might be indicated and provide better accuracy than auditory or visual systems (Kaufmann, Holz, & Kübler, 2013).

BCIs can have a tremendous effect on the quality of life of severely disabled patients when communication can be established, restored or maintained while a disease leads to increasing impariment. Further, BCIs also allow for the implementation of daily life applications such as browsing the internet (Mugler, Ruf, Halder, Bensch, & Kübler, 2010), chatting with friends (Hutchison et al., 2011) or creative expression using brain painting (Holz, Botrel, & Kübler, 2014). Thus, the scope of possible activities of the patients can be significantly enlarged.

4.4.3 Challenges

Albeit the important fields of application of ERPs in patients with DOC or neurodegenerative diseases like ALS, in practice, these studies face many obstacles. First of all, patients in severe states often live in clinics or nursing homes and even if they live at home, their room resembles hospital environment. In such settings, user and researcher have to deal with acoustic and electrical noise from medical devices that can complicate the measurements, impede concentration, and disturb the EEG signal. Additionally, these patients are often enrolled in an intense program of therapeutic sessions such as physiotherapy. Thus, time available for measurements is limited and further shortened by an often brief attention span of the patients. As a consequence, measurements need to be as short as possible and well planned. For most of the patients, the forenoon is assumed to be the time of best physical and mental fitness but in general, an individual assessment at different times of the day should be conducted.

Depending on the condition of the patient, also injuries of the head following trauma or operations can be an issue. Open wounds, scar tissue, or implants can disturb the signal or even make EEG measurements impossible. Other medical conditions may include the infection with bacteria or germs like methycillin-resistant Staphylococcus aureus (MRSA). Such infections are generally harmless for healthy people but constitute a severe risk for people with open wounds or a vulnerable immune system. When working with several patients, MRSA can be transferred from one patient to the other through experimenters and caregivers. Thus, special procedures of disinfection are necessary and tight hygienic regulations must be followed at all times. Taken together, measurements with patients need to be well planned regarding the given preconditions, necessary hardware and software, best possible time slots, and hygienic conditions.

4.5 Motivation and general hypotheses

The present work was designed to foster the research of ERPs suitable to be applied to DOC patients. In this context, it was first investigated, if practitioners working with these patients, judge a complementation of diagnostic assessment through ERPs as useful and which preconditions would have to be met. Subsequently, ERPs were recorded in DOC patients diagnosed with UWS to detect if these patients show signs of residual cognitive functioning independently from their diagnosis. The last two studies focused on the detailed analyses of

ERPs often used in clinical settings, questioning their reliability under different attentional instructions and in terms of specific features of the paradigms they are elicited with. All studies refer to auditory ERPs because patients in late stage of ALS or in UWS might be unable to control their eye gaze and often, the auditory channel is the only remaining channel for communication (Laureys, 2000; Murguialday et al., 2011).

The following studies investigate practical preconditions of the application of ERPs in patients with DOC, and report on the measurements of ERPs in patients with DOC as well as healthy participants basing on the following general hypotheses:

a) Practitioners working with DOC patients have a general interest in the complementation of current diagnostic procedures by psychophysiological methods comprising ERPs.
b) ERPs can also be elicited in non-responsive patients with DOC.
c) Attentional instructions do affect ERPs such as P300, N400, and MMN. In this context, focused instructions elicited larger and therefore more reliable ERPs compared to passive or ignore instructions.

Study 1 addresses hypotheses a, study 2 addresses hypotheses b and c, studies 3 and 4 focus on hypothesis c.

5 Study 1 – Interviews with practitioners

The following study has been published elsewhere (Guger et al., 2014). The methodological approach and the results were adopted.

5.1 Study aims

In the past years, studies have repeatedly indicated a high proportion of misdiagnosis in MCS and UWS patients (Schnakers et al., 2009). Thus, diagnosis in such minimal or non-responsive states needs to be improved and ongoing research aims at developing diagnostic means based on imaging and electrophysiological techniques. Application of ERPs has been shown to be a suitable tool to complement clinical assessment and to detect residual cognitive functions (Kotchoubey, Lang, Bostanov, & Birbaumer, 2002). However, such tools have to meet the requirements of physicians in the field and must be developed in close collaboration with these practitioners who are the target user group for such an EEG or imaging based diagnostic battery.

In the present study, representatives from acute care clinics and rehabilitation centers dealing with DOC patients were questioned regarding their diagnostic methods and their opinion on the complementation of diagnosis through ERP techniques following a user-centered approach in which a product is developed in an iterative process between users and developers (Kübler et al., 2014). This study was designed to investigate potential weaknesses of the diagnostic procedures leading to high rates of misdiagnosis. In addition, an overview on the opinions and preconditions expressed by the practicing physicians may serve as a starting point for the development and implementation of an integrated diagnostic battery ready for usage.

In practice, daily routines are expected to vary greatly between different institutions dealing with DOC patients. After the incident leading to a DOC, patients are firstly admitted to an acute care clinic to restore living functions. In these clinics, emergency treatment within the first days is in the foreground. When the patient is stable, he or she is usually admitted to a rehabilitation center focusing on therapeutic procedures to restore as many functions as possible. The present study included representatives from both institutions to assess differences and commonalities and to identify which institutions provide the most appropriate conditions for the application of ERP-based diagnostics.

5.2 Method

Semi structured interviews were conducted in nine different institutions across Germany – four in acute care clinics (ACC) and five in neurological rehabilitation centers (NRC). Interviewees were five medical directors, two chief physicians and two senior physicians in the field of neurology. All interviews were conducted in the private offices of the participants as a guided interview and recorded using a voice recorder after receiving the permission of the participants. First of all, interviewees were told about the development of a new diagnostic battery based on auditory ERPs recorded via EEG. They were told that this device is still subject to research but shall be made available for clinical studies within the next years. Subsequently, the interview started and covered three main topics: current diagnostic procedures, weaknesses of the current process, and expectations concerning a new diagnostic battery (see Appendix A). All interviews were conducted in German language, lasted between 20 and 45 minutes and were recorded and transcribed. Answers to each question were grouped into clusters and counted.

5.3 Results

For reasons of clarity, answers of ACCs and NRCs will be presented together unless a differentiation is of importance for the result.

5.3.1 Current diagnostic procedures

A diagnosis in ACCs is made quickly within few hours. NRCs acknowledge the diagnosis provided by the referring ACC but review it on admission of the patient. A diagnosis is checked regularly on an hourly (ACCs), daily or weekly (NRCs) basis depending on the status and medical history of the patient. When making a diagnosis, physicians primarily rely on the clinical assessment comprising the observation of reactions to auditory, sensory and visual stimuli. All institutions apply EEG, especially in comatose, UWS, and MCS patients. One institution (NRC) also applies measurements of evoked potentials. In some cases computer tomography (n = 6) or MRI (n = 4) are used additionally. The Glasgow Coma Scale is administered in six, the Barthel Index in five and the Coma Recovery Scale revised in two institutions. Seven institutions consider their diagnosis to be of primary importance for treatment decisions and future therapeutic processes. Two institutions (NRC) consider the diagnosis to be important but put a greater focus on prognosis and treatment.

5.3.2 Weaknesses in the current procedures

According to the participants, results in the current diagnostic process partially depend on experience and observational skills of the responsible physician (n = 5). Therefore, there is a wish for a stronger focus on different aspects of diagnostics already in the education of becoming a neurologist (n = 3). Another critical issue is the lack of methods to estimate the further development of patients in terms of regaining consciousness or rehabilitative progress (n = 3). Furthermore, a lack of sufficient resources to apply imaging techniques was mentioned (n = 3). Finally, the consideration for psychic matters and cognitive performance (as the entity that makes us humans) is regarded as insufficient in neurological diagnostics (n = 2).

5.3.3 Requirements and expectations

A general interest in applying a new, more reliable diagnostic tool was evident in six institutions (one ACC, five NRCs). Three representatives from ACCs could not imagine using it in their institutions but consider it interesting, particularly for therapeutic institutions such as NRCs. Reasons against the application of such a system were limited resources of time and personnel. All interviewees named reliability and validity as mandatory. Additionally, the tool must not be affected by disturbances typical for a medical environment (*n* = 6) and needs to be practical regarding time, personnel, financing and the setup (*n* = 7). However, it was also mentioned that the amount of resources available to invest will largely depend on the benefit of the resulting output (*n* = 4). Taking into account the weaknesses of the current diagnostics, the most relevant expectations are the prognostic value of the results (*n* = 7) and a support in therapeutic decision-making (*n* = 5). Thus, the output is expected to be accurate in terms of a selective differentiation between various diagnoses and prognoses.

5.4 Discussion and summary

A correct diagnosis is vital for minimally and non-responsive patients, not only because prospects for MCS patients are more favorable than for UWS patients but also to prevent that consciousness in a behaviorally non-responsive patient remains undetected (Healy, 2010). The results shed light on two important aspects: Firstly, there are weaknesses in the current diagnostic process that physicians are aware of and practitioners are generally interested in new measures to overcome them. Secondly, practitioners have clear expectations regarding a potential new diagnostic EEG-based tool: it must be valid, work reliably, allow for prognostic statements and not add to the burden of limited financial and personnel resources. The necessity of such an EEG-based tool to improve reliability of the diagnosis is widely acknowledged as current clinical assessment is influenced by individual skills of the physician.

The results point at some potential reasons for high rates of misdiagnosis in DOC. All institutions apply the clinical observations and EEG for diagnosis. Clinical observations, however, only focus on visible reactions of the patient to various stimuli. As explained in chapter 4.3 the lack of motor movements does not imply the lack of awareness and consciousness. The recording of EEG seems promising but usually a resting state EEG is applied, solely focusing on general activity and leaving out specific reactions in response to distinct stimuli. Thus, diagnostic procedures as reported by the clinicians in the present study are subject to several constraints potentially leading to diminished discriminatory power.

The study was conducted to obtain an overview on the opinion and requirements of practitioners regarding an ERP-based diagnostic system. It is limited by the small amount of participants. Timetables of medical directors and chief physicians are busy and thus, recruitment of a larger number of interviewees was not possible. Furthermore, the present results provide a general idea on the topic but no detailed requirements analysis which would also include the interrogation of different experts including nurses and therapists, different use cases, and the implementation of a prototype.

To conclude, a practical, reliable and valid EEG-based diagnostic tool would be highly welcome in clinical and rehabilitative routine, affirming general hypothesis a) introduced in chapter 4.5. Thus, the ERP-based paradigms to delineate the level of consciousness and cognitive function in otherwise non-responsive patients need to be validated such that only the most reliable and informative paradigms are applied when time is limited.

6 Study 2 – Event-related potentials in non-responsive patients

A part of the data presented in the following study is about to be published elsewhere (Real et al., 2015). For the present study, the data were re-analyzed.

6.1 Study aims

Study 1 revealed a general interest of practitioners working with DOC patients in the complementation of diagnostic procedures by ERP measures. The assessment of specific brain reactions in response to certain stimuli can deliver important information on the state of awareness and the prognosis of the patient. Study 2 connects to these findings and investigates the elicitation of ERPs in low- and non-responsive patients diagnosed with UWS or MCS.

The present study was conducted to answer four topics. Firstly, it shall be clarified, how many patients in UWS or MCS show ERPs in general. Secondly, the pattern of arising ERPs is compared to the hierarchical approach as pointed out in 4.3.1. Thirdly, the number of ERPs from a passive task will be compared to the number of ERPs in a focused task. Fourthly, it is investigated if there is a connection between behavioral measures and emerging ERPs.

It is predicted that at least some patients in UWS and MCS show ERPs in response to auditory stimulation (Kotchoubey et al., 2005). Further, ERPs are expected to be smaller, delayed and, potentially, reversed in polarity (Perrin et al., 2006; Pokorny et al., 2013). In addition, it is predicted that the focused task leads to a higher number of arising ERPs in comparison to the passive task (Bennington & Polich, 1999).

6.2 Methods

6.2.1 Participants

EEG was recorded in 19 DOC patients (11 males) at the Clinic for Intensive Care in Schwaig and Hersbruck in Bavaria/Germany. The patients were between 31 and 69 years old (*M* = 50.74, *SD* = 13.75 years) and all measurements were undertaken at bedside. The patients had been suffering a DOC for at least 2 months and for at most 192 months (*M* = 76.95, *SD* = 48.13 months). Written informed consent was given by the legal representatives of the patients after they were informed about the nature of the study. Sixteen patients were examined twice within an interval of two to eight weeks. The remaining three could not be visited a second time due to an alloyed health status. Right before each measurement, the Coma Recovery Scale revised (CRS-R; Giacino, Kalmar, & Whyte, 2004) was carried out. The study was conducted in accordance to the Declaration of Helsinki and was approved by the Ethical Review Board of the University Hospital Würzburg. Important demographic data of all patients enrolled in the study are listed in Table 1.

Table 1: Demographic data of the patient sample in study 2: Sex (f-female, m-male), age at the time of measurement, CRS scores at the first (t1) and second (t2) measurement, if applicable, short diagnosis, and months since onset.

code	sex	age	CRS t1	CRS t2	diagnosis	months since onset
P01	f	47	3	4	hypoxia	192
P02	m	50	12	6	bleeding basal ganglia	63
P03	m	58	0	0	bleeding basal ganglia	30
P04	m	35	3	4	trauma	82
P05	m	69	3	2	hypoxia	56
P06	f	59	13	13	hypoxia	39
P07	f	53	2	N/A	hypoxia	2
P08	f	31	3	2	hypoxia	119
P09	f	66	6	1	hypoxia	135
P10	m	30	4	4	trauma	44
P11	f	52	22	N/A	hypoxia	80
P12	m	32	2	N/A	hypoxia	112
P13	m	26	3	4	hypoxia	77
P14	f	63	14	6	Guillain-Barré syndrome	40
P15	f	64	6	4	intracerebral bleeding	141
P16	m	52	5	2	hypoxia	68
P17	m	61	5	4	meningitis	8
P18	m	66	3	5	trauma	70
P19	m	50	3	6	ischemic stroke	104

6.2.2 Experimental procedure and stimuli

The experiment comprised four paradigms that were named according to the ERP they aimed to elicit: MMN Duration, P300, N400 Words, and N400 Sentences. The MMN Duration paradigm comprised 1000 three-component harmonic sounds of 440+880+1760 Hz, with 900 standard stimuli with a duration of 50 ms and 100 deviant stimuli with a duration of 20 ms. The stimulus onset asynchrony (SOA) between the onset of two successive tones was 350 ms. The first five tones were always standards and a deviant was always followed by a standard. The P300 paradigm comprised 480 three-component harmonic tones of which 420 were standards with a frequency of 440+880+1760 Hz and 60 were deviants with a frequency of 247+494+988 Hz. The SOA in the P300 paradigm was 900 ms. All tones had a 5 ms rise and 5 ms fall-time and lasted 50 ms.

The N400 Words paradigm comprised 100 semantically related (i.e. mountain-valley) and 100 semantically unrelated word-pairs (i.e. place-bravery), resulting in 400 words altogether. The inter-stimulus interval (ISI) was 300 ms within and 1200 ms between the word-pairs. The word-pairs were defined in a pre-experiment in which 45 participants rated the relation of various word-pairs. Only related word-pairs with a prime strength above 90% and unrelated word-pairs with a prime strength below 10% were selected for the resulting paradigm. The same words were used for the related and unrelated condition, such that each word was presented twice.

The N400 Sentences paradigm comprised 200 short sentences of which 100 ended with an incorrect word (e.g., “The eel is a bird.”) and 100 with a correct word (e.g., “The eel is a fish.”). The ISI between the sentences was 1200 ms. The sentences were selected in the same pre-experiment as the word-pairs. The participants rated the sentences as correct or incorrect and only sentences which were rated with a certainty above 90% were included. All correct end words also appeared as incorrect end words. All stimuli were spoken by a young female

German native speaker with a clear voice free of any dialect inflexion. All sounds in the semantic paradigms had a sampling rate of 44.1 kHz, a resolution of 32 bits and were presented at a sound level of 70 dB.

Each paradigm was presented once with the following passive instruction given in German: “You will now hear a tone sequence including one frequent and one rare tone/a list of word-pairs of which some belong together and some do not/a list of sentences of which some make sense and some do not. Please listen.” In addition, the P300 paradigm was presented a second time with the following focused instruction: “You will now hear a tone sequence including one frequent and one rare tone. Please count the rare tone. If you miscount, just restart with one again.” Thus, for P300, there was one passive and one focused task. All paradigms were presented within a single session with breaks in-between. Absolute recording time was approximately 45 minutes. Paradigms were presented in a pseudorandom order, such that the P300 passive task always preceded the P300 focused task.

All auditory stimuli were presented via pneumatic transducer in-ear headphones (3M™ E-A-RTONE™ Insert Earphone 3A ABR, 50 ohm) equipped with foam eartips (Etymotic research, inc., eartips for ER-3 & ER-5).

6.2.3 Material and data acquisition

EEG was recorded according to the international 10-20 system with a g.tec system and g.recorder (g.tec, Graz, Austria) using 31 Ag/AgCl active electrodes at the following scalp sites: F8, F4, Fz, F3, F7, FC6, FC2, FC1, FC5, T8, C4, Cz, C3, T7, CP6, CP2, CP1, CP5, P8, P4, Pz, P3, P7, O2, O1, and on the left and right mastoids. The ground electrode was placed at AFz and the data were online referenced to the nose. Four additional electrodes were attached to the two external canthi, as well as above and below the right eye, to monitor eye movements (EOG). The EEG and EOG had a sampling rate of 500 Hz and were online band-pass filtered between 0.01 Hz and 250 Hz.

6.2.4 Data pre-processing and analysis

Pre-processing and analysis of EEG data were carried out in Brain Vision Analyzer, Version 2.0.4.368 (Brain Products GmbH, Gilching, Germany). Statistical calculations were performed in SPSS 17.0 (SPSS Inc., IL).

The EEG data were re-referenced to the linked mastoids and offline band-pass filtered between 0.1 and 25 Hz (time constant 15.91549, 12 dB/oct). The ocular channels were bipolarized into vertical and horizontal EOG. Furthermore, epochs were created from -100 to 500 ms for the MMN Duration paradigm, from -200 to 800 ms for the P300 paradigms and from -200 to 1000 for the N400 paradigms. Time windows from -100 to 0 ms for the MMN Duration paradigm and -200 to 0 for the P300 and N400 paradigms were used as a baseline. Eye movement artefacts were corrected using a regression-based procedure (Gratton, Coles, & Donchin, 1983) and all trials containing signal changes of ± 100 µV were excluded from further analysis. Finally, grand averages were obtained for each patient. A paradigm was only included into analysis when at least 50 % of the trials remained after pre-processing.

In all paradigms, difference waves were obtained by subtracting the standards(related word-pairs/correct sentences from the deviants/unrelated word-pairs/incorrect sentences. The relevant time windows for all analyses were defined for each patient and paradigm individually. First, local negative maxima were automatically detected in the time intervals from 100 to 300 ms for MMN Duration, and from 300 to 800 ms for N400 Words and Sentences. Local positive maxima were automatically detected from 250 to 700 ms for P300. Subsequently, mean amplitudes under the curve in an interval of 100 ms (MMN Duration) or 200 ms (P300, both N400 paradigms) around that peak were exported. For statistical analyses, the mean amplitudes of the scalp electrodes F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 were selected.

For each patient, t-tests comparing the mean amplitudes to zero were conducted for all nine electrode sites to detect the elicitation of a component. In a second step, repeated measures ANOVAs including the factors stimulus (standard vs. deviant), region (frontal, central, parietal), and laterality (left, middle, right) were conducted. For all ANOVAs, the Greenhouse-Geisser corrected results are reported (Greenhouse & Geisser, 1959) since the assumption of sphericity was violated in all the analyses and values of epsilon were smaller than .75, which is the recommended threshold for application of the Greenhouse-Geisser correction (Girden, 1992). All averages of each patient were screened visually for ERPs distinguishing standards from deviants, independently from the results of statistical analyses.

Every paradigm aimed at the elicitation of a certain ERP. However, in patients, also unexpected ERPs may arise, i.e. N400 or P600 in response to semantic violations (Neumann & Kotchoubey, 2004) or MMN in classical P300 paradigms (Pokorny et al., 2013). Therefore, each waveform was carefully inspected visually and, if necessary, re-analyzed.

6.3 Results

Altogether, 35 datasets from 19 patients were processed. However, the data of the second measurement of P14 had to be excluded due to a poor signal-to-noise ratio, resulting in 34 datasets that entered statistical and visual analyses.

6.3.1 MMN Duration

Table 2 lists all statistically significant or marginally significant effects, the results of t-tests and ANOVAs, and findings from the visual inspection.

Table 2: Summary of the statistical and visual analysis in all patients for the MMN Duration paradigm. The table includes results from *t*-test against zero and from the ANOVA including the factor stimulus. It lists significant ($p \leq .05$) and marginally significant ($p \leq .10$) results.

patient	time	*t*-test	ANOVA	visual inspection
P03	t2	-	stimulus*region*laterality $F(4, 368) = 2.76$, $p = .054$	no distinct deflection
P04	t2	Cz ($p = .069$)	stimulus*region $F(2, 184) = 3.85$, $p = .036$	no distinct deflection
P06	t1	Cz ($p = .061$)	stimulus *laterality	no distinct deflection

			F(2, 180) = 2.86, *p* = .075 stimulus*region*laterality *F*(4, 360) = 2.28, *p* = .078	
P10	t2	Cz (*p* = .023) C3, C4 (*p* ≤ .066)	stimulus *F*(1, 89) = 3.38, *p* = .069	no distinct deflection
P11	t1	Fz, C4 (*p* ≤ .045) F3 (*p* = .065)	-	negative deflection (frontal and central 100-200 ms)
P13	t2	-	stimulus*laterality *F*(2, 186) = 4.02, *p* = .020	no distinct deflection
P15	t2	-	stimulus* laterality *F*(2, 198) = 3.95, *p* = .039	no distinct deflection
P16	t2	F3, Fz, C3, Cz, P3, Pz (*p* ≤ .041)	stimulus *F*(1, 99) = 7.32, *p* = .008 stimulus*laterality *F*(2, 168) = 7.02, *p* = .006	no distinct deflection
P17	t1	F3, Fz, (*p* ≤ .049) C3, F4 (*p* ≤ .097)	stimulus *F*(1, 99) = 3.11, *p* = .081 stimulus*region *F*(2, 198) = 2.78, *p* = .091	negative deflection (frontal, central, 150-300 ms)
P18	t2	P4, C4 (*p* ≤ .049) F4 (*p* = .096)	stimulus *F*(1, 92) = 3.20, *p* = .077 stimulus*laterality *F*(2, 184) = 4.36, *p* = .028	no distinct deflection
P19	t2	-	stimulus*region *F*(2, 160) = 2.84, *p* = .081	no distinct deflection

In five patients (P10, P11, P16, P17, P18), a deflection significantly different from zero at one or more of the nine electrodes was elicited. In two more patients a marginally significant difference from zero in the t-tests (P04, P06) was detected. In five patients, ANOVA analysis revealed significant (P04, P13, P15, P16, P18) and in five more marginally significant (P03, P06, P10, P17, P19) results. In all patients, significant or marginally significant results were only present at one of the two measurements, except from P11 who could only be examined once in total. However, these statistical indicators of an ERP were only supported by visual analysis in two patients (P11, P17). In the other patients, significant statistics stem from predominant drifts, artifacts or other oscillations that cannot be classified as an ERP. Exemplary figures of the recorded brain signals are included in Appendix B. Figure 2 and Figure 3 depict the negative deflections in P11 and P17 revealed by visual analyses. They could be interpreted as an MMN. In P11, the ANOVA did not deliver a significant result which could be due to a large standard deviation of the curves.

In three patients, amplitudes elicited by deviants were positive and amplitudes elicited by standards were negative, indicating a reversed potential (P06, P10, P16). Also in three patients amplitudes elicited by deviants were negative, amplitudes elicited by standards were positive (P17, P13, P18). In another three patients, both, amplitudes elicited by deviants and standards were positive (P03, P13, P19). In one patient, both, amplitudes elicited by deviants and standards were negative (P04).

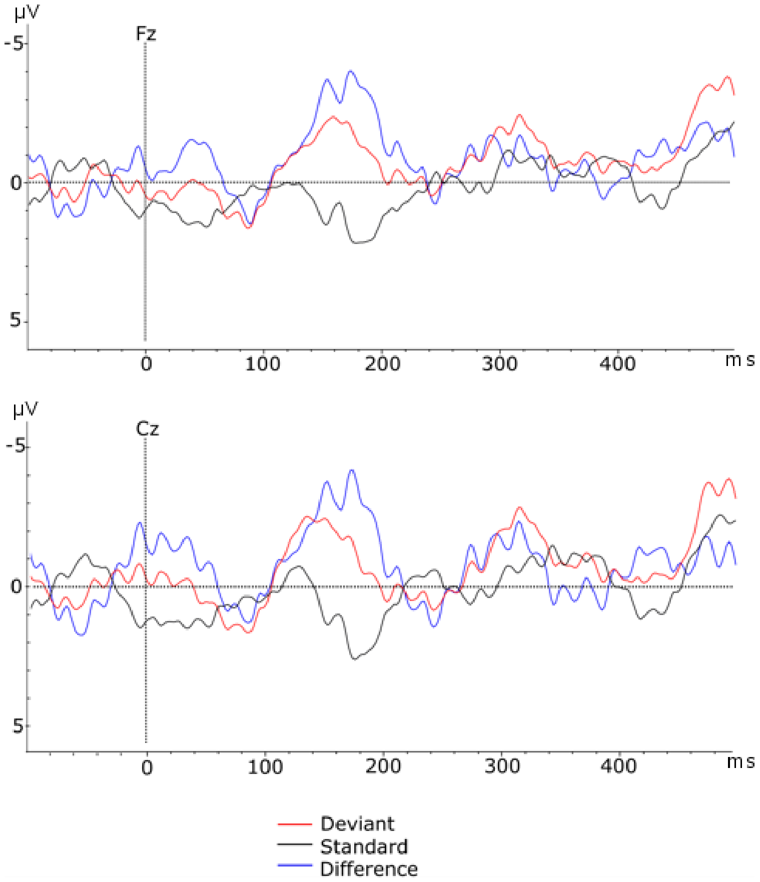

Figure 2: Distinct negative deflection elicited in the MMN Duration paradigm in P11 (t1) at Fz and Cz between 100 and 200 ms.

