LIVING WITH SEVERE MOTOR IMPAIRMENTS – FROM CONSCIOUSNESS TO QUALITY OF LIFE

LEBEN MIT SCHWEREN MOTORISCHEN EINSCHRÄNKUNGEN – BEWUSSTSEIN UND LEBENSQUALITÄT

Doctoral thesis for a doctoral degree
at the Graduate School of Life Sciences,
Julius-Maximilians-Universität Würzburg,
Section *Neuroscience*
submitted by

Ruben G.L. Real

from

Salé, Marokko

Würzburg 2015

Submitted on: ………………………………………………………………..……..

Office stamp

Members of the *Promotionskomitee*:

Chairperson: **Prof. Dr. Michael Sendtner**

Primary Supervisor: **Prof. Dr. Andrea Kübler**

Supervisor (Second): **Prof. Dr. Karl Mertens**

Supervisor (Third): **Prof. Dr. Claudia Sommer**

Date of Public Defence: ……………………………………………….…………

Date of Receipt of Certificates: ……………………………………………….

LIVING WITH SEVERE MOTOR IMPAIRMENTS

From consciousness to quality of life

RUBEN G.L. REAL

You know, i learned something today.

— Kyle Broflovski

ABSTRACT

BACKGROUND The impact of acquired severe motor impairments is pervasive and may lead to a complete loss of communication and voluntary motor control, rendering the patient behaviourally unresponsive. In routine clinical care it may thus be unclear, whether some of these patients are even conscious. Given that finding a cure is unlikely, care focuses on providing the best possible quality of life (QoL), and knowing its predictors might contribute to that aim. Patients who still can communicate often report a high QoL, and several predictors have been identified. However, many instruments used to assess QoL require at least residual verbal and motor abilities. Thus, a method to assess QoL independent of these requirements is desirable. In addition, many instruments assume QoL to be temporarily stable, and little information is available on predictors of instantaneous QoL, i.e. QoL as it fluctuates from moment to moment throughout the day.

RESEARCH QUESTIONS

1. Is it possible to differentiate behaviorally unresponsive but conscious patients from unconscious patients in routine clinical care?

2. Is is possible to validate a passive psychophysiological paradigm as a predictor of QoL?

3. Which factors predict instantaneous QoL?

RESULTS AND DISCUSSION 1) Analysis of EEG-data obtained from patients with very severe motor impairments while listening to a short active–passive two-tone oddball paradigm did not provide evidence that (minimally) conscious patients could be reliably differentiated from unconscious vegetative state patients. It, thus, appears that paradigms which are reliably associated with conscious processing in otherwise healthy participants, cannot be transferred directly to research on information processing in severely motor impaired patients.

2) Results from a study in motor-impaired patients with Amyotrophic Lateral Sclerosis (ALS) showed that the N400 event-related potential (ERP) was selectively reduced in patients reporting low QoL after reading disease-related words. Thus, the N400 ERP might serve as a predictor of QoL in future studies.

3) Results from an experience-sampling study in ALS-patients confirmed previous findings of a robust association between the perception of control and QoL. Results further revealed that the perception of demands can also contribute to QoL, as long as demands are perceived as controllable. Thus, pursuing, within limits, demanding activities may contribute to patients' QoL.

SIGNIFICANCE 1) A short widely-applicable EEG-based auditory paradigm was not successful in differentiation between conscious and unconscious patients with very severe motor impairments. 2) In motor impaired but responsive patients with ALS, a new N400-ERP based psychophysiological predictor of QoL was identified, and 3) pursuing demanding activities might help to increase these patients' QoL.

ZUSAMMENFASSUNG

HINTERGRUND Die Auswirkungen erworbener motorischer Einschränkungen sind verheerend, und können bis hin zu einem völligen Verlust der Kommunikationsfähigkeit und Willkürmotorik führen. In der klinischen Praxis bedeutet dies, dass bei einigen Patienten unklar ist, ob sie überhaupt bei Bewusstsein sind. Da bei vielen dieser Erkrankungen eine Heilung derzeit unwahrscheinlich ist, steht die Förderung einer möglichst hohen Lebensqualität (LQ) im Fokus der Behandlung. Unabdingbare Voraussetzung hierzu ist eine genaue Kenntnis möglicher Prädiktoren der LQ. Bei Patienten, mit denen noch kommuniziert werden kann, konnten einer Reihe von Prädiktoren der –meist hohen– LQ identifiziert werden. Alle bislang verwendeten Instrumente erfordern jedoch zumindest residuale motorische und verbale Fähigkeiten, so dass ein Verfahren zur Erfassung der LQ, welches nicht oder kaum auf diese Fähigkeiten angewiesen ist, wünschenswert ist. Des Weiteren unterstellen viele Instrumente zur Erfassung der LQ eine Zeitstabilität der LQ, so dass vergleichsweise weniger Informationen über Prädiktoren der momentanen LQ vorliegen, beispielsweise Fluktuationen der LQ im Tagesverlauf.

FORSCHUNGSFRAGEN

1. Kann in einem klinischen Anwendungsbereich zwischen bewussten und bewusstlosen Patienten mit schwersten motorischen Beeinträchtigungen unterschieden werden?

2. Eignet sich ein passives psychophysiologisches Paradigma als Prädiktor der LQ?

3. Welche Faktoren sagen die momentane LQ vorher?

ERGEBNISSE UND DISKUSSION 1) Es wurde eine EEG-Studie (auditorisches 2-Ton oddball Paradigma) bei Patienten mit schwersten motorischen Einschränkungen durchgeführt. Dieses Paradigma konnte jedoch nicht zwischen bewusstlosen Patienten im Wachkoma und bewussten Patienten im minimalem Bewusstseinszustand unterscheiden. Obwohl das verwendete Paradigma bei gesunden Personen zuverlässig mit bewusster Verarbeitung assoziiert ist, scheiterte eine direkte Übertragung auf Patienten mit schweren motorischen Einschränkungen.

2) Ergebnisse einer Untersuchung an motorisch schwer beeinträchtigten Patienten mit Amyotropher Lateralsklerose (ALS) zeigten eine selektiv reduzierte Amplitude des Ereignis-korrelierten Potentials (EKP) N400 nach dem Lesen krankheitsassoziierter Wörtern bei Patienten, die eine niedrige Lebensqualität berichteten. Diese Ergebnisse sprechen für eine erhöhte Zugänglichkeit krankheitsrelevanter Begriffe bei niedriger Lebensqualität. Dieser Effekt wäre somit ein möglicher Prädiktor zur Vorhersage der LQ.

3) Ergebnisse einer Untersuchung an ALS-Patienten unter Verwendung der längschnittlichen experience-sampling method bestätigten frühere Befunde einer positiven Assoziation zwischen wahrgenommener Kontrolle und LQ. Darüberhinaus wurde gezeigt, dass auch das Ausmaß wahrgenommener Herausforderungen positiv mit LQ assoziiert sein kann, solange die Herausforderungen noch als kontrollierbar erlebt werden. Somit besteht die Möglichkeit, die LQ von Patienten durch die Aufnahme auch potentiell herausfordernder Aktivitäten zu steigern.

RELEVANZ 1) Die Validierung eines routinemäßig einsetzbaren EEG-basierten Verfahrens zur Differenzierung von Patienten mit schweren motorischen Einschränkungen im Wachkoma von Patienten mit minimalem Bewusstseinszustand war nicht erfolgreich. 2) Bei motorisch beeinträchtigten ALS-Patienten konnte das N400-EKP als neuer neurophysiologischer Prädiktor der LQ identifiziert werden. 3) Die Aufnahme herausfordernder Aktivitäten könnte die LQ von Patienten mit ALs erhöhen.

ACKNOWLEDGMENTS

Die vorliegende Arbeit wurde am Lehrstuhl für Psychologie I der Julius-Maximilians-Universität Würzburg verfasst.

Für die Unterstützung während meiner Arbeit bedanke ich mich ganz herzlich bei Prof. Dr. Andrea Kübler und den Mitgliedern meines Promotionskomitees, Prof. Dr. Claudia Sommer und Prof. Dr. Karl Mertens.

Diese Arbeit wäre ohne die freundliche Zusammenarbeit mit meinen Kollegen nicht zustande gekommen. Besonders danke ich Dr. Sonja C. Kleih auf deren Fachwissen ich jederzeit zurückgreifen konnte. Ebenfalls bedanken möchte ich mich bei den vielen Kollegen, die ich im Rahmen der EU-Projekte DECODER, CONTRAST und BNCI Horizon 2020 kennenlernen durfte.

Von ganzen Herzen danke ich Svenja Vollmering, ohne deren Rücksicht, Anteilnahme und fachliches Interesse ich diese Arbeit nicht hätte schreiben können.

CONTENTS

FIGURES

ACRONYMS

ALS Amyotrophic Lateral Sclerosis

BCI Brain-Computer Interface

CLIS Completely Locked-In Syndrome

DOC Disorders Of Consciousness

EEG Electroencephalography

EKP Ereigniskorreliertes Potential

EOG Electrooculography

ERP Event Related Potential

fMRI functional Magnetic Resonance Imaging

LIS Locked-In Syndrome

LMN Lower Motor Neuron

LQ Lebensqualität

MCS Minimally Conscious State

MND Motor Neuron Disease

PLS Primary Lateral Sclerosis

PMA Progressive Muscular Atrophy

PVS Persistent Vegetative State, also: Permanent Vegetative State

QoL Quality of Life

R-EEC Revised El Escorial Criteria

RRS Ruminative Responses Scale

SWB Subjective Well-Being

t-CWT Studentized Continuous Wavelet Transformation

UMN Upper Motor Neuron

VS Vegetative State

Part I

INTRODUCTION

The impact of acquired motor impairments is pervasive. However, many patients, if able to do so, report a surprisingly high subjective quality of life, despite the severe limitations these patients are confronted with.

Two medical conditions leading to severe motor impairments are described, followed by an overview on empirical findings and theoretical models of quality of life.

1

LIVING WITH SEVERE MOTOR IMPAIRMENTS

1.1 DISORDERS OF CONSCIOUSNESS

Due to improved medical care more patients than ever survive severe damage to the brain (Lu et al., 2005). Whereas some fifty years ago life expectancy was low, many patients are now able to survive for several years. In healthy people, being awake and consciousness are closely related. However, in some patients with severe damage to the brain, these phenomena become dissociated, i.e. they are awake but appear to be unresponsive to their environment (Schnakers & Laureys, 2012). Complicating matters, other conditions exist, such as end stage Amyotrophic Lateral Sclerosis (ALS), in which patients are nearly completely unresponsive, but nevertheless conscious (see section 1.2). Thus, unresponsiveness alone is only a coarse indicator of lost consciousness.

1.1.1 *Diagnostic criteria*

If patients recover from severe brain injuries, they may pass through several stages of disorders of consciousness (DOC, Laureys, 2007): **Coma** is marked by a severe disruption of vigilance and consciousness (Giacino et al., 2009) with no signs of sleep-wake cycles, or auditory, visual, emotional or communicative functions (Giacino et al., 2002). Motor responses are limited to reflex or postural changes in response to certain external stimulation and consciousness is deemed absent.

In contrast, patients in the **vegetative state** (VS) show preserved sleep-wake cycles, defensive reflexes to auditory or visual stimulation, and withdrawal or postural changes in response to noxious stimulation. Some patients may also show brief orienting responses to visual or auditory stimuli, or reflexive facial emotional expressions. Again, consciousness appears to be absent and communication impossible. The term "vegetative" was chosen purposeful since, "vegetate is defined in the Oxford English Dictionary as 'to live a merely physical life, devoid of intellectual activity or social intercourse [...]' and vegetative is used to describe 'an organic body capable of growth and development but devoid of sensation and thought [...]" (Jennett & Plum, 1972, p. 736). If the condition persists for longer than one month, the term **persistent vegetative state** may be used, and, if recovery is deemed unlikely, **permanent vegetative state**. It should be noted, however, that whereas the former is a diagnostic term, the latter term constitutes a prediction. It is, thus, unfortunate that both terms are sometimes abbreviated to "PVS" (Bernat, 2006).

Patients in a **minimally conscious state** (MCS) show preserved sleep-wake cycles and behavioural evidence of conscious processing. Motor responses to external stimulations include visual pursuit or localisation of noxious stimuli and reaching/touching of objects while accommodating for simple physical features, e.g. shape or size (MCS-, Bruno, Majerus, et al., 2012). Auditory functions may include localisation of sounds and patients may show inconsistent command following (MCS+, Bruno, Majerus, et al., 2012). Communication is not functional and emotional expression may be inconsistent but can be contingent.

Finally, the **locked-in syndrome** (LIS) is characterised by preserved consciousness, sleep-wake cycles, and eye-coded communication. However, motor responses are absent in the **completely locked-in state (CLIS)**, which makes communication impossible (Giacino et al., 2002). Consequently, while (C)LIS is not a DOC, it may sometimes be confused with e.g. VS, because the absence of motor responses complicates the differentiation between these two states (Bernat, 2006).

1.1.2 *Epidemiology*

VS and MCS are most often caused by traumatic injuries, with lesions damaging cortical neurons, the thalami, and (predominantly) white matter, but typically sparing the brain stem and the hypothalamus. Differential sheering between grey and white matter during strong rotations results in diffuse severing of axons, which isolate cortical areas from each other (Bernat, 2006). Non-traumatic causes, e.g. stroke, encephalitis, and cardiopulmonary arrest, involve diffuse hypoxic-ischaemic injuries with widespread damage to cortical and thalamic neurons, while brain stem neurons are typically spared, most likely because cortical areas have higher metabolic demands (Bernat, 2006). While MCS pathology is less well described, generally, cortical damage is less severe as compared to VS.

LIS, on the other hand, results from hemorrhage or infarction in the pons, which subsequently cause de-efferentation of all higher motor pathways, except for vertical eye movements. However, other causes exist, e.g. late stage Amyotrophic Lateral Sclerosis or Guillain-Barré syndrome (c.f. Bernat, 2006).

PROGNOSIS Recovery in DOC patients can be evaluated at the levels of mortality/survival, recovery of consciousness, and return of functioning (Bruno, Ledoux, et al., 2012).

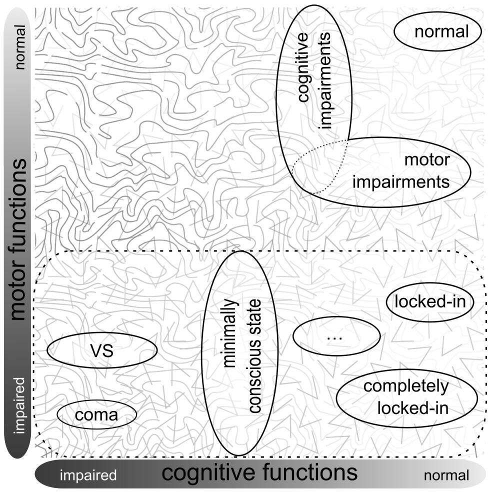
In the acute or post-acute phase, the most frequent causes of death after brain injury are infections of the pulmonary or urinary tract, generalised systemic failure, or disease related causes, e.g. recurrent strokes (The Multi-Society Task Force on PVS, 1994). Medical complications such as hyperthermia or epilepsy may further decrease chances of survival (Sazbon & Groswasser, 1990). In a recent large scale Belgian study one-year mortality was lower for MCS patients (traumatic origin: 23%, non-traumatic: 33%) than for VS patients (traumatic origin: 42%, non-traumatic: 70%) and traumatic onset was consistently associated with lower mortality than non-traumatic onset (c.f Bruno, Gosseries, Vanhaudenhuyse, Chatelle, & Laureys, 2010; Bruno, Ledoux, et al., 2012). However, it should be noted that mortality estimates may be biased, such that not all patients received the most aggressive medical treatment available, and many might have been let to die from otherwise treatable causes (Bernat, 2006).

Functional recovery, defined as the return of signs of awareness, may be as high as 52% within one year after a traumatic brain injury, but drops sharply thereafter (only seven percent regain consciousness after a period of 12 month in VS; The Multi-Society Task Force on PVS, 1994). Further, a "good" recovery is also unlikely, with 45% of patients showing at least moderate levels of disabilities. Again, functional recovery is less frequent in patients in VS of non-traumatic origin (15% recovery within 1 year). In the Belgian study cited above, transition from VS to MCS was 14% for traumatic and eight percent for non-traumatic patients. Rates of functional recovery, i.e. emergence from MCS, was 23% for VS and 48% for MCS patients. Predictors of recovery and, thus, return of consciousness, include –among others– age of onset (more favorable for younger patients) and time spent in the VS (less if more than one year (traumatic) or six months (non-traumatic, Bruno, Ledoux, et al., 2012)).

1.1.3 *Diagnostic instruments*

Several instruments have been designed to facilitate the assessment of consciousness in DOC patients. As of now, these instruments all rely on careful observation of the patient to distinguish voluntary behavioural responses to certain external stimulations from simple reflexes (Giacino et al., 2009).

Figure 1: Continuum of motor and disorders of consciousness.



Note. Modified from DECODER (2010)

Nevertheless, reliable assessment of consciousness is difficult due to the fact that signs of consciousness detectable by observation are often subtle and therefore easy to miss. Indeed, many instruments based on pure behavioural assessment demonstrate low inter-rater reliability making misdiagnoses a major issue (Giacino et al., 2009; Schnakers, Perrin, et al., 2009). Further, even studies using the most accurate behavioural assessment procedures, identified some "VS" patients who were behaviourally completely unresponsive, but who, nevertheless, showed clear evidence of command following using functional MRI (fMRI) or EEG-based paradigms (c.f. Kotchoubey, Lang, Bostanov, & Birbaumer, 2002; Owen et al., 2006; Monti et al., 2010; Cruse et al., 2011; Goldfine et al., 2013; Cruse et al., 2013; Schnakers, Vanhaudenhuyse, et al., 2009).

In this section, several medical conditions were presented in which patients may have vastly different cognitive abilities, but share the presence of a severe loss of voluntary motor control (see Figure 1). Given the high rate of misdiagnoses, at least some of these patients are deprived from shaping their environments according to their needs and from contributing to their QoL. Thus, accurately identifying these patients has a high priority.

The next sections focus on another medical condition (Amyotrophic Lateral Sclerosis, ALS) leading to severe motor impairments. In this condition, however, consciousness is spared, leading to questions on how patients experience being confronted with an incurable neurodegenerative disease.

1.2 AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is a rare neurodegenerative disease leading to progressive paralysis and, ultimately, death, mainly from respiratory failure (Logroscino et al., 2008; Kurian, Forbes, Colville, & Swingler, 2009).

1.2.1 *Symptoms and diagnostic criteria*

Clinical symptoms of ALS can be described in relation to different neurological regions (Mitchell & Borasio, 2007), with bulbar-onset occurring in about 25% and limb-onset, i.e. onset in cervical and lumbar regions, occurring in about 70% of all cases (Kiernan et al., 2011): Patients with bulbar-onset show predominantly signs of dysphagia (difficulty swallowing) and dysarthria (slurring of speech). Additional features may include emotional lability (upper motor neuron, UMN, involvement) or facial weakness, and atrophy and fasciculations of the tongue (Mitchell & Borasio, 2007). Symptoms of cervical-onset ALS can be delimited into signs of proximal weakness (e.g. difficulties with shoulder abduction during hair washing) and distal weakness with marked atrophy and fasciculation in hands and arms. Finally, lumbar-onset symptoms manifest in symptoms such as a limited ability to climb stairs or to lift the foot, which may result in frequent tripping (Mitchell & Borasio, 2007). Not all types of motor neurons are equally affected, with oculomotor neurons and sacral motor neurons controlling the sphincter muscle remaining unaffected, except in some rare long-term surviving patients (Robberecht & Philips, 2013).

DIAGNOSTIC CRITERIA Clinical findings in ALS patients show high variability, which, in combination with the absence of biological diagnostic markers, complicates diagnosing ALS. To standardise clinical diagnoses several diagnostic criteria have been developed, the Revised El Escorial criteria (Brooks, Miller, Swash, & Munsat, 2000, R-EEC, p. 293) being widely accepted:

Depending on the extent to which the above criteria are fulfilled, diagnoses of *clinically definite ALS* (UMN and LMN signs in a bulbar and at least two spinal regions, *or* UMN and LMN signs in more than three spinal regions) or *clinically probable ALS* (UMN and LMN signs in at least two regions, with some UMN signs rostral of LMN signs) are made. If patients show only UMN signs, the disease is classified as Primary Lateral Sclerosis (PLS) or, if only LMN signs are present, Progressive Muscular Atrophy (PMA). However, many patients with PLS develop LMN signs during the course of their disease and are later rediagnosed as having ALS, and PMA patients show a course of disease similar to ALS (Robberecht & Philips, 2013). However, with the diagnosis of ALS being primarily clinical, misdiagnoses do occur, although rarely so (Kurian et al., 2009).

1.2.2 *Epidemiology*

Most cases of ALS occur sporadic, i.e. without a family history, with only a minority of cases (5%) occurring within genetic relatives (Byrne et al., 2011). Further, the majority of familial ALS and sporadic ALS cases are clinically identical (Hand & Rouleau, 2002).

INCIDENCE Incidence rates are approximately 1.5 to 2.5 / 100.000 per year (Logroscino et al., 2008; in Europe 2.16 / 100.000 per year Logroscino et al., 2010), and rates increase rapidly after the age of 40, reaching a peak at approximately 70 years (median 65 years) in men and 65 years (median 57 years) in women. Generally, men are at greater risk than women (1.4 incidence ratio). In Europe, approximately 66% of patients registered with ALS clinics fulfill the R-EEC defined diagnoses of clinically definite or clinically probable ALS. Mean time from symptom onset to diagnosis is 370 days (with large variation between countries).

prognosis The most common cause of death is related to respiratory failure (52%), either because of bronchopneumonia (41%) or aspiration pneumonia (11%, Kurian et al., 2009). Median survival after diagnoses is 19 month (32 month after symptom onset) and less than seven percent of patients live longer than five years after diagnosis. Negative prognostic indicators include older age, bulbar onset, being female, and a faster disease progression (del Aguila, Longstreth, McGuire, Koepsell, & van Belle, 2003).

Being married is associated with increased survival, possibly because spouses recognise initial symptoms and insist on an early medical evaluation (del Aguila et al., 2003). Whereas earlier studies indicated a possible role of mental health in predicting survival (McDonald, Wiedenfeld, Carpenter, & Walter, 1994), this could not be replicated in later studies (del Aguila et al., 2003).

1.2.3 *Management of ALS*

Research into the pathogenesis of ALS suggests the presence of multiple pathogenic factors, each contributing to the clinical picture of ALS (Kiernan et al., 2011). This may be a reason why only one drug, Riluzole, a glutamate release inhibitor, has been shown to be effective in extending life expectancy (c.f. R. G. Miller, Mitchell, & Moore, 2012), but only marginally so (2-3 months). Thus, in the absence of a cure, management of ALS focuses on the treatment of the disease's symptoms aiming to improve survival and quality of life (Kiernan et al., 2011). Generally, multidisciplinary care, i.e. care provided by teams of experts in rehabilitation medicine, physical therapists, occupational therapists, speech pathologists, dietitians and social workers has been shown to be most effective in the care of patients with ALS (Van den Berg et al., 2005).

Compromised respiratory functions are frequent in ALS and require special attention. Hypoxia, initially most often nocturnal, is associated with lethargy, inability to concentrate, headaches and tiredness throughout the day (Kiernan et al., 2011). Thus, non-invasive ventilation techniques should be considered and applied where possible, especially, as they have been shown to increase patients' quality of life (c.f. Bourke & Gibson, 2004), and prolong survival (Andersen et al., 2005).

2

QUALITY OF LIFE

Given the extent of motor impairments, the completely locked-in syndrome being the extreme, it seems almost implausible that the well-being of these patients is, on average, comparable to non-disabled study participants. The following sections present theoretical models of quality of life, and how it can be maintained even in severe diseases. The chapter closes with the observation that some behaviourally unresponsive DOC patients exhibit clear signs of awareness, and highlights the lack of knowledge about their quality of life.

Throughout history, the term "happiness" has been difficult to define, with ideas as luck, virtue, salvation, and pleasure all having been associated with happiness (Holt, 2012; Kesebir & Diener, 2008). For science to advance, however, concepts of interests need to be clearly defined and suitable for operationalisation. Thus, the term *subjective well-being* (SWB) has been proposed to refer to people's evaluations of their lives, including their cognitive as well as affective appraisals (Kesebir & Diener, 2008). Two aspects of this definition deserve special attention. First, SWB is entirely subjective, thus, relations between objective factors such as health (see below) are empiric not a priori [1]. Secondly, the definition calls for positive measures, i.e. measures that

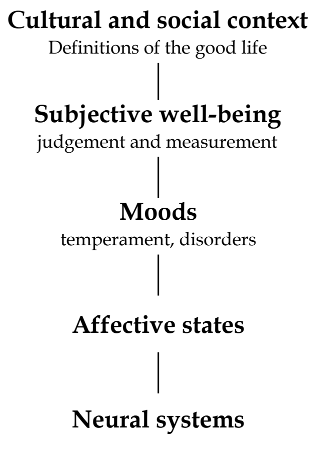
1 In this regard, subjective well-being differs from concepts such as health-related quality of life (HRQoL) in that HRQoL-instruments such as the SF-36 (Ware & Sherbourne, 1992) often presuppose a close association of health and well-being. SWB on

capture the experience of well-being, and excludes measures which infer well-being from the absence of negative factors (Diener, 1984). This conceptualisation is also reflected in the WHO's definition of quality of life (QoL).

> Quality of life [is] defined, therefore, as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept, incorporating in a complex way individuals' physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of the environment. This definition highlights the view that quality of life is subjective, includes both positive and negative facets of life and is multi-dimensional. (WHOQOL, 1995, p. 1405)

Whereas initially questions arose on the precise relationship of SWB and QoL, detailed empirical as well as theoretical analyses suggest that SWB and QoL are virtually synonymous (c.f. Camfield & Skevington, 2008). SWB –or, from now on, QoL– can be analysed at the cultural and social level, at the levels of cognitive evaluations, mood, affective states, or even at the neural systems level (Kahneman et al., 2003, see also Figure 2).

Figure 2: Levels of analysis of subjective well-being.



Note. Modified after Kahneman, Diener, and Schwarz (2003)

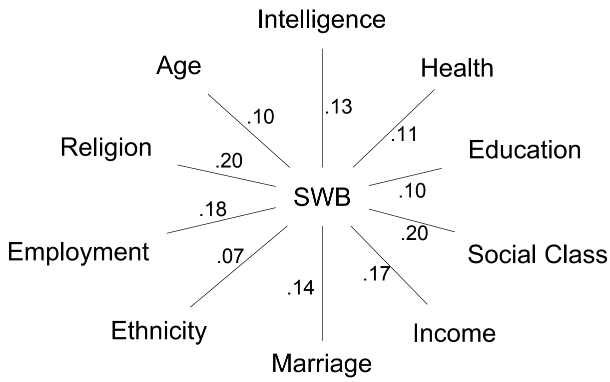
---

the other hands suggests that health can have, but does not need to have an influence on well-being (Bakas et al., 2012)

2.1 OBJECTIVE CORRELATES OF QOL

National governments (e.g. Bundesregierung, 2014) and international bodies (e.g. WHOQOL, 1995) are highly interested in the conditions which might influence QoL, and several objective factors have been associated with QoL, a subset of which are shown in Figure 3.

Figure 3: Objective correlates of QoL.



Note. From data presented in Argyle (2003)

However, as can be seen from Figure 3, correlations between objective predictors, e.g. frequency of attending religious services, and QoL are often small (c.f J. Cohen, 1992). Even when multiple measures are taken into account, explained variances of QoL rarely exceed 15% (Argyle, 2003). Most strikingly, the relation of objective health status to QoL is among the smallest (rank six of eight unique ranks in Figure 3), despite the high importance health is usually assigned to (Ridder & Wit, 2006).

2.2 QOL IN SEVERE DISEASES - PARADOXICAL FINDINGS

As described in the previous section, the correlation between objective health and QoL is small, and this finding is not limited to surveys, in which, it may be argued, severely ill people may be underrepresented.

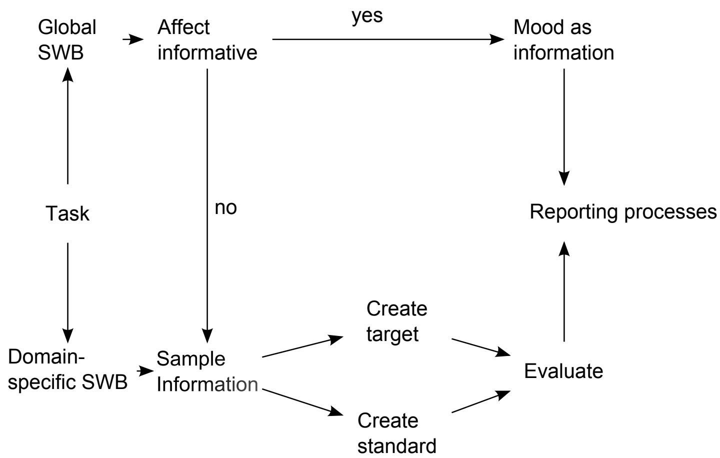
Instead, this seemingly paradoxical result –variously referred to as the "well-being paradox", "satisfaction paradox" (Herschbach, 2002), or "disability paradox" (Albrecht & Devlieger, 1999)– has also been found in patients waiting for a bone marrow transplant (Andrykowski & Hunt, 1993), patients with traumatic tetraplegia (Bach & Tilton, 1994), breast cancer (Groenvold et al., 1999; Carver, Smith, Petronis, & Antoni, 2006), and, multiple times, in patients with ALS (e.g. Robbins, Simmons, Bremer, Walsh, & Fisher, 2001; Kübler, Winter, Ludolph, Hautzinger, & Birbaumer, 2005; Lulé, Häcker, Ludolph, Birbaumer, & Kübler, 2008; Matuz, Birbaumer, Hautzinger, & Kübler, 2010), and even in LIS (Lulé et al., 2009). Further, in ALS patients, the degree of functional impairment is often unrelated to QoL (e.g. Robbins et al., 2001), or, even inversely related, such that more impaired patients report a higher QoL (Lulé et al., 2008). Even aggressive measures such as long term artificial ventilation are usually tolerated (Kaub-Wittemer, Steinbüchel, Wasner, Laier-Groeneveld, & Borasio, 2003) and may even improve QoL (Bourke & Gibson, 2004). However, it should be noted that while these findings are true for the majority of patients, some patients decline (the continuation of) potentially life-prolonging treatments (Meyer et al., 2008), or request, where legal, assisted suicide (c.f. Ganzini & Block, 2002). Reasons for this decision include a fear of losing the ability to pursue pleasurable activities and an anticipated loss of autonomy, control and independence (Ganzini & Block, 2002, p. 1664). While research into ALS and QoL is unlikely to eliminate the wish for hastened death in all patients, it may help to increase QoL in at least some of them.

In the next sections, theoretical models will be presented which can account for findings of high QoL in severely ill patients.

2.3 A JUDGEMENT MODEL OF QOL

Findings such as those presented above, have led some to question the validity of self-reported QoL and even to caution against their use (e.g. Breetvelt & Van Dam, F S, 1991; Groenvold et al., 1999). Others, however, started researching the conditions that might explain the experience of high QoL despite poor health. Important in this regard was a shift from viewing QoL as a stable inner state toward conceptualising QoL reports as reflecting the operation of a context-dependent judgement process (Calman, 1984; Schwarz & Strack, 2003). Figure 4 summarises this view.

Figure 4: A judgement model of subjective well-being.



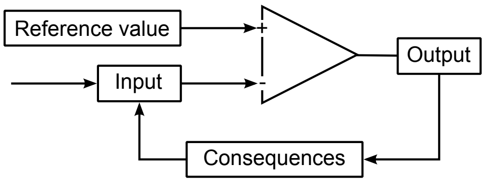
Note. Modified after Schwarz and Strack (2003)

In this model, a first distinction is made according to how QoL reports are elicited. If a global question is asked, such as "Taking all things together, how would you say things are these days – would you say you are happy, pretty happy, or not too happy?" (Campbell, 1981, p. 27) people tend to answer based on their momentary affective state (unless they have reason to discount their momentary affect). In contrast, when people are asked to report their QoL in a variety of distinct life aspects, i.e. their satisfaction in domains like finance, health, or social life, they engage in highly complex cognitive processes. This complexity arises, primarily, because a multitude of aspects of one's life could potentially be relevant to answer a question on QoL. Thus, an important step is to identify information that is relevant to the question, and often, highly accessible aspects, i.e. information that happens to be in the mind, are used. In line with the idea that QoL reflects an evaluation of one's position in life (see page 13), this model suggests that information concerning one's life domains (the target domain) is not judged in isolation, but against another set of information (the standard domain). Following the judgement model, findings of high QoL despite poor health, can then be explained with reference to the information used in the evaluation process.

2.4 CYBERNETIC MODELS OF QOL

While the judgement model explains how QoL statements depend on ad hoc comparisons, it does not provide –apart from accessibility– a mechanism through which inter- or intra-individual differences in the representation of targets and standards can arise. This missing link is filled by another set of models, which emphasise a cybernetic view on QoL. Generally these models, e.g. the revision by Park and Folkman (1997) of the Transactional Stress Model (Folkman, 1984), or the model of response shift and quality of life by Sprangers and Schwartz (1999) involve two components.

Figure 5: A simple feedback loop.



A *monitoring process* compares a desired state with the individual's current state and a *discrepancy reduction loop* is activated whenever desired and current states differ (Koole, van Dillen, & Sheppes, 2011; c.f. TOTE model: Test-Operate-Test-Exit, G. A. Miller, Galanter, & Pribram, 1960). The overall function of these processes is to bring sensed and intended conditions into conformity (Carver & Scheier, 2000, 2011) [2], and a rich literature exists on how coping strategies – "cognitive and behavioural efforts to master, reduce, or tolerate the internal and/or external demands" (Folkman, 1984, p. 843) – can be used to restore conformity (c.f. Chronister & Chan, 2007).

Support for the existence of such a feedback loop is only indirect, as no studies have directly tested the full TOTE cycle for behaviour (Ridder & Wit, 2006). Indirect support comes from studies that confirm some rather subtle predictions of the model. For example, the model predicts that detection of a *positive* mismatch should lead to a reduction of efforts (Carver, 2003), since positive affect is generated only when progress is better than expected, allowing for a reduction of efforts. This hypothesis was confirmed in a study showing that people increase their efforts when progress toward goals is less than expected, but, importantly, reduce their efforts when progress is better than expected (Fulford, Johnson, Llabre, & Carver, 2010).

2 Technically, models in the tradition of Carver and Scheier (1990, 2000, 2011) propose that well-being is not directly influenced by a discrepancy between sensed and intended conditions, but by the rate by which the discrepancy is reduced. Thus, merely noting a discrepancy would not influence well-being whereas well-being is reduced if the rate of discrepancy reduction is less than expected. Conversely, low well-being indicates a less-than-optimal discrepancy reduction rate and, hence, the presence of a discrepancy between sensed and intended conditions.

2.5 QUALITY OF LIFE IN DISORDERS OF CONSCIOUSNESS? - THE NEED AND THE GAP

A HIERARCHY OF GOALS - THE ROLE OF COMMUNICATION Although the above discussion might suggest otherwise, it is important to note that not just any perceived mismatch is relevant for QoL but only those mismatches, which involve an individual's important goals (Sprangers & Schwartz, 1999; Carver & Scheier, 2000, 2011). The models by Sprangers and Schwartz (1999) and Carver and Scheier (2011) assume that goals form a hierarchy of importance and different sub-goals can lead to the attainment of the same higher-order goal. Further, goals are not necessarily static, but may change, especially, when some routes to a higher-order goal become disrupted. Generally, flexibility in goal adjustment has been related to increased well-being (Brandtstädter & Renner, 1990; Wrosch, Scheier, Miller, Schulz, & Carver, 2003). Evidence for the validity of this suggestion in ALS-patients comes from a study by Lulé et al. (2008) who compared ALS-patients with and without clinically relevant depression, and found depressed patients to place stronger emphasis on unachievable goals such as health and mobility, whereas non-depressed patients placed stronger value on achievable goals like personal well-being. Together with similar findings (e.g. Fegg et al., 2010), this suggests that at least some patients with chronic severe diseases such as ALS do relinquish unattainable goals but find and pursue new goals that still can be attained.

However, ALS-patients do not give up all goals just because they become increasingly difficult to attain. Matuz (2008) found that *communication* –an activity, which becomes increasingly difficult and even impossible in late stage ALS–, was rated consistently of increasing importance across four time points over the course of one year (see also

Lulé et al., 2008). It, thus, appears that communication is such a high-order goal that disengagement is unlikely and patients remain committed to this goal, even if it becomes increasingly difficult. Indeed, patients in LIS go to great lengths to learn alternative communication systems, such as the use of spelling boards containing letters (e.g. León-Carrión, Eeckhout, & Domínguez-Morales, 2002), or train to regulate their cortical activity over the course of several hundred training sessions to be able to communicate again via a BCI (Birbaumer et al., 1999, 2000).

THE GAP The previous section suggested that the ability to communicate is of increasing importance in patients with severe motor impairments. It is thus tragic to note that at least some behaviourally unresponsive patients are not unconscious but show signs of conscious processing, yet still have no possibility of interacting with their environment. However, providing these patients with reliable communication tools requires to first identify wrongly diagnosed VS patients.

Whereas traditionally, DOC diagnoses depend on the evaluation of the absence of behavioural signs, new developments in imaging techniques and experimental paradigms have shown that at least some behaviourally non-responsive patients are in fact not in a vegetative state, but show signs of consciousness (Kotchoubey et al., 2002; Owen et al., 2006; Monti et al., 2010; Cruse et al., 2011; Schnakers, Vanhaudenhuyse, et al., 2009). For example, using functional magnetic resonance imaging (fMRI) Owen and colleagues (2006) were able to demonstrate that a patient diagnosed with VS at the time of testing was able to perform two types of mental imagery in a command following task, thus demonstrating preserved cognitive processing. Similar results have been found in an extensive study by

Monti et al. (2010) investigating 54 patients with disorders of consciousness: one – per definition then wrongly diagnosed– VS patient was able to manipulate his own brain activation to answer five of six yes and no questions correctly. Whereas the use of fMRI is expensive with regard to time, effort, and money, several studies suggest that consciousness can be detected in behaviourally non-responsive patients using more affordable technologies. For example, Cruse et al. (2011) demonstrated that event related desynchronisation/synchronisation (Pfurtscheller & Lopes da Silva, 1999) as measured by electroencephalography (EEG) could be used to detect command following in three of 16 (19%) VS patients. These findings, however, have been challenged by Goldfine et al. (2013) on statistical grounds. Reanalyzing the data from Cruse et al. (2011) using an arguably more accurate approach showed that no evidence for successful command following could be detected in VS patients (but see the reply in Cruse et al., 2013).

To summarise, there exists a subgroup of patients who are, judging from clinical impression, behaviourally unresponsive, but who nevertheless can show signs of conscious awareness. Of these patients' lives, their experiences, the factors affecting their well-being, virtually nothing is known. Thus, these patients are confronted with two problem areas. First, there is a *diagnostic gap* by which at least some patients are wrongly diagnosed as vegetative, and may thus not receive the optimal treatment of their condition. Secondly, there is an *output gap*, which prevents wrongly diagnosed VS patients from shaping their environments according to their needs and from contributing to their QoL (L. Johnson, 2013). Further, given the major implications of identifying behaviourally unresponsive yet conscious patients for medicine (Goldfine et al., 2013), ethics, and law (Eisenberg, 2008), it is clear that any analysis methods used in this enterprise should not only be plausible but have its statistical properties demonstrated.

