STIMULUS INTENSITY DEPENDENT ERP COMPONENTS IN THE PHARMACOTHERAPY OF MAJOR DEPRESSIVE DISORDER

THOMAS LINKA

STIMULUS INTENSITEIT AFHANKELIJKE ERP COMPONENTEN IN DE BEHANDELING VAN DEPRESSIEVE STOORNISSEN

STIMULUS INTENSITY DEPENDENT ERP COMPONENTS IN THE PHARMACOTHERAPY OF MAJOR DEPRESSIVE DISORDER

STIMULUS INTENSITEIT AFHANKELIJKE ERP COMPONENTEN IN DE BEHANDELING VAN DEPRESSIEVE STOORNISSEN

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificicus

Prof.dr. H. G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
donderdag 1 oktober 2009 om 15.30 uur

door

Thomas Linka

geboren te Wattenscheid (Duitsland)

Promotiecommissie

Promotor:
Prof.dr. W.M.A. Verhoeven

Overige leden:
Prof.dr. M.W. Hengeveld
Prof.dr. F. Verhey
Prof.dr. G. Sartory

Copromotor:
Dr. J.H.M. Tulen

The research described in this thesis was carried out at the Clinics for Psychiatry and Psychotherapy of the University of Duisburg-Essen, Germany.

Für meine Familie

Cover design: T. Linka
Printing: V+V Sofortdruck GmbH

Contents

Abbreviations

BDI	Beck Depression Inventory
CGI	Clinical Global Impression
CNS	central nervous system
CSF	cerebrospinal fluid
DA	dopamine
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalography
ERP	event related potentials
HDRS	Hamilton Depression Rating Scale
HPA	hypothalamic-pituitary-adrenal axis
HPT	hypothalamic-pituitary-thyroid axis
5-HT	serotonin
IDAP	Intensity Dependence of Auditory Evoked Potentials
MDD	major depressive disorder
NE	norepinephrine
SNRI	selective NE re-uptake inhibitor
SSRI	selective serotonin re-uptake inhibitor
STAI	State Trait Anxiety Inventory
TCA	tricyclic antidepressants

CHAPTER 1

GENERAL INTRODUCTION

General Introduction

1. Introduction

This dissertation deals with original research results obtained from investigations on the role and the predictive value of stimulus intensity dependent ERP components in the pharmacotherapy of major depressive disorder (MDD). The Intensity Dependence of Auditory Evoked potentials (IDAP) is the key parameter that has been assessed in the five clinical studies which have been performed by our research group and are presented here.

This general introduction starts with a concise overview of the epidemiology, clinical characteristics and current theories on the etiology and pathophysiology of depression. Subsequently, certain aspects of the pharmacological treatment with antidepressants, with special attention to existing strategies and methods of treatment efficacy prediction, are described followed by an overview of the general methodology of the electroencephalography (EEG) and of event related potentials (ERP). Furthermore, methodological assessment strategies of the IDAP particularly with regard to aspects of reliability are evaluated. Finally, the aims of the presented studies will be introduced.

2. Major depressive disorder

Major depressive disorder belongs to the most common mental diseases in Europe and in the United States. The European Study of the Epidemiology of Mental Disorders (ESEMeD) analyzed diagnostic interviews of a random sample of non-institutionalized inhabitants from Belgium, France, Germany, Italy, The Netherlands and Spain aged 18 years or older (n = 21425). This study revealed that 14 per cent reported a lifetime history of any mood disorder of whom 4.2 per cent reported any mood disorder in the last year. Major depression and specific phobia were the most common single mental disorders (Alonso et al., 2004). For the United States, the National Comorbidity Survey Replication (NCS-R) revealed a lifetime prevalence of 16.2 per cent and a 12-month prevalence of 6.6 per cent for major depressive disorder (Kessler et al., 2003). Bijl et al. (1997) found a lifetime prevalence of major depressive disorder of 15.4 per cent in the Dutch population.

According to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association, 1994), major depressive disorder is characterized by a single major depressive episode or several recurrent episodes in individuals without a history of mixed, hypomanic or manic episodes. The DSM-IV defines 5 of 9 commonly observed symptoms as a minimum criterion for the diagnosis of a major depressive episode. During the same 2-week period at least one of these symptoms must be either (1) depressed mood or (2) loss of interest or pleasure. Further symptoms are: (3) significant weight loss when not dieting or weight gain, (4) insomnia or hypersomnia (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or inappropriate guilt, (8) diminished ability to think or concentrate, or indecisiveness, (9) recurrent thoughts of death, recurrent suicidal ideation. The symptoms are present permanently or almost daily, cause significant impairment in social, occupational, or other important areas of functioning and are not due to the direct physiological effects of a substance or a general medical condition.
Van Praag (1998) pointed out that the wide use of the DSM more or less led to a disappearance of the syndromal differentiation from the diagnosis of depression. The major constructs of affective disorders represented by the DSM (major depression and dysthymia) cover a variety of syndromes. According to van Praag (1998), the diagnostic differentiation of depressive syndromes is of enormous scientific value in biological psychiatry and psychopharmacology, because the etiological and syndromal heterogeneity of the major depressive disorder concept constrains the demonstration of the specificity of a given compound. Furthermore, van Praag (1998) suggests the formulation of hypotheses regarding the relationships between personality structure and depressive syndromes and the systematic analysis of psychological dysfunctions constituting the depressive syndrome.

2.1 The Etiology of depression

The multifactorial etiology of depression is widely accepted, but there is no agreement over the exact contributional value of psychosocial, neurobiological and genetic factors.

2.1.1 Neurobiological factors

Disturbances in various neuroendocrine and neurotransmitter systems have been associated with the pathophysiological mechanisms that are assumed to contribute to the origin of depressive disorders, e.g. in the glutamatergic, cholinergic, GABAergic

systems and the hypothalamic-pituitary-thyroid axis (HPT). Mainly the discussion of the role of the monoaminergic system and the hypothalamic-pituitary-adrenal axis (HPA) has a long tradition and will be introduced here.

The monoamine hypothesis

In the 1960s, the hypothesis was postulated that a central nervous (synaptic) deficit of one or more monoamine neutransmitters (serotonin, norepinephrine and dopamine) might be the neuronal basis of depressive disorders (Bunney and Davis, 1965; Schildkraut, 1965; van Praag, 1970). Findings in the 1950s that the depletion of central nervous monoamine stores by reserpin (antihypertensivum) was accompanied by symptoms of depression (Shore et al., 1955) and that drug induced elevation of monoamnine levels in the brain by iproniazid (tuberculostaticum) and by imipramine had an antidepressive effect (Kline,1958; Kuhn,1958), formed the basis for the monoamine hypothesis of depression.

The inhibition of the monoamine oxydase and the transporter mediated reuptake of serotonin and norepinephrine were assumed to be the most important mechanisms of action of antidepressive agents. A revised monoamine theory suggested that the monoamine systems are only modulating "other" brain neurobiologic systems which have a more primary role in depression (Heniger et al., 1996, review in: Delgado and Moreno, 2000).

From the late 1960s, a deficit in serotonin (5-HT) metabolism as a potentially underlying mechanism in the pathophysiology of at least a subgroup of depression became the focus of neurobiological research. The major metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), is found in the cerebrospinal fluid (CSF) as well as in the brain itself. Low CSF 5-HIAA, thus, suggests a decrease of 5-HT metabolism in the central nervous system (CNS). Van Praag and Korf (1971) described a lowering of cerebrospinal fluid (CSF) concentration of 5-HIAA in a sample of depressive subjects. Various classes of antidepressants as well as electroconvulsive treatment improve the efficiency of serotonergic transmission, particularly of 5-HT1A receptor-mediated transmission, either by sensitization of postsynaptic 5-HT receptors or by desensitization of presynaptic 5-HT receptors that normally reduce the release of 5-HT in the synaptic cleft or inhibit the firing rate of the 5-HT neuron (Blier and De Montigny, 1994). The role of 5HT-metabolism in the pathophysiology of depression has also been investigated by the tryptophan-depletion method. Tryptophan is an essential amino acid and the precursor of 5-HT. Thus, a shortage of tryptophan leads to a deficiency of 5-HT. Such a state can be generated by ingesting a mixture of amino acids, devoided of tryptophan and rich in

competing amino acids. This strategy has been shown to lead to a decrease of 5-HIAA in the CSF (Williams et al., 1999) and to a substantial lowering of brain 5-HT in animals (Moja et al., 1989). Applied to healthy volunteers, this procedure leads to mood lowering (Young et al., 1985). Furthermore, depletion of 5-HT induces a relapse in depressed patients who were in remission after treatment with 5-HT specific antidepressants (Delgado and Moreno, 2000). Van Praag (1992) demonstrated that a low CSF 5-HIAA in depressive individuals did not disappear after remission of the depression and might thus be a neurobiological trait-marker.

Disturbances of 5-HT receptors are another important mechanism that appears to be of pathophysiological relevance in depression. The 5-HT system operates via at least 15, probably function-specific, 5-HTreceptors (Van Praag, 2004). They are divided in seven subtypes, named 5-HT1, 5-HT2...5-HT7 receptors. The 5-HT1 receptor family is subdivided into four subgroups 5-HT1A up to 5-HT1D, the 5-HT2 family counts three subtypes: 5-HT2A up to 5-HT2C receptors. In humans, 5-HT receptors have been predominantly studied with challenge tests. Indirect 5-HT agonists have been used such as the 5-HT precursors tryptophan and 5-HTP, as well as fenfluramine, a 5-HT releaser and inhibitor of its reuptake (Newman et al., 1998). The secretion of prolactin and adrenocorticotrophic hormone (ACTH) by the pituitary gland and of cortisol by the adrenal cortex have been mostly used as serotonergically mediated variables. Most of these studies reported blunting of the hormonal responses to indirect 5-HT agonists in a subgroup of depression (Ansseau, 1997; Newman et al., 1998), indicating down-regulation of 5-HT receptors. The prolactin responses to fenfluramine and to the selective serotonin reuptake inhibitor (SSRI) citalopram remained blunted in recovered patients (Florey et al., 1998). These findings suggest that some aspects of impaired serotonergic transmission are trait-related phenomena.

A widespread reduction in 5-HT1A receptor binding was reported in patients with major depression, both presynaptically in the raphe nuclei and postsynaptically, i.e. in several cortical regions (Drevets et al., 1999; Sargent et al., 2000). As low 5-HT1A receptor binding did not increase after clinical remission of depression, these disturbances might be regarded as trait-marker and therefore represent a neurobiological risk factor for depression. Additional support for the hypothesis that 5-HT1A receptor disturbances are involved in the pathophysiology of depression or certain subtypes of depression has been obtained from animal data. In animal models of depression, highly selective 5-HT1A receptor agonists possess antidepressant properties (Mayorga et al., 2001).

HPA axis hyperactivity hypothesis

Although studies over the last 40 years have demonstrated that hyperactivity of the hypothalamic-pituitary-adrenal axis is one of the most consistent neurobiological

findings in the research of depressive disorders, there is no agreement regarding the underlying mechanisms. In the 1950s, elevated plasma cortisol levels in indivuals suffering from a depressive state were described by Board et al. (1956). Further studies revealed that patients suffering from depressive disorders showed a reduced suppression of cortisol secretion by the adrenal cortex in response to dexamethasone, an elevated cortisol secretion in response to the adrenocorticotropic hormone (ACTH) and a hypersecretion of corticotropin-releasing hormone (CHR), which stimulates ACTH secretion (Holsboer and Barden, 1996; McQuade and Young, 2000). An impairment of the glucocorticoid receptor system in HPA axis sensitive structures and the hippocampus, resulting in a dysregulation of the feedback inhibition by endogenous corticosteroids may explain the HPA axis hyperactivity in depression (for review see: Pariante and Lightman, 2008).

Genetic influences

A medline search based metanalysis of studies on the genetic epidemiology of major depression revealed that the heritability of this disturbance probably ranges from 31% to 41% (Sullivan et al., 2000). It is assumed that mainly alterations in the expression of neurotransmitters, neuropeptides and receptors rather than structural gene changes underly genetic influences, which might be relevant in the origin of depression. This assumption is also reflected by the concept of gene-environment interaction ,meaning that genetic vulnerability to depression comes to expression only in individuals exposed to specific environmental factors, e.g. emotional stress (Sullivan et al., 2000). Studies of the interaction of the serotonin transporter 5-HTTLPR polymorphism genotype and environment on the development of depression in aldulthood have suggested a role for both childhood maltreatment and stressful life events. Childhood maltreatment might trigger early changes in brain function associated with the polymorphism explaining the link of such negative events with adult depressive episodes by an increased vulnerability for stressful life events (for review see: Brown and Harris, 2008).

2.1.2 Psychosocial factors

The etiological impact of stressful life events, economic status, social relationships and personality on the depressive disorders has been investigated extensively, but there are hardly theoretical concepts, that have been widely accepted. The personality model of Cloninger, which has been established in 1987 (Cloninger, 1987), has been linked with the individual risk of developing a depressive disorder. A high score of Harm Avoidance,

which is defined as the tendency to respond intensely to aversive stimuli, was found to increase the susceptibility to depressive disorders (Cloninger, 1987). Temperament following Cloningers personality model was also identified as a predictive factor of treatment succes in 50 % of a patient sample suffering from severe depressive disorder unter treatment with clomipramine and desipramine (Joyce et al., 1993).

3. Pharmacotherapy with antidepressants

The pharmacological treatment of depressive disorders started in the 1950s after the discovery of tricyclic antidepressants (TCA) and monoamine oxydase inhibitors (MAO-Inhibitors). Most antidepressants primarily enhance norepinephrine (NE), dopamine (DA) and serotonin (5-HT) activity in brain, although their antidepressive effect is likely to be modulated by other neurotransmitter and neurohormonal systems such as the HPA axis (Nemeroff and Owens, 2004). MAO-Inhibitors have been shown to be effective antidepressants. They prevent the catabolism of NE, DA and 5-HT neurotransmitters, but their use is limited due to the risk of severe adverse events such as serotonin syndrome and hypertensive crises. NE-selective antidepressants, such as the TCA desipramine and the selective NE re-uptake inhibitor (NRI) reboxetine, have been shown to be effective in the treatment of MDD. In a review by Montgomery et al. (1997) istwas concluded that reboxetine may have an equipotent antidepressant efficacy as compared to TCAs and to selective serotonin re-uptake inhibitors (SSRIs). Selective antidepressants such as serotonin reuptake inhibitors preserve the ability to block the serotonin (5HT) reuptake, but have no effect on e.g. M1, H1 or α1 receptors, which increases their tolerability compared to TCAs. Thus, SSRIs have become established as the first-line therapy for the treatment of MDD although many patients (28 - 55%) fail to respond sufficiently to this class of compounds (Trivedi et al., 2006). Dual-acting antidepressants (SNRIs), such as duolextine, have shown similar but not superior rates of response to the SSRIs (Detke et al., 2004).

As a consequence of the assumed role of the HPA axis in the pathophysiology of depression, antagonistic compounds to stress-hormones have been studied in animals and humans with regard to their antidepressive potential. In animals, such compounds reduce a repertoire of behaviours associated with anxiety (Basso et al., 1999; Arborelius et al., 2000). Recently, CP-316,311, a selective nonpeptide antagonist of corticotropin-releasing hormone type 1 (CRH(1)) receptors, was randomly assigned to a sample of patients with recurrent major depression in a 6-week fixed-dose, double-blind placebo-

and sertraline-controlled trial. Although CP-316,311 was safe and well tolerated in this study population, it failed to demonstrate any efficacy in the treatment of major depression (Binneman et al., 2008).
It is becoming increasingly evident that depression is a heterogeneous, systemic illness, involving an array of different neurotransmitters, neurohormones, and neuronal pathways. Considering that a generally superior mode of antidepressive action has not been found during more than half a century, reliable prediction methods of treatment response to seronotonergic versus non-serotonergic antidepressants could be of considerable clinical value in order to avoid an unnecessarily delayed onset of antidepressant effect.

4. The stimulus intensity dependence of ERP components (IDAP)

4.1 Background: The methodology of EEG and ERP

Electroencephalography (EEG) is a diagnostic method based on the measurement of electrical activity produced by the brain as recorded from electrodes placed on the scalp. The electrical activity of the brain derives from microanatomic structures, e. g. currents within a single dendrite of a single neuron, which reach the scalp surface. Resulting voltage differences on the scalp can be recorded as the electroencephalogram. EEG electrodes positioned on different locations at the surface of the head receive electrical signals which can be amplified and digitalized for later processing (figure 1).

The scalp EEG measures the summed activity of post-synaptic currents. The result is a flow of ions into or out of the dendrite, which is followed by compensatory currents in the extracellular space. These extracellular currents generate EEG voltages. Thus, a surface EEG reading is the summation of the synchronous activity of thousands of neurons that have similar spatial orientation, radial to the scalp. As currents that are tangential to the scalp cannot be detected by this method, the EEG benefits from the parallel, radial arrangement of apical dendrites in the cortex. Because voltage fields decrease with the fourth power of the radius, activity from deep sources is more difficult to detect than currents near the skull.

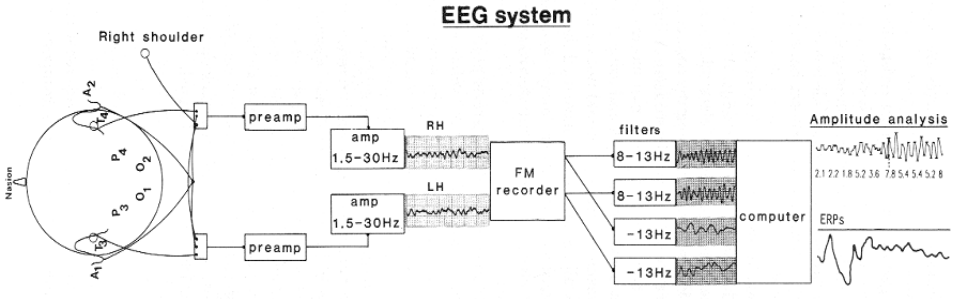

Figure 1
A typical EEG laboratory, with the subject to the left and examples of EEG recordings to the right. Only two electrode leads are shown here, but the principle is the same when more leads are added. RH = right hemisphere, LH left hemisphere, amp = amplifier. The settings for the filters are only examples of possible settings. (Hugdahl, Kenneth, 1995. Psychophysiology. The mind-body perspective. Cambridge, MA & London, England; Harvard University Press.)

Scalp EEG activity oscillates at multiple frequencies having different characteristic spatial distributions associated with different states of brain functioning. These oscillations represent synchronized activity over a network of neurons (Hughes and John, 1999).

In conventional scalp EEG, the recording is obtained by placing electrodes on the scalp with a conductive gel or paste, usually after preparing the scalp area by light abrasion to reduce impedance due to dead skin cells. Many systems typically use electrodes, each of which is attached to an individual wire. Some systems use caps (figure 2) or nets into which electrodes are embedded; this is particularly common when high-density arrays of electrodes are needed.

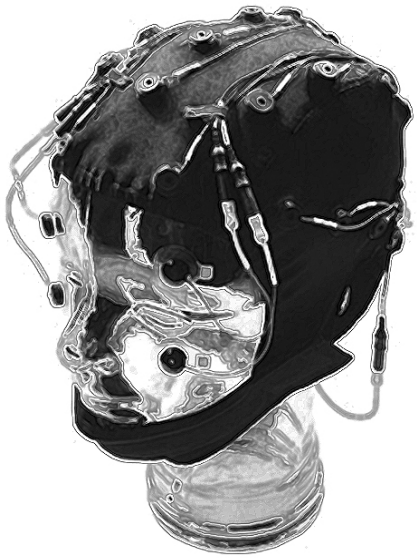

Figure 2
EEG Cap (32 channels)

Electrode locations and names are specified by the International 10–20 system for most clinical and research applications (figure 3). This system ensures that the naming of electrodes is consistent across laboratories. In most clinical applications, 19 recording electrodes (plus ground and system reference) are used. Each electrode is connected to one input of a differential amplifier (one amplifier per pair of electrodes); a common system reference electrode is connected to the other input of each differential amplifier. These amplifiers augment the voltage between the active electrode and the reference (typically 1.000–100.000 times, or 60–100 dB of voltage gain).

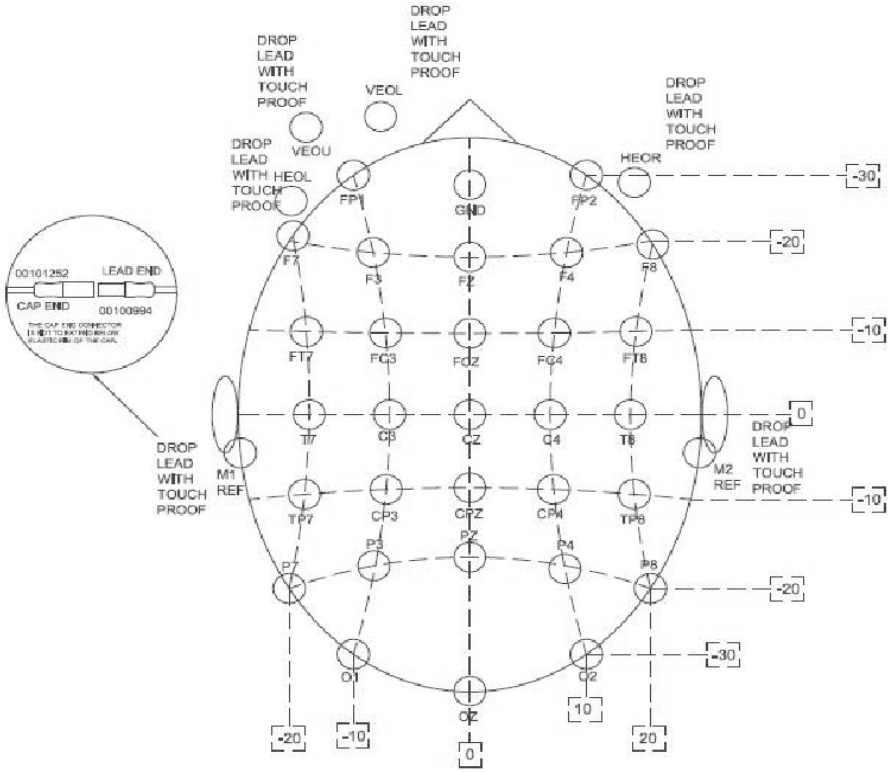

Figure 3
32-channel EEG: positions of electrodes (10 -20 system)

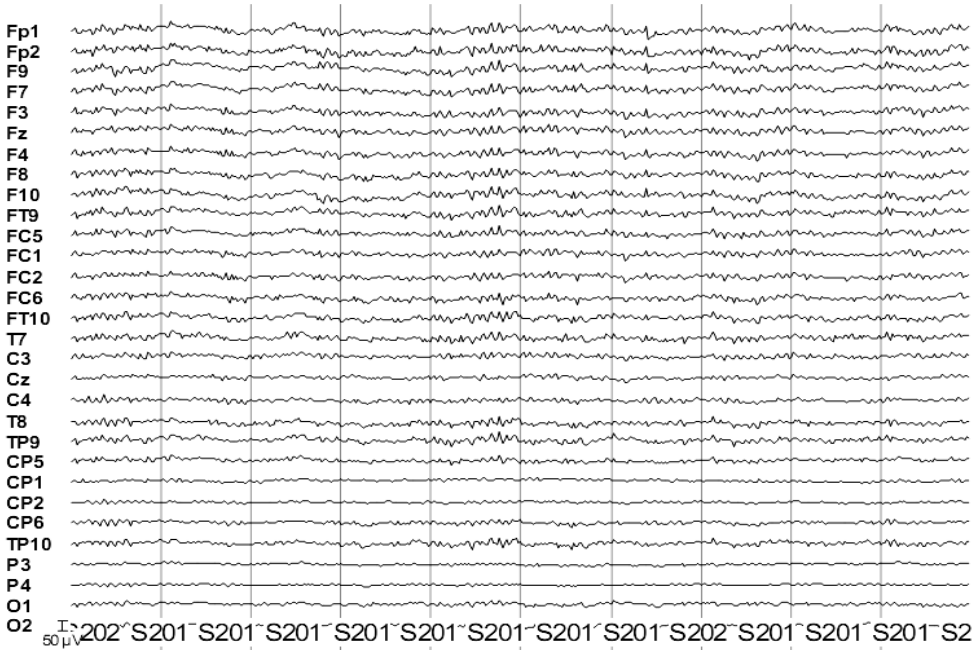

Figure 4
Normal (calm) EEG

In digital EEG systems the amplified signal is digitized via an analog-to-digital converter, after being passed through an anti-aliasing filter. Analog-to-digital sampling typically occurs at 256-512 Hz in clinical scalp EEG; sampling rates of up to 10 kHz are used in some research applications.The digital EEG signal is stored electronically and can be filtered for display. Typical settings for the high-pass filter and a low-pass filter are 0.5-1 Hz and 35–70 Hz, respectively. The high-pass filter typically filters out slow artifacts, such as electrogalvanic signals and movement artifacts, whereas the low-pass filter filters out high-frequency artifacts, such as electromyographic signals.

A typical adult human EEG signal (figure 4) is about 10µV to 100 µV in amplitude when measured from the scalp and is about 10–20 mV when measured from subdural electrodes.The EEG is typically described in terms of (1) rhythmic activity and (2) transients. The rhythmic activity is divided into bands by frequency. To some degree, these frequency bands are a matter of nomenclature (i.e., any rhythmic activity between 8-12 Hz can be described as "alpha"), but these designations were chosen because rhythmic activity within a defined frequency range was noted to have a typical distribution over the scalp or a certain biological significance. Most of the cerebral

signals observed in the scalp EEG falls in the range of 1-20 Hz. Under standard clinical recording techniques, activity below or above this range is likely to be artefactual .