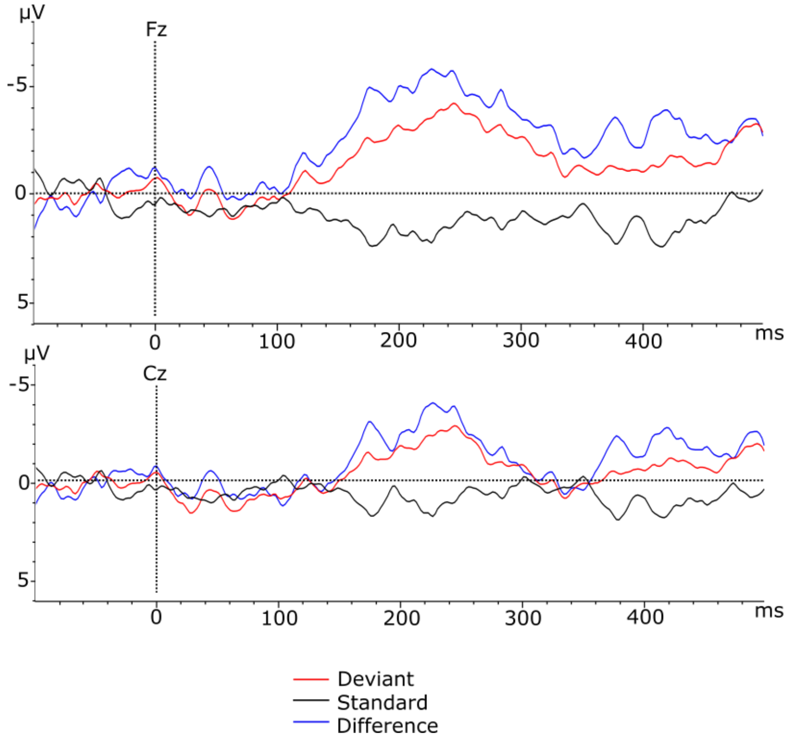

Figure 3: Distinct negative deflection elicited in the MMN Duration paradigm in P17 (t1) at Fz and Cz between 150 and 300 ms.

6.3.2 P300

6.3.2.1 Passive task

In the P300 paradigm with the passive instruction, data from P01 at t1, and P06 and P08 at t2 could not be analyzed due to an insufficient number of trials after pre-processing. Thus, 31 datasets from 19 patients entered analyses. Table 3 lists all statistically significant or marginally significant results of t-tests and ANOVAs, and findings from the visual inspection.

In four patients (P05, P15, P16, P18), a deflection significantly different from zero at one or more of the nine electrodes was elicited. In all four patients, these significant results were only present at one of the two measurements. In six more patients, there was a marginally significant difference from zero in the t-tests. In three patients, only one measurement revealed marginally significant deflections in the t-tests (P03, P04, P10). In three patients, only one dataset entered analyses from the start (P07, P08, P11) because only one measurement could be undertaken. In one patient, only one measurement revealed significant results while the other one remained inconclusive (P17).

Table 3: Summary of the statistical and visual analysis in all patients for the P300 paradigm with the passive task. The table lists results from *t*-test against zero and the ANOVA including the factor stimulus. It lists significant ($p \leq .05$) and marginally significant ($p \leq .10$) results.

patient	time	*t*-test	ANOVA	visual inspection
P02	t1	-	stimulus*region*laterality $F(4, 224) = 2.20, p = .086$	negative deflection (frontal, central, 300-500ms
	t2	-	stimulus*laterality $F(2, 96) = 3.93, p = .042$	no distinct deflection
P03	t1	-	stimulus*laterality $F(2, 70) =4.45, p = .027$	no distinct deflection
	t2	F3, P4 ($p \leq .085$)	stimulus*region $F(2, 94) =5.08, p = .020$ stimulus*laterality $F(2, 94) = 5.79, p = .009$	no distinct deflection
P04	t1	F3 ($p = .080$)	-	no distinct deflection
	t2	-	stimulus*laterality $F(2, 98) = 3.95, p = .031$	no distinct deflection
P05	t2	all P ($p \leq .044$)	stimulus*region $F(2, 102) = 3.55, p = .059$	no distinct deflection, but parietal drift
P07	t1	all F ($p \leq .098$)	-	negative deflection (frontal, central, 50-150ms)
P08	t1	P4 ($p = .051$)	stimulus*region*laterality $F(4, 236) = 2.54, p = .092$	no distinct deflection
P10	t1	-	-	no distinct deflection
	t2	F3 ($p = .052$)	stimulus*laterality $F(2, 106) = 3.18, p = .063$	no distinct deflection
P11	t1	-	stimulus*region $F(2, 66) = 2.55, p = .091$	no distinct deflection
P15	t1	Pz, P4 ($p \leq .046$)	-	no distinct deflection
P16	t2	Pz ($p = .039$) P3, P4 ($p \leq .060$)	-	no distinct deflection
P17	t1	F3 ($p = .095$)	-	no distinct deflection
P18	t1	F4, C4 ($p \leq .010$) P3 ($p = .053$)	stimulus*region $F(2, 106) =4.95, p = .022$ stimulus*laterality $F(2, 106) =16.77, p = .000$	no distinct deflection

In four patients, ANOVA analyses revealed significant (P02 at t2, P03, P04 at t2, P18) and in five patients (P02 at t1, P05, P08, P10 at t2, P11) marginally significant results. In seven patients (P04, P05, P10, P15, P16, P17, P18), significant or marginally significant results were only present at one of the two measurements. In two patients (P02, P03), both measurements revealed significant or marginally significant results. From three patients (P07, P08, P11) only one dataset was included in the analysis from the start.

The statistical indicators of an ERP in 11 patients were supported by the results of visual inspection in only two. In the other patients, significant statistics stem from predominant drifts, artifacts or other oscillations that cannot be classified as an ERP. Exemplary figures of the recorded brain signals are included in Appendix B. In P02, a distinct long-drawn negative deflection between 300 and 500 ms over frontal and central sites was noticeable at t1 (Figure 4). It remains unclear whether it constitutes a reversed P300, a late MMN or a different kind of brain response. In P07, a negative deflection at about 50-150 ms was elicited by deviants and standards that could be interpreted as N1.

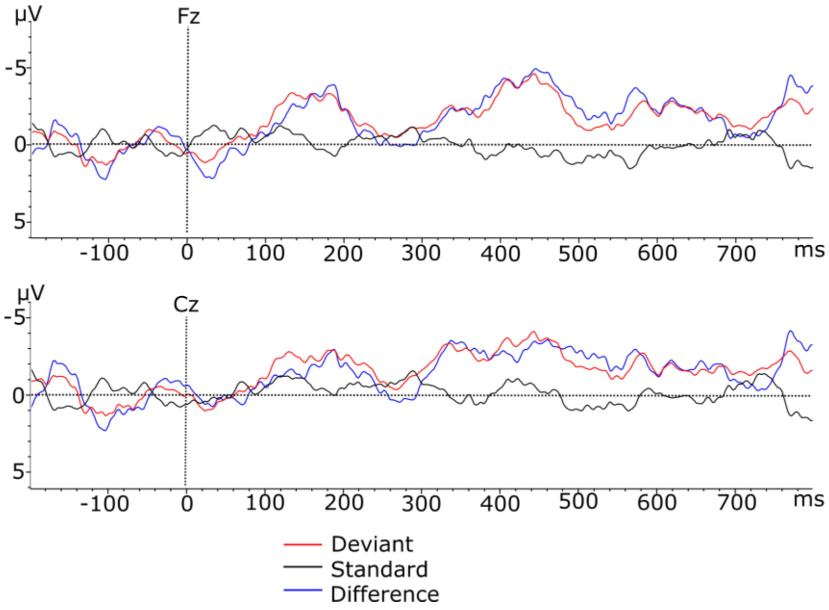

Figure 4: Distinct negative deflection elicited in the P300 paradigm with the passive task in P02 (t1) at Fz and Cz between 300 and 500 ms.

In two patients, amplitudes elicited by deviants were positive and amplitudes elicited by standards were negative (P11, P15). In six datasets from five patients, amplitudes elicited by deviants were negative and amplitudes elicited by standards were positive (P04 both, P05, P08, P10 t1, P17). In six datasets from five patients, both amplitudes were positive (P02 t2, P03 both, P10 t2, P16, P18,) and in one patient, both amplitudes were negative (P02 t1).

6.3.2.2 Focused task

In the P300 paradigm with the focused task, data from P01 and P19 at t1, and P06 and P10 at t2 could not be analyzed due to an insufficient number of trials after pre-processing. Thus, 30 datasets from 19 patients entered analyses. Table 4 lists all statistically significant or marginally significant results of t-tests and ANOVAs, and findings from the visual inspection.

Table 4: Summary of the statistical and visual analysis in all patients for the P300 paradigm with the focused task. The table lists the *t*-test against zero and the ANOVA including the factor stimulus with significant ($p \leq .05$) and marginally significant ($p \leq .10$) results.

patient	time	*t*-test	ANOVA	visual inspection
P02	t1	Cz, C4 ($p \leq .083$)	-	no distinct deflection
	t2	Pz ($p = .040$) P3 ($p = .096$)	-	no distinct deflection
P03	t1	-	stimulus*region*laterality $F(4, 128) = 2.41$, $p = .097$	no distinct deflection
	t2	F4 ($p = .053$)	stimulus*region $F(2, 92) = 2.99$, $p = .084$ stimulus*laterality $F(2, 92) = 2.66$, $p = .095$	positive deflection, double peak (frontal, 250-700 ms)
P05	t1	F3 ($p = .089$)	-	no distinct deflection
	t2	Cz ($p = .025$)	stimulus $F(1, 53) = 5.48$, $p = .023$	positive deflection (frontal, central, 400-600 ms)
P09	t1	all F and C ($p \leq .016$) Pz ($p = .088$)	stimulus*region $F(2, 104) = 4.90$, $p = .030$	no distinct deflection
P13	t2	Fz, F4 ($p \leq .097$)	stimulus $F(1, 48) = 3.18$, $p = .081$	no distinct deflection
P14	t1	C3, P3, Pz ($p \leq .048$) Cz ($p = .054$)	stimulus $F(1, 28) = 5.02$, $p = .033$	no distinct deflection
P15	t1	Fz, all C ($p \leq .080$)	-	no distinct deflection
	t2	Pz ($p = .091$)	-	no distinct deflection
P16	t2	P3, Pz ($p \leq .034$) Cz ($p = .068$)	-	no distinct deflection
P17	t2	-	-	negative deflection (frontal, central, 250-350 ms)
P18	t1	-	stimulus*region*laterality $F(4, 208) = 4.26$, $p = .015$	no distinct deflection
P19	t2	C4 ($p = .076$)	stimulus $F(1, 47) = 3.86$, $p = .055$	no distinct deflection

In five patients (P02, P05, P09, P14, P16), a deflection significantly different from zero at one or more of the nine electrodes was elicited. In six more patients a marginally significant deflection different from zero in the t-tests. In two of those, the other measurement had already shown significant results (P02, P05), in one patient, both measurements revealed marginally significant deflections (P15) and in three patients, only one measurement revealed marginally significant deflections (P03, P13, P19).

In five patients, ANOVA analyses revealed significant (P05, P09, P14, P18) and in three more (P03 at t1 and t2, P13, P19) marginally significant results. In six patients (P09, P13, P14, P16, P17, P18), significant or marginally significant results were only present at one of the two measurements. In four patients (P02, P03, P05, P15), both measurements revealed significant or marginally significant results. In one patient (P19) only one dataset was included in the analysis from the start. However, these statistical indicators of an ERP in 10 patients altogether were supported by visual analysis in only three (P03, P05, P17). In the other patients, significant statistics stem from drifts, artifacts or other oscillations that cannot be classified as an ERP. In two patients, amplitudes elicited by deviants were positive and amplitudes elicited by standards were negative (P11, P15). In six datasets from five patients, amplitudes elicited by deviants were negative and amplitudes elicited by standards were positive (P04 both, P05, P08, P10 t1, P17). In six datasets from five patients, both amplitudes were positive (P02 t2, P03 both, P10 t2, P16, P18,) and in one patient, both amplitudes were negative (P02 t1).

Figure 5 depicts the distinct positive deflection at Fz and Cz in P03, which could be interpreted as a P300. In P17, a negative deflection between 250 and 350 ms was detected instead of the expected positive P300. Re-analysis of the data in that time window did not reveal any significant effect. Also in P04, visual inspection revealed a positive deflection between 350 and 450 ms, that was not supported by statistical re-assessment.

In eight datasets from six patients, amplitudes elicited by deviants were positive and amplitudes elicited by standards were negative (both from P02, P03 t2, P05, P13, P14, both from P15). In one patient, amplitudes elicited by deviants were negative and amplitudes elicited by standards were positive (P09). In two patients, both amplitudes were positive (P16, P19) and in one patient, both amplitudes were negative (P03 t1).

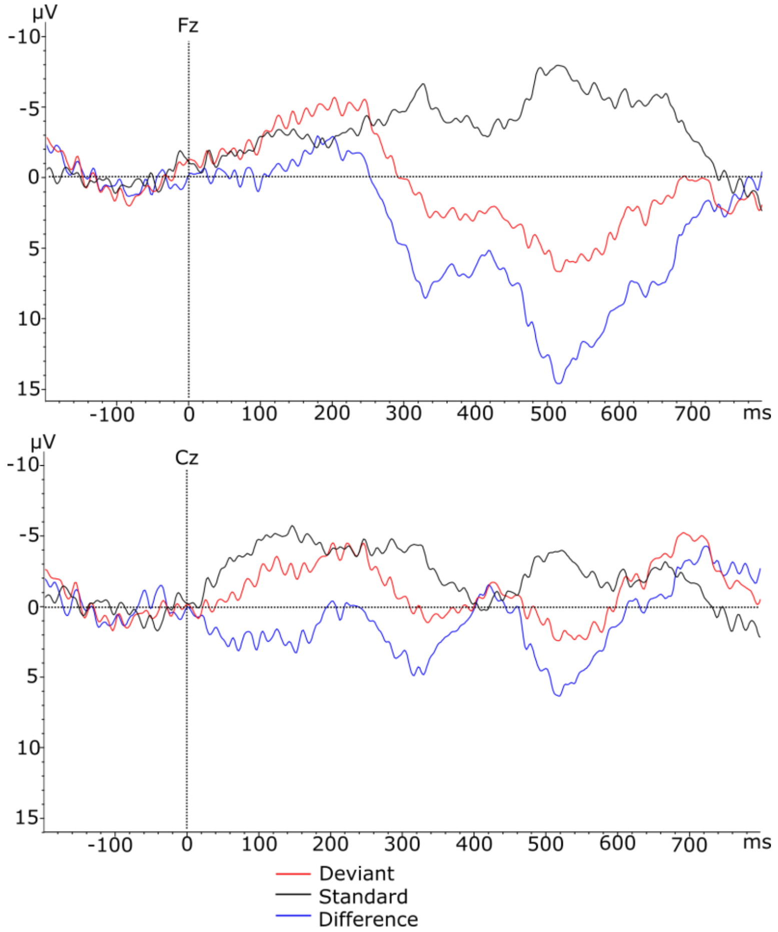

Figure 5: Distinct positive deflection elicited in the P300 paradigm with the focused task in P03 (t2) at Fz and Cz between 250 and 700.

6.3.3 N400 Words

In the N400 Words paradigm, data from P01 at t1, from P06 at t2, respectively, and from P07 and P19 could not be analyzed due to an insufficient number of trials after pre-processing. Thus, 29 datasets from 17 patients entered analyses. Table 5 lists all statistically significant or marginally significant results of t-tests and ANOVAs, and findings from the visual inspection.

In six patients (P03, P04 t2, P05 t1, P06, P13, P16 t2), a deflection significantly different from zero at one or more of the nine electrodes was elicited. In three patients there was a marginally significant difference from zero in the t-tests (P05 t2, P08, P16 t1). In two of those, the other measurement had already shown significant results (P05, P16).

Table 5: Summary of the statistical and visual analysis in all patients for the N400 Words paradigm. The table includes results from *t*-test against zero and from the ANOVA including the factor stimulus. It lists significant ($p \leq .05$) and marginally significant ($p \leq .10$) results.

patient	time	*t*-test	ANOVA	visual inspection
P02	t1	-	stimulus*region*laterality $F(4, 234) = 4.42$, $p = .008$	no distinct deflection
P03	t1	all F ($p \leq .036$)	stimulus $F(1, 57) = 4.38$, $p = .041$	no distinct deflection
P04	t1	-	stimulus*region*laterality $F(4, 384) = 2.57$, $p = .057$	no distinct deflection
	t2	F3, F4 ($p \leq .050$)	-	no distinct deflection
P05	t1	P3 ($p = .020$) Pz ($p = .079$)	stimulus*region $F(2, 162) = 3.08$, $p = .080$	no distinct deflection
	t2	C3 ($p = .051$)	stimulus*laterality $F(2, 128) = 2.67$, $p = .083$	no distinct deflection
P06	t1	all F, all C ($p \leq .043$)	stimulus $F(1, 85) = 5.44$, $p = .022$ stimulus*region $F(2, 170) = 3.35$, $p = .062$	negative deflection (frontal, central, parietal, 50-150ms)
P08	t1	P3 ($p = .094$)	-	no distinct deflection
P13	t1	Fz ($p = .003$) C3 ($p = .080$)	stimulus*region $F(2, 156) = 3.59$, $p = .044$ stimulus*region*laterality $F(2, 156) = 3.97$, $p = .024$	no distinct deflection
P16	t1	Pz, P4 ($p \leq .099$)	stimulus $F(1, 87) = 3.13$, $p = .080$	no distinct deflection
	t2	P3, Pz ($p \leq .016$)	stimulus*laterality $F(2, 182) = 5.05$, $p = .012$ stimulus*region*laterality $F(4, 364) = 2.33$, $p = .076$	no distinct deflection
P18	t1	-	stimulus*region $F(2, 172) = 3.00$, $p = .078$	no distinct deflection

In five patients, ANOVA analyses revealed significant (P02, P03, P06, P13, P16) and in four patients (P04, P05, P16, P18) marginally significant results. In six patients (P02, P03, P04, P06, P13, P18), significant or marginally significant results were only present at one of the two measurements. In two patients (P05, P16), both measurements revealed significant or marginally significant results. From one patient (P06) only one dataset was included in the analysis because no second measurement was undertaken. However, these statistical indicators of an ERP in nine patients altogether were not supported by visual analysis in any of them with the exception of P06 who exhibited a negative deflection between 50-150 ms over all channels. The effect was elicited by deviants and standards and could be interpreted as N1. Brain signals from P06 and one more example are depicted in Appendix B. In the other patients, significant statistics stem from predominant drifts, artifacts or other oscillations that cannot be classified as an ERP.

In four datasets from three patients, amplitudes elicited by deviants were positive and amplitudes elicited by standards were negative (P02, both from P04, P06). In three patients, respectively, amplitudes elicited by deviants were negative and amplitudes elicited by standards were positive, both amplitudes were positive (P05 t1, P13, P16 t2), and both amplitudes were negative (P03 t2, P05 t1, P18).

6.3.4 N400 Sentences

In the N400 Sentences paradigm, data from P01 at t1, from P02, P03, P06, P10, P13, and P19 at t2, respectively, and from P07 and P14 could not be analyzed due to an insufficient number of trials after pre-processing. Thus, 25 datasets from 17 patients entered analyses. Table 6 lists all statistically significant or marginally significant results of t-tests and ANOVAs, and findings from the visual inspection.

In five datasets from four patients (both from P05, P12, P13, P17), a deflection significantly different from zero at one or more of the nine electrodes was elicited. In three patients there was a marginally significant difference from zero in the t-tests (P09, P11, P15).

In six datasets from five patients, ANOVA analyses revealed significant (P03, both from P05, P08, P15, P17) and in three patients (P03, P06, P13) marginally significant results.

In five patients (P08, P09, P15, P17, P18), significant or marginally significant results were only present at one of the two measurements. In one patient (P05), both measurements revealed significant or marginally significant results. From five patients (P03, P06, P11, P12, P13) only one dataset was included in the analysis from the start.

Table 6: Summary of the statistical and visual analysis in all patients for the N400 Sentences paradigm. The table includes results from *t*-test against zero and from the ANOVA including the factor stimulus. It lists significant ($p \leq .05$) and marginally significant ($p \leq .10$) results.

patient	time	*t*-test	ANOVA	visual inspection
P03	t1	-	stimulus*region *F*(2, 122) = 2.63, *p* = .084	no distinct deflection
P05	t1	Fz, F4 (*p* ≤ .029) C4, P3, P4 (*p* ≤ .088)	stimulus*region *F*(2, 166) = 4.24, *p* = .022	positive deflection (frontal, 500-800 ms)
	t2	Fz, F4 (*p* ≤ .048) F3 (*p* = .097)	stimulus*region *F*(2, 136) = 4.14, *p* = .042	positive deflection (frontal, central, 200-600 ms)
P06	t1	-	stimulus*laterality *F*(2, 154) = 2.64, *p* = .078	no distinct deflection
P08	t1	-	stimulus*laterality *F*(2, 174) = 3.54, *p* = .044 stimulus*region*laterality *F*(4, 348) = 3.24, *p* = .050	no distinct deflection
P09	t1	Fz (*p* = .073)	-	no distinct deflection
P11	t1	Pz (*p* = .088)	-	no distinct deflection
P12	t1	all P (*p* ≤ .028)	-	no distinct deflection
P13	t1	C3 (*p* = .028) F3, Cz (*p* ≤ .093)	stimulus *F*(1, 82) = 2.79, *p* = .098	no distinct deflection
P15	t1	P3, Pz (*p* ≤ .070)	stimulus*region*laterality *F*(4, 200) = 3.42, *p* = .040	no distinct deflection
P17	t2	F4, all C, all P (*p* ≤ .044) F3, Fz (*p* ≤ .069)	stimulus *F*(1, 92) = 8.45, *p* = .005	no distinct deflection
P18	t2	-	-	positive deflection (frontal, central, parietal, 200-600 ms)

These statistical indicators of an ERP in ten patients altogether were only supported by visual analysis in two patients. In the other patients, significant statistics stem from predominant drifts, artifacts or other oscillations that cannot be classified as an ERP. Exemplary figures of the recorded brain signals are included in Appendix B. Patient P05 exhibited a distinct positive deflection over frontal sites in both measurements that could be interpreted as a P600.

The deflection elicited at t1 is depicted in Figure 6. P18 exhibited a distinct positive deflection over all sites that could be interpreted as a P300 (Figure 7). No N400 was observed.

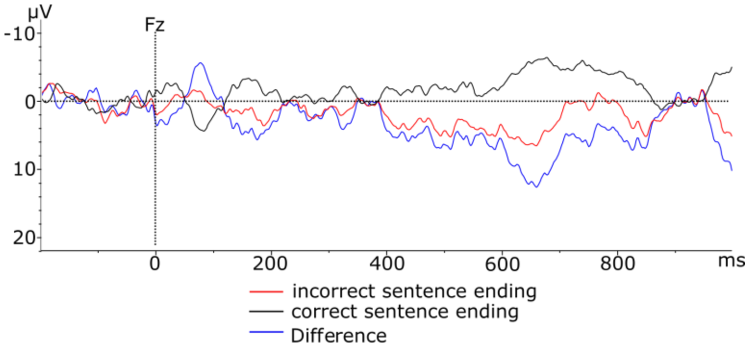

Figure 6: Distinct positive deflection elicited in the N400 Sentences paradigm in P05 (t1) at Fz between 400 and 800 ms.