3

STUDIES OF THE DISSERTATION

3.1 RESEARCH QUESTIONS

1. Can we overcome the diagnostic gap in patients with disorders of consciousness?

   Mounting evidence exists that a subgroup of patients with a diagnosis of vegetative state is wrongly diagnosed, i.e. they are behaviourally non-responsive but, nevertheless, can show functional signs of consciousness. While experimental studies are carried out in highly specialised medical centres, the technology is far from being widely available for routine clinical use. Thus, the ability of a short auditory paradigm to differentiate between conscious MCS and unconscious VS patients was evaluated in a routine clinical setting.

2. Is it possible to identify psychophysiological correlates of quality of life in patients with chronic diseases?

   Cybernetic models of quality of life suggest that low quality of life is an indicator of a mismatch between internal standards (or, goals) and perceived conditions, and that the individual has not (yet) found a way to reduce this difference. The proposed feedback-loop suggests that this individual should repeatedly circle through perceiving a mismatch, trying to reduce this mismatch and again testing for a difference between standards and conditions. Typically, research on quality of life uses questionnaires or interviews, which may not be suitable for patients with severe motor impairments. Thus, the question arises whether it is possible to identify alternative ways to gather information about the quality of life of patients with severe motor impairments. Combining findings from models of quality of life (see section 2.4) and on the event-related potential N400 it is suggested that amplitude modulations of the N400 might serve as a psychophysiological correlate of QoL (see section 3.2.2).

3. How do chronic diseases affect instantaneous QoL?

   Research on quality of life in patients with chronic disease often depends on the use of aggregate measures, e.g. by asking them how they felt (on average) during the past days (Robbins et al., 2001; S. R. Cohen, Mount, Strobel, & Bui, 1995), or even weeks (Hammer, Häcker, Hautzinger, Meyer, & Kübler, 2008). Thus, little is known about the factors which are associated with instantaneous well-being, i.e. well-being as it fluctuates from moment to moment throughout the day.

3.2 studies of the dissertation & synopses

In the following, the studies conducted to answer the above questions are described.

3.2.1 *Closing the diagnostic gap in patients with disorders of consciousness*

Clinical studies as well as studies relying on novel neuroscientific paradigms indicate that at least some patients diagnosed with being in a vegetative state show in fact some evidence of conscious awareness, and this number does not appear to have changed over the last decade (Schnakers, Vanhaudenhuyse, et al., 2009). Despite their comparable complexity, neuroscientific approaches promise a standardised and objective assessment of cognitive functions in DOC patients. For these approaches to be used by non-(EEG-) experts in clinical routine, automaticity and reliability are considered key factors (Guger et al., 2013).

In light of these requirements, the EU-sponsored (FP7-ICT-2009-4) project DECODER aimed at developing an easy-to-use and reliable battery for the assessment of consciousness. While early ERPs can provide valuable information about the intactness of sensory processing, only later ERPs, especially the P300, are sensitive to voluntary shifts of attention. Demonstrating successful command following, as indicated by increased P300 amplitudes, can consequently be taken as evidence of conscious processing.

Given the major implications of identifying behaviourally unresponsive yet conscious patients for medicine (Goldfine et al., 2013), ethics, and law (Eisenberg, 2008) a first study evaluated the statistical properties of a promising ERP-detection routine. A variant of the Studentized Continuous Wavelet Transform (t-CWT) (Bostanov & Kotchoubey, 2006) was implemented, and validated using a total of 12.000 artificial EEG datasets. Results, published in Frontiers in Brain Imaging Methods (Real, Kotchoubey, & Kübler, 2014), indicated that sensitivity and specificity were higher for the t-CWT than for several alternative methods.

In a second study, the t-CWT was applied to EEG data from healthy participants and N = 61 DOC patients while they listened to an auditory oddball paradigm, presented in an active –count the odd tones– and a passive –just listen– condition. Results, in press at Clinical Neurophysiology (Real et al., 2015) suggests that the paradigm implemented in this study does differentiate between healthy participants and DOC patients, but does not distinguish between MCS and VS patients.

- Real, R. G. L., Kotchoubey, B., & Kübler, A. (2014). Studentized Continuous Wavelet Transform (*t*-CWT) in the Analysis of Individual ERPs: Real and Simulated data. *Frontiers in Brain Imaging Methods, 8*, 279. doi: 10.3389/fnins.2014.00279
- Real, R. G. L., Veser, S., Erlbeck, H., Risetti, M., Vogel, D., Müller, F., Kotchoubey, B., Mattia, D., & Kübler, A. (2015). Information processing in patients in vegetative and minimally conscious states. *Clinical Neurophysiology, in press*,. doi:10.1016/j.clinph.2015.07.020

3.2.2 *Psychophysiological correlates of quality of life*

The cybernetic model described in section 2.4 suggests that persons experiencing low quality of life tend to compare their experiences repeatedly with their expectancies, but are unable to reduce a discrepancy. Repeatedly circling through the feedback-loop should then increase the amount with which individuals are confronted with aspects related to the source of the discrepancy. Consequently, these aspects, e.g. words such as *wheelchair* or *diagnosis* should become more accessible in patients reporting low QoL in relation to patients reporting high QoL. To test this hypothesis the N400 event related potential

(ERP) following disease related and disease unrelated words was investigated in patients with ALS and healthy controls. The N400 is a negative ERP deflection with a peak latency about 400 ms after the onset of a meaningful stimulus (usually, a word) that is incongruent with the preceding context. Besides semantic congruence, predictability in general has been found to modulate the N400, with larger amplitudes following non-predictable sentence endings even when the ending itself is semantically congruent with the sentence content. Thus, amplitudes of the N400 potential are inversely related to the ease of lexical access, with lower amplitudes reflecting facilitated access to the mental lexicon. The model suggests that ALS patients who report low QoL should be confronted with disease specific concepts more often than patients who report high QoL, and this should show as a reduced difference N400 (congruent - incongruent) following disease-related in comparison to disease unrelated words.

This hypothesis was tested in a sample of N = 18 patients with ALS and N = 20 age-matched healthy controls. As expected, N400-amplitudes were reduced in patients with low QoL when reading sentences ending in disease-related words, but not when reading sentences ending in disease-unrelated words. Patients reporting high QoL did not show a difference in N400 amplitudes between disease-related and disease-unrelated words. Finally, ERPs in healthy subjects showed no difference between disease-related or non disease-related words, regardless of QoL. Results of the study were published in Clinical Neurophysiology (Real, Herbert, et al., 2014).

- Real, R. G. L., Herbert, C., Kotchoubey, B., Wessig, C., Volkmann, J., & Kübler, A. (2014). Psychophysiological correlates of coping and quality of life in patients with ALS. *Clinical Neurophysiology, 125*, 955-961. doi: 10.1016/j.clinph.2013.09.040.

3.2.3 *How do chronic diseases affect instantaneous QoL*

A rich literature exists on factors influencing QoL and coping with diseases. However, many of the questionnaires used in research on well-being and quality of life in patients with ALS require participants to generate aggregate statements about their experiences, e.g. by asking them how they felt (on average) during the past days or even weeks. Thus, little is known about the factors which are associated with instantaneous well-being, i.e. well-being as it fluctuates from moment to moment throughout the day. In this study, therefore, the experience sampling method (ESM) was used to analyse possible predictors of well-being. The ESM asks participants to record their experiences directly at the moment of sampling. By randomising sampling times throughout the study period, it is possible to collect representative data on participants' experiences, such as well-being and possible influencing factors. A sample of N = 10 patients with ALS provided data on perceived demands, perceived control and well-being three times a day over the course of two weeks. Results, published in Frontiers in Psychology for Clinical Settings (Real, Dickhaus, Ludolph, Hautzinger, & Kübler, 2014), confirmed the importance of perceived control for increased well-being. Importantly, however, perceived demands were also associated with increased well-being, as long as they were perceived as controllable. Within the limitations of the study, e.g. small sample size, these findings suggests that encouraging patients to pursue, within limits, potentially demanding activities, may help to increase their well-being.

- Real, R. G. L., Dickhaus, T., Ludolph, A. Hautzinger, M., & Kübler, A. (2014). Well-being in Amyotrophic Lateral Sclerosis: a pilot Experience Sampling Study. *Frontiers in Psychology for Clinical Settings, 5*, 704. doi: 10.3389/fpsyg.2014.00704

Part II

PUBLICATIONS

frontiers in
NEUROSCIENCE

METHODS ARTICLE
published: 10 September 2014
doi: 10.3389/fnins.2014.00279

Studentized continuous wavelet transform (*t*-CWT) in the analysis of individual ERPs: real and simulated EEG data

Ruben G. L. Real[1]*, Boris Kotchoubey[2] and Andrea Kübler[1]

[1] Department of Psychology I, Institute of Psychology, University of Würzburg, Würzburg, Germany
[2] Institute for Medical Psychology and Behavioural Neurobiology, University of Tübingen, Tübingen, Germany

Edited by:
John J. Foxe, Albert Einstein College of Medicine, USA

Reviewed by:
Stephan Moratti, Universidad Complutense de Madrid, Spain
Ladislav Kristoufek, Academy of Sciences of the Czech Republic, Czech Republic

***Correspondence:**
Ruben G. L. Real, Institute of Psychology, University of Würzburg, Marcusstr. 9-11, 97070 Würzburg, Germany
e-mail: ruben.real@uni-wuerzburg.de

This study aimed at evaluating the performance of the Studentized Continuous Wavelet Transform (*t*-CWT) as a method for the extraction and assessment of event-related brain potentials (ERP) in data from a single subject. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of the *t*-CWT were assessed and compared to a variety of competing procedures using simulated EEG data at six low signal-to-noise ratios. Results show that the *t*-CWT combines high sensitivity and specificity with favorable PPV and NPV. Applying the *t*-CWT to authentic EEG data obtained from 14 healthy participants confirmed its high sensitivity. The *t*-CWT may thus be well suited for the assessment of weak ERPs in single-subject settings.

Keywords: electroencephalogram, EEG, wavelet, *t*-CWT, ERP, significance, detection

1. INTRODUCTION

A wide variety of traumatic and non-traumatic brain injuries can lead to disorders of consciousness (DOC), the vegetative state (aka. apallic syndrome) and the minimally conscious state being the most severe forms (Laureys et al., 2006). Event-related potentials (ERPs) promise to objectively assess residual cognitive functions in these patients (Kotchoubey et al., 2002, 2005; Kübler and Kotchoubey, 2007; Monti, 2012). However, several factors have been noted which make the reliable assessment of ERPs in these patients challenging: EEG recorded at the patients bed-side is often contaminated by artifacts from the surrounding medical equipment or sudden changes in the patient's sympathetic activity, e.g., excessive sweating, changes in body temperature, blood pressure, heart and respiratory rate, or body posture. Further, increasing the number of trials, a method often used to increase the signal-to-noise ratio (SNR), is limited by the rapidly fluctuating vigilance and the short attention span of these patients (Neumann and Kotchoubey, 2004; Laureys et al., 2006). These issues are all the more important, since neuroscientific findings of preserved cognitive functioning in DOC patients may influence the patient's further medical treatment (Laureys et al., 2006), or questions concerning end-of-life decisions (Eisenberg, 2008).

Thus, any EEG analysis technique should fulfill at least four requirements. Firstly, to maintain reliability and, thus, validity, it should be independent of the experimenter's expertise (Valdes-Sosa et al., 1987). Secondly, it should allow for the statistical evaluation of identified ERPs. Thus, the technique must be applicable to single subject analysis and, therefore, must use single trials for statistical evaluation. Thirdly, the technique should be able to differentiate temporarily distinct ERPs (Bostanov and Kotchoubey, 2006). Finally, it should show high sensitivity, i.e., correctly identifying those subjects showing the ERP of interest, and high specificity, correctly identifying those subjects who do not show the ERP of interest.

It should be noted that here the term ERP is used in a mathematical/statistical sense, i.e., it means a time-locked deflection which discriminates between two experimental conditions or between one experimental condition and baseline activity. This definition makes no assumption as to the underlying physiological or psychological generators.

In this paper, we describe an ERP detection method based on the continuous wavelet transform (CWT), and compare its performance to a variety of competing analysis techniques in detecting ERP components in artificial and authentic EEG data under varying SNRs.

2. METHODS

2.1. THE STUDENTIZED CONTINUOUS WAVELET TRANSFORM (*t*-CWT)

Classical techniques for ERP detection in data obtained from a single subject include template matching (Woody, 1967) or peak picking after low-pass filtering (Ruchkin and Glaser, 1978), which, incidentally, are virtually the same, since low-pass filtering can be thought of as determining the cross-covariance of a signal with a predefined template. Later, the discrete wavelet transform (DWT) has been suggested (Samar et al., 1999). While DWTs provide for a very economical signal representation, the resulting coefficients are difficult to interpret in terms of the characteristics of an ERP: Typically, one ERP is reflected in several coefficients and, conversely, one coefficient may also reflect several ERPs. Further, in ERP assessment, complete representation of a signal is a minor requirement in comparison to the overall aim of extracting meaningful features from the data. Thus, our approach concentrates on

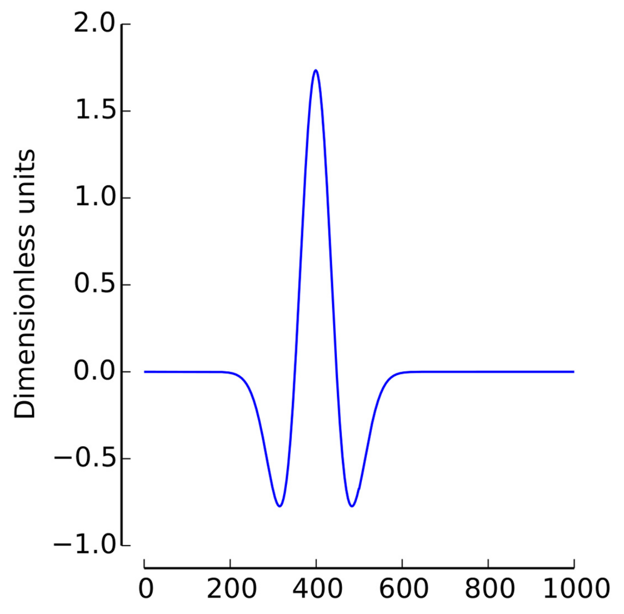


FIGURE 1 | A Mexican Hat Wavelet with a scale of 200 and a time shift of 400 ms.

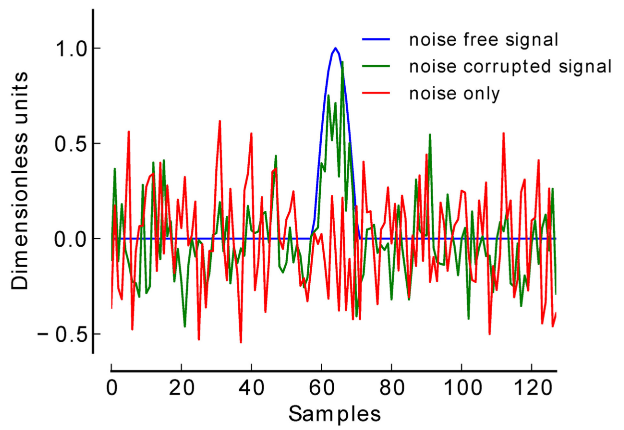


FIGURE 2 | Average of simulated EEG data at −16 dB.

feature extraction and uses the continuous wavelet transform (CWT) to represent EEG signals as a function of two parameters: time and scale. The resulting coefficients can be thought of forming a map with the axes corresponding to time and scale—a scalogram (see **Figures 1–3**). In this map, local extrema indicate salient features of the EEG signal, such as peaks or oscillations.

In the following, we describe and evaluate a variant of the Studentized Continuous Wavelet Transform (t-CWT), in which Student t-values are calculated for each wavelet coefficient (Bostanov and Kotchoubey, 2006) and evaluated using a t_{max} randomization test (Blair and Karniski, 1993; Groppe et al., 2011). Previous implementations of the t-CWT (Bostanov, 2004; Bostanov and Kotchoubey, 2006) included a time-dependent low-pass filtering procedure, which attenuated short deflections occurring late in an epoch. This procedure was originally implemented to account for the phenomenon that earlier ERPs are shorter than late ERPs and that short deflections occurring late in an epoch are less unlikely to represent a true ERP. However, this procedure makes rather strict assumptions on the distribution of ERP components, thus running the risk of attenuating ERPs, which do not match the filter specifications. In data from healthy participants this assumption may be less critical than in patients with acquired brain damage, who often exhibit substantial variation in latencies. For example, analyzing EEG data obtained from patients with severe disorders of consciousness, Guérit et al. (1999) found that latencies of a P300-like component ranged from 260 to more than 620 ms after stimulus onset. With this in mind, we chose not to implement the time-dependent low pass filtering procedure thus avoiding the risk of attenuating ERPs outside the filter's specification.

First step: Calculation of the Continuous Wavelet Transform (Mallat, 2007)

For a digitally sampled EEG signal $f^{mo}[t]$ of length N, where m denotes the channel, o denotes the trial, and t denotes the time variable, the wavelet coefficients $W^{mo}[s, \tau]$ are calculated as follows:

$$W^{mo}[s,\tau] = \frac{1}{\sqrt{s}} \sum_{t=0}^{t=N-1} f^{mo}[t]\psi\left(\frac{t-\tau}{s}\right) \quad (1)$$

where τ denotes the time shift and $s > 0$ denotes the scale. Both τ and s are measures in time units, and ψ is the wavelet function.

$$-\psi(\tau) = \frac{2}{\pi^{1/4}\sqrt{3\sigma}}\left(1 - \frac{\tau^2}{\sigma^2}\right)\exp\left(\frac{-\tau^2}{2\sigma^2}\right) \quad (2)$$

In the current study, the Mexican Hat wavelet was used (2, with $\sigma = 1/4$, see **Figure 1**)[1].

Equation (1) implies that the CWT's representation of a signal is highly redundant. While this redundancy is not very efficient, i.e., the CWT generates many more coefficients than the DWT, it does allow for the precise localization of ERPs.

Second step: Calculation of Student t-values

In standard ERP analysis, comparison of within-condition averages is often used to decide where activation differs between experimental conditions. The same logic is followed here, with the exception that Student t-values are calculated instead of means. In the two-sample case, as when comparing two experimental conditions, t-values are calculated using the two-sample t-test. In the one-sample case, when comparing activity against the

[1]Note, the use of $\sigma = 1/4$ instead of the standard $\sigma = 1$ in (2). In the standard definition, σ corresponds to half the width between the zeroes of the Mexican Hat, while in our definition σ corresponds to the distance between the minima. This was done for convenience, as, thus defined, the scale parameter corresponds to the approximate wavelength of the Mexican Hat (inverse frequency). In ERP applications, scales can then be interpreted as the approximate durations of components.

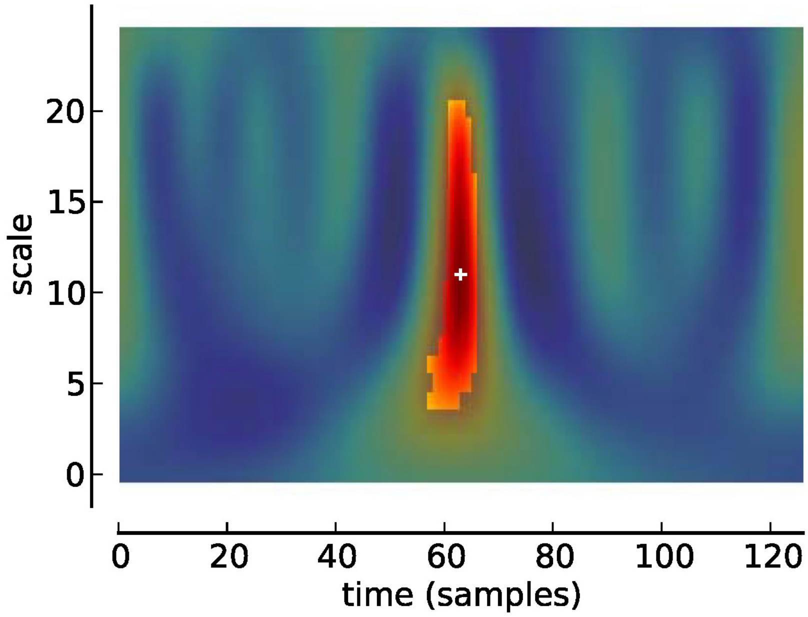


FIGURE 3 | Scalogram of Studentized wavelet coefficients corresponding to Figure 2. Highlighted area indicates location of significant ($p < 0.05$) differences. Plus sign indicates local maximum.

baseline, a one-sample *t*-test can be used. The result of this procedure is a statistical map, which shows the reliability of each wavelet coefficient across trials. However, the *t*-values are not directly used for statistical analysis. The primary reason is that the statistical map corresponds to many individual *t*-test, thereby introducing the problem of multiple comparison. Another reason is that the distribution of Studentized wavelet coefficients is unknown, rendering the statistical validity of parametric statistical tests questionable. The solution to this problem is addressed in Section 2.2.

Third step: Detection of local extrema

From the statistical map local extrema (s^{mi}, τ^{mi}) are detected. These are the locations in the time-frequency plane of locally maximal differences (weighted by variance) between experimental conditions. Note that no weighting procedure is used in the detection of local extrema. Spurious local extrema—which do not correspond to true differences in activity in the data—are deleted during significance testing (see Fourth Step).

Fourth step: Calculation of significance

The purpose of this step is to ascertain whether the local extrema identified in the previous step truly differentiate between the two experimental conditions. The wavelet coefficients calculated in the First step are subjected to a randomization test, described in the next section. After randomization testing, a *p*-value can be assigned to each local extremum indicating significance.

2.2. RANDOMIZATION TESTS

Two-sample tests are designed to assess whether a statistic differs between two experimental conditions. Under the null hypothesis of no difference, the information that an observation originated from a particular condition is quite meaningless, since the same observation could just as likely have originated from the other condition, i.e., the condition labels assigned to each observation are *exchangeable*. Under the null hypothesis, then, the significance of a statistic expressing the group difference, such as a two-sample *t*-value, can be assessed by comparing the original statistic with the distribution of this statistic obtained when the condition labels have been permuted, or, if permutation is not feasible, when they have been randomly exchanged many times.

Importantly, this procedure can be easily extended to compensate for the increased chance of false positive findings due to increased number of comparisons. As the number of comparisons increases, so does the likelihood of getting extreme observations by chance. By computing the distribution of the most extreme statistic, the maximal *t*-value ($t_{\max}$) in our study, across the number of tests for each permutation, the distribution obtained through randomization automatically adapts for the increased likelihood of extreme values (Blair and Karniski, 1993; Groppe et al., 2011).

2.3. APPLICATION TO SIMULATED DATA

Previously, the *t*-CWT was validated on real EEG data from healthy subjects. The underlying assumption is that the most common ERPs should be present in every healthy subject. Then, an analysis method is the better the more subjects it identifies as showing the ERPs of interest (Bostanov and Kotchoubey, 2006). However, it is also known that even highly prototypical ERPs, such as the P300, may be absent in as much as 31% of healthy subjects (e.g., Lulé et al., 2013). Therefore, the number of subjects in which an ERP can be detected may be a spurious criterion. An arguably better criterion may then be the evaluation of sensitivity, i.e., the number of subjects in which an ERP is truly present and detected, and specificity, i.e., the number of subjects in which a component is truly absent and not detected. However, accurate knowledge of the true presence or absence of ERPs is typically not available. In the past, this problem has been approached by using experts' ratings as a "gold" standard against which automated ERP detection procedures could be validated. However, this procedure finds its difficulties in that inter-rater agreement varies between studies (Valdes-Sosa et al., 1987; Wilson et al., 1996), and that this procedure does not allow for the easy analysis of ERP datasets with different signal-to-noise ratios (Schneider et al., 2003). Lastly, obtaining ratings from two or more experts is expensive and time consuming.

However, simulating ERPs allows for precisely controlling presence or absence of defined components. We therefore generated artificial EEG datasets which either contained or did not contain a signal of interest, and compared the performance of the t-CWT to a variety of other ERP detection methods.

2.3.1. Generation of artificial EEG signals

The signal-to-noise ratio (SNR) of EEG signals is often very low and subject to considerable heterogeneity. While ERPs of some subjects exhibit exceptionally high SNRs of up to 3 dB, SNRs in around 50% of healthy participants are lower than approximately −9 dB (Coppola et al., 1978).

To validate our procedure, we simulated a total of 12.000 EEG datasets at six low levels of SNR. For each SNR level (−18 to −13 dB) 1000 datasets were generated in which a simulated ERP (centered positive half wave of a 3 Hz cosine wave) (Yeung et al., 2004) was truly present, and 1000 datasets in which this component was truly absent (see **Figure 2**). Each dataset consisted of 60 trials of simulated EEG data of one-second duration (sampling rate 128 Hz). In datasets belonging to the present condition, 30 trials contained the positive peak, and the remaining 30 trials did not contain such a peak, thus simulating two experimental conditions. Gaussian white noise was added to each trial to achieve the desired SNR. Datasets belonging to the absent condition were pure Gaussian white noise. The number of 30 trials per condition was chosen following reports that in a classical P300 oddball paradigm at least 20 trials are needed to be able to detect a P300 (Cohen and Polich, 1997).

2.3.2. EEG analysis methods

The performance of the t-CWT was compared to five other signal processing methods. Given the tremendous amount of effort invested into the development of new signal processing methods, it is clear that our choice of comparison methods is restricted. The t-CWT as proposed in this paper is a combination of two factors, wavelet analysis (which may be understood as simultaneous filtering) and the t_{max} randomization test to correct for multiple comparisons. Consequently, data filtering and correction for multiple comparisons were also considered in the choice of comparisons methods. A further consideration was the availability of analysis methods, with filtering and peak picking procedures being implemented in all major EEG analysis software packages (e.g., BrainVision Analyzer, Brain Products, Gilching, Germany) and (t_{max}) randomization testing being freely available as a software package for the EEGLAB suite (Delorme and Makeig, 2004; Groppe et al., 2011). The t-CWT was compared to the following procedures:

1. *Simple peak detection:* A difference signal was calculated by subtracting the average of trials which might contain a peak from the average of trials without a peak, and a two-sample t-test performed at the location of the maximum difference. It was expected to provide very high sensitivity but very low specificity. Low specificity was hypothesized since this procedure does not control for α error inflation due to multiple comparisons.
2. *Peak detection after band pass filtering:* As above, but here a fourth order Butterworth band pass filter (0.1–20 Hz) was used before calculation of averages. Filtering of EEG data is often used to increase the SNR, so we expected this procedure to increase sensitivity and specificity. However, because no adjustment for multiple comparisons was performed in this analysis, the false positive rate was expected to exceed the nominal α level.
3. t_{max} *based peak detection:* A t_{max} randomization test was performed on the unfiltered EEG signal, and the minimal p-value selected. This method was expected to show high specificity, reflecting effective control of α-error inflation built into the t_{max} randomization test, but at the same time low sensitivity, confirming the low levels of SNR in our datasets.
4. t_{max} *based peak detection after band pass filtering:* A t_{max} randomization test was used on the fourth order Butterworth band pass filtered (0.1–20 Hz) EEG signal. This procedure was expected to show high sensitivity, reflecting the increased SNR after filtering, and high specificity.
5. *Range based peak picking after band pass filtering:* As (2.), but here the means around the detected peak (± 83 ms) were used for statistical analysis. This method resembles a popular approach of visually determining the latency of the ERP of interest and then calculating the mean-amplitude in an interval surrounding the identified peak.
6. *t-CWT:* The t-CWT was calculated using five steps per octave to generate logarithmically spaced scales between 1 Hz and half the Nyquist frequency (32 Hz). It was expected to show superior performance to all other methods.

One-thousand repetitions (Groppe et al., 2011) were used for randomization testing of the t_{max} tests and the t-CWT and $\alpha = 0.05$ was the nominal false positive rate used for all analyses.

2.3.3. Statistical analysis

Statistical analysis was based on the F_1-score, the harmonic mean of the positive predictive value, $PPV = TP/(TP + FP)$, and sensitivity, $TP/(TP + FN)$.

$$F_1 = \frac{2 \cdot PPV \cdot sensitivity}{PPV + sensitivity} \quad (3)$$

$$= \frac{2 \cdot \mathrm{TP}}{2 \cdot \mathrm{TP} + \mathrm{FN} + \mathrm{FP}} \quad (4)$$

F_1 scores are a popular metric in research on information retrieval. In this application setting, a "good" algorithm would retrieve not only all relevant documents (i.e., high sensitivity), but at the same time ensure that the proportion of relevant documents is high in relation to the total number of findings (i.e., high PPV).

While the exact distribution of F_1 is unknown, Goutte and Gaussier (2005) have shown that Monte Carlo simulations can be used to estimate the probability that the F_1 scores of one system (F_1^1) exceed the scores of another system (F_1^2). This can be achieved by creating large (50.000 in our case) samples ($\{f_i^1\}_{i=1...L}$ and $\{f_i^2\}_{i=1...L}$) of the distributions of F_1 scores using random gamma variates.

$$F_1 = \frac{U}{U+V} \text{ with } \begin{cases} U \sim \Gamma(TP + 0.5, 2) \\ V \sim \Gamma(FP + FN + 1, 1) \end{cases} \quad (5)$$

The probability $P(F_1^1 > F_1^2)$ is then estimated by:

$$\hat{P}(F_1^1 > F_1^2) = \frac{1}{L}\sum_{i=1}^{L} \mathrm{I}\left(f_i^1 > f_i^2\right) \quad (6)$$

where the indicator function $\mathrm{I}(\cdot)$ is 1 if the condition is true, 0 otherwise.

A potential problem associated with the sole reliance on F_1 scores is that they are insensitive to the number of true negatives (Sokolova and Lapalme, 2009). While this is not a problem in the classic domain of information retrieval, in individual ERP assessment knowledge about the absence of a particular ERP is often important information. Thus, to complement the traditional F_1 score, we defined the "negative" F_1 score as the harmonic mean of the NPV and specificity:

$$\text{negative } F_1 = \frac{2 \cdot \mathrm{TN}}{2 \cdot \mathrm{TN} + \mathrm{FP} + \mathrm{FN}} \quad (7)$$

Finally, we also calculated 95% confidence intervals for the F_1 scores. This was performed by first calculating the distribution of F_1 scores according to (4, 7, 5) and then selecting the F_1 scores delimiting the 2.5 to 97.5% interval.

2.4. APPLICATION TO REAL EEG DATA

Anticipating results presented later (see Section 3.1), results from simulation studies indicated an overall favorable performance of the *t*-CWT, closely followed by the t_{max} randomization test after band pass filtering (see **Figure 4**, **Table 2**). To confirm these findings in real EEG datasets, we analyzed EEG data recorded from 14 healthy participants (9 female; mean age = 27.6, *SD* = 9.5) while they listened to a two-tone auditory oddball paradigm. Participants were instructed to silently count the number of odd tones. EEG recordings were performed at the psychophysiological laboratories at the Universities of Tübingen and Würzburg. The study was approved by the local Ethical Review Boards of

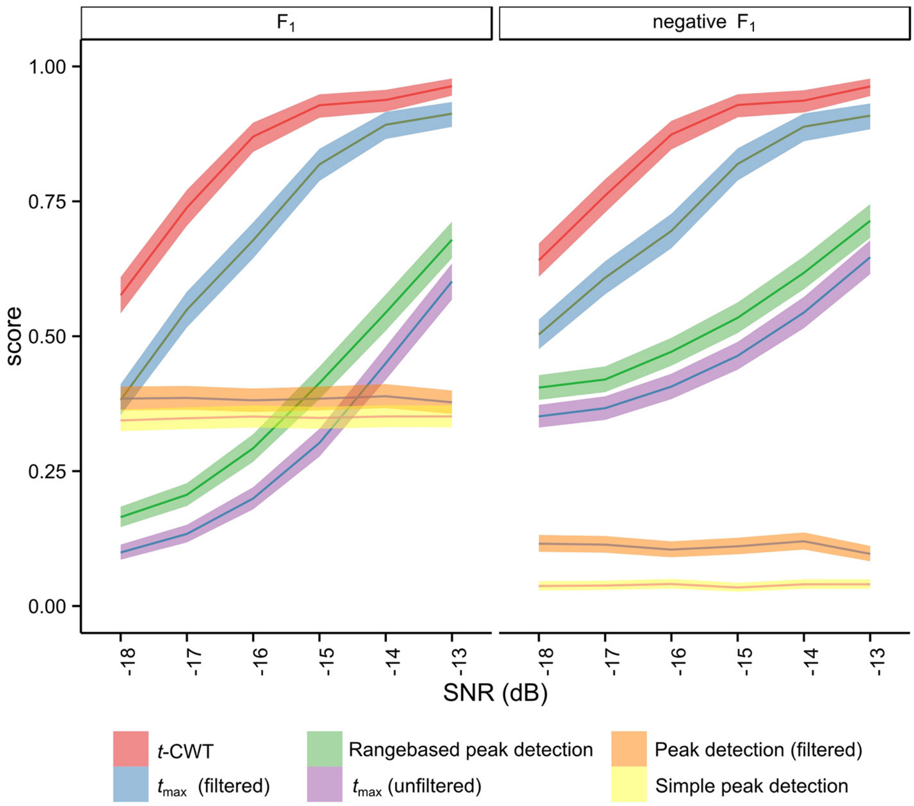


FIGURE 4 | Means and 95% confidence intervals of the distribution of F_1 after Monte Carlo simulation (5).

the institutions involved and conformed to the Declaration of Helsinki (World Medical Association, 2008).

2.4.1. Stimuli

Stimuli were delivered via in-ear headphones (E-A-RTONE Gold, Auditory Systems, Indianapolis, Indiana). Participants were presented with a binaural stream of 420 short complex high (440 + 880 + 1760 Hz) tones into which 60 short complex low (247 + 494 + 988 Hz) tones were pseudo-randomly interspersed (Kotchoubey et al., 2005). Stimulus duration was 50 ms, linear rise-fall time was 5 ms, intensity was 70 dB (Polich, 1986), and SOA was 850 ms.

2.4.2. EEG recording and preprocessing

EEG was recorded with a sampling rate of 512 Hz using a 31-channel active electrodes cap (LADYbird, g.tec medical engineering, Schiedlberg, Austria; nose reference). Vertical and horizontal eye movement was recorded with two pairs of electrodes at the outer canthi and above and below one eye. Offline, data was bandpass (0.01–70 Hz) and notch (50 Hz) filtered, segmented into epochs of 850 ms, and aligned to the 100 ms pre-stimulus baseline. Ocular artifacts were corrected with a regression-based approach after which segments with absolute voltages exceeding 120 μV were rejected as artifacts. Segments were re-referenced to linked-mastoids, and all odd tone trials and the preceding frequent tone trials selected for further analysis. Mean number of trials after artifact rejection was 52.93 ($SD = 9.88$) for each condition. Inspection of the grand average (see **Figure 5**) indicated the presence of a broad positive difference ERP (odd minus frequent tone trials) which was maximal at electrode Pz. Therefore, analysis was restricted to identifying a positivity at electrode Pz in the 250 ms long interval starting at 250 ms after stimulus onset (Polich, 2007). SNR estimates for these datasets were calculated on the basis of the sample correlation coefficient (Coppola et al., 1978, Equations 3–6, coefficient $\hat{\alpha}_R$).

2.4.3. Analysis

The t-CWT was hypothesized to be especially suited for the analysis of data with low SNRs. However, real EEG data from healthy participants only offers a limited range of SNRs. Therefore, analysis focused on EEG datasets obtained from healthy participants with degraded SNRs. First, datasets were split into "signal" and "noise" trials by calculating the "signal" as the single-subject difference ERP (activation in odd minus activation in frequent tone trials) and then calculating surrogate (Fell et al., 1996) "noise" trials by subtracting the signal from the single trials. Then, the signal's amplitude was reduced to achieve a desired SNR (ranging from −18 to −13 dB). Finally, the degraded signal and noise were recombined and subjected to further analysis. During the generation of datasets with degraded SNRs only those datasets in which the original SNR was above the to be simulated SNR were used (see **Table 3**). For example, a dataset with an original SNR of −12 dB would be used to generate degraded datasets ranging from −13 dB to −18 dB, while a dataset with an SNR of −14 dB would not be used to generate a dataset of −13 dB, as doing so would correspond to amplification instead of degradation. This method allowed us to analyze the performance of the t-CWT and the t_{max} test under several low SNRs while simultaneously maintaining properties of authentic EEG data (Fell et al., 1996). We hypothesized increased performance of the t-CWT at low SNRs. Differences between the number of identified datasets between the t-CWT and the t_{max} procedure were evaluated using a permutation test (1000 repetitions). Development of the t-CWT and t_{max} procedures was done in Python using the SciPy and NumPy libraries (Jones et al., 2001) and R (R Development Core Team, 2011) was used for statistical analysis.

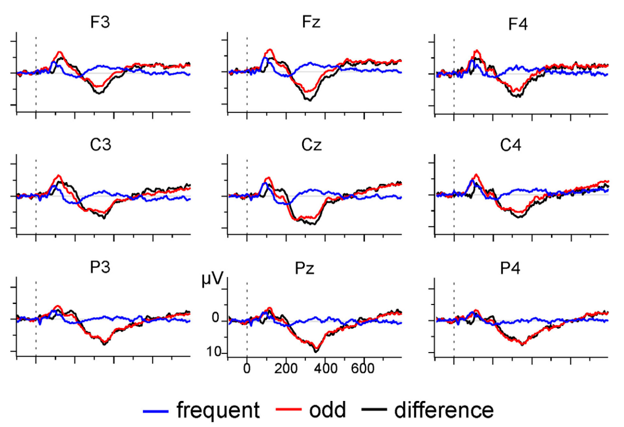


FIGURE 5 | Grand average of activation following odd and frequent tone trials (N = 14).

3. RESULTS

3.1. RESULTS OF SIMULATION STUDIES

Table 1 shows mean sensitivities and specificities for each analysis method and level of SNR. Procedures that do not correct for multiple testing [Simple peak detection and Peak detection (filtered)] show very high sensitivity but at the same time very high rates of false positives which exceed the nominal α-level of 0.05. In contrast, procedures based on the t_{max} randomization test do not show inflated false positive rates. The range-based peak detection procedure does not show α error inflation, however, sensitivity is lower as compared to the t_{max} (filtered) or the t-CWT procedure.

Figure 4 shows the mean F_1 scores and associated 95% confidence intervals for each method studied. The non-overlapping confidence intervals for the t-CWT show that its F_1 scores are significantly higher than those of the competing methods. From **Figure 4** it also appears that the difference between the t-CWT and the t_{max} (filtered) procedure is smaller at higher levels of SNR. However, **Table 2** confirms that the t-CWT achieves higher F_1 scores than the t_{max} (filtered) procedure.

3.2. RESULTS OF EEG ANALYSIS

The median $\hat{\alpha}_R$ SNR for the difference in activation between odd and frequent tone trials in data recorded from healthy participants was −9.28 dB ($M = -9.26$, $SD = 3.09$), and 50% of participants had values between −8.99 and −1.87 dB. These estimates closely replicate previous findings on the distribution of SNRs obtained from healthy participants during auditory paradigms (Coppola et al., 1978, median = −9.35 dB, 50% range: −7.17 to −1.31 dB).

Table 1 | Sensitivity (SE) and 1-specificity (SP) by analysis method and SNR.