Cognitive research performed with EEG most frequently makes use of the event-related potential (ERP) technique. Most ERP paradigms involve a subject being provided with a stimulus to react to, either overtly or covertly (figure 5). Depending on the hypothesis tested, there are at least two conditions that vary in some manner, e.g. high versus low tone freuency. As the stimulus-response is going on, an EEG is being recorded from the subject. The ERP is obtained by averaging the EEG signal from each of the trials under a certain condition; averages from one stimulus-response condition can then be compared with averages from the other stimulus-response condition(s). Stimuli of various sensory qualities can be applied albeit that visual and auditory stimuli are most frequently used.
ERPs to auditory stimulation consist of early and late components (figure 6). There are three major early components: the electrically positive P1 component at about 50 ms following stimulus onset, the negative N1 component at about 100 ms and the positive P2 component at about 200 ms. Furthermore, the P300 or P3 component, which occurs 300 ms (mean) after stimulus onset, is the most important late component in sensory evoked potentials. Enhancement of auditory stimulus intensities, are mainly reflected by increases in the amplitudes of the P1/N1, N1, N1/P2 and the P2. Thus, interindividual differences in the stimulus intensity dependence of ERP components (IDAP) are phenomena that predominantly, refer to early ERP components. Typically, several stimulus intensities are used to elicit amplitude changes, which can be transformed into slope values that give the amplitude change in µV per 10/dB (Beauducel et al., 2000).

4.2 The stimulus intensity dependence of ERP components (IDAP)

Research on the stimulus intensity dependence of ERP components has a long tradition, but broad scientific interest arose only 15 years ago when Hegerl and Juckel (1993) introduced their hypothesis and theory of the IDAP as an indicator of central serotonergic neurotransmission (Hegerl and Juckel, 1993).

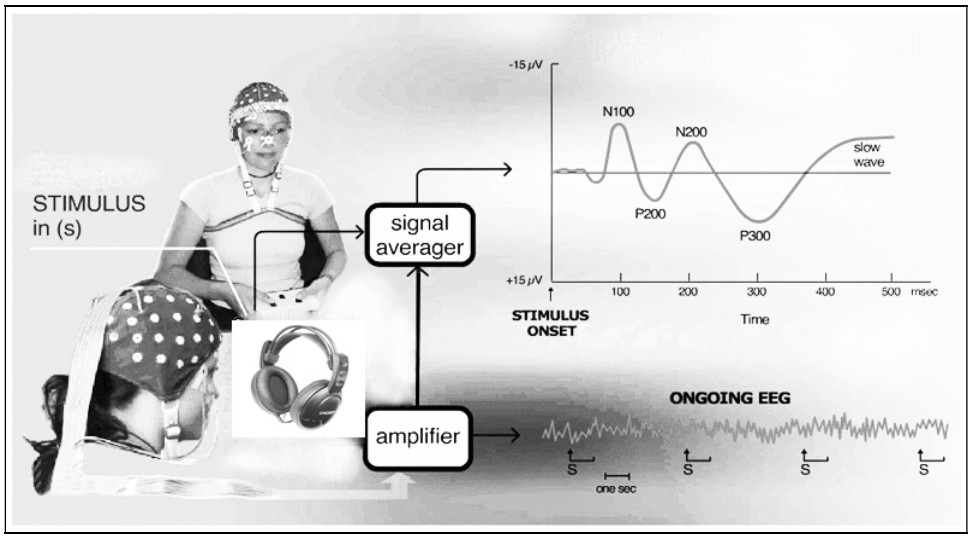

Figure 5
Schematic depiction of the measurement and averaging of event-related potentials. Singular "waves" temporally associated with a specific experimental event are usually labeled according to their polarity and latency from the triggering event. (e.g. N100 = negatively poled ERP with peak latency at roughly 100 milliseconds; P300 = positively poled ERP with peak latency at roughly 300 milliseconds). Negative potential deflections are often presented facing upwards (modified from MPI for neurological Research, Cologne).

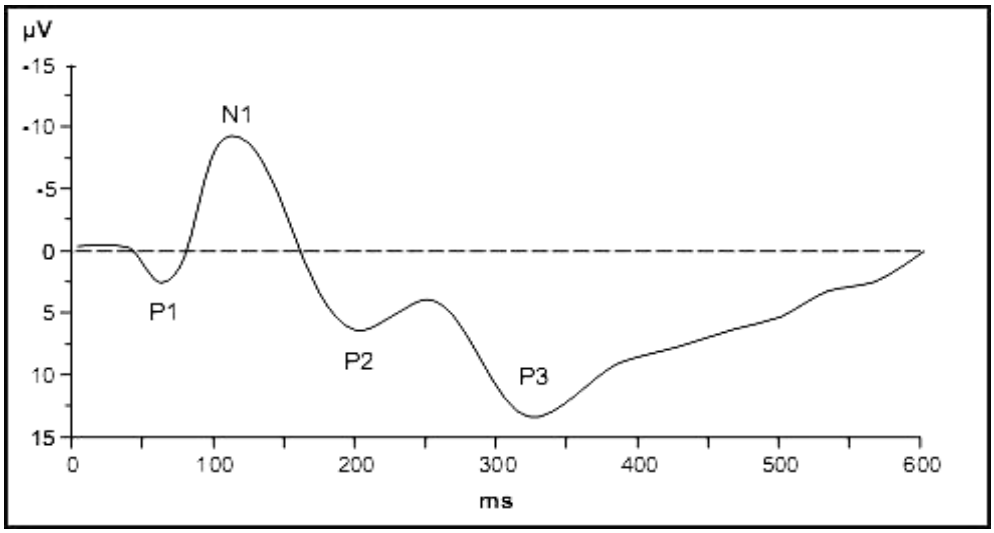

Figure 6
Auditory evoked potential with early (P1, N1, P2) and late components (P3).

Neurophysiology

An ERP results mainly from the summation of cortical excitatory and inhibitory postsynaptic potentials triggered by the release of neurotransmitters like GABA and glutamate. An ERP is therefore likely to directly reflect functional aspects of these neurotransmitters. Furthermore, it may indirectly reflect modulating effects of neurotransmitters like serotonin and acetylcholine on cortical functioning. The highest concentrations of cortical serotonin have consistently been found in the primary sensory cortices, especially in the primary auditory cortex. The theory of Hegerl and Juckel (1993) postulates that serotonergic neurotransmission modulates sensory processing in the auditory cortex, mainly in the primary auditory cortex. Serotonergic projections to the auditory cortices might modulate neuronal activity in an initial stage of signal processing in the cortex. The observed loudness dependence of auditory ERP components is therefore assumed to occur as a consequence of cortical serotonergic modulatory effects. An increased serotonergic neurotransmission, for example as a consequence of a high firing rate of serotonergic neurons in the raphe nuclei, is assumed to result in an only small increase in the auditory evoked cortical response with increasing loudness (intensity) of the stimuli (tones), or in other words, in a low IDAP. The inverse relationship between central nervous serotonergic activity and IDAP is assumed to exist vice versa as well.

Method

Although many studies found reliable results either for the N1/P2 derived IDAP or for the N1 derived IDAP, it is still not definitely known which ERP component gives the best correlation with central nervous serotonergic activity. The N1 or N1/P2-component of the auditory evoked potential occurs about 70 – 200 ms after the stimuli, exhibits pronounced interindividual differences in its loudness dependence, and can be reliably observed. In the 1980s, intracranial recordings and lesion studies provided evidence that the N1 and N1/P2 component is generated by primary as well as secondary auditory cortices (for review see Vaughan an Arezzo, 1988).

The serotonergic modulation theory of the IDAP (Hegerl et al., 1994) results in the following main assumption: a high IDAP is assumed to be mainly caused by low serotonergic neurotransmission in the primary auditory cortex that is known to be highly innervated with serotonergic neurons. According to Hegerl et al. (1993), the IDAP should be ideally assessed in the primary auditory cortex. In human studies this can indirectly be done by using multichannel-EEG combined with source analysis techniques such as Brain Electrical Source Analysis (BESA; Gallinat and Hegerl, 1994; Scherg, 1990; Scherg

and Von Cramon, 1986) or Low Resolution Electromagnetic Source Analysis (LORETA; Mulert et al., 2002; Pascual-Marqui et al., 1994). By means of BESA, it has been demonstrated that the scalp N1/P2 can be explained by two dipoles per hemisphere, a radial and a tangential dipole (Hegerl et al., 1994). The latter accounts for most of the variance and is located in the primary auditory cortex, whereas the former touches the secondary cortex. Thus, dipole source analysis allows separating the influence of the serotonergic modulated primary auditory cortex from other structures. However, dipole source analysis requires special expertise and is often too time consuming and expensive for clinical practice and even research. In clinical settings, low-cost, easy applicable, fast, automated and objective methods are needed. This is perhaps the reason why there are still many successful studies using only one or a few EEG channels at central sites, mostly Cz (e.g. Carrillo-de-la-Pena et al.,2006; Gallinat et al., 2003). In the study by Dierks et al. (1999), using an acute tryptophan depletion paradigm, a high correlation of the IDAP of tangential dipoles with the IDAP at Cz was found.

Despite its wide acceptation, data on the reliability of the IDAP are limited, possibly for two reasons. *First*, the visual modality was preferred in the beginning of intensity dependence research, at that time usually called augmenting/reducing (Buchsbaum an Pfefferbaum, 1971). This explains why most studies reporting reliabilities on single channel intensity dependence, deal with results derived from visual stimuli. However, visual and auditory intensity dependence are not clearly associated (Raine et al., 1981), and the serotonin hypothesis as proposed by Hegerl and coworkers is exclusively based on the auditory modality. *Second*, having focused to auditory intensity dependence following the serotonin hypothesis by Hegerl, the majority of studies no longer reported the reliability of single and multichannel IDAP, but only that of tangential and radial dipoles. Dipole analyses in these studies revealed mostly good test–retest reliabilities for the IDAP of the tangential dipole from r = .77 (Gohle, 2005) to r = .88 in a study by Hegerl et al. (1994). The coefficients for the radial dipole were much lower, ranging from r = .38 for N1/P2 amplitude (Hegerl et al., 1994) to r = .66 (Carrillo-de-la-Pena, 2001).

Despite the above mentioned shortcomings, there are studies on the methodology of IDAP in which single electrodes were applied and auditory stimuli were used. Most of these studies detected reliabilities between r =.7 and .8. In a sample including 8 men and 16 women (mean age = 47, SD = 11), Beauducel et al. (2000) revealed a retest-stability of the IDAP after about three weeks of .71, .77 and .59 at Cz, C3, C4, respectively. Applying Principal Component Analysis (PCA) improved the reliability in this study to .78, .80 and .76 at Cz, C3, C4, respectively. In a sample comprising 5 males and 16 women (18–23 years, mean age = 18.8; SD = 1.2), Carrillo-de-la-Pena (2001) found correlations of .79

and .76 with an extraordinarily long test–retest interval of one year for the central electrodes Fz and Cz, respectively. In a study by Hegerl et al. (1988), two retests in a sample of 17 males and 16 females (19–63 years, mean = 40; SD = 13) were performed: one retest after 20 min and another after three weeks. While the first revealed reliabilities of .70, .58 and .53 for Cz, C3, C4, respectively, even higher reliabilities coefficients of .74, .77, and .71 were found with the test–retest interval comprising three weeks. In a study by Sandor et al. (1999), the stabilities were in a similar range of .71 to .76 after 1, 2 or 24 hours, when the stimuli were presented with a fixed repetition rate. However, in the same study variable interstimulus intervals revealed only a reliability coefficient of .52 irrespective of the test–retest interval. These lower reliability coefficients as found by Sandor et al. (1999) might be caused by a higher proportion of men in the sample (4 women and 8 men; 24 ± 3 years). Friedman and Meares (1979b) examined only males (N = 29; 18–30 years old; mean age not given) and found a significant stability of r = .6 over one week for the N1/P2 slope. Another gender homogeneous study by Debener et al. (2002) including 18 women between 19 and 34 years (M = 22.4, SD = 3.4) revealed stabilities of the N1/P2 slope between r = .56 and r = .58. The results of the latter gender homogeneous studies demonstrated much lower coefficients. It should be stressed, however that the EEGs of Debener et al. (2002) were run in subjects fasting just before treatment within a cross-over placebo controlled tryptophan depletion paradigm. This experimental condition might have caused more state-related error variance than an usual IDAP test-retest paradigm. In summary, most stability coefficients for single central electrodes in gender-mixed samples vary between .7 and .8, while more homogeneous samples showed lower reliabilities.

Most of the above cited studies have limitations with respect to three factors that have potential impact on reliability, namely gender, age and variability of IDAP parameters. Females showed a higher IDAP in several studies (Bruneau et al., 1986; Camposano and Lolas, 1992; Schwerdtfeger et al., 1999; Silverman et al., 1973). Age also impacts the IDAP as a higher age generally seems to coincide with lower IDAP (Hegerl et al., 1994; Siniatchkin et al., 2000). Thus, an age- and gender-heterogeneous sample might generate artificially elevated test–retest reliabilities partly due to the constant factors of age and sex from test to retest, assuming that every IDAP-correlated variable that remains constant from test to retest could lead to an overestimation of test–retest reliability.

In addition to the assumed confounding effects of age and gender, different parameterizations of the IDAP might also influence the reliability. The most common way to parameterize the IDAP seems to be the calculation of a linear regression of ERP

amplitudes against stimulus intensities. The slope of this linear regression (called ‘‘amplitude-stimulus function slope’’ or ASF slope) indicates the linear amplitude change with increasing stimulus intensity. Another slope (called median slope) does not require linearity of the IDAP. It is calculated as the median of all possible slopes between pairs of two amplitudes each. For example, if five intensities are used, then there are 10 possible slopes between pairs of intensities from which the median is calculated. The reliability of all slope measurements will depend on the reliabilities of the single evoked potentials at each intensity from which the slope is calculated. These reliabilities of the amplitudes are of special interest, as some studies dealing with the serotonin hypothesis of IDAP abstain from calculating slopes but rely on the ERP amplitude derived from a single high intensity stimulus (Manjarrez et al., 2005). Most studies describe test–retest reliabilities, which indicate both stability of the IDAP over time and accuracy of measurement. Other relevant reliability indices are the odd–even and split-half reliability. In the case of evoked potentials, all sweeps are virtually the same. The comparison of the averaged odd sweeps with the averaged even sweeps does not provide much information on internal consistency or homogeneity, but instead gives information on the ability of the paradigm to get a sufficient signal-to-noise ratio if only half of the sweeps are averaged. Therefore, odd–even reliability will substantially depend on the length of the paradigm, i.e. how many stimuli are presented. The split-half reliability compares the IDAP of the first half of the testing session with the IDAP of the second half. Besides measurement accuracy, the correlation coefficient between first and second half’s IDAP will be influenced by time-on-task processes like habituation, fatigue and test anxiety that could alter the ranking of interindividual differences in the IDAP. By comparing the split-half and odd–even reliabilities, the influence of such time-on-task effects can be estimated.

Hensch et al. (2008) examined test–retest, split-half and odd–even reliabilities of the IDAP and of single ERP amplitudes at central positions (Cz, C3, C4) simultaneously (Hensch et al., 2008). The authors evaluated auditory-evoked potentials from 166 students, of whom 37 women and 25 men were retested after three weeks. Furthermore, they compared two manners of IDAP slope calculation: the ASF slope (based on linear regression) and the median slope. The possibly confounding effects of age and gender were controlled for. Test–retest and odd–even reliabilities were remarkably high at Cz in both females (r = .88/.86) and males (r = .82/.79). Reliabilities were higher in women, higher with linear than median slopes and best at Cz. Hensch and coworkers (2008) concluded that reliabilities, especially at Cz, can reach the same level as previously reported by dipole-source-localization methods, if sufficient sweep numbers are applied.

Animal studies

Juckel et al. (1999) reported differential effects of microinjection of a 5-HT1A agonist and a 5-HT1A antagonist into the dorsal raphe nucleus (DRN) on the intensity dependence of auditory evoked potentials (AEP) recorded epidurally from the primary and secondary auditory cortex in behaving cats. Recently, Wutzler et al. (2008) performed in vivo measurement of cortical extracellular serotonin levels simultaneously with the recording of auditory evoked potentials in the epidura of rats. Extracellular serotonin levels in the primary auditory cortex were measured by in vivo microdialysis before and after application of the selective serotonin reuptake inhibitor citalopram. The increase of serotonin levels after citalopram application was significantly related to a decrease of the IDAP of the N1 component (Wutzler et al, 2008).

Preclinical studies

Strobel et al. (2003) described an association of a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) with the N1/P2 amplitude intensity dependence. This result has been replicated by Hensch et al. (2006). Juckel et al. (2007a) reported an association between a 5-HT_{1B} receptor polymorphism and IDAP.. On the other hand, Debener et al.(2002) found no effects of acute tryptophan depletion on AEP N1/P2 amplitude stimulus intensity function (ASF-slope) in a placebo controlled trial in healthy women. Uhl et al. (2006), measured the IDAP in female subjects during infusion of citalopram versus placebo before and for a period of up to 60 min after drug/placebo administration, and performed dipole source analysis. They found no significant change of the IDAP in response to citalopram compared to the placebo condition. Finally, Norra et al. (2008) performed a tryptophan depletion test versus placebo in healthy women and monitored tryptophan levels and mood states while measuring the IDAP followed by dipole source analysis. Calculated IDAP slopes neither differed significantly between treatments nor correlated with states of mood, suggesting that the IDAP might reflect individual (trait) rather than state differences of serotonergic neurotransmission.

Clinical studies

In clinical research, the role of the IDAP has been studied in several psychiatric disturbances and diseases. Tuchtenhagen et al. (2000) and Croft et al. (2001) found an elevated intensity dependence of auditory evoked dipole source activity in abstinent ecstasy (MDMA) users and long-term MDMA abuse, respectively. Juckel et al. (2003)

reported that the IDAP of the primary auditory cortex derived from dipole source analysis in 25 in-patients suffering from schizophrenia is significantly decreased compared to a healthy control group. Wang et al. (2006) described an elevation of the IDAP in female patients with histrionic personality disorder. Furthermore, the IDAP was found to be elevated in patients suffering from bipolar affective disorder (Brocke et al., 2000) and from fibromyalgia (Carrillo-de-la-Pena et al., 2006). However, despite the hypothesized pathophysiological role of serotonin in obsessive compulsive disorder, Carrillo-de-la-Pena et al. (2000) could not demonstrate any difference between patients and controls. Senkowski et al. (2003) described a significantly lower IDAP derived from bilateral tangential dipoles in 31 medication-free patients with general anxiety disorder in comparison to matched healthy control subjects.

The concept of the IDAP as an electrophysiological indicator of central serotonergic neurotransmission in major depressive disorder with special relevance to treatment-response to serotonergic versus non-serotonergic antidepressants and to other medication that influence the serotonergic system, has been evaluated in several studies (Gallinat et al., 2000; Juckel et al., 2004; Lee et al., 2005; Mulert et al., 2007, Guille et al., 2008). At the time, however, we started our studies on the IDAP, the value of this method in clinical psychiatric practice was still unclear.

Shortcomings and questions

At the start of our research program, there were no sufficient data on the predictive value of the IDAP in the differentiated psychopharmacotherapy of depressive disorders. Whereas earlier studies from 1990s evaluated the IDAP in samples of patients who were treated with a variety of antidepressants during the period of the test procedures, we performed two studies in groups of patients, who were exclusively treated with one selective serotonergic or with one selective noradrenergic antidepressant, respectively. In order to obtain a range of normal values, we measured the IDAP in a sample of healthy subjects. These IDAP results were subsequently compared with those obtained from a sample of unmedicated patients with major depressive disorder in order to learn whether MDD is paralled by a general abnormality of the IDAP. In a further study, we investigated whether there is a relationship between symptom clusters of MDD and the level of the IDAP.

5. Aims of the performed studies and outline of this thesis

The specific aims of the presented studies are the following:

1. To evaluate the predictive value of the of pre-treatment intensity dependent auditory evoked ERP component (P1, N1, P2, P1/N1, N1/P2) amplitude slopes in a sample of patients with major depression exclusively treated with the SSRI citalopram.
2. To assess the predictive value of pre-treatment intensity dependent auditory evoked ERP component (P1, N1, P2, P1/N1, N1/P2) amplitude slopes in a sample of patients with major depression, who were exclusively treated with the selective norepinephrine re-uptake inhibitor (SNRI) reboxetine.
3. To investigate whether the IDAP is mainly a state or a trait indicator of central serotonergic neurotransmission, whether serotonergic and non-serotonergic antidepressants differently influence the IDAP and whether the pre-treatment IDAP changes during the course of treatment of MDD.
4. To investigate the hypothesis that unmedicated patients suffering from major depression exhibit a higher IDAP compared to healthy control subjects.
5. To investigate the hypothesis that the IDAP is associated with certain psychometrically assessed symptom clusters of depression and to identify, describe and discuss those dimensions that are indirectly associated with a favourable outcome to SSRI treatment as predicted by a strong IDAP.

Our research group evaluated the IDAP in patients suffering from MDD and in healthy control subjects. We assessed the predictive value of the IDAP for treatment with the SSRI citalopram (Chapter 2) as well as for treatment with the selective norepinephrine re-uptake inhibitor reboxetine in MDD (Chapter 3). We compared the IDAP of auditory ERP components in unmedicated patients with MDD with the results from healthy controls (Chapter 4) and evaluated treatment effects of serotonergic and noradrenergic antidepressants in MDD on the IDAP itself (Chapter 6). Furthermore, we studied associations of certain clinical symptom clusters of MDD with the auditory ERP components (Chapter 5). In Chapter 7 we discuss the results and present the final conclusions of this thesis.

References

- Alonso J et al. ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project.Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl. 2004; 420:21-7.
- Ansseau, M. Hormonal disturbances in depression. In: Honig, A.,Van Praag, H.M. (Eds.). 1997. Depression. Neurobiological, Psychopathological and Therapeutic Advances. John Wiley, Chichester.
- Beauducel A, Debener S, Brocke B, Kayser J. On the reliability of augmenting/reducing. Peak amplitudes and principal component analysis of auditory evoked potentials. J Psychophysiol 2000; 14:226–40.
- Beck AT, Ward CH, Mendelson M, Mock J,Erbaugh J. Archives of General Psychiatry 1961; 4:561-571.
- Bijl RV, van Zessen G, Ravelli A. Psychiatric morbidity among adults in The Netherlands: the NEMESIS-Study. II. Prevalence of psychiatric disorders. Netherlands Mental Health Survey and Incidence Study. Ned Tijdschr Geneeskd. 1997; 141(50):2453-60.
- Binneman B, Feltner D, Kolluri S, Shi Y, Qiu R, Stiger T. A 6-week randomized, placebo-controlled trial of CP-316,311 (a selective CRH1 antagonist) in the treatment of major depression. Am J Psychiatry. 2008 May;165(5):617-20.
- Blier, P and De Montigny, C. Current advances and trends in the treatment of depression. Trends Pharmacol. Sci. 1994. 15:220–226.
- Brocke B, Beauducel A, John R, Debener S, Heilemann H. Sensation seeking and affective disorders: characteristics in the intensity dependence of acoustic evoked potentials. Neuropsychobiology 2000; 41:24–30.
- Brown GW, Harris TO. Depression and the serotonin transporter 5-HTTLPR polymorphism: a review and a hypothesis concerning gene-environment interaction. J Affect Disord. 2008 Nov;111(1):1-12.
- Bruneau N, Barthelemy C, Jouve J, Lelord G. Frontal auditory-evoked potential augmenting-reducing and urinary homovanillic acid. Neuropsychobiology 1986; 16:78–84.
- Buchsbaum, M and Silverman, J. Stimulus intensity control and the cortical evoked response. Psychosom Med 1968; 30: 12-22.
- Buchsbaum M and Pfefferbaum A. Individual differences in stimulus intensity response. Psychophysiology 1971; 8:600–11.