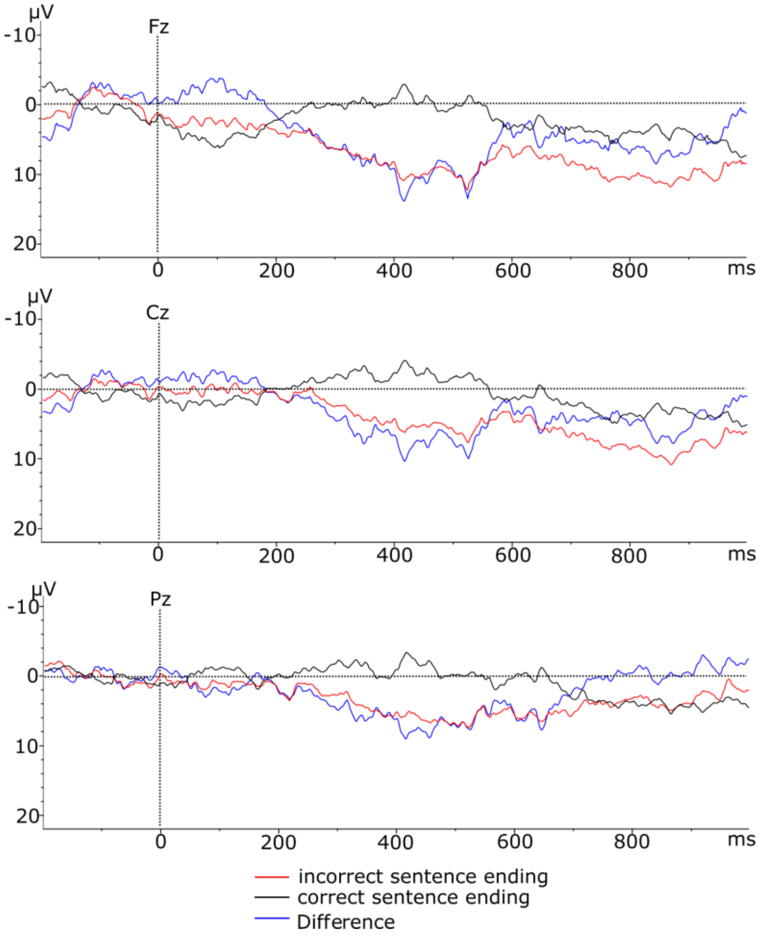

Figure 7: Distinct positive deflection elicited in the N400 Sentences paradigm in P18 (t2) at Fz, Cz, and Pz between 200 and 600 ms.

In three datasets from two patients, amplitudes elicited by deviants were positive and amplitudes elicited by standards were negative (both from P05, P18), indicating a reversed potential. In two patients amplitudes elicited by deviants were negative, amplitudes elicited by standards were positive (P09, P17). In six patients, both, amplitudes elicited by deviants and standards were negative (P03, P06, P08, P11, P12, P15), and in one patient, both amplitudes were positive (P13).

6.3.5 CRS and ERPs

The CRS comprised assessment in six domains (auditory, visual, motor, verbal, communication, arousal) with 23 tasks and observations in total. Eleven of the checkpoints indicate MCS and two indicate emergence from MCS. Two patients exhibited signs for MCS at one time of measurement (P09 t1, P14 t1). Two more patients exhibited signs for emergence from MCS at one time of measurement (P02 t1, P11 t1). One patient exhibited signs for emergence from MCS in the first measurement and signs for MCS in the second one (P06). In all of these six datasets, statistically significant results were found and in four of them, visual analyses revealed some kind of ERP, albeit no semantic one. In turn, however, the two patients who exhibited two ERPs within one single measurement (P05 at t2, P18 at t2) had relatively low CRS scores of 2 and 5, respectively, at that time. None of those patients with two ERPs exhibited signs of MCS or emergence from MCS.

6.3.6 Summary

Table **7** summarizes the presented results and gives an overview in which of the patients statistically significant or marginally significant results or visually distinct components were found.

Table 7: Summary of the statistical and visual results for all patients. For each dataset of each patient, it is listed, if t-tests (t), ANOVA (F) or visual inspection (v) indicated the existence of a component. For visual inspection, v is written in brackets, if the found component differed from the expected one. The symbol # is added if the statistical result was only marginally significant. Grey fields mark datasets that were excluded.

patient	time	MMN Duration	P300 passive	P300 focused	N400 Words	N400 Sentences
P01	t1		▨	▨	▨	▨
	t2					
P02	t1		F#, (v)	t#	F	
	t2		F	t		▨
P03	t1		F	F#	t, F	F#
	t2	F#	t#, F	t#, F#, v		▨
P04	t1		t#		F#	
	t2	t#, F	F		t	
P05	t1			t#	t, F#	t, F, (v)
	t2		F	t, F, v	t#, F#	t, F, (v)
P06	t1	t#, F#			t, F, (v)	F
	t2		▨	▨	▨	▨
P07	t1		t#, F#, (v)		▨	▨
P08	t1		t#, F#		t#	
	t2		▨			
P09	t1			t, F		t#
	t2					
P10	t1					
	t2	t, F#	t#, F#	▨		▨
P11	t1	t, v	F#			t#
P12	t1					t
P13	t1				t, F	t, F#
	t2	F		t#, F#		▨
P14	t1			t, F		▨
P15	t1		t	t#		t#, F
	t2	F		t#		
P16	t1				t#, F#	
	t2	t, F	t	t	t, F	
P17	t1	t, F#, v	t#			
	t2			(v)		t, F
P18	t1		t, F	F	F#	
	t2	t, F, v				(v)
P19	t1			▨		
	t2	F#		t#, F#	▨	▨

6.4 Discussion and summary

The goal of the present study was to investigate the elicitation of ERPs in DOC patients and to study the effect of differential attentional instructions on P300. Auditory stimulation through oddball and semantic paradigms lead to the elicitation of MMN, P300, and P600 in eight out of 19 patients. The attentional instructions presented with the P300 paradigm required the participants to either focus on the stimuli or listen passively. More ERPs could be identified when the focused instruction was used. The following chapter discusses these findings and their implications.

6.4.1 Hierarchical approach

The hierarchical approach as outlined in chapter 4.3.1 (Kotchoubey et al., 2005; Kübler & Kotchoubey, 2007; Owen et al., 2005) is an appealing idea to limit strenuous measuring time to a minimum and to work efficiently in clinical settings where time is a limited resource. Complex paradigms would only have to be applied to patients that have shown positive responses to simple stimulus material (Kotchoubey et al., 2005). In the present sample, P03 exhibited a P300, while no MMN was detected. P05 exhibited a presumed P600 but no other ERP at t1 while at t2 a P300 in the focused task was detected but an MMN was similarly lacking. An N1, representing basic processing of auditory stimuli, was only identified in two patients. Thus, the present results do not support the hierarchical approach. However, the authors themselves reported patterns contradicting their hierarchical approach (Kotchoubey et al., 2005). They report that even though they found more responses in simple paradigms compared to more complex ones, this rule was not valid for all patients included in the study. The authors conclude that varying levels of attentional awareness may be one reason for these irregularities.

Variation in wakefulness was also observed in the present study. The experimenters thoroughly monitored the patients during measurements and drew their attention to the stimuli by gentle touch at the shoulders or by speech, whenever it seemed necessary. However, exactly estimating the level of awareness remains impossible and it may, thus, have had an effect on the recorded ERPs. False-negative results in neuroimaging studies are not uncommon and also healthy volunteers may fail to show the expected signal changes (Owen et al., 2005).

The existence or absence of ERPs in DOC patients needs to be interpreted with great care. On the one hand, responses to passive paradigms cannot be considered a proof of consciousness, but only reveal that some brain region is still able to process the incoming stimulation (Boly et al., 2007). On the other hand, Jones and colleagues (2000) for example did not find any auditory evoked potential in two patients who had shown behaviorally clear signs of discriminative hearing. A more reliable proof consists in the application of paradigms including specific instructions or volitional tasks. However, patients who exhibit responses to passive stimulation might be aware, but still unable to understand and follow complex instructions (Kübler & Kotchoubey, 2007).

6.4.2 Focused and passive tasks

An increased P300 following an active task compared to a passive one is a common finding in ERP research (i.e. Polich, 1986; Spencer & Polich, 1999; Wickens, Kramer, Vanasse, & Donchin, 1983). In patients who often show diminished ERPs in general (i.e. Duncan, Kosmidis, & Mirsky, 2005; Elting, Naalt, Weerden, Keyser, & Maurits, 2005; Knuepffer, Murdoch, Lloyd, Lewis, & Hinchliffe, 2012; Münte & Heinze, 1994; Segalowitz, Bernstein, & Lawson, 2001), responses may thus only be detectable when attention is directed towards the stimuli and even then may still be overlooked. The usage of a focused instruction has proven beneficial in the present study. In the focused task, visual analysis revealed a distinct positive deflection in two datasets in two patients, and a negative deflection in one patient. In the passive task, a distinct deflection differentiating between standard and deviant was detected in only one patient. Thus, it is assumed that the focused instruction had a positive effect engaging the patients more strongly in the task and therefore leading to more distinct ERPs.

6.4.3 Behavioral assessment and ERPs

Regarding a connection between CRS scores and elicitation of ERPs, it can be concluded that high CRS scores may be an indicator for the presence of ERPs, but low CRS scores do not mean that no ERP can be found. The CRS solely relies on different kinds of motor functions. In its course, the patients are for example required to follow a moving object with their gaze, to reach out for objects, to open and close their mouth, and they are carefully observed while different stimuli such as loud noise, touch, and soft pain are applied. Thus, most tasks depend on intact vision and hearing and on at least the residual ability to voluntary move limbs, mouth and eyes. However, all these functions might be impaired in DOC patients and the lack of motor responses does not imply the lack of awareness or consciousness. Hence, low CRS scores do not automatically denote a lack of conscious perception and should not be taken as a guarantee that the patient is unaware of the self or the environment. Differentiating UWS and MCS from each other and from coma remains a complex and difficult task. A correct diagnosis requires prolonged periods of observation, profound training and repeated assessment (Childs, Mercer, & Childs, 1993; Kotchoubey et al., 2005). The recording of ERPs can complement the behavioral assessment and provide important indicators of the patients' cognitive functioning.

6.4.4 Altered ERPs in patients

ERPs in DOC patients can differ a lot from ERPs in healthy participants. Latency range of components might be delayed (Perrin et al., 2006; Schnakers et al., 2008) and even inversed ERPs have been reported before: Negative deflections in P300 paradigm, for example, may indicate a delayed MMN instead of the expected P300 (Pokorny et al., 2013). In the present study, unexpected ERPs were detected in six patients in all paradigms except from the MMN Duration paradigm. In the P300 passive and focused paradigms, deflections of reversed polarity were found, that might be interpreted as delayed MMNs (Pokorny et al., 2013). In the N400 Sentences paradigm, P300s and P600s were identified and in the N400 Words paradigm, only N1 was present. A P600 usually only occurs in response to grammatical and syntactic errors (Osterhout & Holcomb, 1992), but in patients both, N400 and P600, should be regarded as a sign of some language comprehension (Neumann & Kotchoubey, 2004). Thus, the present results underline that it is important to analyze each paradigm for different kinds of ERPs and to not focus on a certain latency range or polarity. Even though unexpected ERPs are no prove for awareness or consciousness as such, their existence might still indicate some kind of preserved processing and might deliver an orientation for future measurements with and treatment of the respective patient.

6.4.5 Significance of the results

Although a considerable number of ERPs has been found in the present study, their mere presence does not automatically prove consciousness of the relevant stimuli in the respective patients (Chennu & Bekinschtein, 2012). In research with healthy participants, a reliable MMN is also elicited without any attention on the stimuli (i.e. Folstein & van Petten, 2007; Muller-Gass, Stelmack, & Campbell, 2005; Näätänen, 1990). A P3a can be elicited even under high distraction, indicating that it might be based on a mostly automatic process (Muller-Gass, Macdonald, Schröger, Sculthorpe, & Campbell, 2007) and even in sleep a P300 and N400 can be identified (Bastuji, García-Larrea, Franc, & Mauguière, 1995; Brualla, Romero, Serrano, & Valdizán, 1998; Niiyama, Fujiwara, Satoh, & Hishikawa, 1994). Thus, even responses to semantic material do not automatically indicate conscious awareness of these stimuli (Owen et al., 2006). However, the presence of ERPs in DOC patients has repeatedly proven to be an indicator of recovery (i.e. Daltrozzo, Wioland, Mutschler, & Kotchoubey, 2007; Faran, Vatine, Lazary, Birbaumer, & Kotchoubey, 2006; Steppacher et al., 2013). Thus, elicitation of ERPs in DOC patients is an important sign of some preserved information processing that might lead to a restoration of awareness or consciousness. In fact, the strong connection of the presence of ERPs and recovery from coma suggests that attention and consciousness, albeit being two separate phenomena, do share some cognitive processes and neural mechanisms in common (Chennu & Bekinschtein, 2012).

6.4.6 Limitations

Even though interesting and valuable results were delivered, the study has some limitations. Firstly, it only included patients from two subsidiaries of a single clinic and only patients that showed at least minimal responses in reaction to sensory stimulation (such as eye opening following touch). Thus, the results presented herein may not be generalizable to other patients in other clinics. Secondly, all patients apart from two had been already suffering a DOC for several years. It is often stated that the probability of recovery and regaining consciousness decreases with increasing duration of coma and/or UWS (i.e. Bricolo, Turazzi, & Feriotti, 1980; Tirschwell, 2006). Therefore, it is likely that the patients included in this study had a poor prognosis of awakening from the start, and thus exhibited less and smaller ERPs in comparisons to other patients.

In addition, a high number of recordings had to be excluded in the N400 Sentences paradigm due to noisy data. This contamination with artifacts may stem from random noise from electrical devices but it is also possible that the auditory stimuli provoked artifacts from eye movements or muscular activities. Regardless of the source of artifacts, less datasets were included in the analyses compared to the other paradigms. Thus, it might be possible that more

ERPs to the N400 Sentences paradigm could have been found if a higher number of datasets was included.

Finally, most importance was attached to the visual analyses because statistical analyses can be complicated by various factors: Usually, only a certain time window is included in the statistics, possibly missing deflections in a different time area. Furthermore, significance of results can be missed due to high variance of the test values. In most patients who exhibited statistically significant results, visual inspection did not affirm an ERP. This ambiguity was caused by significant statistics stemming from drifts and artifacts that can only be identified visually. However, also visual analysis may include mistakes. In any way, in a patient setting it seems most appropriate to minimize type II errors (missing an existing effect) and to accept an increased type I error (stating an effect that is not present). Thus, visually detected deflections were also interpreted when statistics were not significant. As a consequence, some effects reported herein might not be reproducible but re-assessment of the relevant patients is still highly advisable.

6.4.7 Conclusion

The present results indicated elicitation of ERPs in eight out of 19 DOC patients, of whom all were diagnosed with UWS or apallic syndrome, respectively, and therefore confirmed general hypothesis b) as outlined in chapter 4.5. Thus, it could be shown that UWS patients do exhibit some degree of cognitive functioning up to semantic processing of spoken sentences. A close observation of those patients and regular re-assessment of their state of consciousness is recommended urgently.

The paradigms used in this study were developed and tested in close relation to the current research applying ERP paradigms to DOC patients. Thus, all paradigms were designed such that a sufficient number of stimuli is comprised without extending the duration of each paradigm more than necessary. These paradigms were shown to work efficiently in the patients enrolled in the present study. An ERP distinguishing deviants from standards was elicited in at least one patient in each paradigm except from the N400 Words paradigm where only an N1 to standards and deviants was identified. However, Münte and Heinze reported before that more ERP responses were found for sentence-based stimulus material compared to word-pairs (1994). For P300, it could be shown that utilization of a focused task elicited ERPs in more patients compared to a passive task, a finding affirming general hypothesis c) as outlined in chapter 4.5 for P300. It is thus recommended to use focused instructions when recording such ERPs in DOC patients.

7 Study 3 – Attention effects on MMN and N400

The description of the following study is taken from the paper published by Erlbeck, Kübler, Kotchoubey, & Veser (2014). For the present study, the data were re-analyzed.

7.1 Study aims

Study 3 connects to results of study 2 in which no ERP responses were observed in the N400 Words paradigm, although ERPs were elicited in the N400 Sentences paradigm. Thus, those two paradigms were presented to healthy participants alongside with different attentional instructions to detect a potential difference in the reliability of the paradigms. In addition, MMN was included in the study to test whether larger amplitudes can be achieved through focused instructions compared to passive or ignore tasks like it is the case with P300 (Bennington & Polich, 1999; Polich, 1986).

Although one can rarely know the current state of consciousness in DOC patients, measurements are often carried out assuming that there is at least residual awareness. On the basis of this assumption, the importance of appropriate instructions to record reliable ERPs is evident. Since there are significant differences in the instructions for patients, it shall be clarified how N400 and MMN, two ERPs with great potential to be used in patient assessment, are influenced by attentional modulations in healthy participants. The study includes the discrete effect of a behaviorally passive attentional instruction alongside with a focused and an ignore one. The passive instruction was covert and unspecific such that no overt responses to the auditory stimuli were required. Furthermore, ERP findings are complemented with subjective ratings of the effort experienced after each task and paradigm.

Differential effects of the attentional instructions on N400 and MMN were expected. ERP components and subjective effort are expected to vary according to the manipulation of attention. The focused task required fast and correct reactions to the auditory stimuli and was thus expected to be the most strenuous. The ignore task only required few key presses in reaction to the presentation of predefined scenes in a movie of emotionally neutral content which was expected to be the least strenuous. The passive task, however, did not require any overt response; therefore the participants were unable to engage in a specific activity. This state may cause boredom accompanied by feelings of negative affect and mental effort (Eastwood, Frischen, Fenske, & Smilek, 2012). Thus, it is expected that the average subjective effort is highest in the focused task, lower in the passive task, and lowest in the ignore task in which attention was drawn away, irrespective of the paradigm,

On the physiological level, an N400 effect is expected in both semantic paradigms. This effect was assumed to be greatest in the focused task, diminished in the passive task, and most strongly attenuated in the ignore task referring to previously found attention effects in the N400 component (Chwilla, Brown, & Hagoort, 1995; McCarthy & Nobre, 1993). In the oddball paradigm, a similar modulation of the MMN effect is assumed. This variation of the MMN is expected because of the assumed effect of the attentional instruction on the standard formation process as postulated by Sussman (2007).

7.2 Method

7.2.1 Participants

EEG was recorded in 18 healthy adults (seven males, two left-handed) at the University of Würzburg. The participants were between 25 and 49 years old (*M* = 33.39, *SD* = 7.55 years) and received an expense allowance of 9 € per hour. All participants had normal hearing and were not in treatment for any psychiatric or neurological disorders at the time of the study. All participants gave their written consent after they were informed about the nature of the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Review Board of the Medical Faculty, University of Würzburg.

7.2.2 Experimental procedure and stimuli

The present study comprised three tasks (ignore, passive, focused) and three paradigms that were named according to the ERP they aimed to elicit (MMN Duration, N400 Words, and N400 Sentences. Each paradigm was presented three times with three different attention tasks. The tasks were presented in a pseudorandom order such that the passive task always preceded the focused task. The paradigms were presented pseudorandomly within the tasks such that consecutive paradigms were never identical. In the ignore task, the presentation of auditory stimuli was accompanied by a documentary silent movie (Vertov, 2006) which did not require any language to follow the content. The participants' task was to press a key when a certain scene appeared. The movie was cut into three parts containing between 20 and 24 occurrences of the relevant scene (2 s long) at intervals of 15 to 45 s. These sections were presented in random order such that each paradigm was accompanied by a different part of the movie.

The instructions were given in German and contained the following information: "In the following experiment, you will hear tones/semantically right or wrong sentences/related and unrelated word-pairs and see a silent movie. Your task is to watch out for a specific scene in the movie and press the 'M' key as soon as the scene appears. Please look out for the following scene. [scene is shown]. Are you ready? The experiment starts in a few seconds." In the passive task, the participants were instructed to just listen to auditory stimuli. The exact instruction was: "In the following experiment, you will hear tones/semantically right or wrong sentences/related and unrelated word-pairs. Please just listen and watch the fixation cross in the center of the screen. Are you ready? The experiment starts in a few seconds." In the focused task, the participants were required to indicate either the odd tone or semantically congruent and incongruent stimuli by pressing a key (oddball) or two different keys (semantic paradigms). The exact instruction was: "In the following experiment, you will hear tones/semantically right or wrong sentences/related and unrelated word-pairs. Please listen carefully and press the 'M' key as soon as you detect a deviant tone/press the 'M' key for related word-pairs/semantically correct sentences and the ‘B’ key for unrelated word-pairs/semantically incorrect sentences. Are you ready? The experiment starts in a few seconds.”

The paradigms MMN Duration, N400 Words, and N400 Sentences were the same paradigms as described in chapter 6.2.2. All auditory stimuli were presented via pneumatic transducer in-ear headphones equipped with foam eartips (se chapter 6.2.2).

To evaluate the perceived effort, the participants indicated their subjective effort after each paradigm on a scale from 0 to 220 with seven labels ranging from “rarely strenuous” at 20 to “extraordinarily strenuous” at about 205 (Eilers, Nachreiner, & Hänecke, 1986).

All the paradigms and tasks were presented within a single session. The absolute recording time was approximately 90 minutes. The whole experiment took between two and three hours depending on breaks, further explanations, etc.

7.2.3 Material and data acquisition

EEG was recorded according to the international 10-20 system with a BrainAmp ActiCap system (Brain Products GmbH, Gilching, Germany) using 32 Ag/AgCl active electrodes at the following scalp sites: Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, O1, O2, and on the right mastoid. The ground electrode was placed at AFz and the data were online referenced to the left mastoid. Four additional electrodes attached to the two external canthi, and above and below the right eye, monitored the eye movements (EOG). The EEG and EOG were sampled with 500 Hz and online bandpass filtered between 0.01 and 250 Hz.

7.2.4 Data preprocessing and analysis

The EEG data were preprocessed and analyzed in MATLAB 2011b (The Math Works, Inc., M.A.) using the EEGlab toolbox (Delorme & Makeig, 2004) and the ERPlab toolbox extensions (http://erpinfo.org/erplab). Statistics were performed in SPSS 17.0 (SPSS Inc., IL).

EEG data were offline band-pass filtered between 0.5 and 35 Hz (Kaiser windowed sinc FIR filter, 3624 points). The four vertical and horizontal ocular channels were bipolarized into vertical and horizontal EOG. Furthermore, the data were re-referenced to the linked mastoids. Epochs were created from -100 to 500 ms for the MMN Duration paradigm and from -200 to 1000 ms for the N400 Words and N400 Sentences paradigms. Time windows from -100 to 0 ms for MMN Duration paradigm and -200 to 0 for the N400 Words and N400 Sentences paradigms were used as a baseline. Eye movement artefacts were corrected using a regression-based procedure (Gratton et al., 1983) and all trials containing signal changes of ± 80 µV were excluded from further analysis using an automatic peak-to-peak detection method. Before entering the statistical analyses, all trials containing key presses in the ignore task and all misclassified sentences and word-pairs as well as missed deviants in the focused task were discarded. Finally, grand averages were obtained.

For the statistical analyses, the electrodes F3, Fz, F4, C3, Cz, and C4 were selected for the MMN Duration paradigm and the electrodes Fz, Cz, and Pz were selected for N400 effects. The relevant time windows for the component analyses in all the paradigms were defined by visual inspection and automatic peak detection. In the MMN Duration paradigm, visual inspection yielded a large negative component with two peaks in the passive and focused task. The first peak which occurred at about the same time as the only peak in the ignore task, was interpreted as an MMN. The mean amplitude in an interval of 40 ms around that peak was used for the analyses. In the semantic paradigms, the time windows were set to 300–600 ms for the N400 Words paradigm and 250–650 ms for the N400 Sentences paradigm. Difference waves were obtained by subtracting the standards from the deviants (MMN Duration), the related word-pairs from the unrelated word-pairs (N400 Words), and the correct sentences from the incorrect sentences (N400 Sentences).

The mean amplitude under the curve entered the statistical analyses. Multivariate repeated-measures ANOVAs with the difference waves as dependent variables including the factors task (ignore, passive, focused), region (frontal, central, parietal), and laterality (left, middle, right) were performed. Furthermore, t-tests comparing the mean amplitudes to zero were conducted for midline electrode sites to detect the elicitation of a component.

ANOVAs were calculated for each paradigm separately and for all results, the Greenhouse-Geisser corrected values are reported (Greenhouse & Geisser, 1959) since the assumption of sphericity was violated in all the analyses and values of epsilon were smaller than .75, which is the recommended threshold for application of the Greenhouse-Geisser correction (Girden, 1992). Post-hoc comparisons were conducted to detect any significant differences between individual tasks as defined in the hypotheses. Reported results were SIDAK corrected as implemented in SPSS 17.0. In addition, the effect size partial eta squared (ηp^2) is reported for all significant main effects of and interactions. According to (Cohen, 1988), ηp^2 = .01 represents a small effect, ηp^2 = .06 a medium effect and ηp^2 = .14 a large effect.

In addition to the amplitudes at scalp electrodes, mastoid amplitudes were analyzed in the MMN Duration paradigm. All eye blinks were eliminated and the data were re-referenced to IO2 (electrode below the eye). The mean amplitude under the curve in a time interval of 40 ms around the most positive peak entered analyses.

7.3 Results

7.3.1 MMN Duration

A t-test for the difference from zero demonstrated large and significant negative components in all three tasks (all $p < .001$). The first deflection peaking at about 150 ms was interpreted as an MMN. The second deflection in the passive and focused task peaked at about 200 ms and reached its maximum over central sites. It was thus interpreted as an N2b. The typical reversal of polarity at the mastoid electrode was only evident for the first peak. Figure 8 depicts the ERP waveforms at the six electrodes that entered analyses.