Analysis	Measure	SNR (dB)					
		−18	−17	−16	−15	−14	−13
Simple peak detection	1-SP	0.9280	0.9270	0.9220	0.9340	0.9230	0.9230
Simple peak detection	SE	0.9870	0.9950	0.9990	1.0000	1.0000	1.0000
Peak detection (filtered)	1-SP	0.7920	0.7960	0.8110	0.8010	0.7860	0.8240
Peak detection (filtered)	SE	0.9950	1.0000	1.0000	1.0000	1.0000	1.0000
t_{max} (unfiltered)	1-SP	0.0590	0.0610	0.0440	0.0380	0.0500	0.0470
t_{max} (unfiltered)	SE	0.1910	0.2500	0.3470	0.4820	0.6520	0.7870
t_{max} (filtered)	1-SP	0.0490	0.0500	0.0660	0.0500	0.0470	0.0450
t_{max} (filtered)	SE	0.5800	0.7450	0.8620	0.9460	0.9880	0.9980
Rangebased peak detection (filtered)	1-SP	0.0120	0.0240	0.0120	0.0240	0.0230	0.0230
Rangebased peak detection (filtered)	SE	0.2860	0.3500	0.4580	0.5990	0.7210	0.8280
t-CWT	1-SP	0.0200	0.0220	0.0190	0.0150	0.0260	0.0180
t-CWT	SE	0.7460	0.8690	0.9490	0.9780	0.9940	1.0000

Table 2 | Results of the statistical comparison of the point estimates $\hat{F}_1(4, 7)$ between the *t*-CWT and the t_{max} (filtered) procedure by SNR.

SNR (dB)	$\hat{F}_1$ scores			Negative $\hat{F}_1$ scores		
	t-CWT	t_{max} (filtered)	*p*	*t*-CWT	t_{max} (filtered)	*p*
−18	0.8448	0.7121	0.0000	0.8774	0.8022	0.0000
−17	0.9191	0.8301	0.0000	0.9275	0.8617	0.0000
−16	0.9644	0.8942	0.0000	0.9656	0.9015	0.0000
−15	0.9814	0.9479	0.0000	0.9816	0.9481	0.0000
−14	0.9842	0.9710	0.0026	0.9838	0.9700	0.0021
−13	0.9911	0.9770	0.0002	0.9909	0.9760	0.0001

Using the t_{max} randomization test after 4th-order Butterworth band pass filtering (0.1–20 Hz) indicated that 6 out of 14 (43%) participants showed a significant difference in activation between odd and frequent tone trials at Pz. In contrast, the *t*-CWT could detect a significant positivity in two additional participants (total: 8 of 14, 57%).

Table 3 shows the results of our main analysis. At high SNRs the *t*-CWT and the t_{max} show increasingly high agreement, but at lower levels of SNR the *t*-CWT identified more significant differences than the t_{max} test. In total, the *t*-CWT identified significantly ($p = 0.001$) more datasets ($n = 39$) than the t_{max} test ($n = 14$).

Table 3 | Percentage of degraded datasets (∼ participants) with a significant positivity in the P300-time range.

	SNR (dB)					
	−18	−17	−16	−15	−14	−13
n^a	13	13	12	11	9	9
t-CWT	15.00	31.00	67.00	82.00	89.00	89.00
t_{max}	0.00	0.00	17.00	27.00	33.00	67.00

[a] *The number of participants whose SNR was higher than that required for simulation (see Section 2.4.3).*

4. DISCUSSION

In this study, we evaluated the performance of a variant of the Studentized Continuous Wavelet Transform (*t*-CWT). Earlier studies based on data from healthy participants suggested favorable performance, however, specificity and performance under different signal-to-noise ratios were not evaluated. Using simulated EEG datasets in which a signal was either present or absent at six levels of low SNR allowed us to systematically analyze the performance of a variety of EEG signal detection methods and compare them to the *t*-CWT. Our results show that for peak detection procedures that do not control for multiple comparisons, false positive rates (greatly) exceed the nominal α level. In contrast, procedures using t_{max} randomization tests effectively control the false positive rate. The *t*-CWT showed superior performance compared to all other examined methods. Analysis of EEG data obtained from healthy participants while listening to a two-tone auditory oddball paradigm showed that the *t*-CWT identified a significant difference ERP in the P300-time range in more participants than the t_{max} test. Further, analysis of surrogate EEG data confirmed that the *t*-CWT is particularly sensitive at low SNRs.

Filtering has long been used to increase SNRs and much effort has been spent on identifying optimal filtering procedures for ERP detection (e.g., Kalyakin et al., 2007 for the MMN, and Farwell et al., 1993 for the P300). However, these approaches rely on using just one optimal filter, thereby running the risk of attenuating ERPs, which do not match the filter specifications. In contrast, the wavelet approach of the *t*-CWT can be thought of simultaneously applying a multitude of filters, thereby increasing the chance of identifying an optimum. Thus, the *t*-CWT also allows for the detection of several ERPs simultaneously, e.g., detecting the N100-(P200) complex and a P300 in an oddball paradigm.

However, this conceptual superiority comes at increased computational costs, as the time required for the t_{max} randomization tests increases with the number of wavelet coefficients, and the number of randomizations. Other methods to control for multiple comparisons exist, e.g., the variants of the false discovery rate (FDR; Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001; Benjamini et al., 2006) and have also been applied to wavelet coefficients (Abramovich and Benjamini, 1995). These were not implemented as they all entail stronger assumption of the underlying data structure than the t_{max} randomization test, which only assumes symmetric distribution around zero under H_0. However, closer examination of the performance of the *t*-CWT when using FDR might still be worthwhile since these procedures work much faster than randomization tests.

EEG analysis methods are complex, results sometimes only depend on subtle differences in the preprocessing procedures (e.g., VanRullen, 2011; Acunzo et al., 2012) or statistical analysis (e.g., Cruse et al., 2011, 2013; Goldfine et al., 2013), and it may not always be easy to decide upon the most appropriate method. However, the use of simulated data offers the possibility of systematically varying the data's properties a particular analysis method is designed to detect. It, thus, offers a controlled testing environment that may help to tailor an analysis for a particular problem. Nevertheless, simulations can only approximate real life data and results are strongly influenced by the underlying assumptions. For example, although our analysis of real EEG data confirmed results obtained during simulation, it appears that sensitivities of both *t*-CWT and t_{max} test are overestimated during simulation (see sensitivities in **Table 1**) in comparison to real EEG data (**Table 3**). We speculate the reason for this to be that the assumptions made during simulation, i.e., a highly localized peak embedded in Gaussian white noise, while statistically convenient, are less than perfect approximations to real EEG data. Importantly, however, the most important finding from our simulation study –high sensitivity of the *t*-CWT– was validated by the analysis of EEG data from healthy participants.

The assessment of ERPs promises to be a valuable tool in determining residual cognitive functions in patients with DOC. However, a variety of factors may lead to reduced signal-to-noise ratios in EEG obtained from these patients, making reliable assessment difficult. At the same time, depending on the results of the assessment, consequences may be far reaching (Laureys et al., 2006; Eisenberg, 2008). Using simulated ERPs at six low levels of SNR we have shown that the *t*-CWT was superior to a variety of other procedures in terms of sensitivity, specificity, positive ($\sim F_1$ scores), and negative predictive values ($\sim$ negative F_1 scores).

While the development of the *t*-CWT was prompted by a desire to evaluate ERPs in DOC patients, the method can be applied in other scenarios, as it can be used whenever detection of ERPs in single subjects is necessary. However, it should be noted that its increased sensitivity might not be noticeable provided high SNRs. Thus, the *t*-CWT may be best for the assessment of weak ERPs. Finally, although we have used a real wavelet in our study, the *t*-CWT can be easily extended to include complex wavelets, thus, allowing for the analysis of non-phase-locked activity, or to compensate for latency jitter.

ACKNOWLEDGMENTS

This work is supported by the European ICT Programme projects FP7-247919 (DECODER) and FP7-287320 (CONTRAST). This paper solely reflects the views of its authors. The European commission is not liable for any use that may be made of the information contained therein. This publication was funded by the German Research Foundation (DFG) and the University of Würzburg in the funding programme Open Access Publishing.

REFERENCES

Abramovich, F., and Benjamini, Y. (1995). "Thresholding of wavelet coefficients as multiple hypotheses testing procedure," in *Lecture Notes in Statistics*, eds P. Bickel, P. Diggle, S. Fienberg, K. Krickeberg, I. Olkin, and N. Wermuth (New York, NY: Springer New York), 5–14.

Acunzo, D. J., MacKenzie, G., and van Rossum, M. C. (2012). Systematic biases in early erp and erf components as a result of high-pass filtering. *J. Neurosci. Methods* 209, 212–218. doi: 10.1016/j.jneumeth.2012.06.011

Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J. R. Stat. Soc. B* 57, 289–300.

Benjamini, Y., Krieger, A. M., and Yekutieli, D. (2006). Adaptive linear step-up procedures that control the false discovery rate. *Biometrika* 93, 491–507. doi: 10.1093/biomet/93.3.491

Benjamini, Y., and Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *Ann. Stat.* 29, 1165–1188. doi: 10.2307/2674075

Blair, R. C., and Karniski, W. (1993). An alternative method for significance testing of waveform difference potentials. *Psychophysiology* 30, 518–524. doi: 10.1111/j.1469-8986.1993.tb02075.x

Bostanov, V. (2004). Bci competition 2003–data sets ib and iib: feature extraction from event-related brain potentials with the continuous wavelet transform and the t-value scalogram. *IEEE Trans. Biomed. Eng.* 51, 1057–1061. doi: 10.1109/TBME.2004.826702

Bostanov, V., and Kotchoubey, B. (2006). The t-cwt: a new erp detection and quantification method based on the continuous wavelet transform and student's t-statistics. *Clin. Neurophysiol.* 117, 2627–2644. doi: 10.1016/j.clinph.2006.08.012

Cohen, J., and Polich, J. (1997). On the number of trials needed for p300. *Int. J. Psychophysiol.* 25, 249–255. doi: 10.1016/S0167-8760(96)00743-X

Coppola, R., Tabor, R., and Buchsbaum, M. S. (1978). Signal to noise ratio and response variability measurements in single trial evoked potentials. *Electroencephalogr. Clin. Neurophysiol.* 44, 214–222. doi: 10.1016/0013-4694(78)90267-5

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T. A., Fernández-Espejo, D., Pickard, J. D., et al. (2011). Bedside detection of awareness in the vegetative state: a cohort study. *Lancet* 378, 2088–2094. doi: 10.1016/S0140-6736(11)61224-5

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T. A., Fernández-Espejo, D., Pickard, J. D., et al. (2013). Reanalysis of "bedside detection of awareness in the vegetative state: a cohort study" – authors' reply. *Lancet* 381, 291–292. doi: 10.1016/S0140-6736(13)60126-9

Delorme, A., and Makeig, S. (2004). Eeglab: an open source toolbox for analysis of single-trial eeg dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21. doi: 10.1016/j.jneumeth.2003.10.009

Eisenberg, J. B. (2008). Schiavo on the cutting edge: functional brain imaging and its impact on surrogate end-of-life decision-making. *Neuroethics* 1, 75–83. doi: 10.1007/s12152-007-9000-6

Farwell, L. A., Martinerie, J. M., Bashore, T. R., Rapp, P. E., and Goddard, P. H. (1993). Optimal digital filters for long-latency components of the event-related brain potential. *Psychophysiology* 30, 306–315. doi: 10.1111/j.1469-8986.1993.tb03357.x

Fell, J., Röschke, J., and Schäffner, C. (1996). Surrogate data analysis of sleep electroencephalograms reveals evidence for nonlinearity. *Biol. Cybern.* 75, 85–92. doi: 10.1007/BF00238742

Goldfine, A. M., Bardin, J. C., Noirhomme, Q., Fins, J. J., Schiff, N. D., and Victor, J. D. (2013). Reanalysis of "bedside detection of awareness in the vegetative state: a cohort study." *Lancet* 381, 289–291. doi: 10.1016/S0140-6736(13) 60125-7

Goutte, C., and Gaussier, E. (2005). "A probabilistic interpretation of precision, recall and f-score, with implication for evaluation," in *Advances in Information Retrieval*, eds D. E. Losada and J. M. Fernández-Luna (Berlin; Heidelberg: Springer), 345–359.

Groppe, D. M., Urbach, T. P., and Kutas, M. (2011). Mass univariate analysis of event-related brain potentials/fields i: A critical tutorial review. *Psychophysiology* 48, 1711–1725. doi: 10.1111/j.1469-8986.2011.01273.x

Guérit, J. M., Verougstraete, D., de Tourtchaninoff, M., Debatisse, D., and Witdoeckt, C. (1999). Erps obtained with the auditory oddball paradigm in coma and altered states of consciousness: clinical relationships, prognostic value, and origin of components. *Clin. Neurophysiol.* 110, 1260–1269. doi: 10.1016/S1388-2457(99)00061-9

Jones, E., Oliphant, T., Peterson, P., and others. (2001). *Scipy: Open Source Scientific Tools for Python.* Available online at: http://www.scipy.org/

Kalyakin, I., Gonzalez, N., Joutsensalo, J., Huttunen, T., Kaartinen, J., and Lyytinen, H. (2007). Optimal digital filtering versus difference waves on the mismatch negativity in an uninterrupted sound paradigm. *Dev. Neuropsychol.* 31, 429–452. doi: 10.1080/87565640701229607

Kotchoubey, B., Lang, S., Bostanov, V., and Birbaumer, N. (2002). Is there a mind? electrophysiology of unconscious patients. *News Physiol. Sci.* 17, 38–42.

Kotchoubey, B., Lang, S., Mezger, G., Schmalohr, D., Schneck, M., Semmler, A., et al. (2005). Information processing in severe disorders of consciousness: vegetative state and minimally conscious state. *Clin. Neurophysiol.* 116, 2441–2453. doi: 10.1016/j.clinph.2005.03.028

Kübler, A., and Kotchoubey, B. (2007). Brain–computer interfaces in the continuum of consciousness. *Curr. Opin. Neurol.* 20, 643–649. doi: 10.1097/WCO.0b013e3282f14782

Laureys, S., Giacino, J. T., Schiff, N. D., Schabus, M., and Owen, A. M. (2006). How should functional imaging of patients with disorders of consciousness contribute to their clinical rehabilitation needs? *Curr. Opin. Neurol.* 19, 520–527. doi: 10.1097/WCO.0b013e3280106ba9

Lulé, D., Noirhomme, Q., Kleih, S. C., Chatelle, C., Halder, S., Demertzi, A., et al. (2013). Probing command following in patients with disorders of consciousness using a brain–computer interface. *Clin. Neurophysiol.* 124, 101–106. doi: 10.1016/j.clinph.2012.04.030

Mallat, S. (2007). *A wavelet Tour of Signal Processing.* 2nd Edn. San Diego, CA: Academic Press.

Monti, M. M. (2012). Cognition in the vegetative state. *Annu. Rev. Clin. Psychol.* 8, 431–454. doi: 10.1146/annurev-clinpsy-032511-143050

Neumann, N., and Kotchoubey, B. (2004). Assessment of cognitive functions in severely paralysed and severely brain-damaged patients: neuropsychological and electrophysiological methods. *Brain Res. Protocols* 14, 25–36. doi: 10.1016/j.brainresprot.2004.09.001

Polich, J. (1986). Normal variation of p300 from auditory stimuli. *Electroencephalogr. Clin. Neurophysiol.* 65, 236–240. doi: 10.1016/0168-5597(86)90059-6

Polich, J. (2007). Updating p300: An integrative theory of p3a and p3b. *Clin. Neurophysiol.* 118, 2128–2148. doi: 10.1016/j.clinph.2007.04.019

R Development Core Team. (2011). *R: A Language and Environment for Statistical Computing.* Vienna: R Foundation for Statistical Computing.

Ruchkin, D. S., and Glaser, E. M. (1978). "Simple digital filters for examining cnv and p300 on a single-trial basis," in *Multidisciplinary Perspectives in Event-Related Brain Potential Research*, ed D. A. Otto (Washington, DC: U.S. Environmental Protection Agency), 579–581.

Samar, V. J., Bopardikar, A., Rao, R., and Swartz, K. (1999). Wavelet analysis of neuroelectric waveforms: a conceptual tutorial. *Brain Lang.* 66, 7–60. doi: 10.1006/brln.1998.2024

Schneider, G., Nahm, W., Kochs, E. F., Bischoff, P., Kalkman, C. J., Kuppe, H., et al. (2003). Quality of perioperative aep: variability of expert ratings. *Br. J. Anaesthesia* 91, 905–908. doi: 10.1093/bja/aeg280

Sokolova, M., and Lapalme, G. (2009). A systematic analysis of performance measures for classification tasks. *Inf. Process. Manag.* 45, 427–437. doi: 10.1016/j.ipm.2009.03.002

Valdes-Sosa, M. J., Bobes, M. A., Perez-abalo, M. C., Perera, M., Carballo, J. A., and Valdes-Sosa, P. (1987). Comparison of auditory-evoked potential detection methods using signal detection theory. *Int. J. Audiol.* 26, 166–178. doi: 10.3109/00206098709078419

VanRullen, R. (2011). Four common conceptual fallacies in mapping the time course of recognition. *Front. Psychol.* 2:365. doi: 10.3389/fpsyg.2011.00365

Wilson, S. B., Harner, R. N., Duffy, F. H., Tharp, B. R., Nuwer, M. R., and Sperling, M. R. (1996). Spike detection. i. correlation and reliability of human experts. *Electroencephalogr. Clin. Neurophysiol.* 98, 186–198. doi: 10.1016/0013-4694(95)00221-9

Woody, C. D. (1967). Characterization of an adaptive filter for the analysis of variable latency neuroelectric signals. *Med. Biol. Eng.* 5, 539–554. doi: 10.1007/BF02474247

World Medical Association. (2008). *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.* World Medical Association. Available online at: http://www.wma.net/en/30publications/10policies/b3/

Yeung, N., Bogacz, R., Holroyd, C. B., and Cohen, J. D. (2004). Detection of synchronized oscillations in the electroencephalogram: an evaluation of methods. *Psychophysiology* 41, 822–832. doi: 10.1111/j.1469-8986.2004.00239.x

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 14 January 2014; accepted: 18 August 2014; published online: 10 September 2014.

*Citation: Real RGL, Kotchoubey B and Kübler A (2014) Studentized continuous wavelet transform (t-CWT) in the analysis of individual ERPs: real and simulated EEG data. Front. Neurosci. **8**:279. doi: 10.3389/fnins.2014.00279*

This article was submitted to Brain Imaging Methods, a section of the journal Frontiers in Neuroscience.

ARTICLE IN PRESS

Clinical Neurophysiology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Information processing in patients in vegetative and minimally conscious states

Ruben G.L. Real[a,*], Sandra Veser[b], Helena Erlbeck[a], Monica Risetti[c], Dominik Vogel[d], Friedemann Müller[d], Boris Kotchoubey[b], Donatella Mattia[c], Andrea Kübler[a]

[a] *Institute of Psychology, University of Würzburg, Germany*
[b] *Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Germany*
[c] *IRCCS, Fondazione Santa Lucia, Rome, Italy*
[d] *Schön Clinics for Neurological Rehabilitation, Bad Aibling, Germany*

ARTICLE INFO

Article history:
Accepted 5 July 2015
Available online xxxx

Keywords:
Vegetative state
Minimally conscious state
DOC
EEG
P300

HIGHLIGHTS

- Rates of misdiagnoses in patients with disorders of consciousness (DOC) are high.
- The auditory P300 was more prevalent in healthy participants than in DOC patients.
- P300 prevalence did not differentiate between VS and MCS patients.

ABSTRACT

Objective: Evaluation of a short two-tone oddball paradigm to discriminate between the vegetative state (VS) and minimal consciousness state (MCS) in a sample of patients with severe disorders of consciousness (DOC).
Method: EEG was recorded from 45 DOC patients and 14 healthy participants while listening to an auditory oddball paradigm presented in a passive – just listen – and an active – count the odd tones – condition. In patients, the experiment was repeated after a minimum of one week.
Results: Prevalence of the P300 was higher in healthy participants (71%) than in patients, but did not discriminate between VS (T1: ~10%; T2: ~11%) and MCS (T1: ~13%; T2: 25%) patients.
Conclusion: Results cast doubt on whether this simple auditory stimulation paradigm, which requires cognitive action from the listener, is sensitive enough to discriminate between patients with DOC.
Significance: The sensitivity of the P300 ERP obtained in a short two-tone oddball paradigm presented in a passive and an active condition appears to be too low for routine application in a clinical setting aiming at distinguishing between VS and MCS patients.

1. Introduction

Disorders of consciousness (DOC) challenge routine diagnostic and clinical practice. After a period of coma, patients may become awake yet still not show behavioural signs of awareness. These patients are assigned the diagnosis "vegetative state" (VS; Plum and Posner, 1972), more recently termed "unresponsive wakefulness syndrome" (Laureys et al., 2010). Later, some of these patients may start to show non-reflexive behaviour, albeit inconsistently, e.g. gaze following, orienting responses or command following. These patients are then diagnosed as minimally conscious (MCS; Giacino et al., 2002). Clinically, correctly diagnosing these patients is difficult, as evidenced by high rates of misdiagnoses (Schnakers et al., 2009).

Originally, the term VS was meant to indicate a complete lack of cortical functioning. However, neuroscientific evidence from passive techniques such as stimulation (e.g. Kotchoubey et al., 2005) or connectivity studies (c.f. Gantner et al., 2013) suggests that some VS patients possess at least some intact cognitive functions, e.g. pitch discrimination, or recognition of nonsensical sentence endings (c.f. Harrison and Connolly, 2013; Monti, 2012; Steppacher et al., 2013). Unfortunately, these studies cannot

* Corresponding author at: Institute of Psychology, University of Würzburg, Marcusstr. 9-11, 97070 Würzburg, Germany. Tel.: +49 931 3180853.
E-mail address: ruben.real@uni-wuerzburg.de (R.G.L. Real).

http://dx.doi.org/10.1016/j.clinph.2015.07.020
1388-2457/© 2015 Published by Elsevier Ireland Ltd. on behalf of International Federation of Clinical Neurophysiology.

answer the question of whether these patterns of activation reflect conscious awareness. Studies using active paradigms, i.e. paradigms requiring the wilful modulation of brain activity, suggest that at least some VS patients do show signs of awareness and volitional control in various paradigms using functional MRI (fMRI; Bardin et al., 2011; Owen et al., 2006), or electroencephalography (EEG; Cruse et al., 2011, but see Cruse et al., 2013; Goldfine et al., 2013). Thus, on a purely functional, but not behavioural basis, at least some of these patients might be more appropriately classified as MCS (Monti, 2012), or even completely locked-in (Lulé et al., 2013).

Yet, these paradigms are restricted to experimental research and have yet to be transferred into routine clinical practice (Harrison and Connolly, 2013). To promote application of psychophysiological paradigms in supporting the clinical assessment of the state of consciousness we developed a short (2×6.8 min) two-tone auditory oddball paradigm, and analysed its performance in a large sample of DOC patients. In the EEG, randomly occurring odd tones within a series of frequent tones are associated with a marked centro-parietal positivity, occurring approximately 300 ms after onset of the odd tone (event-related potential, ERP, P300). Apart from physiological factors, such as arousal (Polich and Kok, 1995), the amplitude of the P300 was shown to be sensitive to shifts of attention. Instructions designed to shift attention towards the odd tones, such as asking participants to count how often such a tone occurs, lead to an increased P300 amplitude (Polich, 1986a,b) as compared to a passive listening condition. Conversely, an increased P300 following an instruction to count the odd tones may be taken as evidence, that the participant successfully followed the instruction which is only possible if he or she is consciously aware during testing.

Passive stimulation paradigms appear not to discriminate between VS and MCS patients (Harrison and Connolly, 2013; Kotchoubey et al., 2005). Thus, in this study we investigated whether a direct comparison of the same paradigm between a passive and an active condition would be able to do so. Specifically, we hypothesised that at least some VS but more MCS would show, (1) undifferentiated cortical activation in relation to the sole presence of tones (N100–P200), (2) differential activation between frequent and odd tones in the passive and active conditions (Kotchoubey et al., 2005), (3) an increased P300 following the odd tones in the active as compared to the passive condition (difference P300). Further, presence/absence of ERPs should be stable across time. In addition, we analysed several possible predictors. Firstly, we hypothesised that the presence of the P300 component (in either condition) would be predicted by the early N100–(P200) complex (Harrison and Connolly, 2013; Kotchoubey et al., 2005). Secondly, we assumed that the time since the incident would predict presence of a P300 since this parameter is known to be an important predictor of recovery (The Multi-Society Task Force on PVS, 1994). Finally, we investigated the role of aetiology, hypothesising that ERPs would be less frequent in patients with hypoxia, in whom cortical injuries are more diffuse, as compared to traumatic patients who present with more focal injuries (Daltrozzo et al., 2007; Kotchoubey, 2005; Kotchoubey et al., 2005).

2. Methods

2.1. Samples

The study was conducted at three clinics specialised in the care for patients with chronic and severe disorders of consciousness between September 2011 and May 2012. We recruited $N = 61$ adult patients who met the definition of VS or MCS according to the revised Coma Recovery Scale (CRS-R; Giacino et al., 2004; see Table 1 and Supplementary Table S1). Exclusion criteria were psychomotor agitation, use of drugs affecting vigilance, infectious diseases, and a history of auditory impairment. Information about their medical histories was obtained from the patients' files. Informed consent was obtained from the legal guardians. In addition, data from $N = 14$ healthy adult participants (5 male, 9 female, mean age = 27.6, $SD = 9.5$) was collected at the psychophysiological laboratories of the Institute of Psychology, University of Würzburg, and the Institute for Medical Psychology and Behavioural Neurobiology, University of Tübingen. In patients, the study was conducted at two time points (T1 and T2) separated by at least one week. The study was approved by the local Ethical Review Boards of the institutions involved (Fondazione Santa Lucia, Rome, Italy; University of Tübingen, and University of Würzburg, both Germany) and conformed to the Declaration of Helsinki (World Medical Association, 2008).

Diagnoses (as per CRS-R) were stable between T1 and T2 in 48 patients, but changed in three patients (from VS to MCS: one patient; from MCS to VS: two patients). CRS-R scores were significantly higher in MCS than in VS patients ($t = 8.49$, $DF = 43$, $p < .001$). VS and MCS patients did not differ in age ($t = 0.15$, $DF = 43$, $p = .88$), time since onset ($t = -0.54$, $DF = 43$, $p = .59$), and aetiology (Fisher's Exact Test, $p = .846$).

2.2. Procedure

Prior to EEG recording, each patient was assessed using the CRS-R. If, during the course of the experiment, patients appeared to be drowsy, recordings were aborted, the Arousal Facilitation Protocol of the CRS-R administered, and the recording restarted. Via in-ear headphones (E-A-RTONE Gold, Auditory Systems, Indianapolis, Indiana), participants were then presented with a binaural stream of 420 short complex (Kotchoubey et al., 2005) high (440 + 880 + 1760 Hz) tones into which 60 short complex low (247 + 494 + 988 Hz) tones were pseudo-randomly interspersed. Stimulus duration was 50 ms, linear rise/fall time was 5 ms, intensity was 70 dB (Polich, 1986b), and ISI was 850 ms. This paradigm was designed to detect the early auditory cortical responses expressed in components N100 (defined as the most negative deflection within 50–200 ms post onset of a tone; Näätänen and Picton, 1987), and P200 (most positive deflection between 100 and 250; Crowley and Colrain, 2004), and – as an indicator of deeper differentiation – the P300 (most positive deflection between 250 and 500 ms; Polich, 2007; in patients the interval was chosen between 300 and 700 ms, to compensate for the delayed latencies of cognitive ERPs in patients with acquired brain damage; Guérit et al., 1999). Tone streams were presented twice, once in a passive (always presented first) and once in an active condition. In the passive condition, participants were told that they were going to listen to a series of tones and that they would just have to listen to the

Table 1
Description of patient sample.

	VS ($n = 29$)	MCS ($n = 16$)
Males/females	19/10	9/7
Age (mean, *SD*)	49.72 (13.58)	50.38 (16.64)
Time since incident, months (mean, *SD*)	36.73 (44.94)	29.46 (39.02)
CRS-R (mean, *SD*)	4.86 (2.1)	11.69 (3.3)
Aetiology (*n*)		
Haemorrhage	4	3
Hypoxia	13	6
TBI	10	5
Other[a]	2	2
Second measurement available (*n*)	28	12

[a] Anaphylactic shock, Guillain–Barre, Aneurism A. Cerebri media, central pontine myelinolysis.

Please cite this article in press as: Real RGL et al. Information processing in patients in vegetative and minimally conscious states. Clin Neurophysiol (2015), http://dx.doi.org/10.1016/j.clinph.2015.07.020

tones. In the active condition, participants were told that they were going to listen to a tone stream, and that their task was to count the occurrence of the odd (low) tones (Neumann and Kotchoubey, 2004). To avoid frustration in behaviourally non-responsive patients, instructions to indicate perception of an odd tone, e.g. by moving the index finger (e.g. Polich, 1989) were not given (Neumann and Kotchoubey, 2004). To maintain comparability between groups, healthy participants were given the same instructions as patients. The active condition served to test, whether subjects were able to focus attention towards the odd tones, when prompted to do so. In patients, the experiment was repeated after a minimum interval of 1 week, to compensate for possible fluctuations in arousal (Polich and Herbst, 2000).

2.3. EEG recording

EEG was recorded with a sampling rate of 512 Hz at the patient's bedside using a 31-channel active electrodes cap (LADYbird, g.tec medical engineering, Schiedlberg, Austria; nose reference), but analysis was restricted to F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4. Vertical and horizontal eye movement was recorded with two pairs of electrodes at the outer cantii and above and below one eye.

2.4. Data reduction and analysis

Offline, data was bandpass (0.01–70 Hz) and notch (50 Hz) filtered, segmented into epochs of 850 ms, and aligned to the 100 ms pre-stimulus baseline. Ocular artefacts were corrected with a regression-based approach (Gratton et al., 1983) and segments with absolute voltages exceeding 120 μV were rejected as artefacts. Segments were re-referenced to linked-mastoids. Datasets were analysed further if at least 20 odd tone (Cohen and Polich, 1997) and 20 frequent tone trials remained after artifact rejection.

Of 61 patients, complete data was available from 57. Factors leading to incomplete datasets included drowsiness from which the patient could not be awakened, or necessity of immediate medical care. After visual inspection (excessive noise, silent electrodes, strong EMG artefacts in target channels) of the recorded EEG, eight patients were removed from further analysis. After pre-processing, data from four patients had too few remaining trials, and therefore, these patients were removed from further analysis. The final sample size at T1 was thus 45. Of the 61 patients entering the study at T1 6 VS and 4 MCS patients did not participate at T2, because they were medically unstable (three VS, one MCS), transferred to another institution (three VS, two MCS), or died (one MCS). Thus, at T2 51 DOC patients participated. Complete data was available from 47 patients. After visual inspection of the recorded EEG, five patients were removed from further analysis. Finally, after preprocessing, data from two patients had too few remaining trials, and therefore, these patients were removed from further analysis. Thus, the final sample size at T2 was 40 (see Table 1).

ERPs (see Fig. 1) were detected and quantified with a variant of the Studentized continuous wavelet transform (*t*-CWT; Real et al., 2014; cf. Bostanov and Kotchoubey, 2006). Firstly, the continuous wavelet transform (Mexican Hat; Mallat, 2007) was calculated for each segment of EEG data, for 25 scales ranging from approximately 1 to 32 Hz. Secondly, a statistical map was created by calculating one-sample (for analyses against baseline activity) or two-sample (for comparisons between experimental conditions) Student *t*-values for each wavelet coefficient across trials. Thirdly, *t*-max randomization tests (Blair and Karniski, 1993; Groppe et al., 2011) with 1000 randomizations were used to assign a *p*-value – adjusted for multiple comparisons – to each Studentized wavelet coefficient. Significant local maxima (minima) in the statistical map were retained if they matched our definitions for the various ERPs and one-tailed tests were used because we had specific hypotheses about the properties of each ERP component (see above). Thus, an ERP was considered present, if a significant activation with suitable latency and polarity was detected. Results from simulation studies show that this method combines high sensitivity with high specificity and is superior to other techniques such as peak detection after low pass filtering (Real et al., 2014).

Fisher Exact Tests were used to compare the prevalence of ERPs (N100, P200, passive P300, active P300, difference P300) between diagnostic and aetiological groups, to determine whether the prevalence of earlier EPRs differed from later ERPs, and to analyse temporal stability of ERPs and whether earlier ERPs predicted later ERPs, and we report two-sided confidence intervals. Since the frequency of some ERPs was low, Mann–Whitney *U* tests, instead of parametric *t*-tests, were used to analyse the predictive value of CRS-R scores and time since the event.

3. Results

3.1. Prevalence of ERPs

The N100, P200, P300, and difference P300 were significantly more prevalent in healthy participants than in VS patients in both conditions (passive condition: N100: $p < .001$; P200: $p < .001$; P300: $p = .03$; active condition N100: $p < .001$; P200: $p < .001$; P300: $p < .001$; difference P300: $p < .001$). It was also higher as compared to MCS patients in both conditions (passive condition: N100: $p < .001$, P200: $p = .003$, P300: $p = .02$; active condition: N100: $p < .001$, P200: $p < .001$, P300: $p < .001$; difference P300: $p = .003$; see Tables 2 and 3).

Within the patient group, diagnosis did not significantly predict the presence of any ERP at T1 or T2, except for a marginally higher prevalence of the P300 in the passive condition in MCS patients in comparison to VS patients at T2 (OR = 8.43, $p = .07$, 95% CI 0.59–487.74). Patients with a significant N100 in the passive condition at T2 ($Z = 1.45$, $p = .08$) or a significant P300 in the active condition at T2 ($Z = 1.41$, $p = .09$) tended to have higher CRS scores than participants without these components.

In healthy participants, prevalence of the N100 and P200 did not differ in any condition. The N100 was more frequent than the P300 in the passive ($p = .02$) but not in the active condition ($p = .5$) and more frequent than the difference P300 (passive: $p = .05$; active: $p = .05$). The P200 was as frequent as the P300 (in both conditions) and the difference P300.

In VS patients, prevalences of the N100 and P200 did not differ in any condition, and at any time point, but the prevalence of the P200 was higher than the prevalence of the P300 at T1 in the active condition ($p = .03$, passive: $p = .19$, ns.), and at T2 in both conditions (passive: $p = .001$; active: $p = .04$). The N100 was significantly more frequent than the difference P300 in all conditions and time points, and more frequent than the P300 except at T1 in the passive condition where only a trend was found ($p = .08$). In MCS patients, the prevalence of ERPs did not differ in any of the conditions and time points (all $p > .10$), except for a marginally higher prevalence of the N100 in comparison to the difference P3 in the passive condition at T1 ($p = .06$).

As reported in Section 2, in three patients the diagnosis (as per CRS-R) differed between T1 and T2. However, this change in observable responses was not accompanied by any consistent change in detected ERPs. The one patient who changed from VS to MCS did not show significant activation in the P300 interval at either time point. Of the two patients who changed from MCS to VS, one patient did not show any significant activation at either

Please cite this article in press as: Real RGL et al. Information processing in patients in vegetative and minimally conscious states. Clin Neurophysiol (2015), http://dx.doi.org/10.1016/j.clinph.2015.07.020

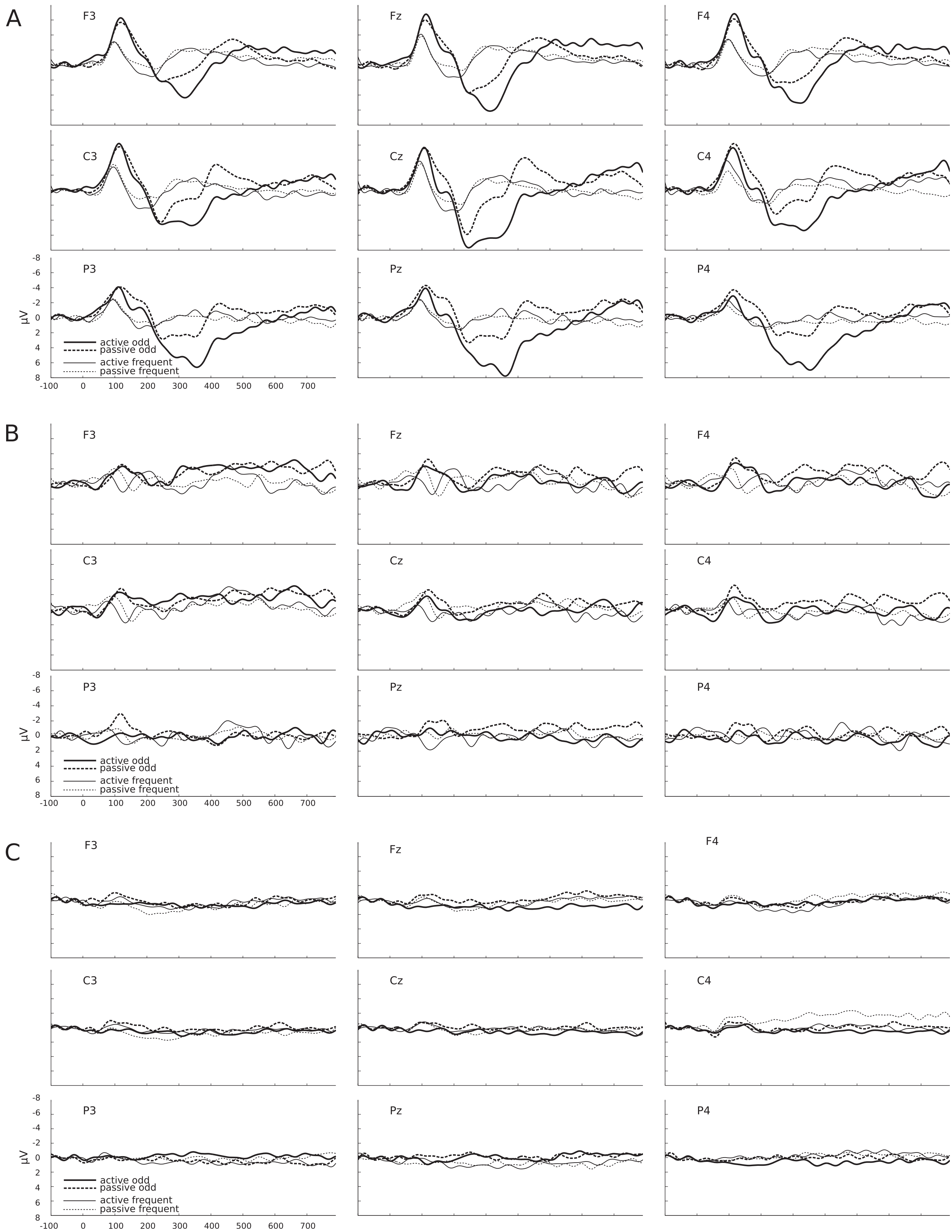


Fig. 1. Evoked activation following odd and frequent tones in the passive and active condition. (A) Healthy participants. (B) MCS patients at T1. (C) VS patients at T1. Within each group, the top row depicts potentials at frontal sites, the middle row at central, and the bottom row at parietal sites.

Please cite this article in press as: Real RGL et al. Information processing in patients in vegetative and minimally conscious states. Clin Neurophysiol (2015), http://dx.doi.org/10.1016/j.clinph.2015.07.020

Table 2
Prevalence of significant activations (in %).

	Passive	Active	Difference	Passive	Active	Difference	Passive	Active	Difference
	Healthy (N = 14)			VS (n = 29)			MCS (n = 16)		
T1									
N100	100.00	100.00		44.83	34.48		43.75	37.50	
P200	86.00	86.00		37.93	34.48		37.50	25.00	
P300	64.00	93.00	71.00	24.14	10.34	10.34	18.75	12.50	12.50
				VS (n = 28)			MCS (n = 12)		
T2									
N100				39.29	46.43		50.00	33.33	
P200				39.29	28.57		50.00	33.33	
P300				3.57	7.14	10.71	25.00	16.67	25.00

Note: T1, first measurement; T2, second measurement. Healthy participants participated only once.

Table 3
Summary of results.