- Bunney WE Jr, Davis JM. Norepinephrine in depressive reactions. A review. Arch Gen Psychiatry. 1965 Dec; 13(6):483-94.
- Board F, Persky H, Hamburg DA. Psychological stress and endocrine functions; blood levels of adrenocortical and thyroid hormones in acutely disturbed patients. Psychosom Med. 1956 Jul-Aug; 18(4):324-33.
- Camposano S, Lolas F. Effects of stimulation intensity, gender and handedness upon auditory evoked potentials. Arq Neuropsiquiatr 1992; 50:43–9.
- Carrillo-de-la-Pena MT, Mavrogiorgou P, Juckel G, Hauke W., Gallinat J, Frodl T, Zaudig M, Hegerl U. Loudness dependence of auditory evoked potentials in obsessive–compulsive disorder: a pilot study. Psychiatry Research 2000; 93: 209–216.
- Carrillo-de-la-Pena MT. One-year test–retest reliability of auditory evoked potentials (AEPs) to tones of increasing intensity. Psychophysiology 2001; 38:417–24.
- Carrillo-de-la-Pena MT, Vallet M, Perez MI, Gomez-Perretta C. Intensity dependence of auditory-evoked cortical potentials in fibromyalgia patients: a test of the generalized hypervigilance hypothesis. J Pain 2006;7:480–7.
- Clayton AH, Zajecka J, Ferguson, JM, Filipiak-Reisner, JK, Brown MT, Schwartz GE. Lack of sexual dysfunction with the selective noradrenaline reuptake inhibitor reboxetine during treatment for major depressive disorder. Int Clin Psychopharmacol 2003 ; 18:151-156.
- Cloninger CR. A systematic method for clinical description and classification of personality variants. A proposal. Arch Gen Psychiatry. 1987 Jun; 44(6):573-88.
- Croft RJ, Klugman A, Baldeweg T, Gruzelier JH. Electrophysiological evidence of serotonergic impairment in long-term MDMA (“ecstasy”) users. American Journal Psychiatry 2001; 158: 1687–1692.
- Cyranowski JM, Frank E., Cherry C, Houck P, Kupfer DJ. Prospective assessment of sexual function in women treated for recurrent major depression. J Psychiatr Res 2004; 38:267-273.
- Debener S, Strobel A, Kurschner K, Kranczioch C, Hebenstreit J, Maercker A, et al. Is auditory evoked potential augmenting/reducing affected by acute tryptophan depletion? Biol Psychol 2002; 59:121–33.
- Delgado PL and Moreno FA. Role of norepinephrine in depression. J Clin Psychiatry. 2000; 61 Suppl 1:5-12.
- Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Neuropsychopharmacol. 2004 Dec; 14(6):457-70.

- Dierks T, Barta S, Demisch L, Schmeck K, Englert E, Kewitz A, et al. Intensity dependence of auditory evoked potentials (AEPs) as biological marker for cerebral serotonin levels: effects of tryptophandepletion in healthy subjects. Psychopharmacology (Berl) 1999; 146:101–7.
- Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, Huang Y, Gautier, C, Mathis C. PET imaging of serotonin 1A receptor binding in depression. Biol. Psychiatry 1999. 46:1375–1387.
- Fava M, Rosenbaum JF, Hoog SL, Tepner RG, Kopp JB, Nilsson ME. Fluoxetine versus sertraline and paroxetine in major depression: tolerability and efficacy in anxious depression. J Affect Disord 2000 ; 59: 119-126.
- Fava M. Daytime sleepiness and insomnia as correlates of depression. J Clin Psychiatry 2004; 65 Suppl 16:27-32.
- Ferguson JM. SSRI Antidepressant Medications: Adverse Effects and Tolerability. Prim Care Companion J Clin Psychiatry 2001; 3:22-27.
- Florey JD, Mann JJ, Manuck SB, Muldoon MF. Recovery from major depression is not associated with normalisation of serotonergic function. Biol. Psychiatry 1998. 43:320–326.
- Friedman J, Meares R. The effect of placebo and tricyclic antidepressants on cortical evoked potentials in depressed patients. Biol Psychol 1979b; 8:291–302.
- Gallinat J, Hegerl U. Dipole source analysis. Linking scalp potentials to their generating neuronal structures. Pharmacopsychiatry 1994; 27:52–3.
- Gallinat J, Bottlender R, Juckel G, Munke-Puchner A, Stotz G, Kuss HJ,et al. The loudness dependency of the auditory evoked N1/P2-component as a predictor of the acute SSRI response in depression. Psychopharmacology (Berl) 2000; 148:404–11.
- Gallinat J, Senkowski D, Wernicke C, Juckel G, Becker I, Sander T, et al. Allelic variants of the functional promoter polymorphism of the human serotonin transporter gene is associated with auditory cortical stimulus processing. Neuropsychopharmacology 2003; 28:530–2.
- Gohle D. Lautstärkeabhängigkeit akustisch evozierter Potentiale bei Patienten mit Zwangserkrankungen. Doctoral dissertation, Medical Faculty Ludwig-Maximilians-University München, München, Germany, 2005.
- Gopal KV, Briley KA, Goodale ES, Hendea OM. Selective serotonin reuptake inhibitors treatment effects on auditory measures in depressed female subjects. Eur J Pharmacol 2005; 520:59–69.
- Guille V, Croft RJ, O'Neill BV, Illic S, Phan KL, Nathan PJ. An examination of acute changes in serotonergic neurotransmission using the loudness dependence measure

of auditory cortex evoked activity: effects of citalopram, escitalopram and sertraline. Hum Psychopharmacol. 2008; 23(3):231-41.

- Hamilton M. A rating scale for depression. J Neurology, Neurosurgery and Psychiatry 1960; 23:56-62.
- Hamilton M., Development of a rating scale for primary depressive illness, Br J Soc Clin Psychol, 1967; 6:278-96.
- Hamilton M., HAMA, Hamilton Anxiety Scale. In: Guy, W. (Ed.), ECDEU Assessment manual for psychopharmacology. US Department of Health and Human Services, Rockville, MD, 1976 ; pp. 194-198.
- Harvey BH and Bouwer CD. Neuropharmacology of paradoxic weight gain with selective serotonin reuptake inhibitors. Clin Neuropharmacol 2000; 23:90-97.
- Hegerl U, Prochno I, Ulrich G, Müller-Oerlinghausen B. Are auditory evoked potentials suitable for predicting the response to lithium prophylaxis? A study on the effects of repeated measurement, age, gender, and personality on the amplitude/stimulus intensity function in healthy volunteers. Pharmacopsychiatry 1988;21:336–7.
- Hegerl U, Juckel G. Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. Biol Psychiatry 1993;33:173–87.
- Hegerl U, Bottlender R, Gallinat J, Kuss HJ, Ackenheil M and Moller HJ. The serotonin syndrome scale: first results on validity, Eur Arch Psychiatry Clin Neurosci, 1998; 248:96-103.
- Hegerl U, Gallinat J, Juckel G. Event-related potentials. Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? J Affect Disord 2001; 62:93-100.
- Heninger GR, Delgado PL, Charney DS.The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. Pharmacopsychiatry. 1996 Jan;29(1):2-11.
- Hensch T, Wargelius HL, Herold U, Lesch KP, Oreland L, Brocke B. Further evidence for an association of 5-HTTLPR with intensity dependence of auditory-evoked potentials. Neuropsychopharmacology 2006; 31:2047-2054.
- Hensch T, Herold U, Diers K, Armbruster D, Brocke B. Reliability of intensity dependence of auditory-evoked potentials. Clinical Neurophysiology 2008; 119: 224–236.
- Hetzel G, Moeller O, Erfurth A, Michael N, Rothermundt M, Arolt V,Evers S. Pharmacopsychiatry 2004; 37:200-205.

- Holsboer F and Barden N. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. Endocr Rev. 1996 Apr;17(2):187-205.
- Hughes JR and John ER. Conventional and Quantitative Electroencephalography in Psychiatry. J Neuropsychiatry Clin Neurosci 1999 May; 11: 190-208.
- Jacobs BL and Azmitia EC. Structure and function of the brain serotonin system, Physiol Rev, 1992; 72: 165-229.
- Joyce PR, Mulder RT, Cloninger CR.Temperament predicts clomipramine and desipramine response in major depression. J Affect Disord. 1994; Jan;30(1):35-46.
- Juckel G, Molnar M, Hegerl U, Csepe V, Karmos G. Auditory-evoked potentials as indicator of brain serotonergic activity - first evidence in behaving cats. Biol Psychiatry 1997; 41:1181–95.
- Juckel G, Hegerl U, Molnar M, Csepe V, Karmos G. Auditory evoked potentials reflect serotonergic neuronal activity – a study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus. Neuropsychopharmacology 1999; 21:710–6.
- Juckel G, Gallinat J, Riedel M, Sokullu S, Schulz C, Moller HJ, Muller N, Hegerl U. Serotonergic dysfunction in schizophrenia assessed by the loudness dependence measure of primary auditory cortex evoked activity. Schizophr Res 2003; 64: 115-124.
- Juckel G, Mavrogiorgou P, Bredemeier S, Gallinat J, Frodl T, Schulz C, et al. Loudness dependence of primary auditory-cortex-evoked activity as predictor of therapeutic outcome to prophylactic lithium treatment in affective disorders – a retrospective study. Pharmacopsychiatry 2004; 37:46–51.
- Juckel G, Pogarell O, Augustin H, Mulert C, Muller-Siecheneder F, Frodl T, Mavrogiorgou P, Hegerl U. Differential prediction of first clinical response to serotonergic and noradrenergic antidepressants using the loudness dependence of auditory evoked potentials in patients with major depressive disorder. 2007; J Clin Psychiatry 68:1206-1212.
- Juckel G, Hegerl U, Giegling I, Mavrogiorgou P, Wutzler A, Schuhmacher C, Uhl I, Brune M, Mulert C, Pogarell O, Rujescu D. Association of 5-HT1B receptor polymorphisms with the loudness dependence of auditory evoked potentials in a community-based sample of healthy volunteers. Am J Med Genet B Neuropsychiatr Genet. 2008; 5 ;147B(4):454-458.
- Kahkonen S, Ahveninen J, Pennanen S, Liesivuori J, Ilmoniemi RJ and Jaaskelainen IP. Serotonin modulates early cortical auditory processing in healthy subjects: evidence

from MEG with acute tryptophan depletion, Neuropsychopharmacology 2002; 27:862-868.

- Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003; 289(23):3095-105.
- Kline NS. Clinical experience with iproniazid (marsilid).J Clin Exp Psychopathol. 1958; Apr-Jun;19(2, Suppl. 1):72-78
- Kuenzel HE, Murck H, Held K, Ziegenbein M,Steiger A. Pharmacopsychiatry 2004; 37:193-195.
- Kuhn R. The treatment of depressive states with G 22355 (imipramine hydrochloride). Am J Psychiatry. 1958 Nov; 115(5):459-464.
- Linka T, Müller BW, Bender S, Sartory G. The intensity dependence of the auditory evoked N1 component as a predictor of response to Citalopram treatment in patients with major depression. Neurosci Lett 2004; 367:375-378.
- Linka T, Müller BW, Bender S, Sartory G, Gastpar M. The intensity dependence of auditory evoked ERP components predicts responsiveness to reboxetine treatment in major depression. Pharmacopsychiatry 2005; 38:139-143.
- Lee TW, Yu YW, Chen TJ, Tsai SJ. Loudness dependence of the auditory evoked potential and response to antidepressants in Chinese patients with major depression. J Psychiatry Neurosci 2005; 30:202–205.
- Mayorga A, Dalvi A, Page M, Zimov-Levinson S, Hen R, Lucki I. Antidepressant-like behavioral effects in 5-hydroxytryptamine1A and 5-hydroxytryptamine1B receptor mutant mice. J. Pharmacol. Exp Ther. 2001. 298:1101– 1107.
- Manjarrez G, Hernandez E, Robles A, Hernandez J. N1/P2 component of auditory evoked potential reflect changes of the brain serotonin biosynthesis in rats. Nutr Neurosci 2005; 8:213–8.
- McQuade R, Young AH. Future therapeutic targets in mood disorders: the glucocorticoid receptor. Br J Psychiatry. 2000 Nov; 177:390-5.
- Montgomery SA. Reboxetine: additional benefits to the depressed patient. J. Psychopharmacol 1997; 11:9-15.
- Mulert C, Juckel G, Augustin H, Hegerl U. Comparison between the analysis of the loudness dependency of the auditory N1/P2 component with LORETA and dipole source analysis in the prediction of treatment response to the selective serotonin reuptake inhibitor citalopram in major depression. Clin Neurophysiol 2002; 113:1566–72.

- Mulert C, Jager L, Pogarell O, Bussfeld P, Schmitt R, Juckel G, Hegerl U. Simultaneous ERP and event-related fMRI: focus on the time course of brain activity in target detection. Methods Find Exp Clin Pharmacol 2002; 24 Suppl D:17-20.
- Moja E, Cipolla P, Castoldi D, Tofanetti O. Dose-response de-crease in plasma tryptophan and in brain tryptophan and serotonin after tryptophan-free amino acid mixtures in rats. Life Sci. 1989. 44:971– 976.
- Mulert C, Juckel G, Brunnmeier M, Karch S, Leicht G, Mergl R, et al. Prediction of treatment response in major depression: integration of concepts. J Affect Disord 2007; 98:215–25.
- Nathan PJ, Segrave R, Phan KL, O'Neill B, Croft RJ. Direct evidence that acutely enhancing serotonin with the selective serotonin reuptake inhibitor citalopram modulates the loudness dependence of the auditory evoked potential (LDAEP) marker of central serotonin function. Hum Psychopharmacol 2006; 21:47–52.
- Nemeroff CB, Owens MJ. Pharmacologic differences among the SSRIs: focus on monoamine transporters and the HPA axis. CNS Spectr. 2004 Jun;9(6 Suppl 4): 23-31.
- Newman ME, Shapira B, Lerer B.. Evaluation of central se-rotonergic function in affective and related disorders by the fenfluramine challenge test: a critical review. Int. J. Neuropsychopharmacol. 1998 ; 1:49– 69.
- NIMH, N.I.o.M.H., CGI. Glinical global impressions. In R. Bonato (Ed.), Manual for the EDCEU assessment battery, 2nd edition, Vol. 12, NIMH, Chevy Chase, 1976.
- Norra C, Mrazek M, Tuchtenhagen F, Gobbele R, Buchner H, Sass H, Herpertz SC. Enhanced intensity dependence as a marker of low serotonergic neurotransmission in borderline personality disorder. J Psychiatr Res 2003; 37:23-33.
- Norra C, Becker S, Bröcheler A, Kawohl W, Kunert HJ, Buchner H. Loudness dependence of evoked dipole source activity during acute serotonin challenge in females. Hum Psychopharmacol. 2008; 23(1):31-42.
- Owens MJ. Selectivity of antidepressants: from the monoamine hypothesis of depression to the SSRI revolution and beyond. J Clin Psychiatry 2004; 6:5-10.
- Paige SR, Fitzpatrick DF, Kline JP, Balogh SE Hendricks SE. Event-related potential amplitude/intensity slopes predict response to antidepressants. Neuropsychobiology 1994; 30:197-201.
- Pariante CM and Lightman SL. The HPA axis in major depression: classical theories and new developments Trends Neurosci. 2008 Sep; 31(9):464-8.
- Pascual-Marqui RD, Michel CM, Lehmann D. Low resolution electro-magnetic tomography: a new method for localizing electrical activity in the brain. International Journal of Psychophysiology 1993; 18: 49–65.

- Perry PJ. Pharmacotherapy for major depression with melancholic features: relative efficacy of tricyclic versus selective serotonin reuptake inhibitor antidepressants. J Affect Disord 1996; 39:1-6.
- Proietti-Cecchini A, Afra J, Schoenen J. Intensity dependence of the cortical auditory evoked potentials as a surrogate marker of central nervous system serotonin transmission in man: demonstration of a central effect for the 5HT1B/1D agonist zolmitriptan (311C90, Zomig). Cephalalgia 1997; 17:849-854; discussion 799.
- Quednow BB, Kuhn KU, Stelzenmueller R, Hoenig K, Maier W and Wagner M. Effects of serotonergic and noradrenergic antidepressants on auditory startle response in patients with major depression, Psychopharmacology (Berl) 2004 Oct; 175 (4): 399-406.
- Raine A, Mitchell DA, Venables PH. Cortical augmenting-reducing-modality specific? Psychophysiology 1981; 18:700–8.
- Riedel WJ, Klaassen T, Griez E, Honig A, Menheere PP, van Praag HM. Dissociable hormonal, cognitive and mood responses to neuroendocrine challenge: evidence for receptor-specific serotonergic dysregulation in depressed mood. Neuropsychopharmacology 2002; 26:358-367.
- Sandor PS, Roon KI, Ferrari MD, van Dijk JG, Schoenen J. Repeatability of the intensity dependence of cortical auditory evoked potentials in the assessment of cortical information processing. Cephalalgia 1999; 19:873–9.
- Scherg M, Von Cramon D. Evoked dipole source potentials of the human auditory cortex.ElectroencephalogrClinNeurophysiol 1986; 65:344–60.
- Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry. 1965 Nov; 122(5):509-22.
- Schwerdtfeger A, Baltissen R. Augmenter vs. Reducer: Kortikale und autonome Reaktivität auf weißes Rauschen unterschiedlicher Intensität in Abhängigkeit vom Persönlichkeitsmerkmal Augmenting-Reducing. Zeitschrift für Differentielle und Diagnostische Psychologie 1999; 20:247–262.
- Sargent PA, Husted Kjaer K, Bench CJ, Rabiner EA, Messa C, Meyer J, Gunn RN, Grasby PM, Cowen PJ. Brain serotonin 1A receptor binding measured by positron emission tomography with [11 C]WAY-100635. Effects of depression and antidepressant treatment. 2000. Arch. Gen. Psychiatry 57, 174– 180.
- Semlitsch HV, Anderer P, Schuster P and Presslich O. A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP, Psychophysiology 1986; 23:695-703.

- Senkowski D, Linden M, Zubragel D, Bar T, Gallinat J. Evidence for disturbed cortical signal processing and altered serotonergic neurotransmission in generalized anxiety disorder. Biol Psychiatry 2003; 53:304-314.
- Shore PA, Silver SL, Brodie BB. Interaction of reserpine, serotonin, and lysergic acid diethylamide in brain. Science. 1955 Aug 12;122(3163):284-5.
- Silverman J, Buchsbaum M, Stierlin H. Sex differences in perceptual differentiation and stimulus intensity control. J Pers Soc Psychol 1973;25:309–18.
- Siniatchkin M, Kropp P, Neumann M, Gerber W, Stephani U. Intensity dependence of auditory evoked cortical potentials in migraine families. Pain 2000; 85:247–54.
- Spielberger CD. Manual for the State-Trait-Anxiety Inventory. Consulting Psychologist Press, Palo Alto. 1970.
- Strobel A, Debener S, Schmidt D, Hunnerkopf R, Lesch KP and Brocke B. Allelic variation in serotonin transporter function associated with the intensity dependence of the auditory evoked potential, Am J Med Genet 2003; 118B: 41-47.
- Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000 Oct; 157(10): 1552-62.
- Tuchtenhagen F, Daumann J, Norra C, Gobbele R, Becker S, Pelz S, Sass H, Buchner H, Gouzoulis-Mayfrank E. High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent ecstasy (MDMA) users. Neuropsychopharmacology 2000; 22: 608-617.
- Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006 Jan; 163(1):28-40.
- Uhl I, Gorynia I, Gallinat J, Mulert C, Wutzler A, Heinz A, Juckel G. Is the loudness dependence of auditory evoked potentials modulated by the selective serotonin reuptake inhibitor citalopram in healthy subjects? Hum Psychopharmacol. 2006; 21(7):463-71.
- von Knorring L and Johansson F. Changes in the augmenter-reducer tendency and in pain measures as a result of treatment with a serotonin-reuptake inhibitor--zimelidine. Neuropsychobiology 1980; 6:313-8.
- von Knorring L and Perris C. Biochemistry of the augmenting-reducing response in visual evoked potentials. Neuropsychobiology 1981; 7:1-8.

- Van Praag HM, Korf J, Puite J. 5-Hydroxyindoleacetic acid levels in the cerebrospinal fluid of depressive patients treated with probenecid. Nature. 1970 Mar 28; 225(5239):1259-60.
- Van Praag HM, Korf J. Endogenous depressions with and without disturbances in the 5-hydroxytryptamine metabolism: a biochemical classification? Psychopharmacology 1971. 19:148– 152.
- Van Praag HM. Make Believes in Psychiatry or the Perils of Progress. 1992. Brunner/Mazel, New York.
- Van Praag HM. The Diagnosis of depression in disorder. Australian and New Zealand Journal of Psychiatry. 1998 ; 32:767-772.
- Van Praag, HM. The debit balance of present day stress research. World J. Biol. Psychiatry 2004. 5:154– 159.
- Vaughan Jr. HG and Arezzo JC. The neural basis of event-related-potentials. In: Picton, TW (Ed.), Human Event-Related Potentials. EEG Handbook Revised Series 1988; Vol. 3. Elsevier, Amsterdam, pp.45-96.
- Wang W, Timsit-Berthier M, Schoenen J. Intensity dependence of auditory evoked potentials is pronounced in migraine: an indication of cortical potentiation and low serotonergic neurotransmission? Neurology 1996; 1404-1409.
- Wang W, Wang Y, Fu X, Liu J, He C, Dong Y, Livesley WJ, Jang KL. Cerebral information processing in personality disorders: I. Intensity dependence of auditory evoked potentials. Psychiatry Res. 2006 Feb 28; 141(2):173-83.
- Willeit M, Praschak-Rieder N, Neumeister A, Zill P, Leisch F, Stastny J, Hilger E, Thierry N, Konstantinidis A, Winkler D, Fuchs K, Sieghart W, Aschauer H, Ackenheil M, Bondy B, Kasper S. A polymorphism (5-HTTLPR) in the serotonin transporter promoter gene is associated with DSM-IV depression subtypes in seasonal affective disorder. Mol Psychiatry 2003; 8:942-946.
- Williams WA, Shoaf SE, Hommer D, Rawlings R, Linnoila M. Effects of acute tryptophan depletion on plasma and cerebrospinal fluid tryptophan and 5-hydroxyindoleacetic acid in normal volunteers. J. Neurochem. 1999. 72:1641– 1647.
- Wutzler A, Winter C, Kitzrow W, Uhl I, Wolf RJ, Heinz A, Juckel G. Loudness dependence of auditory evoked potentials as indicator of central serotonergic neurotransmission: simultaneous electrophysiological recordings and in vivo microdialysis in the rat primary auditory cortex. Neuropsychopharmacology 2008; 33(13):3176-81.
- Young S, Smith S, Pihl R, Ervin F. Tryptophan depletion causes a rapid lowering of mood in normal males. Psychopharmacology (Berl.) 1985. 87:173– 177.

- Yoshida K, Takahashi H, Higuchi H, Kamata M, Ito K, Sato K, Naito S, Shimizu T, Itoh K, Inoue K, Suzuki T, Nemeroff CB. Prediction of antidepressant response to milnacipran by norepinephrine transporter gene polymorphisms. Am J Psychiatry 2004; 161:1575-1580.
- Zuckerman M, Murtaugh T, Siegel J. Sensation seeking and cortical augmenting-reducing. Psychophysiology 1974; 11:535-542.

CHAPTER 2

THE INTENSITY DEPENDENCE OF THE AUDITORY EVOKED N1 COMPONENT AS A PREDICTOR OF RESPONSE TO CITALOPRAM TREATMENT IN PATIENTS WITH MAJOR DEPRESSION.

The intensity dependence of the auditory evoked N1 component as a predictor of response to Citalopram treatment in patients with major depression.

Thomas Linka, Bernhard Müller, Stefan Bender, Gudrun Sartory

Published in Neuroscience Letters 2004 Sep 9;367(3):375-8

1. Abstract

The intensity dependence of the auditory evoked N1 ERP component (IDAP) has been suggested as an indicator of central serotonergic neurotransmission with relevance to pharmacological treatment. Here we report results of a study evaluating the IDAP in 16 in-patients fulfilling DSM-IV criteria for major depressive episode in the course of treatment with the Selective Serotonin Reuptake Inhibitor citalopram. Our data revealed a significant correlation between the intensity slopes of the N1 amplitude prior to citalopram-treatment and treatment-response: patients with higher intensity slopes of N1 amplitude showed a significantly stronger decrease of HDRS-Score after citalopram-treatment than patients within the lower intensity slope ranges. Our results indicate an association of N1 amplitude intensity dependence with response to antidepressant treatment with citalopram.

2. Introduction

The search for reliable electrophysiological indicators of serotonergic dysfunction in major depression with relevance for psychopharmacological therapy has attracted scientific interest recently [5, 7, 16]. The involvement of serotonin in auditory cortical processing has been demonstrated e.g. in studies examining the effects of acute tryptophan depletion [11]. Amplitude changes of the N1 and the

N1/P2 ERP component in response to different tone intensities have been suggested as a correlative of central nervous serotonergic activity [3, 7, 10, 18, 21] with a strong loudness dependent amplitude increase (“strong intensity dependence”) presumably reflecting low serotonergic neurotransmission and vice versa [10]. This psychophysiological finding might be of clinical relevance with regard to the modulating role of serotonin in the pathogenetic concept of depression [8] and of other psychiatric disorders [4, 19]. While first investigations on the intensity dependence of sensory evoked potentials and their relation to psychiatric disorders by Buchsbaum et al. (1968) and von Knorring et. al. (1978) were based on the hypothesis of "augmenting/reducing" [3], recently the same phenomenon has been described by different terms. As to the acoustic modality, the term "IDAP" (intensity dependence of the cortical auditory evoked potentials) is widely used, especially in the context of migraine research [15], whereas in the context of psychiatric research the term "LDAEP" ("loudness dependence of the auditory evoked potentials") has been suggested [5, 7].