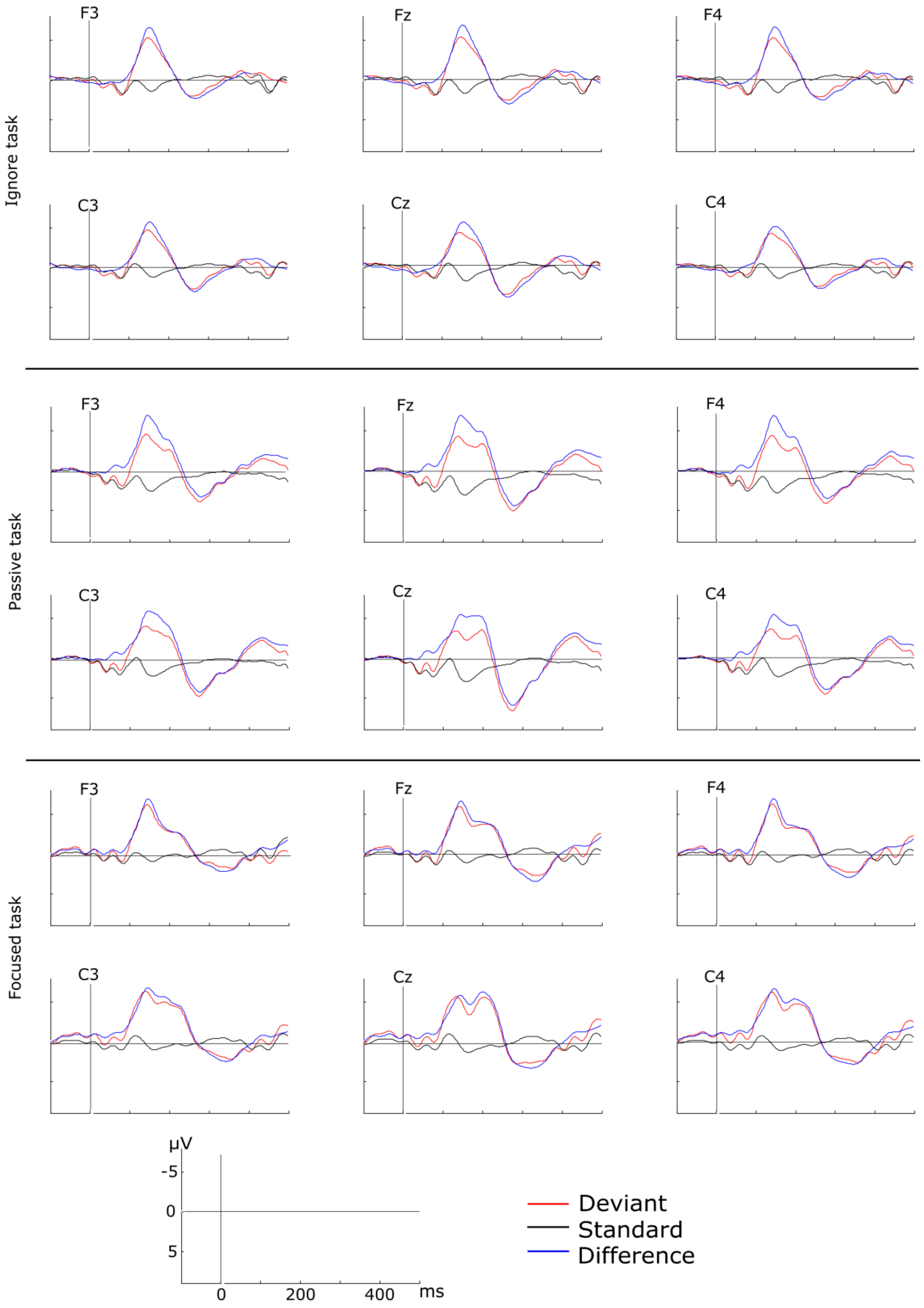

Figure 8: Grand averages across all subjects elicited in the MMN Duration paradigm at F3, Fz, F4, C3, Cz, and C4 in all three tasks. In the ignore task, a distinct single peak was elicited. In the passive and focused task, a double peak emerged. The first peak was interpreted as MMN while the second peak was interpreted as N2b.

A repeated measures ANOVA including the factors task, region, and laterality was conducted. Amplitudes were larger over frontal regions compared to central ones (Mf_{rontal} = -6.14 µ; $M_{central}$ = -5.41 µV; *F*(1, 17) = 10.54, *p* = .005, η_p^2 = .383). Task interacted with region (*F*(2, 34) = 5.01, *p* = .031, η_p^2 = .228) and laterality (*F*(4, 68) = 9.27, *p* < .001, η_p^2 = .353) but post-hoc comparisons did not reveal significant differences. In addition, task interacted with region and laterality (*F*(4, 68) = 5.07, *p* = .003, η_p^2 = .230): Larger amplitudes were elicited in the focused task compared to the ignore task at C3 (*p* = .030) and C4 (marginally significant; *p* = .085), and significantly larger amplitudes were elicited in the focused task compared to the passive task at C4 (*p* = .037). In addition, an ANOVA with the amplitudes at the right mastoid including the factor task was calculated. Mastoid amplitudes did not differ according to task.

Taken together, the amplitudes at the scalp electrodes indicated a small effect of attention over central regions. However, this effect was not supported by mastoid data.

7.3.2 N400 Words

A t-test for the difference from zero indicated a significant negative deflection at Pz in the passive task (*p* = .02) and at Fz, Cz, and Pz in the focused task (*p* < .001). It was interpreted as an N400. No N400 was observed in the ignore task. Figure 9 depicts the recorded brain signals in all three tasks in the N400 Words paradigm at the three electrodes that entered analyses.

A repeated-measures ANOVA including the factors task and region revealed amplitudes to differ as a function of task (*F*(2, 34) = 38.17, *p* < .001, ηp^2 = .692) and region (*F*(2, 34) = 32.54, *p* < .001, ηp^2 = .657). In addition, task interacted with region (*F*(4, 68) = 13.87, *p* < .001, ηp^2 = .449). Amplitudes in the focused task (*M* = -1.87 µV) were significantly larger compared to amplitudes in the passive (*M* = -.32 µV) and ignore task (*M* = -.06 µV, all *p* <

.001). This effect was found over all regions (all $p \leq .048$), apart from the difference between the ignore and the focused task over frontal regions which was only marginally significant ($p = .056$). With respect to region, amplitudes were largest over parietal regions, smaller over central ones and smallest over frontal regions (all $p \leq .006$).

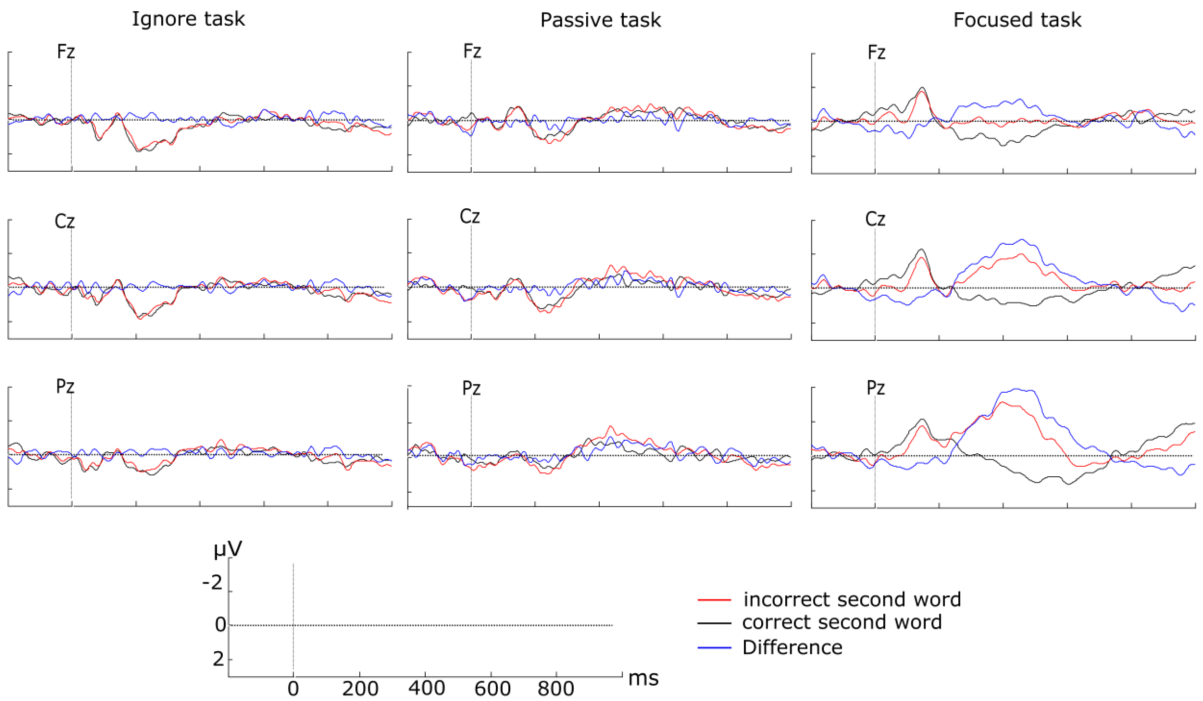

Figure 9: Grand averages across all subjects elicited in the N400 Words paradigm at Fz, Cz, and Pz in all three tasks. No N400 was visible in the ignore task. In the passive task, an N400 is difficult to visually identify. A clear N400 only emerged in the focused task between 200 and 600 ms.

In addition to the N400 component, noticeable deflections could be seen in several time windows. To test whether these deflections reflected different brain processes in reaction to related and unrelated word-pairs, separate repeated-measures ANOVAs including the factors task and region were extended by the factor stimulus (related vs. unrelated): In the focused task a positivity occurred between 0 and 190 ms, but related and unrelated second words did not differ significantly. In the passive task a positive deflection occurred between 110 and 160 ms. Again, related and unrelated second words did not differ significantly. In the ignore and passive task, respectively, two positive deflections ranging from 40 to 100 ms and 170 to 300 ms were elicited. Again, related and unrelated second words did not differ significantly in either time window.

Taken together, the N400 was the only component that reflected different processes in reaction to related and unrelated word-pairs. The results for the N400 Words paradigm revealed an N400 effect in the focused task, but no N400 in the ignore task. In the passive task, amplitudes at Pz differed from zero, but the ANOVA did not detect any significant difference between the passive and the ignore task.

7.3.3 N400 Sentences

In the N400 Sentences paradigm, one participant's data were excluded due to technical problems during recording. A t-test for difference from zero revealed an N400 component in the passive task (at Cz and Pz, both $p \leq .021$) and the focused task (all $p \leq .016$). No N400 component was elicited in the ignore task. Figure 10 depicts the recorded brain signals in all three tasks at the three electrodes that entered analyses.

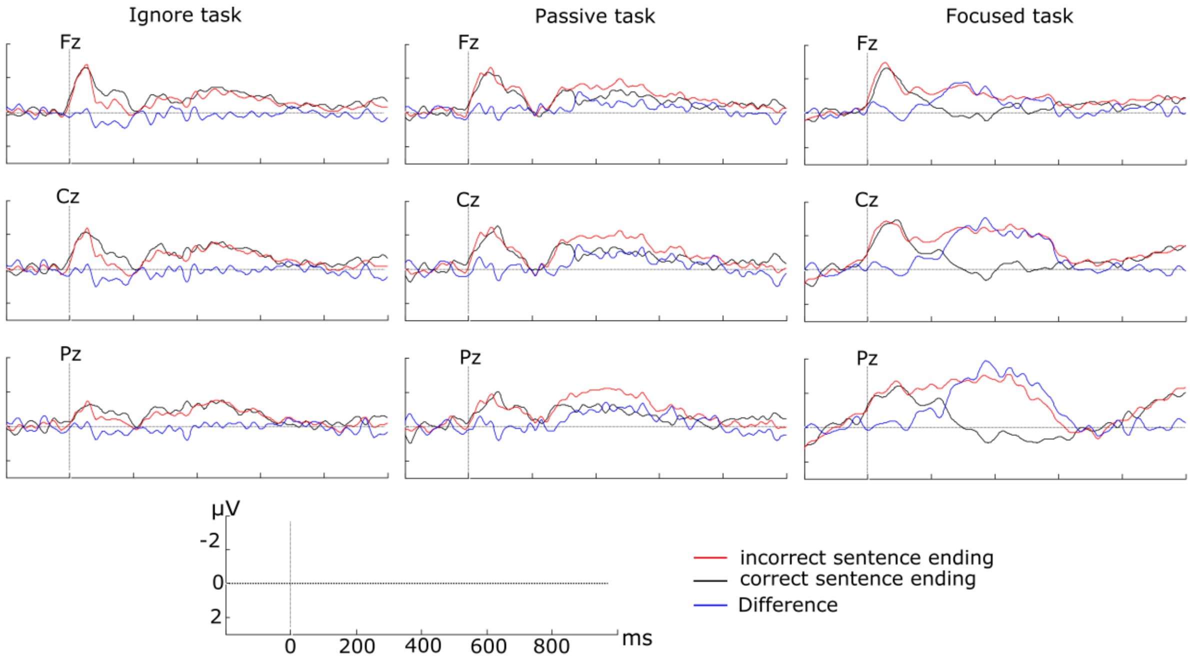

Figure 10: Grand averages across all subjects elicited in the N400 Sentences paradigm at Fz, Cz, and Pz in all three tasks. No N400 was visible in the ignore task. In the passive task, a small N400 was visually identifiable. A large N400 was detected in the focused task between 200 and 600 ms.

A repeated-measures ANOVA including the factors task and region revealed amplitudes to differ as a function of task ($F(2, 32) = 12.93$, $p < .001$, $\eta p^2 = .447$) and region ($F(2, 32) = 14.81$, $p < .001$, $\eta p^2 = .481$). In addition, task interacted with region ($F(4, 64) = 8.61$, $p < .001$, $\eta p^2 = .350$). In general, amplitudes in the focused ($M = -1.68$ µV) and passive task ($M = -.65$ µV) were significantly larger compared to amplitudes in the ignore task ($M = -.11$ µV, all $p < .044$). Post-hoc comparisons revealed amplitudes over parietal regions to be smallest in the ignore task, larger in the passive one, and largest in the focused one (all $p \leq .026$). The same pattern emerged over central regions, whereas the differences between the ignore and the passive task and the focused and the passive task were only marginally significant ($p \leq .072$). Frontally, amplitudes in the focused task were significantly larger compared to the ignore task ($p = .005$), while the passive task did not differ significantly from the others. Overall, amplitudes were largest over central and parietal regions as compared to frontal ones (all $p \leq .001$).

In addition to the N400 component, a negative deflection could be observed between 0 and 170 ms in all three tasks. This negative deflection did not distinguish between correct and incorrect sentence endings and was interpreted as a continuing negativity in response to the previous words of the sentences.

Taken together, the N400 was the only component reflecting different brain processes in response to correct and incorrect sentences. The largest N400 effect was found in the focused task, a by trend smaller one in the passive task and no N400 in the ignore task.

7.3.4 Comparison of N400 Sentences and N400 Words

A repeated measures ANOVA including the factors paradigm (N400 Words vs. N400 Sentences), task, and region was conducted to test whether the two paradigms elicited potentials of different amplitudes. No significant main effect or interaction of paradigm was detected. Thus, amplitudes in the two paradigms did not differ significantly from each other.

7.3.5 Subjective effort and performance

The participants indicated their subjective effort after the completion of each paradigm in each task (Table 8). Repeated-measures ANOVA with the two factors task (ignore, passive, focused) and paradigm (MMN Duration, N400 Words, N400 Sentences) were performed to detect any significant variation as a function of task and auditory stimuli.

Table 8: The mean values (*M*) and standard deviations (*SD*) of stated subjective effort listed for all three paradigms (columns) and tasks (rows)

		N400 Words	N400 Sentences	MMN Duration	*M* per task
ignore task	*M*	32.55	55.99	46.89	45.15
	SD	22.08	56.99	40.52	42.66
passive task	*M*	72.91	80.01	89.39	80.77
	SD	47.24	58.11	55.82	53.34
focused task	*M*	73.76	85.98	83.71	81.15
	SD	46.09	59.84	54.37	52.98

Subjectively experienced effort varied significantly according to the task ($F(2, 34) = 9.93$, $p = .001$, $\eta p^2 = .369$) with the passive and focused tasks being judged as more effortful than the ignore task (both $p = .001$). Subjective effort did not vary according to the paradigms. This result partially confirms the expected variation since the ignore task was least effortful, but the passive and focused tasks were judged as equally demanding.

The ignore task required the participants to press a button in response to a predefined scene in a silent movie. Eleven participants (61.1%) detected all the scenes in one of the three paradigms, six participants (33.3%) detected all the scenes in two paradigms, and one participant (5.6%) correctly detected all the scenes in all of the paradigms. The number of missed scenes ranged between one and four. Three participants indicated the scene although it had not appeared. The number of missed scenes varied according to paradigm ($F(2, 34) = 4.34$, $p = .022$, $\eta p^2 = .203$). However, post-hoc comparisons only revealed a by trend significant difference between the N400 Words and the N400 Sentences paradigm ($p = .054$).

Table 9 lists the number of correct and incorrect detections as well as misses in the three paradigms in the focused task. In the MMN Duration and N400 Sentences paradigm, two participants were excluded because their results differed from the group mean by more than two standard deviations.

Table 9: Amount of correct and incorrect answers and misses for the focused task for N400 Words, N400 Sentences, and MMN Duration.

		deviant detection/ correct answers	wrong detections/ incorrect answers	misses
MMN Duration	*M*	94.24	5.76	5.59
deviant detection	*SD*	6.22	6.22	4.82
N400 Words	*M*	95.33	4.17	0.5
related	*SD*	3.12	3.09	1.04
N400 Words	*M*	93.00	4.83	2.17
unrelated	*SD*	5.58	3.26	2.97
N400 Sentences	*M*	82.82	12.47	4.35
correct	*SD*	8.44	1.28	7.91
N400 Sentences	*M*	80.47	13.53	6.00
incorrect	*SD*	7.65	1.55	7.71

For each of the two answer categories (correct and incorrect), a repeated-measures ANOVA including the factors paradigm (N400 Words vs. N400 Sentences) and stimuli (related/correct vs. unrelated/incorrect) was performed. The ANOVA for correct answers yielded a significant main effect of paradigm ($F(1, 15) = 154.88$, $p < .001$, $\eta p^2 = .912$) and stimuli ($F(1, 15) = 7.10$, $p = .018$, $\eta p^2 = .321$), indicating that the participants identified more related word-pairs as related than correct sentences as correct and in general made less errors detecting related word-pairs and correct sentences than detecting unrelated word-pairs and incorrect sentences. The ANOVA for incorrect answers confirmed this result by revealing a main effect of paradigm ($F(1, 15) = 279.57$, $p < .001$, $\eta p^2 = .949$), indicating that generally more errors occurred in the sentence paradigm.

7.4 Discussion and summary

The goal of the present study was to investigate the effect of different attentional instructions on ERP measures. The attentional instructions required the participants to either focus on the stimuli, listen passively, or to focus on a concurrent sensory input. All the ERP effects described in the corresponding literature (MMN, single word N400, sentence N400) were successfully replicated and it was shown that these effects depended on the direction of attention. In addition, also subjective effort was affected by the attentional tasks. The following chapter discusses these findings and their implications.

7.4.1 Attentional effects on MMN

A significant MMN was elicited at all levels of attention, with attention being directed away, passive, or highly focused on the auditory stimuli. Even though there is still debate about the possible effect of voluntary attention on the MMN, it was hypothesized that the MMN would also be modulated by attention because of the standard formation process postulated by Sussman (2007). At central electrodes, the results indicated slightly larger amplitudes in the focused task compared to the passive and ignore task. However, when interpreting these findings, a potential overlap of the MMN with N1 and N2b should be taken into account.

In an oddball paradigm, the MMN might be overlapped by an N1 which renders them difficult to differentiate (Näätänen & Picton, 1987). However, the MMN usually peaks well after the time window of the N1 and short analyses intervals are chosen to minimize potential overlap effects (Duncan et al., 2009). Studies analyzing N1 amplitude usually use an interval ranging from about 80 ms to about 120 ms (i.e. Davis, Mast, Yoshie, & Zerlin, 1966; Näätänen, 1992; Ruhnau, Herrmann, & Schröger, 2012). All intervals used in the present study started after 120 ms, making a contamination of MMN amplitudes by an N1 effect unlikely.

In the present data, a single peak at about 150 ms was elicited in all tasks while a second peak at about 200 ms was only found in the passive and focused task. The first peak was interpreted as MMN while the second peak was assumed to represent an N2b. Even though both, MMN and N2b, are elicited by rare events in an oddball paradigm, it is assumed that the MMN is elicited by both attended and unattended stimuli, whereas the N2b only occurs when attention is directed to target stimuli (Folstein & van Petten, 2007; Muller-Gass, Stelmack, & Campbell, 2005). In the focused task, participants were specifically instructed to attend to the stimuli, leading to elicitation of an N2b. In the passive task, participants did not receive a specific instruction, leaving them without a task. In this situation, it is likely that at least some attention was directed towards the auditory stimuli. Thus, an N2b can only be ruled out for the ignore task. However, the narrow time interval of 40 ms that entered analyses precludes the inclusion of a negativity caused by N2b. In the passive and focused task, the second decline in the difference curve, representing an N2b, started after the end of the time interval used for analyses. This might also be due to the fact that MMN tends to arise earlier in shorter ISIs like the ones used here (Näätänen, 1992). Thus, elicitation of N2b was inevitable in the present design, but an overlap is very unlikely.

No effect of attention was found at the mastoid electrodes. However, the signal at mastoid electrodes was much noisier compared to scalp electrodes, minimizing the probability of finding a significant effect. Presumably, this was due to the smaller amount of epochs included after elimination of all epochs containing blinks.

Referring to the two component models of MMN (Näätänen & Michie, 1979; Näätänen, Paavilainen, Rinne, & Alho, 2007), the present results argue for an attentional effect on the frontal component of the MMN, but not on the supratemporal one, because an attentional effect was found at scalp electrodes, but not at mastoid electrodes. This is in line with a previous argumentation only linking the frontal component to attentional modulation (Rinne, 2001).

To sum up, the data render the MMN a potential tool to detect basic cognitive functions in the absence of directed attention. Attentional effects could be detected at scalp electrodes, but not at mastoid electrodes. An overlap with N1 and N2b cannot be fully excluded but seems unlikely.

7.4.2 Attentional effects on N400

The N400, representing higher cognitive functions, gradually decreased with decreasing attention from the focused to the passive task and was completely absent in the ignore task. Thus, the hypothesis expecting varying amplitudes according to attention for N400 was confirmed for word-pairs and sentences. These weakened semantic ERPs in the semantic paradigms in the passive task could be attributed to the vigilance decrement due to the high mental effort and feelings of boredom caused by the monotonous situation (discussed in chapter 7.4.3).

Attention toward a stimulus enhances the N400 component, irrespective of whether it is elicited by word-pairs or sentences. These results not only confirm the expected variation according to attention allocation theories, but also highlight the importance of appropriate instructions in ERP measurements, especially in semantic paradigms designed to elicit an N400. If ERPs are recorded in DOC patients to detect basic or higher cognitive functions, passive instructions might lead to attenuated potentials, which are difficult to interpret, and thus to misjudgment of the patients’ cognitive capacity. A positive finding in a passive version of a language paradigm provides strong evidence for the patient’s ability of semantic processing, but a negative finding remains ambiguous, because it can result not only from the real lack of semantic competence but also from many other factors such as a low arousal level. In the N400 Words paradigm, a significant deflection in the passive task was detected at Pz, but the amplitudes of the passive task did not differ significantly from those in the ignore task where no N400 was elicited. Thus, N400 in the passive task could be easily overlooked. This was also evident in Figure 9 and Figure 10 depicting grand averages in the N400 Words and Sentences paradigm, respectively. In the N400 Words paradigm, visual identification of an N400 in the passive task was very difficult and the potential could easily be missed whereas in the N400 Sentences paradigm a small but clear N400 in the passive task was detectable. Thus, although no statistical difference was found between the two ERPs, visual identification as it is also conducted in patients yielded more reliable results for the N400 Sentences paradigm.

In addition, the N400 Words and Sentences paradigm differed in terms of the participants' performance in distinguishing related/correct from unrelated/incorrect stimuli. Generally more errors occurred in the sentence based paradigm. This might be due to the more complex structure of a sentence compared to simple word-pairs. The focused task required the participants to decide and react quickly and thus, more complex stimuli like the sentences could have led to more errors.

The present findings support the N400 as a potential to detect higher cognitive functions that require directed attention and confirm previous studies showing strong attenuation or extinction of the N400 effect when attention is not directed toward the eliciting stimuli (Chwilla, Brown, & Hagoort, 1995; McCarthy & Nobre, 1993). However, other studies did not find that N400 is modulated by the depth of processing level (Connolly, 1990; Relander, Rämä, & Kujala, 2009). In their review, Deacon and Shelley-Tremblay concluded that the N400 does not necessarily require attention but only occurs if the processing of the stimuli is not actively inhibited by some other task (2000). This view is supported by the present data insofar that active inhibition in the ignore task led to extinction of the N400 potential. In the passive task, where no specific tasks had to be performed apart from mere listening, the N400 was strongly attenuated but still present.