Comparisons	N100	P200	P300	Difference P300
Prevalence in healthy participants and patients	• More frequent in healthy participants than in patients	• More frequent in healthy participants than in patients	• More frequent in healthy participants than in patients	• More frequent in healthy participants than in patients
Prevalence in VS and MCS patients	• No difference	• No difference	• Marginally higher in MCS patients (T2 passive)	• No difference
Association with CRS-R	• No association except marginally positive at T2 passive	• No association	• No association except marginally positive at T2 active	• No association
Relative prevalence				
In healthy participants:	• As frequent as P200	• As frequent as P300	• Less frequent than N100 (passive) • As frequent as P200	• Less frequent than N100 • As frequent as P200 and P300
In VS:	• As frequent as P200	• More frequent than P300 (except T1 passive)	• Less frequent than N100 and P200 (except T1 passive)	• Less frequent than N100 • As frequent as P200 and P300
In MCS:	• As frequent as P200	• As frequent as P300	• As frequent as N100 and P200	• As frequent as N100, except at T1 (passive) • As frequent as P200 and P300
Early ERP	• Predicts presence of P200	• Does not predict P300, except marginally at T2 (active)	• Does not predict difference P300	• Not predicted by any other ERP
Temporal stability	• Marginally stable	• Not stable	• Marginally not stable	• Marginally stable
Time since the event	• Marginally negative association (T1 passive)	• Marginally negatively associated (T1 active)	• No association	• No association
Aetiology	• No association	• No association	• Marginally less frequent in HYP (T1 passive) versus TBI and HAEM • No difference between TBI and HYP	• No association
Sex/age	• No association	• No association	• No association	• No association

Note: HYP, patients with hypoxia; TBI, patients with traumatic brain injury; HAEM, patients with intracerebral haemorrhage.

time point, and the other patient showed a difference P300 at T1 but not at T2.

Since VS and MCS patients did not differ in prevalence of ERPs, we merged the groups for the following analyses.

3.2. Temporal stability

Presence of an N100 at T1 marginally predicted its presence at T2 in the passive (OR = 3.77, p = .07, 95% CI 0.69–23.74) and significantly in the active condition (OR = 5.11, p = .05, 95% CI 0.82–41.79). Further, a P300 in the passive condition at T1 marginally predicted its presence at T2 (OR = 13.56, p = .06, 95% CI 0.56–972.39) but not in the active condition (OR = 0, p = 1, 95% CI 0–18.38). Finally, patients who showed an increased activation in response to odd tones in the active as compared to the passive condition at T1, tended to show the same response at T2 (OR = 10.14, p = .09, 95% CI 0.44–702.37).

3.3. Early ERP components

At T1 and T2, presence of an N100 predicted the presence of a P200 (T1: OR = 3.75, p = .03, 95% CI 0.92–16.88; T2: OR = 4.96, p = .02, 95% CI 1.11–25.31) in the passive condition. Similarly, presence of an N100 in the active condition predicted the presence of the P200 at T1 (OR = 3.71, p = .05, 95% CI 0.84–17.81) and T2 (OR = 7.08, p = .01, 95% CI 1.33–51.5). Finally, the presence of a P200 at T2 in the active condition tended to predict the presence of a P300 in the active condition (OR = 8.43, p = .07, 95% CI 0.59–487.74). The difference P300 was not predicted by any earlier ERP component.

3.4. Time since the event

The time since the event was marginally negatively associated with the presence of the N100 in the passive condition

Please cite this article in press as: Real RGL et al. Information processing in patients in vegetative and minimally conscious states. Clin Neurophysiol (2015), http://dx.doi.org/10.1016/j.clinph.2015.07.020

($Z = -1.39$, $p = .08$) and the P200 in the active condition ($Z = -1.45$, $p = .08$) at T1, but not at T2 (all $p > .10$).

3.5. Aetiology, age and sex

Prevalence of ERPs did not differ between patients with intracerebral haemorrhage and TBI patients (all $p > .10$), but in hypoxic patients, the prevalence of the P300 obtained in the passive condition was marginally lower as compared to TBI patients (T1: OR = 0.12, $p = .07$, 95% CI 0.00–1.27; T2: $p = .23$, ns.) and as compared to patients with intracerebral haemorrhage (T1: OR = 0.09, $p = .05$, 95% CI 0.00–1.35, T2:, $p = .24$).

No influence of age or sex was found on the prevalence of ERPs (all $p > .10$). Table 3 shows a comprehensive summary of our results.

4. Discussion

In this study, we evaluated the potential of a short two-tone oddball paradigm presented in an active and a passive condition to differentiate between VS and MCS patients. Whereas the prevalence of ERPs differed between healthy participants and patients, no difference was found between patient groups. At T1, the P300 in the passive condition was marginally less prevalent in hypoxic patients in comparison to TBI patients and significantly less in comparison to patients with intracerebral haemorrhage. In patients, we found close associations between early ERPs (N100–P200) in both experimental conditions and at both time points, but the P300 in the active or passive condition or difference P300 was not predicted by earlier ERPs. Presence of an N100 at T1 in the passive and active conditions marginally predicted the presence of an N100 at T2. Further, the P300 in the passive condition and the presence of a difference in response to odd tones in the active versus passive condition tended to be stable across time.

While the absolute prevalence of the early ERPs in our patient group was somewhat reduced, the low prevalence of the P300 in both VS and MCS patients has been reported before (Kotchoubey et al., 2005). Similarly, the finding of a (marginally) reduced prevalence of the P300 in hypoxic patients confirms previous studies (Daltrozzo et al., 2007) and supports that a widespread cortical activation is necessary for the generation of this response (Polich and Criado, 2006).

As can be seen in Table 2, the earlier N100–P200 was more frequent than the late P300 in both patient groups, although the difference reached significance only in VS but not in MCS patients (which might be due to the smaller number of MCS patients). While this result seems to support a weak hierarchical hypothesis of information processing, in which more complex responses such as the P300 depend on the successful operation of earlier processing steps (Kotchoubey et al., 2005), other results speak against this view. Specifically, the P300 was only inconsistently predicted by earlier ERPs (see Table 3), and the difference P300 was not at all predicted. Unfortunately, further conclusions are limited by the fact that information about intactness of brainstem auditory evoked potentials was not available from our patients.

An important finding is the high number of false negatives, i.e. healthy participants and MCS patients not showing a difference between the active and the passive condition, in our study. In 29% of all healthy participants no difference between responses to odd tones in the active versus the passive condition could be detected. The same was true for as many as 87% of MCS patients, although these patients showed behavioural evidence of consciousness at bedside. Some of these negative findings might be attributed to fluctuations of arousal as is common in DOC patients (Laureys et al., 2004), which might have led to an increased number of missed odd tone trials, thereby reducing the P300 amplitude (Connolly et al., 2006). However, care was taken to minimise the influence of arousal by performing the CRS-R prior to EEG recording, and monitoring the patient throughout the experiment for signs of drowsiness. Further, reduced arousal is unlikely to account for the high number of false negatives in healthy participants. In addition, false negatives in active paradigms have also been reported by others, (c.f. Daltrozzo et al., 2009; Harrison and Connolly, 2013; Kotchoubey, 2005; Lulé et al., 2013). Thus, it appears that the paradigm itself is not sufficiently sensitive to discriminate between different DOCs and cannot be recommended for routine clinical application. However, it is important to keep in mind that the P300 is not a unitary phenomenon, i.e. it is sensitive to several (partially overlapping) processes. Therefore, it is possible that subcomponents of the P300 may be useful to differentiate between DOC patients. However, in the following we restrict our discussion to factors which may have been relevant in our implementation of the paradigm.

Instruction-dependent tasks require a whole set of intact cognitive functions, e.g. working memory, language comprehension, motivation, and understanding of instructions (Kotchoubey et al., 2013; Kotchoubey and Lang, 2011). If such high levels of cognitive and motivational functioning were impaired in MCS patients – even if they were consciously aware – this might explain the apparent inability of our paradigm to differentiate between VS and MCS patients. Based on our results, we may assume a sensitivity of the task of approximately 0.7, albeit the sample of healthy participants was too small to draw solid conclusions. This reduces the probability of positive results by 30%, which may have added to the negative results in MCS and VS patients.

Another potential problem concerns the choice of modality used in our study. The visual domain is often impaired in DOC patients and, therefore, much research on passive and active paradigms in DOC patients concentrates on the auditory domain (Monti, 2012). In our study, a two-tone oddball paradigm presented in an active and passive condition was used to elicit a P300. While complex tones were shown to be superior to simple sines (Kotchoubey et al., 2005), other stimuli, such as emotional interjections (Neumann and Kotchoubey, 2004), or different stimulus properties might give different, but not necessarily better (Pokorny et al., 2013) results. An important argument concerns the number of stimuli (60 odd, 420 frequent tones) used in our study. While the number of stimuli was chosen following the respective literature (Guérit et al., 1999; Neumann and Kotchoubey, 2004), one might suspect that the low signal-to-noise ratio in DOC patients would have required an increased number of stimuli. However, given the risk of fluctuating arousal, we abstained from prolonging the experiment by increasing the number of stimuli.

In addition, there is evidence that using other modalities, e.g. tactile stimulation, may be more appropriate for demonstrating successful command following (Kaufmann et al., 2013). Although a single case study, these authors found in a patient with classic locked-in syndrome that tactile event-related potentials were most suitable for communication with an ERP-based brain–computer interface despite opposite results in healthy participants (Riccio et al., 2012).

While the above discussion focused on properties of our paradigm, a recent review by Liberati et al. (2014) questioned the validity of assuming a dichotomy between VS and MCS altogether. Reviewing neurophysiological as well as behavioural evidence regarding the distinction between VS and MCS, these authors found that no combination of variables allowed for a reliable and consistent differentiation of the two diagnostic categories. Although unexpected, our results integrate very well with these findings, and support the need of a more diversified and multifaceted evaluation procedure in DOC patients (Liberati et al., 2014).

5. Conclusion

We evaluated the performance of a short auditory two-tone oddball paradigm presented in an active and a passive condition to differentiate between VS and MCS patients. Results revealed that the paradigm could differentiate between healthy participants and DOC patients, but not between patient groups. Further, significant differences between the active and the passive condition were not found in all healthy participants, indicating a low sensitivity of this paradigm. While there seems to be a potential for the application of neuroscientific paradigms to differentiate between states of consciousness, those have to be evaluated with a significant number of participants in all those states (normal, MCS, VS) under bedside conditions before paradigms can be recommended for clinical routine. Based on our results, the sensitivity of this complex tone passive–active P300 paradigm (Kotchoubey et al., 2005) is too low to recommend it for routine application in a clinical setting aimed at differentiating between VS and MCS patients. However, given the intuitive appeal of detecting voluntary shifts of attention to aid in the diagnosis of disorders of consciousness, further research into factors maximising the sensitivity of the active–passive P300 paradigm is necessary.

Acknowledgements

This work was supported by the European ICT Program Project FP7-247919. Possible inaccuracies of information are under the responsibility of the project team. The text reflects solely the views of its authors. The European Commission is not liable for any use that may be made of the information contained therein.

The authors thank all participants and clinics whose contributions have made this research possible.

Conflict of interest: The sponsor of the study had no role in study design, data collection, analysis, interpretation, or writing of the report. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication. The authors declare no competing financial interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2015.07.020.

References

Bardin JC, Fins JJ, Katz DI, Hersh J, Heier LA, Tabelow K, et al. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. Brain 2011;134:769–82.
Blair RC, Karniski W. An alternative method for significance testing of waveform difference potentials. Psychophysiology 1993;30:518–24.
Bostanov V, Kotchoubey B. The *t*-CWT: a new ERP detection and quantification method based on the continuous wavelet transform and Student's *t*-statistics. Clin Neurophysiol 2006;117:2627–44.
Cohen J, Polich J. On the number of trials needed for P300. Int J Psychophysiol 1997;25:249–55.
Connolly J, Marchand Y, Major A, D'Arcy R. Event-related brain potentials as a measure of performance on WISC-III and WAIS-R NI similarities sub-tests. J Clin Exp Neuropsyc 2006;28:1327–45.
Crowley KE, Colrain IM. A review of the evidence for P2 being an independent component process: age, sleep and modality. Clin Neurophysiol 2004;115:732–44.
Cruse D, Chennu S, Chatelle C, Bekinschtein TA, Fernández-Espejo D, Pickard JD, et al. Bedside detection of awareness in the vegetative state: a cohort study. Lancet 2011;378:2088–94.
Cruse D, Chennu S, Chatelle C, Bekinschtein TA, Fernández-Espejo D, Pickard JD, et al. Reanalysis of "Bedside detection of awareness in the vegetative state: a cohort study" – Authors' reply. Lancet 2013;381:291–2.
Daltrozzo J, Wioland N, Mutschler V, Kotchoubey B. Predicting coma and other low responsive patients outcome using event-related brain potentials: a meta-analysis. Clin Neurophysiol 2007;118:606–14.
Daltrozzo J, Wioland N, Mutschler V, Lutun P, Calon B, Meyer A, et al. Cortical information processing in coma. Cogn Behav Neurol 2009;22:53–62.
Gantner IS, Bodart O, Laureys S, Demertzi A. Our rapidly changing understanding of acute and chronic disorders of consciousness: challenges for neurologists. Future Neurol 2013;8:43–54.
Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology 2002;58:349–53.
Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004;85:2020–9.
Goldfine AM, Bardin JC, Noirhomme Q, Fins JJ, Schiff ND, Victor JD. Reanalysis of "Bedside detection of awareness in the vegetative state: a cohort study". Lancet 2013;381:289–91.
Gratton G, Coles MGH, Donchin E. A new method for off-line removal of ocular artifact. Electroencephalogr Clin Neurophysiol 1983;55:468–84.
Groppe DM, Urbach TP, Kutas M. Mass univariate analysis of event-related brain potentials/fields I: a critical tutorial review. Psychophysiology 2011;48:1711–25.
Guérit JM, Verougstraete D, de Tourtchaninoff M, Debatisse D, Witdoeckt C. ERPs obtained with the auditory oddball paradigm in coma and altered states of consciousness. clinical relationships, prognostic value, and origin of components. Clin Neurophysiol 1999;110:1260–9.
Harrison AH, Connolly JF. Finding a way in: a review and practical evaluation of fMRI and EEG for detection and assessment in disorders of consciousness. Neurosci Biobehav Rev 2013;37:1403–19.
Kaufmann T, Holz EM, Kübler A. Comparison of tactile, auditory, and visual modality for brain–computer interface use: a case study with a patient in the locked-in state. Front Neurosci 2013;7:129.
Kotchoubey B. Apallic syndrome is not apallic: is vegetative state vegetative? Neuropsychol Rehabil 2005;15:333–56.
Kotchoubey B, Lang S. Intuitive versus theory-based assessment of consciousness: the problem of low-level consciousness. Clin Neurophysiol 2011;122:430–2.
Kotchoubey B, Lang S, Mezger G, Schmalohr D, Schneck M, Semmler A, et al. Information processing in severe disorders of consciousness: vegetative state and minimally conscious state. Clin Neurophysiol 2005;116:2441–53.
Kotchoubey B, Veser S, Real RGL, Herbert C, Lang S, Kübler A. Towards a more precise neurophysiological assessment of cognitive functions in patients with disorders of consciousness. Restor Neurol Neurosci 2013;31:473–85.
Laureys S, Celesia GG, Cohadon F, Lavrijsen J, Leon-Carrrion J, Sannita WG, et al. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med 2010;8:68.
Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 2004;3:537–46.
Liberati G, Huenefeldt T, Olivetti Belardinelli M. Questioning the dichotomy between vegetative state and minimally conscious state: a review of the statistical evidence. Front Hum Neurosci 2014;8:865.
Lulé D, Noirhomme Q, Kleih SC, Chatelle C, Halder S, Demertzi A, et al. Probing command following in patients with disorders of consciousness using a brain–computer interface. Clin Neurophysiol 2013;124:101–6.
Mallat S. A wavelet tour of signal processing. San Diego, CA: Academic Press; 2007.
Monti MM. Cognition in the vegetative state. Annu Rev Clin Psychol 2012;8:431–54.
Näätänen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 1987;24:375–425.
Neumann N, Kotchoubey B. Assessment of cognitive functions in severely paralysed and severely brain-damaged patients: neuropsychological and electrophysiological methods. Brain Res Protocol 2004;14:25–36.
Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard. Detecting awareness in the vegetative state. Science 2006;313:1402.
Plum F, Posner JB. The diagnosis of stupor and coma. Contemp Neurol Ser 1972;10:1–286.
Pokorny C, Klobassa DS, Pichler G, Erlbeck H, Real RGL, Kübler A, et al. The auditory P300-based single-switch brain–computer interface: paradigm transition from healthy subjects to minimally conscious patients. Artif Intell Med 2013;59:81–90.
Polich J. Attention, probability, and task demands as determinants of P300 latency from auditory stimuli. Electroencephalogr Clin Neurophysiol 1986a;63:251–9.
Polich J. Normal variation of P300 from auditory stimuli. Electroencephalogr Clin Neurophysiol 1986b;65:236–40.
Polich J. P300 from a passive auditory paradigm. Electroencephalogr Clin Neurophysiol 1989;74:312–20.
Polich J. Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 2007;118:2128–48.
Polich J, Criado JR. Neuropsychology and neuropharmacology of P3a and P3b. Int J Psychophysiol 2006;60:172–85.
Polich J, Herbst KL. P300 as a clinical assay: rationale, evaluation, and findings. Int J Psychophysiol 2000;38:3–19.
Polich J, Kok A. Cognitive and biological determinants of P300: an integrative review. Biol Psychol 1995;41:103–46.

Real RGL, Kotchoubey B, Kübler A. Studentized continuous wavelet transform (*t*-CWT) in the analysis of individual ERPs: real and simulated EEG data. Front Neurosci 2014;8:279.

Riccio A, Mattia D, Simione L, Olivetti M, Cincotti F. Eye-gaze independent EEG-based brain–computer interfaces for communication. J Neural Eng 2012;9:045001.

Schnakers C, Vanhaudenhuyse A, Giacino JT, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol 2009;9:35.

Steppacher I, Eickhoff S, Jordanov T, Kaps M, Witzke W, Kissler J. N400 predicts recovery from disorders of consciousness. Ann Neurol 2013;73:594–602.

The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state. N Engl J Med 1994;330:1499–508.

World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research involving Human Subjects [Online]. <www.wma.net/en/30publications/10policies/b3/17c.pdf> [18 Nov. 2011].

Clinical Neurophysiology 125 (2014) 955–961

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Psychophysiological correlates of coping and quality of life in patients with ALS

R.G.L. Real [a,*], C. Herbert [b], B. Kotchoubey [c], C. Wessig [d], J. Volkmann [d], A. Kübler [a]

[a] Department of Psychology I, University of Würzburg, 97070 Würzburg, Germany
[b] Institute of Psychology, German Sport University Cologne, 50933 Cologne, Germany
[c] Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, 72074 Tübingen, Germany
[d] Department of Neurology, University Hospital of Würzburg, 97080 Würzburg, Germany

ARTICLE INFO

Article history:
Accepted 27 September 2013
Available online 6 November 2013

Keywords:
ALS
N400
EEG
Coping
Quality of life

HIGHLIGHTS

- N400 event-related potentials can be reliably elicited in patients with amyotrophic lateral sclerosis and quality of life modulates the N400 amplitude in response to incongruent disease-related words.
- Healthy subjects do not show this effect.
- N400 modulation might serve as a psychophysiological correlate of quality of life.

ABSTRACT

Objective: Self-regulation models of coping suggest that patients with chronic diseases reporting low quality of life (QoL), an indicator of failed coping efforts, should show facilitated access to disease related words. Here we investigated whether a reduced N400 amplitude within an incongruent, i.e. unpredictable disease-related context would be a correlate of this facilitated access.

Methods: ERPs were recorded in $N = 18$ patients with amyotrophic lateral sclerosis (ALS) and $N = 20$ age-matched healthy controls during reading of sentences, ending either with congruent or incongruent words. Incongruent and congruent words were disease related or disease unrelated. Mean N400 amplitudes were analyzed with mixed models.

Results: Generally, incongruent words elicited a more negative N400 amplitude than congruent words in all groups and conditions, i.e. an N400 effect. In patients with high QoL this N400 effect did not differ between disease related and unrelated words. In patients with low QoL, however, the N400 effect was significantly smaller for disease related than for disease unrelated words. In healthy controls N400 amplitudes showed no such interaction between congruence, disease relatedness and QoL. Results remained stable when controlling for disease severity, duration and depression.

Conclusion: The N400 indicates increased accessibility to disease related information in ALS patients with low QoL. The increased access may imply a constantly activated disease related context which is linked to low QoL.

Significance: N400 modulation by disease related information may serve as a psychophysiological correlate of coping and the patient's QoL.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rare degenerative disorder marked by progressive paralysis and ultimately death. However, many studies have demonstrated that subjective quality of life (QoL), an important indicator of the impact of, or coping with, a disease, can be rather high in patients with ALS. Moreover, QoL was found to be relatively independent of medical aspects of the ALS, such as disease severity or duration (Kübler et al., 2005; Rabkin et al., 2000; Robbins et al., 2001), but strongly influenced by psychosocial factors (Lulé et al., 2009; Matuz et al., 2010; McDonald et al., 1994; Plahuta et al., 2002). In the present study, we aimed at establishing a psychophysiological correlate of subjective QoL and thus, coping with a severe and terminal disease.

Subjective QoL may be defined as "the difference between the hopes and expectations of the individual and that individual's

* Corresponding author. Address: Department of Psychology I, University of Würzburg, Marcusstr. 9-11, 97070 Würzburg, Germany. Tel.: +49 9313180853.
E-mail address: ruben.real@uni-wuerzburg.de (R.G.L. Real).

1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2013.09.040

present experiences" (Calman, 1984). It is low if the difference is large, e.g. because of a serious disease, and high if the difference is low, e.g. due to successful coping (Lazarus and Folkman, 2008; Rapkin and Schwartz, 2004). The relation between these differences and the use of coping strategies has been described (Cameron and Leventhal, 2002) with reference to a simple feedback loop (TOTE model: test-operate-test-exit; Miller et al., 1986): Individuals first test for the presence of a difference between their expectations and their experiences and then engage in various operations to reduce this difference. The difference is then tested again, and the cycle iterates until expectations and experiences match. This model predicts that individuals who report low QoL repeatedly compare their experiences with their expectations but might be unsuccessful in effectively reducing the difference between the two. In the context of a severe disease, patients who report low QoL might therefore tend to compare their experiences with their expectancies repeatedly, without being able to bridge the gap between their hopes and their current situation.

To test this hypothesis we examined the N400 event related potential (ERP) to disease related and disease unrelated words in patients with ALS and healthy controls. The N400 is a negative ERP deflection with a peak latency about 400 ms after the onset of a meaningful stimulus (usually, a word) that is incongruent with the preceding context (Kutas and Hillyard, 1980). However, the absolute value of the N400 does not need to be negative. It is, therefore, typically examined by evaluating a difference ERP created by subtracting the EEG signal in one condition from the signal in another condition (Kutas and Federmeier, 2011). Besides semantic congruence, predictability in general has been found to modulate the N400, with larger amplitudes following non-predictable sentence endings even when the ending itself is semantically congruent with the sentence content (Kutas and Hillyard, 1984; Lau et al., 2008). N400 effects are further modulated by word frequency such that unpredictable high frequency words elicit a smaller N400 amplitude than unpredictable low frequency words (Allen et al., 2003; van Petten and Kutas, 1990).

In summary, applying the TOTE model to coping with diseases suggests that disease related concepts are repeatedly processed in patients reporting low QoL. When such concepts are presented in a sentence context, amplitudes of the N400 potential are inversely related to the ease of lexical access, with lower amplitudes reflecting facilitated access to the mental lexicon. ALS patients who report low QoL should be confronted with disease specific concepts more often than patients who report high QoL. This should make the processing of disease related words easier in ALS patients with poor QoL than in patients with high QoL. Therefore, an N400 effect between incongruent and congruent disease related words should be reduced in patients with low QoL as compared to patients with high QoL. Further, these differences should be specific for disease-related material, and not be obtained for disease unrelated words, i.e. N400 effects to disease unrelated words should be independent of QoL. To ensure that our proposed results would be truly disease related, healthy age-matched volunteers served as controls. Healthy controls were expected to show only an effect of congruence, but not an interaction of congruence, disease relatedness, and QoL.

2. Methods

2.1. Participants

Patients were recruited at the ALS outpatient clinic of the Department of Neurology, University Hospital of Würzburg. The initial patient sample comprised $N = 21$ patients fulfilling the revised El Escorial criteria of clinically definite or clinically probable ALS (Brooks et al., 2000). Exclusion criteria were a history of any other neurological or psychiatric disorder and disease duration of less than 3 months. The three-month criterion was chosen because coping processes in the acute phase (i.e., immediately after the diagnosis) can considerably differ from those in the later stages of ALS. One male patient aborted the experiment due to excessive drowsiness, one female patient refused to complete the questionnaires due to emotional burden, and one male patient died before data collection was completed. The final patient sample size was thus $n = 18$ (13 male). Twenty age-matched healthy controls were recruited via the local newspaper, of which none had to be excluded (see Table 1 for description of the patient and control samples).

All participants were German native speakers and had normal or corrected to normal vision. Handedness was assessed using a German version of the Edinburgh Handedness Inventory (Oldfield, 1971). Seventeen patients and 18 controls were right-handed.

All participants gave written informed consent. The study was approved by the Ethical Review Board of the Medical Faculty, University of Würzburg and conformed to the Declaration of Helsinki (World Medical Association, 2011). Healthy participants received reimbursement (EUR 40) for participation. The sponsor of the study had no role in study design, data collection, analysis, interpretation, or writing of the report. The first author had full access to the data and had final responsibility for the decision to submit for publication.

2.2. Materials

2.2.1. Stimuli

To generate disease related and disease unrelated words, 217 words originating from patients' quality of life questionnaires and interviews were collected. Ten patients with ALS rated these words for valence, arousal, subjective frequency of occurrence, and disease relatedness. These ten patients did not participate in this study, as prior knowledge of disease related and disease unrelated words, might have increased accessibility of these words and thus led to a reduction of the N400 effect which would have been unrelated to QoL. Valence and arousal were rated on 9-point visual scales of the Self-Assessment Mannequin (Bradley and Lang, 1994). Subjective frequency ("Please indicate how frequent this word is in your daily life") was assessed with a 9 point Likert scale (1: "very rare" to 9: "very frequent"); disease relatedness ("Please indicate the extent to which this word is related to your disease") was assessed with a 6 point Likert scale (1: "disease related" to 6: "disease unrelated"). $N = 120$ words comparable in valence, arousal,

Table 1
Sample characteristics. Means, standard deviations and intercorrelations.

Measure	*M* (SD)	2	3	4	5	6
Patients with ALS (n = 18)						
Age	60.39 (10.35)	−.25	−.30	.14	−.05	−.34
BDI-12	10.88 (4.80)		.63**	−.35	−.64**	.26
ADI-12	12.35 (4.66)			−.34	−.34	.03
SEIQOL-DW	72.0 (17.99)				.24	.06
ALSFRS-R	23.94 (9.28)					−.34
range	6–36					
Duration (years)	2.23 (1.8)					
Age matched healthy participants (n = 20)						
Age	59.9 (10.34)	−.20	−.40	.38	−.18	
BDI-II	7.30 (6.73)		.62**	−.33	.28	
ADI-12	6.6 (4.11)			−.35	.37	
SEIQOL-DW	77.77 (9.23)				−.22	
FSL	153.75 (36.22)					

Note. $^{**}p < .01$.

and frequency but differing in disease relatedness were chosen as experimental stimuli and incorporated as the last word in two congruent (congruent condition) and two incongruent sentences (incongruent condition). Overall, 480 sentences were generated (see Supplementary Table S1 for sentence examples and further details).

2.2.2. Questionnaires

Subjective quality of life was assessed in patients and healthy controls with the Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQOL-DW; O'Boyle et al., 1993). The SEIQOL is a semi-structured interview asking patients to name and describe the five domains which contribute the most to their QoL. Then, they are required to rate their current satisfaction within each domain and finally to weigh the importance of each domain by distributing 100 "importance points" among their chosen life domains. A final score ranging from 0 to 100 with higher scores indicating higher quality of life is computed by calculating the weighted sum of satisfaction scores across the domains and then dividing by 100.

Depression was assessed using the revised Beck Depression Inventory (BDI-II) (Beck et al., 1996; Hautzinger et al., 2006) and the ALS specific ALS Depression inventory (ADI-12; Hammer et al., 2008).

In the patient sample, functional status was defined with the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (Cedarbaum et al., 1999). To obtain a comparable "physical" measure for healthy participants, those filled out the Freiburg Symptom List (FSL) (Fahrenberg, 1994), a questionnaire assessing the presence and intensity of bodily symptoms.

2.2.3. Procedure

After obtaining informed consent, questionnaires were mailed to the participants of the study shortly before the EEG recording. For the EEG recording patients were visited at home during the late morning hours. Care was taken to seat patients as comfortable as possible in bed, wheelchair or armchair. Healthy participants were tested in the Electrophysiological Laboratory of the Department of Psychology I of the University of Würzburg.

Sentences were presented pseudo-randomly in black font on a white background on a computer monitor in four blocks of 120 sentences each, using E-Prime Software (Psychology Software Tools, Sharpsburg, PA). Each trial started with a fixation cross (+) presented on the screen for 700 ms. Sentences were then presented word-by-word with each word appearing for 700 ms. After the last word, the screen turned white, indicating an intertrial interval of 1500 ms before the next trial started. After each block, the presentation paused for 5 min for rest. Participants were instructed to read each sentence quietly for comprehension and to try to restrict eye blinks to the intertrial interval. If possible, caregivers, family members and the experimenter left the room during the experiment. The whole presentation lasted 80 min.

EEG was recorded from 32 active electrodes mounted in an elastic cap (32-channel BrainVision actiCAP), which provides for electrode locations at Fp1, Fp2, F7, F3, Fz, F4, F8, Fc5, Fc1, Fc2, Fc6, T7, C3, Cz, C4, T8,Cp5, Cp1, Cp2, Cp6, Tp9, P7, P3, Pz, P4, P8, Tp10, Po9, O1, Oz, O2, Po10. One electrode (Fp2) was mounted left infraorbital to record vertical eye movements. EEG-signals were recorded at 256 Hz and digitized online using BrainVision DCAmp with BrainVision Recorder software. Offline EEG analysis was performed with BrainVision Analyzer 2.0 and included notch (50 Hz) and band pass (0.0159–30 Hz) filtering, rereferencing to a common average, correction for eye movements (Gratton et al., 1983), and exclusion of artefacts (visual inspection, amplitudes in excess of ±70 μV, and low activation, i.e. the difference between maximal and minimal amplitudes should exceed 0.5 μV). All in all 3.6% of all trials were rejected as artefacts (see also Supplementary Table S2). The proportion of trials identified as artefacts was independent of patients' QoL ($p = .89$) and disease severity ($p = .78$). Data was segmented from −200–900 ms after target word onset and the 200 ms interval prior to target onset was used for baseline correction before averaging.

Functional status (ALSFRS-R) and subjective quality of life (SEIQOL-DW) were assessed with a delay of approximately 20 min after the end of the EEG session. Completed questionnaires were then inspected for missing items, and patients asked to answer the missing items.

2.2.4. Data analysis

High density mapping of the N400 in healthy subjects shows that the N400 is most pronounced at centro parietal electrode locations Cz, CP1, CP2, P3, Pz, and P4 (Johnson and Hamm, 2000). Since patients with ALS may show altered ERPs (Hanagasi et al., 2002; Paulus et al., 2002; Raggi et al., 2008; Vieregge et al., 1999; Westphal et al., 1998), we identified the electrode position Pz as the electrode of interest, because in visual inspection of grand average waveforms Pz displayed the strongest difference between congruent and incongruent disease unrelated words. We then analyzed the mean activation (in μV) at Pz in the 400–500 ms time window.

2.2.5. Statistical analysis

Our hypothesis predicted a triple interaction between the patients' QoL, a continuous variable, and disease relatedness and congruence, both categorical variables. In addition, we hypothesized this effect to be only present in patients, but not in healthy controls, a fourth-order interaction.

Thus, our data consists of multiple observations per subject and we predicted interactions of between-subjects and within-subjects variables. Using the usual linear regression model to analyze this data would ignore the fact that observations on the same subject are dependent and, thus, would violate a basic assumption of this model. Alternatively, using a repeated measures ANOVA would, under certain assumptions, account for the within-subject dependence, but would require us to transform the continuous variable of interest (QoL) to a categorical variable, a procedure which is discouraged (Cohen, 1983; Maxwell and Delaney, 1993). Mixed models are an extension of the regression and ANOVA approach, that recognize the within-subject level dependence (like repeated measures ANOVA) while at the same time allow for the analysis of both, continuous and categorical predictor variables (like regression). Consequently we analyzed mean amplitudes using a full factorial linear mixed model (R Development Core Team, 2011) with the within subject factors disease relatedness (disease related vs. disease unrelated) and congruence (congruent vs. incongruent), and the between subject factors QoL (z-standardized SEIQOL-DW score), and subject group (ALS patients vs. healthy controls). Results from the mixed model are reported as F-statistics (Pinheiro et al., 2012) and may be interpreted just as in conventional ANOVA.

In mixed models, like in regression, follow-up analysis is based on the fact that the effect of a term is evaluated when all higher-order interactions involving this term are zero. Thus, it is possible to analyze the effect of a given variable at a specific level of another variable, just by re-calculating the model with appropriately set reference levels for the variables of interest. z-Standardized continuous predictors may be used in follow-up analysis by simply adding 1 to the predictor, thereby shifting the zero-point 1 SD towards the lower end or by subtracting 1, thereby shifting the zero-point 1 SD towards the higher end. Further details on this procedure can be found in (Aiken et al., 1993). In our study, significant effects involving congruence, QoL, and disease relatedness were followed up one standard deviation above and below the mean QoL score.

Initial analyses also controlled for a possible role of valence of the target word, but this term was dropped from the analysis since valence did not interact with congruence or the hypothesized triple interaction between congruence, disease relatedness, and quality of life. We also examined a possible role of disease severity and duration. These covariates were chosen, because disease severity or disease duration may increase the extent to which patients are confronted with disease related information, and may thus render disease related information more accessible. In addition, depression was also included as a potential covariate, as it is known that depressed individuals process environmental stimuli more detailed and more accurately than non-depressed subjects (Alloy et al., 1981), which may increase the accessibility of disease related information. No such influences were found and thus, these variables were not entered into the final analysis. A sensitivity analysis (DFBETA Belsley et al., 2005) – identifying and excluding potentially influential observations – indicated that our results were not influenced by outlying data values.

Two-sample *t*-tests were used to analyze differences in age, and depression (ADI-12, and BDI-II). The difference in QoL between patient and controls was analyzed using Welch's *t*-test, as the standard deviation of QoL was larger in patients as compared to controls ($F(17,19) = 3.80$, $p < .01$).

3. Results

3.1. Description of samples

Sample characteristics are shown in Table 1. Patients and controls did not differ in age, $t(36) = 0.15$, $p = .89$, or quality of life $t(24.77) = -1.22$, $p = .23$, but patients showed a trend towards higher depression scores in the BDI-II, $t(35) = 1.83$, $p = .07$, and significantly higher scores in the ADI-12, $t(35) = 3.99$, $p < .01$.

Grand mean ERP waveforms of congruent vs. incongruent, and disease related vs. disease unrelated target words are presented in Fig. 1, separately for patients (top) and healthy controls (bottom) with a QoL above vs. below the median QoL.

Visual inspection of the first two panels of Fig. 1 demonstrates that patients with high QoL presented with an N400-like negativity peaking around 450 ms in response to incongruent disease-unrelated (left most upper panel) and incongruent disease-related words (middle-left upper panel). The last two panels of Fig. 1 indicate that patients with low QoL also showed a similar negativity to incongruent disease-unrelated words (middle right upper panel), but that this negativity was markedly reduced for disease-related words (right most panel of Fig. 1).

Statistical analysis (see Fig. 2) indicated a strong effect of congruence ($F(1,482) = 19.28$, $p < .001$), indicating a larger N400 to incongruent than to congruent words. The effect of congruence was modified by a significant triple interaction of congruence, disease relatedness and QoL ($F(1,482) = 8.42$, $p < .01$), which in turn was modified by the quadruple interaction of congruence, disease relatedness, QoL and subject group ($F(1,482) = 6.13$, $p < .05$). The quadruple interaction of congruence, disease relatedness, QoL, and group, was followed up by separate models for the patient and control samples.

3.2. Patient sample

Statistical analysis indicated a strong main effect of congruence, ($F(1,228) = 17.31$, $p < .001$), indicating a larger N400 to incongruent than to congruent words, i.e. an N400 effect. The triple interaction between congruence, disease relatedness, and QoL was significant ($F(1,228) = 7.56$, $p < .01$). Fig. 2 shows that patients reporting low QoL showed a significant effect of congruence only for disease-unrelated words, but not for disease-related words. In contrast, in patients reporting high QoL the effect of congruence did not differ between disease related and disease unrelated words.

3.3. Healthy participants (control group)

As shown in Fig. 1 (lower half) healthy controls reporting high QoL presented with a negativity peaking around 450 ms in response to incongruent disease unrelated (left most lower panel) and incongruent disease related words (middle-left lower panel). ERP waveforms in healthy controls with high and low quality of life were identical.

Statistical analysis confirmed a strong main effect of congruence ($F(1,254) = 29.86$, $p < .0001$) indicating a larger negativity to incongruent than to congruent target words. In contrast to the

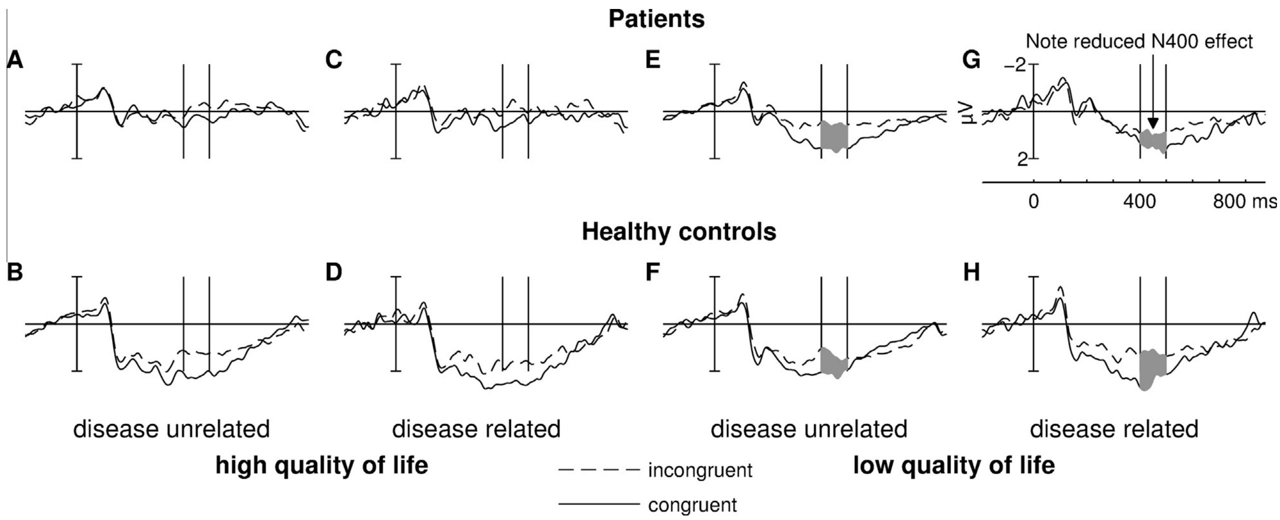


Fig. 1. Grand averages (Pz) from 200 ms before until 900 ms after onset of the target word, for congruent vs. incongruent, and disease related vs. disease unrelated target words separately for patients (top) and healthy controls (bottom) with a QoL above vs. below the median QoL. *Note*: Patients reporting lower than median QoL present with reduced negativity for incongruent disease related words in (panel G). Groups are defined by median QoL. Median QoL in the patient sample = 78 (below: $n = 8$, above: $n = 10$). Median QoL in healthy participants = 77.5 (below: $n = 10$, above: $n = 10$).