As the auditory cortex belongs to those cortical areas with the highest density of serotonergic fibers in brain [9], Juckel et al. examined the effects of microinjection of a $5HT_{1A}$agonist and a $5HT_{1A}$antagonist into the dorsal raphe nucleus (DRN) on AEP recorded epidurally from the primary and secondary auditory cortex in behaving cats. Injection of a $5HT_{1A}$agonist (8-OH-DPAT), which inhibits the firing rate of serotonergic DRN neurons, lead to a stronger intensity dependence of AEP from the primary auditory cortex, whereas injection of a $5HT_{1A}$antagonist (spiperone) reduced AEP intensity dependence compared to baseline[10]

Several studies corroborated the concept of the IDAP as an indicator of central serotonergic neurotransmission. The concentration of 5-hydroxyindoleacetic acid (main metabolite of serotonin) in cerebrospinal fluid was found to be inversely correlated with the intensity dependence of sensory evoked potentials [21] and serotonin agonists reduced the intensity dependence of the N1 amplitude [10, 20]. In patients under treatment with serotonin reuptake inhibitors (SSRI) Hegerl et al. (1998) found high scores in the serotonin syndrome scale (SSS) to be associated with low IDAP and vice versa [7]. Tuchtenhagen et al. (2000) reported a high intensity dependence of auditory evoked dipole source activity in abstinent ecstasy (MDMA) users indicating a decreased serotonergic activity [19]. Similar results have been described by Croft et al. (2001) for long-term MDMA abuse [4]. Recently, Strobel et al. (2003) found a functional polymorphism in the promoter

region of the serotonin transporter gene (5-HTTLPR) to be associated with the N1/P2 amplitude intensity dependence [18].

Based on these findings the IDAP has been suggested as an psychophysiological indicator of central serotonergic neurotransmission in depression with special relevance to treatment-response to SSRI. Indeed, Paige et al. (1994) found responders to different serotonergic antidepressants to show significantly higher P2 amplitude slopes (as a function of stimulus intensity) prior to treatment than nonresponders [14]. Gallinat et al. (2000) reported an association of pre-treatment N1/P2 amplitude slope with treatment success as indicated by a decrease of Hamilton scores after 4 weeks in patients treated with different SSRI (paroxetine, sertraline, citalopram) [5].

The aim of our study was to assess the predictive value of pre-treatment intensity dependent auditory evoked ERP component (P1, N1, P2, P1/N1, N1/P2) amplitude slopes in a sample of patients with major depression exclusively treated with the SSRI citalopram.

3. Method

Sixteen acutely depressed in-patients (DSM-IV: 296.2, 296.3, 296.5, 300.4; APA 1994), who were admitted consecutively to the Department of Psychiatry and Psychotherapy of the University of Duisburg-Essen and considered as candidates for an antidepressant medication with citalopram, were included in the study. Patient characteristics are given in Table 1. Clinical symptoms of major depression were assessed by means of psychiatric rating scales: Clinical Global Impression (CGI) [13], Hamilton Rating Scale for Depression (HDRS, 21 items) [6] and Beck Depression Inventory (BDI) [1]. Clinical ratings were performed by experienced psychiatrists, who had no information on patients' ERP data. The total score of HDRS had to be 20 at least.

Patients gave their informed written consent prior to their inclusion in the study. The study was approved by the local ethics committee. ERP data were recorded one day before the start of pharmacological treatment with citalopram (baseline). The CGI, HDRS and BDI scores, were obtained at the day of ERP recordings and

again after three weeks of treatment (D25). Pre-treatment antidepressants (eight patients, non-SSRI) were stopped at least 2 days before the ERP recording. Central neurological disorders, abuse of illicit drugs and alcohol dependence were excluded, as was pre-treatment with electroconvulsive therapy. The auditory threshold with respect to 1000 Hz tones was below 30 dB as measured by an audiometer. Following the ERP-recording, patients were treated with citalopram (range: 20 to 40 mg) for 25 (21 – 28) days. Concomitant medication with antipsychotics, moodstabilizers, additional antidepressants were not allowed. Concomittant benzodiazepine treatment (n=3) was restricted to a maximum dose of 1.5mg lorazepam per day. Lorazepam was not given 12 hours before ERP-recording.

Table 1
Subject characteristics

n	16
Age	39.38 (±14.5)
Gender (m/f)	5/11
Education (y)	13.0 (±2.6)
Nicotine (n; mg/d)	9; 12.9 (6.3)
Episodes of depression (n)	2.37(±1.7)
Duration (y)	8.3 (±7.3)
Dose of citalopram (Day 25)	37.5 (±10.0)
CGI (Baseline/25)	4.56 (±0.7)/3.9 (±0.8)
HDRS (Baseline)	25.13 (±3.5)/14.6 (±5.5)
BDI (Baseline)	29.50 (±12.5)/21.6 (11.0)

ERP data were recorded in a sound-attenuated and electrically shielded room and subjects were seated in a comfortable armchair. Auditory stimulation was done in two runs of 500 stimuli each with an interstimulus-interval randomized between 500 ms and 900 ms. Auditory stimuli of 1000 Hz, with 80 ms duration (10 ms rise / fall) were presented at five intensities of 60, 70, 80, 90 and 100 dB sound pressure level via TDH-39p headphones (Telephonics Inc.) in randomized order. Stimulus presentation was generated by Neuroscan Stim 3.3 Software. Evoked potentials were recorded from 27 scalp electrodes (extended international 10-20 system) with linked earlobes as reference using a 32-channel EEG amplifier (Neuroscan Inc.). Additionally, vertical and horizontal electro-oculogram (EOG) was recorded

for offline artifact removal [17]. ERP data were recorded with a sampling rate of 500 Hz in the frequency range of 0.1 to 100 Hz. ERP data were offline filtered with a 0.1 Hz to 30 Hz bandpass filter (Neuroscan Edit 4.1). EEG data were segmented into periods of 600 ms starting 100 ms prior to stimulus onset. Segments with artifacts exceeding +/- 50 µV were rejected from further analysis. ERP averages were computed for each stimulus intensity level. Mean sweep numbers ranged between 117.5 and 133.4 sweeps for intensities between 60 dB up to 100 dB. Amplitudes of the N100 and the P200 components were computed from electrode Fz, Fcz, Cz, C3 and C4. Intensity slopes (linear regression) were computed for the P1, N1, P2 amplitudes and the P1/N1 and N1/P2 peak to peak amplitudes. All statistical analyses were performed using SPSS 11.5.

4. Results

Psychiatric rating scores significantly improved from baseline to retest after 25 days of treatment: HDRS total score decreased from 25.1 (±3.5) to 14.6 (±5.5), BDI total score from 29.5 (±12.5) to 21.6 (11.0) and CGI severity of illness score from 4.6 (±0.7) to 3.9 (±0.8) as presented in table 1. A multivariate analysis of variance including the HDRS and the BDI (scale factor) at baseline and day 25 (time factor) revealed a significant main effect for the time factor ($F=38.5$, $p<.001$). The amount of symptom reduction did not differ between patient self-ratings (BDI) and psychiatrist ratings (HDRS) as indicated by the lack of a significant time x scale interaction.

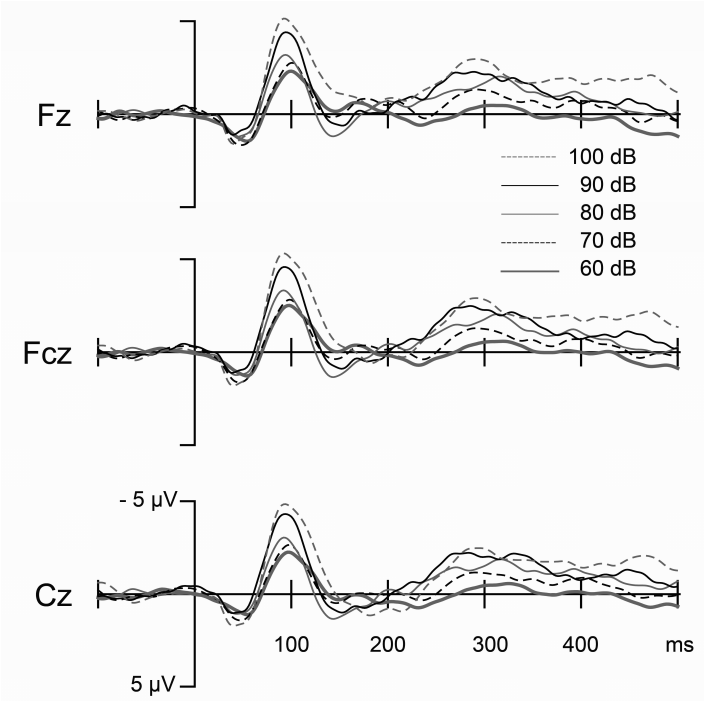

Figure 1
N1 evoked potential amplitudes at electrodes Fz, Fcz and Cz. Lines indicate 5 stimulus intensity levels ranging from 60 dB to 100 dB. The amplitude of the N1 component rises with higher stimulus intensities.

Intensity slopes of the N1 amplitudes significantly correlated with HDRS reduction at Fz (r=0.56, p=.025) at Fcz (r=0.55, p=.029) and at Cz (r=0.50, p=.048). No correlations with HDRS reduction were found for N1 amplitude slopes from C3 and C4. As illustrated in figure 2, higher intensity slopes of N1 amplitude were associated with better outcome as indicated by reduction of HDRS scores during treatment. N1 amplitude intensity slopes were not affected by sex, age, duration of illness, frequency of episodes of depression, smoking habits (Pearson's correlation). No correlation emerged for N1 intensity slopes with BDI and CGI scores. Additionally, no correlations with psychiatric ratings were found for P1, P1/N1, P2 and N1/P2 amplitude slopes.

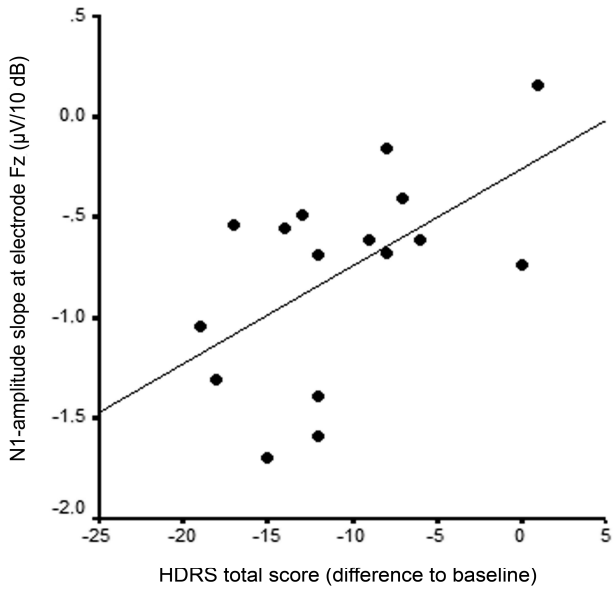

Figure 2
Scatterplot of N1 amplitude slopes at electrode Fz (µV/10dB) correlates with decrease of HDRS total score within the first three to four weeks of treatment (mean 25 days) with r=.56, p=.025.

5. Discussion

Our data revealed a significant correlation between intensity slopes of N1 amplitude prior to citalopram-treatment and treatment-response (decrease of HDRS total score) thus supporting the hypothesis of a strong IDAP being related to a favorable outcome in SSRI-treatment of major depression. In contrast to earlier reports, in our study SSRI-treatment was restricted to citalopram [5, 14] and patients were free of concomitant medication except for three patients treated with lorazepam in low doses.

In our study, we evaluated a mean period of 25 days. Although this may be characterized as an initial treatment outcome, our data revealed a significant improvement in symptoms in the self rated BDI as well as in the psychiatrist rated HDRS in the course of treatment.

While several previous studies applied reverse problem solutions like BESA or LORETA in the evaluation of the N1 auditory intensity dependence [5, 12, 19] other studies evaluated raw data with regard to N1 [[2, 18], N1/P2 [4, 18] and P2 [14] amplitude slopes. Here we investigated auditory stimulus intensity with regard to raw data P1, P1/N1, P2, N1 as well as N1/P2 amplitude slopes. We found associations of amplitude slopes with treatment outcome only for the N1 but neither for the P1/N1 nor for the N1/P2 component, probably due to the relatively small sample of patients.

In summary, our data confirm the hypothesis of a strong intensity dependence of the auditory evoked potential being associated with a favorable reponse to SSRI treatment in a group of acutely depressed in-patients treated exclusively with citalopram. In contrast to previous treatment-studies we found a significant correlation between pre-treatment intensity dependence of N1 ERP component and decrease of HDRS scores based on the analysis of raw amplitudes thus providing a non-invasive, easy applicable method of response-prediction to pharmacotherapy with citalopram in major depression. Further studies considering other antidepressants are needed to verify the clinical utility of this approach in differential indication of serotonergic versus noradrenergic antidepressants, especially corroborating the hypothesis of a better responsiveness to Selective Noradrenalin Reuptake Inhibitors (SNRI) in individuals with major depression showing a low IDAP.

6. Acknowledgements

The authors are grateful to Arndt Hesse, R. Windelschmidt, R. Franzke, Nora Löbbecke and Oliver Ligneth-Dahm for help in data collection and to Prof. M. Gastpar for support.

References

[1] Beck, A.T., Ward, C.H., Mendelson, M., Mock, J. and Erbaugh, J., An inventory for measuring depression, Archives of General Psychiatry, 4 (1961) 561-571.

[2] Brocke, B., Beauducel, A., John, R., Debener, S. and Heilemann, H., Sensation seeking and affective disorders: characteristics in the intensity dependence of acoustic evoked potentials, Neuropsychobiology, 41 (2000) 24-30.

[3] Buchsbaum, M. and Silverman, J., Stimulus intensity control and the cortical evoked response, Psychosom Med, 30 (1968) 12-22.

[4] Croft, R.J., Klugman, A., Baldeweg, T. and Gruzelier, J.H., Electrophysiological evidence of serotonergic impairment in long-term MDMA ("ecstasy") users, Am J Psychiatry, 158 (2001) 1687-92.

[5] Gallinat, J., Bottlender, R., Juckel, G., Munke-Puchner, A., Stotz, G., Kuss, H.J., Mavrogiorgou, P. and Hegerl, U., The loudness dependency of the auditory evoked N1/P2-component as a predictor of the acute SSRI response in depression, Psychopharmacology (Berl), 148 (2000) 404-11.

[6] Hamilton, M., Development of a rating scale for primary depressive illness, Br J Soc Clin Psychol, 6 (1967) 278-96.

[7] Hegerl, U., Bottlender, R., Gallinat, J., Kuss, H.J., Ackenheil, M. and Moller, H.J., The serotonin syndrome scale: first results on validity, Eur Arch Psychiatry Clin Neurosci, 248 (1998) 96-103.

[8] Heninger, G.R., Delgado, P.L. and Charney, D.S., The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans, Pharmacopsychiatry, 29 (1996) 2-11.

[9] Jacobs, B.L. and Azmitia, E.C., Structure and function of the brain serotonin system, Physiol Rev, 72 (1992) 165-229.

[10] Juckel, G., Hegerl, U., Molnar, M., Csepe, V. and Karmos, G., Auditory evoked potentials reflect serotonergic neuronal activity--a study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus, Neuropsychopharmacology, 21 (1999) 710-6.

[11] Kahkonen, S., Ahveninen, J., Pennanen, S., Liesivuori, J., Ilmoniemi, R.J. and Jaaskelainen, I.P., Serotonin modulates early cortical auditory processing in healthy subjects: evidence from MEG with acute tryptophan depletion, Neuropsychopharmacology, 27 (2002) 862-8.

[12] Mulert, C., Jager, L., Pogarell, O., Bussfeld, P., Schmitt, R., Juckel, G. and Hegerl, U., Simultaneous ERP and event-related fMRI: focus on the time course of brain activity in target detection, Methods Find Exp Clin Pharmacol, 24 Suppl D (2002) 17-20.

[13] (NIMH), N.I.o.M.H., CGI. Glinical global impressions. In R. Bonato (Ed.), Manual for the EDCEU assessment battery, 2nd edition, Vol. 12, NIMH, Chevy Chase, 1976.

[14] Paige, S.R., Fitzpatrick, D.F., Kline, J.P., Balogh, S.E. and Hendricks, S.E., Event-related potential amplitude/intensity slopes predict response to antidepressants, Neuropsychobiology, 30 (1994) 197-201.

[15] Proietti-Cecchini, A., Afra, J. and Schoenen, J., Intensity dependence of the cortical auditory evoked potentials as a surrogate marker of central nervous system serotonin transmission in man: demonstration of a central effect for the 5HT1B/1D agonist zolmitriptan (311C90, Zomig), Cephalalgia, 17 (1997) 849-54; discussion 799.

[16] Quednow, B.B., Kuhn, K.U., Stelzenmueller, R., Hoenig, K., Maier, W. and Wagner, M., Effects of serotonergic and noradrenergic antidepressants on auditory startle response in patients with major depression, Psychopharmacology (Berl) (2004).

[17] Semlitsch, H.V., Anderer, P., Schuster, P. and Presslich, O., A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP, Psychophysiology, 23 (1986) 695-703.

[18] Strobel, A., Debener, S., Schmidt, D., Hunnerkopf, R., Lesch, K.P. and Brocke, B., Allelic variation in serotonin transporter function associated with the intensity dependence of the auditory evoked potential, Am J Med Genet, 118B (2003) 41-7.

[19] Tuchtenhagen, F., Daumann, J., Norra, C., Gobbele, R., Becker, S., Pelz, S., Sass, H., Buchner, H. and Gouzoulis-Mayfrank, E., High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent ecstasy (MDMA) users, Neuropsychopharmacology, 22 (2000) 608-17.

[20] von Knorring, L. and Johansson, F., Changes in the augmenter-reducer tendency and in pain measures as a result of treatment with a serotonin-reuptake inhibitor--zimelidine, Neuropsychobiology, 6 (1980) 313-8.

[21] von Knorring, L. and Perris, C., Biochemistry of the augmenting-reducing response in visual evoked potentials, Neuropsychobiology, 7 (1981) 1-8.

[22] Wang W, Timsit-Berthier M, Schoenen J. Intensity dependence of auditory evoked potentials is pronounced in migraine: an indication of cortical potentiation and low serotonergic neurotransmission? Neurology 1996; 1404-1409.

CHAPTER 3

THE INTENSITY DEPENDENCE OF AUDITORY EVOKED ERP COMPONENTS PREDICTS RESPONSIVENESS TO REBOXETINE TREATMENT IN PATIENTS WITH MAJOR DEPRESSION.

The intensity dependence of auditory evoked ERP components predicts responsiveness to reboxetine treatment in major depression.

Thomas Linka, Bernhard Müller, Stefan Bender, Gudrun Sartory , Markus Gastpar

Published in Pharmacopsychiatry 2005 May;38(3):139-43

1. Abstract

The intensity (loudness) dependent amplitude change (IDAP) of auditory evoked Event Related Potential (ERP) components has been suggested as an indicator of central serotonergic neurotransmission. In patients with major depression, associations of high IDAP with favorable SSRI treatment outcome have been reported. This is the first study to assess the predictive value of the IDAP in SNRI treatment. We evaluated the pre-treatment intensity dependent change of auditory evoked P1, N1, P2 as well as P1/N1 and N1/P2 peak to peak amplitudes in 14 in-patients with major depressive episode (DSM IV) in the course of 24 days of treatment with the SNRI Reboxetine (6 to 12 mg/d). Our data revealed a highly significant correlation between lower intensity dependent N1 amplitude slopes prior to Reboxetine treatment and stronger decrease of HDRS total score at Fz ($r=.86$, $p<.001$), Fcz ($r=.91$, $p<.001$) and Cz ($r=.93$, $p<.001$). This result corroborates the hypothesis of the IDAP as a differential indicator of serotonergic versus noradrenergic antidepressant psychopharmacotherapy.

2. Introduction

Predicting treatment response to antidepressant medication has been a challenge to psychiatric research for decades. The decision either to start psychopharmacological treatment of major depression with a serotonergic or a noradrenergic antidepressant has been mainly based on clinical observations, that led up to now, to a considerable number of initial non-responders. The search for reliable electrophysiological indicators of serotonergic and noradrenergic

dysfunction in major depression therapy has therefore recently attracted scientific interest [6,9,10,12,13,20].

Changes of the N1 and P2 ERP component amplitudes as well as of the P1/N1 and the N1/P2 peak-to-peak amplitudes in response to different tone intensities have been suggested as a correlative of central nervous serotonergic activity [4,9,11,22,25]. The ”intensity dependence” of certain auditory evoked ERP components means that their amplitude increases with increasing loudness (= stimulus intensity) of the presented auditory stimuli. A strong loudness dependent amplitude increase (”strong intensity dependence”) presumably reflects low serotonergic neurotransmission and vice versa [11]. First investigations on the intensity dependence of sensory evoked potentials and their relation to psychiatric disorders by Buchsbaum et al. (1968) and von Knorring et. al. (1978) were based on the hypothesis of "augmenting/reducing" [4], and recently the same phenomenon has been described by different terms. The term "IDAP" (intensity dependence of the cortical auditory evoked potentials) is widely used, especially in the context of migraine research [19,26] whereas in the context of psychiatric research, the term "LDAEP" ("loudness dependence of the auditory evoked potentials") has been suggested [6,9].

Several studies corroborated the concept of the IDAP as an indicator of central serotonergic neurotransmission. The concentration of 5-hydroxyindoleacetic acid (main metabolite of serotonin) in cerebrospinal fluid was found to be inversely correlated with the intensity dependence of sensory evoked potentials [25] and serotonin agonists reduced the intensity dependence of the N1 amplitude [11,24]. Juckel et al. examined the effects of microinjection of a 5-HT1A agonist and a 5-HT1A antagonist into the dorsal raphe nucleus (DRN) on auditory evoked potentials (AEP) recorded epidurally from the primary and secondary auditory cortex in behaving cats. Injection of a 5-HT1A agonist (8-OH-DPAT), which inhibits the firing rate of serotonergic DRN neurons, led to a stronger intensity dependence of AEP from the primary auditory cortex whereas injection of a 5-HT1A antagonist (Spiperone) reduced AEP intensity dependence when compared to baseline [11]. In patients under treatment with Serotonin Reuptake Inhibitors (SSRI) Hegerl et al. (1998) found that high scores in the serotonin syndrome scale (SSS) were associated with low IDAP and vice versa [9]. Tuchtenhagen et al. (2000) reported a high intensity dependence of auditory evoked dipole source activity in abstinent ecstasy (MDMA) users which indicates decreased serotonergic activity

[23]. Similar results have been decribed by Croft et al. (2001) regarding long-term MDMA abuse [5]. Strobel et al. (2003) recently found a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) to be associated with the N1/P2 amplitude intensity dependence [22]: individuals with the ll genotype exhibited a stronger intensity dependence compared to individuals with the ls genotype. Conversely, Gallinat et al. (2003) described a weaker IDAP in individuals homozygous for the l allele compared to heterozygous subjects [7].

Based on these findings the IDAP has been suggested as an psychophysiological indicator of central serotonergic neurotransmission in depression with special relevance to treatment-response to SSRI. Paige et al. (1994) found responders to different serotonergic antidepressants demonstrate significantly higher P2 amplitude slopes (as a function of stimulus intensity) prior to treatment than nonresponders [18]. Gallinat et al. (2000) reported an association of pre-treatment N1/P2 amplitude slope with treatment success as indicated by a decrease of Hamilton scores after 4 weeks in patients treated with various SSRI [6]. Our research group recently found a better responsiveness to Citalopram treatment in depressive subjects exhibiting a strong pre-treatment intensity dependence of the auditory evoked N1 raw amplitude [14].

Considering that all effective antidepressants until now either modify serotonergic, noradrenergic or both functional systems in brain [17] , in clinical practice non-responders to SSRI treatment of Major Depression are frequently treated with selectively or additionally noradrenergic antidepressants. Studies regarding the predictive value of pre-treatment auditory evoked ERP component amplitude slopes for treatment outcome with noradrenergic antidepressants are lacking. The clinical utility of the pre-treatment IDAP in differential prediction of response to serotonergic versus noradrenergic antidepressants is basically influenced by the question, whether the IDAP is not only related to SSRI response but to responsiveness to noradrenergic antidepressants as well. Therefore, the aim of our study was to assess the predictive value of pre-treatment intensity dependent auditory evoked ERP component (P1, N1, P2, P1/N1, N1/P2) amplitude slopes in a sample of patients with major depression, who were exclusively treated with the Selective Noradrenalin Reuptake Inhibitor (NARI) Reboxetine.

3. Method

Subjects: Fourteen in-patients with major depressive episode (DSM-IV: 296.2, 296.3, 296.5; APA 1994), who were admitted consecutively to the Department of Psychiatry and Psychotherapy of the University of Duisburg-Essen and considered candidates for an antidepressant medication with Reboxetine, were included in the study. Patient characteristics are given in Table 1.

Table 1
Subject characteristics

n	14
Age	45.2 (±11.8)
Gender (m/f)	4/10
Education (y)	12.9 (±2.0)
Nicotine (n; mg/d)	6; 14.9 (±20.4)
Episodes of depression (n)	2.7(±2.4)
Duration (y)	10.0 (±8.6)
Dose of citalopram (Day 25)	8.4 (±1.4)
CGI (Baseline/25)	4.6 (±1.4)/3.4 (±1.1)
HDRS (Baseline)	24.1 (±3.7)/11.6 (±7.2)
BDI (Baseline)	23.7 (±10.6)/15.4 (10.7)

Rating scales and procedure: Clinical symptoms of major depression were assessed by means of psychiatric rating scales: Clinical Global Impression (CGI) [16], Hamilton Rating Scale for Depression (HDRS, 21 items) [8] and Beck Depression Inventory (BDI) [2]. Clinical ratings were performed by a senior psychiatrist who had no information on patients' ERP data. The total score of HDRS had to be at least 20. Patients gave their written informed consent prior to their inclusion in the study. The study was approved by the local Ethics Committee. ERP data were recorded one day before beginning pharmacological treatment with Reboxetine (baseline). The CGI, HDRS and BDI scores were obtained at the day of ERP recordings and again after three to four weeks of treatment (mean: 24 days). Pre-treatment antidepressants (six patients) were stopped at least two days before the ERP recording. Central neurological disorders, abuse of illicit drugs and alcohol

dependence were excluded, as was pre-treatment with electroconvulsive therapy. Following the ERP-recording, patients were treated with Reboxetine (range: 6 to 12 mg) for 24 (21 – 28) days. Concomitant medication with antipsychotics, mood stabilizers or additional antidepressants was not allowed. Concomittant benzodiazepine treatment (n=2) was restricted to a maximum dose of 1.5mg Lorazepam per day. Lorazepam was not given 12 hours before ERP-recording.