7.4.3 Subjective effort

The three tasks required different levels of attention to be allocated to the auditory stimuli, resulting in different levels of subjective effort. The prediction of the highest subjective effort in the focused task, lower effort in the passive task, and the lowest effort in the ignore task was not fully confirmed. Subjective effort in the passive and focused task was equally high. Thus, listening to the stimuli without mental and behavioral engagement was judged to be as effortful as having to respond to each word-pair or sentence, or monitoring the tone stream for deviants.

It is assumed that the passive task, especially when directly compared to the ignore and focused tasks, shared commonalities with vigilance and sustained attention tasks, which are characterized by a low rate of relevant stimuli and require concentrated attention over a prolonged period of time (i.e. Haga, 1984; Noyes, 2009; Warm, Dember, & Hancock, 1996). In this respect, the passive task can be considered to require sustained attention as defined by Coull (1998) (see chapter 4.1). Although the passive task was shorter and simpler than the usual vigilance task, some characteristics are similar in both, such as a low level of signal input, and having to sustain attention over a prolonged period of time (up to 15 minutes in the N400 Sentences paradigm), especially when directly compared to the other, more engaging, ignore, and focused tasks. A vigilance decrement in such sustained tasks (Colquhoun & Baddeley, 1964) leads to a drop in performance, sometimes already within five minutes after the initiation of the task (for a review, see Warm, Matthews, & Finomore Jr, 2008). Warm and colleagues rejected the previous view that the decline of arousal and performance is exclusively due to monotony (Warm, Parasuraman, & Matthews, 2008). Instead, they concluded that vigilance tasks require a large amount of information processing, and are exhausting and capacity draining. As a task continues for a prolonged period of time, the level of arousal declines and the person must increase the degree of attention to maintain task performance (Parasuraman, 1984). Therefore, individuals experience high levels of subjective workload and stress (Grier et al., 2003).

In support of these findings, Eastwood and colleagues (2012) defined the aversive state of boredom as correlating with high mental effort in terms of attentional processes: boredom arises when individuals are unable to engage attention to internal or external information, focus on the fact of this unsatisfactory state, and consider the reason for this state to be caused by the environment. Thus, participants in the present study may have experienced boredom in the passive task, leading to high ratings of subjective effort.

7.4.4 Limitations

The present study is subject to a few limiting factors outlined in the following. An external behavioral measure of the level of processing was only applied in the focused task where participants had to press a key in reaction to each sentence or word-pair. In this course, error trials with presumed low vigilance were excluded. The passive and ignore tasks did not demand a behavioral reaction to the auditory stimuli thereby making it impossible to eliminate trials with low vigilance or errors. This effect might have contributed to lower N400 amplitudes in the passive task compared to the focused task. However, such behavioral information is similarly lacking when ERPs are used in the clinical assessment of DOC and other non- and low-responsive patients.

Furthermore, there are alternative explanations for the ERP response decrement in the passive and ignore tasks. Firstly, it is possible that psychological states such as frustration and mood led to an attenuation of the ERP components (Federmeier, Kirson, Moreno, & Kutas, 2001; Kübler, Blankertz, Müller, & Neuper, 2011; Nijboer, Birbaumer, & Kübler, 2010). However, a close monitoring of mood and emotional status was not included in the study. Moreover, the instructions might have caused the participants to allocate different levels of motivation to the tasks, which can also influence ERP responses (Johnson, 1986; Kleih, Nijboer, Halder, & Kübler, 2010).

7.4.5 Conclusion

Taken together, the present study revealed differential effects of attentional modulation on MMN and N400. In the semantic paradigms, N400 can be considered a measure of performance, which has been shown to decrease in vigilance and sustained attention tasks that are similar to the passive task performed in the present study. The application of passive instructions diminishes N400 amplitudes and thus, in clinical settings, a focused instruction is strongly recommended. For the MMN Duration paradigms, the present results indicate only small attentional effects on MMN in favor of the focused task. Thus, general hypothesis c) as outlined in chapter 4.5 can be confirmed for N400 while results for MMN were less clear. Nevertheless, in clinical settings a focused instruction might be beneficial to maximize the probability of eliciting reliable ERPs if cognitive processing is preserved.

8 Study 4 – Effects of attention and stimulus features on MMN and P300

8.1 Study aims

Study 3 revealed small effects of attentional modulation on MMN amplitudes measured in an oddball paradigm. Study 4 builds up on these first results investigating attentional effects on MMN, varying different stimulus parameters including the design of the oddball paradigm itself, several dimensions of deviation, and the deviant-to-standard distance (DSD). Typical paradigms like the ones used in study 2 and study 3 comprise one standard and one rare deviant that are identical in all but one dimension, i.e. frequency or duration. Thus, these paradigms only focus on one feature of auditory stimuli. However, attention span of DOC patients is short and it is therefore important that the applied paradigms are brief but at the same time provide a maximum of information and allow for a reliable detection of MMNs also in single subjects. Using oddball paradigms comprising several deviant tones in various dimensions may be a promising tool to record ERPs in response to more than one deviating stimulus within a short period of time. These so-called multifeature oddball paradigms were first developed by Näätänen and colleagues whose tone sequence comprised deviants in five different dimensions: frequency, intensity, location, duration, and a silent gap in the middle of a tone (Näätänen, Pakarinen, Rinne, & Takegata, 2004). MMN responses in the multifeature paradigm were found to be as large as in the traditional unifeature oddball. Similar results were presented by Pakarinen and colleagues (2009) who also report highly similar amplitudes in multifeature and unifeature paradigms. Furthermore, it is not only possible to include different dimensions of deviation, but also different levels of DSD as defined by the magnitude of change between deviating and standard stimuli. A study of six levels of deviation in four dimensions (frequency, duration, intensity, location) revealed increased MMN amplitudes with increasing deviation (Pakarinen, Takegata, Rinne, Huotilainen, & Näätänen, 2007).

With this study it shall be clarified whether (1) the MMN amplitudes elicited by physically identical stimuli differ as a function of paradigm (uni- vs. multifeature oddball), and (2) the amplitude of the MMN increases with the increasing DSD in terms of the target stimulus feature in four different dimensions (frequency, intensity, location, and duration). It is assumed that amplitudes in the unifeature and multifeature paradigms are equally high and that amplitudes increase when DSD increases.

Furthermore, a P300 paradigm was included to follow up on study 2 where more responses of DOC patients were found when a P300 paradigm was applied using a focused instruction compared to a passive one. With this study, past research findings reporting smaller P300 potentials in passive compared to focused tasks shall be replicated (i.e. Bennington & Polich, 1999; Mertens & Polich, 1997; Polich, 1987; Rappaport, Clifford, & Winterfield, 1990). In addition, this study allows for a direct comparison of attentional effects on MMN and P300 because both are presented under identical instructions. It is assumed that an MMN is elicited in all three tasks with higher amplitudes in the focused task compared to the ignore task. For P300 it is expected that no P300 is elicited when attention is drawn away from the auditory stimuli. In the passive and focused task, a P300 is expected whereas amplitudes in the focused task should be larger compared to the passive task.

An additional purpose of the study was to investigate a potential order effect on P300 and MMN amplitudes. In the study of P300, the use of different attentional instructions is common and the passive task is usually given before the focused one as explained in chapter 4.2.2.1. This approach is chosen to prevent that participants continue counting in the passive task as it was required in the focused one (Bennington & Polich, 1999), may it be unintended (Mertens & Polich, 1997), due to conditioning effects (Rappaport et al., 1990), or due to the unmeant continuation of the focused instruction in the passive task (Polich, 1987). Ford and colleagues randomized the order of tasks in their study, but did not examine potential effects on P300 amplitudes in the passive task (Ford, Roth, & Kopell, 1976). In studies investigating

MMN, the use of different attentional instructions is less common, but like in P300 research, the passive or ignore task is usually presented before the active one (i.e. Oades & Dittmann-Balcar, 1995; Sussman, Ritter, & Vaughan, 1998; Sussman, Winkler, & Wang, 2003). These approaches are chosen to avoid an increase of amplitudes in passive tasks that is not caused by the task itself but by the transfer of the preceding focused instruction. Thus, in this study, it shall be clarified, if the order of tasks (ignore, passive, focused) influences the elicited amplitudes in the passive task.

Furthermore, it is assumed that the effects on subjective effort found in study 3 can be replicated. The focused task required sustained attention to the counting of deviant stimuli and was thus expected to be the most strenuous. The ignore task only required few key presses in reaction to predefined scenes in a movie which was expected to be the least strenuous. In accordance with study 3, highest subjective effort is expected in the focused and passive task as compared to the ignore task.

8.2 Methods

8.2.1 Participants

EEG was recorded in 32 healthy adults (12 males) at the University of Würzburg. The participants were between 25 and 55 years old (*M* = 35.66, *SD* = 10.68 years) and received an expense allowance of 8 € per hour. All participants had normal hearing and were not in treatment for any psychiatric or neurological disorder at the time of the experiment. All participants gave written informed consent after they were informed about the nature of the study. The study was conducted in accordance to the Declaration of Helsinki and was approved by the Ethical Review Board of the University Hospital Würzburg.

8.2.2 Experimental procedure and stimuli

The experiment comprised three tasks (ignore, passive, and focused) and four paradigms (two unifeature paradigms, namely MMN Absolute and MMN Proportion, one MMN Multifeature paradigm, P300 paradigm).

MMN Absolute, MMN Proportion, and MMN Multifeature shared the same three-component harmonic tone as a standard with a frequency of 500+1000+1500 Hz, a duration of 75 ms and an intensity of 65 dB. MMN Absolute and MMN Proportion consisted of 900 standard tones and 100 deviants each that differed in duration (MMN Absolute 50 ms, MMN Proportion 37 ms). Thus, the MMN Absolute represents a paradigm with a small DSD, whereas the MMN Proportion represents a paradigm with a large DSD. The first 15 tones were always standards and a deviant was always followed by a standard.

The MMN Multifeature paradigm comprised 800 standards and 800 deviants in four dimensions (duration, frequency, intensity, location). In each dimension, 200 deviants were used of whom 100 differed only slightly from the standard and 100 differed distinctly. In the duration domain, the same deviants as in MMN Absolute and Proportion were used (50 ms and 37 ms, respectively). In the frequency domain, 100 deviants were modified by 10 % (450+900+1350 Hz) and 100 deviants by 20 % (400+800+1200 Hz) of the original frequency. Intensity deviants were either slightly (60 dB) or distinctly (55 dB) quieter than standards. In the location domain, a perceived shift of 5° to either the left or the right ear was produced by introducing an inter-aural time difference of 50 µs between the stereo channels. Thus, the MMN Multifeature paradigm comprised deviants with small and large DSDs in each dimension except from the location deviant.

The MMN Multifeature paradigm was presented in two blocks of approximately eight to nine minutes and each block was preceded by 15 standard tones to implement a memory trace. To prevent confounding effects of intensity and duration deviants, a pre-experiment was conducted, in which participants had to up- and down-regulate the intensity of the duration deviants until they were perceived as equally loud. SOA was 500 ms in all MMN paradigms.

Finally, the P300 paradigm was the same as described in chapter 6.2.2 and comprised 480 three-component harmonic tones of which 420 were standards (440+880+1760 Hz) and 60 were deviants (247+494+988 Hz). SOA in the P300 paradigm was 850 ms.

MMN Absolute, MMN Proportion, and the P300 paradigm were presented three times under three different instructions: ignore task, passive task, and focused task. The instructions were the same as described in chapter 7.2.2 with the change that in the focused task, participants did not have to press a key, but to only count silently and report the number of scenes verbally to the experimenter. The MMN Multifeature paradigm was not presented in the focused task since counting is not applicable when every other tone is a deviant.

All auditory stimuli were presented via pneumatic transducer in-ear headphones (3M™ E-A-RTONE™ Insert Earphone 3A ABR, 50 ohm) equipped with foam eartips (Etymotic research, inc., eartips for ER-3 & ER-5).

Presentation of the three tasks was divided into two appointments with a time interval of one to seven days in-between. The tasks were presented in a pseudorandom order such that in the session with two tasks, one always was the ignore task to limit fatigue and monotony due to mere listening in the focused and passive tasks. The order of the tasks varied in four versions: focused-passive-ignore, passive-ignore-focused, ignore-focused-passive, passive-focused-ignore. Within the tasks, paradigms were presented in a random order, but such that a paradigm was never presented twice in a row when changing to the next task.

Finally, participants indicated their subjective effort after each paradigm on a scale ranging from 0 to 220 with seven labels ranging from “rarely strenuous” at 20 to “extraordinarily strenuous” at about 205 (Eilers et al., 1986). Participants could mark the scale at an arbitrary position.

8.2.3 Material and data acquisition

EEG was recorded according to the international 10-20 system with a g.tec system and g.recorder (g.tec, Graz, Austria) using 31 Ag/AgCl active electrodes at the following scalp sites: Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FCz, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, O1, O2, and on the right mastoid. The ground electrode was placed at AFz and the data were online referenced to the left mastoid. Four additional electrodes were attached to the two external canthi, as well as above and below the right eye, to monitor eye movements (EOG). The EEG and EOG had a sampling rate of 500 Hz and were online band-pass filtered between 0.01 Hz and 250 Hz.

8.2.4 Data pre-processing and analysis

Pre-processing and analysis of EEG data was carried out in MATLAB 2011b (The Math Works, Inc., M.A.) using the EEGlab toolbox (Delorme & Makeig, 2004) and the ERPlab toolbox extensions (http://erpinfo.org/erplab). Statistical calculations were performed in SPSS 17.0 (SPSS Inc., IL).

EEG data were offline band-pass filtered between 0.5 and 25 Hz (Kaiser windowed sinc FIR filter, 3624 points). The ocular channels were bipolarized into vertical and horizontal EOG. Furthermore, the data was re-referenced to the linked mastoids and epochs from -100 to 500 ms for the MMN paradigms and from -200 to 1000 ms for the P300 paradigms were created. Time windows from -100 to 0 ms for the MMN paradigms and -200 to 0 for the P300 paradigms were used as a baseline. Eye movement artefacts were corrected using a regression-based procedure (Gratton et al., 1983) and all trials containing signal changes of ± 80 µV were excluded from further analysis using an automatic peak-to-peak detection method.

Finally, grand averages were obtained. For statistical analyses, the electrodes F3, Fz, F4, C3, Cz, and C4 were selected for the MMN paradigms. In the P300 paradigm, Fz, Cz, and Pz were selected (Duncan et al., 2009). The relevant time windows for all analyses were defined by visual inspection and automatic peak detection. For the MMN paradigms, the mean amplitudes 40 ms around the relevant peaks entered analyses. In the P300 paradigm, a time window ranging from 220 to 400 ms was selected.

In all paradigms, difference waves were obtained by subtracting the standards from the deviants. The mean amplitude under the curve in the corresponding time windows entered into the statistical analyses. For all ANOVAs, the Greenhouse-Geisser corrected results are reported (Greenhouse & Geisser, 1959) since the assumption of sphericity was violated in all the analyses and values of epsilon were smaller than .75, which is the recommended threshold for application of the Greenhouse-Geisser correction (Girden, 1992). Post-hoc comparisons were conducted for significant main effects and interactions. Reported results were SIDAK corrected as implemented in SPSS 17.0. The effect size partial eta square (ηp^2) is reported for each significant effect, whereas $\eta p^2 = .01$ represents a small, $\eta p^2 = .06$ a medium and $\eta p^2 = .14$ a large effect (Cohen, 1988).

In addition to the amplitudes at scalp electrodes, mastoid amplitudes were analyzed in the MMN paradigms. All eye blinks were eliminated and the data were re-referenced to IO2 (electrode below the eye). The mean amplitude under the curve in a time interval of 40 ms around the most positive peak entered analyses.

To analyze the ERP data, multivariate ANOVAs with repeated-measures with the difference waves as dependent variables were performed including the following factors: task (ignore, passive, focused), DSD (small vs. large), paradigm (unifeature vs. multifeature), dimension (duration, frequency, intensity), region (frontal, central, parietal), and laterality (left, middle, right). Furthermore, t-tests comparing the mean amplitudes to zero were conducted for midline electrode sites to detect the elicitation of a component.

8.3 Results

8.3.1 Unifeature paradigms

8.3.1.1 MMN Absolute

A significant negative component was elicited in all tasks. Visual analysis identified double peaks in the focused task at about 155 ms and 240 ms and in the passive task at about 165 ms and 215 ms, and a broad single peak at about 160 ms in the ignore task. The first peak was interpreted as an MMN while the second peak was assumed to represent an N2b. Reversed amplitudes at mastoid sites were only detected for the first peak.

A repeated measures ANOVA was conducted including the factors task, region, and laterality. Amplitudes varied as a function of task ($F(2, 62) = 5.68$, $p = .006$, $\eta p^2 = .155$). Post-hoc comparisons revealed that amplitudes in the focused task ($M = -2.89$ µV) were significantly larger than amplitudes in the passive task ($M = -2.07$ µV; $p = .019$) and marginally significantly larger compared to the ignore task ($M = -2.25$ µV; $p = .056$). Clarification of the significant interaction of task and region ($F(2, 62) = 3.95$, $p = .025$, $\eta p^2 = .113$) revealed these effects to be present over central sites (both $p \leq .015$), but not over frontal ones. No further significant main effects or interactions were found. For further clarification mastoid amplitudes were analyzed. Amplitudes did not differ as a function of task.

Taken together, the amplitudes at the scalp electrodes indicated an effect of attention. However, this effect was not supported by mastoid amplitudes. Figure 11 depicts the amplitudes at frontal and central electrodes in all three tasks for the MMN Absolute paradigm.

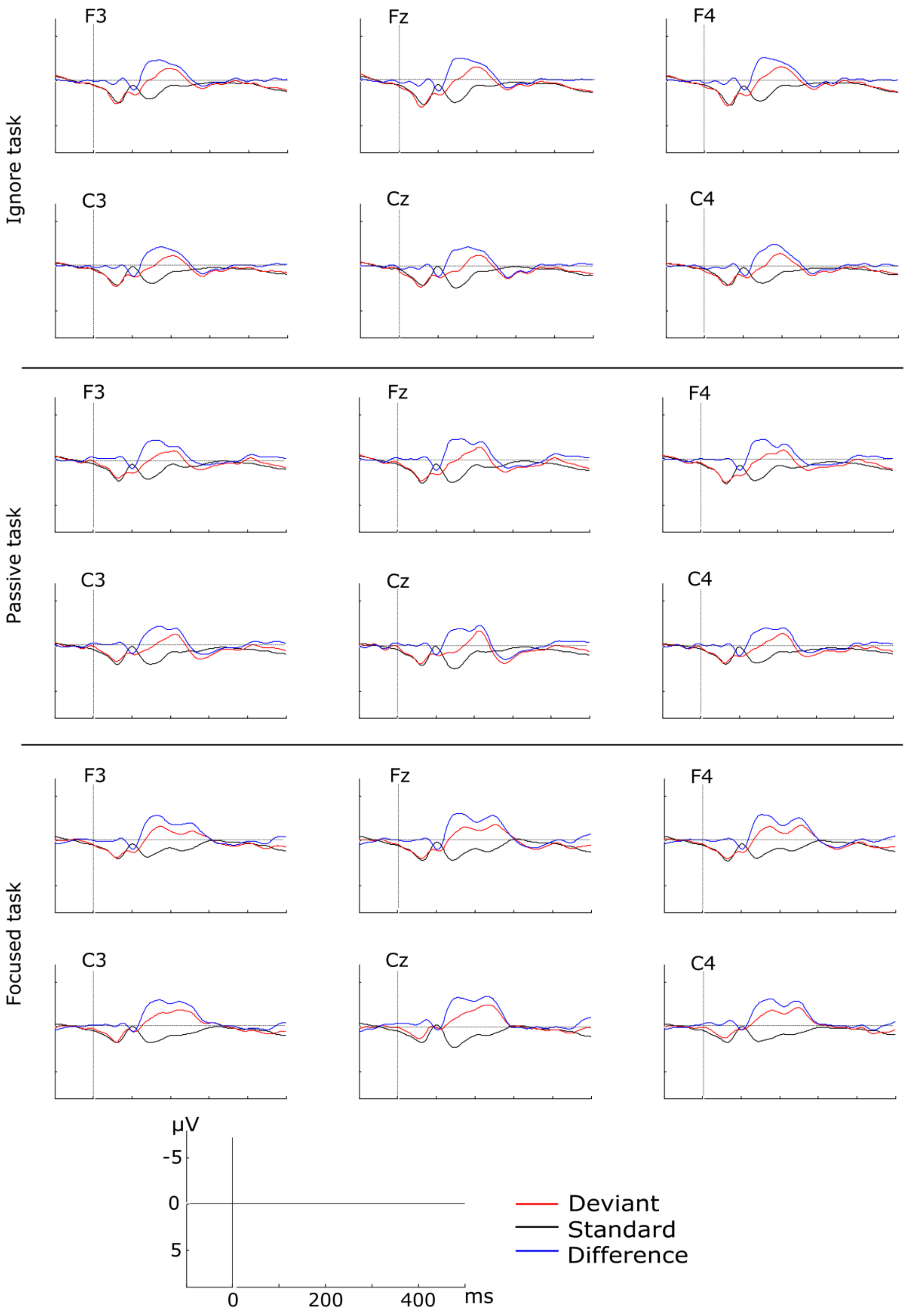

Figure 11: Grand averages across all subjects elicited in the MMN Absolute paradigm at F3, Fz, F4, C3, Cz, and C4 in all three tasks. In the ignore task, a broad single peak was elicited. In the passive and focused task, a double peak emerged. The first peak was interpreted as MMN while the second peak was interpreted as N2b.

8.3.1.2 MMN Proportion

In the MMN Proportion paradigm, visual analysis identified a double peak at about 140 ms and 230 ms in the focused task, a single peak at about 145 ms in the ignore task and a single peak at about 145 ms with a later bulge at about 215 ms in the passive task. The first peak was interpreted as an MMN while the second peak was assumed to represent an N2b. Reversed amplitudes at mastoid sites were only detected for the first peak. Amplitudes of MMN entered analyses.

A repeated measures ANOVA including the factors task, region, and laterality was conducted. Amplitudes varied as a function of task ($F(2, 62) = 9.33$, $p = .001$, $\eta p^2 = .231$). Post-hoc comparisons revealed that amplitudes in the focused task ($M = -3.39$ µV) were significantly smaller as compared to amplitudes in the passive ($M = -4.00$ µV; $p = .014$) and ignore task ($M = -4.25$ µV; $p = .004$). Further analysis of the marginally significant interaction of task and laterality ($F(4, 124) = 2.65$, $p = .056$, $\eta p^2 = .079$) revealed this effect to be present over all lateralities (all $p \leq .049$). In addition, amplitudes were larger over frontal regions as compared to central ones ($F(1, 31) = 11.38$, $p = .002$, $\eta p^2 = .268$). No further significant main effects or interactions were found. For further clarification mastoid amplitudes were analyzed. One participant had to be excluded due to data exportation problems. Amplitudes did not differ as a function of task.

Taken together, the amplitudes at the scalp electrodes indicated an effect of attention. However, this effect was not supported by mastoid amplitudes. Figure 12 depicts the amplitudes at frontal and central electrodes in all three tasks for the MMN Proportion paradigm.

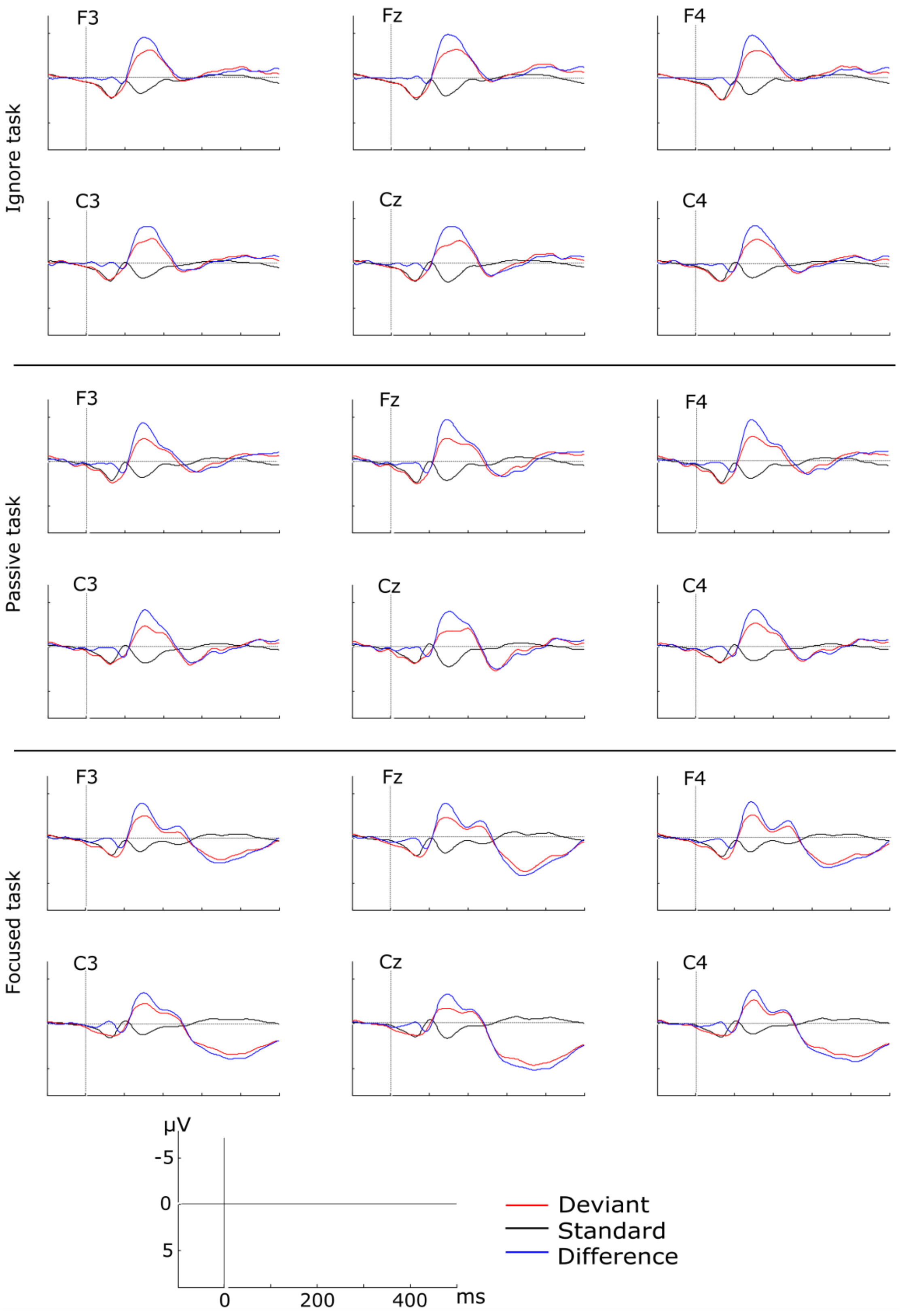

Figure 12: Grand averages across all subjects elicited in the MMN Proportion paradigm at F3, Fz, F4, C3, Cz, and C4 in all three tasks. In the ignore task, a distinct single peak was elicited. In the passive task, the peak was followed by a later bulge. In the focused task, two distinct peaks were detected. The first peak was interpreted as MMN while the second peak was interpreted as N2b. In the focused task, a distinct P300 starting at about 250 ms can be detected.