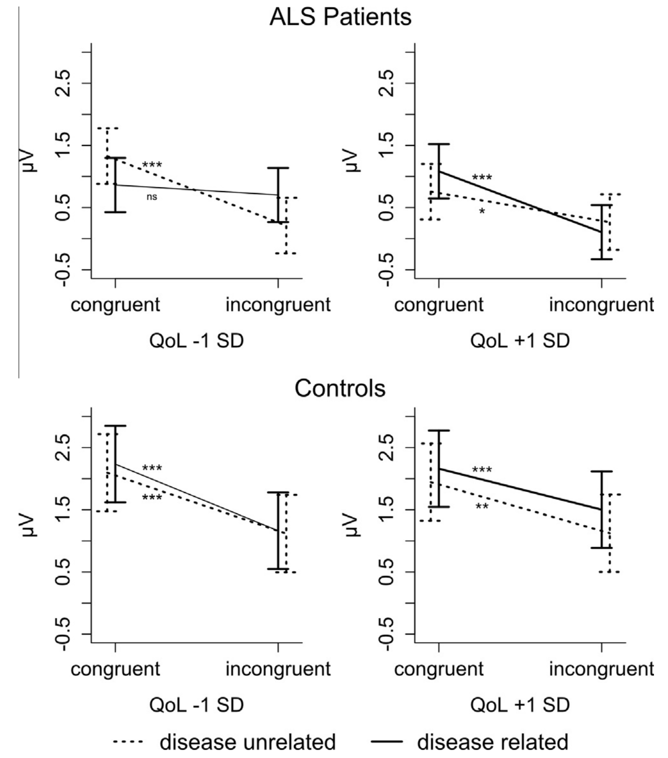


Fig. 2. Interaction between congruence, disease relatedness and QoL in patients (top) and controls (bottom). Vertical lines indicate standard errors. *Note*: $^{*}p < .05$, $^{**}p < .01$, $^{**}p < .001$, *ns*: not significant. *p*-Values are one-sided.

patient group the triple interaction of congruence, disease relatedness, and quality of life was not significant ($F(1,254) = 0.32$, $p = .57$).

4. Discussion

In this study, the accessibility of disease related words was investigated in patients with a severe and terminal disease. N400 effects were examined as a function of self-reported QoL to determine if N400 effects could serve as an psychophysiological correlate of coping with a disease. Theoretically, our approach is based on models and previous research, according to which QoL serves as a measure of coping with a disease (Matuz et al., 2010). In line with this view, patients who have difficulties with coping are expected to have disease-related information more readily available. Accordingly, we hypothesized that ALS patients with low QoL have facilitated access to disease related words in comparison with patients reporting high quality of life.

Healthy controls varying in quality of life were investigated to demonstrate the specificity of these effects, i.e. quality of life dependent disease related effects. Generally, in healthy controls, semantically incongruent words elicited a more negative going amplitude than congruent words (i.e., a well-known N400 effect).

In healthy individuals with high or low QoL, and in patients with high QoL, the size of this effect did not differ between disease-related and disease-unrelated words. In contrast, as predicted, patients reporting low quality of life did show this effect only for disease unrelated words, but not for disease related words.

In patients with ALS amplitudes of event-related potentials are generally lower, and compared to healthy controls, may occur with prolonged latencies and altered scalp distributions, e.g. (Hanagasi et al., 2002). Nevertheless, many studies report task related differences in ERPs in ALS patients similar to healthy controls (e.g. Hanagasi et al., 2002; Nijboer et al., 2008).

Likewise, we found the N400 amplitude to vary as a function of congruence in both healthy controls and patients with ALS (N400 effect). In addition, we found the size of the N400 effect to vary as a function of the target word's disease relatedness and patients' QoL.

The N400 effect may be described as a function of the predictability of the target stimulus (Lau et al., 2008). Our finding of a selectively reduced N400 effect in patients reporting low QoL thus suggests that disease related words are more accessible in patients reporting low QoL.

An alternative explanation would be that disease related words are of stronger emotional valence in patients with low quality of life. Patients reporting low QoL might thus show a reduced effect of incongruence to words with higher valence, e.g. (Lulé et al., 2005). However, initial analyses controlling for the effect of valence did not reveal any influence of valence on the triple interaction of congruence, disease relatedness, and QoL. Furthermore, possible effects of disease duration and severity (one might argue that patients with low QoL are either more severely ill or have been suffering from the disease for a longer time) were also controlled for and did not reveal effects on the decisive triple interaction.

As quality of life and degree of depressive symptoms usually moderately correlate, $\rho = -.35$ in our sample, one might argue that accessibility of disease related words was moderated by depression rather than quality of life, e.g. via increased disease-related ruminative thoughts (Nolen-Hoeksema et al., 2008). However, we can exclude this explanation, because analyses controlling for depression yielded no moderating role of depression.

From Fig. 1 (top left) it appears that amplitudes in patients reporting high QoL are generally less positive than in patients with low QoL. Although unexpected, this finding might be explained with reference to studies on the impact of mood on sentence processing. For example, early behavioral studies showed that positive mood tends to increase creative problem solving (Isen et al., 1987), and the production of unusual (Isen et al., 1985) and remote (Bolte et al., 2003) associations. This suggest that being in a positive mood facilitates the processing of semantic material, e.g. words. Given that the N400 amplitude indexes ease of lexical processing, one might then expect a general effect of mood on N400 amplitudes. A study by Pinheiro and colleagues (Pinheiro et al., 2013) supports this hypothesis by showing that when subjects were in a positive mood, N400 amplitudes where generally shifted towards less positive values, i.e. amplitudes following congruent as well as incongruent sentence endings were less positive than when subjects were in a negative mood. However, it is difficult to judge whether this explanation pertains to our results, since participants' current mood was not assessed in this study.

Our finding that ALS patients and healthy controls did not differ in QoL may seem surprising. Similar results were found, however, not only in ALS (Lulé et al., 2008) but across a wide range of severe diseases (Sprangers and Schwartz, 1999) and are thought to reflect continuous (and successful) adaption to a disease (Rapkin and Schwartz, 2004; Sprangers and Schwartz, 1999). Indeed, the model on which our study is based, describes the consequences of inter-individual differences in the effectiveness of these adaptation processes.

A possible limitation of the present study is related to the fact that our sample was not representative for ALS patients in general, as we did not include all patients that visited the outpatient clinic, but only those who volunteered to take part in the study. Thus, future studies are needed to replicate our findings in a sample of unselected ALS patients. Despite this constraint, we found the predicted selective attenuation of the N400 effect in disease related words in patients with low QoL. We may thus speculate that in a full random sample, this effect might be even more pronounced.

Our approach is based on the assumption, that unsuccessful coping leads to repeatedly circling through the feedback loop presented in the Introduction, thereby increasing the frequency with which unsuccessful copers are confronted with disease specific information. Our results support this prediction. However, we did not yet address the role of the extent of the mismatch between expectations and experiences, and whether our model suggests ways of increasing QoL. In the following, we try to answer these questions within the limits of this article.

Research on the relation of problem solving skills and QoL suggests that problem-solving works in a step-by-step mode, where large numbers of possible solutions are generated and their effectiveness in reducing the discrepancy tested (D'Zurilla and Nezu, 2010). Since it is plausible to assume, that not all of these solutions are equally effective, the discrepancy between perceptions and expectations is likely to persist for some time, i.e. until a viable solution is finally found. It may then follow, that experiencing larger discrepancies should lead to engaging the feedback loop more frequent in comparison to when experiencing smaller discrepancies (for which viable solutions might be found faster). If this is true, the effect we found may not distinguish between subjects experiencing a single "large" discrepancy, and subjects experiencing many "small" discrepancies. This prediction integrates with findings on the predictors of everyday well-being, which state that the detrimental effect of many small "daily hassles" on QoL is comparable to more severe negative life events (Kanner et al., 1981).

Our approach rests on the assumption that QoL derives from a discrepancy between perceptions and expectations (Calman, 1984). From this follows, that one way of maintaining high QoL in the face of adversity may be the lowering of one's expectations to match one's experiences. However, lowering standards may only be part of the story and it may not always be beneficial. While our model suggests that low standards may contribute to high QoL, it also suggests that low standards reduce the use of coping strategies which might, if successful, increase the rate of positive experiences, which have been associated with a decreased risk of depression (Dimidjian et al., 2011). Paradoxically, very low standards may thus lead, if taken to the extreme, to a state of passiveness, where individuals have ceased all efforts to shape their surroundings according to their needs. Further, there is also evidence that changing standards does not work in isolation, but may be supplanted by attempts to redefine the meaning of "high" QoL, or to re-weigh the contributions of different life domains to QoL (Rapkin and Schwartz, 2004; Sprangers and Schwartz, 1999).

Finally, one may ask whether QoL affects the processing of congruent and incongruent words per se. From our data, this does not seem to be the case. No effect of QoL on the difference between congruent and incongruent words was found in healthy participants, and patients did also show an effect of congruence for disease unrelated words. It thus seems that the processing of incongruent information is independent of QoL, and that QoL only alters the accessibility of information subjects consider important for their QoL, e.g. being diagnosed with an incurable disease.

To summarize, our results indicate that disease related words are more accessible in ALS patients with low QoL than in those with high QoL as indexed by an attenuated N400 to incongruent disease related words. We cautiously conclude that the modulations of the N400 effect by disease related words may serve as a neuropsychological correlate of coping with a severe and terminal disease. These results are in line with models of self-regulation which propose the operation of a feedback loop in coping with a disease, or, more generally, any stressor. Thus, our findings might not be limited to ALS but transfer to other severe diseases. We would expect the modulation of the N400 effect by disease related vs. disease unrelated words to be even more pronounced in patients with severe diseases that do not affect cortical neurons.

5. Conflict of interest statement

The authors declare no competing financial interests.

Acknowledgements

R. Real received a grant by the Graduate School of Life Sciences of the University of Würzburg (RTG 1253/1). Funded by FP7-ICT-2009-4, Grant 247919 (DECODER). B. Kotchoubey was supported by German Research Society (Deutsche Forschungsgemeinschaft) Grant KO-1753-10.

This work was supported by the European ICT Program Project FP7-247919. Possible inaccuracies of information are under the responsibility of the project team. The text reflects solely the views of its authors. The European Commission is not liable for any use that may be made of the information contained therein.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2013.09.040.

References

Aiken LS, West SG, Reono RR. Multiple Regression. Testing and Interpreting Interactions. London: SAGE; 1993.
Allen M, Badecker W, Osterhout L. Morphological analysis in sentence processing: an ERP study. Lang Cogn Process 2003;18:405–30.
Alloy LB, Abramson LY, Viscusi D. Induced mood and the illusion of control. J Pers Soc Psychol 1981;41:1129–40.
Beck AT, Steer RA, Brown GK. BDI-II. Beck Depression Inventory. Manual. San Antonio, Tex, Boston: Psychological Corp., Harcourt Brace; 1996.
Belsley DA, Kuh E, Welsch RE. Regression Diagnostics. Identifying Influential Data and Sources of Collinearity. New York: Wiley; 2005.
Bolte A, Goschke T, Kuhl J. Emotion and intuition: effects of positive and negative mood on implicit judgments of semantic coherence. Psychol Sci 2003;14:416–21.
Bradley MM, Lang PJ. Measuring emotion: the self-assessment manikin and the semantic differential. J Behav Ther Exp Psychiatry 1994;25:49–59.
Brooks BR, Miller RG, Swash M, Munsat TL. For the world federation of neurology research group on motor neuron diseases. El escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000;1:293–9.
Calman KC. Quality of life in cancer patients – a hypothesis. J Med Ethics 1984;10:124–7.
Cameron LD, Leventhal H, editors. The Self-Regulation of Health and Illness Behaviour. London: Routledge; 2002.
Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci 1999;169:13–21.
Cohen J. The cost of dichotomization. Appl Psychol Meas 1983;7:249–53.
Dimidjian S, Barrera M, Martell C, Muñoz RF, Lewinsohn PM. The origins and current status of behavioral activation treatments for depression. Annu Rev Clin Psychol 2011;7:1–38.
D'Zurilla TJ, Nezu AM. Problem-solving therapy. In: Dobson KS, editor. New York: Guilford Press; 2010. p. 197–225.
Fahrenberg J. Freiburger Beschwerdenliste. Form FBL-G und revidierte Form FBL-R. Göttingen: Hogrefe; 1994.
Gratton G, Coles MGH, Donchin E. A new method for off-line removal of ocular artifact. Electroencephalogr Clin Neurophysiol 1983;55:468–84.
Hammer EM, Häcker S, Hautzinger M, Meyer TD, Kübler A. Validity of the ALS-depression-inventory (ADI-12) – a new screening instrument for depressive disorders in patients with amyotrophic lateral sclerosis. J Affect Disord 2008;109:213–9.
Hanagasi HA, Gurvit IH, Ermutlu N, Kaptanoglu G, Karamursel S, Idrisoglu HA, et al. Cognitive impairment in amyotrophic lateral sclerosis: evidence from neuropsychological investigation and event-related potentials. Brain Res Cogn Brain Res 2002;14:234–44.
Hautzinger M, Keller F, Kühner C. BDI-II. Beck Depressions Inventar Revision. Harcourt Test Services: Frankfurt a. M; 2006.
Isen AM, Johnson MMS, Mertz E, Robinson GF. The influence of positive affect on the unusualness of word associations. J Pers Soc Psychol 1985;48:1413–26.

Isen AM, Daubman KA, Nowicki GP. Positive affect facilitates creative problem solving. J Pers Soc Psychol 1987;52:1122–31.
Johnson BW, Hamm JP. High-density mapping in an N400 paradigm: evidence for bilateral temporal lobe generators. Clin Neurophysiol 2000;111:532–45.
Kanner AD, Coyne JC, Schaefer C, Lazarus R. Comparison of two modes of stress measurement. Daily hassles and uplifts versus major life events. J Behav Med 1981;4:1–39.
Kübler A, Winter S, Ludolph AC, Hautzinger M, Bierbaumer N. Severity of depressive symptoms and quality of life in patients with amyotrophic lateral sclerosis. Neurorehabil Neural Repair 2005;19:182–93.
Kutas M, Federmeier KD. Thirty years and counting: finding meaning in the N400 component of the event-related brain potential (ERP). Annu Rev Psychol 2011;62:621–47.
Kutas M, Hillyard SA. Reading senseless sentences. Brain potential reflect semantic incongruity. Science 1980;207:203–5.
Kutas M, Hillyard SA. Brain potentials during reading reflect word expectancy and semantic association. Nature 1984;307:161–3.
Lau EF, Phillips C, Poeppel D. A cortical network for semantics. (de)constructing the N400. Nature Rev Neurosci 2008;9:920–33.
Lazarus RS, Folkman S. Stress, Appraisal, and Coping. New York: Springer; 2008.
Lulé D, Kurt A, Jürgens R, Kassubek J, Diekmann V, Kraft E, et al. Emotional responding in amyotrophic lateral sclerosis. J Neurol 2005;252:1517–24.
Lulé D, Häcker S, Ludolph A, Birbaumer N, Kübler A. Depression und Lebensqualität bei Patienten mit Amyotropher Lateral Sklerose. Deutsches Ärzteblatt 2008;105:307–403.
Lulé D, Zickler C, Hacker S, Bruno MA, Demertzi A, Pellas F, et al. Life can be worth living in locked-in syndrome. Prog Brain Res 2009;177:339–51.
Matuz T, Birbaumer N, Hautzinger M, Kübler A. Coping with amyotrophic lateral sclerosis: an integrative view. J Neurol Neurosurg Psychiatry 2010;81:893–8.
Maxwell SE, Delaney HD. Bivariate median splits and spurious statistical significance. Psychol Bull 1993;113:181–90.
McDonald ER, Wiedenfeld SA, Carpenter CL, Walter RA. Survival in amyotrophic lateral sclerosis. The role of psychological factors. Arch Neurol 1994;51:17–23.
Miller GA, Galanter E, Pribram KH. Plans and the Structure of Behavior. New York: Adams-Bannister-Cox; 1986.
Nijboer F, Sellers EW, Mellinger J, Jordan MA, Matuz T, Furdea A, et al. A P300-based brain-computer interface for people with amyotrophic lateral. Clin Neurophysiol 2008;119:1909–16.
Nolen-Hoeksema S, Wisco BE, Lyubomirsky S. Rethinking rumination. Perspect Psychol Sci 2008;3:400–24.
O'Boyle CA, Browne J, Hickey A, McGee HM, Joyce CRB. The Schedule for the Evaluation of Individual Quality of Life (SEIQoL): A Direct Weighting Procedure for Quality of Life Domains (SEIQoL-DW). Dublin: Department of Psychology, Royal College of Surgeons in Ireland; 1993.
Oldfield RC. The assessment and analysis of handedness. The Edinburgh inventory. Neuropsychologia 1971;9:97–113.
Paulus KS, Magnano I, Piras MR, Solinas MA, Solinas G, Sau GF, et al. Visual and auditory event-related potentials in sporadic amyotrophic lateral sclerosis. Clin Neurophysiol 2002;113:853–61.
Pinheiro AP, del Re E, Nestor PG, McCarley RW, Goncalves OF, Niznikiewicz M. Interactions between mood and the structure of semantic memory: event-related potentials evidence. Soc Cogn Affect Neurosci 2013;8:579–94.
Plahuta JM, McCulloch BJ, Kasarskis EJ, Ross MA, Walter RA, McDonald ER. Amyotrophic lateral sclerosis and hopelessness: psychosocial factors. Soc Sci Med 2002;55:2131–40.
R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2011.
Rabkin JG, Wagner GJ, del Bene M. Resilience and distress among amyotrophic lateral sclerosis patients and caregivers. Psychosom Med 2000;62:271–9.
Raggi A, Consonni M, Iannaccone S, Perani D, Zamboni M, Sferrazza B, et al. Auditory event-related potentials in non-demented patients with sporadic amyotrophic lateral sclerosis. Clin Neurophysiol 2008;119:342–50.
Rapkin BD, Schwartz CE. Toward a theoretical model of quality-of-life appraisal. Implications of findings from studies of response shift. Health Qual Life Outcomes 2004;2:14.
Robbins RA, Simmons Z, Bremer BA, Walsh SM, Fisher S. Quality of life in ALS is maintained as physical function declines. Neurology 2001;56:442–4.
Sprangers MAG, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999;48:1507–15.
van Petten C, Kutas M. Interactions between sentence context and word frequency in event-related brain potentials. Mem Cognit 1990;18:380–93.
Vieregge P, Wauschkuhn B, Heberlein I, Hagenah J, Verleger R. Selective attention is impaired in amyotrophic lateral sclerosis – a study of event-related EEG potentials. Brain Res Cogn Brain Res 1999;8:27–35.
Westphal KP, Heinemann HA, Grözinger B, Kotchoubey BJ, Diekmann V, Becker W, et al. Bereitschafts potential in amyotrophic lateral sclerosis (ALS): lower amplitudes in patients with hyperreflexia (spasticity). Acta Neurol Scand 1998;98:15–21.
World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects [Online]. <http://www.wma.net/en/30publications/10policies/b3/17c.pdf> [21 Jul. 2011].
Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., 2012. R Development Core Team. nlme: Linear and Nonlinear Mixed Effects Models. [Online] R. package version 3.1-110.

frontiers in
PSYCHOLOGY

ORIGINAL RESEARCH ARTICLE
published: 08 July 2014
doi: 10.3389/fpsyg.2014.00704

Well-being in amyotrophic lateral sclerosis: a pilot experience sampling study

Ruben G. L. Real[1]*, Thorsten Dickhaus[2], Albert Ludolph[3], Martin Hautzinger[4] and Andrea Kübler[1,5]

[1] Department of Psychology I, Institute of Psychology, University of Würzburg, Würzburg, Germany
[2] Weierstrass Institute for Applied Analysis and Stochastics, Research Group "Stochastic Algorithms and Nonparametric Statistics," Berlin, Germany
[3] Department of Neurology, University of Ulm, Ulm, Germany
[4] Department of Clinical Psychology and Psychotherapy, University of Tübingen, Tübingen, Germany
[5] Institute for Medical Psychology and Behavioural Neurobiology, University of Tübingen, Tübingen, Germany

Edited by:
Francesco Pagnini, Catholic University of Milan, Italy

Reviewed by:
Michelle Dow Keawphalouk, Harvard/MIT, USA
Donatella Mattia, IRCCS Fondazione Santa Lucia, Italy
Eleonora Volpato, Fondazione Don Gnocchi, Milan, Italy

****Correspondence:***
Ruben G. L. Real, Department of Psychology I, Insitute of Psychology, University of Würzburg, Marcusstr. 9-11, 97070 Würzburg, Germany
e-mail: ruben.real@uni-wuerzburg.de

Objective: The aim of this longitudinal study was to identify predictors of instantaneous well-being in patients with amyotrophic lateral sclerosis (ALS). Based on flow theory well-being was expected to be highest when perceived demands and perceived control were in balance, and that thinking about the past would be a risk factor for rumination which would in turn reduce well-being.

Methods: Using the experience sampling method, data on current activities, associated aspects of perceived demands, control, and well-being were collected from 10 patients with ALS three times a day for two weeks.

Results: Results show that perceived control was uniformly and positively associated with well-being, but that demands were only positively associated with well-being when they were perceived as controllable. Mediation analysis confirmed thinking about the past, but not thinking about the future, to be a risk factor for rumination and reduced well-being.

Discussion: Findings extend our knowledge of factors contributing to well-being in ALS as not only perceived control but also perceived demands can contribute to well-being. They further show that a focus on present experiences might contribute to increased well-being.

Keywords: amyotrophic lateral sclerosis, ALS, coping, well-being, experience sampling, ESM, reminiscence, rumination

1. INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a rare neurodegenerative disease characterized by progressive paralysis (Logroscino et al., 2008). In the absence of a cure (Logroscino et al., 2008, 2010) the treatment of ALS focuses on the alleviation of symptoms and the maintenance of the best possible degree of functioning (Clarke et al., 2001). A rich literature exists on factors influencing quality of life and coping with the disease (c.f. Pagnini, 2013). For example, different styles of coping (Matuz et al., 2010; Montel et al., 2012a), spirituality (McLeod and Clarke, 2007), or care-giver relations (Chiò et al., 2004) have all been related to psychosocial well-being in patients with ALS. In line with psychological theories on subjective quality of life (e.g., Rapkin and Schwartz, 2004) the great physical burden of ALS shows no simple relationship to well-being, with many studies showing small and insignificant correlations (Robbins et al., 2001; Pagnini, 2013) or even positive associations (Lulé et al., 2009). However, many of the questionnaires used in research on well-being and quality of life in patients with ALS require participants to generate aggregate statements about their experiences, e.g., by asking them how they felt (on average) during the past days (Cohen et al., 1995; Robbins et al., 2001) or even weeks (Hammer et al., 2008). Thus, little is known about the factors which are associated with instantaneous well-being, i.e., well-being as it fluctuates from moment to moment throughout the day.

In this study, therefore, the experience sampling method (ESM) was used (Larson and Csikszentmihalyi, 1983; Stone et al., 2003) to analyze possible predictors of well-being. Experience sampling, originally developed because of concerns of how accurate people are in "reconstructing their experience[s] after the fact" (Larson and Csikszentmihalyi, 1983, p. 42), asks participants to record their experiences directly at the moment of sampling. By randomizing sampling times throughout the study period, it is possible to collect representative data on the participants' experiences, such as well-being, and possible influencing factors (Shiffman et al., 2008; Scollon et al., 2009).

At its most basic level, flow theory assumes that the physical and mental activities people engage in, influence their well-being. More specifically, it predicts that well-being is highest if perceived control and perceived demands match in a given situation (Csikszentmihalyi, 1990). Any imbalance between demands and abilities results in reduced well-being, e.g., feelings of frustration, when demands exceed abilities, or of boredom, when abilities exceed situational demands (Csikszentmihalyi, 1990). Given that the progressive loss of motor functions requires constant adaptation and change (King et al., 2009), we hypothesized that finding this balance would be of crucial importance in patients with ALS. A second prediction of flow theory is that well-being depends on the extent to which thoughts are focused on present experiences (Schmidt et al., 2007). However, the little data available from patients with ALS is heterogeneous. Support comes from a study by Plahuta et al. (2002), which found that hopelessness, a future oriented direction of thought, is related to increased suffering and higher intentions of suicide in patients with ALS. However, the use of the coping strategy "planning" (Carver, 1997), an arguably more direct and less negatively valenced indicator of "thoughts directed toward the future" does not seem to be strongly related to well-being (Montel et al., 2012b). Qualitative findings from interviews with patients are also mixed (Fanos et al., 2008). On the one hand, several subjects indicated the use of "living in the moment" as a successful coping strategy while others sought consolation in remembering positive past experiences. The constant adaptation and change required for coping with ALS (King et al., 2009), necessitates disengaging from goals no longer attainable, or anticipating disengagement from goals which may become unattainable in the future. Generally, confrontation with unattainable goals—even more so when the factors which make a goal unattainable are essentially uncontrollable as is the case in ALS (Nolen-Hoeksema et al., 2008)—has been shown to be a risk factor for rumination, and, thus, decreased well-being (Nolen-Hoeksema, 1991; Martin and Tesser, 1996). Therefore, we hypothesized that thinking about the past and future would be associated with reduced well-being, and that rumination would mediate this effect.

2. METHODS

2.1. PATIENTS

A convenience sample of ten patients (seven male; see **Table 1**) fulfilling the revised El Escorial criteria for clinically definite ALS (Brooks et al., 2000) was recruited via the Institute for Medical Psychology and Behavioral Neurobiology of the University of Tübingen and the Department of Neurology of the University of Ulm. All participants contacted for inclusion agreed to participate in this study. Mean time since diagnosis was 38.10 months ($SD = 35.96$, range = 12–129). One patient had a percutaneous endoscopic gastrostomy (PEG), and three were non-invasively ventilated. The study was approved by the Ethical Review Board of the Medical Faculty, University of Tübingen. Written informed consent was obtained from all participants.

Table 1 | Patients' Characteristics.

	ALSFRS-R	ADI-12	well-being	*M*	*SD*	Range
Age (years)	0.52	0.32	−0.09	52.30	11.56	35–71
ALSFRS-R		0.59[#]	−0.75[*]	19.20	10.57	1–35
ADI-12			−0.63[#]	20.70	7.41	12–34
well-being				4.79	0.69	3.93–5.86

Intercorrelations, means, and standard correlations.

Note: $N = 10$. [#]$p < 0.10$, [*]$p < 0.05$.

2.2. PROCEDURE

We collected data on well-being, perceived demands, perceived control, temporal direction of thoughts and rumination over the course of two weeks at three randomly chosen times per day using the ESM. Patients were provided with a pager that beeped when they should record their experiences using a standardized questionnaire. To avoid interference with morning and evening caring routines, sampling was restricted to between 10 a.m. and 6 p.m. Patients were instructed to answer the ESM-questionnaires immediately after the beep and while answering the questions to refer only to the situation in which the beep occurred. At the beginning of the two weeks study period, patients were visited at their homes and the procedure was explained in full detail and questions concerning the study protocol were answered.

2.3. MEASURES

Functional status was assessed with the revised ALS Functional Rating Scale (ALSFRS-R) (Cedarbaum et al., 1999), and the extent of depressive symptoms with the ALS specific ALS Depression Inventory (ADI-12) (Hammer et al., 2008). These standardized measures were collected once at the beginning of the two week study period.

The ESM-questionnaire used in this study was previously used by Csikszentmihalyi and Larson (1987) and assessed the extent of perceived demands and control with two items, "How challenging was your activity?" and "Was the situation under your control?" To minimize participants' burden in terms of time and effort, rumination was measured with the single item "Did your thoughts turn round in circles?" (Jong-Meyer et al., 2009) and temporal direction of thoughts with two face-valid items ("Did you look ahead/to the past?"). Each item was scored on a 10-point Likert-type scale ranging from 0 (low) to 9 (high). Patients' well-being was measured with 13 well-being-related items developed by Larson and Csikszentmihalyi (1983). Each item was scored on a 7-point Likert-type scale, and a composite score reflecting well-being was derived by averaging ESM-items of the well-being category. To determine the reliability of this scale while taking the inter-correlation of repeated measurements into account Cronbach's α was calculated across subjects for every time point during the 2-week study period, yielding 42 coefficients. Reliability of the well-being scale was satisfactory (median $\alpha = 0.86$).

Patients completed an average of 33.30 assessments (range 13–43). Fifty percent of all questionnaires were answered within 10 min and 75% within 45 min after the beep. Further analysis revealed that without the most disabled participant (one male who used a personal computer to answer the questionnaires) 75% of all questionnaires were answered within 30 min after the beep. One patient was excluded from the following analyses because of excessive numbers of missing items, leading to a final sample size of $N = 9$.

2.4. STATISTICAL ANALYSES

Random intercept multiple regression analysis was used to test the hypothesis that well-being depended on the balance of demands and control (Edwards and Cooper, 1990; Edwards, 1994, also see Supplementary Material). The analysis was also performed with functional status included as a covariate, which indicated that the results we report here were independent of functional status. Mediation analysis (MacKinnon et al., 2002; Kenny et al., 2003) was used to test the hypothesis that thinking about the past would have a negative effect on well-being and that this effect would be mediated by rumination. We report 95% confidence intervals for the mediated effect (Tofighi and MacKinnon, 2011). The same analysis was repeated for thinking about the future. Analyses were performed in R (R Development Core Team, 2011). Cohen's f^2 was calculated as a measure of the effect size (Selya et al., 2012).

3. RESULTS

Average well-being (see **Table 1**) was marginally negatively associated with symptoms of depression, but significantly positively associated with functional status. Functional status was marginally positively associated with symptoms of depression. Patient's age was not associated with functional status, symptoms of depression, or well-being.

Our first hypothesis suggested that well-being would depend on the balance of perceived control and demands. However, no support was found for this prediction (see Supplementary Material). Instead, results indicated that perceived control was associated with increased well-being ($b = 0.18$, $SE = 0.03$, $p < 0.001$, $f^2 = 0.22$), regardless of the level of perceived demands. In contrast, the effect of perceived demands depended on whether these demands were perceived as controllable: Only, if demands were perceived as *controllable*, they were associated with increased well-being ($b = 0.09$, $SE = 0.02$, $p < 0.001, f^2 = 0.17$). If demands were perceived as *uncontrollable*, the positive effect of demands was significantly reduced ($b = -0.14$, $SE = 0.05, p < 0.01, f^2 = 0.03$), rendering the effect of demands on well-being non-significant ($b = 0.02$, $SE = 0.05$, $p > 0.70$, $f^2 = 0.01$).

Our second hypothesis proposed that thinking about the past would lead to increased rumination which in turn would reduce well-being. **Table 2** shows that thinking about the past (Row 1), thinking about the future (Row 2), and rumination (Row 3) were associated with lower well-being, and that thinking about the past (Row 4) was significantly and thinking about the future (Row 5) was marginally associated with higher rumination. Mediation analysis confirmed a negative effect of thinking about the past on well-being via rumination ($b = -0.03$, 95% CI [-0.05 -0.02]). No evidence was found that the negative effect of thinking about the future on well-being was mediated via increased rumination ($b = -0.01$, 95% CI [-0.02 0.001]).

4. DISCUSSION

Little is known about how patients with ALS cope with their disease from moment to moment in daily life. Thus, in this study the ESM was used to record patients' experiences throughout the day. Despite their severe physical disability, patients were able to complete the ESM-questionnaires within a short time after the scheduled signal. These results provide evidence that even a potentially demanding procedure such as the ESM may be a valuable tool in assessing patients' thoughts, well-being and cognitive state. The relationships between functional status, presence of depressive symptoms and well-being indicated that depressive symptoms were more present and well-being was lower in early stages of the disease. This result mirrors findings of better quality of life in patients who are longer affected by the disease (Lulé et al., 2008, 2009).

Flow theory predicts that well-being depends on finding the optimal balance between perceived demands and control (Csikszentmihalyi, 1990), and we hypothesized that finding this balance would be of crucial importance in patients with ALS. However, our data did not support this hypothesis. Instead, but in line with previous findings (Plahuta et al., 2002), perceived control was associated with increased well-being, regardless of the level of perceived demands. However, our results extend this idea, by showing that increased demands can also contribute to increased well-being, as long as they are perceived as controllable. While flow theory is primarily concerned with experiences related to activities in the present, experiences may also differ in their temporal orientation. We hypothesized that if attention is not focused on the here and now, but directed toward the past or the future, this would increase the risk for rumination, which in turn would reduce well-being. Our results indicate that thinking about the past was indeed associated with decreased well-being and that this effect was mediated by rumination. While some patients may find solace in remembering the good times they have had (Fanos

Table 2 | Results of mediation analysis.

	Predicted	Predictor	*b*	*SE*	*DF*	*t*	*p*	f^2
PREDICTORS OF WELL-BEING								
1	Well-being	Thinking about the past	−0.03	0.01	250.83	−2.73	0.01	0.02
2	Well-being	Thinking about the future	−0.03	0.01	250.97	−2.08	0.04	0.01
3	Well-being	Rumination	−0.08	0.01	255.84	−5.60	<0.001	0.10
PREDICTORS OF RUMINATION								
4	Rumination	Thinking about the past	0.41	0.04	252.89	10.34	<0.001	0.40
5	Rumination	Thinking about the future	0.09	0.05	252.50	1.70	0.09	0.01
MEDIATION MODELS								
6	Well-being	Thinking about the past	0.00	0.01	247.77	0.17	0.87	
7		Rumination	−0.08	0.02	254.12	−4.79	<0.001	
8	Well-being	Thinking about the future	−0.02	0.01	250.30	−1.66	0.10	
9		Rumination	−0.08	0.01	254.83	−5.43	<0.001	

et al., 2008), reminiscing may also introduce the risk of being reminded of unattainable goals, thus, in turn, increasing the risk of reduced well-being. Likewise, thinking about the future was negatively associated with well-being; however, it was only loosely related to rumination, and no support was found for rumination mediating a negative effect of thinking about the future on well-being. We may thus speculate that thoughts about the future are not necessarily ruminative, possibly only in patients experiencing hopelessness (Plahuta et al., 2002).

4.1. LIMITATIONS AND CONSIDERATIONS FOR FUTURE STUDIES

4.1.1. Sampling

Several limiting factors of the current study deserve attention. To minimize interruption of daily routine, time slots in which patients had pre-set appointments (e.g., occupational therapy) were excluded from the experience sampling and sampling was restricted to the time between 10 a.m. and 6 p.m. This restriction may have prevented us from sampling several activities of daily living, e.g., personal hygiene, which may be very demanding and frustrating for severely ill patients (Foley et al., 2014).

4.1.2. Economic considerations

From a research perspective it is often desirable to use longer rather than shorter instruments, if only to increase reliability (Spearman, 1910). However, in a repeated measures context, this desire needs to be balanced with economic considerations, especially in a sample in which motor difficulties, e.g., when holding a pen, are common. Thus, to avoid spurious results, e.g., low well-being due to the frustrating experience of having to repeatedly answer a long questionnaire, and to reduce the risk of high levels of non-reponse (Iglesias and Torgerson, 2000) the questionnaires we used were kept as short as possible. Yet it is clear, that assessing rumination with only one item is a simplification of a complex construct. However, both empirical (Jong-Meyer et al., 2009) as well as theoretical accounts (Carver, 1996) suggest, that the item we used possesses high face validity for assessing rumination.

4.1.3. Sample size and generalizability

Finally, although not uncommon in ESM studies (e.g., Teuchmann et al., 1999), the small sample size limits generalization of results, until future studies can replicate our findings. Further, our analyses focused on within-subject variables, but between-subject factors and their interactions could also play an important role. For example, care-givers tend to underestimate the patient's quality of life (Trail et al., 2003), and it might be interesting to know, whether this is accompanied by a tendency to shield the patient from demanding activities, which according to our findings, might actually improve the patient's well-being. To the best of our knowledge, our study is the first to employ the ESM in patients with ALS. Thus, little information on appropriate sample sizes was available beforehand, demonstrating the pilot character of this study. Judging from the obtained effect sizes, mainly small to medium according to Cohen (1992), we suggest increasing sample sizes in future studies. Results from simulation studies (Snijders and Bosker, 1993) suggest, that an increase in the number of participants might be of greater interest than increasing the number of observations per participant. Further, if a research question focused primarily on between-subject factors (see above) a larger sample size would also be recommended. Thus, it should be kept in mind, that the optimal balance between number of participants and the number of observations per participant is dependent on the particular research question.

The ESM methodology has been applied in a variety of chronic diseases, e.g., in patients with cancer, chronic pain, cardiovascular diseases, or patients requiring hemodialysis (c.f. Smyth and Stone, 2003), testifying to the wide applicability of the method (c.f. Christensen et al., 2003). However, depending on the research questions, sophisticated data analysis methods, and technical equipment, e.g., electronic paging and recording devices with a user-friendly and unobstrusive interface, may be needed. Given the large challenge of living with ever progressing motor impairments, we suggest that future studies may take full advantage of the widespread availability of smartphones which lend themselves to ESM-studies (e.g., Runyan et al., 2013). Using such a system it might even become possible to densely track the evolution of coping with ALS over prolonged periods of time. However, apart from generating valuable data for research purposes, such a procedure might also affect patients' well-being, e.g., by making relations between certain situations and well-being transparent to the patient.

4.2. SUMMARY

Our results suggest that the ESM may be a valuable tool to elucidate components of coping and well-being in daily life in patients with ALS. Perceived control over challenging situations seems to be of major importance for maintaining high well-being. We further show that well-being may not only depend on perceived control, but that it also depends on the level of perceived demands. Encouraging patients to pursue, within limits, potentially demanding activities might help to improve their well-being.

Both thoughts directed toward the past and the future may negatively affect well-being, whereas rumination mediates this effect when thoughts are directed toward the past. We speculate that patients who experience poor well-being and may even be depressed might benefit from interventions which not only strengthen an internal locus of control (Nonnenmacher et al., 2013; Foley et al., 2014) but also encourage living in the present.

On a more global perspective the flow-theoretical approach and our results correspond well with recent work aiming at evaluating mindfulness-based (Kocovski et al., 2009) interventions in patients with ALS (Pagnini et al., 2014a,b). These interventions aim to help focusing on the experiences in the here and now, and thus to reduce the risk of reactive, e.g., ruminative, thoughts, which may otherwise reduce well-being or even lead to depression (Bishop et al., 2004). Our results provide further evidence for this promising approach, by highlighting the importance of the temporal direction of thoughts and the importance of perceived demands and control for the experience of well-being in patients with ALS.

FUNDING

Funding for this study was provided by a grant to Ruben G. L. Real of the research training group 1253/1 which is supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) by Federal and Länder funds. The study sponsor had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

ACKNOWLEDGMENTS

We thank Petra Nedele who assisted in data collection. This publication was funded by the German Research Foundation (DFG) and the University of Wuerzburg in the funding programme Open Access Publishing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fpsyg.2014.00704/abstract

REFERENCES

Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., et al. (2004). Mindfulness: a proposed operational definition. *Clin. Psychol. Sci. Pract.* 11, 230–241. doi: 10.1093/clipsy.bph077

Brooks, B. R., Miller, R. G., Swash, M., Munsat, T. L., and for the World Federation of Neurology Research Group on Motor Neuron Diseases. (2000). El escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph. Lateral Scler. Other Motor Neuron Disord.* 1, 293–299. doi: 10.1080/146608200300079536

Carver, C. S. (1996). "Goal engagement and the human experience," in *Ruminative Thoughts*, Volume IX of *Advances in Social Cognition*, ed R. S. Wyer (Mahwah, NJ: Lawrence Erlbaum), 49–59.