Electrophysiological assessment and data analysis: ERP data were recorded in a sound-attenuated and electrically shielded room. Subjects were seated in a comfortable armchair. Auditory stimulation was done in two runs of 500 stimuli each with an interstimulus-intervall randomized between 500 ms and 900 ms. Auditory stimuli of 1000 Hz, with 80 ms duration (10 ms rise / fall) were presented at five intensities of 60, 70, 80, 90 and 100 dB sound pressure level via TDH-39p headphones (Telephonics Inc.) in randomized order. The auditory threshold with respect to 1000 Hz tones was below 30 dB as measured by an audiometer. Stimulus presentation was generated by Neuroscan Stim 3.3 Software. Evoked potentials were recorded from 27 scalp electrodes (extended international 10-20 system) with linked earlobes as reference using a 32-channel EEG amplifier (Neuroscan Inc.). A vertical and horizontal electro-oculogram (EOG) was recorded for offline artifact removal [21]. ERP data were recorded with a sampling rate of 500 Hz in the frequency range of 0.1 to 100 Hz. ERP data were filtered offline with a 0.1 Hz to 30 Hz bandpass filter (Neuroscan Edit 4.1). EEG data were segmented into periods of 600 ms starting 200 ms prior to stimulus onset. The 200 ms baseline was chosen because of slightly more stable results when compared to more traditional 100 ms baseline [1]. Segments with artifacts exceeding +/- 50 µV were rejected from further analysis. ERP averages were computed for each stimulus intensity level. Mean sweep numbers ranged between 114.5 and 137.5 sweeps for intensities between 60 dB up to 100 dB. Amplitudes of the N100 and the P200 components were computed from electrode Fz, Fcz, Cz, C3 and C4. Intensity slopes (amplitude slope function derived by linear regression across stimulus intensity levels) were computed for the P1, N1, P2 amplitudes and the P1/N1 and N1/P2 peak to peak amplitudes. All statistical analyses were performed using SPSS 11.5. All used variables showed a normal distribution (Kolmogorov-Smirnov-Test) and were therefore computed as Pearson's correlation.

4. Results

Rating scales: Psychiatric rating scores significantly improved from baseline to follow-up after 24 days of treatment: HDRS total score decreased from 24.1 (±3.7) to 11.6 (±7.2), BDI total score from 23.7 (±10.6) to 15.4 (±10.7) and CGI severity of illness score from 4.9 (±0.5) to 3.4 (±1.1) as presented in Table 1. A multivariate analysis of variance including the HDRS and the BDI (scale factor) at baseline and day 24 (time factor) revealed a significant main effect for the time factor ($F=44.8$, $p<.001$). The amount of symptom reduction did not differ between patient self-ratings (BDI) and psychiatrist ratings (HDRS) as indicated by the lack of a significant time x scale interaction.

ERP data: Mean amplitudes of the N1 at electrode Fz increased from –2.93 µV (±2.17) at 60 dB to –5.70 µV (±3.40) at 100 dB; at electrode Fcz from –3.20 µV (±2.17) at 60 dB to –5.9 µV (±3.14) at 100 dB; at electrode Cz from –3.15 µV (±2.0) at 60 dB up to –5.64 µV (±2.63) at 100 dB; at C3 from –2.96 µV (2.0) to –5.57 µV (±3.23), and at C4 from –2.96 µV (±1.64) to –5.25 µV (±2.88). N1 intensity slopes (µV / 10 dB) at Fz, Fcz, Cz, C3 and C4 were 0.64 (±0.53), 0.65 (0.45), 0.61 (±0.37), 0.64 (±0.47) and 0.57 (±0.47) respectively. The P1/N1 intensity slopes were 0.64 (±0.47), 0.68 (±0.47), 0.69 (±0.45), 0.69 (±0.50) and 0.66 (±0.58) respectively and the N1/P2 intensity slopes were 0.65 (±0.64), 0.83 (±0.58), 0.89 (±0.55), 0.65(±0.73) and 0.59 (±0.68) respectively. Group averages for electrodes Fz, Fcz and Cz are shown in Figure 1.

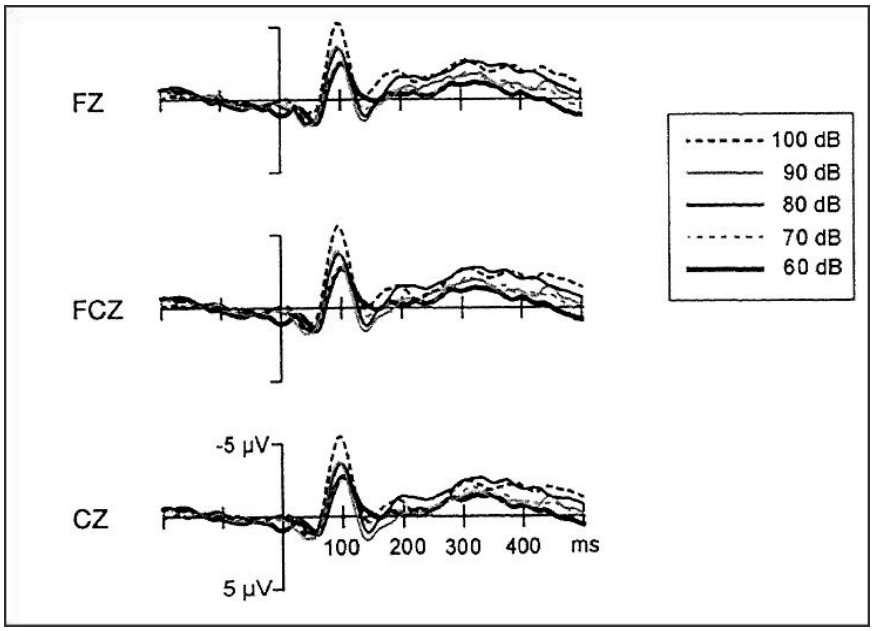

Figure 1
N1 evoked potential amplitudes at electrodes Fz, Fcz and Cz. Lines indicate 5 stimulus intensity levels ranging from 60 dB to 100 dB. The amplitude of the N1 component rises with higher stimulus intensities.

Correlations with treatment response: We found highly significant correlations of low intensity slopes of the N1 and high HDRS reduction at Fz (r=.86, p<.001) at Fcz (r=.91, p<.001), at Cz (r=.93, p<.001), C3 (r=.81, p<.001) and C4 (r=.75, p<.001). As illustrated in Figure 2, higher intensity slopes of N1 amplitude were associated with better outcome as indicated by reduction of HDRS scores during treatment.

N1 amplitude intensity slopes were not affected by sex, age, duration of illness, frequency of depression episodes or smoking habits (Pearson's correlation). Significant correlations ((Pearson's) with HDRS reduction were found for P1/N1 peak to peak amplitude slopes at Fz (r=.68, p<.001) at Fcz (r=.63, p=.015), at Cz (r=.56, p=.038) and C3 (r=.63, p=.017) and N1/P2 amplitude slopes at Fz (r=.70, p<.001) and at Fcz (r=.56, p=.036). No correlations emerged from the assessment of P2 amplitude slopes or from ERP intensity slopes and BDI or CGI scores.

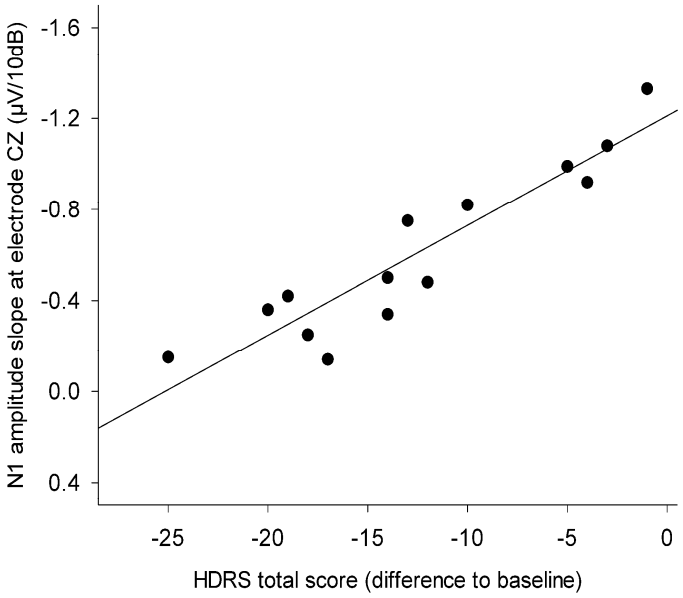

Figure 2
Scatterplot of N1 amplitude slopes at electrode Cz (µV/10dB) correlates with decrease of HDRS total score within the first three to four weeks of treatment (mean 24 days) with r=.93, p<.001.

Split-half reliabilities for the N1 amplitude at Fz, Fcz and Cz were calculated separately for each level of intensity. Correlation coefficients ranged between 0.879 and 0.919 ($p < 0.001$) at Fz, 0.89 and 0.93 ($p < 0.001$) at Fcz and 0.90 and 0.93 ($p < 0.001$) at Cz, which indicates a good temporal stability across the two runs.

5. Discussion

Our data revealed a significant correlation between low intensity slopes of N1 amplitude prior to Reboxetine treatment and favorable treatment response (decrease of HDRS total score) thus supporting the hypothesis of a low IDAP being related to a favorable outcome in SNRI-treatment of major depression.

In contrast to earlier reports [6,18] patients were free of concomitant medication with the exception of two patients treated with low doses of Lorazepam. In these two cases the daily doses of Lorazepam were 0, 5 mg since 2 days and 1 day respectively and the last dose was given 24 h before ERP recording in both cases.

Due to organizational reasons the final psychiatric ratings were done after a minimum of 21 and a maximum of 28 days. The date of the final ratings for each patient was chosen independently from patients' psychiatric state. We evaluated a mean period of 24 days in our study. Although this might be characterized as an initial treatment outcome, our data revealed a significant mean improvement of symptoms in the self-rated BDI as well as in the psychiatrist rated HDRS during the course of treatment.

While several previous studies applied reverse problem solutions like BESA or LORETA in the evaluation of the N1/P2 auditory intensity dependence [6,12,15,23] other studies evaluated raw data with regard to N1 [3,14,22], N1/P2 [5,14,22] and P2 [14,18] amplitude slopes. Here we investigated auditory stimulus intensity with regard to raw data P1, P1/N1, P2, N1 and N1/P2 amplitude slopes. In comparison to several other authors we applied a relatively short interstimulus interval (ISI). The ISI varied randomly around 700 ms +/- 200 ms in order to avoid the theoretical problem of a faster habituation to tone intensity differences. Speculatively, our clear results from the analyses of ERP components' raw amplitudes are due to the short but varying ISI.

We found highly significant associations of ERP amplitude slopes with treatment outcome predominantly for the N1 amplitude and to a lesser extent for P1/N1 and the N1/P2 component as well, but not for P2 component. Paige et al. (1994) found a significant correlation of P2 amplitude intensity dependence with SSRI treatment outcome [15] and Beauducel et al. (2000) suggested that the P2 amplitude slopes reflect stimulus intensity changes more precisely than other ERP component slopes [1]. In contrast, in our data the intensity dependence of P2 amplitudes was not significantly associated with NARI treatment outcome. This negative result may have been due to our relatively small sample or to methodological differences, i.e. the short ISI in our paradigm. However, considering high split-half

coefficients indicating high internal consistency and intensity slopes compatible with previously reported studies, a lack of data quality seems unlikely.

Although the amount of symptom reduction did not differ between BDI and HDRS, we could not find a significant correlation between these rating scales in our sample, which indicates an inconsistency between patients' and psychiatrists' ratings. That is probably the reason for the missing correlation between decrease of BDI and IDAP in our study.

Our data confirm the hypothesis of a low intensity dependence of the auditory evoked potential being associated with a favorable response to SNRI treatment in a group of acutely depressed in-patients treated exclusively with Reboxetine. In contrast to previous treatment-studies we found a significant correlation between pre-treatment intensity dependence of ERP component amplitude slopes and decrease of HDRS scores based on the analysis of raw amplitudes. As a low IDAP is associated with a favorable response to SNRI treatment and a high IDAP with a favorable response to SSRI treatment in major depression, this approach may provide an easily applicable method for clinicians in the initial differential indication of serotonergic versus noradrenergic antidepressants.

Nevertheless, further studies are needed in order to replicate these results in a larger sample of patients comparing SSRI and SNRI treatment in a randomized and double-blind setting. Future studies may investigate the impact of the norepinephrine transporter gene polymorphism on the IDAP in a large sample of healthy subjects in order to clarify connections between noradrenergic function and ERP measures of auditory intensity processing [27] as demonstrated in studies, which assessed the 5-HTTLPR polymorphism [7,22].

6. Acknowledgements

The authors are grateful to R. Franzke, A. Hesse, O. Ligneth-Dahm, N. Löbbecke and R. Windelschmidt for help in data acquisition.

References

[1] Beauducel A, Debener S, Brocke B, Kayser J. On the reliability of augmenting/reducing. Peak amplitudes and principal component analysis of auditory evoked potentials. J Psychophysiol 2000; 14:226–40.

[2] Beck AT, Ward CH, Mendelson M, Mock J,Erbaugh J. Archives of General Psychiatry 1961; 4:561-571.

[3] Brocke B, Beauducel A, John R, Debener S, Heilemann H. Sensation seeking and affective disorders: characteristics in the intensity dependence of acoustic evoked potentials. Neuropsychobiology 2000; 41:24–30.

[4] Buchsbaum, M and Silverman, J. Stimulus intensity control and the cortical evoked response. Psychosom Med 1968; 30: 12-22.

[5] Croft RJ, Klugman A, Baldeweg T, Gruzelier JH. Electrophysiological evidence of serotonergic impairment in long-term MDMA ("ecstasy") users. American Journal Psychiatry 2001; 158: 1687–1692.

[6] Gallinat J, Bottlender R, Juckel G, Munke-Puchner A, Stotz G, Kuss HJ,et al. The loudness dependency of the auditory evoked N1/P2-component as a predictor of the acute SSRI response in depression. Psychopharmacology (Berl) 2000; 148:404–11.

[7] Gallinat J, Senkowski D, Wernicke C, Juckel G, Becker I, Sander T, et al. Allelic variants of the functional promoter polymorphism of the human serotonin transporter gene is associated with auditory cortical stimulus processing. Neuropsychopharmacology 2003; 28:530–2.

[8] Hamilton M., HAMA, Hamilton Anxiety Scale. In: Guy, W. (Ed.), ECDEU Assessment manual for psychopharmacology. US Department of Health and Human Services, Rockville, MD, 1976 ; pp. 194-198.

[9] Hegerl U, Bottlender R, Gallinat J, Kuss HJ, Ackenheil M and Moller HJ. The serotonin syndrome scale: first results on validity, Eur Arch Psychiatry Clin Neurosci, 1998; 248:96-103.

[10] Hetzel G, Moeller O, Erfurth A, Michael N, Rothermundt M, Arolt V,Evers S. Pharmacopsychiatry 2004; 37:200-205.

[11] Juckel G, Hegerl U, Molnar M, Csepe V, Karmos G. Auditory evoked potentials reflect serotonergic neuronal activity – a study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus. Neuropsychopharmacology 1999; 21:710–6.

[12]Juckel G, Mavrogiorgou P, Bredemeier S, Gallinat J, Frodl T, Schulz C, et al. Loudness dependence of primary auditory-cortex-evoked activity as predictor of therapeutic outcome to prophylactic lithium treatment in affective disorders – a retrospective study. Pharmacopsychiatry 2004; 37:46–51.

[13]Kuenzel HE, Murck H, Held K, Ziegenbein M,Steiger A. Pharmacopsychiatry 2004; 37:193-195

[14]Linka T, Müller BW, Bender S, Sartory G. The intensity dependence of the auditory evoked N1 component as a predictor of response to Citalopram treatment in patients with major depression. Neurosci Lett 2004; 367:375-378.

[15]Mulert C, Juckel G, Augustin H, Hegerl U. Comparison between the analysis of the loudness dependency of the auditory N1/P2 component with LORETA and dipole source analysis in the prediction of treatment response to the selective serotonin reuptake inhibitor citalopram in major depression. Clin Neurophysiol 2002; 113:1566–72.

[16]NIMH, N.I.o.M.H., CGI. Glinical global impressions. In R. Bonato (Ed.), Manual for the EDCEU assessment battery, 2nd edition, Vol. 12, NIMH, Chevy Chase, 1976.

[17]Owens MJ. Selectivity of antidepressants: from the monoamine hypothesis of depression to the SSRI revolution and beyond. J Clin Psychiatry 2004; 6:5-10.

[18]Paige SR, Fitzpatrick DF, Kline JP, Balogh SE Hendricks SE. Event-related potential amplitude/intensity slopes predict response to antidepressants. Neuropsychobiology 1994; 30:197-201.

[19]Proietti-Cecchini A, Afra J, Schoenen J. Intensity dependence of the cortical auditory evoked potentials as a surrogate marker of central nervous system serotonin transmission in man: demonstration of a central effect for the 5HT1B/1D agonist zolmitriptan (311C90, Zomig). Cephalalgia 1997; 17:849-854; discussion 799.

[20]Quednow BB, Kuhn KU, Stelzenmueller R, Hoenig K, Maier W and Wagner M. Effects of serotonergic and noradrenergic antidepressants on auditory startle response in patients with major depression, Psychopharmacology (Berl) 2004 Oct; 175 (4): 399-406.

[21]Semlitsch HV, Anderer P, Schuster P and Presslich O. A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP, Psychophysiology 1986; 23:695-703.

[22]Strobel A, Debener S, Schmidt D, Hunnerkopf R, Lesch KP and Brocke B. Allelic variation in serotonin transporter function associated with the intensity

dependence of the auditory evoked potential, Am J Med Genet 2003; 118B: 41-47.

[23]Tuchtenhagen F, Daumann J, Norra C, Gobbele R, Becker S, Pelz S, Sass H, Buchner H, Gouzoulis-Mayfrank E. High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent ecstasy (MDMA) users. Neuropsychopharmacology 2000; 22: 608-617.

[24]von Knorring L and Johansson F. Changes in the augmenter-reducer tendency and in pain measures as a result of treatment with a serotonin-reuptake inhibitor--zimelidine. Neuropsychobiology 1980; 6:313-8.

[25]von Knorring L and Perris C. Biochemistry of the augmenting-reducing response in visual evoked potentials. Neuropsychobiology 1981; 7:1-8.

[26]Wang W, Timsit-Berthier M, Schoenen J. Intensity dependence of auditory evoked potentials is pronounced in migraine: an indication of cortical potentiation and low serotonergic neurotransmission? Neurology 1996; 1404-1409.

[27]Yoshida K, Takahashi H, Higuchi H, Kamata M, Ito K, Sato K, Naito S, Shimizu T, Itoh K, Inoue K, Suzuki T, Nemeroff CB. Prediction of antidepressant response to milnacipran by norepinephrine transporter gene polymorphisms. Am J Psychiatry 2004; 161:1575-1580.

CHAPTER 4

THE INTENSITY DEPENDENCE OF AUDITORY ERP COMPONENTS IN UNMEDICATED PATIENTS WITH MAJOR DEPRESSION AND HEALTHY CONTROLS. AN ANALYSIS OF GROUP DIFFERENCES.

The intensity dependence of auditory ERP components in unmedicated patients with major depression and healthy controls. An analysis of group differences.

Thomas Linka, Gudrun Sartory, Stefan Bender, Markus Gastpar, Bernhard Müller

Publsihed in the Journal of Affective Disorders 2007 Nov; 103(1-3):139-45

1. Abstract

The intensity dependent amplitude change (IDAP) of auditory evoked Event Related Potential (ERP) components has been found to correlate with the level of central serotonergic neurotransmission and to be associated with response to certain antidepressants. However, it is currently unknown whether there is a general abnormality of the IDAP in patients with major depression. Therefore, the purpose of the present study was to compare the IDAP in unmedicated depressed patients with that of healthy control subjects. We report the results of a study evaluating the change of auditory evoked P1, N1, P2 as well as P1/N1 and N1/P2 peak to peak amplitudes in 34 in-patients with major depressive episode prior to antidepressant treatment, and 44 healthy control subjects. Clinical symptoms of depression were assessed by means of standardized psychiatric rating scales (CGI, HDRS, HAMA and BDI). In multivariate analyses of variance we found no group differences in the intensity dependent increase neither of the P1, N1, and P2 nor of the P1/N1 and N1/P2 peak to peak amplitudes between patients and controls. Our data revealed no general abnormality of the IDAP in patients with major depression in comparison to healthy control subjects. This result suggests that specific alterations of the IDAP are not to be expected in major depression in general, these may be confined to subgroups of depressed patients.

2. Introduction

Major concepts on the pathophysiology of depression comprise alterations in serotonergic and noradrenergic systems in brain (Owens, 2004) and changes in the hypothalamic-pituitary-adrenal axis (Riedel et al., 2002). In particular, the search for reliable indicators of central serotonergic and noradrenergic dysfunction in major depression has recently attracted scientific interest. Beside genetic approaches (Yoshida et al., 2004) several authors used auditory event related potential (ERP) components in the investigation of serotonergic dysregulation in patients with major depression (review in: Hegerl et al., 2001).

Cortical responses to auditory stimulation derived from EEG in the form of ERPs consist of three typical components: An electrically positive P1 component at about 50 ms following stimulus onset, a negative N1 component at 100 ms and a positive P2 component at about 200 ms. Increases in auditory stimulus intensities are reflected by increases in ERP amplitudes. Typically, several stimulus intensities are used to elicit amplitude changes which can be transformed into slope values which give the amplitude change in µV per 10/dB (Beauducel et al., 2000).

Changes of the N1 and P2 ERP component amplitudes as well as of the P1/N1 and the N1/P2 peak-to-peak amplitudes in response to different tone intensities have been identified as a correlative of central nervous serotonergic activity (Buchsbaum and Silverman, 1968; Hegerl et al., 1998; Juckel et al., 1999; Strobel et al., 2003; von Knorring and Perris, 1981). A high loudness dependent amplitude increase (“high intensity dependence”, “high IDAP”) presumably reflects low serotonergic neurotransmission and vice versa (Juckel et al., 1999).

Buchsbaum et al. (1968) et al. described the phenomenon of augmenting/reducing, which is considered to reflect individual differences in the modulation of sensory input (Buchsbaum and Silverman, 1968). Individuals who showed an increase of ERP amplitudes with increasing stimulus intensity were classified as augmenters and individuals who showed a decrease of ERP amplitudes with increasing stimulus intensity as reducers. First investigations on the intensity dependence of sensory evoked potentials and their relation to psychiatric disorders by Zuckerman et a. (1974) focused on the relation between stimulus intensity dependence and personality factors like impulsiveness, aggressiveness and sensation seeking behaviour (Zuckerman et al., 1974).

Based on theories about the role of serotonin in the pathophysiology of migraine the stimulus intensity dependence of ERP components has been investigated in the context of migraine research, where the term "IDAP" (intensity dependence of the cortical auditory evoked potentials) is widely used (Proietti-Cecchini et al., 1997a; Wang et al., 1996). Within psychiatric research Hegerl et al. introduced the term "LDAEP" ("loudness dependence of the auditory evoked potentials") (Gallinat et al., 2000; Hegerl et al., 1998), whereas other authors used the term “IDAP” in psychological and psychiatric investigations as well (Hensch et al., 2006). In the description of our investigations we decided to use the “traditional” term of IDAP.

Several studies corroborated the concept of the IDAP as an indicator of central serotonergic neurotransmission. Juckel et al. reported differential effects of microinjection of a 5-HT_{1A} agonist and a 5-HT_{1A} antagonist into the dorsal raphe nucleus (DRN) on the intensity dependence of auditory evoked potentials (AEP) recorded epidurally from the primary and secondary auditory cortex in behaving cats. (Juckel et al., 1999). Strobel et al. (2003) found a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) to be associated with the N1/P2 amplitude intensity dependence. This result has been recently replicated by Hensch et al. (2006).

The role of the IDAP has been studied in several fields of psychiatric research: Tuchtenhagen et al. (2000) reported a high intensity dependence of auditory evoked dipole source activity in abstinent ecstasy (MDMA) users which indicates decreased serotonergic activity (Tuchtenhagen et al., 2000). Similar results have been decribed by Croft et al. (2001) regarding long-term MDMA abuse. A high IDAP has been described to correlate with aspects of impulsiveness in 15 female patients suffering from borderline personality disorder (Norra et al., 2003). Juckel et al. found the IDAP of the primary auditory cortex derived from dipole source analysis in 25 inpatients with schizophrenia to be significantly lower compared to 25 healthy controls. After treatment with the 5-HT(2) antagonistic antipsychotics Clozapine and Olanzapine, the IDAP tended to be increased, indicating normalization of serotonergic function in the patients with schizophrenia under antipsychotic treatment (Juckel et al., 2003). Applying dipole source analysis Senkowski et al. described a significantly lower IDAP derived from bilateral tangential dipoles in 31 medication-free patients with General Anxiety Disorder in comparison to 31 matched control subjects (Senkowski et al., 2003). In patients

under treatment with Serotonin Reuptake Inhibitors (SSRI) Hegerl et al. (1998) found that high scores in the serotonin syndrome scale (SSS) were associated with low IDAP and vice versa (Hegerl et al., 1998).