8.3.2 Multifeature paradigm

Visual analysis identified different ERP waveforms according to task, dimension and DSD. Duration deviants elicited a single peak at about 145 ms when DSD was large and a single peak at about 160 ms with a second bulge at about 210 ms when DSD was small. Frequency deviants elicited a single peak in both conditions, small (about 155 ms) and large DSD (about 145 ms). Intensity deviants with small DSD elicited a double peak at about 115 and 210 ms in the passive task and an expanded peak at about 210 in the ignore task. Intensity deviants with large DSD elicited a single peak at about 185 ms with a preceding bulge at about 125 ms. Duration and frequency deviants elicited only one distinct peak which was interpreted as MMN. For intensity deviants, the first peak was interpreted as N1 and the second peak was interpreted as MMN. A significant negative component was elicited at all sites in both, the passive and ignore task (all $p \leq .008$), for duration, frequency, and intensity deviants. No significant component was elicited by location deviants.

A repeated measures ANOVA including the factors task, DSD, dimension, region, and laterality was conducted. Overall amplitudes were larger for large DSDs ($M = -4.57$ µV) as compared to small DSDs ($M = -2.85$ µV; $F(1, 31) = 148.52$, $p < .001$, $\eta p^2 = .827$) and post-hoc comparisons confirmed that effect in all three dimensions (all $p < .001$). In addition, DSD interacted with dimension ($F(2, 62) = 5.78$, $p = .007$, $\eta p^2 = .157$) and post-hoc comparisons revealed that for both DSD levels, amplitudes were smaller for intensity deviants as compared to duration and frequency deviants (all $p \leq .027$). Furthermore, task interacted with laterality ($F(2, 62) = 7.42$, $p = .002$, $\eta p^2 = .193$) and post-hoc comparisons revealed significantly larger amplitudes in the passive task as compared to the ignore task ($p = .038$) over the left laterality, but not over the other lateralities. Another by trend significant interaction was found for task and DSD ($F(1, 31) = 3.24$, $p = .082$, $\eta p^2 = .094$): Amplitudes in the passive task were by trend larger than in the ignore task for small DSD ($p = .056$), but not for large DSD. All significant main effects and interactions are listed in Table 10.

Table 10: Results of the repeated measures ANOVA for MMN Multifeature including the factors DSD (small vs. large), dimension (duration, frequency, intensity), task (ignore, passive), region (frontal, central), and laterality (left, middle, right)

factor		
DSD	*F*	148.52
	df	1, 31
	p	.000
	ηp²	.827
dimension	*F*	14.58
	df	2, 62
	p	.000
	ηp²	.320
region	*F*	26.99
	df	1, 31
	p	.000
	ηp²	.466
laterality	*F*	18.61
	df	2, 62
	p	.000
	ηp²	.375
DSD*dimension	*F*	5.78
	df	2, 62
	p	.007
	ηp²	.157
dimension*region	*F*	5.98
	df	2, 62
	p	.005
	ηp²	.162
DSD*dimension* region	*F*	3.51
	df	2, 62
	p	.042
	ηp²	.102
task* laterality	*F*	7.42
	df	2, 62
	p	.002
	ηp²	.193
region*laterality	*F*	7.64
	df	2, 62
	p	.003
	ηp²	.198
dimension* region* laterality	*F*	2.91
	df	4, 124
	p	.030
	ηp²	.086

For further clarification mastoid amplitudes were analyzed. Amplitudes varied significantly as a function of dimension (*F*(2, 62) = 3.96, *p* = .029, ηp^2 = .113) and post hoc comparisons revealed that amplitudes elicited by duration deviants were significantly larger than those elicited by intensity deviants (*p* = .025) and by trend significantly larger than those elicited by frequency deviants (*p* = .094). In addition, amplitudes elicited by deviants with large DSD were by trend significantly larger than those elicited by deviants with small DSD (*F*(1, 31) = 3.32, *p* = .078, ηp^2 = .097). Amplitudes did not differ as a function of task.

An additional ANOVA including scalp electrodes was calculated to detect whether the difference between amplitudes for deviants with small vs. large DSD depended on the dimension of deviance. The ANOVA included the difference between amplitudes elicited by deviants with small vs. large DSD (DA) and contained the factors dimension, task, region, and laterality. Amplitudes differed significantly as a function of dimension (*F*(2, 62) = 5.78, *p* = .007, ηp^2 = .157). For frequency deviants, DA was significantly larger as compared to intensity deviants (*p* = .014), while DA for duration deviants did not differ from the two. Overall, DA was marginally significantly smaller in the passive task as compared to the ignore task (*F*(1, 31) = 3.24, *p* = .082, ηp^2 = .094).

Taken together, amplitudes were largest for large DSD and in the duration and frequency dimension. In addition, amplitudes at scalp electrodes indicated a small effect of attention for small DSD and a small effect of attention on DA. However, no attention effect was found in the mastoid data. Figure 13, Figure 14, and Figure 15 depict the amplitudes elicited by duration, frequency and intensity deviants at frontal and central electrodes in the ignore and passive task for the MMN Multifeature paradigm.

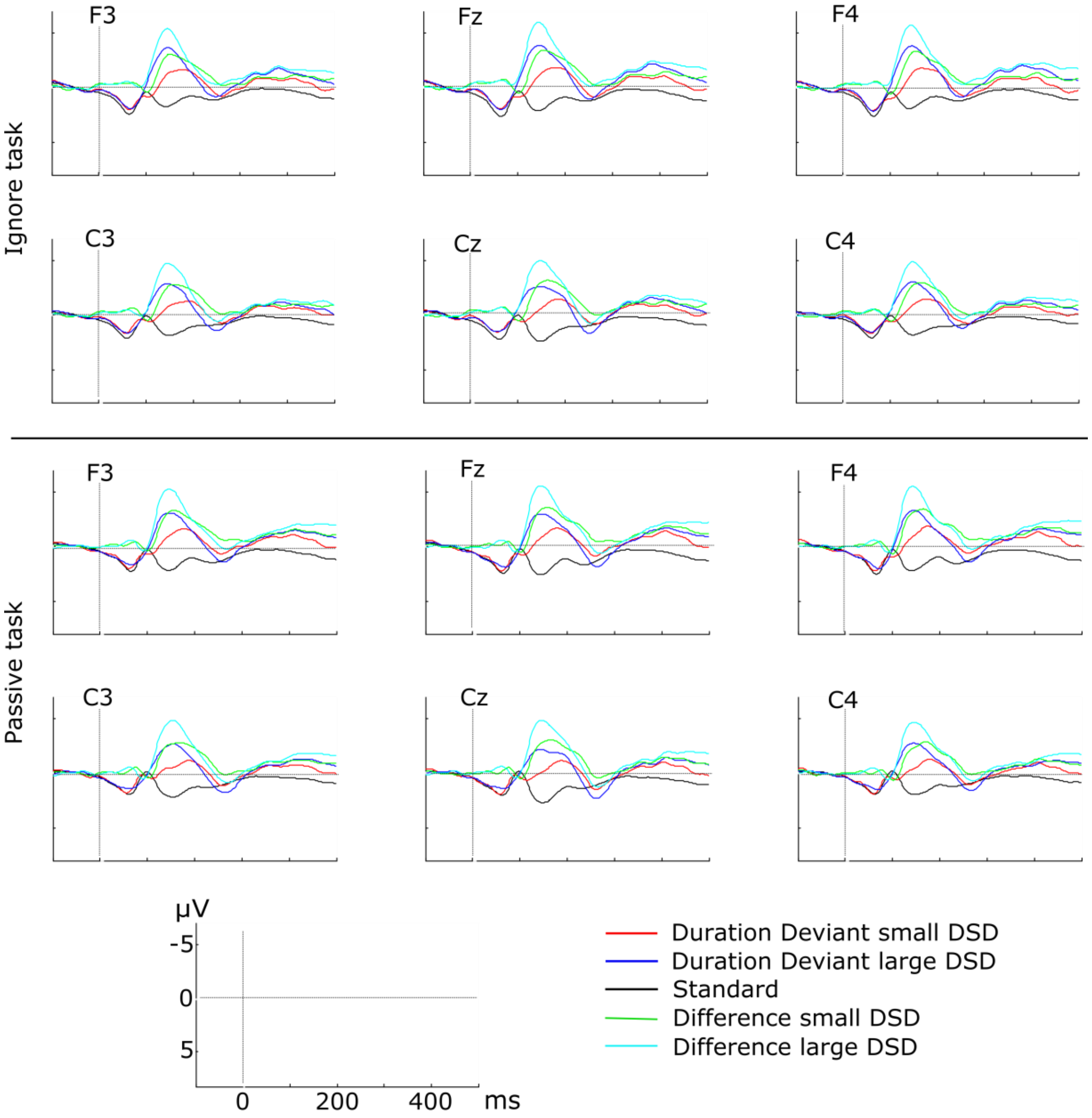

Figure 13: MMN grand averages across all subjects for duration deviants elicited in the MMN Multifeature paradigm in the ignore and passive task. In the ignore task, a distinct single peak was elicited. In the passive task, the peak was followed by a later bulge. The peak was interpreted as MMN while the later bulge might indicate an N2b.

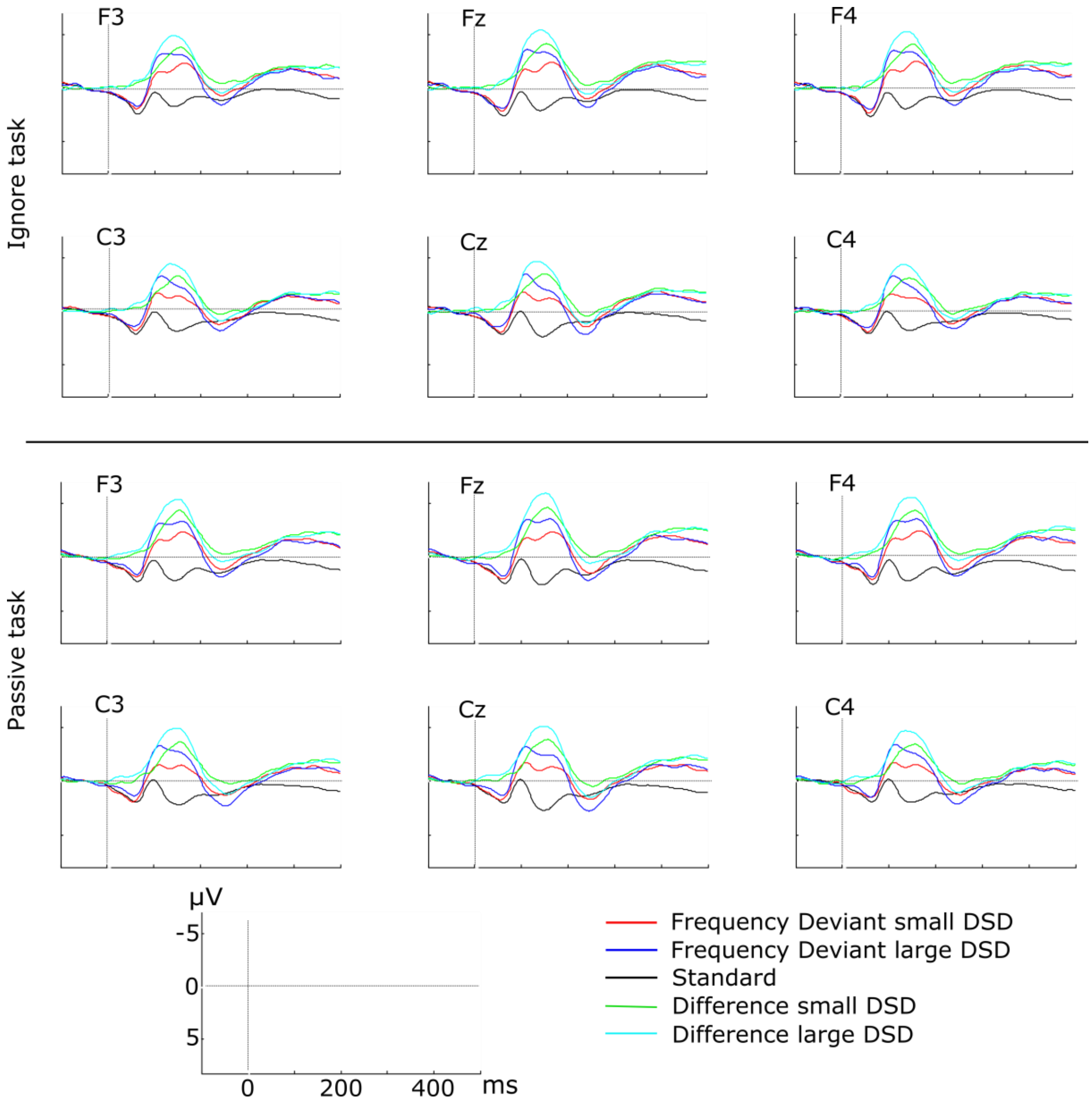

Figure 14: MMN grand averages across all subjects for frequency deviants elicited in the MMN Multifeature paradigm in the ignore and passive task. In both tasks, a distinct single peak was elicited which was interpreted as an MMN.

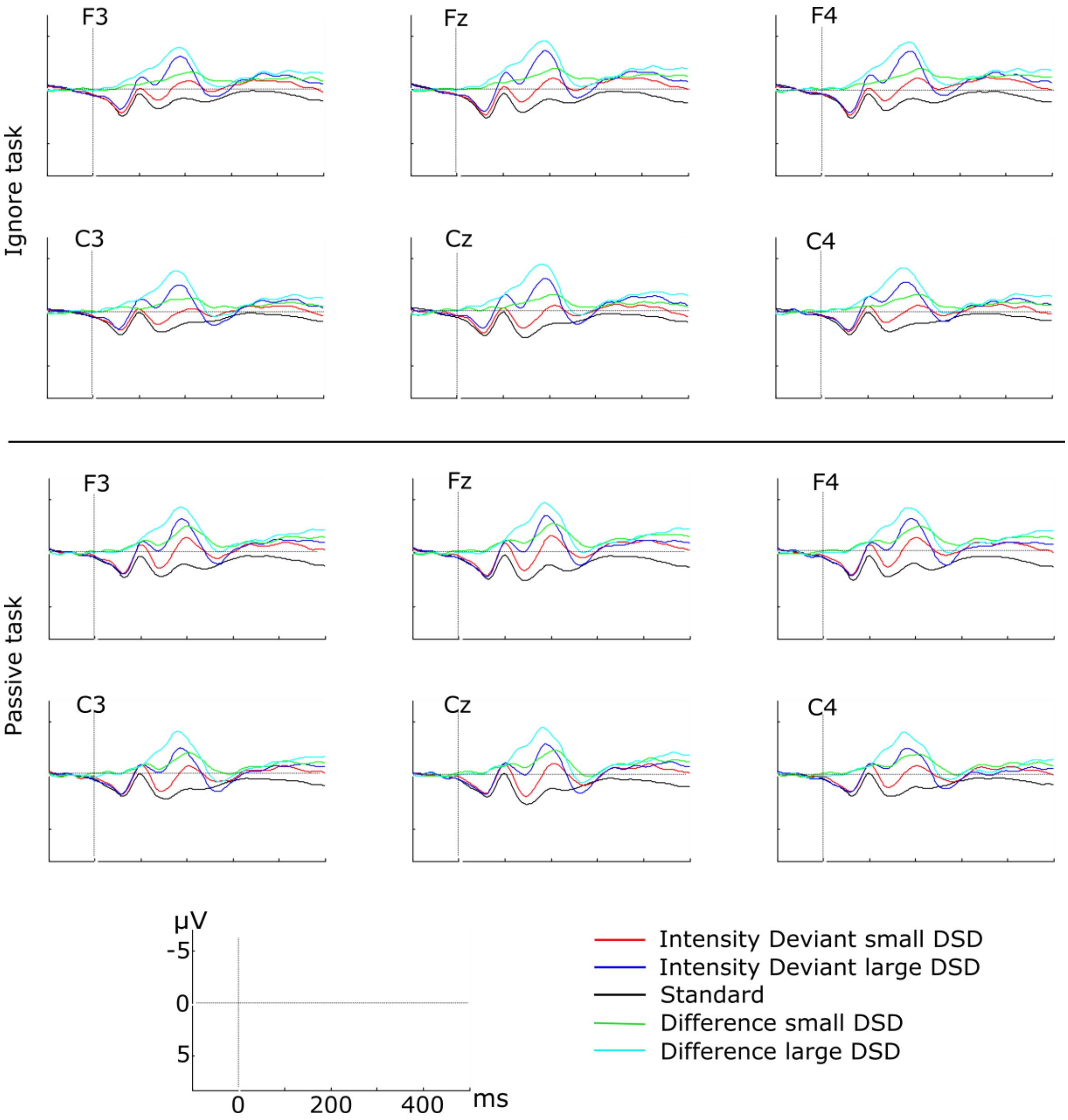

Figure 15: MMN grand averages across all subjects for intensity deviants elicited in the MMN Multifeature paradigm in the ignore and passive task. In both tasks, a single peak with a preceding bulge was elicited. The peak was interpreted as MMN and the preceding bulge was interpreted as an N1.

8.3.3 Effects of paradigm and deviant-to-standard distance

A repeated measures ANOVA including the factors task (ignore and passive), paradigm unifeature and multifeature), DSD, region, and laterality was conducted for the duration deviants in the unifeature vs. multifeature paradigm in the ignore and passive task. Overall amplitudes were higher in the multifeature paradigm (*M* = -3.91 µV) as compared to the unifeature paradigm (*M* = -3.14 µV; *F*(1, 31) = 22.65, *p* < .001, ηp^2 = .422). In addition, deviants with large DSD elicited higher amplitudes as compared to deviants with small DSD (*F*(1, 31) = 147.17, $p < .001$, $\eta p^2 = .826$), which was the case in both paradigms (both $p < .001$). Amplitudes did not vary as a function of task. All significant main effects and interactions are listed in Table 11.

Table 11: Results of the repeated measures ANOVA for MMN Multifeature, MMN Absolute and MMN Proportion for duration deviants including the factors: DSD (small vs. large), paradigm (unifeature, multifeature), task (ignore, passive), region (frontal, central), and laterality (left, middle, right)

factor		
paradigm	*F*	22.65
	df	1, 31
	p	.000
	ηp^2	.422
DSD	*F*	147.17
	df	1, 31
	p	.000
	ηp^2	.826
region	*F*	16.97
	df	1, 31
	p	.000
	ηp^2	.354
laterality	*F*	6.96
	df	2, 62
	p	.003
	ηp^2	.183
DSD*region	*F*	8.93
	df	1, 31
	p	.005
	ηp^2	.224
paradigm*laterality	*F*	4.69
	df	2, 62
	p	.018
	ηp^2	.132
region*laterality	*F*	5.86
	df	2, 62
	p	.006
	ηp^2	.159

For further clarification mastoid amplitudes were analysed. Deviants with large DSD elicited higher potentials compared to deviants with small DSD (*F*(1, 30) = 8.37, $p = .007$, $\eta p^2 = .218$). Amplitudes did not vary as a function of task or paradigm.

Taken together, both, scalp electrodes and mastoid amplitudes indicate larger amplitudes when DSD is high. Larger amplitudes in the multifeature paradigm were found at scalp electrodes, but not at mastoid sites.

8.3.4 P300

A significant positive component was elicited in the focused and the passive task (all $p < .001$) at Fz, Cz, and Pz. It was interpreted as a P300. No deflection significantly different from zero was elicited in the ignore task. Figure 16 depicts the amplitudes in all three tasks for the P300 paradigm at the three electrodes that entered analyses.

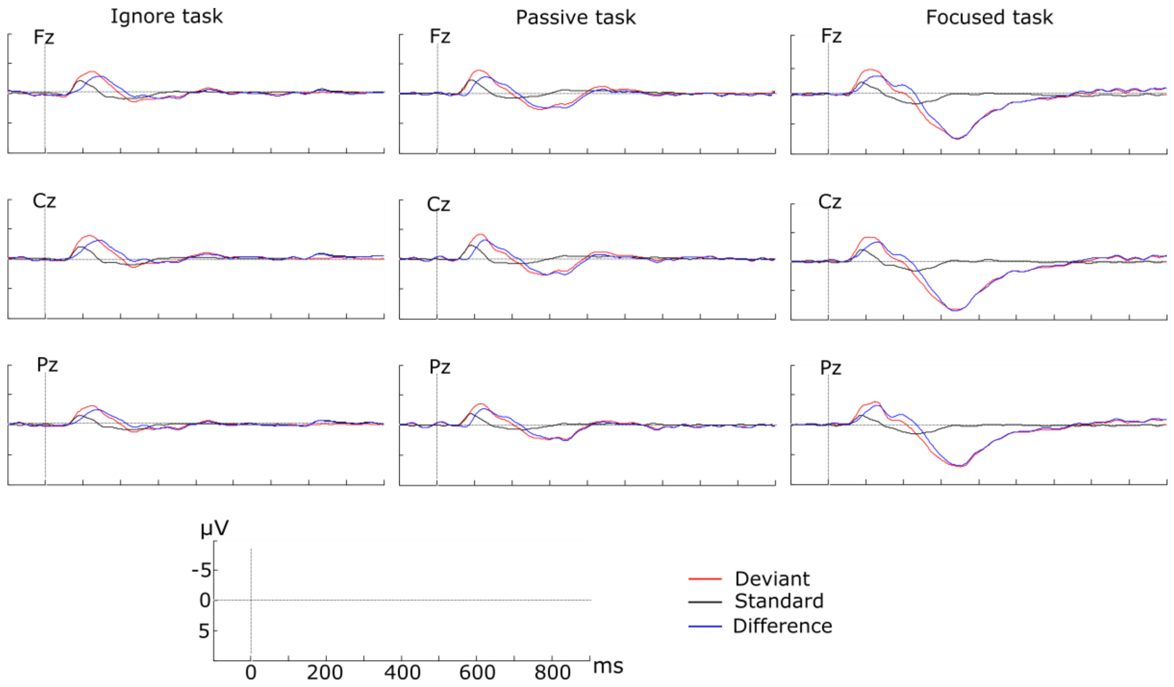

Figure 16: Grand averages across all subjects elicited in the P300 paradigm in all three tasks. In all tasks, a negative deflection at about 100 ms was elicited which can be interpreted as N1. No P300 was elicited in the ignore task. In the passive task, a small P300 was visible and in the focused task, a distinct P300 could be identified. In all tasks, a N1 in response to standards and deviants peaking at about 100 ms can be detected.

A repeated measures ANOVA including the factors task and region was conducted to detect significant variation according to task. P300 amplitudes were largest in the focused task ($M = 5.05$ µV), smaller in the passive task ($M = 1.89$ µV), and not significantly different from zero in the ignore task ($F(2, 62) = 61.71$, $p < .001$, $\eta p^2 = .666$; all post-hoc $p < .001$). This effect was present in all regions (all post-hoc $p \leq .001$). In addition, task interacted with region ($F(4, 124) = 10.09$, $p < .001$, $\eta p^2 = .246$). Post-hoc comparisons revealed largest amplitudes over central and parietal regions as compared to frontal sites (both $p \leq .011$) in the focused task. In the passive task, amplitudes were largest over central regions as compared to frontal and parietal ones while frontal and parietal amplitudes did not differ from each other (both $p \leq .002$). No such difference was found in the ignore task.