Carver, C. S. (1997). You want to measure coping but your protocol's too long: consider the brief cope. *Int. J. Behav. Med.* 4, 92–100. doi: 10.1207/s15327558ijbm0401_6

Cedarbaum, J. M., Stambler, N., Malta, E., Fuller, C., Hilt, D., Thurmond, B., et al. (1999). The alsfrs-r: a revised als functional rating scale that incorporates assessments of respiratory function. *J. Neurol. Sci.* 169, 13–21. doi: 10.1016/S0022-510X(99)00210-5

Chiò, A., Gauthier, A., Montuschi, A., Calvo, A., Di Vito, N., and Mutani, R. (2004). A cross sectional study on determinants of quality of life in als. *J. Neurol. Neurosurg. Psychiatry* 75, 1597–1601. doi: 10.1136/jnnp.2003.033100

Christensen, T., Barrett, L., Bliss-Moreau, E., Lebo, K., and Kaschub, C. (2003). A practical guide to experience-sampling procedures. *J. Happiness Stud.* 4, 53–78. doi: 10.1023/A:1023609306024

Clarke, S., Hickey, A., O'Boyle, C., and Hardiman, O. (2001). Assessing individual quality of life in amyotrophic lateral sclerosis. *Qual. Life Res.* 10, 149–158. doi: 10.1023/A:1016704906100

Cohen, J. (1992). A power primer. *Psychol. Bull.* 112, 155–159. doi: 10.1037/0033-2909.112.1.155

Cohen, S. R., Mount, B. M., Strobel, M. G., and Bul, F. (1995). The mcgill quality of life questionnaire: a measure of quality of life appropriate for people with advanced disease. a preliminary study of validity and acceptability. *Palliative Med.* 9, 207–219. doi: 10.1177/026921639500900306

Csikszentmihalyi, M. (1990). *Flow: The Psychology of Optimal Experience*. New York, NY: Harper and Row.

Csikszentmihalyi, M., and Larson, R. (1987). Validity and reliability of the experience-sampling method. *J. Nerv. Ment. Dis.* 175, 526–536. doi: 10.1097/00005053-198709000-00004

Edwards, J. R. (1994). The study of congruence in organizational behavior research: critique and a proposed alternative. *Organ. Behav. Hum. Decis. Process.* 58, 51–100. doi: 10.1006/obhd.1994.1029

Edwards, J. R., and Cooper, C. L. (1990). The person-environment fit approach to stress: recurring problems and some suggested solutions. *J. Organ. Behav.* 11, 293–307. doi: 10.1002/job.4030110405

Fanos, J. H., Gelinas, D. F., Foster, R. S., Postone, N., and Miller, R. G. (2008). Hope in palliative care: From narcissism to self-transcendence in amyotrophic lateral sclerosis. *J. Palliative Care* 11, 470–475. doi: 10.1089/jpm.2007.0098

Foley, G., Timonen, V., and Hardiman, O. (2014). Exerting control and adapting to loss in amyotrophic lateral sclerosis. *Soc. Sci. Med.* 101, 113–119. doi: 10.1016/j.socscimed.2013.11.003

Hammer, E. V., Häcker, S., Hautzinger, M., Meyer, T. D., and Kübler, A. (2008). Validity of the als-depression-inventory (adi-12): a new screening instrument for depressive disorders in patients with amyotrophic lateral sclerosis. *J. Affect. Disord.* 109, 213–219. doi: 10.1016/j.jad.2007.11.012

Iglesias, C., and Torgerson, D. (2000). Does length of questionnaire matter? a randomised trial of response rates to a mailed questionnaire. *J. Health Serv. Res. Policy* 5, 219–221. doi: 10.1177/135581960000500406

Jong-Meyer, R. D., Parthe, T., and Projektgruppe (2009). Einfluss von achtsamkeitsübung und dezentrierung auf rumination und spezifität autobiographischer erinnerungen. *Z. Klin. Psychol. Psych.* 38, 240–249. doi: 10.1026/1616-3443.38.4.240

Kenny, D. A., Bolger, N., and Korchmaros, J. D. (2003). Lower level mediation in multilevel models. *Psychol. Methods* 8, 115–128. doi: 10.1037/1082-989X.8.2.115

King, S. J., Duke, M. M., and O'Connor, B. A. (2009). Living with amyotrophic lateral sclerosis/motor neurone disease (als/mnd): decision-making about 'ongoing change and adaptation'. *J. Clin. Nurs.* 18, 745–754. doi: 10.1111/j.1365-2702.2008.02671.x

Kocovski, N. L., Segal, Z. V., and Battista, S. R. (2009). "Mindfulness and psychopathology: problem formulation," in *Clinical Handbook of Mindfulness*, ed F. Didonna (New York, NY: Springer New York), 85–98.

Larson, R., and Csikszentmihalyi, M. (1983). "The experience sampling method," in *Naturalistic Approaches to Studying Social Interaction*, Vol. 15, ed H. T. Reis (San Francisco, CA: Jossey-Bass), 41–46.

Logroscino, G., Traynor, B. J., Hardiman, O., Chiò, A., Couratier, P., Mitchell, J. D., et al. (2008). Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *J. Neurol. Neurosurg. Psychiatry* 79, 6–11. doi: 10.1136/jnnp.2006.104828

Logroscino, G., Traynor, B. J., Hardiman, O., Chio, A., Mitchell, D., Swingler, R. J., et al. (2010). Incidence of amyotrophic lateral sclerosis in europe. *J. Neurol. Neurosurg. Psychiatry* 81, 385–390. doi: 10.1136/jnnp.2009.183525

Lulé, D., Häcker, S., Ludolph, A., Birbaumer, N., and Kübler, A. (2008). Depression and quality of life in patients with amyotrophic lateral sclerosis. *Deutsch. Ärztebl. Int.* 105, 397–403. doi: 10.3238/arztebl.2008.0397

Lulé, D., Zickler, C., Häcker, S., Bruno, M. A., Demertzi, A., Pellas, F., et al. (2009). Life can be worth living in locked-in syndrome. *Prog. Brain Res.* 177, 339–351. doi: 10.1016/S0079-6123(09)17723-3

MacKinnon, D. P., Lockwood, C. M., Hoffman, J. M., West, S. G., and Sheets, V. (2002). A comparison of methods to test mediation and other intervening variable effects. *Psychol. Methods* 7, 83–104. doi: 10.1037/1082-989X.7.1.83

Martin, L. L., and Tesser, A. (1996). "Some ruminative thoughts," in *Ruminative Thoughts*, Vol. IX of *Advances in Social Cognition*, ed R. S. Wyer (Mahwah, NJ: Lawrence Erlbaum), 1–47.

Matuz, T., Birbaumer, N., Hautzinger, M., and Kübler, A. (2010). Coping with amyotrophic lateral sclerosis: an integrative view. *J. Neurol. Neurosurg. Psychiatry* 81, 893–898. doi: 10.1136/jnnp.2009.201285

McLeod, J. E., and Clarke, D. M. (2007). A review of psychosocial aspects of motor neurone disease. *J. Neurol. Sci.* 258, 4–10. doi: 10.1016/j.jns.2007.03.001

Montel, S., Albertini, L., and Spitz, E. (2012a). Coping strategies as related to medical and demographic data in amyotrophic lateral sclerosis. *Acta Neurol. Scand.* 125, 136–141. doi: 10.1111/j.1600-0404.2011.01513.x

Montel, S., Albertini, L., and Spitz, E. (2012b). Coping strategies in relation to quality of life in amyotrophic lateral sclerosis. *Muscle Nerve* 45, 131–134. doi: 10.1002/mus.22270

Nolen-Hoeksema, S. (1991). Responses to depression and their effects on the duration of depressive episodes. *J. Abnorm. Psychol.* 100, 569–582. doi: 10.1037/0021-843X.100.4.569

Nolen-Hoeksema, S., Wisco, B. E., and Lyubomirsky, S. (2008). Rethinking rumination. *Perspect. Psychol. Sci.* 3, 400–424. doi: 10.1111/j.1745-6924.2008.00088.x

Nonnenmacher, S., Hammer, E. M., Lulé, D., Hautzinger, M., and Kübler, A. (2013). Psychische störungen und individuelle lebensqualität bei der chronisch progredient-terminalen erkrankung amyotrophe lateralsklerose (als). *Z. Klin. Psychol. Psych.* 42, 55–63. doi: 10.1026/1616-3443/a000186

Pagnini, F. (2013). Psychological wellbeing and quality of life in amyotrophic lateral sclerosis: a review. *Int. J. Psychol.* 48, 194–205. doi: 10.1080/00207594.2012.691977

Pagnini, F., Di Credico, C., Gatto, R., Fabiani, V., Rossi, G., Lunetta, C., et al. (2014a). Meditation training for people with amyotrophic lateral sclerosis and their caregivers. *J. Altern. Complement. Med.* 20, 272–275. doi: 10.1089/acm.2013.0268

Pagnini, F., Phillips, D., and Langer, E. (2014b). A mindful approach with end-of-life thoughts. *Front. Psychol.* 5:138. doi: 10.3389/fpsyg.2014.00138

Plahuta, J. M., McCulloch, B. J., Kasarskis, E. J., Ross, M. A., Walter, R. A., and McDonald, E. R. (2002). Amyotrophic lateral sclerosis and hopelessness: psychosocial factors. *Soc. Sci. Med.* 55, 2131–2140. doi: 10.1016/S0277-9536(01)00356-2

Rapkin, B. D., and Schwartz, C. E. (2004). Toward a theoretical model of quality-of-life appraisal: implications of findings from studies of response shift. *Health Qual. Life Out.* 2:14. doi: 10.1186/1477-7525-2-14

R Development Core Team (2011). *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing.

Robbins, R. A., Simmons, Z., Bremer, B. A., Walsh, S. M., and Fisher, S. (2001). Quality of life in als is maintained as physical function declines. *Neurology* 56, 442–444. doi: 10.1212/WNL.56.4.442

Runyan, J. D., Steenbergh, T. A., Bainbridge, C., Daugherty, D. A., Oke, L., and Fry, B. N. (2013). A smartphone ecological momentary assessment - intervention app for collecting real-time data and promoting self-awareness. *PLoS ONE* 8:e71325. doi: 10.1371/journal.pone.0071325

Schmidt, J. A., Shernof, D. J., and Csikszentmihalyi, M. (2007). "Individual and situational factors related to the experience of flow in adolescence," in *Oxford Handbook of Methods in Positive Psychology, Series in Positive Psychology*, eds A. D. Ong and M. H. M. Van Dulmen (Oxford; New York, NY: Oxford University Press), 542–558.

Scollon, C. N., Prieto, C. K., and Diener, E. (2009). "Experience sampling: promises and pitfalls, strength and weaknesses," in *Assessing Well-Being*, Volume 39 of *Social Indicators Research Series*, ed E. Diener (Dordrecht: Springer), 157–180.

Selya, A. S., Rose, J. S., Dierker, L. C., Hedeker, D., and Mermelstein, R. J. (2012). A practical guide to calculating cohen's f2, a measure of local effect size, from proc mixed. *Front. Psychol.* 3:111. doi: 10.3389/fpsyg.2012.00111

Shiffman, S., Stone, A. A., and Hufford, M. R. (2008). Ecological momentary assessment. *Annu. Rev. Clin. Psychol.* 4, 1–32. doi: 10.1146/annurev.clinpsy.3.022806.091415

Smyth, J. M., and Stone, A. A. (2003). Ecological momentary assessment research in behavioral medicine. *J. Happiness Stud.* 4, 35–52. doi: 10.1023/A:1023657221954

Snijders, T. A. B., and Bosker, R. J. (1993). Standard errors and sample sizes for two-level research. *J. Educ. Behav. Stat.* 18, 237–259. doi: 10.3102/10769986018003237

Spearman, C. (1910). Correlation calculated from faulty data. *Br. J. Psychol.* 3, 271–295.

Stone, A. A., Shiffman, S. S., and DeVries, M. W. (2003). "Ecological momentary assessment," in *Well-Being*, eds D. Kahneman, E. Diener, and N. Schwarz (New York, NY: Russell Sage Foundation), 26–39.

Teuchmann, K., Totterdell, P., and Parker, S. K. (1999). Rushed, unhappy, and drained: an experience sampling study of relations between time pressure, perceived control, mood, and emotional exhaustion in a group of accountants. *J. Occup. Health Psychol.* 4, 37–54. doi: 10.1037/1076-8998.4.1.37

Tofighi, D., and MacKinnon, D. P. (2011). Rmediation: an r package for mediation analysis confidence intervals. *Behav. Res. Methods* 43, 692–700. doi: 10.3758/s13428-011-0076-x

Trail, M., Nelson, N. D., Van, J. N., Appel, S. H., and Lai, E. C. (2003). A study comparing patients with amyotrophic lateral sclerosis and their caregivers on measures of quality of life, depression, and their attitudes toward treatment options. *J. Neurol. Sci.* 209, 79–85. doi: 10.1016/S0022-510X(03)00003-0

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 07 May 2014; paper pending published: 29 May 2014; accepted: 19 June 2014; published online: 08 July 2014.

*Citation: Real RGL, Dickhaus T, Ludolph A, Hautzinger M and Kübler A (2014) Well-being in amyotrophic lateral sclerosis: a pilot experience sampling study. Front. Psychol. **5**:704. doi: 10.3389/fpsyg.2014.00704*

This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology.

Frontiers in Psychology for Clinical Settings

Research Article
1 July 2014

Supplementary Material: Well-being in Amyotrophic Lateral Sclerosis: a pilot Experience Sampling Study

Ruben GL Real[1,*], Thorsten Dickhaus[2], Albert Ludolph[3], Martin Hautzinger[4] and Andrea Kübler[1,5]

[1] *Institute of Psychology, Department of Psychology I, University of Würzburg, Würzburg, Germany*
[2] *Weierstrass Institute for Applied Analysis and Stochastics, Research Group "Stochastic Algorithms and Nonparametric Statistics", Berlin, Germany*
[3] *Department of Neurology, University of Ulm, Ulm, Germany*
[4] *Department of Clinical Psychology and Psychotherapy, University of Tübingen, Tübingen, Germany*
[5] *Institute for Medical Psychology and Behavioural Neurobiology, University of Tübingen, Tübingen, Germany*

Correspondence*:
Ruben GL Real
Insitute of Psychology, University of Würzburg, Marcusstr. 9-11, 97070 Würzburg, Germany, ruben.real@uni-wuerzburg.de

Psychological issues in Amyotrophic lateral sclerosis

Flow theory predicts that well-being depends on finding the optimal balance between perceived demands and control. In the following we describe in some detail the methods we used to the test this hypothesis.

1 TESTING AN ABSOLUTE DIFFERENCE MODEL

The hypothesis that well-being would be highest when the demands associated with an activity were matched by one's abilities implies an absolute difference model ($|X - Y|$) such that deviations in either direction reduce well-being (see Figure 1).

Let the variables Z, X, Y, and ϵ represent well-being, perceived control, perceived demands, and a random error term. The absolute difference model may then be expressed using the following regression equation (**Edwards**, 1994, 2001):

$$Z = \beta_0 + \beta_1(1 - 2W)(X - Y) + \epsilon \quad (1)$$

where $W = 0$ if $X \geq Y$, else $W = 1$. The notion of absolute differences is captured by the interplay of the definition of W and the difference term (X-Y). If X is greater than or equal to Y, the difference (X-Y) is positive and 1-2W reduces to 1, leaving the difference term unchanged. However, if X is smaller than Y the difference is negative but 1-2W reduces to -1, reversing the sign of the difference term. Equation 1 may be expanded to

$$Z = \beta_0 + \beta_1 X - \beta_1 Y - 2\beta_1 WX + 2\beta_1 WY + \epsilon \quad (2)$$

Equation 2 may then be compared to a standard multiple regression equation with terms X, Y and the product terms WX and WY. Conceptually, the product terms serve to capture the moderating effect of the difference between control (X) and demands (Y) on the effect of control and demands. However, it has been shown that product terms may only be interpreted as interactions when the constituent terms of the interaction are included in the regression (**Cohen**, 1978; **Brambor et al.**, 2006). This means, to be able to interpret WX or WY as the moderating effects of W on X and Y, W would have to be included in the equation. Equation 2 does not include a term W, as it assumes W's regression weight to be zero thereby dropping the term from the equation. Further, the multiple occurrences of β_1 in Equation 2 reveal that all these regression weights are assumed to be the same. To be able to test this assumption, the regression weights for X, Y, WX, WY, and W in Equation 2 are set free,

$$Z = \beta_0 + \beta_1 X + \beta_2 Y + \beta_3 W + \beta_4 WX + \beta_5 WY + \epsilon \quad (3)$$

and Equation 3 may then be used to estimate the empirical relation between the predictors and well-being.

EXAMPLE

After fitting the model specified by Equation 3, the obtained coefficients are compared to the constraints as defined in Equation 2. The logic behind this step is best illustrated by an example: Imagine applying Equation 3 to some data yielded the following parameter estimates. $\beta_0 = 0$, $\beta_1 = 1$, $\beta_2 = -1$, $\beta_3 = 0$, $\beta_4 = -2$, $\beta_5 = 2$. Note that the following conditions hold for these fictitious estimates: All coefficients are different from zero but not β_3, b) coefficients β_1 and β_2 are of equal absolute magnitude but opposite sign, c) coefficients β_4 and β_5 are of equal absolute magnitude but opposite sign, and d) β_4 is twice the negative of β_1. Inserting these estimates into Equation 3 yields,

$$Z = 0 + 1X - 1Y + 0W - 2WX + 2WY + \epsilon$$

After rearranging and conversion:

$$Z = 0 + 0W + 1(X - Y) - 2W(X - Y) + \epsilon$$

Since the parameter for W is zero, we can eliminate it from the equation and rearrange the equation:

$$Z = 0 + 1(1 - 2W)(X - Y) + \epsilon$$

Comparing this equation with Equation 1 shows they are the same. Thus, the parameters in this example would support an absolute difference model.

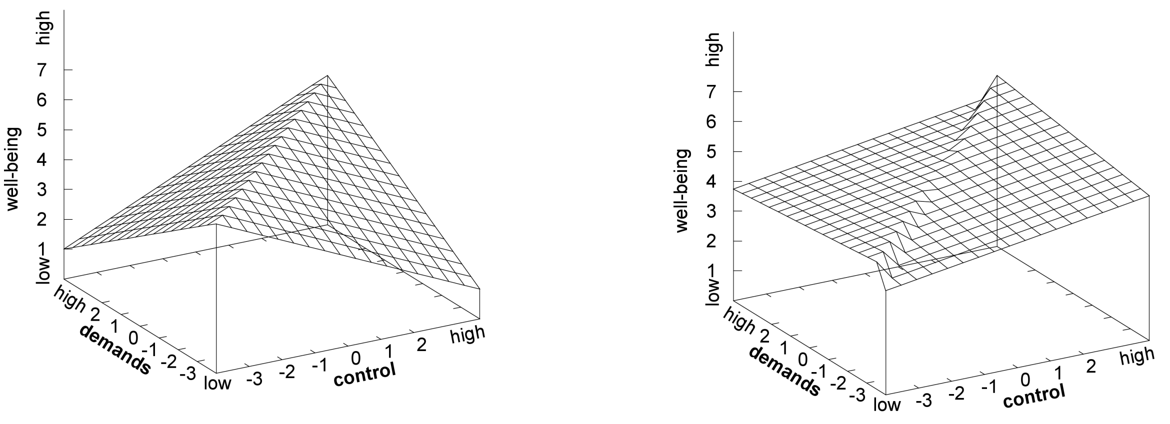
Any set of empirical coefficients β_1, β_2, β_3, β_4, and β_5 supports an absolute difference model if the following conditions hold: a) all coefficients to be significantly different from zero but not β_3, b) coefficients β_1 and β_2 to be of equal absolute magnitude but opposite sign, c) coefficients β_4 and β_5 to be of equal absolute magnitude but opposite sign, and d) β_4 to be twice the negative of β_1.

Finally, Equation 3 can be slightly adapted by introducing a random intercept ξ_j per subject to account for multiple measurements per subject:

$$Z_{i,j} = \beta_0 + \xi_j + \beta_1 X_{i,j} + \beta_2 Y_{i,j} + \beta_3 W_{i,j} + \beta_4 W_{i,j} X_{i,j} + \beta_5 W_{i,j} Y_{i,j} + \epsilon_{i,j} \tag{4}$$

with measurements i nested in subjects j, X=control, Y=demands, Z=well-being, and W=0 if control exceeded demands, and W=1 if demands exceeded control. In thirty-nine measurements patients reported equal values of perceived demands and control. These ties were corrected by pseudo-randomly setting Wij to 0 or 1, and all predictors were centered on their shared mean (**Edwards**, 1994). Linear contrasts were used to test our hypothesis.

Figure 1: Illustration of the hypothesized (Panel a) and empirical (Panel b) relationship between well-being, perceived control and perceived demands.



(a) hypothesized (b) empirical

Note. Panel a depicts the hypothesized relation between perceived control, perceived demands and well-being. Well-being is hypothesized to be highest, if perceived control and perceived demands are in balance. Panel b depicts the empirical relationship between these variables. If perceived control exceeds perceived demands, both, control and demands are associated with increased well-being . However, if perceived demands exceed perceived control increasing demands are associated with reduced well-being, while the positive association of perceived control with well-being remains unchanged.

2 RESULTS

Applying the model described in Equation 4 to our data indicated a significant fit for the whole model (AIC 288.35, BIC 315.53, $\chi^2 = 91.26, DF = 5, p < .001$). Provided that perceived control exceeded perceived demands, both, control and demand were associated with increased well-being ($b_1 = 0.18, SE = 0.03, p < .001$, $b_2 = 0.09, SE = 0.02, p < .001$). However, if demands exceeded perceived control increasing demands were associated with reduced well-being ($b_5 = -0.14, SE = 0.05, p < .01$), while the positive association of perceived control with well-being remained unchanged ($b_4 = -0.004, SE =$

$0.06, p > .93$). The effect of W, i.e. the point when demands begin to exceed control (see Equation 1) was not significantly different from zero ($b_3 = 0.6, SE = 0.10, p > .55$).

The first constraint required all coefficients but b_3 to be significant. Instead, only coefficients b_1, b_2 and b_5 were significant, while coefficient b_4 was not significant.

Formal testing of the model's other constraints showed that b_1 was not of equal magnitude but opposite sign as b_2, ($t(5) = 4.30, p < .01$), and b_4 was not twice the negative of b_1, ($t(5) = 3.02, p < .05$). However, coefficient b_4 was of equal magnitude but opposite sign as $b_5, t(5) = 1.26, p > .13$). Since all constraints have to be fulfilled simultaneously the pattern of coefficients did not support the idea of a necessary balance between situational demands and perceived control for optimal well-being.

REFERENCES

Brambor, T., Clark, W. R., and Golder, M. (2006), Understanding interaction models: Improving empirical analyses, *Political Analysis*, 14, 63–82

Cohen, J. (1978), Partialed products are interactions: Partialed powers are curve components, *Psychological Bulletin*, 85, 4, 858–866

Edwards, J. R. (1994), The study of congruence in organizational behavior research: Critique and a proposed alternative, *Organizational Behavior and Human Decision Processes*, 58, 51–100

Edwards, J. R. (2001), Ten difference score myths, *Organizational Research Methods*, 4, 265–287

Part III

GENERAL DISCUSSION

4

GENERAL DISCUSSION

The following questions formed the basis for this dissertation (see chapter 3):

1. Can we overcome the diagnostic gap in patients with disorders of consciousness?
2. Is it possible to identify psychophysiological correlates of QoL?
3. How do chronic diseases affect instantaneous QoL?

In the following sections, results of the studies performed to answer these questions are discussed and suggestions for future work are made.

4.1 CLOSING THE DIAGNOSTIC GAP IN PATIENTS WITH DISORDERS OF CONSCIOUSNESS?

In Real et al. (2015) a reliable (Real, Kotchoubey, & Kübler, 2014) ERP quantification method was used to evaluate the performance of a short auditory two-tone oddball paradigm for detecting evidence of command following and, hence, consciousness, in severely motor impaired patients with disorders of consciousness. Results suggest that the paradigm could differentiate healthy participants from patients, but no difference between VS and MCS patients was found. Further, prevalence of the late P300 ERP was low even in MCS patients, although these patients show –at the behavioural level– evidence for conscious processing.

It, thus, appears that paradigms, which work successfully in healthy participants, cannot be easily transferred to DOC patients. Part of this difficulty may lie in the fact that much research on paradigms similar to the one used in Real et al. (2015) was performed using group statistics on data obtained from healthy subjects, and these results do not necessarily hold true for the single subject. For example, although the P300 is robustly associated with conscious processing at the group level, there is strong evidence for a less than perfect reliability even in healthy subjects, with estimates ranging from $r_{tt} = .50$ to $r_{tt} = .80$ (c.f. Polich, 1998) and evidence for significant yet unexplained heterogeneity (Segalowitz & Barnes, 1993). Thus, one could argue that using a single potential (P300) is not sufficient to differentiate between VS and MCS patients, and that analyses, which include more data features might be more effective. However, this does not seem to be the case:

Lulé et al. (2013) used an auditory oddball paradigm in which participants were asked several yes/no questions while they listened to a stream of randomised words (yes, no, stop, go) and had their EEG recorded. Their task was to indicate the correct answer to each question by counting the occurrence of the word (yes or no) which stood for the correct answer. Importantly, analysis was based on a stepwise linear discriminant analysis (SWLDA) classifier (Krusienski, Sellers, McFarland, Vaughan, & Wolpaw, 2008), which makes no a priori assumptions on the discriminant features. Despite this potential advantage results from offline analyses show that a significant number of correct answers was found in only 14 of 16 healthy participants (88%), in one of two LIS patients (50%), in one of thirteen MCS patients (8%), and in no VS patient (of three). Similar evidence comes from a (co-authored) study by Pokorny et al. (2013). This study was based on the observation that severely motor impaired patients are not only confronted with a diagnostic gap, but also with an output gap, which is characterised by the absence of reliable and easy-to-use communication technologies (see section 2.5). To overcome this gap, the performance of a simple-to-use auditory single-switch brain-computer interface (ssBCI) was evaluated in healthy participants and MCS patients. In this study, evidence of command following could be detected in a maximum of eight of ten healthy participants (80%) but not in a single MCS patient (of 12)[1]. Whereas these studies focused on EEG recordings during auditory paradigms, a similar pattern can be found with motor-imagery based paradigms in fMRI. For example, in the already mentioned extensive study by Monti et al. (2010) willful modulation of brain activity could be detected in only one of 31 (3%) MCS patients. These findings –although not exhaustive– suggest that the problem of less-than-perfect reliability even in healthy participants and under (presumably) optimal recording conditions cannot be solved by simple measures, such as different recording methods, or using more electrodes. Indeed, a review of the literature on factors influencing BCI performance, Kübler (2011) suggests that at least four major categories of factors influence performance: *1)* individual differences, *2)* technical aspects, *3)* instructions/feedback, and *4)* applications/task complexity. Optimising each group of factors is likely to improve BCIs and, by transference, to impact on research on disorders of consciousness.

Thus, future developments might focus on *interindividual differences in physiology* (e.g. Kotchoubey et al., 2005) or *anatomy* (e.g. Irimia et al., 2013). It might even be possible to use information about *psychological*

1 Using a more lenient approach, designed to improve the signal-to-noise ratio, a P300 was detected in one MCS patient (8%)

factors. For example, instead of using stimuli such as (abstract) words or tones, future paradigms might use more salient stimuli such as names which hold a special relevance to the subject (e.g. Qin et al., 2008) or even different tastes (e.g. sweet vs. sour).

Similarly, *advances in technical aspects*, such as improved sensors and recording caps or signal processing methods might help to alleviate some of the problems associated with EEG recording from DOC patients (c.f. Real, Kotchoubey, & Kübler, 2014).

Special attention should also be given to the stimulus *modality*, as e.g. the visual domain is often markedly impaired in patients with severe DOCs. A study by Kaufmann, Holz, and Kübler (2013) is illustrative. These authors used a collection of several paradigms targeting different modalities (visual, auditory, tactile) and found that a LIS patient who did not show reliable responses in the visual and auditory modalities, responded, nevertheless, with a clear P300 in the tactile domain[2]. This result is all the more important, as in healthy subjects, the tactile domain is typically less reliable than other domains (Aloise et al., 2007; Riccio, Mattia, Simione, Olivetti, & Cincotti, 2012).

Finally, the *complexity of tasks* needs to be kept in mind. While it is true that, e.g. command following suggests preserved consciousness (Kotchoubey et al., 2013), successful performance requires the smooth operation of a variety of cognitive functions, e.g. language comprehension, attention, working memory, memory storage, and motivation (Polich, 2007; Kotchoubey & Lang, 2011). If only one of these faculties is impaired, the patient might not be able to complete the task (Kotchoubey et al., 2013). In addition, this interconnectedness might also introduce spurious associations between performances in different paradigms. For example, if, in a series of experiments all instructions were given verbally, performance across experiments might

2 Online communication was, nevertheless, not possible.

covary because they all depend on language comprehension. Thus, it is desirable to develop sets of paradigms, which are able to address unique, non-overlapping cognitive functions. (Kotchoubey et al., 2013)

Earlier (see section 2.5) it was noted that the ability to communicate is of increasing importance for the QoL of ALS patients with severe motor impairments. Unfortunately, many instruments designed to assess QoL rely on at least residual motor functions. For other patients, conscious but severely motor impaired, an assessment procedure which places minimal demands on motor functioning is highly desirable (see the following section 4.2, L. Johnson, 2013).

4.2 PSYCHOPHYSIOLOGICAL CORRELATES OF QOL

Cybernetic models of QoL suggest that individuals, e.g. patients with ALS, reporting low QoL are repeatedly comparing their experiences with their expectations but are unsuccessful in effectively reducing a discrepancy between the two. The hypothesis that this process should lead to increased accessibility of disease-related words was tested in patients with ALS using an N400 sentence paradigm. In this paradigm, sentences ended with a congruent or incongruent word, and this word could be related or unrelated to ALS. Results showed that the N400 ERP following incongruent vs. congruent sentence endings was reduced in patients reporting low QoL if the sentence ended in a disease related word, but not if the word was unrelated to the disease (Real, Herbert, et al., 2014). Further, this modulatory effect of QoL was absent in healthy age-matched controls. These findings support the idea of increased accessibility of disease-related words in patients with low QoL and, thus, the operation of the proposed feedback-loop.

It may be tempting to assume that the extent of the discrepancy and the N400 reduction would be linearly related. However, findings on problem solving suggests that it might not be so simple. Generally, problem solving is hypothesized to proceed in a stepwise fashion, where large numbers of possible solutions are generated and their effectiveness in reducing the extent of a problem tested (D'Zurilla & Nezu, 2010). Assuming that not all of these solutions are equally effective, it follows that a large discrepancy between e.g. perceptions and expectations is likely to persist for some time, which should lead to frequent engagement of the feedback loop. If this was true, the mechanism identified in Real, Herbert, et al. (2014) might not distinguish between dealing with a single large or many small discrepancies. This prediction integrates with findings that the negative effect of many small "daily hassles" on QoL is comparable to more severe life events (Kanner, Coyne, Schaefer, & Lazarus, 1981).

reliability and validity The work in Real, Herbert, et al. (2014) provided further evidence that QoL is an inherently psychological phenomenon, which shows no simple relation to objective factors. For example, QoL did not differ between healthy participants and patients with ALS, and disease severity (functional status) did not modulate the N400 following disease related or disease unrelated words. However, given the continued questioning of the validity of self-reports of QoL (see section 2.3), one might wonder, whether the N400 paradigm might be more "objective" than other methods. Several processes such as social desirability (c.f. Schwarz & Strack, 2003) affect the reporting of QoL statements. Given the rapid time course of ERPs, it might then be argued that willful manipulation of ERPs is not possible. While this is true in the strict sense, manipulation of ERPs is possible by changing one's psychological processes, e.g.

by focusing attention. For example, Vliet, Mühl, Reuderink, and Poel (2010) showed that the N400 can be wilfully manipulated by actively thinking of an object, thereby increasing its accessibility which leads to a reduced N400 amplitude. Consequently, these authors proposed the N400 as a potential control signal for BCI applications.

However, it seems implausible that the naïve participants in the study by Real, Herbert, et al. (2014) actively sought to manipulate their ERPs following disease related words, as this would have required detailed knowledge of the paradigm and our hypotheses. In addition, the words and sentences used were carefully matched on e.g. valence, to ensure that disease-related and unrelated words did not differ in salience. Finally, any attempt of explaining these findings in terms of wilful manipulation would also have to provide a mechanism why the effect of reduced N400 amplitudes following disease-related words was specific to patients with ALS reporting low QoL.

More generally, it is important to analyse precisely what is meant by terms such as "reliability" or "objective" with regard to QoL (Larsen & Fredickson, 2003). Often, reliability is understood to mean "high retest-correlation", i.e. the correlation between two measurements separated in time. However, it should be noted that this approach assumes the measured process to be temporarily stable. If the process changes over time, retest-correlations cannot adequately inform about the instrument's reliability. To alleviate this difficulty Larsen and Fredickson (2003) suggested three alternatives:

1) If retest reliability cannot be used, e.g. because the measured process is assumed to be varying over time, estimates of internal consistency may be used. *2)* If, however, multiple items are not feasible, one may remind oneself that reliability is just an estimate of the "upper bound on validity correlations" (Larsen & Fredickson, 2003, p. 43). Thus, reliability may also be estimated via one of the multiple measures of validity, e.g. by using different instruments designed to measure the same underlying construct (construct validity). *3)* The strongest evidence for validity, however, is found when psychological and measurement theory can be combined to derive highly specific predictions about a phenomenon.

Especially with regard to the last aspect, it may then be concluded that the approach used by Real, Herbert, et al. (2014) is reliable and valid, even if no statistical coefficient can be reported.

OTHER PSYCHOPHYSIOLOGICAL CORRELATES OF QOL Real, Herbert, et al. (2014) are not the only to relate psychophysiological signals to QoL measures. For example, Urry et al. (2004) found a significant association between greater-left-than-right frontal activation in the α band of the EEG and well-being, and Geisler, Vennewald, Kubiak, and Weber (2010) report a mediated effect of heart rate variability (Thayer & Lane, 2000) on well-being via executive emotion regulation. Despite differences in methodology, these approaches share the aim of relating interindividual differences in physiology to differences in executive functions, which are hypothesized to influence the choice and success of emotion regulation strategies (Zelazo & Cunningham, 2007). With regard to the levels of subjective well-being model (see Figure 2), these studies are, thus, positioned at a more fundamental level than Real, Herbert, et al. (2014). It may then be interesting to examine the relation between high-level cybernetic models of QoL and inter- and intra-individual differences in physiology and executive functioning.

The study by Real, Herbert, et al. (2014) rested on the hypothesis that the progressive loss of motor functions in ALS requires constant adaptation and that patients might differ in how successfully they cope with the disease. Within this model, self-regulation, i.e.

"attempts to change the self in order to fit the world." (Baumeister, Schmeichel, & Vohs, 2007, p. 6) appears to be the most important executive function, as patients have to constantly decide which goals to give up and which to pursue (Wrosch, Scheier, Carver, & Schulz, 2003). Consequently, a high capacity for self-regulation should make this process easier and facilitate adaptation to the progression of ALS. Within the cybernetic model, patients high in self-regulatory capacity may then be expected to cycle the loop less frequently, which should lead to a reduced modulation of QoL on N400 amplitudes.

This prediction shares some similarities with research on physiological correlates on depression and rumination. Here, rumination is seen as a pattern of repetitive negative intrusions (c.f. Siegle & Thayer, 2003), whose presence has been associated with decreased prefrontal activity, but increased activity in the amygdala, hippocampus and anterior cingulate cortex. Given the similarities between models of rumination and cybernetic models of QoL (Carver, 1996) it may then be that the same processes found to be associated with rumination also influence the operation of the feedback loop, and hence QoL. However, it should be noted that this association is somewhat speculative, as the specificity of disturbed physiological processes is unclear (c.f. Siegle & Thayer, 2003). For example, although rumination is primarily thought of being a cognitive phenomenon (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008), similarly disrupted physiological processes have also been found in relation to phenomena such as anxiety (Siegle & Thayer, 2003) and even in animal models of depression (e.g. Zangen, Overstreet, & Yadid, 1999).

4.3 how do chronic diseases affect instantaneous qol?

Research on QoL in patients with ALS often requires participants to generate aggregate statements about their experiences (e.g. Hammer et al., 2008; S. R. Cohen et al., 1995), and it is unclear how these aggregates relate to well-being as it fluctuates from moment to moment throughout the day (c.f. Larson & Csikszentmihalyi, 1983). Flow theory places a strong focus on momentary experiences, suggesting that well-being is highest, if, in any given situation, perceived demands and perceived control are in balance. However, results from Real, Dickhaus, et al. (2014) only partly supported these hypotheses. In line with previous findings, perceived *control* was positively related to well-being, regardless of the level of perceived demands. In addition, however, it was also found that perceived *demands* were associated with well-being, as long as they were perceived as controllable.

The theory further suggests that well-being should be highest, if thoughts are directed towards momentary experiences, but not towards the future or past. Again, support (Real, Dickhaus, et al., 2014) was only partial. Reminiscing was negatively associated with well-being and mediation analysis suggested that this negative association was mediated via increased rumination. However, thoughts directed towards the future were only marginally associated with well-being and no evidence for a role of rumination was found. While some patients may find solace in remembering the good times they have had (Fanos, Gelinas, Foster, Postone, & Miller, 2008), reminiscing may also introduce the risk of being reminded of unattainable goals, thus, in turn, increasing the risk of reduced well-being. Finally, although thinking about the future was negatively related to well-being, no support for rumination mediating this effect was found. It may thus be speculated that, even in patients with a progressive and terminal disease, thoughts about the future are not necessarily ruminative, possibly only in patients experiencing hopelessness (Plahuta et al., 2002).

CLINICAL IMPLICATIONS Although the prevalence of major depression is only marginally elevated in ALS (Rabkin, Wagner, & Bene, 2000; Rabkin et al., 2005), psychological treatment is virtually not existent yet much sought after (Kurt, Nijboer, Matuz, & Kubler, 2007).

Extending previous finding on the crucial role of perceived control (Nonnenmacher, Hammer, Lulé, Hautzinger, & Kübler, 2013; Foley, Timonen, & Hardiman, 2014), the findings in Real, Dickhaus, et al. (2014) offer the possibility that encouraging patients to focus on current experiences might also contribute to high well-being. Further, these findings also integrate well with recent work aimed at evaluating mindfulness-based interventions (Kocovski, Segal, & Battista, 2009) in patients with ALS (Pagnini et al., 2013; Pagnini, Phillips, & Langer, 2014). These treatments try to help the patient focus on current experiences and may, thus, help to reduce ruminative thoughts, which might otherwise lead to reduced well-being or even depression (Bishop et al., 2004). The findings by Real, Dickhaus, et al. (2014) provide further evidence for these promising approaches by highlighting the importance of the temporal direction of thought and the importance of perceived demands and control for the well-being of patients with ALS.

Moreover, this line of research might also benefit from the finding detailed in Real, Herbert, et al. (2014). While many questionnaires (Nolen-Hoeksema & Morrow, 1991; Trapnell & Campbell, 1999; Treynor, Gonzalez, & Nolen-Hoeksema, 2003) and models (c.f. Smith & Alloy, 2009) of rumination exist, they all agree that rumination involves repeated exposure to an object of thought. In line with the theory put forward in Real, Herbert, et al. (2014) one might then expect ruminators to show preferential access to these thought objects, which should be reflected in a decreased N400. Correspondingly, interventions which effectively block ruminations, either by mindfulness-based approaches (see above), or, e.g. behavioral activation (c.f. Dimidjian, Barrera, Martell, Muñoz, & Lewinsohn, 2011), should lead to increasing N400 responses.

further implications To the best of my knowledge, Real, Dickhaus, et al. (2014) were the first to apply the experience-sampling method in patients with ALS. Previously, the methodology has been applied in patients with other severe and chronic diseases, e.g. with cancer, chronic pain, cardiovascular diseases, or in patients requiring hemodialysis (c.f. Smyth & Stone, 2003), testifying to the wide applicability of the method (c.f. Christensen, Barrett, Bliss-Moreau, Lebo, & Kaschub, 2003). However, it should be noted that the method might place high demands on patients with progressing and severe motor impairments. Thus, the tools used in such studies should be designed with maximum user-friendliness and usability in mind. Thus, future studies might want to evaluate the use of smart phones for ESM studies. They combine the potential for sophisticated online data analysis, immediate relay of data to the investigators, with unobtrusiveness and wide availability (e.g. Runyan et al., 2013).