Based on such preclinical and clinical studies the IDAP has been suggested as a psychophysiological indicator of central serotonergic neurotransmission in depression with special relevance to treatment-response to SSRI. This concept has been corroborated in several studies applying various antidepressants (Paige et al., 1994; Gallinat et al., 2000; Lee et al., 2005; Linka et al., 2004; Linka et al., 2005).

Although preclinical and clinical studies indicate that the IDAP can be useful in the evaluation of serotonergic dysfunction, it is still unknown, if the IDAP in unmedicated depressed patients basically differs from that of healthy control individuals. However, the IDAP in major depression has been compared to control subjects only in the context of a treatment response study by Gallinat et al. 2000. In this study nonresponders but not responders to SSRI showed a reduced loudness dependent increase of the tangential dipole of the N1/P2 complex (dipole source analysis). While these data indicate at least some differences between control subjects and patients with major depression, it remains unknown, whether patients with major depression show a general alteration in the IDAP.

In summary, there is accumulating evidence, that the IDAP is an indirect indicator of central serotonergic neurotransmission in major depression and other psychiatric disorders. As central nervous serotonergic dysfunction is suggested to be one of the major pathophysiological factors in depression, healthy controls and patients should differ with regard to this indicator. As most studies suggest that a high IDAP is associated with superior responsiveness to SSRI-treatment in depression, this study aims to investigate the hypothesis that individuals suffering from major depression exhibit a higher IDAP compared to healthy control subjects.

3. Method

3.1 Subjects

Thirty-four in-patients with major depressive episode (DSM-IV: 296.2, 296.3, 296.5; APA 1994), who were admitted consecutively to the Department of Psychiatry and Psychotherapy of the University of Duisburg-Essen and 44 matched

healthy control subjects, were included for participation in the study. Patients and controls gave their written informed consent prior to their inclusion in the study. The study was approved by the local ethics committee. Controls were recruited via advertisements in local community centers and stores. Control subjects recruitement was done with regard to the matching criteria age, gender and education of the patient sample. Patients and controls did not differ with regard to age and gender (table 1).

3.2 Rating scales and procedure

Clinical symptoms of major depression were assessed by means of psychiatric rating scales: Clinical Global Impression (CGI) ((NIMH), 1976), Hamilton Rating Scale for Depression (HDRS, 21 items, range of scores: 0 - 63) (Hamilton, 1960), Beck Depression Inventory (BDI, 21 items, range of scores: 0 - 63) (Beck et al., 1961), Hamilton Anxiety Scale (HAMA, 14 items, range of scores: 0 – 56) (Hamilton, 1976)and State-Trait-Anxiety Inventory (STAI range of scores: 40, 40 – 160) (Spielberger, 1970).

Table 1

Subject characteristics

	Patients with Major Depression means (sd)	Healthy Control Subjects means (sd)
Age	41.4 (± 12.6)	39.2 (± 10.4)
Gender (m/f)	11 / 23	16 / 28
Education (y)	10.6 (± 1.6)	13.9 (± 2.6)
Nicotine (n; mg/d)	18; 19.6 (± 17.4)	22; 14.11 (± 9.2)
Episodes of depression (n)	1.9 (± 1.9)	-
Duration of illness (y)	8.9 (± 7.6)	-
CGI total score	4.7 (± 1.0)	-
HDRS total score	24.5 (± 4.1)	-
HAMA total score	8.5 (± 7.6)	-
BDI total score	27.8 (±10.7)	3.1 (±3.1)
STAI total score	58.7 (±13.3)	33.3 (±8.8)

Clinical ratings were performed by a experienced senior psychiatrist who was blind to patients' ERP data. The BDI and STAI self rating scales were completed by all subjects in order to exclude individuals with clinically relevant anxiety and depression within the controlgroup. The total score of HDRS in patients had to be 20 at least. The CGI, HDRS and BDI scores were obtained at the day of ERP recording. Pre-treatment antidepressants were stopped at least two days before ERP recording. Patients with central neurological disorders, abuse of illicit drugs and alcohol dependence were excluded, as was pre-treatment with electroconvulsive therapy. Concomitant medication with antipsychotics, mood stabilizers or additional antidepressants was not permitted and patients receiving antidepressants within three months before hospitalisation were excluded from the study. Concomittant benzodiazepine treatment (n=2) was restricted to a maximum dose of 1.5 mg Lorazepam per day. Lorazepam was not given 12 hours before ERP-recording.

3.3 Electrophysiological assessment and data analysis

EEG-recording took place in a sound-attenuated and electrically shielded room. Subjects were seated in a comfortable chair. Auditory stimulation consisted of two runs of 500 stimuli each with the interstimulus-intervall being randomized between 500 and 900 ms. Tones of 1000 Hz and 80 ms duration (10 ms rise and fall times) were presented with five intensities namely 60, 70, 80, 90 and 100 dB sound pressure level via TDH-39p headphones (Telephonics Inc.). The stimulus intensities where presented in randomized order. The auditory threshold with respect to 1000 Hz tones was below 30 dB as measured by an audiometer. Stimulus presentation was generated by Neuroscan Stim 3.3 Software. Evoked potentials were recorded from 27 scalp electrodes (extended international 10-20 system) with linked earlobes as reference using a 32-channel EEG amplifier (Neuroscan Inc.). The vertical and horizontal electro-oculogram (EOG) was recorded for offline artifact removal (Semlitsch et al., 1986). EEG data were recorded with a sampling rate of 500 Hz in the frequency range of 0.1 to 100 Hz and filtered offline with a 0.1 Hz to 30 Hz bandpass filter (Neuroscan Edit 4.2). ERP sweeps extended over 600 ms starting 100 ms prior to stimulus onset. Sweeps with artifacts exceeding +/- 50 µV were rejected from further analysis. ERP averages were computed separately for each stimulus intensity level. Mean number of sweeps ranged from 114.5 to 137.5. Amplitudes of the N100 and the P200 components were computed from electrodes Fz, Fcz, Cz, C3 and C4.

Amplitude slopes (amplitude slope function derived by linear regression across stimulus intensity levels) were computed for the P1, N1, P2 amplitudes and the P1/N1 and N1/P2 peak to peak amplitudes.

3.4. Statistical analysis

ERP Amplitude data of the P1, N1, P2 amplitudes and the P1/N1 and N1/P2 peak to peak amplitudes were analysed in separate multivariate analyses of variance with stimulus intensities (60, 70, 80, 90, 100 dB) and electrodes (Fz, Fcz, Cz, C3, C4) as within factors and group (patients / control) as between factor. Reports on results are restricted to effects involving the group factor and group x intensity interactions. Group effects indicate differences in mean amplitudes between patients and controls and group x intensity interactions indicate differences in the auditory intensity dependent amplitude slopes between patients and control subjects. Effects of gender, and smoking habit on amplitude slopes were assessed with Chi^2 tests and the effects of age, education and the amount of nicotine consumption among smoking subjects were assessed with analysis of variance. The impact of duration of illness and the frequency of depression episodes on evoked potentials were assessed with Pearson correlations.

4. Results

4.1 Rating scales

Patients and controls did not differ significantly with regard to age, gender, smoking status and the amount of nicotine intake per day in smoking subjects. Patients spent a lower time in school education than control subjects ($p = .015$). Results of clinical ratings are shown in table 1.

4.2 ERP data

N1 amplitude slopes were not affected by sex, age, education, duration of illness, frequency of depression episodes or smoking habits. Results of ERP-data analysis are presented in table 2. Group averages in patients and controls for electrode Cz are shown in figure 1.

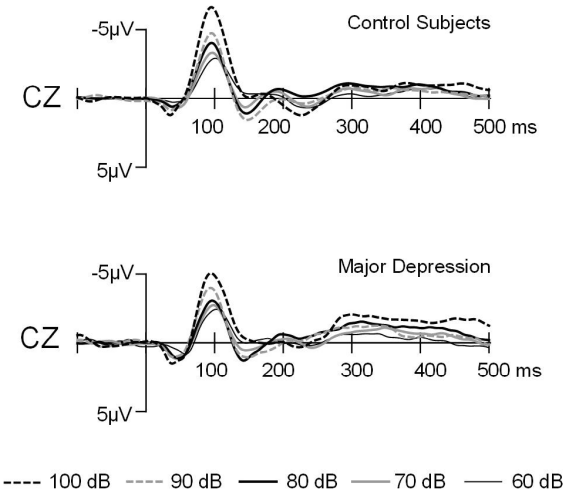

Figure 1
Group averages of the N1 component at electrode CZ in patients with major depression and control subjects. Lines indicate five stimulus intensity levels ranging from 60 to 100 dB. The amplitude of the N1 component increases with higher stimulus intensities.

Five multivariate analyses of variance including group (between factor: patients, controls) and stimulus intensities (within factor: 60, 70, 80, 90, 100 dB) were computed for P1, N1, P2 amplitudes and the P1/N1 and N1/P2 peak to peak amplitudes. We found no significant effects for the group factor or for group x intensity interactions at the Bonferoni corrected level of $p<.01$ ($p=.05 / 5$ analyses). Figure 2 shows mean amplitudes over the five auditory intensity levels for patients with major depression and healthy control subjects at electrode Cz.

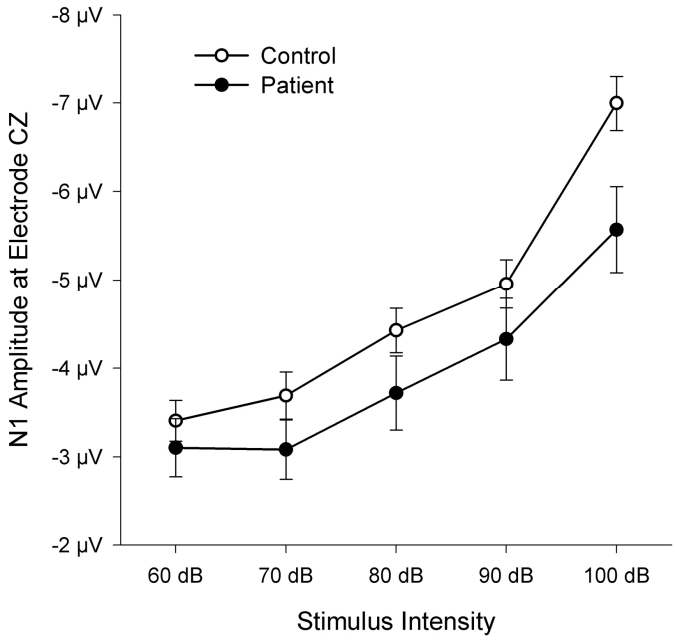

Figure 1
N1 group means of the amplitudes at electrode Cz evoked by stimulus intensities 60 to 100 dB. Compared to patients, controls showed a slightly higher intensity dependent amplitude increase at Cz, in an overall analysis of electrodes Fz, Fcz, Cz, C3, C4 we found no significant group differences.

Table 2
ERP Data: N1 amplitudes and N1, P1/N1, N1/P2 amplitude slopes

	Major Depression mean (sd)	Healthy Control Subjects mean (sd)
N1 amplitude 60 dB/100 dB (μV) *		
Fz	–3.25 (±2.1) / –5.80 (±3.6)	–3.69 (±1.8) / –6.91 (±2.3)
Fcz	–3.29 (±2.1) / –5.92 (±3.1)	–3.67 (±1.8) / –7.18 (±2.6)
Cz	–3.10 (±1.9) / –5.57 (±2.8)	–3.41 (±1.5) / –7.00 (±2.1)
C3	–2.90 (±1.9) / –5.18 (±2.7)	–3.10 (±1.4) / –6.19 (±1.9)
C4	–2.87 (±1.7) / –4.92 (±2.6)	–2.96 (±1.3) / –5.90 (±1.8)
N1 amplitude slope (μV / 10 dB)#		
Fz	0.62 (±0.5)	0.77 (±0.5)
Cz	0.66 (±0.5)	0.84 (±0.5)
Fcz	0.62 (±0.4)	0.84 (±0.4)
C3	0.56 (±0.4)	0.71 (±0.3)
C4	0.52 (±0.4)	0.69 (±0.3)
P1/N1 amplitude slope (μV/10 dB)#		
Fz	0.69 (±0.5)	0.86 (±0.5)
Fcz	0.77 (±0.5)	1.01 (±0.5)
Cz	0.76 (±0.5)	1.03 (±0.4)
C3	0.63 (±0.5)	0.86 (±0.4)
C4	0.71 (±0.5)	0.70 (±0.4)
N1/P2 amplitude slope (μV/10 dB		
Fz	0.64 (±0.6)	0.84 (±0.6)
Cz	0.80 (±0.6)	1.10 (±0.6)
Fcz	0.85 (±0.6)	1.16 (±0.6)
C3	0.67 (±0.5)	0.85 (±0.4)
C4	0.63 (±0.5)	0.93 (±0.5)

* Evoked response (ERP) amplitude data are given for the lowest (60 dB) and the highest (100 dB) auditory stimulus intensities at electrode positions Fz, Cz, Fcz, C3 and C4 in μV.
# Amplitude slopes give the absolute value of the mean increase in ERP amplitudes within the five (60, 70, 80, 90 and 100 dB) stimulus intensities in μV per 10 dB.

5. Discussion

This is the first report to compare a large sample of unmedicated patients with major depression with a group of healthy control subjects with regard to general abnormalities in the IDAP. We conducted analyses over five commonly used methods in the calculation of amplitudes (P1/baseline, N1/baseline, P2/baseline, P1/N1, N1/P2).

Although, compared to patients, controls showed a slightly higher intensity dependent amplitude increase at Cz (see figure 2), in an overall analysis of electrodes Fz, Fcz, Cz, C3, C4 we found no significant group differences. Given the sample size and compared to the highly significant predictive power of the IDAP with regard to treatment outcome (Gallinat et al., 2000; Lee et al., 2005; Linka et al., 2004; Linka et al., 2005) the IDAP baseline, differences between patients and controls at Cz were small (Figure 2) and after adjustment for multiple testing (Bonferoni) turned out to be non-significant.

While several previous studies applied reverse problem solutions like BESA (dipole source analysis) or LORETA in the evaluation of the N1/P2 auditory intensity dependence (Gallinat et al., 2000; Mulert et al., 2002; Tuchtenhagen et al., 2000) other studies evaluated raw data with regard to N1 [(Brocke et al., 2000; Strobel et al., 2003), N1/P2 (Croft et al., 2001; Strobel et al., 2003) and P2 (Paige et al., 1994) amplitude slopes. However, there is no unambiguous evidence that reverse methods of ERP analysis are superior to the evaluation of raw amplitudes. In line with earlier studies in this field, here we assessed auditory stimulus intensity with regard to raw data P1, P1/N1, P2, N1 and N1/P2 amplitude slopes.

The intensity dependent amplitude slopes of the subjects in our study can be compared to those obtained in previous studies using similar procedures and measures. While our inter-stimulus interval between 500 ms and 900 ms is at the lower end of what has been used by other groups, stimulus intensities, electrode positions and stimulus intensity slope calculation are in keeping with previously employed methods (Beauducel et al., 2000). The resulting N1/P2 amplitude slopes in our study are in line with results reported by Sandor et al. (Sandor et al., 1999). They are however lower than those reported by Croft et al. (Croft et al., 2001) and higher than those in a study by Cecchini et al. (Proietti-Cecchini et al., 1997b). Therefore we may conclude, that results from our experimental setup are

comparable to previously reported results assessing healthy subjects with similar methods and that the lack of significant differences in auditory evoked potentials between patients with major depression and matched healthy control subjects is unlikely to be related to methodological factors.

The lack of a difference between patients and controls with regard to the IDAP in our study seems to be contradictory to those studies, which support the significance of the IDAP as a clinically relevant indicator of the central nervous serotonergic dysfunction in depressive disorders.

Paige et al. (1994) found responders to different serotonergic antidepressants demonstrate significantly higher P2 amplitude slopes (as a function of stimulus intensity) prior to treatment than non-responders (Paige et al., 1994). Our research group recently reported a superior responsiveness to Citalopram treatment in depressed patients exhibiting a high pre-treatment intensity dependence of the auditory evoked N1 raw amplitude (Linka et al., 2004), and to Reboxetine treatment in depressed patients exhibiting low pre-treatment intensity dependence (Linka et al., 2005). These studies support the clinically relevant sensitivity of the IDAP as an indicator of central nervous serotonergic dysfunction.

In a study by Gallinat et al. (2000) patients with a high pre-treatment IDAP (based on dipole source analysis; bilateral tangential dipoles) showed significantly lower HDRS scores after 4 weeks of treatment with SSRI than patients with a low IDAP (Gallinat et al., 2000). However, in this study authors failed to show changes in the IDAP after four weeks of SSRI treatment in a subsample of 19 patients between the first and the second assessment. Although Gallinat et al. in line with our results did not find a general abnormality of the IDAP when comparing the whole sample of depressed patients with the healthy control group, their data revealed a lower mean IDAP within the group of depressed non-responders to SSRI treatment compared to controls.

In our study variances of the IDAP were only slightly larger in patients than in controls (table 2). It can be hypothized that a subgroup of controls as well as patients shows some kind of dysregulation of the serotonergic system. Considering the results from MDMA-users (Croft et al., 2001; Tuchtenhagen et al., 2000), the findings in schizophrenia [13], borderline personality disorder [20] an general anxiety disorder [28] and the association between IDAP and the Serotonin

Syndrom Scale (Hegerl et al., 1998) the IDAP seems to reflect the sensitivity of the central serotonergic system. The results of our study do not necessarily contradict the assumed role of the IDAP as an indicator a central nervous serotonergic sensitivity in major depression and other psychiatric disorders. The phenomenon, that only a subgroup of depressed individuals shows associations with a biological factor, assumed to reflect serotonergic sensitivity, is known from genetic approaches. This might be exemplified by a study by Willeit et al. (2003) over the role of a polymorphism in the promoter region of the serotonin transporter (5-HTTLPR) in seasonal affective disorder. While Willeit found no difference between patients and controls for genotype distribution and s-allele frequency, genotype distribution and allele frequencies were associated with DSM-IV depression subtypes. Melancholic depression was associated with the 5-HTTLPR long (l) allele and atypical depression with the 5-HTTLPR s-allele (Willeit et al., 2003). Similarly, the lack of a difference between patients and controls with regard to the IDAP in our study might be due to the independence of this factor from the clinically observed, general depressive state and from major depression itself. Thus alterations of the IDAP in major depression may be expected in a subgroup of depressed patients only, which is affected by a potentially higher degree of dysfunction in the central nervous serotonergic neurotransmission.

Our study presents normal values for the IDAP derived from 44 healthy control subjects and reveals that there is no general abnormality of the IDAP in major depression. These results should be helpful in further studies combining ERP, genetic approaches (NET- and 5HT polymorphisms) in a double blind, randomized setting with different classes of antidepressants (SSRI, NARI, SNRI). Furthermore it could be of interest to evaluate if there is a link between abnormalities in the IDAP and subgroups of patients with depressive disorders and whether these can be identified by certain patterns of clinical symptomatology of depression.

6. Acknowledgements

The authors are grateful to R. Franzke, A. Hesse, O. Ligneth-Dahm, N. Löbbecke and R. Windelschmidt for help in data acquisition.

References

- Beauducel, A., Debener, S., Brocke, B., Kayser, J., 2000. On the reliability of augmenting / reducing. Peak amplitudes and principal component analysis of auditory evoked potentials. Journal of Psychophysiology 14, 226-240.
- Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Archives of General Psychiatry 4, 561-571.
- Brocke, B., Beauducel, A., John, R., Debener, S., Heilemann, H., 2000. Sensation seeking and affective disorders: characteristics in the intensity dependence of acoustic evoked potentials. Neuropsychobiology 41, 24-30.
- Buchsbaum, M., Silverman, J., 1968. Stimulus intensity control and the cortical evoked response. Psychosom Med 30, 12-22.
- Croft, R.J., Klugman, A., Baldeweg, T., Gruzelier, J.H., 2001. Electrophysiological evidence of serotonergic impairment in long-term MDMA ("ecstasy") users. Am J Psychiatry 158, 1687-1692.
- Gallinat, J., Bottlender, R., Juckel, G., Munke-Puchner, A., Stotz, G., Kuss, H.J., Mavrogiorgou, P., Hegerl, U., 2000. The loudness dependency of the auditory evoked N1/P2-component as a predictor of the acute SSRI response in depression. Psychopharmacology (Berl) 148, 404-411.
- Hamilton, M., 1960. A rating scale for depression. J Neurol Neurosurg Psychiatry, pp. 56-62.
- Hamilton, M., 1976. HAMA, Hamilton Anxiety Scale. In: Guy, W. (Ed.), ECDEU Assessment manual for psychopharmacology. US
- Hegerl, U., Bottlender, R., Gallinat, J., Kuss, H.J., Ackenheil, M., Moller, H.J., 1998. The serotonin syndrome scale: first results on validity. Eur Arch Psychiatry Clin Neurosci 248, 96-103.
- Hegerl, U., Gallinat, J., Juckel, G., 2001. Event-related potentials. Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? J Affect Disord 62, 93-100.
- Hensch, T., Wargelius, H.L., Herold, U., Lesch, K.P., Oreland, L., Brocke, B., 2006. Further Evidence for an Association of 5-HTTLPR with Intensity Dependence of Auditory-Evoked Potentials. Neuropsychopharmacology.
- Juckel, G., Gallinat, J., Riedel, M., Sokullu, S., Schulz, C., Moller, H.J., Muller, N., Hegerl, U., 2003. Serotonergic dysfunction in schizophrenia assessed by the

loudness dependence measure of primary auditory cortex evoked activity. Schizophr Res 64, 115-124.

- Juckel, G., Hegerl, U., Molnar, M., Csepe, V., Karmos, G., 1999. Auditory evoked potentials reflect serotonergic neuronal activity--a study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus. Neuropsychopharmacology 21, 710-716.
- Lee, T.W., Yu, Y.W., Chen, T.J., Tsai, S.J., 2005. Loudness dependence of the auditory evoked potential and response to antidepressants in Chinese patients with major depression. J Psychiatry Neurosci 30, 202-205.
- Linka, T., Müller, B.W., Bender, S., Sartory, G., 2004. The intensity dependence of the auditory evoked N1 component as a predictor of response to Citalopram treatment in patients with major depression. Neurosci Lett 367, 375-378.
- Linka, T., Müller, B.W., Bender, S., Sartory, G., Gastpar, M., 2005. The intensity dependence of auditory evoked ERP components predicts responsiveness to reboxetine treatment in major depression. Pharmacopsychiatry 38, 139-143.
- Mulert, C., Jager, L., Pogarell, O., Bussfeld, P., Schmitt, R., Juckel, G., Hegerl, U., 2002. Simultaneous ERP and event-related fMRI: focus on the time course of brain activity in target detection. Methods Find Exp Clin Pharmacol 24 Suppl D, 17-20.
- (NIMH), N.I.o.M.H., 1976. CGI. Glinical global impressions. In: Bonato, R. (Ed.), Manual for the EDCEU assessment battery, 2nd edition. NIMH, Chevy Chase.
- Norra, C., Mrazek, M., Tuchtenhagen, F., Gobbele, R., Buchner, H., Sass, H., Herpertz, S.C., 2003. Enhanced intensity dependence as a marker of low serotonergic neurotransmission in borderline personality disorder. J Psychiatr Res 37, 23-33.
- Owens, M.J., 2004. Selectivity of antidepressants: from the monoamine hypothesis of depression to the SSRI revolution and beyond. J Clin Psychiatry, pp. 5-10.
- Paige, S.R., Fitzpatrick, D.F., Kline, J.P., Balogh, S.E., Hendricks, S.E., 1994. Event-related potential amplitude/intensity slopes predict response to antidepressants. Neuropsychobiology 30, 197-201.
- Proietti-Cecchini, A., Afra, J., Schoenen, J., 1997a. Intensity dependence of the cortical auditory evoked potentials as a surrogate marker of central nervous system serotonin transmission in man: demonstration of a central effect for

the 5HT1B/1D agonist zolmitriptan (311C90, Zomig). Cephalalgia, pp. 849-854; discussion 799.