Taken together, a P300 was only elicited in the passive and focused task while the scalp distribution in terms of the most prominent occurrence was slightly different between the two.

8.3.5 Order effects

To test for potential effects of the order of tasks, amplitudes in the passive task were compared between the groups defined by the order of tasks in the paradigms MMN Absolute, MMN Proportion, and P300. The MMN Multifeature paradigm was not included because it was not presented under the focused instruction. Repeated measures ANOVA including the factors region for P300 and including the factors region and laterality for MMN Absolute and MMN Proportion, respectively, were conducted. In addition, the between-subject factor order (focused-passive, passive-focused) was included. The between-subject factor order did not reach a level of significance for any of the paradigms.

8.3.6 Subjective effort and performance

The participants indicated their subjective effort after the completion of each paradigm in each task (Table 12). Repeated-measures ANOVA with the two factors task (ignore, passive, focused) and paradigm (MMN Absolut, MMN Proportion, P300) were performed to detect any significant variation as a function of the attentional instruction and auditory stimuli.

MMN Multifeature was not included in this analysis because it was not presented under the focused task.

Table 12: The mean values (*M*) and standard deviations (*SD*) of stated subjective effort listed for all paradigms (columns) and tasks (rows)

		MMN Absolute	MMN Proportion	P300	MMN Multifeature
ignore task	*M*	61.25	58.75	61.25	62.03
	SD	43.25	43.11	52.89	51.07
passive task	*M*	51.41	57.18	45.16	44.84
	SD	40.96	41.81	35.16	35.19
focused task	*M*	108.59	109.84	79.37	
	SD	54.72	60.10	50.68	

Task interacted significantly with paradigm ($F(4, 124) = 4.76$, $p = .004$, $\eta p^2 = .133$). Post-hoc comparisons revealed that in all paradigms, the focused task was most strenuous (all $p \leq .046$) while the ignore and passive task did not differ from each other. In the MMN Multifeature paradigm, subjective effort in the ignore and passive task did not differ significantly. These results contradict the previous assumption of the passive and focused task being equally more demanding compared to the ignore task.

In the analysis of the counting results of the movie scenes in the ignore task, the two blocks of MMN Multifeature were treated separately, resulting in five sequences. Some participants had to be excluded due to technical problems. Relevant scenes were shown and counted but counting results were not recorded. In the MMN Absolute and the Multifeature (block 1) paradigms, data of five participants was missing, in the MMN Proportion and in the P300 paradigm data of four participants was missing, in the MMN Multifeature (block 2) paradigm data of six participants was missing. In the MMN Absolute paradigm, 19 out of 27 participants detected all scenes correctly. In the MMN Proportion paradigm, 16 out of 28 participants detected all scenes, in the P300 paradigm nine out of 28 participants detected all scenes, in the MMN Multifeature (block 1) 15 out of 28 participants detected all scenes, and in the MMN Multifeature (block 2) 16 out of 26 participants detected all scenes correctly. The number of missed scenes ranged between one and six. Four participants counted the scene between one and four times although it had not appeared. The number of missed scenes did not vary according to the paradigms.

In the analysis of the counting of deviants in the focused task, some participants had to be excluded. In the MMN Absolute paradigm, one participant had to be excluded because data was missing and three participants had to be excluded because their counting results differed from the group mean by more than two standard deviations. In the MMN Proportion paradigm, one participant had to be excluded because his counting results differed from the group mean by more than two standard deviations. The difference in counting results between MMN Absolute and MMN Proportion was not significant. Table 13 lists the mean counting results for each paradigm.

Table 13: Counting results in the focused task for MMN Absolute, MMN Proportion, and P300. The correct number of deviants was 100 for both MMN paradigms and 60 for the P300 paradigm.

		counting result
MMN Absolute	*M*	89.43
	SD	26.96
MMN Proportion	*M*	97.29
	SD	10.89
P300	*M*	59.97
	SD	3.49

8.4 Discussion and summary

The goal of the present study was to investigate the effect of different attentional instructions and stimulus features on MMN and P300. Following the attentional instructions the participants either focused on the stimuli, listened passively, or focused on a concurrent sensory input. All the ERP effects described in the corresponding literature (MMN, P300) were successfully replicated with the exception of the location deviant by which no MMN was elicited. Larger MMN amplitudes were elicited by deviants highly different from the standard and in multifeature paradigms. The ERP effects depended on the direction of attention, and attentional effects were larger for P300 as compared to MMN. In addition, also subjective effort was affected by the three attentional tasks. The following chapter discusses these findings and their implications.

8.4.1 Effects of attention

Differential effects of attention were found in the different paradigms. In the MMN Absolute paradigm, smallest amplitudes were elicited in the ignore task, larger ones in the passive task and the largest ones in the focused task. In the MMN Proportion paradigm, amplitudes were smallest in the focused task as compared to the ignore and passive task. However, these small amplitudes in the focused task might have been caused by the large and dominant P300 following the MMN (see Figure 12). A P300 was not present in the ignore and passive task. In the MMN Multifeature paradigm, results at some electrodes indicated higher amplitudes in the passive task as compared to the ignore task. These results are in line with a former study finding an effect of attention only for low deviant stimuli and only for one of two recording sessions (Müller, Achenbach, Oades, Bender, & Schall, 2002). Thus, attention effects on MMN seem to be of an inconsistent nature. None of the attention effects found in this study was present at the respective mastoid electrodes. Thus, the results argue for an attentional effect on the frontal component of the MMN, but not on the supratemporal one as outlined by Rinne (2001), replicating the findings of study 3.

A potential overlap of MMN with N1 and N2b has already been discussed in study 3 (see chapter 7.4.1). Like in study 3, short intervals of analyses were chosen to minimize the risk of overlap. These intervals started well after the N1 range and well before the N2b range. Distinct second peaks could be observed in the passive task in the MMN Absolute paradigm and in the focused task in the MMN Absolute and the MMN Proportion paradigm. These second peaks were interpreted as N2b and did not occur in the MMN Multifeature paradigm. As an exception, two peaks were observed in the MMN Multifeature paradigm for intensity deviants with small DSD in the passive task. However, for intensity deviants, MMN occurs later than for frequency and duration deviants (Pakarinen et al., 2007). The two peaks occurred at latencies of about 115 and 205 ms. Thus, the first one was interpreted as N1 and the second one as MMN. Because of the late latency of intensity deviants (between 180 and 210 ms), for these deviants an overlap with N2b in the passive task cannot be excluded. However, no distinct attentional effect on intensity deviants was detected in the first place. This is contradictory to former studies reporting no effect of attention on frequency MMN, but on intensity MMN (Näätänen, Paavilainen, Titinen, Jiang, & Alho, 1993; Schröger, 1996).

In the P300 paradigm, strong attentional effects as already reported in the literature (Bennington & Polich, 1999; Spencer & Polich, 1999) could be replicated. No P300 was elicited when attention was withdrawn, a small P300 emerged in the passive task and a large P300 was elicited in the focused task. In the passive task, the P300 exhibited a scalp distribution reaching its maximum over central sites while in the focused task, amplitudes where highest over central and parietal sites. Thus, the P300 in the focused task was most likely a P3b while classification of the P300 in the passive task remains inconclusive since no predominance of frontal or parietal sites was observed (Polich, 2007).

In the comparison between different orders of task, no effect was evident for amplitudes in the passive task in either paradigm, MMN Absolute, MMN Proportion, or P300. Thus, amplitudes in the passive task were not larger when it was preceded by the focused one. These results indicate that a potential transfer of the focused instruction on the passive task (Bennington & Polich, 1999; Mertens & Polich, 1997; Polich, 1987; Rappaport, Clifford, & Winterfield, 1990) has either not taken place or has not lead to larger amplitudes in the passive task.

Taken together, attentional effects on P300 were found as expected while the exact impact of attention on MMN remains inconclusive in the present study. Its investigation is complicated by confounding effects like a following P300 in the focused task as it was the case in the MMN Proportion paradigm. Amplitudes at scalp electrodes indicate amplitudes to be affected by attentional modulation while no effect of attention was found at mastoid amplitudes. However, when oddball paradigms are applied to patient samples, the focus of analyses is clearly on scalp electrodes, thus emphasizing the importance of the present results.

8.4.2 Effects of paradigm and deviant-to-standard distance

Duration, frequency and intensity deviants elicited reliable MMNs also in multifeature paradigms. For duration deviants, physically identical deviants elicited even higher MMN amplitudes in the multifeature as compared to the unifeature paradigms (MMN Absolute and MMN Proportion). At the same time, the multifeature paradigm was not judged to be more stressful than the unifeature paradigms.

Like in previous studies, the present results show an increase in MMN amplitudes for large DSDs (Jaramillo, Paavilainen, & Näätänen, 2000; Pakarinen, Takegata, Rinne, Huotilainen, & Näätänen, 2007). This effect was found for all deviants eliciting an MMN, namely frequency, duration, and intensity deviants. No MMN was detected for location deviants that were shifted by 5° to the left or to the right, although location MMN has been shown before in numerous studies (Näätänen, Pakarinen, Rinne, & Takegata, 2004; Paavilainen, Karlsson, Reinikainen, & Näätänen, 1989; Pakarinen, Takegata, Rinne, Huotilainen, & Näätänen, 2007). However, the usual shift is larger than the ones used in the current study: Previous studies applied a shift of 90° (Näätänen et al., 2004) or 70° of deviation (Vuust, Brattico, Seppänen, Näätänen, & Tervaniemi, 2012). He and colleagues (2013) included numerous location deviants with a deviation between 10 and 90°. Nonetheless, Pakarinen and colleagues (2007) comprised location deviants of varying deviation and an MMN was also elicited for deviants of 5°, albeit being very small. To draw a conclusion, a deviation of at least 10° or more should be applied to observe a reliable MMN.

8.4.3 Subjective effort

Highest ratings of subjective effort were reported in the focused task, whereas the passive and ignore task did not differ from each other. This finding contradicts the original hypothesis and the results of study 3 in which the passive and focused task were equally strenuous. The ignore and passive task of study 4 were identical to the tasks used in study 3. The focused task was slightly different since in study 3, participants had to press a key and were required to react to semantic content, also, while in study 4, only silent counting was necessary.

Low subjective effort in the passive task contradicts the postulate according to which tasks with low signal input for a prolonged period of time require high amounts of processing capacities and are stressful (Warm, Parasuraman et al., 2008; see chapter 7.4.3). In the present study, the passive task, sharing some commonalities with such vigilance tasks, was not perceived as more stressful than watching a video and looking out for a predefined scene occurring every 15 to 45 seconds, thus engaging the participants minds. It is still likely that participants experienced boredom due to a lack of sufficient environmental stimulation (Eastwood et al., 2012). However, in the current context, this aversive state did not cause the participants to rate the passive task itself as strenuous.

8.4.4 Limitations

While significant effects of attention were found at scalp electrodes no distinct effects at mastoid electrodes could be detected. However, the signal at mastoid electrodes was noisier compared to scalp electrodes, thus reducing the probability of finding significant results. Presumably, this was due to the smaller amount of epochs included after elimination of all epochs containing blinks. Especially in the MMN Absolute paradigm, no distinct deflections were found at mastoid electrodes, thus rendering the analysis less reliable in the first place.

No effect of task order was found for MMN or P300. However, this result is limited by the fact that the present study also included an ignore task and that the presentation of the passive and focused task was always on two different days of measurement. Potential effects of a transfer of the focused instruction to the passive task might thus have been reduced in the first place due to the time period in-between.

8.4.5 Conclusion

The present study provided evidence for a strong attentional effect on P300 amplitudes and a smaller attentional effect on MMN amplitudes. General hypothesis c) as outlined in chapter 4.5 can thus be confirmed for P300, but not for MMN where attentional effects depended on DSD. Furthermore, the present results illustrate the advantage of multifeature paradigms and deviants with large DSD, rendering these stimulus features especially interesting for measurements with patients. Higher amplitudes in the multifeature paradigm may be of benefit in patient settings for several reasons: Firstly, patients often exhibit smaller amplitudes and paradigms eliciting generally larger amplitudes are promising. Secondly, measurements with patients are based on single subject analysis, being even more dependent on distinct deflections than analyses including grand averages. Thirdly, time and attentional awareness are limited resources and paradigms providing more information on cognitive processing within comparable time slots allow for an effective expolitation of these resources. These benefits are supported by our finding that listening to a multifeature paradigm is judged to be as effortless as listening to a unifeature oddball. Taken together, our results indicate multifeature oddball paradigms to be a suitable tool to investigate auditory discrimination profiles. Eliciting larger duration MMNs than the unifeature oddball paradigm renders them especially interesting for research in DOC patients. When applied to patients, a focused instruction is advisable for P300 but not without restrictions for MMN where attentional effects depended on DSD.

9 General discussion and summary

The present work comprised four studies investigating three main topics: a) the opinion of practitioners working with DOC patients on the complementation of current diagnostic procedures by psychophysiological methods comprising ERPs, b) elicitation of ERPs in non-responsive patients with DOC, and c) attentional effects on MMN, N400, and P300. It could be shown that practitioners working with DOC patients have a general interest in new diagnostic measures complementing current procedures. Furthermore, different kinds of ERPs could be detected in patients diagnosed with UWS and MCS indicating preserved cognitive processing. Finally, in studies with healthy participants, attentional effects on MMN, N400, and P300 could be shown and stimulus parameters and instructions eliciting the most prominent ERPs were identified. The following chapter summarizes the most important findings and integrates them into recommendations for future measurements with patients.

9.1 Attention effects on MMN, P300, and N400

9.1.1 Attention and MMN

As outlined in chapter 4.2.1.1, no final conclusion on the debate on attention and MMN has been drawn yet. In the studies presented herein, the frontal component of the MMN, as reflected by amplitudes at scalp electrodes, was affected by attention. Studies 3 and 4 revealed attentional effects on amplitudes over central sites and when DSD was small. At the same time, the supratemporal component of the MMN, as reflected by amplitudes at mastoid sites, was not altered by attention. However, the mastoid signal was noisier and thus less reliable. In their review, Näätänen and colleagues (2007) summarized that attention effects on MMN might vary according to the magnitude of change and the attribute of stimulus deviation. This assumption was supported by the results presented in the present studies: Differential effects of attention were found for different DSDs and dimensions. The authors also postulate that visual task load usually has no effect on MMN amplitude, further strengthening to hypothesis of attentional effects. The three tasks used in the present studies involved different degrees of visual task load. Given the fact, that visual input has no effect on MMN amplitude, the present effects can be attributed to the attentional variation.

Taken together, studies 3 and 4 presented clear evidence that MMN amplitude is affected by attention. It is assumed that amplifying neurons (Näätänen, 1991) generate these effects. Following the two-component models outlined in 4.2.1, the frontal component of MMN was affected by the attentional modulation caused by the three different tasks. The supratemporal component, as reflected by mastoid amplitudes, was not. Thus, the present results support this model and the related assumption of differential proneness to attentional modulation (Rinne, 2001). This model may also co-exist with Sussmans (2007) postulation of two distinct processes leading to the elicitation of an MMN, namely standard formation and deviant detection (see chapter 4.2.1.1). The present work did not aim at testing this model, however, it can by hypothesized that the attentional tasks influenced the standard formation process, thus leading to differing amplitudes.

9.1.1.1 Overlap of MMN with N1

The overlap between MMN and N1 poses a problem in most studies investigating these ERPs. Both potentials arise as early negativities in response to unexpected stimuli and both reverse polarity at mastoid sites. Thus, even though MMN and N1 are regarded as spatiotemporally distinct (i.e. Campbell, Winkler, & Kujala, 2007), separating them is problematic. Following the MMN-N1 additivity hypothesis (Campbell et al., 2007), differentiating and eliminating the N1 effect from the MMN would have required a second control condition, in which the deviant tones are presented in a sequence of many other tones to control for the frequency specific refractoriness. By using such a control condition, it is possible to differentiate the processing of deviant and control tones as reflected by N1 and MMN amplitudes using the components' distributions in the N1/MMN latency range. The negative ERP amplitudes following deviant tones would be larger at fronto-central sites than following the physically identical tones used in the control condition. Thus, this comparison differentiates the memory-based and refractoriness effect of the N1 and MMN (Jacobsen & Schröger, 2001; Schröger & Wolff, 1996). Such a separate condition was not included in the present work because a short paradigm which has already proven to be applicable in DOC patients was used (Kotchoubey et al., 2005).

In the studies presented in this work, an overlap of N1 and MMN cannot be fully excluded. However, the probability that such an overlap may have contaminated the MMN effect, is low for two reasons: Firstly, the time intervals used for analyses of MMN all started after 120 ms, so in a time window in which an N1 potential should already be in decline. Secondly, N1 amplitude heavily depends on the SOA and is smallest when SOA is around 350-500 ms like in the present studies (Budd & Michie, 1994; Davis, Mast, Yoshie, & Zerlin, 1966; Rosburg, Boutros, & Ford, 2008; Sable, Low, Maclin, Fabiani, & Gratton, 2004). Thus, if existent, the potential overlap should be negligible.

In contrast to time-consuming control conditions (Campbell et al., 2007), May and Tiitinen (2010) argue for a completely different point of view, called the adaptation model: The authors consider the MMN to be a part of an amplitude- and latency-modulated N1 response. Following this approach, the response to the deviant, the MMN, is an enhanced N1 response and thus, there is no danger of contamination because it is one and the same potential.

9.1.2 Attention and P300

Attention effects on P300 are widely known (see chapter 4.2.2.1) and results of studies 2 and 4 support these findings. In DOC patients, more ERPs were found when using a focused instruction, thus indicating a benefit of directly guiding the participants' attention toward the relevant stimuli. In healthy participants, the P300 in a focused task was significantly larger as compared to the passive task and no P300 was elicited when attention was withdrawn. Commonly, the P300 is seen as proportional to the amount of attentional resources invested in a task (for a review, see Polich & Kok, 1995) and is even regarded as an index of attention paid to certain stimuli (i.e. Gray, Ambady, Lowenthal, & Deldin, 2004; Wickens, Heffley, Kramer, & Donchin, 1980). Thus, the importance of the usage of focused instructions in clinical settings including patients cannot be overstated.

9.1.3 Attention and N400

Study 3 replicated former studies revealing strong attentional effects on N400. The deflection was significantly smaller in a passive task as compared to a focused one. No N400 was elicited when attention was withdrawn. Differential effects were found for stimulus material comprising full sentences or word-pairs in patients and healthy participants. In patients, no N400 was elicited by word-pairs while a P600 was found in response to sentences. In healthy participants, a clear N400 to word-pairs was only evident in the focused task, while effects in the passive task did not differ significantly from those in the ignore task and were difficult to identify visually.

Kutas and Federmeier described in their review that the N400 incorporates characteristics of both, automatic and controlled processing (2011). Daltrozzo and colleagues came to the conclusion that sentence N400 is mainly a reflection of controlled processes, but did not rule out that single word N400 might also include automatic aspects (Daltrozzo et al., 2012). The results of study 3 tend to support the view that both single word and sentence N400 manifest controlled processes: A pronounced N400 component was only evident when attention was deliberately focused on the verbal stimuli.

The attentional effects on N400 exemplify the problem of applying passive instructions in semantic paradigms. Even in healthy participants no distinct N400 was elicited when attention was not directly guided to the stimuli. In settings including DOC patients, this circumstance can lead to the misjudgment of a patient's information processing capabilities. Thus, the application of focused instructions is vital.

9.2 Subjective effort

Differential effects of the different tasks on subjective effort were found. In study 3, the passive task was experienced as similarly stressful as the focused task. However, in study 4, both, the passive and ignore task were judged to be less strenuous as compared to the focused one. However, considering the range of the scale (0 to 220), all ratings very reasonably low (rarely exceeding 100). In study 3, it was assumed that the experience of boredom and the lack of a specific task to engage attention in, led to increased subjective effort (see chapter 7.4.3). This hypothesis was not supported in study 4 revealing similarly low effort in the passive task as in the ignore task. However, the length of the semantic paradigms was up to 14 minutes in study 3, while in study 4 no paradigm lasted longer than nine minutes. This difference might have heavily contributed to the perception of boredom and thus to the experience of subjective effort. Vigilance tasks are characterized by a low input of stimuli over a prolonged period of time (i.e. Haga, 1984; Noyes, 2009) and it might be possible that paradigms in study 4 were too short to be judged as strenuous.

Moreover, differences in the subjective perception of the tasks might have been caused by the differences in the experimental settings. Study 3 was conducted in only one session while study 4 required the participants to come in twice. In addition, study 3 also included semantic material while study 4 only comprised oddball paradigms. Thirdly, the focused task in study 3 required the participants to press a key and to react to semantic material, also, while the same task in study 4 required silent counting, only. Thus, the judgment of a certain task seems to depend on other tasks it is compared to, and on the general experimental setting.

Taken together, undesired subjective effort may arise especially in lengthy tasks without specific instructions.

9.3 Implications for the measurement with patients with disorders of consciousness

The presented results have important implications for applying ERP-based paradigms in non-responsive patients for assessment of their cognitive functioning. High subjective effort can be caused by passive instructions in healthy participants, which may be due to the passiveness being experienced as stressful and straining. In DOC patients whose attention span is much shorter than that of healthy individuals, requiring sustained attention in the absence of attention attractors may result in failed task performance and a consequent lack of the respective ERP components despite the intact neuronal sources. For the use in patients, a passive instruction might be problematic but it remains unclear to what extent judgments from healthy participants can be transferred to patients. While for healthy participants, two stimuli trains like in the ignore task are suitable to engage their minds, this situation can be overwhelming for patients. Thus, an ignore task is probably inappropriate in patient settings, also regarding potentially disturbed sensory perception. A focused task, albeit risking slightly higher subjective effort, may be beneficial to motivate the patients, to catch their attention, and as a consequence to elicit more reliable ERPs.

Looking at the psychophysiological results, experimenters need to bear in mind that instructions to passively listen to the stimuli can attenuate ERP effects in semantic paradigms. In this case, the expected differences in ERP components might be difficult to find even though the same stimuli would elicit large ERP effects under an active instruction specifically engaging the participant’s attention in a goal-directed task. Particularly at the single subject level, where the signal/noise ratio is relatively low, the aim of stimulation paradigms has to be the elicitation of strong and robust ERP differences, which in semantic paradigms are unlikely to occur without active instructions. In the oddball paradigm, the effect of attention was less clear. Study 3 indicated smaller MMN amplitudes in the ignore and passive task as compared to the focused task. Study 4 revealed differential effects according to DSD and paradigm: For MMN Multifeature and MMN Absolute, amplitudes were larger in the passive task as compared to the ignore task. In the MMN Absolute paradigm, amplitudes in the focused task were still larger than in the passive task. Amplitudes in the MMN Proportion paradigm were smallest in the focused task but this might be due to the following N2b-P300 complex. However, results in the MMN Multifeature and Absolute paradigm indicate smaller amplitudes in the traditional ignore task than in the passive or focused task.

To draw a conclusion, the implementation of passive instruction bears the risk of diminished ERPs in semantic paradigms, while in oddball paradigms, a passive instruction should be preferred to ignore tasks and if possible (unifeature paradigms), a focused instruction can be beneficial. In any case, it has been shown that the application of different instructions can have distinct effects on the size of arising ERPs – a finding that must be taken into account when working with DOC patients.

Further conclusions can be drawn for the stimulus material. One major result of study 4 is the suitability of multifeature paradigms since they evoked ERPs of comparable size to the ones in unifeature paradigms. The MMN Multifeature paradigm was shown to be little strenuous but at the same time it permits the investigation of responses to different stimulus features. This analysis of deviants in several dimensions allows for the identification of the most appropriate dimension for individual patients. While some patients might respond with larger amplitudes to frequency deviants, others might exhibit larger amplitudes in response to duration deviants. Identifying the most appropriate dimension of deviation can also provide valuable information on the BCI to be used. For duration deviants, amplitudes in the MMN Multifeature paradigm were even larger as compared to unifeature paradigms, albeit the deviants used were physically identical. Importantly, no distinct N2b was elicited in the passive task in the MMN Multifeature paradigm while a clear N2b was visible in the MMN Absolute unifeature paradigm. Thus, MMN Multifeature paradigms are a promising tool to be included in patient assessments. Study 4 also revealed larger amplitudes for duration and frequency deviants compared to intensity deviants and higher amplitudes for deviants with larger DSD. Thus, future studies should present multifeature paradigms to patients to investigate their suitability in that special population. In patient settings, deviants with high magnitude of change, preferably in the frequency and duration domain, should deliver the best results. Regarding semantic material, full sentences should be preferred to simple word-pairs as indicated in study 2 and 3.

Regarding the hierarchical model outlined in chapter 4.3.1, study 2 indicated that following this approach might lead to a precocious termination of measurements with a patient due to a lack of basic responses although responses requiring more complex information processing might still be elicited. As already pointed out by Kotchoubey and colleagues (2005), some patients exhibit responses to semantic material albeit no reaction to simple tone streams was detected beforehand. This finding can be caused by various factors. On the one hand, fluctuation in arousal and attention may lead to some paradigms being presented in time slots of higher or lower reagibility irrespective of the stimulus material (Kotchoubey et al., 2005). Furthermore, single modules of cortical information processing might be preserved in patients with severe brain damage and this may lead to single responses to certain stimuli while others do not elicit any response (Kotchoubey et al., 2005; Schiff et al., 2002; Schiff, Ribary, Plum, & Llinás, 1999). Thus, instead of following a hierarchical approach, complex paradigms should also be applied to patients if no basic responses were found.