Health monitoring While the experience sampling method was primarily developed to test the predictions of flow theory, it can easily be adapted to general patient monitoring purposes. For example, it might be useful to track patients' experiences in relation to quality of care, or interpersonal relationships, but also to monitor disease and medication related aspects, e.g. tiredness, sialorrhea, or spasticity (R. G. Miller et al., 1999, 2009). Further, recent advances in biosensor design have made it possible to provide smartphones with sensors for ECG, blood oxygenation level, blood glucose level, or body temperature (e.g. ADITECH, 2014). It should, thus, be possible to integrate physiological measures with the patient's self-report to provide a more comprehensive picture of the patient's medical and psychological status.

Evolution of coping Such a technology would also offer the possibility of densely tracking the evolution of coping with ALS over prolonged periods. For example, it is known that caregivers often underestimate the quality of life of ALS patients (Kübler et al., 2005; Lulé et al., 2009), and maybe this tendency is accompanied by a trend towards overprotection. The negative association of overprotection with well-being in patients with chronic diseases (c.f. Berg & Upchurch, 2007) could thus be explained via caregivers shielding the patient from potentially demanding activities, which, according to the results of Real, Dickhaus, et al. (2014), could actually improve the patient's well-being.

Reducing caregiver burden Finally, the method could also benefit caregivers of patients. Caring for patients with chronic severe diseases places a substantive burden on (family) caregivers (Emanuel, 2000; Rabkin et al., 2000; Chio, Gauthier, Calvo, Ghiglione, & Mutani, 2005), and the fear of being a burden is related to the wish for a hastened death in patients with ALS (Ganzini et al., 2002). Existing models found caregiver burden to be associated with essentially unchangeable factors, such older age, low income, poor physical function, and incontinence (Emanuel, 2000). It appears that the experience sampling methodology could extend these models by providing important information into the dynamics of caregiver well-being across time and tasks. It should then be possible to develop targeted interventions to help caregivers in their most challenging tasks.

5

CONCLUSION AND OUTLOOK

This work aimed at providing insights into the dynamics of living with severe motor impairments. Results replicated previous findings on the importance of perceived control for well-being. However, they further suggest that perceived demands can also contribute to well-being, as long as demands are perceived as controllable (Real, Dickhaus, et al., 2014). Results from Real, Herbert, et al. (2014) identified a reduced N400 amplitude following incongruent vs. congruent disease related words as a psychophysiological correlate of quality of life in patients with ALS, supporting cybernetic models of quality of life and well-being (Carver & Scheier, 1990).

Although ALS is a very severe disease, communication is typically possible. However, other condition exists in which patients with very severe motor impairments have lost the ability to communicate, and it may even be unclear, whether some of these patients are still conscious. Results from Real et al. (2015), however, show that a short two-tone auditory oddball paradigm could not differentiate behaviorally unresponsive VS from behaviorally responsive MCS patients. Although information processing in DOC is a field of active research, it, thus, appears premature to leap from experimental findings in a select group of patients to its introduction into routine clinical practice. Further, the failure to detect evidence of conscious processing, let alone to establish reliable communication with behaviourally non-responsive patients, is not only a problem of basic research, but has real and direct consequences for the affected patients. Bearing in mind the dangers of analogies, some insights on how life would be for these patients may be drawn from studies in patients with ALS. While the heightened dependency on others offers the possibility for close personal relations (e.g. Young & McNicoll, 1998), the corresponding lack of autonomy is much regretted (e.g. the patient in the study by Kaufmann et al. (2013, p.9) indicated her present condition as "the worst time in her life" citing the strong dependency on others). Thus, it is encouraging to note that further efforts are devoted to this issue. For example, the EU Joint Program - Neurodegenerative Disease Program (JPND) "NEEDS in ALS" (Network for determining existential decisions in Amyotrophic Lateral Sclerosis) aims at using advanced neuroscientific methods to determine quality of life in unresponsive patients. Although this program targets primarily patients with ALS, investigating QoL of very late-stage ALS patients promises to provide important information, which may also be of use for patients with disorders of consciousness.

Part IV

APPENDIX

REFERENCES

Abramovich, F., & Benjamini, Y. (1995). Thresholding of wavelet coefficients as multiple hypotheses testing procedure. In P. Bickel et al. (Eds.), *Lecture notes in statistics* (pp. 5–14). New York, NY: Springer New York. doi: 10.1007/978-1-4612-2544-7-1

Acunzo, D. J., MacKenzie, G., & van Rossum, M. C. (2012). Systematic biases in early erp and erf components as a result of high-pass filtering. *Journal of neuroscience methods*, *209*(1), 212–218. doi: 10.1016/j.jneumeth.2012.06.011

ADITECH. (2014). *Lifewatch v: Smartphone android con sensori medicali e app.* Retrieved 06.10.2014, from http://www.aditechsrl.com/healthcare/mobile-care/lifewatch

Aiken, L. S., West, S. G., & Reono, R. R. (1993). *Multiple regression: Testing and interpreting interactions*. London: SAGE.

Albrecht, G. L., & Devlieger, P. J. (1999). The disability paradox: high quality of life against all odds. *Social Science & Medicine*, *48*(8), 977–988. doi: 10.1016/S0277-9536(98)00411-0

Allen, M., Badecker, W., & Osterhout, L. (2003). Morphological analysis in sentence processing: An erp study. *Language and Cognitive Processes*, *18*(4), 405–430. doi: 10.1080/01690960244000054

Alloy, L. B., Abramson, L. Y., & Viscusi, D. (1981). Induced mood and the illusion of control. *Journal of Personality and Social Psychology*, *41*(6), 1129–1140. doi: 10.1037/0022-3514.41.6.1129

Aloise, F., Lasorsaa, I., Schettini, F., Brouwer, A. M., Mattiaa, D., Babilonia, F., . . . Cincotti, F. (2007). Multimodal stimulation for a p300-based bci. *International Journal of Bioelectromagnetism*, *9*(3), 128–130.

Andersen, P. M., Borasio, G. D., Dengler, R., Hardiman, O., Kollewe, K., Leigh, P. N., . . . Tomik, B. (2005). Efns task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives. *European Journal of Neurology*, *12*(12), 921–938. doi: 10.1111/j.1468-1331.2005.01351.x

Andrykowski, M. A., & Hunt, J. W. (1993). Positive psychosocial adjustment in potential bone marrow transplant recipients: Cancer as a psychosocial transition. *Psycho-Oncology*, *2*(4), 261–276. doi: 10.1002/pon.2960020406

Argyle, M. (2003). Causes and correlates of happiness. In D. Kahneman, E. Diener, & N. Schwarz (Eds.), *Well-being* (pp. 354–373). New York: Russell Sage Foundation.

Bach, J. R., & Tilton, M. C. (1994). Life satisfaction and well-being measures in ventilator assisted individuals with traumatic tetraplegia. *Archives of Physical Medicine and Rehabilitation*, *75*(6), 626–632.

Bakas, T., McLennon, S. M., Carpenter, J. S., Buelow, J. M., Otte, J. L., Hanna, K. M., ... Welch, J. L. (2012). Systematic review of health-related quality of life models. *Health and Quality of Life Outcomes*, *10*, 134. doi: 10.1186/1477-7525-10-134

Baumeister, R. F., Schmeichel, B. J., & Vohs, K. D. (2007). Self-regulation and the executive function: The self as controlling agent. In A. W. Kruglanski & E. T. Higgins (Eds.), *Social psychology* (pp. 516–540). New York: Guilford Press.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Bdi-ii, beck depression inventory: Manual* (2nd ed.). San Antonio, TX: Psychological Corporation.

Belsley, D. A., Kuh, E., & Welsch, R. E. (2005). *Regression diagnostics: Identifying influential data and sources of collinearity*. New York: Wiley. doi: 10.1002/0471725153

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, *57*(1), 289–300. doi: 10.2307/2346101

Benjamini, Y., Krieger, A. M., & Yekutieli, D. (2006). Adaptive linear step-up procedures that control the false discovery rate. *Biometrika*, *93*(3), 491–507. doi: 10.1093/biomet/93.3.491

Benjamini, Y., & Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *The Annals of Statistics*, *29*(4), 1165–1188. doi: 10.2307/2674075

Berg, C. A., & Upchurch, R. (2007). A developmental-contextual model of couples coping with chronic illness across the adult life span. *Psychological Bulletin*, *133*(6), 920–954. doi: 10.1037/0033-2909.133.6.920

Bernat, J. L. (2006). Chronic disorders of consciousness. *Lancet*, *367*(9517), 1181–1192. doi: 10.1016/S0140-6736(06)68508-5

Birbaumer, N., Ghanayim, N., Hinterberger, T., Iversen, I., Kotchoubey, B., Kübler, A., ... Flor, H. (1999). A spelling device for the paralysed. *Nature*, *398*(6725), 297–298. doi: 10.1038/18581

Birbaumer, N., Kubler, A., Ghanayim, N., Hinterberger, T., Perelmouter, J., Kaiser, J., ... Flor, H. (2000). The thought translation device (ttd) for completely paralyzed patients. *IEEE Transactions on Rehabilitation Engineering*, *8*(2), 190–193. doi: 10.1109/86.847812

Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., ... Devins, G. (2004). Mindfulness: A proposed operational definition. *Clinical Psychology: Science and Practice*, *11*(3), 230–241. doi: 10.1093/clipsy.bph077

Blair, R. C., & Karniski, W. (1993). An alternative method for significance testing of waveform difference potentials. *Psychophysiol-*

ogy, *30*(5), 518–524. doi: 10.1111/j.1469-8986.1993.tb02075.x

Bolte, A., Goschke, T., & Kuhl, J. (2003). Emotion and intuition: Effects of positive and negative mood on implicit judgments of semantic coherence. *Psychological Science*, *14*(5), 416–421. doi: 10.1111/1467-9280.01456

Bostanov, V., & Kotchoubey, B. (2006). The t-cwt: a new erp detection and quantification method based on the continuous wavelet transform and student's t-statistics. *Clinical Neurophysiology*, *117*(12), 2627–2644. doi: 10.1016/j.clinph.2006.08.012

Bourke, S. C., & Gibson, G. J. (2004). Non-invasive ventilation in als: current practice and future role. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders*, *5*(2), 67–71. doi: 10.1080/14660820410020330

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: The self-assessment manikin and the semantic differential. *Journal of Behavior Therapy and Experimental Psychiatry*, *25*(1), 49–59. doi: 10.1016/0005-7916(94)90063-9

Brandtstädter, J., & Renner, G. (1990). Tenacious goal pursuit and flexible goal adjustment: Explication and age-related analysis of assimilative and accommodative strategies of coping. *Psychology and Aging*, *5*(1), 58–67. doi: 10.1037/0882-7974.5.1.58

Breetvelt, I. S., & Van Dam, F S. (1991). Underreporting by cancer patients: the case of response-shift. *Social science & medicine (1982)*, *32*(9), 981–987. doi: 10.1016/0277-9536(91)90156-7

Brooks, B. R., Miller, R. G., Swash, M., & Munsat, T. L. (2000). El escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders*, *1*, 293–299. doi: 10.1080/146608200300079536

Bruno, M.-A., Gosseries, O., Vanhaudenhuyse, A., Chatelle, C., & Laureys, S. (2010). État végétatif et état de conscience minimale: Un devenir pire que la mort ? In L. Puybasset (Ed.), *Enjeux éthiques en réanimation* (pp. 119–127). Springer Paris. doi: 10.1007/978-2-287-99072-4{\textunderscore}13

Bruno, M. A., Ledoux, D., Vanhaudenhuyse, A., Gosseries, O., Thibaut, A., & Laureys, S. (2012). Prognosis of patients with altered state of consciousness. In C. Schnakers & S. Laureys (Eds.), *Coma and disorders of consciousness* (pp. 11–23). London: Springer.

Bruno, M.-A., Majerus, S., Boly, M., Vanhaudenhuyse, A., Schnakers, C., Gosseries, O., ... Laureys, S. (2012). Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients. *Journal of Neurology*, *259*(6), 1087–1098. doi: 10.1007/s00415-011-6303-7

Bundesregierung. (2014). *Lebensqualität in ländlichen räumen und integrative stadtpolitik fördern.* Retrieved 24.04.2014, from `http://www.bundesregierung.de/Content/DE/_Anlagen/Demografie/4-lebensqualitaet.pdf?__blob=publicationFile&v=2`

Byrne, S., Walsh, C., Lynch, C., Bede, P., Elamin, M., Kenna, K., ... Hardiman, O. (2011). Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *82*(6), 623–627. doi: 10.1136/jnnp.2010.224501

Calman, K. C. (1984). Quality of life in cancer patients–a hypothesis. *Journal of medical ethics*, *10*(3), 124–127. doi: 10.1136/jme.10.3.124

Cameron, L. D., & Leventhal, H. (Eds.). (2002). *The self-regulation of health and illness behaviour*. London: Routledge.

Camfield, L., & Skevington, S. M. (2008). On subjective well-being and quality of life. *Journal of Health Psychology*, *13*(6), 764–775. doi: 10.1177/1359105308093860

Campbell, A. (1981). *The sense of well-being in america: Recent patterns and trends*. New York: McGraw-Hill. Retrieved 29.04.2014, from `http://hdl.handle.net/2027/mdp.39015071885714`

Carver, C. S. (1996). Goal engagement and the human experience. In R. S. Wyer (Ed.), *Ruminative thoughts* (Vol. IX, pp. 49–59). Mahwah, N.J.: Lawrence Erlbaum.

Carver, C. S. (1997). You want to measure coping but your protocol's too long: consider the brief cope. *International Journal of Behavioral Medicine*, *4*(1), 92–100. doi: 10.1207/s15327558ijbm0401{\textunderscore}6

Carver, C. S. (2003). Pleasure as a sign you can attend to something else: Placing positive feelings within a general model of affect. *Cognition & Emotion*, *17*(2), 241–261. doi: 10.1080/02699930302294

Carver, C. S., & Scheier, M. F. (1990). Origins and functions of positive and negative affect: A control-process view. *Psychological Review*, *97*(1), 19–35. doi: 10.1037/0033-295X.97.1.19

Carver, C. S., & Scheier, M. F. (2000). Scaling back goals and recalibration of the affect system are processes in normal adaptive self-regulation: understanding 'response shift' phenomena. *Social Science & Medicine*, *50*, 1715–1722. doi: 10.1016/S0277-9536(99)00412-8

Carver, C. S., & Scheier, M. F. (2011). Self-regulation of action and affect. In K. D. Vohs & R. F. Baumeister (Eds.), *Handbook of self-regulation* (pp. 3–21). New York: Guilford Press.

Carver, C. S., Smith, R. G., Petronis, V. M., & Antoni, M. H. (2006). Quality of life among long-term survivors of breast cancer: different types of antecedents predict different classes of outcomes. *Psycho-Oncology*, *15*(9), 749–758. doi: 10.1002/pon.1006

Cedarbaum, J. M., Stambler, N., Malta, E., Fuller, C., Hilt, D., Thurmond, B., ... BDNF ALS Study Group (1999). The alsfrs-r: a revised als functional rating scale that incorporates assessments of respiratory function. *Journal of the Neurological Sciences*, *169*, 13–21.

Chio, A., Gauthier, A., Calvo, A., Ghiglione, P., & Mutani, R. (2005). Caregiver burden and patients' perception of being a burden in als. *Neurology*, *64*(10), 1780–1782. doi: 10.1212/01.WNL.0000162034.06268.37

Chiò, A., Gauthier, A., Montuschi, A., Calvo, A., Di Vito, N., & Mutani, R. (2004). A cross sectional study on determinants of quality of life in als. *Journal of Neurology, Neurosurgery & Psychiatry*, *75*, 1597–1601. doi: 10.1136/jnnp.2003.033100

Christensen, T., Barrett, L., Bliss-Moreau, E., Lebo, K., & Kaschub, C. (2003). A practical guide to experience-sampling procedures. *Journal of Happiness Studies*, *4*(1), 53–78. doi: 10.1023/A:1023609306024

Chronister, J., & Chan, F. (2007). Hierarchical coping: A conceptual framework for understanding coping within the context of chronic illness and disability. In E. Martz, H. Livneh, & B. A. Wright (Eds.), *Coping with chronic illness and disability* (pp. 49–71). Boston, MA: Springer.

Clarke, S., Hickey, A., O'Boyle, C., & Hardiman, O. (2001). Assessing individual quality of life in amyotrophic lateral sclerosis. *Quality of Life Research*, *10*(2), 149–158. doi: 10.1023/A:1016704906100

Cohen, J. (1983). The cost of dichotomization. *Applied Psychological Measurement*, 7(3), 249–253. doi: 10.1177/014662168300700301

Cohen, J. (1992). A power primer. *Psychological Bulletin*, *112*(1), 155–159. doi: 10.1037/0033-2909.112.1.155

Cohen, J., & Polich, J. (1997). On the number of trials needed for p300. *International journal of psychophysiology*, *25*(3), 249–255. doi: 10.1016/S0167-8760(96)00743-X

Cohen, S. R., Mount, B. M., Strobel, M. G., & Bui, F. (1995). The mcgill quality of life questionnaire: a measure of quality of life appropriate for people with advanced disease. a preliminary study of validity and acceptability. *Palliative Medicine*, *9*, 207–219. doi: 10.1177/026921639500900306

Coppola, R., Tabor, R., & Buchsbaum, M. S. (1978). Signal to noise ratio and response variability measurements in single trial evoked potentials. *Electroencephalography and clinical neurophysiology*, *44*(2), 214–222. doi: 10.1016/0013-4694(78)90267-5

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T. A., Fernández-Espejo, D., Pickard, J. D., ... Owen, A. M. (2011). Bedside detection of awareness in the vegetative state: a cohort study. *The Lancet*, *378*(9809), 2088–2094. doi: 10.1016/S0140-6736(11)61224-5

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T. A., Fernández-Espejo, D., Pickard, J. D., ... Owen, A. M. (2013). Reanalysis of "bedside detection of awareness in the vegetative state: a cohort study" – authors' reply. *The Lancet*, *381*(9863), 291–292. doi: 10.1016/S0140-6736(13)60126-9

Csikszentmihalyi, M. (1990). *Flow: The psychology of optimal experience*. New York: Harper & Row.

Csikszentmihalyi, M., & Larson, R. (1987). Validity and reliability of the experience-sampling method. *The Journal of Nervous and Mental Disease*, *175*(9), 526–536. doi: 10.1097/00005053-198709000-00004

DECODER. (2010). *Aims.* Retrieved 25.06.2014, from `http://www.decoder.i1.psychologie.uni-wuerzburg.de/images/aims.png` del Aguila, M. A., Longstreth, W. T., McGuire, V., Koepsell, T. D., & van Belle, G. (2003). Prognosis in amyotrophic lateral sclerosis: A population based study. *Neurology*, *60*, 813–819. doi: 10.1212/01.WNL.0000049472.47709.3B

Delorme, A., & Makeig, S. (2004). Eeglab: an open source toolbox for analysis of single-trial eeg dynamics including independent component analysis. *Journal of neuroscience methods*, *134*(1), 9–21. doi: 10.1016/j.jneumeth.2003.10.009

Diener, E. (1984). Subjective well-being. *Psychological Bulletin*, *95*(3), 542–547. doi: 10.1037/0033-2909.95.3.542

Dimidjian, S., Barrera, M., Martell, C., Muñoz, R. F., & Lewinsohn, P. M. (2011). The origins and current status of behavioral activation treatments for depression. *Annual Review of Clinical Psychology*, *7*(1), 1–38. doi: 10.1146/annurev-clinpsy-032210-104535

D'Zurilla, T. J., & Nezu, A. M. (2010). Problem-solving therapy. In K. S. Dobson (Ed.), *Handbook of cognitive-behavioral therapies* (pp. 197–225). New York: Guilford Press.

Edwards, J. R. (1994). The study of congruence in organizational behavior research: Critique and a proposed alternative. *Organizational Behavior and Human Decision Processes*, *58*, 51–100. doi: 10.1006/obhd.1994.1029

Edwards, J. R., & Cooper, C. L. (1990). The person-environment fit approach to stress: Recurring problems and some suggested solutions. *Journal of Organizational Behavior*, *11*(4), 293–307. doi: 10.1002/job.4030110405

Eisenberg, J. B. (2008). Schiavo on the cutting edge: Functional brain imaging and its impact on surrogate end-of-life decision-making. *Neuroethics*, *1*(2), 75–83. doi: 10.1007/s12152-007-9000-6

Emanuel, E. J. (2000). Understanding economic and other burdens of terminal illness: The experience of patients and their caregivers. *Annals of internal medicine*, *132*(6), 451. doi: 10.7326/0003-4819-132-6-200003210-00005

Fahrenberg, J. (1994). *Freiburger beschwerdenliste: Form fbl-g und revidierte form fbl-r*. Göttingen: Hogrefe.

Fanos, J. H., Gelinas, D. F., Foster, R. S., Postone, N., & Miller, R. G. (2008). Hope in palliative care: From narcissism to self-transcendence in amyotrophic lateral sclerosis. *Journal of Palliative Care*, *11*(3), 470–475. doi: 10.1089/jpm.2007.0098

Farwell, L. A., Martinerie, J. M., Bashore, T. R., Rapp, P. E., & Goddard, P. H. (1993). Optimal digital filters for long-latency components of the event-related brain potential. *Psychophysiology*, *30*(3), 306–315. doi: 10.1111/j.1469-8986.1993.tb03357.x

Fegg, M. J., Kögler, M., Brandstätter, M., Jox, R., Anneser, J., Haarmann-Doetkotte, S., … Borasio, G. D. (2010). Meaning in life in patients with amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders*, *11*(5), 469–474.

Foley, G., Timonen, V., & Hardiman, O. (2014). Exerting control and adapting to loss in amyotrophic lateral sclerosis. *Social Science & Medicine*, *101*, 113–119. doi: 10.1016/j.socscimed.2013.11.003

Folkman, S. (1984). Personal control and stress and coping processes: a theoretical analysis. *Journal of Personality and Social Psychology*, *46*(4), 839–852. doi: 10.1037/0022-3514.46.4.839

Fulford, D., Johnson, S. L., Llabre, M. M., & Carver, C. S. (2010). Pushing and coasting in dynamic goal pursuit: coasting is attenuated in bipolar disorder. *Psychological Science*, *21*(7), 1021–1027. doi: 10.1177/0956797610373372

Ganzini, L., & Block, S. (2002). Physician-assisted death–a last resort? *The New England Journal of Medicine*, *346*(21), 1663–1665. doi: 10.1056/NEJM200205233462113

Ganzini, L., Harvath, T. A., Jackson, A., Goy, E. R., Miller, L. L., & Delorit, M. A. (2002). Experiences of oregon nurses and social workers with hospice patients who requested assistance with suicide. *The New England Journal of Medicine*, *347*(8), 582–588. doi: 10.1056/NEJMsa020562

Geisler, F. C., Vennewald, N., Kubiak, T., & Weber, H. (2010). The impact of heart rate variability on subjective well-being is mediated by emotion regulation. *Personality and Individual Differences*, *49*(7), 723–728. doi: 10.1016/j.paid.2010.06.015

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., ... Zasler, N. D. (2002). The minimally conscious state: definition and diagnostic criteria. *Neurology*, *58*(3), 349–353. doi: 10.1212/WNL.58.3.34

Giacino, J. T., Schnakers, C., Rodriguez-Moreno, D., Kalmar, K., Schiff, N., & Hirsch, J. (2009). Behavioral assessment in patients with disorders of consciousness: gold standard or fool's gold? *Progress in Brain Research*, *177*, 33–48. doi: 10.1016/S0079-6123(09)17704-X

Goldfine, A. M., Bardin, J. C., Noirhomme, Q., Fins, J. J., Schiff, N. D., & Victor, J. D. (2013). Reanalysis of "bedside detection of awareness in the vegetative state: a cohort study". *The Lancet*, *381*(9863), 289–291. doi: 10.1016/S0140-6736(13)60125-7

Goutte, C., & Gaussier, E. (2005). A probabilistic interpretation of precision, recall and f-score, with implication for evaluation. In D. E. Losada & J. M. Fernández-Luna (Eds.), *Advances in information retrieval* (pp. 345–359). Berlin: Springer. doi: 10.1007/978-3-540-31865-1-25

Gratton, G., Coles, M. G. H., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and clinical neurophysiology*, *55*, 468–484. doi: 10.1016/0013-4694(83)

90135-9

Groenvold, M., Fayers, P. M., Sprangers, M. A., Bjorner, J. B., Klee, M. C., Aaronson, N. K., ... Mouridsen, H. T. (1999). Anxiety and depression in breast cancer patients at low risk of recurrence compared with the general population. *Journal of Clinical Epidemiology*, *52*(6), 523–530. doi: 10.1016/S0895-4356(99)00022-0

Groppe, D. M., Urbach, T. P., & Kutas, M. (2011). Mass univariate analysis of event-related brain potentials/fields i: A critical tutorial review. *Psychophysiology*, *48*(12), 1711–1725. doi: 10.1111/j.1469-8986.2011.01273.x

Guger, C., Sorger, B., Noirhomme, Q., Naci, L., Monti, M. M., Real, R. G. L., ... Kübler, A. (2013). Brain-computer interfaces for coma assessment and communication. In G. R. Naik & Y. Guo (Eds.), *Emerging theory and practice in neuroprosthetics* (pp. 181–215). Hershey, PA: IGIGLOBAL Press.

Hammer, E. M., Häcker, S., Hautzinger, M., Meyer, T. D., & Kübler, A. (2008). Validity of the als-depression-inventory (adi-12)— a new screening instrument for depressive disorders in patients with amyotrophic lateral sclerosis. *Journal of Affective Disorders*, *109*(1-2), 213–219. doi: 10.1016/j.jad.2007.11.012

Hanagasi, H. A., Gurvit, I. H., Ermutlu, N., Kaptanoglu, G., Karamursel, S., Idrisoglu, H. A., ... Demiralp, T. (2002). Cognitive impairment in amyotrophic lateral sclerosis: evidence from neuropsychological investigation and event-related potentials. *Cognitive Brain Research*, *14*(2), 234–244. doi: 10.1016/S0926-6410(02)00110-6

Hand, C. K., & Rouleau, G. A. (2002). Familial amyotrophic lateral sclerosis. *Muscle & Nerve*, *25*(2), 135–159. doi: 10.1002/mus.10001

Hautzinger, M., Keller, F., & Kühner, C. (2006). *Bdi-ii: Beck depressions inventar revision*. Frankfurt a. M.: Harcourt Test Services.

Herschbach, P. (2002). Das „zufriedenheitsparadox” in der lebensqualitätsforschung - wovon hängt unser wohlbefinden ab? -. *Psychotherapie · Psychosomatik · Medizinische Psychologie*, *52*(3/4), 141–150. doi: 10.1055/s-2002-24953

Holt, J. (2012). *Oh, joy: Review of 'happiness: A history,' by darrin m. mcmahon.* Retrieved 09.09.2014, from `http://www.nytimes.com/2006/02/12/books/review/12holt.html?pagewanted=all&_r=0`

Iglesias, C., & Torgerson, D. (2000). Does length of questionnaire matter? a randomised trial of response rates to a mailed questionnaire. *Journal of Health Services Research and Policy*, *5*(4), 219–221. doi: 10.1177/135581960000500406

Irimia, A., Goh, S.-Y. M., Torgerson, C. M., Stein, N. R., Chambers, M. C., Vespa, P. M., & Van Horn, John D. (2013). Electroencephalographic inverse localization of brain activity in acute traumatic brain injury as a guide to surgery, monitoring and treatment. *Clinical Neurology and Neurosurgery*, *115*(10), 2159–2165. doi: 10.1016/j.clineuro.2013.08.003

Isen, A. M., Daubman, K. A., & Nowicki, G. P. (1987). Positive affect facilitates creative problem solving. *Journal of Personality and Social Psychology*, *52*(6), 1122–1131. doi: 10.1037/0022-3514.52.6.1122

Isen, A. M., Johnson, M. M. S., Mertz, E., & Robinson, G. F. (1985). The influence of positive affect on the unusualness of word associations. *Journal of Personality and Social Psychology*, *48*, 1413–1426. doi: 10.1037/0022-3514.48.6.1413

Jennett, B., & Plum, F. (1972). Persistent vegetative state after brain damage. a syndrome in search of a name. *Lancet*, *1*(7753), 734–

737. doi: 10.1016/S0140-6736(72)90242-5

Johnson, B. W., & Hamm, J. P. (2000). High-density mapping in an n400 paradigm: evidence for bilateral temporal lobe generators. *Clinical Neurophysiology*, *111*, 532–545. doi: 10.1016/S1388-2457(99)00270-9

Johnson, L. (2013). Can they suffer? the ethical priority of quality of life research in disorders of consciousness. *Bioethica Forum*, *6*(4), 129–136.

Jong-Meyer, R. d., Parthe, T., & Projektgruppe. (2009). Einfluss von achtsamkeitsübung und dezentrierung auf rumination und spezifität autobiographischer erinnerungen. *Zeitschrift für Klinische Psychologie und Psychotherapie*, *38*(4), 240–249. doi: 10.1026/1616-3443.38.4.240

Kahneman, D., Diener, E., & Schwarz, N. (2003). Preface. In D. Kahneman, E. Diener, & N. Schwarz (Eds.), *Well-being* (pp. ix–xii). New York: Russell Sage Foundation.

Kalyakin, I., Gonzalez, N., Joutsensalo, J., Huttunen, T., Kaartinen, J., & Lyytinen, H. (2007). Optimal digital filtering versus difference waves on the mismatch negativity in an uninterrupted sound paradigm. *Developmental neuropsychology*, *31*(3), 429–452. doi: 10.1080/87565640701229607

Kanner, A. D., Coyne, J. C., Schaefer, C., & Lazarus, R. (1981). Comparison of two modes of stress measurement: Daily hassles and uplifts versus major life events. *Journal of Behavioral Medicine*, *4*(1), 1–39. doi: 10.1007/BF00844845

Kaub-Wittemer, D., Steinbüchel, N. v., Wasner, M., Laier-Groeneveld, G., & Borasio, G. D. (2003). Quality of life and psychosocial issues in ventilated patients with amyotrophic lateral sclerosis and their caregivers. *Journal of Pain and Symptom Management*, *26*(4), 890–896. doi: 10.1016/S0885-3924(03)00323-3

Kaufmann, T., Holz, E. M., & Kübler, A. (2013). Comparison of tactile, auditory, and visual modality for brain-computer interface use: a case study with a patient in the locked-in state. *Frontiers in Neuroscience*, *7*, 129. doi: 10.3389/fnins.2013.00129

Kenny, D. A., Bolger, N., & Korchmaros, J. D. (2003). Lower level mediation in multilevel models. *Psychological Methods*, *8*(2), 115–128. doi: 10.1037/1082-989X.8.2.115

Kesebir, P., & Diener, E. (2008). In pursuit of happiness: Empirical answers to philosophical questions. *Perspectives on Psychological Science*, *3*(2), 117–125. doi: 10.1111/j.1745-6916.2008.00069.x

Kiernan, M. C., Vucic, S., Cheah, B. C., Turner, M. R., Eisen, A., Hardiman, O., ... Zoing, M. C. (2011). Amyotrophic lateral sclerosis. *The Lancet*, *377*(9769), 942–955. doi: 10.1016/S0140-6736(10)61156-7

King, S. J., Duke, M. M., & O'Connor, B. A. (2009). Living with amyotrophic lateral sclerosis/motor neurone disease (als/mnd): decision-making about 'ongoing change and adaptation'. *Journal of Clinical Nursing*, *18*(5), 745–754. doi: 10.1111/j.1365-2702.2008.02671.x

Kocovski, N. L., Segal, Z. V., & Battista, S. R. (2009). Mindfulness and psychopathology: Problem formulation. In F. Didonna (Ed.), *Clinical handbook of mindfulness* (pp. 85–98). New York, NY: Springer New York.

Koole, S. L., van Dillen, L. F., & Sheppes, G. (2011). The self-regulation of emotion. In K. D. Vohs & R. F. Baumeister (Eds.), *Handbook of self-regulation* (pp. 22–40). New York: Guilford Press.

Kotchoubey, B., & Lang, S. (2011). Intuitive versus theory-based assessment of consciousness: the problem of low-level consciousness. *Clinical Neurophysiology*, *122*(3), 430–432. doi: 10.1016/j.clinph.2010.07.011

Kotchoubey, B., Lang, S., Bostanov, V., & Birbaumer, N. (2002). Is there a mind? electrophysiology of unconscious patients. *News in physiological sciences*, *17*, 38–42.

Kotchoubey, B., Lang, S., Mezger, G., Schmalohr, D., Schneck, M., Semmler, A., … Birbaumer, N. (2005). Information processing in severe disorders of consciousness: Vegetative state and minimally conscious state. *Clinical Neurophysiology*, *116*(10), 2441–2453. doi: 10.1016/j.clinph.2005.03.028

Kotchoubey, B., Veser, S., Real, R. G. L., Herbert, C., Lang, S., & Kübler, A. (2013). Towards a more precise neurophysiological assessment of cognitive functions in patients with disorders of consciousness. *Restorative neurology and neuroscience*, *31*(4), 473–485. doi: 10.3233/RNN-120307

Krusienski, D. J., Sellers, E. W., McFarland, D. J., Vaughan, T. M., & Wolpaw, J. R. (2008). Toward enhanced p300 speller performance. *Journal of neuroscience methods*, *167*(1), 15–21. doi: 10.1016/j.jneumeth.2007.07.017

Kübler, A. (2011). A model of bci control. In G. R. Müller-Putz, R. Scherer, M. Billinger, A. Kreilinger, V. Kaiser, & C. Neuper (Eds.), *Proceedings of the 5th international brain-computer interface* (pp. 100–103). Graz.

Kübler, A., & Kotchoubey, B. (2007). Brain–computer interfaces in the continuum of consciousness. *Current Opinion in Neurology*, *20*(6), 643–649. doi: 10.1097/WCO.0b013e3282f14782

Kübler, A., Winter, S., Ludolph, A. C., Hautzinger, M., & Birbaumer, N. (2005). Severity of depressive symptoms and quality of life in patients with amyotrophic lateral sclerosis. *Neurorehabilitation and Neural Repair*, *19*(3), 182–193. doi: 10.1177/1545968305276583

Kurian, K. M., Forbes, R. B., Colville, S., & Swingler, R. J. (2009).

Cause of death and clinical grading criteria in a cohort of amyotrophic lateral sclerosis cases undergoing autopsy from the scottish motor neurone disease register. *Journal of Neurology, Neurosurgery & Psychiatry*, *80*, 84–87. doi: 10.1136/jnnp.2008.149708

Kurt, A., Nijboer, F., Matuz, T., & Kubler, A. (2007). Depression and anxiety in individuals with amyotrophic lateral sclerosis: Epidemiology and management. *CNS Drugs*, *21*(4), 279–291. doi: 10.2165/00023210-200721040-00003

Kutas, M., & Federmeier, K. D. (2011). Thirty years and counting: Finding meaning in the n400 component of the event-related brain potential (erp). *Annual Review of Psychology*, *62*(1), 621–647. doi: 10.1146/annurev.psych.093008.131123

Kutas, M., & Hillyard, S. A. (1980). Reading senseless sentences: Brain potential reflect semantic incongruity. *Science*, *207*(4427), 203–205. doi: 10.1126/science.7350657

Kutas, M., & Hillyard, S. A. (1984). Brain potentials during reading reflect word expectancy and semantic association. *Nature*, *307*(5947), 161–163. doi: 10.1038/307161a0

Larsen, R. J., & Fredickson, B. L. (2003). Measurement issues in emotion research. In D. Kahneman, E. Diener, & N. Schwarz (Eds.), *Well-being* (pp. 40–60). New York: Russell Sage Foundation.

Larson, R., & Csikszentmihalyi, M. (1983). The experience sampling method. In H. T. Reis (Ed.), *Naturalistic approaches to studying social interaction* (Vol. 15, pp. 41–56). San Francisco: Jossey-Bass.

Lau, E. F., Phillips, C., & Poeppel, D. (2008). A cortical network for semantics: (de)constructing the n400. *Nature Reviews Neuroscience*, *9*, 920–933. doi: 10.1038/nrn2532

Laureys, S. (2007). Eyes open, brain shut. *Scientific American*, *296*(5), 84–89. doi: 10.1038/scientificamerican0507-84

Laureys, S., Giacino, J. T., Schiff, N. D., Schabus, M., & Owen, A. M. (2006). How should functional imaging of patients with disorders of consciousness contribute to their clinical rehabilitation needs? *Current Opinion in Neurology*, *19*(6), 520–527. doi: 10.1097/WCO.0b013e3280106ba9

Lazarus, R. S., & Folkman, S. (2008). *Stress, appraisal, and coping*. New York: Springer.

León-Carrión, J., Eeckhout, P. v., & Domínguez-Morales, M. d. R. (2002). The locked-in syndrome: a syndrome looking for a therapy. *Brain Injury*, *16*(7), 555–569. doi: 10.1080/02699050110119466

Logroscino, G., Traynor, B. J., Hardiman, O., Chiò, A., Couratier, P., Mitchell, J. D., ... Beghi, E. (2008). Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *Journal of Neurology, Neurosurgery & Psychiatry*, *79*, 6–11. doi: 10.1136/jnnp.2006.104828

Logroscino, G., Traynor, B. J., Hardiman, O., Chio, A., Mitchell, D., Swingler, R. J., ... Beghi, E. (2010). Incidence of amyotrophic lateral sclerosis in europe. *Journal of Neurology, Neurosurgery & Psychiatry*, *81*, 385–390. doi: 10.1136/jnnp.2009.183525

Lu, J., Marmarou, A., Choi, S., Maas, A., Murray, G., & Steyerberg, E. W. (2005). Mortality from traumatic brain injury. In W. S. Poon et al. (Eds.), *Acta neurochirurgica supplementum* (Vol. 95, pp. 281–285). Vienna: Springer. doi: 10.1007/3-211-32318-X{\textunderscore}58

Lulé, D., Häcker, S., Ludolph, A., Birbaumer, N., & Kübler, A. (2008). Depression and quality of life in patients with amyotrophic lateral sclerosis. *Deutsches Ärzteblatt International*, *105*(23), 397–403. doi: 10.3238/arztebl.2008.0397

Lulé, D., Kurt, A., Jürgens, R., Kassubek, J., Diekmann, V., Kraft, E.,

... Anders, S. (2005). Emotional responding in amyotrophic lateral sclerosis. *Journal of Neurology*, *252*, 1517–1524. doi: 10.1007/s00415-005-0907-8

Lulé, D., Noirhomme, Q., Kleih, S. C., Chatelle, C., Halder, S., Demertzi, A., ... Laureys, S. (2013). Probing command following in patients with disorders of consciousness using a brain–computer interface. *Clinical Neurophysiology*, *124*(1), 101–106. doi: 10.1016/j.clinph.2012.04.030

Lulé, D., Zickler, C., Häcker, S., Bruno, M. A., Demertzi, A., Pellas, F., ... Kübler, A. (2009). Life can be worth living in locked-in syndrome. *Progress in Brain Research*, *177*, 339–351. doi: 10.1016/S0079-6123(09)17723-3

MacKinnon, D. P., Lockwood, C. M., Hoffman, J. M., West, S. G., & Sheets, V. (2002). A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods*, *7*(1), 83–104. doi: 10.1037/1082-989X.7.1.83

Martin, L. L., & Tesser, A. (1996). Some ruminative thoughts. In R. S. Wyer (Ed.), *Ruminative thoughts* (Vol. IX, pp. 1–47). Mahwah, N.J.: Lawrence Erlbaum.