- Proietti-Cecchini, A., Afra, J., Schoenen, J., 1997b. Intensity dependence of the cortical auditory evoked potentials as a surrogate marker of central nervous system serotonin transmission in man: demonstration of a central effect for the 5HT1B/1D agonist zolmitriptan (311C90, Zomig). Cephalalgia 17, 849-854; discussion 799.
- Riedel, W.J., Klaassen, T., Griez, E., Honig, A., Menheere, P.P., van Praag, H.M., 2002. Dissociable hormonal, cognitive and mood responses to neuroendocrine challenge: evidence for receptor-specific serotonergic dysregulation in depressed mood. Neuropsychopharmacology 26, 358-367.
- Sandor, P.S., Roon, K.I., Ferrari, M.D., van Dijk, J.G., Schoenen, J., 1999. Repeatability of the intensity dependence of cortical auditory evoked potentials in the assessment of cortical information processing. Cephalalgia 19, 873-879.
- Semlitsch, H.V., Anderer, P., Schuster, P., Presslich, O., 1986. A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. Psychophysiology, pp. 695-703.
- Senkowski, D., Linden, M., Zubragel, D., Bar, T., Gallinat, J., 2003. Evidence for disturbed cortical signal processing and altered serotonergic neurotransmission in generalized anxiety disorder. Biol Psychiatry 53, 304-314.
- Spielberger, C.D., 1970. Manual for the State-Trait-Anxiety Inventory. Consulting Psychologist Press, Palo Alto.
- Strobel, A., Debener, S., Schmidt, D., Hunnerkopf, R., Lesch, K.P., Brocke, B., 2003. Allelic variation in serotonin transporter function associated with the intensity dependence of the auditory evoked potential. Am J Med Genet 118B, 41-47.
- Tuchtenhagen, F., Daumann, J., Norra, C., Gobbele, R., Becker, S., Pelz, S., Sass, H., Buchner, H., Gouzoulis-Mayfrank, E., 2000. High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent ecstasy (MDMA) users. Neuropsychopharmacology 22, 608-617.
- von Knorring, L., Perris, C., 1981. Biochemistry of the augmenting-reducing response in visual evoked potentials. Neuropsychobiology, pp. 1-8.

- Wang, W., Timsit-Berthier, M., Schoenen, J., 1996. Intensity dependence of auditory evoked potentials is pronounced in migraine: an indication of cortical potentiation and low serotonergic neurotransmission? , Neurology, pp. 1404-1409.
- Willeit, M., Praschak-Rieder, N., Neumeister, A., Zill, P., Leisch, F., Stastny, J., Hilger, E., Thierry, N., Konstantinidis, A., Winkler, D., Fuchs, K., Sieghart, W., Aschauer, H., Ackenheil, M., Bondy, B., Kasper, S., 2003. A polymorphism (5-HTTLPR) in the serotonin transporter promoter gene is associated with DSM-IV depression subtypes in seasonal affective disorder. Mol Psychiatry 8, 942-946.
- Yoshida, K., Takahashi, H., Higuchi, H., Kamata, M., Ito, K., Sato, K., Naito, S., Shimizu, T., Itoh, K., Inoue, K., Suzuki, T., Nemeroff, C.B., 2004. Prediction of antidepressant response to milnacipran by norepinephrine transporter gene polymorphisms. Am J Psychiatry 161, 1575-1580.
- Zuckerman, M., Murtaugh, T., Siegel, J., 1974. Sensation seeking and cortical augmenting-reducing. Psychophysiology 11, 535-542.

CHAPTER 5

CLINICAL SYMPTOMS OF MAJOR DEPRESSION ARE ASSOCIATED WITH THE INTENSITY DEPENDENCE OF AUDITORY ERP COMPONENTS.

Clinical symptoms of major depression are associated with the intensity dependence of auditory ERP components

Thomas Linka, Gudrun Sartory, Markus Gastpar, Norbert Scherbaum, Bernhard W. Müller

Psychiatry Research 2009 (in press)

1. Abstract

The intensity (loudness) dependent amplitude change (IDAP) of auditory Event Related Potential (ERP) has been shown to be associated with the outcome of SSRI treatment in major depression. The purpose of the present study is to evaluate associations between clinical symptoms of major depression and the IDAP as an indirect indicator of cortical serotonergic function. We assessed 40 in-patients suffering from a major depressive episode (DSM-IV) prior to antidepressant treatment. Psychometric characteristics of depression were assessed by means of psychiatric rating scales (CGI, HDRS, HAMA, STAI and BDI) and evaluated for associations with auditory evoked P1, N1, P2 as well as P1/N1 and N1/P2 peak to peak amplitude slopes. Our data revealed a positive correlation of the intensity dependent N1 amplitude slope with the degree of certain somatic symptoms of depression: loss of appetite and weight, insomnia, and sexual dysfunction. The results of our study might contribute to a more specific clinical basis in the differential indication of serotonergic versus noradrenergic antidepressants.

2. Introduction

The increasing number of available antidepressants leads to a growing interest in the prediction of treatment reponse to different classes of antidepressants. The traditional clinical way of deciding, whether to use a serotonergic or noradrenergic antidepressant in the pharmacotherapy of depression, is often based on more or less clearly identifiable clinical subtypes of depression, for instance “anxious

depression" (Fava et al., 2000) or "melancholic depression" (Perry, 1996) and thus leads to a considerable number of initial non-responders. Therefore it seems to be of clinical interest to evaluate if certain symptoms of depression might be associated with an altered central serotonergic sensitivity.
In human electrophysiology research the search for reliable indicators of central serotonergic dysfunction in major depression has particularly attracted scientific interest in recent years. Considering that main concepts on the pathophysiology of depression comprise alterations in the central serotonergic neurotransmission and sensitivity (Owens, 2004), several authors used auditory Event Related Potential (ERP) components in the investigation of serotonergic dysregulation in patients with major depression (review in: Hegerl et al., 2001).

ERPs to auditory stimulation are characterized by three major components: An electrically positive P1 component at about 50 ms following stimulus onset, a negative N1 component at 100 ms and a positive P2 component at about 200 ms. Increases in auditory stimulus intensities are reflected by increases in ERP amplitudes. Typically, several stimulus intensities are used to elicit amplitude changes which can be transformed into slope values which give the amplitude change in µV per 10/dB (Beauducel et al., 2000).

Changes of the N1 and P2 amplitudes, P1/N1 and the N1/P2 peak-to-peak ERP component amplitudes in response to different tone intensities have been identified as a correlative of central nervous serotonergic activity (Buchsbaum, Silverman, 1968; Hegerl et al., 1998; Juckel et al., 1999; Strobel et al., 2003; von Knorring, Perris, 1981). A high loudness dependent amplitude increase ("high intensity dependence", "high IDAP") presumably reflects low serotonergic neurotransmission and vice versa (Juckel et al., 1999).

Studies in animals and human individuals corroborated the concept of the IDAP as an indicator of central serotonergic neurotransmission. Juckel et al. reported differential effects of microinjection of a 5-HT_{1A} agonist and a 5-HT_{1A} antagonist into the dorsal raphe nucleus (DRN) on the intensity dependence of auditory evoked potentials (AEP) recorded epidurally from the primary and secondary auditory cortex in behaving cats (Juckel et al., 1999). Strobel et al. (2003) found a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) to be associated with the N1/P2 amplitude intensity dependence. This result has been replicated by Hensch et al.(2006). However Debener et al. (2002)

found no effects of acute tryptophan depletion on AEP N1/P2 amplitude stimulus intensity function (ASF-slope) in a placebo controlled trial with 18 healthy women, suggesting that the IDAP might reflect individual rather than state differences of serotonergic neurotransmission. More recently, Juckel et al. reported an association between a specific 5-HT1B receptor polymorphism and the loudness dependence of the N1/P2 component of the auditory evoked potential (Juckel et al., 2007a).

The psychophysiological phenomenon of augmenting/reducing, firstly described by Buchsbaum et al. (1968), is assumed to reflect individual differences in the modulation of sensory input. Individuals who showed an increase of ERP amplitudes with increasing stimulus intensity were classified as augmenters and individuals who showed a decrease of ERP amplitudes with increasing stimulus intensity as reducers. First investigations on the intensity dependence of sensory evoked potentials and their relation to psychiatric disorders by Zuckerman et al. (1974) focused on the relation between stimulus intensity dependence and personality factors like impulsiveness, aggressiveness and sensation seeking behaviour (Zuckerman, Murtaugh, 1974).

In psychiatric research the role of the IDAP has been studied in several fields: Juckel et al. found the IDAP of the primary auditory cortex derived from dipole source analysis in 25 inpatients with schizophrenia to be significantly lower compared to 25 healthy controls. After treatment with the 5-HT2 antagonistic antipsychotics clozapine and olanzapine, the IDAP tended to be increased, indicating normalization of serotonergic function in the patients with schizophrenia under antipsychotic treatment (Juckel et al., 2003). Tuchtenhagen et al. (2000) reported a high intensity dependence of auditory evoked dipole source activity in abstinent ecstasy (MDMA) users which indicates decreased serotonergic activity (Tuchtenhagen et al., 2000). Similar results have been decribed by Croft et al. (2001) regarding long-term MDMA abuse. A high IDAP has been described to correlate with aspects of impulsiveness in 15 female patients suffering from borderline personality disorder (Norra et al., 2003). Wang et al. found a high IDAP in histrionic personality disorder (Wang et al., 2006). However, applying dipole source analysis Senkowski et al. found a significantly lower IDAP derived from bilateral tangential dipoles in 31 medication-free patients with General Anxiety Disorder in comparison to 31 matched control subjects (Senkowski et al., 2003). In

patients under treatment with Serotonin Reuptake Inhibitors (SSRI) Hegerl et al. (1998) found that high scores in the serotonin syndrome scale (SSS) were associated with low IDAP and vice versa (Hegerl et al., 1998). Despite the hypothesised pathophysiological role of serotonin in obsessive compulsive disorder, Carrillo-de-la-Pena found no difference between patients and controls (Carrillo-de-la-Pena et al., 2000).

Based on such preclinical and clinical studies, the IDAP has been established as an electrophysiological indicator of central serotonergic neurotransmission in depression with special relevance to treatment-response to SSRI. This concept has been corroborated in several studies applying various antidepressants (Juckel et al., 2007b; Paige et al., 1994).

As a strong IDAP is considered a predictor of superior response to SSRI treatment in major depression, this study aims to investigate the hypothesis that the IDAP is associated with certain patterns of psychometrically assessed symptoms of depression evaluated by psychiatric rating scales. Moreover we aim to identify, describe and discuss those psychometric symptoms, which are indirectly associated with a favourable outcome to SSRI treatment as predicted by a strong IDAP.

3. Method

3.1 Subjects

Forty in-patients with major depressive episode (DSM-IV: 296.2, 296.3, 296.5; APA 1994), who were admitted consecutively to the Department of Psychiatry and Psychotherapy of the University of Duisburg-Essen were included in the study. The study was approved by the local ethics committee. Patients gave their written informed consent prior to their inclusion in the study. Subjects' characteristics are presented in table 1.

3.2 Rating scales and procedure

Symptoms of major depression were assessed by means of psychiatric rating scales: Clinical Global Impression (CGI) ((NIMH), 1976), Hamilton Rating Scale for

Depression (HDRS, 21 items) (Hamilton, 1960), Beck Depression Inventory (BDI) (Beck et al., 1961) and State-Trait-Anxiety Inventory (STAI state anxiety form X1 (Spielberger, 1970)). Symptom ratings were performed by a senior psychiatrist who had no information on patients' ERP data. The total score of HDRS in patients had to be 20 at least. The CGI, HDRS and BDI scores were obtained at the day of ERP recording. Pre-treatment antidepressants were stopped at least two days before ERP recording. Six patients received antidepressants before they were included into the study (substance, wash out, duration of treatment: Amitriptyline n=2, 2 and 3 days, 11 and 8 months; Mirtazapine n=1, 3 days, 5 weeks; Paroxetine n=1, 2 days, 5 weeks; Venlafaxine n=1, 3 days, 4 weeks; Hypericum extract n=1, 4 days, 4 weeks).Central neurological disorders, abuse of illicit drugs and alcohol dependence were excluded, as was pre-treatment with electroconvulsive therapy. Concomitant medication with antipsychotics, mood stabilizers or additional antidepressants was not allowed. Concomitant benzodiazepine treatment (n=2) was restricted to a maximum dose of 1.5mg Lorazepam per day. Lorazepam was not given 12 hours before EEG-recording.

Table 1
Subject characteristics

Total	40
Age	41.9 (± 12.4)
Gender (m/f)	13 / 27
Education (y)	12.8 (± 2.2)
Nicotine (n; mg/d)	22; 18.3 (± 16.2)
Episodes of depression (n)	2.2 (± 2.0)
Time since the beginning of the first episode (y)	9.0 (± 8.6)
CGI total score	4.6 (± 1.0)
HDRS total score	24,5 (±3.8)
HAMA (psychic anxiety)	6.0 (± 4.9)
HAMA (somatic anxiety)	3.3 (± 3.1)
HAMA total score	8.3 (± 7.6)
BDI total score	28.9 (±12,0)
STAI total score	58.7 (±12.8)

3.3 Electrophysiological assessment and data analysis

EEG data were recorded in a sound-attenuated and electrically shielded room. Subjects were seated in a comfortable armchair. Auditory stimulation was done in two runs of 500 stimuli each with an interstimulus-intervall randomized between 500 ms and 900 ms. Auditory stimuli of 1000 Hz, with 80 ms duration (10 ms rise / fall) were presented at five intensities of 60, 70, 80, 90 and 100 dB sound pressure level via TDH-39p headphones (Telephonics Inc.) in randomized order. The auditory threshold with respect to 1000 Hz tones was below 30 dB as measured by an audiometer. Stimulus presentation was generated by Neuroscan Stim 3.3 Software. Evoked potentials were recorded from 27 scalp electrodes (extended international 10-20 system) with linked earlobes as reference using a 32-channel EEG amplifier (Neuroscan Inc.). A vertical and horizontal electro-oculogram (EOG) was recorded for offline eyeblink artifact removal (Semlitsch et al., 1986). EEG data were recorded with a sampling rate of 500 Hz in the frequency range of 0.1 to 100 Hz. ERP data were filtered offline with a 0.1 Hz to 30 Hz bandpass filter (Neuroscan Edit 4.1). EEG data were segmented into periods of 600 ms starting 100 ms prior to stimulus onset. Segments with amplitudes exceeding +/- 50 µV were rejected from further analysis. ERP averages were computed for each stimulus intensity level. Mean sweep numbers ranged between 114.5 and 137.5 sweeps for intensities between 60 dB up to 100 dB. Amplitudes of the N1 and the P2 components were computed from electrodes Fz, Fcz, Cz, C3 and C4. According to Beauducel et al. we restricted our analysis to those five electrodes which have been most commonly used in IDAP research (Beauducel et al., 2000).

3.4 Statistical analysis

Intensity slopes (amplitude slope function derived by linear regression across stimulus intensity levels) were computed for the P1, N1, P2 amplitudes and the P1/N1 and N1/P2 peak to peak amplitudes. For within-subject tests on stimulus intensity and electrode effects, epsilon-corrected averaged F-tests (Greenhouse-Geisser) were used. To assess associations between ERP data and psychometric symptoms of major depression we restricted correlation analyses to electrode Fz where we previously found the largest amplitude increases with increasing auditory stimulus intensity (Linka et al., 2004). With the limitations of a larger number of relevant symptoms and a sample size of 40 patients we had to abstain from multivariate analyses. Following Pearson correlations between the N1

intensity slope at electrode Fz and the sum scores of our psychometric scales, we screened the single items of our scales (HDRS, BDI, HAMA and STAI) for correlations with the N1 amplitude intensity slope at electrode Fz. We identified seven items with significant correlation coefficients ($r \geq .2$) between psychometric rating scales and the IDAP. For the construction of a composite variable, we first computed z-transformations on each of these seven variables in order to adjust for different dimensions in scaling between these items. In a second step we averaged the seven z-transformed single item rating scale scores in each subject, thereby constructing a composite value. The new composite score values were then correlated with the N1 amplitude slope data. All statistical analyses were performed using SPSS.

4. Results

4.1 Rating scales

Results of clinical ratings (Clinical Global Impression, CGI ((NIMH), 1976), Hamilton Rating Scale for Depression, HDRS, 21 items (Hamilton, 1960), Hamilton Anxiety Scale, HAMA (Guy, 1976), Beck Depression Inventory, BDI (Beck et al., 1961) and the State-Trait-Anxiety Inventory, STAI (Spielberger, 1970)) are shown in Table 1.

4.2 ERP data

N1 amplitude intensity slopes were not affected by sex, age, duration of illness, frequency of depression episodes or smoking habits (Pearson's correlation). Details on ERP data are given in Table 2.

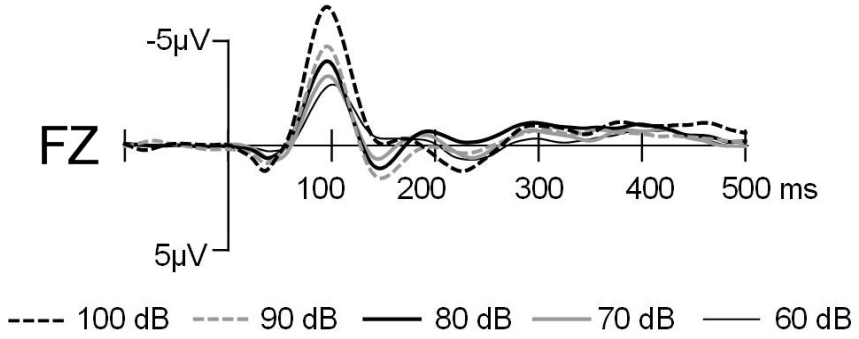

Figure 1
N1 evoked potential group averages at electrode Fz. Lines indicate five stimulus intensity levels ranging from 60 to 100 dB. The amplitude of the N1 component rises with higher stimulus intensities.

N1 amplitudes and slopes and P1/N1 and N1/P2 slopes were analysed with regard to electrode position effects in multivariate analysis of variance with electrode as within factor (Fz, Fcz, Cz, C3, C4) for slopes and electrode and intensity. N1 amplitudes increased with stimulus intensity ($F[3.3;202.4] = 28.8$, $p<.001$). Amplitudes differed between electrode positions ($F[1.7;202.4] = 15.1$, $p<.001$) and there was an interaction between the intensity dependent amplitude increase and electrode position ($F[5.2;202.4] = 2.7$, $p=.020$). Amplitude slopes differed between electrodes with $F[2.1;177.0] = 10.3$, $p<.001$ for the N1, with $F[2.1;174.0] = 11.4$, $p<.001$ for the P1/N1 and with $F[2.3;194.0] = 20.8$, $p<.001$ for the N1/P2 component (Table 2).

4.3 Correlations with rating scale items

We found associations of amplitude slopes at electrode Fz with the sum scores of our psychometric rating scales only for the N1 (HDRS $r=-.38$, $p=.02$) but neither for the P1/N1 nor for the N1/P2 component. There was no significant correlation between the state of anxiety as measured by the STAI (X1) total score and the IDAP. In the screening of the single items within the psychiatric rating scales we found highly significant correlations with the intensity slopes of the N1 amplitude

at Fz: HAMA item “Depressed Mood” (decreased interest in activities, anhedonia, insomnia): r=.41, p=.008, BDI item “Lack of interest in sex“: r=.40, p=.010 and HDRS items “insomnia, early“: r=.40, p=.011 and “decreased libido or menstrual disturbance”: r=.33, p=.037 correlated positively with the IDAP. There was a statistical trend for a positive correlation for BDI items “hopelessness”: r=.29, p=.073 and “decreased appetite”: r=.28, p=.079 and HDRS item “weight loss”: r=.26, p=.10. The overall correlation for these 7 rating scale items was r=.64, p<.001 (Fig. 2).

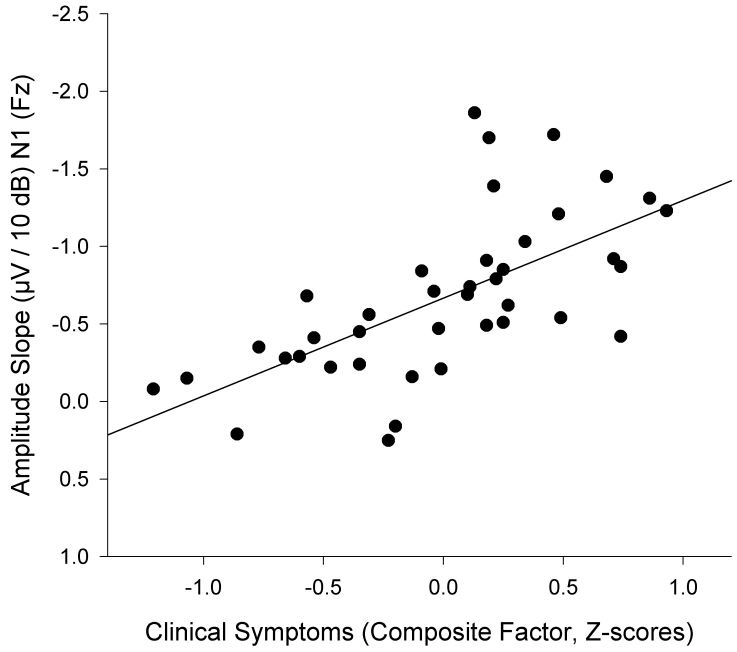

Figure 2

Scatterplot of overall correlation for 7 rating scale items with intensity dependent N1 amplitudes increase (slopes at µV / 10 dB) r=.64, p<.001.

Table 2

ERP Data: N1 amplitudes and N1, P1/N1, N1/P2 amplitude slopes.

	n=40 mean (sd)
N1 amplitude 60 dB / 100 dB (μV) *	
Fz	–3.22 (±2.0); –5.87 (±3.5)
Fcz	–3.28 (±1.9); –6.04 (±3.0)
Cz	–3.09 (±1.9); –5.65 (±2.8)
C3	–2.94 (±1.8); –5.34 (±2.6)
C4	–2.89 (±1.6); –5.02 (±2.5)
N1 amplitude slope (μV/10 dB) #	
Fz	0.67 (±0.52)
Fcz	0.71 (±0.46)
Cz	0.66 (±0.43)
C3	0.61 (±0.39)
C4	0.55 (±0.39)
P1/N1 amplitude slope (μV/10 dB) #	
Fz	0.73 (±0.51)
Fcz	0.83 (±0.54)
Cz	0.81 (±0.54)
C3	0.67 (±0.50)
C4	0.76 (±0.47)
N1 / P2 amplitude slope (μV/10 dB) #	
Fz	0.64 (±0.61)
Fcz	0.85 (±0.70)
Cz	0.88 (±0.74)
C3	0.70 (±0.56)
C4	0.67 (±0.56)

* Evoked response (ERP) amplitude data are given in μV for the lowest (60 dB) and the highest (100 dB) auditory stimulus intensities at electrode positions Fz, Cz, Fcz, C3 and C4.

Amplitude slopes give the absolute value of the mean increase in ERP amplitudes within the five (60, 70, 80, 90 and 100 dB) stimulus intensities in μV per 10 dB.

5. Discussion

Our analysis revealed a significant correlation between the intensity dependent slope of the N1 raw amplitude and specific symptoms assessed by means of psychiatric rating scales in unmedicated depressive subjects. We especially aimed to investigate the hypothesis of the IDAP being associated with certain patterns of psychometric symptoms of major depression and to identify, describe and discuss those symptoms, which may thus be indirectly associated with the outcome to SSRI treatment. In healthy subjects, the IDAP has been assessed and associated with personality traits by other authors. As this study focuses on the analysis of psychometric symptoms of major depression, we abstained from the assessment of healthy control subjects.

Among those six patients, who had been pretreated with antidepressants two subjects actually had a wash out phase of two days, whereas three subjects had a wash out phase of three days and one subject of four days. Exclusion of these pretreated subjects from evoked potential data analysis did not reveal significant differences in comparison to the analysis of the whole patient sample. Therefore we abstained from excluding these subjects from our analysis.

While several previous studies applied reverse problem solutions like BESA or LORETA in the evaluation of the N1/P2 auditory intensity dependence (Gallinat et al., 2000, Tuchtenhagen et al., 2000, Mulert et al., 2002) other studies evaluated raw data with regard to N1 (Brocke et al., 2000, Strobel et al., 2003), N1/P2 (Strobel et al., 2003, Croft et al., 2001) and P2 (Paige et al., 1994) amplitude slopes. In line with our earlier studies, here we investigated auditory stimulus intensity with regard to raw data P1, P1/N1, P2, N1 and N1/P2 amplitude slopes. We found associations of amplitude slopes at electrode Fz with psychometric symptoms of depression only for the N1 but neither for the P1/N1 nor for the N1/P2 component.

The intensity dependent amplitude slopes of the subjects in our study are comparable with those obtained in previous studies using similar procedures and measures. While our inter-stimulus interval between 500 ms and 900 ms is at the lower end of what has been used by other groups, stimulus intensities, electrode positions and stimulus intensity slope calculation are in keeping with previously employed methods (Beauducel et al., 2000). The resulting N1/P2 amplitude slopes in our study are in line with results reported by Sandor et al. (1999). They are however lower than those reported by Croft et al. (2001) and higher than those in

a study by Proietti-Cecchini et al. (1997). Therefore we may conclude that our experimental setup is principally comparable with that applied in previous studies in this field. However, the result that our data revealed no significant associations between psychometric symptoms of depression and P1/N1, N1/P2 and P2 slopes may be attributed to characteristics of our paradigm. In our data the N1 amplitude slope at electrode Fz slope was significantly correlated with the N1/P2 ($r=.57$, $p<.001$), with the P1/N1 ($r=.65$, $p>.001$) but to a much lower degree with the P2 ($r=.32$, $p=.043$). We suggest that in our experimental setup the N1 is the most sensitive variable. This is in line with our previous reports using the same experimental setup (Linka et al., 2004; Linka et al., 2005) .