One obstacle in measurements with patients is the problematic classification of significant deflections as a specific ERP. Delayed latency, modified scalp distribution and reversed polarity render it difficult to differentiate between P3a and P3b as well as between MMN, N1, and N2b. The prognostic value of P3a versus P3b is different such that only P3b represents an ERP that allows inference on preserved conscious processing (Guérit, Verougstraete, Tourtchaninoff, Debatisse, & Witdoeckt, 1999). In addition, the prognostic value of MMN is larger than that of N1 (Daltrozzo et al., 2007). Thus, the presence of an ERP is not always of prognostic value, but in any case should be taken very seriously. In addition, study 2 revealed that a P600 instead of N400 is possible when applying semantic material. Thus, experimenters need to closely analyze EEG data obtained from patients also for unexpected ERPs. Only repeated assessment of a patient with different stimulus material and, if possible, different imaging technologies can provide reliable evidence of preserved information processing.

9.4 Conclusive recommendations

The results presented herein allow for a number of important recommendations for the assessment of patients with DOC using ERPs.

(1) Experimenters should refrain from a hierarchical approach but apply more complex paradigms even if no responses to basic stimulus material were found.

(2) Patients should be assessed more than once and ideally during different times of the day since arousal may differ according to individual circadian rythms.

(3) The duration of a single session should be as short as possible. Experimenters need to closely observe the patient and potentially interrupt or terminate the assessment if arousal declines. As a consequence of these first recommendations, different sets of paradigms could be presented randomly during several times of measurements.

(4) Assessments for diagnostic reasons should include paradigms aiming at the elicitation of MMN, P300 and N400 for their special prognostic value. MMN paradigms should be presented with a short ISI to minimize a potential overlap with N1. N400 paradigms should contain sentences instead of word-pairs.

(5) Volitional tasks should be included in patient assessment because only these tasks allow for an inference on consciousness.

(6) Instructions presented with the paradigms should engage the patients' attention to the stimuli to increase the probability of eliciting an ERP.

(7) Multifeature paradigms aiming at the elicitation of an MMN have been proven beneficial in healthy participants and seem promising for the use in patients for their high information output within a short period of time.

9.5 Perspectives

The stimuli used in the present studies delivered reliable ERPs in healthy participants and some ERPs in patients. They thus represent appropriate stimulation material for future studies. The decision of which paradigm works best for which level of consciousness or cognition requires normative studies with representative healthy and patient samples. In addition, the true prognostic value of such paradigms can only be determined in longitudinal research settings. Studies should enroll patients right after the onset of a DOC and reassess them on a regular basis over a prolonged period of time. In this context, it might also be of a benefit to slightly vary stimuli parameters to be able to judge which paradigms work best for the patients. At the same time, normative studies in healthy participants could deliver important implications on the most appropriate instructions and stimulus features.

The importance of a correct diagnosis for the life of a low- or non-responsive patient cannot be overstated. In the worst case, a consciously aware patient might be trapped in a paralyzed body with no means of communication for years. Widespread application of ERPs in clinical assessment can help to minimize this risk and interrogation of practitioners revealed that such a development is welcome and awaited with large interest.

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11 Appendix

A: Guided Interview

B: Additional figures from study 2

C: Curriculum Vitae

Appendix A: Guided Interview

Leitfadeninterview

Datum: _______________

Ansprechpartner: ____

Position: ____

1. Wie wird der Zustand eines Patienten mit Störung des Bewusstseins diagnostiziert?

a. Welche Maßnahmen und Mittel werden verwendet?

b. Wie viel Zeit verstreicht bis eine endgültige Diagnose steht?

c. Gibt es bestimmte Zeitpunkte im Behandlungsprozess, zu denen eine Diagnosestellung erfolgt?

d. Welchen Stellenwert hat die Diagnosestellung im Behandlungsprozess an ihrer Institution?

e. Welche Bedeutung hat die Diagnose für den weiteren Therapieverlauf?

f. Wenden Sie spezifische Verfahren an, um den Bewusstseinszustand des Patienten festzustellen – unabhängig von der rein medizinischen Diagnose?

g. Halten Sie eine gesonderte Diagnose des Bewusstseinszustandes für notwendig und möglich?

2. Welche Aspekte sind im momentanen Diagnoseprozess verbesserungswürdig?

a. Wo sehen Sie Probleme? Wo besteht Verbesserungspotential?

3. Einstellung zu einem neuen Diagnoseinstrument

a. Besteht Ihrer Meinung nach grundsätzliches Interesse an einem gesonderten Diagnoseinstrument für den Bewusstseinszustand?

b. Welche Anforderungen müsste das Diagnoseinstrument erfüllen, um einen Zugewinn zu den momentanen Abläufen darzustellen bzw. diese zu ersetzen?
z. B. zeitlicher Bedarf, Umfang der Geräte, Erlernbarkeit, Anschaffungspreis, …

c. Welchen Output wünschen Sie sich vom System?

d. Wie gut/schnell könnten Sie ein solches Diagnosesystem in Ihre momentanen Abläufe integrieren? Welche Vorbereitungen/Veränderungen wären notwendig?

B: Additional figures from study 2

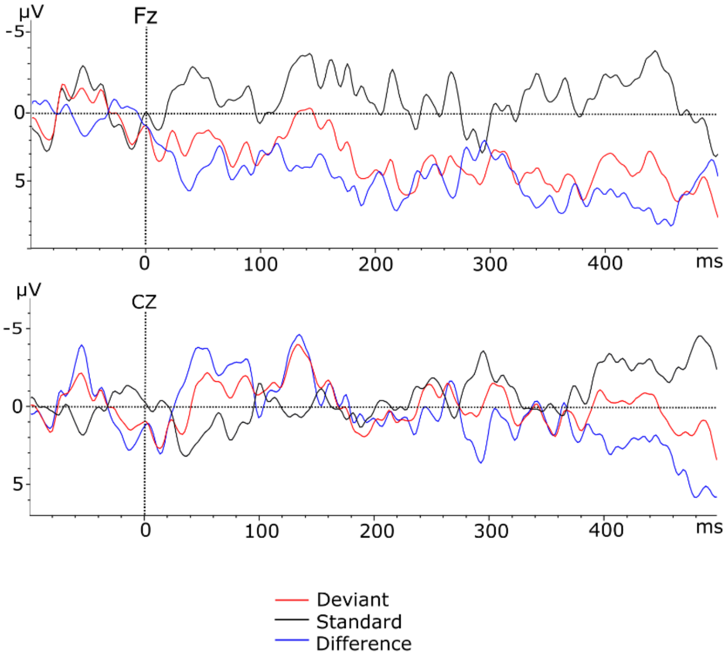

Figure 17: Brain signal recorded in P05 (t2) in the MMN Duration paradigm.

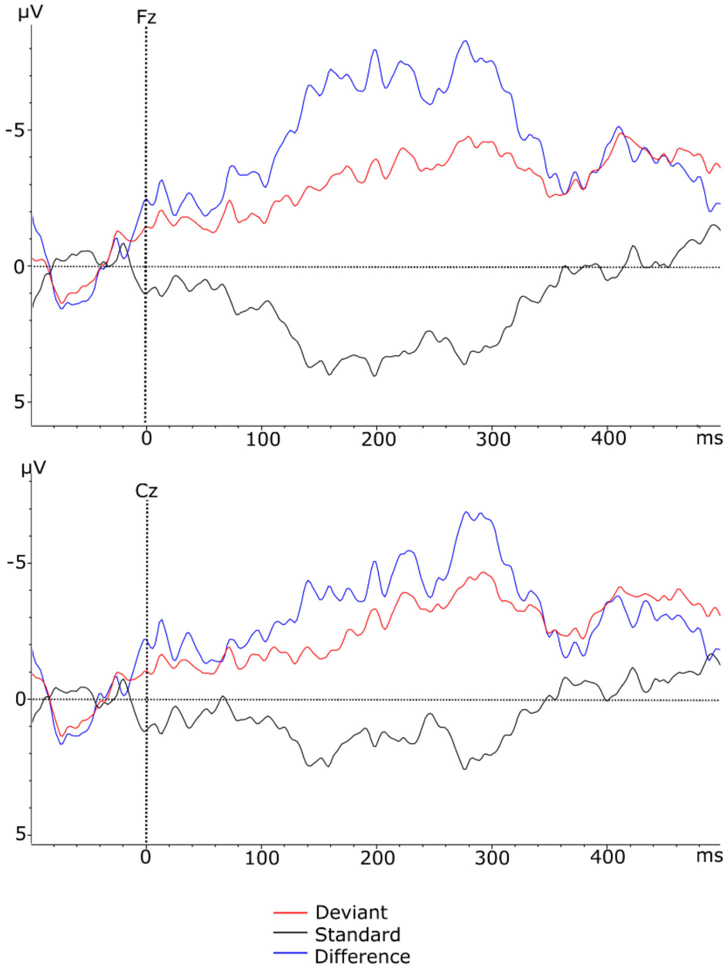

Figure 18: Brain signal recorded in P18 (t2) in the MMN Duration paradigm.

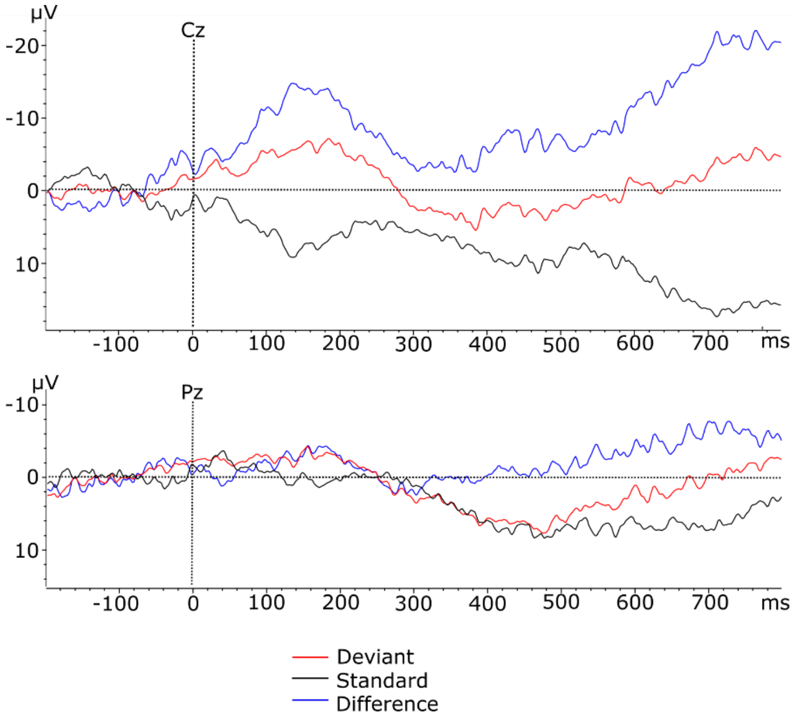

Figure 19: Brain signal recorded in P03 (t1) in the P300 paradigm with the passive task.

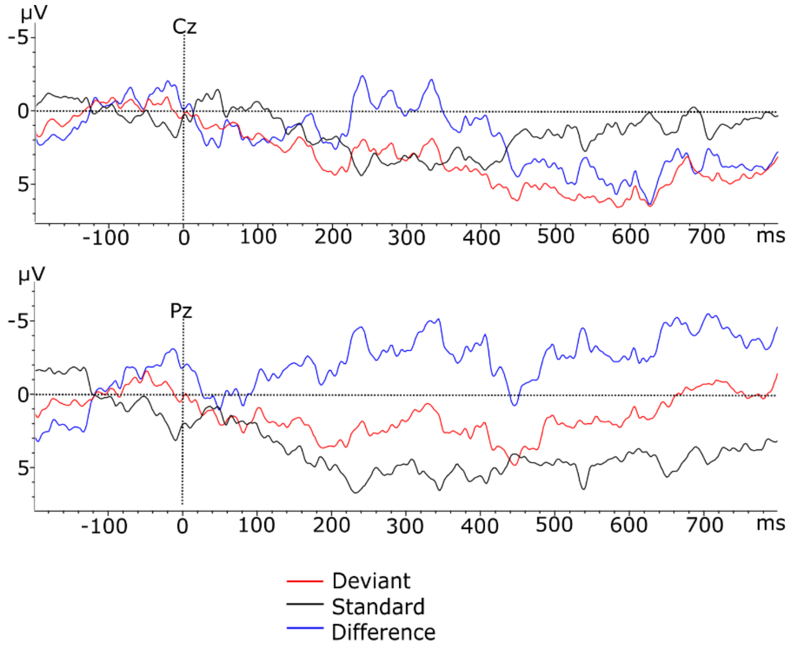

Figure 20: Brain signal recorded in P18 (t1) in the P300 paradigm with the passive task.

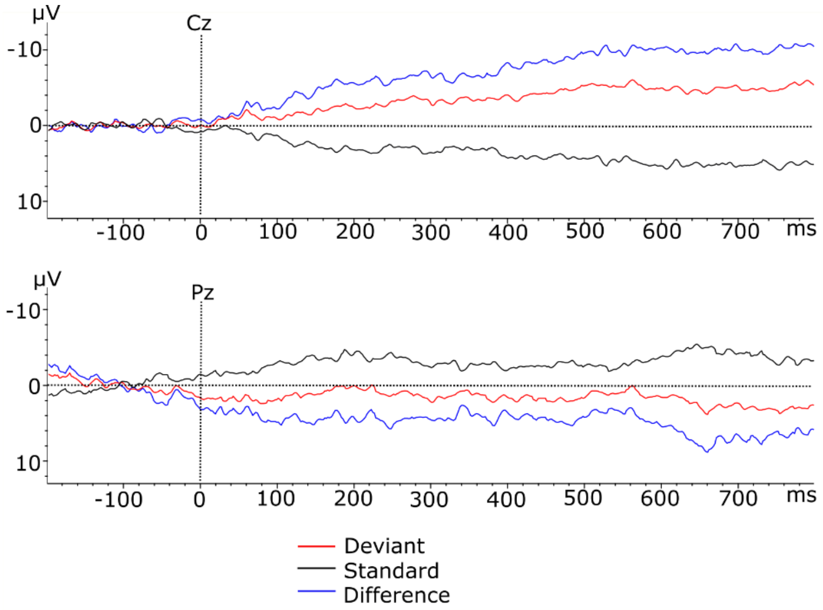

Figure 21: Brain signal recorded in P09 (t1) in the P300 paradigm with the focused task.

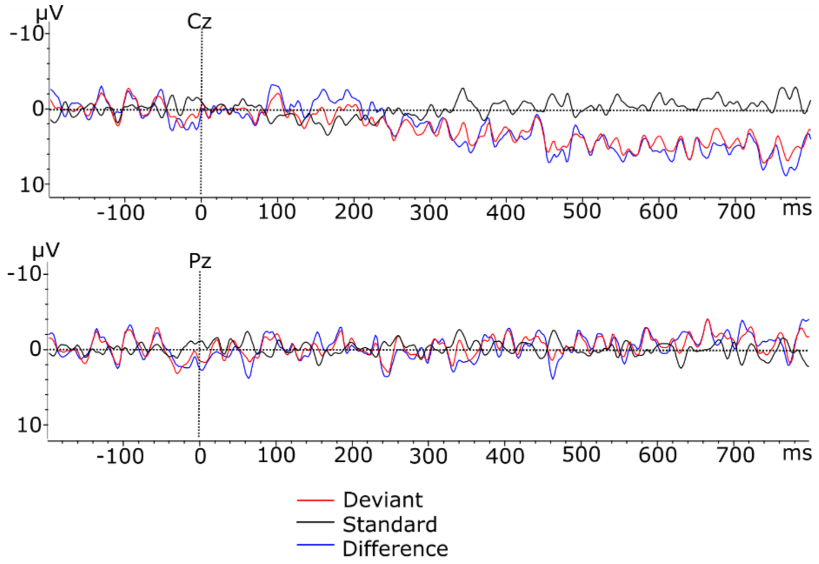

Figure 22: Brain signal recorded in P13 (t2) in the P300 paradigm with the focused task.

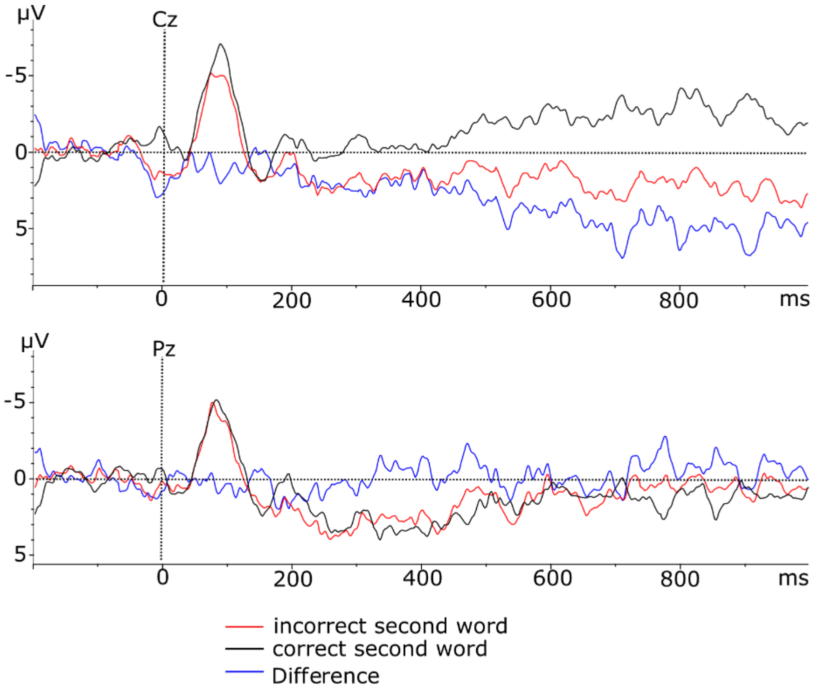

Figure 23: Brain signal recorded in P06 (t1) in the N400 Words paradigm.

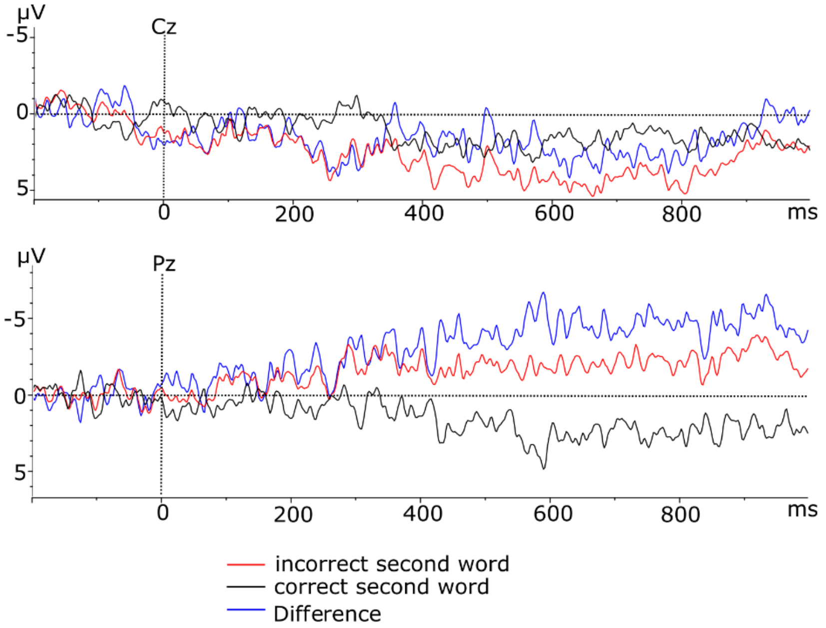

Figure 24: Brain signal recorded in P16 (t2) in the N400 Words paradigm.

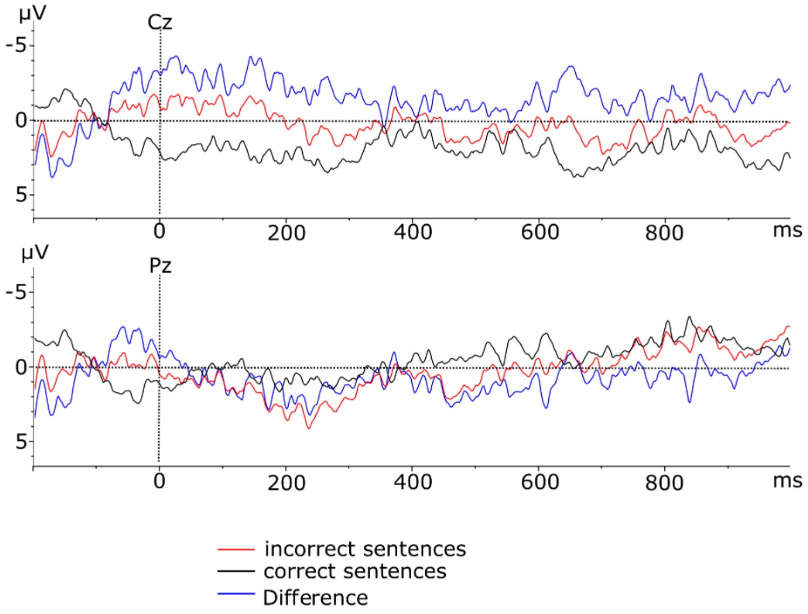

Figure 25: Brain signal recorded in P15 (t1) in the N400 Sentences paradigm.

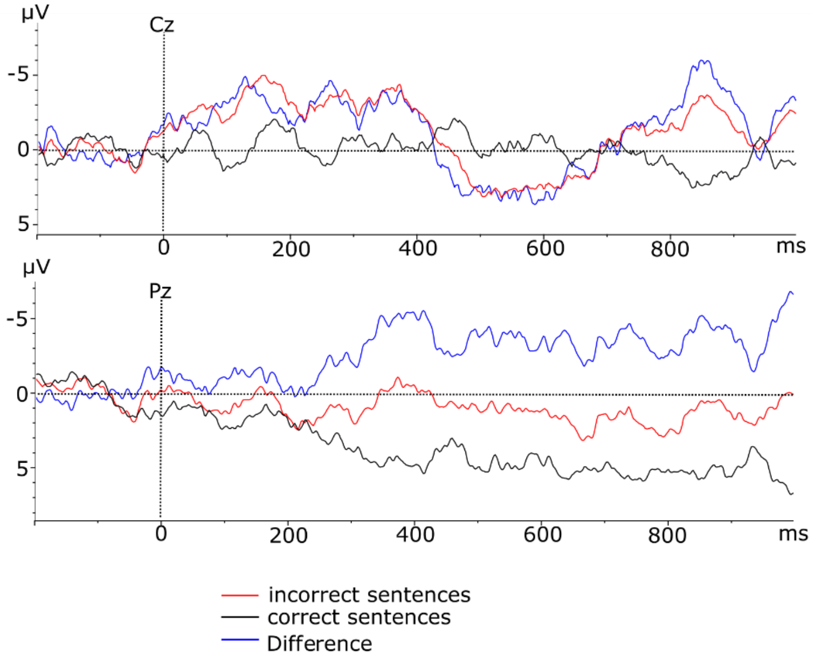

Figure 26: Brain signal recorded in P17 (t1) in the N400 Sentences paradigm.

Appendix C: Curriculum Vitae

Lebenslauf

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Geboren: 24.10.1985 in Dresden

Universitäre Ausbildung

2006 bis 2011	Studium der Psychologie an der Technischen Universität in Chemnitz 2009: Bachelor of Science (Abschlussnote 1,3) 2011: Master of Science (Abschlussnote 1,1)
2000 bis 2004	Humboldt-Gymnasium Radeberg (Abitur, Abschlussnote 1,4)

Beschäftigungsverhältnisse

seit Oktober 2011	wissenschaftliche Mitarbeiterin am Lehrstuhl für Psychologie I, Arbeitsgruppe für Interventionspsychologie, Verhaltensanalyse und Verhaltensregulation
September 2007 bis August 2011	studentische Hilfskraft an der Professur für Wirtschafts-, Arbeits- und Organisationspsychologie der Technischen Universität Chemnitz
Juni 2009 bis Juli 2011	studentische Hilfskraft an der Professur für Allgemeine und Arbeitspsychologie der Technischen Universität Chemnitz
März bis Mai 2009	Praktikum bei BMW Forschung und Technik GmbH, Team Mensch-Maschine-Interaktion (München)

Weiterbildungen

2012 bis 2014	Zertifikatsstudium Mediation
2010	Kursleiterschein für Stressbewältigungstrainings

Eidesstattliche Erklärung

Hiermit versichere ich, Helena Erlbeck, geboren am 24.10.1985 in Dresden, an Eides statt, dass ich die vorliegende Dissertation eigenständig, d.h. insbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt habe. Alle Ausführungen, die anderen Schriften wörtlich oder sinngemäß entnommen wurden, sind kenntlich gemacht.

Die vorgelegte Dissertation wurde bisher bei keinem anderen Prüfungsverfahren in gleicher oder ähnlicher Form eingereicht; sie ist nicht identisch mit einer von mir verfassten Magister-, Diplom- oder Zulassungsarbeit.

Würzburg, den 01.06.2015

…………………………………………….

Helena Erlbeck