Matuz, T. (2008). *Betreuungsstrategien für schwerstgelähmte patienten: empirische ehtik und neurowissenschaftliche ansätze* (Unpublished doctoral dissertation). Ebehard-Karls-Universität, Tübingen.

Matuz, T., Birbaumer, N., Hautzinger, M., & Kübler, A. (2010). Coping with amyotrophic lateral sclerosis: an integrative view. *Journal of Neurology, Neurosurgery & Psychiatry*, *81*(8), 893–898. doi: 10.1136/jnnp.2009.201285

Maxwell, S. E., & Delaney, H. D. (1993). Bivariate median splits and spurious statistical significance. *Psychological Bulletin*, *113*(1), 181–190. doi: 10.1037/0033-2909.113.1.181

McDonald, E. R., Wiedenfeld, S. A., Carpenter, C. L., & Walter, R. A.

(1994). Survival in amyotrophic lateral sclerosis: The role of psychological factors. *Archives of Neurology*, *51*, 17–23. doi: 10.1001/archneur.1994.00540130027010

Meyer, T., Dullinger, J. S., Münch, C., Keil, J.-P., Hempel, E., Rosseau, S., . . . Linke, P. (2008). Elektive termination der beatmungstherapie bei der amyotrophen lateralsklerose. *Der Nervenarzt*, *79*(6), 684–690. doi: 10.1007/s00115-008-2439-9

Miller, G. A., Galanter, E., & Pribram, K. H. (1960). *Plans and the structure of behavior*. New York, NY: Holt Rinehart and Winston.

Miller, R. G., Jackson, C. E., Kasarskis, E. J., England, J. D., Forshew, D., Johnston, W., . . . Woolley, S. C. (2009). Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies: an evidence-based review. *Neurology*, *73*(15), 1218–1226. doi: 10.1212/WNL.0b013e3181bc0141

Miller, R. G., Mitchell, J. D., & Moore, D. H. (2012). Riluzole for amyotrophic lateral sclerosis (als)/motor neuron disease (mnd). *The Cochrane database of systematic reviews*, *3*, CD001447. doi: 10.1002/14651858.CD001447.pub3

Miller, R. G., Rosenberg, A. J., Gelinas, D., Mitsumoto, H., Newman, D., Sufit, R., . . . Oppenheimer, E. A. (1999). Practice parameter: The care of the patient with amyotrophioc lateral sclerosis (an evidence based review): Reports of the quality standards subcommittee of the american academy of neurology. *Neurology*, *52*, 1311-.

Mitchell, J. D., & Borasio, G. D. (2007). Amyotrophic lateral sclerosis. *Lancet*, *369*(9578), 2031–2041. doi: 10.1016/S0140-6736(07)60944-1

Montel, S., Albertini, L., & Spitz, E. (2012a). Coping strategies as related to medical and demographic data in amyotrophic lateral sclerosis. *Acta Neurologica Scandinavica*, *125*(2), 136–141. doi: 10.1111/j.1600-0404.2011.01513.x

Montel, S., Albertini, L., & Spitz, E. (2012b). Coping strategies in relation to quality of life in amyotrophic lateral sclerosis. *Muscle & Nerve*, *45*(1), 131–134. doi: 10.1002/mus.22270

Monti, M. M. (2012). Cognition in the vegetative state. *Annual Review of Clinical Psychology*, *8*(1), 431–454. doi: 10.1146/annurev-clinpsy-032511-143050

Monti, M. M., Vanhaudenhuyse, A., Coleman, M. R., Boly, M., Pickard, J. D., Tshibanda, L., ... Laureys, S. (2010). Willful modulation of brain activity in disorders of consciousness. *The New England Journal of Medicine*, *362*(7), 579–589. doi: 10.1056/NEJMoa0905370

Nijboer, F., Sellers, E. W., Mellinger, J., Jordan, M. A., Matuz, T., Furdea, A., ... Kubler, A. (2008). A p300-based brain-computer interface for people with amyotrophic lateral. *Clinical Neurophysiology*, *119*(8), 1909–1916. doi: 10.1016/j.clinph.2008.03.034

Nolen-Hoeksema, S. (1991). Responses to depression and their effects on the duration of depressive episodes. *Journal of Abnormal Psychology*, *100*(4), 569–582. doi: 10.1037/0021-843X.100.4.569

Nolen-Hoeksema, S., & Morrow, J. (1991). A prospective study of depression and posttraumatic stress symptoms after a natural disaster: the 1989 loma prieta earthquake. *Journal of Personality and Social Psychology*, *61*(1), 115–121.

Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking rumination. *Perspectives on Psychological Science*, *3*(5), 400–424. doi: 10.1111/j.1745-6924.2008.00088.x

Nonnenmacher, S., Hammer, E. M., Lulé, D., Hautzinger, M., & Kübler, A. (2013). Psychische störungen und individuelle lebensqualität bei der chronisch progredient-terminalen erkrankung amyotrophe lateralsklerose (als). *Zeitschrift für Klinische Psychologie und Psychotherapie*, *42*(1), 55–63. doi: 10.1026/1616-3443/a000186

O'Boyle, C. A., Browne, J., Hickey, A., McGee, H. M., & Joyce, C. R. B. (1993). *The schedule for the evaluation of individual quality of life (seiqol): a direct weighting procedure for quality of life domains (seiqol-dw)*. Dublin: Department of Psychology, Royal College of Surgeons in Ireland.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the edinburgh inventory. *Neuropsychologia*, *9*, 97–113. doi: 10.1016/0028-3932(71)90067-4

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard. (2006). Detecting awareness in the vegetative state. *Science*, *313*(5792), 1402. doi: 10.1126/science.1130197

Pagnini, F. (2013). Psychological wellbeing and quality of life in amyotrophic lateral sclerosis: a review. *International Journal of Psychology*, *48*(3), 194–205. doi: 10.1080/00207594.2012.691977

Pagnini, F., Di Credico, C., Gatto, R., Fabiani, V., Rossi, G., Lunetta, C., ... Amadei, G. (2013). Meditation training for people with amyotrophic lateral sclerosis and their caregivers. *Journal of Alternative and Complementary Medicine*, *0*, 1–4. doi: 10.1089/acm.2013.0268

Pagnini, F., Phillips, D., & Langer, E. (2014). A mindful approach with end-of-life thoughts. *Frontiers in Psychology*, *5*, 138. doi: 10.3389/fpsyg.2014.00138

Park, C. L., & Folkman, S. (1997). Meaning in the context of stress and coping. *Review of General Psychology*, *1*(2), 115–144. doi: 10.1037/1089-2680.1.2.115

Paulus, K. S., Magnano, I., Piras, M. R., Solinas, M. A., Solinas, G., Sau, G. F., & Aiello, I. (2002). Visual and auditory event-related potentials in sporadic amyotrophic lateral sclerosis. *Clinical Neurophysiology*, *113*(6), 853–861. doi: 10.1016/S1388-2457(02)00082-2

Pfurtscheller, G., & Lopes da Silva, F. (1999). Event-related eeg/meg synchronization and desynchronization: basic principles. *Clinical Neurophysiology*, *110*(11), 1842–1857. doi: 10.1016/S1388-2457(99)00141-8

Pinheiro, A. P., del Re, E., Nestor, P. G., McCarley, R. W., Goncalves, O. F., & Niznikiewicz, M. (2012). Interactions between mood and the structure of semantic memory: Event-related potentials evidence. *Social Cognitive and Affective Neuroscience*, *March 19, 2012*, [Epub ahead of print]. doi: 10.1093/scan/nss035

Pinheiro, J. C., Bates, D., DebRoy, S., Sarkar, D., & R Development Core Team. (2012). nlme: Linear and nonlinear mixed effects models: [online] r. package version 3.1-110.

Plahuta, J. M., McCulloch, B. J., Kasarskis, E. J., Ross, M. A., Walter, R. A., & McDonald, E. R. (2002). Amyotrophic lateral sclerosis and hopelessness: psychosocial factors. *Social Science & Medicine*, *55*(12), 2131–2140. doi: 10.1016/S0277-9536(01)00356-2

Pokorny, C., Klobassa, D. S., Pichler, G., Erlbeck, H., Real, R. G. L., Kübler, A., ... Müller-Putz, G. R. (2013). The auditory p300-based single-switch brain–computer interface: Paradigm transition from healthy subjects to minimally conscious patients. *Artificial Intelligence in Medicine*, *59*(2), 81–90. doi: 10.1016/j.artmed.2013.07.003

Polich, J. (1998). P300 clinical utility and control of variability. *Journal of clinical neurophysiology*, *15*(1), 14–33. doi: 10.1097/00004691-199801000-00004

Polich, J. (2007). Updating p300: An integrative theory of p3a and p3b. *Clinical Neurophysiology*, *118*(10), 2128–2148. doi: 10.1016/j.clinph.2007.04.019

Qin, P., Di, H., Yan, X., Yu, S., Yu, D., Laureys, S., & Weng, X. (2008). Mismatch negativity to the patient's own name in chronic disorders of consciousness. *Neuroscience Letters*, *448*(1), 24–28. doi: 10.1016/j.neulet.2008.10.029

R Development Core Team. (2011). *R: A language and environment for statistical computing*. Vienna and Austria: R Foundation for Statistical Computing. Retrieved from http://www.R-project.org

Rabkin, J. G., Albert, S. M., Del, B. M. L., O'Sullivan, I., Tider, T., Rowland, L. P., & Mitsumoto, H. (2005). Prevalence of depressive disorders and change over time in late-stage als. *Neurology*, *65*(1), 62–67. doi: 10.1212/01.wnl.0000167187.14501.0c

Rabkin, J. G., Wagner, G. J., & Bene, M. d. (2000). Resilience and distress among amyotrophic lateral sclerosis patients and caregivers. *Psychosomatic Medicine*, *62*(2), 271–279. doi: 10.1097/00006842-200003000-00020

Raggi, A., Consonni, M., Iannaccone, S., Perani, D., Zamboni, M., Sferrazza, B., & Cappa, S. F. (2008). Auditory event-related potentials in non-demented patients with sporadic amyotrophic lateral sclerosis. *Clinical Neurophysiology*, *119*(2), 342–350. doi: 10.1016/j.clinph.2007.10.010

Rapkin, B. D., & Schwartz, C. E. (2004). Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift. *Health and Quality of Life Outcomes*, *2*(14). doi: 10.1186/1477-7525-2-14

Real, R. G. L., Dickhaus, T., Ludolph, A., Hautzinger, M., & Kübler, A. (2014). Well-being in amyotrophic lateral sclerosis: a pilot experience-sampling study. *Frontiers in Psychology for Clinical Settings*, *5*, 704. doi: 10.3389/fpsyg.2014.00704

Real, R. G. L., Herbert, C., Kotchoubey, B., Wessig, C., Volkmann, J.,

& Kübler, A. (2014). Psychophysiological correlates of coping and quality of life in patients with als. *Clinical Neurophysiology*, *125*, 955–961. doi: 10.1016/j.clinph.2013.09.040

Real, R. G. L., Kotchoubey, B., & Kübler, A. (2014). Studentized continuous wavelet transform (t-cwt) in the analysis of individual erps: real and simulated eeg data. *Frontiers in Neuroscience*, *8*, 279. doi: 10.3389/fnins.2014.00279

Real, R. G. L., Veser, S., Erlbeck, H., Risetti, M., Vogel, D., Müller, F., . . . Kübler, A. (2015). Information processing in patients in vegetative and minimally conscious states. *Clinical Neurophysiology*(in press). doi: 10.1016/j.clinph.2015.07.020

Riccio, A., Mattia, D., Simione, L., Olivetti, M., & Cincotti, F. (2012). Eye-gaze independent eeg-based brain–computer interfaces for communication. *Journal of Neural Engineering*, *9*(4), 045001. doi: 10.1088/1741-2560/9/4/045001

Ridder, D. T. D. d., & Wit, J. B. F. d. (2006). Self-regulation in health behavior: Concepts, theories, and central issues. In D. T. D. d. Ridder & J. B. F. d. Wit (Eds.), *Self-regulation in health behavior* (pp. 1–23). Chichester, England: John Wiley & Sons.

Robberecht, W., & Philips, T. (2013). The changing scene of amyotrophic lateral sclerosis. *Nature Reviews Neuroscience*, *14*(4), 248–264. doi: 10.1038/nrn3430

Robbins, R. A., Simmons, Z., Bremer, B. A., Walsh, S. M., & Fisher, S. (2001). Quality of life in als is maintained as physical function declines. *Neurology*, *56*, 442–444. doi: 10.1212/WNL.56.4.442

Ruchkin, D. S., & Glaser, E. M. (1978). Simple digital filters for examining cnv and p300 on a single-trial basis. In D. A. Otto (Ed.), *Multidisciplinary perspectives in event-related brain potential research* (pp. 579–581). Washington, DC: U.S. Environmental Protection Agency.

Runyan, J. D., Steenbergh, T. A., Bainbridge, C., Daugherty, D. A., Oke, L., & Fry, B. N. (2013). A smartphone ecological momentary assessment - intervention app for collecting real-time data and promoting self-awareness. *PLoS ONE*, *8*(8), e71325. doi: 10.1371/journal.pone.0071325

Samar, V. J., Bopardikar, A., Rao, R., & Swartz, K. (1999). Wavelet analysis of neuroelectric waveforms: A conceptual tutorial. *Brain and Language*, *66*(1), 7–60. doi: 10.1006/brln.1998.2024

Sazbon, L., & Groswasser, Z. (1990). Outcome in 134 patients with prolonged posttraumatic unawareness. part 1: Parameters determining late recovery of consciousness. *Journal of neurosurgery*, *72*(1), 75–80. doi: 10.3171/jns.1990.72.1.0075

Schmidt, J. A., Shernof, D. J., & Csikszentmihalyi, M. (2007). Individual and situational factors related to the experience of flow in adolescence. In A. D. Ong & Van Dulmen, Manfred H. M (Eds.), *Oxford handbook of methods in positive psychology* (pp. 542–558). Oxford: Oxford University Press.

Schnakers, C., & Laureys, S. (2012). Preface. In C. Schnakers & S. Laureys (Eds.), *Coma and disorders of consciousness* (pp. xi–xii). London: Springer.

Schnakers, C., Perrin, F., Schabus, M., Hustinx, R., Majerus, S., Moonen, G., ... Laureys, S. (2009). Detecting consciousness in a total locked-in syndrome: An active event-related paradigm. *Neurocase*, *15*(4), 271–277. doi: 10.1080/13554790902724904

Schnakers, C., Vanhaudenhuyse, A., Giacino, J. T., Ventura, M., Boly, M., Majerus, S., ... Laureys, S. (2009). Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology*, *9*(1), 35. doi: 10.1186/1471-2377-9-35

Schneider, G., Nahm, W., Kochs, E. F., Bischoff, P., Kalkman, C. J., Kuppe, H., & Thornton, C. (2003). Quality of perioperative aep: variability of expert ratings. *British journal of anaesthesia*, *91*(6), 905–908. doi: 10.1093/bja/aeg280

Schwarz, N., & Strack, F. (2003). Reports of subjective well-being: Judgmental processes and their methodological implications. In D. Kahneman, E. Diener, & N. Schwarz (Eds.), *Well-being* (pp. 61–84). New York: Russell Sage Foundation.

Scollon, C. N., Prieto, C. K., & Diener, E. (2009). Experience sampling: Promises and pitfalls, strength and weaknesses. In E. Diener (Ed.), *Assessing well-being* (Vol. 39, pp. 157–180). Dordrecht: Springer.

Segalowitz, S. J., & Barnes, K. L. (1993). The reliability of erp components in the auditory oddball paradigm. *Psychophysiology*, *30*(5), 451–459. doi: 10.1111/j.1469-8986.1993.tb02068.x

Selya, A. S., Rose, J. S., Dierker, L. C., Hedeker, D., & Mermelstein, R. J. (2012). A practical guide to calculating cohen's f2, a measure of local effect size, from proc mixed. *Frontiers in Psychology*, *3*. doi: 10.3389/fpsyg.2012.00111

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Review of Clinical Psychology*, *4*(1), 1–32. doi: 10.1146/annurev.clinpsy.3.022806.091415

Siegle, G. J., & Thayer, J. F. (2003). Physiological aspects of depressive rumination. In C. Papageorgiou & A. Wells (Eds.), *Rumination* (pp. 79–104). Chichester: Wiley.

Smith, J. M., & Alloy, L. B. (2009). A roadmap to rumination: a review of the definition, assessment, and conceptualization of this multifaceted construct. *Clinical Psychology Review*, *29*(2), 116–128. doi: 10.1016/j.cpr.2008.10.003

Smyth, J. M., & Stone, A. A. (2003). Ecological momentary assessment research in behavioral medicine. *Journal of Happiness Studies*, *4*(1), 35–52. doi: 10.1023/A:1023657221954

Snijders, T. A. B., & Bosker, R. J. (1993). Standard errors and sample sizes for two-level research. *Journal of Educational and Behavioral Statistics*, *18*(3), 237–259. doi: 10.3102/10769986018003237

Sokolova, M., & Lapalme, G. (2009). A systematic analysis of performance measures for classification tasks. *Information Processing & Management*, *45*(4), 427–437. doi: 10.1016/j.ipm.2009.03.002

Spearman, C. (1910). Correlation calculated from faulty data. *British Journal of Psychology, 1904-1920*, *3*(3), 271–295. doi: 10.1111/j.2044-8295.1910.tb00206.x

Sprangers, M. A. G., & Schwartz, C. E. (1999). Integrating response shift into health-related quality of life research: a theoretical model. *Social Science & Medicine*, *48*, 1507–1515. doi: 10.1016/S0277-9536(99)00045-3

Stone, A. A., Shiffman, S. S., & DeVries, M. W. (2003). Ecological momentary assessment. In D. Kahneman, E. Diener, & N. Schwarz (Eds.), *Well-being* (pp. 26–39). New York: Russell Sage Foundation.

Teuchmann, K., Totterdell, P., & Parker, S. K. (1999). Rushed, unhappy, and drained: an experience sampling study of relations between time pressure, perceived control, mood, and emotional exhaustion in a group of accountants. *Journal of Occupational Health Psychology*, *4*(1), 37–54. doi: 10.1037/1076-8998.4.1.37

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders*, *61*, 201–216. doi: 10.1016/S0165-0327(00)00338-4

The Multi-Society Task Force on PVS. (1994). Medical aspects of the persistent vegetative state. *New England Journal of Medicine*, *330*(22), 1572–1579. doi: 10.1056/NEJM199406023302206

Tofighi, D., & MacKinnon, D. P. (2011). Rmediation: an r package for mediation analysis confidence intervals. *Behavior Research Methods*, *43*(3), 692–700. doi: 10.3758/s13428-011-0076-x

Trail, M., Nelson, N. D., Van, J. N., Appel, S. H., & Lai, E. C. (2003). A study comparing patients with amyotrophic lateral sclerosis and their caregivers on measures of quality of life, depression, and their attitudes toward treatment options. *Journal of the Neurological Sciences*, *209*(1-2), 79–85. doi: 10.1016/S0022-510X(03)00003-0

Trapnell, P. D., & Campbell, J. D. (1999). Private self-consciousness and the five-factor model of personality: distinguishing rumination from reflection. *Journal of Personality and Social Psychology*, *76*(2), 284–304. doi: 10.1037/0022-3514.76.2.284

Treynor, W., Gonzalez, R., & Nolen-Hoeksema, S. (2003). Rumination reconsidered: A psychometric analysis. *Cognitive Therapy and Research*, *27*(3), 247–259. doi: 10.1023/A:1023910315561

Urry, H. L., Nitschke, J. B., Dolski, I., Jackson, D. C., Dalton, K. M., Mueller, C. J., ... Davidson, R. J. (2004). Making a life worth living: neural correlates of well-being. *Psychological Science*, *15*(6), 367–372. doi: 10.1111/j.0956-7976.2004.00686.x

Valdes-Sosa, M. J., Bobes, M. A., Perez-abalo, M. C., Perera, M., Carballo, J. A., & Valdes-Sosa, P. (1987). Comparison of auditory-evoked potential detection methods using signal detection theory. *International Journal of Audiology*, *26*(3), 166–178. doi: 10.3109/00206098709078419

Van den Berg, J. P., Kalmijn, S., Lindeman, E., Veldink, J. H., Visser, M. d., Van der Graaff, M M, ... Van den Berg, L H (2005). Multidisciplinary als care improves quality of life in patients with als. *Neurology*, *65*(8), 1264–1267. doi: 10.1212/01.wnl.0000180717.29273.12

van Petten, C., & Kutas, M. (1990). Interactions between sentence context and word frequency in event-related brainpotentials. *Memory & Cognition*, *18*(4), 380–393. doi: 10.3758/BF03197127

VanRullen, R. (2011). Four common conceptual fallacies in mapping the time course of recognition. *Frontiers in Psychology*, *2*, 365. doi: 10.3389/fpsyg.2011.00365

Vieregge, P., Wauschkuhn, B., Heberlein, I., Hagenah, J., & Verleger, R. (1999). Selective attention is impaired in amyotrophic lateral sclerosis–a study of event-related eeg potentials. *Cognitive Brain Research*, *8*(1), 27–35. doi: 10.1016/S0926-6410(99)00004-X

Vliet, M. v., Mühl, C., Reuderink, B., & Poel, M. (2010). Guessing what's on your mind: Using the n400 in brain computer interfaces. In Y. Yao, R. Sun, T. Poggio, J. Liu, N. Zhong, & J. Huang (Eds.), *Brain informatics* (Vol. 6334, pp. 180–191). Berlin: Springer. doi: 10.1007/978-3-642-15314-3{\textunderscore}17

Ware, J. E. J., & Sherbourne, C. D. (1992). The mos 36-item short-form health survey (sf-36): I. conceptual framework and item selection. *Medical Care*, *30*(6), 473–483.

Westphal, K. P., Heinemann, H. A., Grözinger, B., Kotchoubey, B. J., Diekmann, V., Becker, W., & Kornhuber, H. H. (1998). Bereitschaftspotential in amyotrophic lateral sclerosis (als): lower amplitudes in patients with hyperreflexia (spasticity). *Acta Neurologica Scandinavica*, *98*(1), 15–21. doi: 10.1111/j.1600-0404.1998.tb07372.x

WHOQOL. (1995). The world health organization quality of life assessment: Position paper from the world health organization. *Social Science & Medicine*, *41*(10), 1403–1409. doi: 10.1016/0277-9536(95)00112-K

Wilson, S. B., Harner, R. N., Duffy, F. H., Tharp, B. R., Nuwer, M. R., & Sperling, M. R. (1996). Spike detection. i. correlation and reliability of human experts. *Electroencephalography and clinical* *neurophysiology*, *98*(3), 186–198. doi: 10.1016/0013-4694(95)00221-9

Woody, C. D. (1967). Characterization of an adaptive filter for the analysis of variable latency neuroelectric signals. *Medical & Biological Engineering*, *5*(6), 539–554. doi: 10.1007/BF02474247

World Medical Association. (2008). *Declaration of helsinki: Ethical principles for medical research involving human subjects.* Retrieved 18.11.2011, from http://www.wma.net/en/30publications/10policies/b3/17c.pdf

Wrosch, C., Scheier, M. F., Carver, C. S., & Schulz, R. (2003). The importance of goal disengagement in adaptive self-regulation: When giving up is beneficial. *Self and Identity*, *2*, 1–20. doi: 10.1080/15298860309021

Wrosch, C., Scheier, M. F., Miller, G. E., Schulz, R., & Carver, C. S. (2003). Adaptive self-regulation of unattainable goals: Goal disengagement, goal reengagement, and subjective well-being. *Journal of Personality and Social Psychology*, *29*(12), 1494–1508. doi: 10.1177/0146167203256921

Yeung, N., Bogacz, R., Holroyd, C. B., & Cohen, J. D. (2004). Detection of synchronized oscillations in the electroencephalogram: an evaluation of methods. *Psychophysiology*, *41*(6), 822–832. doi: 10.1111/j.0048-5772.2004.00239.x

Young, J. M., & McNicoll, P. (1998). Against all odds: positive life experiences of people with advanced amyotrophic. *Health & Social Work*, *23*(1), 35–43. doi: 10.1093/hsw/23.1.3

Zangen, A., Overstreet, D. H., & Yadid, G. (1999). Increased catecholamine levels in specific brain regions of a rat model of depression: normalization by chronic antidepressant treatment. *Brain Research*, *824*(2), 243–250. doi: 10.1016/S0006-8993(99)01214-7

Zelazo, P. D., & Cunningham, W. A. (2007). Executive functions: Mechanisms underlying emotion regulation. In J. J. Gross (Ed.), *Handbook of emotion regulation.* New York, NY: Guilford Press.

A

AFFIDAVIT (EIDESSTATTLICHE ERKLÄRUNG)

I hereby confirm that my thesis *Living with severe motor impairments From consciousness to quality of life* is the result of my own work. I did not receive any help or support from commercial consultants. All sources / materials applied are listed and specified in the thesis.

I confirm that this thesis has not been submitted as part of any other examination process neither in identical nor similar form.

Würzburg, September 2015

Ruben G.L. Real

B

PUBLICATIONS RESULTING FROM THIS THESIS

First author only

- Real, R. G. L., Veser, S., Erlbeck, H., Risetti, M., Vogel, D., Müller, F., Kotchoubey, B., Mattia, D., & Kübler, A. (2015). Information processing in patients in vegetative and minimally conscious states. *Clinical Neurophysiology, in press*. doi: 10.1016/j.clinph.2015.07.020
- Real, R. G. L., Herbert, C., Kotchoubey, B., Wessig, C., Volkmann, J., & Kübler, A. (2014). Psychophysiological correlates of coping and quality of life in patients with ALS. *Clinical Neurophysiology, 125*, 955-961. doi: 10.1016/j.clinph.2013.09.040
- Real, R. G. L., Dickhaus, T., Ludolph, A. Hautzinger, M., & Kübler, A. (2014). Well-being in Amyotrophic Lateral Sclerosis: a pilot Experience Sampling Study. *Frontiers in Psychology for Clinical Setting, 5*, 704. doi: 10.3389/fpsyg.2014.00704
- Real, R. G. L., Kotchoubey, B., & Kübler, A. (2014). Studentized Continuous Wavelet Transform (t-CWT) in the Analysis of Individual ERPs: Real and Simulated data. *Frontiers in Brain Imaging Methods, 8*, 279. doi: 10.3389/fnins.2014.00279

C

CURRICULUM VITAE

CURRICULUM VITÆ

personal information

Dipl.-Psych. Ruben G.L. Real

born 22.02.1981 in Salé, Morocco
Department of Psychology I, University of Würzburg, Marcusstr. 9-11, 97070 Würzburg, Germany, +49-931-31-80853, ruben.real@uni-wuerzburg.de

education & research experience

2009-2015 Doctoral Student at the Institute of Psychology, Department of Psychology I, University of Würzburg, Würzburg, Germany

2008 Graduation in Psychology (Diplom) at the Georg-Elias-Müller-Institut of Psychology, University of Göttingen, Göttingen, Germany

2002-2008 Studies in Psychology at the Georg-August University of Göttingen

2001-2002 Studies in Psychology and Computer Sciences at the University of Aberdeen, Aberdeen, UK

professional experience

since 2010 Supervision and guide of five diploma students, one Master, three bachelor students and an intern in Psychology and cognitive sciences

2013 Reviewer for Journals, Conferences and Projects

JOURNALS Journal of Neural Engineering, Journal of Medical and Biological Engineering, Clinical Neurophysiology, Frontiers in Eating Behavior

CONFERENCES 5^{th} International Brain Computer Interface Meeting, 4^{th} TOBI Workshop, 1^{st} International DECODER Workshop

PROJECTS DECODER, CONTRAST, BNCI Horizon 2020

2008-2009 Clinical Psychologist at the intensive care unit of the Vitos Klinik für Psychiatrie and Psychotherapie, Bad Emstal, Germany

grants

2009 Research grant from the research group Emotion (1513/1), Graduate School of Life Sciences, supported by Federal and Länder Funds, at the University of Würzburg, Würzburg, Germany.

research articles

2015 **Real, R. G. L.**, Veser, S., Erlbeck, H., Risetti, M., Vogel, D., Müller, F., Kotchoubey, B., Mattia, D., & Kübler, A. (2015). Information processing in patients in vegetative and minimally conscious states. *Clinical Neurophysiology, in press*. doi: 10.1016/j.clinph.2015.07.020

2014 **Real, R. G. L.**, Herbert, C., Kotchoubey, B., Wessig, C., Volkmann, J., & Kübler, A. (2014). Psychophysiological correlates of coping and quality of life in patients with ALS. *Clinical Neurophysiology, 125*:955-961. doi: 10.1016/-j.clinph.2013.09.040

2014 **Real, R. G. L.**, Dickhaus, T., Ludolph, A. Hautzinger, M., & Kübler, A. (2014). Well-being in Amyotrophic Lateral Sclerosis: a pilot Experience Sampling Study. *Frontiers in Psychology for Clinical Settings, 5*, 704. doi: 10.3389/-fpsyg.2014.00704

2014 **Real, R. G. L.**, Kotchoubey, B., & Kübler, A. (2014). Studentized Continuous Wavelet Transform (t-CWT) in the Analysis of Individual ERPs: Real and Simulated data. *Frontiers in Brain Imaging Methods, 8*, 279. doi: 10.3389/-fnins.2014.00279

2013 Pokorny, C., Klobassa, D. S., Pichler, G., Erlbeck, H., **Real, R. G.**, Kübler, A., & Müller-Putz, G. R. (2013). The auditory P300-based single-switch brain–computer interface: Paradigm transition from healthy subjects to minimally conscious patients. *Artificial Intelligence in Medicine, 59*(2), 81–90. doi:10.1016/j.artmed.2013.07.003

2013 Kotchoubey, B., Veser, S., **Real, R.**, Herbert, C., Lang, S., & Kübler, A. (2013). Towards a more precise neurophysiological assessment of cognitive functions in patients with disorders of consciousness. *Restorative neurology and neuroscience, 31*(4), 473–485. doi:10.3233/RNN-120307

2013 Meule, A., Fath, K., **Real, R. G. L.**, Sütterlin, S., Vögele, C., & Kübler, A. (2013). Quality of life, emotion regulation, and heart rate variability in individuals with intellectual disabilities and concomitant impaired vision. *Psychology of Well-Being: Theory, Research and Practice, 3*(1), 1. doi:10.1186/2211-1522-3-1

2012 Müller-Putz, G. R., Klobassa, D. S., Pokorny, C., Pichler, G., Erlbeck, H., **Real, R.**, & Mattia, D. (2012). The auditory p300-based SSBCI: A door to minimally conscious patients? *34th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*: 4672–4675. doi: 10.1109/EMBC.2012.6347009

other articles

2011 **Real, R.** & Kübler, A. (2011). DECODER – Gehirn-Computer Schnittstellen und die Erkennung von Bewusstsein. *Unterstützte Kommunikation, 11*(3), 18-22.

other

2015 Müller-Putz, G. R., Brunner, C., Bauernfeind, G., Blefari, M. L., Millán, J. D. R., **Real, R. G. L.**, Kübler, A., Mattia, D., Pichiorri, F., Schettini, F., Ramsey, N. F., Höhne, J., Blankertz, B., Miralles, F., Otal, B., Guger, C., Ortner, R., Poel, M., Nijholt, A., Reuderink, B., Birbaumer, N., Pobes, A., Salomon, P., van Steensel, M., Soekader, S., Opisso, E., Opisso, E. (2015). *Roadmap: The future in brain-neural-computer interaction: Horizon 2020*. Graz: Verl. der Techn. Univ. Graz. doi: http://dx.doi.org/10.3217/978-3-85125-379-5

2013 Guger, C., Noirhomme, Q., Naci, L., **Real, R.**, Lugo, Z., Veser, S., Sorger, B., Quitadamo, L., Lesenfants, D., Risetti, M., Formisano, R., Toppi, J., Astolfi, L., Emmerling, T., Erlbeck, H., Monti, M. M., Kotchoubey, B., Bianchi, L., Mattia, D., Goebel, R., Owen, A. M., Pellas, F., Müller-Putz, G., & Kübler. (2013). Brain-computer interfaces for coma assessment and communication. In Ganesh R Naik (Ed.), *Emerging Theory and Practice in Neuroprosthetics*. IGIGLOBAL Press

talks

2015 **Real, R. G. L.** (2015). Communication with low-responsive patients: a multi-dimensional approach. *Establishing communication with low reponsive patients - perspectives for 'cognitive interaction technology'*, Bielefeld, Germany, September 3-5.

2014 **Real, R. G. L.**, Kübler, A., & Kleih, S. C. (2014). Specific effects of slow cortical potentials neurofeedback training on attentional performance. *6th International Brain-Computer Interface Conference 2014*, Graz, Austria, September 16-19.

2013 **Real, R.**, Erlbeck, H., Veser, S., Kotchoubey, B. & Kübler, A. (2013). Information processing in patients with chronic and severe disorders of consciousness, *TOBI Workshop IV:*

Practical Brain-Computer Interfaces for End-Users: Progress and Challenges, Sion, Switzerland, January 23-25.

2012 **Real, R.**, Kaufmann, T., Erlbeck, H., Veser, S., Herbert, C., & Kübler, A. (2012). Correcting ocular artefacts in patients with disorders of consciousness. *1st international DECODER workshop*, Boulogne-Court (Paris), France, April 11-13.

2012 **Real, R.**, Herbert, C., Mattia, D., & Kübler, A. (2012). Informed consent in patients in a vegetative state. *1st international DECODER workshop*, Boulogne-Court (Paris), France, April 11-13.

2011 **Real, R.G.L.** & Kübler, A. (2011). Elektrophysiologische Korrelate der Krankheitsbewältigung bei Amyotropher Lateralsklerose. *Psychologie und Gehirn*. Heidelberg, Germany, June 23-25.

2011 **Real, R.G.L.** & Kübler, A. (2011). Elektrophysiologische Korrelate der Krankheitsbewältigung bei Amyotropher Lateralsklerose. *13. Kongress der Deutschen Gesellschaft für Verhaltensmedizin und Verhaltensmodifikation*. Luxembourg-Kirchberg, Luxembourg, September 29-October 1.

poster presentations (first author only)

2013 **Real, R.**, Erlbeck, H., Veser, S., Kotchoubey, B., & Kübler, A. (2013). Assessing information processing in patients with long-term and severe disorders of consciousness. *Brain Computer Interface 2013, Pacific Grove, California (USA), June 3-7*.

2012 **Real, R.**, Veser, S., Kotchoubey, B., & Kübler, A. (2012). Sensitivity and specificity of the studentized continuous wavelet transform for ERP detection – a simulation study. *TOBI Workshop IV: Practical Brain-Computer Interfaces for End-Users: Progress and Challenges. Sion, Switzerland, January 23-25.*

2012 **Real, R.**, Kaufmann, T., Erlbeck, H., Kübler, A., & Herbert, C. (2012). Correcting ocular artifacts in patients with disorders of consciousness. *48. Kongress der Deutschen Gesellschaft für Psychologie. Bielefeld, Germany, Septembre 23-27.*

2012 **Real, R.**, Kaufmann, T., Erlbeck, H., Veser, S., Herbert, C., & Kübler, A. (2012). Adjusting for autocorrelation in single trial EEG analysis. *Psychologie und Gehirn 2012, Jena, Germany, June 8-10.*

2012 **Real, R.**, Herbert, C., Mattia, D., & Kübler, A. (2012). Informed consent in patients in a vegetative state. *TOBI Workshop III Bringing BCIs to End-Users: Facing the Challenge – Evaluation, User Perspectives, User Needs, and Ethical Questions. Würzburg, Germany, March 20-22.*

2010 **Real, R.**, Nedele, P. Sorg, S., Hautzinger, M., & Kübler, A. (2010). Coping with motoneurone disease: an experience sampling approach. *28. Symposium der Fachgruppe Klinische Psychologie und Psychotherapie der Deutschen Gesellschaft für Psychologie (DGPs), Mainz, Germany, May 13-15.*

Würzburg, September 2015

____

Ruben G.L. Real

„Dissertation unter Einschluss mehrerer publizierter Manuskripte" in der GSLS –

Erklärung zu Eigenanteilen an Publikationen und Zweitpublikationsrechten

(ggf. weitere Blätter dieses Formblatts verwenden)

Publikation (Vollständiges Zitat):

Real, R. G. L., Herbert, C., Kotchoubey, B., Wessig, C., Volkmann, J., & Kübler, A. (2014). Psychophysiological correlates of coping and quality of life in patients with ALS. *Clinical Neurophysiology*, *125*, 955–961. doi:10.1016/j.clinph.2013.09.040

Beteiligt an	**Autoren-Initialen,** Verantwortlichkeit abnehmend von links nach rechts					
Planung der Untersuchungen	RR	AK	BK			
Datenerhebung	RR	CW	JV			
Daten-Analyse und Interpretation	RR	CH	BK	AK		
Schreiben des Manuskripts	RR	CH	BK	CW	JV	AK

ggf. Erläuterung:

Publikation (Vollständiges Zitat):

Real, R. G. L., Dickhaus, T., Ludolph, A., & Kübler, A. (2014). Well-being in Amyotrophic Lateral Sclerosis: a pilot Experience-Sampling Study. *Frontiers in Psychology for Clinical Settings*, *9*, 703. doi: 10.3389/fpsyg.2014.00704

Beteiligt an	**Autoren-Initialen,** Verantwortlichkeit abnehmend von links nach rechts				
Planung der Untersuchungen	AK	AL			
Datenerhebung	AK				
Daten-Analyse und Interpretation	RR	TD	AK	AL	
Schreiben des Manuskripts	RR	AK	TD	AL	

ggf. Erläuterung:

Publikation (Vollständiges Zitat):

Real, R. G. L., Kotchoubey, B., & Kübler, A. (2014). Studentized Continuous Wavelet Transform (*t*-CWT) in the Analysis of Individual ERPs: Real and Simulated data. *Frontiers in Brain Imaging Methods*, *8*, 279. doi: 10.3389/fnins.2014.00279

Beteiligt an	**Autoren-Initialen,** Verantwortlichkeit abnehmend von links nach rechts				
Planung der Untersuchungen	RR	BK			
Datenerhebung	RR				
Daten-Analyse und Interpretation	RR	BK			
Schreiben des Manuskripts	RR	BK	AK		

ggf. Erläuterung:

Publikation (Vollständiges Zitat):

Real, R. G. L., Veser, S., Erlbeck, H., Risetti, M., Vogel, D., Müller, F., Kotchoubey, B., Mattia, D., & Kübler, A. Information processing in patients in vegetative and minimally conscious states. *Clinical Neurophysiology, in revision.*

Beteiligt an	**Autoren-Initialen,** Verantwortlichkeit abnehmend von links nach rechts								
Planung der Untersuchungen	RR	AK	DM	SV					
Datenerhebung	RR	HE	SV	MR	DV	FM			
Daten-Analyse und Interpretation	RR	BK							
Schreiben des Manuskripts	RR	SV	AK	BK	DM	HE	MR	DV	FM

ggf. Erläuterung:

Für alle in dieser „Dissertation unter Einschluss mehrerer publizierter Manuskripte“ verwendeten Manuskripte liegen die notwendigen Genehmigungen der Verlage und Co-Autoren für die Zweitpublikation vor.

Mit meiner Unterschrift bestätige ich die Kenntnisnahme und das Einverständnis meines direkten Betreuers.

Ruben Real	20.09.2016	Würzburg	
Name Doktorand(in)	Datum	Ort	Unterschrift