We found 7 rating scale items to correlate with more than $r = 0.2$ with the IDAP. The correlation of the composite score of these 7 items was statistically highly significant with $r = .64$. The composite score can be viewed at as a construction of a kind of questionnaire derived from the pool of questions obtained in our study. The fact, that the correlation of the composite score with the N1 amplitude slope is considerably higher than each of the correlations with the single items may be taken as indirect evidence for the relevance of the selected items. The first four of these single items correlated significantly with the IDAP while the latter three showed statistical trends. Of special relevance are those items which tag congruent symptoms from psychiatrist's assessment (HDRS) as well as from patients self rating (BDI). Here, this applies to HDRS item "decreased libido or menstrual disturbance" and BDI item "lack of interest in sex" as well as to HDRS item "weight loss" and BDI item "decreased appetite".

The correlation of BDI item "Lack of interest in sex" and HDRS item "decreased libido or menstrual disturbance" points to the important finding, that a high score in sexual disturbance in patients self rating as well as in psychiatrists rating was associated with a high IDAP. This finding is of special clinical interest as a high IDAP correlates with a favorable response to SSRI-treatment (Gallinat et al., 2000; Paige et al., 1994) and the existence of sexual dysfunction associated with depression has so far not been described as a criterion for pharmacotherapy with an SSRI. However, our finding seems to be in contrast to a study results suggesting a benefit for depressive patients with sexual dysfunction when treated with Reboxetine (Clayton et al., 2003). In line with the latter result, many clinicians tend to avoid SSRI in the treatment of major depression associated with sexual disturbances. On the other hand a recent study by Cyranowksi et al (2004) found that SSRI induced sexual dysfunction in a group of 68 women treated for recurrent

major depression was restricted to orgasmic difficulty only, whereas libido and sexual interest were related to depression itself (Cyranowski et al., 2004). As a consequence of our findings, future studies might evaluate the hypothesis, that the existence of sexual dysfunction (apart from orgasmic difficulty) in major depressive episodes may be one among other criteria for treatment with SSRI.

While the effects of SSRI-treatment on appetite and weight are still under discussion (Harvey, Bouwer, 2000), the statistical trend in the correlation between high IDAP indicating favorable SSRI treatment response (Gallinat et al., 2000; Linka et al., 2004) and high scores in BDI items "decreased appetite" and HDRS item "weight loss" is of interest as it implies that the presence of these symptoms may be an indicator for successful SSRI treatment of major depression. However, considering the low statistical association of this finding, this hypothesis may be taken as preliminary.

The statistically significant correlation between high IDAP and a high score in HDRS item "insomnia, early" is of clinical relevance because insomnia is closely related to depressive symptomatology (Fava, 2004). Insomnia has also been reported as a frequent side-effect in SSRI treatment of major depression (Ferguson, 2001). Our finding might give indirect support to the clinical practice of continuing SSRI treatment despite a temporary worsening of sleep disturbance.

In summary, the results of our study may contribute to a more specific clinical basis in the differential indication of serotonergic versus noradrenergic antidepressants and indicate an association of specific somatic symptoms of major depression with the IDAP. While or study is exploratory, further studies are needed to further assess and verify the relevance of our findings. Moreover, studies combining ERP, genetic approaches (NET- and 5HT-polymorphisms) and clinical symptomatology in a double blind, randomized setting with different classes of antidepressants (SSRI, NARI, SNRI) are needed.

6. Acknowledgements

We acknowledge help in data collection by S. Bender, R. Franzke, A. Hesse, O. Ligneth-Dahm, N. Löbbecke, R. Windelschmidt.

References

- Beauducel, A., Debener, S., Brocke, B., Kayser, J., 2000. On the reliability of augmenting / reducing. Peak amplitudes and principal component analysis of auditory evoked potentials. Journal of Psychophysiology 14, 226-240.
- Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Archives of General Psychiatry 4, 561-571.
- Buchsbaum, M., Silverman, J., 1968. Stimulus intensity control and the cortical evoked response. Psychosom Med 30, 12-22.
- Carrillo-de-la-Pena, M.T., Mavrogiorgou, P., Juckel, G., Hauke, W., Gallinat, J., Frodl, T., Zaudig, M., Hegerl, U., 2000. Loudness dependence of auditory evoked potentials in obsessive-compulsive disorder: a pilot study. Psychiatry Res 93, 209-216.
- Clayton, A.H., Zajecka, J., Ferguson, J.M., Filipiak-Reisner, J.K., Brown, M.T., Schwartz, G.E., 2003. Lack of sexual dysfunction with the selective noradrenaline reuptake inhibitor reboxetine during treatment for major depressive disorder. Int Clin Psychopharmacol 18, 151-156.
- Croft, R.J., Klugman, A., Baldeweg, T., Gruzelier, J.H., 2001. Electrophysiological evidence of serotonergic impairment in long-term MDMA ("ecstasy") users. Am J Psychiatry 158, 1687-1692.
- Cyranowski, J.M., Frank, E., Cherry, C., Houck, P., Kupfer, D.J., 2004. Prospective assessment of sexual function in women treated for recurrent major depression. J Psychiatr Res 38, 267-273.
- Debener, S., Strobel, A., Kurschner, K., Kranczioch, C., Hebenstreit, J., Maercker, A., Beauducel, A., Brocke, B., 2002. Is auditory evoked potential augmenting/reducing affected by acute tryptophan depletion? Biol Psychol 59, 121-133.
- Fava, M., Rosenbaum, J.F., Hoog, S.L., Tepner, R.G., Kopp, J.B., Nilsson, M.E., 2000. Fluoxetine versus sertraline and paroxetine in major depression: tolerability and efficacy in anxious depression. J Affect Disord 59, 119-126.
- Fava, M., 2004. Daytime sleepiness and insomnia as correlates of depression. J Clin Psychiatry 65 Suppl 16, 27-32.
- Ferguson, J.M., 2001. SSRI Antidepressant Medications: Adverse Effects and Tolerability. Prim Care Companion J Clin Psychiatry 3, 22-27.
- Gallinat, J., Bottlender, R., Juckel, G., Munke-Puchner, A., Stotz, G., Kuss, H.J., Mavrogiorgou, P., Hegerl, U., 2000. The loudness dependency of the auditory

evoked N1/P2-component as a predictor of the acute SSRI response in depression. Psychopharmacology (Berl) 148, 404-411.

- Guy, W., 1976. ECDEU Assessment manual for psychopharmacology, US Department of Health and Human Services Rockville, MD, pp. 194-198.
- Hamilton, M. 1960. A rating scale for depression, J Neurol Neurosurg PsychiatryVol. 23, 56-62.
- Harvey, B.H., Bouwer, C.D., 2000. Neuropharmacology of paradoxic weight gain with selective serotonin reuptake inhibitors. Clin Neuropharmacol 23, 90-97.
- Hegerl, U., Bottlender, R., Gallinat, J., Kuss, H.J., Ackenheil, M., Moller, H.J., 1998. The serotonin syndrome scale: first results on validity. Eur Arch Psychiatry Clin Neurosci 248, 96-103.
- Hegerl, U., Gallinat, J., Juckel, G., 2001. Event-related potentials. Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? J Affect Disord 62, 93-100.
- Hensch, T., Wargelius, H.L., Herold, U., Lesch, K.P., Oreland, L., Brocke, B., 2006. Further evidence for an association of 5-HTTLPR with intensity dependence of auditory-evoked potentials. Neuropsychopharmacology 31, 2047-2054.
- Juckel, G., Hegerl, U., Molnar, M., Csepe, V., Karmos, G., 1999. Auditory evoked potentials reflect serotonergic neuronal activity--a study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus. Neuropsychopharmacology 21, 710-716.
- Juckel, G., Gallinat, J., Riedel, M., Sokullu, S., Schulz, C., Moller, H.J., Muller, N., Hegerl, U., 2003. Serotonergic dysfunction in schizophrenia assessed by the loudness dependence measure of primary auditory cortex evoked activity. Schizophr Res 64, 115-124.
- Juckel, G., Hegerl, U., Giegling, I., Mavrogiorgou, P., Wutzler, A., Schuhmacher, C., Uhl, I., Brune, M., Mulert, C., Pogarell, O., Rujescu, D., 2007a. Association of 5-HT1B receptor polymorphisms with the loudness dependence of auditory evoked potentials in a community-based sample of healthy volunteers. Am J Med Genet B Neuropsychiatr Genet.
- Juckel, G., Pogarell, O., Augustin, H., Mulert, C., Muller-Siecheneder, F., Frodl, T., Mavrogiorgou, P., Hegerl, U., 2007b. Differential prediction of first clinical response to serotonergic and noradrenergic antidepressants using the loudness dependence of auditory evoked potentials in patients with major depressive disorder. J Clin Psychiatry 68, 1206-1212.

- Linka, T., Müller, B.W., Bender, S., Sartory, G., 2004. The intensity dependence of the auditory evoked N1 component as a predictor of response to Citalopram treatment in patients with major depression. Neurosci Lett 367, 375-378.
- Linka, T., Müller, B.W., Bender, S., Sartory, G., Gastpar, M., 2005. The intensity dependence of auditory evoked ERP components predicts responsiveness to reboxetine treatment in major depression. Pharmacopsychiatry 38, 139-143.
- (NIMH), N.I.o.M.H. 1976. CGI. Glinical global impressions. In R. Bonato (Ed.), Manual for the EDCEU assessment battery, 2nd editionVol. 12. Chevy Chase: NIMH.
- Norra, C., Mrazek, M., Tuchtenhagen, F., Gobbele, R., Buchner, H., Sass, H., Herpertz, S.C., 2003. Enhanced intensity dependence as a marker of low serotonergic neurotransmission in borderline personality disorder. J Psychiatr Res 37, 23-33.
- Owens, M.J. 2004. Selectivity of antidepressants: from the monoamine hypothesis of depression to the SSRI revolution and beyond, J Clin PsychiatryVol. 65 Suppl 4, 5-10.
- Paige, S.R., Fitzpatrick, D.F., Kline, J.P., Balogh, S.E., Hendricks, S.E., 1994. Event-related potential amplitude/intensity slopes predict response to antidepressants. Neuropsychobiology 30, 197-201.
- Perry, P.J., 1996. Pharmacotherapy for major depression with melancholic features: relative efficacy of tricyclic versus selective serotonin reuptake inhibitor antidepressants. J Affect Disord 39, 1-6.
- Proietti-Cecchini, A., Afra, J., Schoenen, J., 1997. Intensity dependence of the cortical auditory evoked potentials as a surrogate marker of central nervous system serotonin transmission in man: demonstration of a central effect for the 5HT1B/1D agonist zolmitriptan (311C90, Zomig). Cephalalgia 17, 849-854; discussion 799.
- Sandor, P.S., Roon, K.I., Ferrari, M.D., van Dijk, J.G., Schoenen, J., 1999. Repeatability of the intensity dependence of cortical auditory evoked potentials in the assessment of cortical information processing. Cephalalgia 19, 873-879.
- Semlitsch, H.V., Anderer, P., Schuster, P., Presslich, O. 1986. A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP, PsychophysiologyVol. 23, 695-703.

- Senkowski, D., Linden, M., Zubragel, D., Bar, T., Gallinat, J., 2003. Evidence for disturbed cortical signal processing and altered serotonergic neurotransmission in generalized anxiety disorder. Biol Psychiatry 53, 304-314.
- Spielberger, C.D. 1970. Manual for the State-Trait-Anxiety Inventory. Palo Alto: Consulting Psychologist Press.
- Strobel, A., Debener, S., Schmidt, D., Hunnerkopf, R., Lesch, K.P., Brocke, B., 2003. Allelic variation in serotonin transporter function associated with the intensity dependence of the auditory evoked potential. Am J Med Genet 118B, 41-47.
- Tuchtenhagen, F., Daumann, J., Norra, C., Gobbele, R., Becker, S., Pelz, S., Sass, H., Buchner, H., Gouzoulis-Mayfrank, E., 2000. High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent ecstasy (MDMA) users. Neuropsychopharmacology 22, 608-617.
- von Knorring, L., Perris, C. 1981. Biochemistry of the augmenting-reducing response in visual evoked potentials, NeuropsychobiologyVol. 7, 1-8.
- Wang, W., Wang, Y., Fu, X., Liu, J., He, C., Dong, Y., Livesley, W.J., Jang, K.L., 2006. Cerebral information processing in personality disorders: I. Intensity dependence of auditory evoked potentials. Psychiatry Res 141, 173-183.
- Zuckerman, M., Murtaugh, T., 1974. Sensation seeking and cotrical augmenting-reducing. Psychophysiology 11, 535-542.

CHAPTER 6

TREATMENT EFFECTS OF SEROTONERGIC AND NORADRENERGIC ANTIDEPRESSANTS ON THE INTENSITY DEPENDENCE OF AUDITORY ERP COMPONENTS IN MAJOR DEPRESSION.

Treatment effects of serotonergic and nor-adrenergic antidepressants on the intensity dependence of auditory ERP components in major depression.

Thomas Linka, Gudrun Sartory, Jens Wiltfang, Bernhard W. Müller

Published in Neuroscience Letters 2009 Sep 29;463(1):26-30

Abstract

The intensity dependent amplitude change of auditory evoked potentials (IDAP), an assumed indicator of the level of central nervous serotonergic neurotransmission, was measured in major depressive disorder (MDD, DSM-IV: 296.2, 296.3; APA 1994) before and after treatment with either a selective serotonin reuptake inhibitor or a selective noradrenaline reuptake inhibitor antidepressant and compared with the results of a healthy control group. Auditory evoked P1, N1, P2, P1/N1 and N1/P2 peak-to-peak amplitudes were evaluated in 26 in-patients with MDD prior to and after antidepressant treatment with citalopram (24 days, n = 14) or reboxetine (25 days, n = 12), and in 43 healthy control subjects. Clinical symptoms of MDD were assessed by means of standardized psychiatric rating scales (CGI, HDRS, HAMA and BDI). The IDAP within the control group remained stable over 24 days (N1 amplitude slope retest ANOVA p = .79). Neither applied antidepressants nor decrease of HDRS total score during treatment had a significant effect on the IDAP in the patients' sample. The conclusion that the IDAP does not reflect the temporary depressive state in MDD is discussed.

Despite significant advances in pharmacologic treatment of major depressive disorder (MDD) over the past 20 years, a substantial proportion of patients (28 - 55%) fail to respond sufficiently to the treatment with the newer serotonin re-uptake inhibitor (SSRI) antidepressants, which have been introduced in the late 1980s [1]. Based on current main pathophysiological concepts of MDD, which comprise alterations in the central serotonergic neurotransmission and sensitivity [2], several authors within the field of human electrophysiology research focused on auditory event related potential (ERP) components in the investigation of serotonergic dysregulation in patients with MDD [3].

The ERP to auditory stimulation consist of three major components: the electrically positive P1 component at about 50 ms following stimulus onset, the negative N1 component at about 100 ms and the positive P2 component at about 200 ms. Typically, increases in auditory stimulus intensities result in increases of these ERP amplitudes. Several stimulus intensities are used to elicit amplitude changes, which can be transformed into slope values rendering the amplitude change in µV per 10/dB [4].

The degree of increase of N1 and P2 amplitudes as well as P1/N1 and the N1/P2 peak-to-peak ERP component amplitudes in response to different tone intensities has been identified as a correlative of central nervous serotonergic activity [5,6]. Animal [7,8], preclinical [9,10] and clinical studies have shown that a high intensity (loudness) dependent amplitude increase ("high intensity dependence", "high IDAP" or "high LDAEP") presumably reflects low central serotonergic neurotransmission and vice versa. A negative result came from Uhl et al., who measured the IDAP in female subjects under infusion of citalopram versus placebo and performed dipole source analysis. The increase of the central serotonin activity in response to citalopram was not accompanied by a significant change of the IDAP compared to the placebo condition [11]. The latter result is in line with an amino acid depletion study by Norra et al. in 16 healthy females. While monitoring tryptophan levels and mood states, the AEP of different loudness stimuli were recorded, followed by dipole source analysis. Calculated IDAP did not differ significantly between treatments and the IDAP was not correlated with states of mood, suggesting that the IDAP might reflect individual (trait) rather than state differences of serotonergic neurotransmission [12].

The concept of the IDAP as an indicator of central nervous serotonergic neurotransmission in MDD has been evaluated with positive results in various studies applying different antidepressants [13,14,15,16]. However, Guille et al.,

who used a double-blind, placebo-controlled cross-over design, in which healthy subjects were tested under acute treatment with pharmacologically equivalent single doses of placebo, escitalopram, citalopram and sertraline and applied two methods of ERP analysis (dipole source analysis and scalp analysis), found no effects of the applied antidepressants on the IDAP [17].

Table 1
Subject characteristics

	MDD, citalopram treatment sample; means (SD)	MDD, reboxetine treatment sample; means (SD)	Control sample; means (SD)
n	14	12	43
Age	39.38 (±14.5)	45.2 (±11.8)	39.2 (±
Gender (m/f)	5/11	4/10	10.4)
Education (y)	13.0 (±2.6)	12.9 (±2.0)	16/27
Nicotine (n; mg/d)	9; 12.9 (6.3)	6; 14.9 (±20.4)	13.9 (± 2.6)
Episodes of depression (n)	2.37(±1.7)	2.7(±2.4)	22; 14.11
Duration of illness (y)	8.3 (±7.3)	10.0 (±8.6)	(± 9.2)
Dose of antidepressant (mg)	37.5 (±10.0)	8.4 (±10.0)	-
CGI total score (baseline)	4.56 (±0.7)	4.6 (±1.4)	-
CGI total score (day 25/24)	3.9 (±0.8)	3.4 (±1.1)	-
HDRS total score (baseline)	25.13 (±3.5)	24.1 (±3.7)	-
HDRS total score (day 25/24)	14.6 (±5.5)	11.6 (±7.2)	3.1 (±3.1)
BDI total score (baseline)	29.50 (±12.5)	23.7 (±10.6)	3.3 (±3.0)
BDI total score (day 25/24)	21.6 (11.0)	15.4 (±10.7)	

Although several reports from independent laboratories considered the IDAP as a pre-treatment indicator in the pharmacologic therapy of MDD and examined acute effects of serotonergic antidepressants, the impact of different

antidepressants applied over several weeks and the effects of the course of treatment of MDD on the IDAP are still unclear. In the present study, we assessed the IDAP in MDD before and after 24 days of treatment with either the selective serotonin reuptake inhibitor citalopram or the selective noradrenaline reuptake inhibitor reboxetine and compared the results with that of a healthy control group.

The essential aim of our study was to investigate, whether serotonergic and non-serotonergic antidepressants differentially influence the IDAP itself. Furthermore we aimed to evaluate, whether the pre-treatment IDAP changes in the course of treatment of MDD and thus shows an association with the degree of the clinically observed depressive state.

Twenty-six in-patients with MDD (DSM-IV: 296.2, 296.3; APA 1994; diagnosed by structured clinical interviews), who were admitted consecutively to the Department of Psychiatry and Psychotherapy of the University of Duisburg-Essen and 43 matched healthy control subjects, were included for participation in the study. Patients and controls gave their written informed consent prior to their inclusion in the study. The study was approved by the local ethics committee and performed in accordance with the ethical recommendations laid down in the Declaration of Helsinki. Control subjects were matched with regard to age, and gender with the patient sample. Patients and controls did not differ significantly with regard to age and gender (table 1).

Central neurological disorders, hearing disability, abuse of illicit drugs and alcohol dependence were excluded, as was pre-treatment with electroconvulsive therapy during the last six months before inclusion. Subjects with a history of other axis-I-disturbances (DSM-IV) than depressive disorders were not included. Concomitant medication with antipsychotics, mood stabilizers or additional antidepressants was not allowed.

Clinical symptoms of major depression were assessed by means of psychiatric rating scales: Clinical Global Impression (CGI) [18], Hamilton Rating Scale for Depression (HDRS, 21 items, range of scores: 0 - 63) [19] and Beck Depression Inventory (BDI, 21 items, range of scores: 0 - 63) [20]. Clinical ratings were performed by an experienced senior psychiatrist who was blind to patients' ERP data. The BDI self rating scale was completed by all subjects in order to exclude individuals with clinically relevant depression within the control group. The pre-treatment total score of HDRS had to be 20 at least for patients to be

included into the study. The CGI, HDRS and BDI scores were obtained on the day of pre-treatment EEG-recording and after a mean of 24 days of treatment with either citalopram or reboxetine. According to the study protocol pre-treatment antidepressants had to be stopped at least 2 days before EEG-recording. Actually four patients of our sample received antidepressants during the last 12 months before they were included into the study (substance, duration of treatment, wash out period: amitriptyline n=1, 8 months, 11 months; mirtazapine n=1, 5 weeks, 3 days; venlafaxine n=1, 4 weeks, 3 days; hypericum extract n=1, 4 weeks, 4 days), which implicates that the minimal wash out time was 3 days. Concomitant benzodiazepine treatment (n=2) was restricted to a maximum dose of 1.5 mg lorazepam per day. Lorazepam was not given 12 hours before EEG-recording.

EEG-recording was repeated in a sub-sample of 14 patients (11 women, 3 men), who had been chosen for therapy with an SSRI antidepressant for clinical reasons, after 25 days of treatment (mean) with citalopram (free dose chosen within a range of 20 - 40 mg per day) and in another sub-sample of 12 patients (10 women, 2 men), who were considered as candidates for an antidepressive medication with a non-serotonergic antidepressant, after 24 days of treatment (mean) with reboxetine (free dose chosen within a range of 6 - 12 mg per day). The control individuals underwent EEG-recording two times as well, with an interval of 28 days.

EEG data were recorded in a sound-attenuated and electrically shielded room. Subjects were seated in a comfortable armchair. Auditory stimulation was administered in two runs of 500 stimuli each with an interstimulus-interval randomized between 500 ms and 900 ms. Auditory stimuli of 1000 Hz, with 80 ms duration (10 ms rise / fall) were presented at five intensities of 60, 70, 80, 90 and 100 dB sound pressure level via TDH-39p headphones (Telephonics Inc.) in randomized order. The auditory threshold with respect to 1000 Hz tones was below 30 dB as measured by an audiometer. Stimulus presentation was generated by Neuroscan Stim 3.3 Software. Evoked potentials were recorded from 27 scalp electrodes (extended international 10-20 system) with linked earlobes as reference using a 32-channel EEG amplifier (Neuroscan Inc.). A vertical and horizontal electro-oculogram (EOG) was recorded for offline eye blink artifact removal. EEG data were recorded with a sampling rate of 500 Hz in the frequency range of 0.1-100 Hz. ERP data were filtered offline with a 0.1-30 Hz band pass filter (Neuroscan Edit 4.1). EEG data were segmented into periods of 600 ms starting 100 ms prior to stimulus onset. Segments with amplitudes exceeding +/- 50 µV

were rejected from further analysis. ERP averages were computed for each stimulus intensity level. Mean sweep numbers ranged between 114.5 and 137.5 sweeps for intensities between 60 and 100 dB. Amplitudes of the N1 and the P2 components were computed from electrodes Fz, FCz, Cz, C3 and C4. In accordance with Beauducel et al. we restricted our analysis to those five electrodes which have been most commonly used in IDAP research [4].

Pre-treatment ERP amplitude of the P1, N1, P2 amplitudes and the P1/N1 and N1/P2 peak-to-peak amplitudes were analysed in separate multivariate analyses of variance with stimulus intensities (60, 70, 80, 90, 100 dB) and electrodes (Fz, FCz, Cz, C3, C4) as within factors and group (patients / control) as between factor. Effects of gender, and smoking habit on amplitude slopes were assessed with Chi^2 tests and the effects of age, education and the amount of nicotine consumption among smoking subjects were assessed with analysis of variance. The impact of duration of illness and the frequency of depression episodes on evoked potentials were assessed with Pearson's correlations.

Detailed results of clinical ratings are presented in table 1. Patients and controls did not show significant group differences with regard to age, gender, smoking status and the amount of nicotine intake per day in smoking subjects. However, patients reported fewer years of education than control subjects ($p = .015$). Within the control group BDI total scores did not reveal any significant symptoms of affective disorder and there was no significant difference between the first and the second ERP measurement.

Results from clinical ratings within the citalopram treatment group: psychiatric rating scores improved significantly from baseline to retest after a mean of 25 days of treatment: HDRS total score decreased from 25.1 (±3.5) to 14.6 (±5.5), BDI total score decreased from 29.5 (±12.5) to 21.6 (11.0) and CGI severity of illness score decreased from 4.6 (±0.7) to 3.9 (±0.8) as presented in table 1. A multivariate analysis of variance including the HDRS and the BDI at baseline and day 25 (time factor) revealed a significant main effect for the time factor ($F=38.5$, $p<.001$). The amount of symptom reduction did not differ between patients' self-ratings (BDI) and psychiatrist's ratings (HDRS) as indicated by the lack of a significant time x scale interaction.

Results from clinical ratings within the reboxetine treatment group: Psychiatric rating scores significantly improved from baseline to follow-up after a mean of 24 days of treatment: HDRS total score decreased from 24.1 (±3.7) to 11.6 (±7.2), BDI total score from 23.7 (±10.6) to 15.4 (±10.7) and CGI severity of illness

score from 4.9 (±0.5) to 3.4 (±1.1) as presented in Table 1. A multivariate analysis of variance including the HDRS and the BDI (scale factor) at baseline and day 24 (time factor) revealed a significant main effect for the time factor ($F=44.8$, $p<.001$). The amount of symptom reduction did not differ between patients' self-ratings (BDI) and psychiatrist's ratings (HDRS) as indicated by the lack of a significant time x scale interaction.

General results from the ERP data analysis: N1 amplitude intensity slopes within the control group were not affected by sex, age or smoking habits (Pearson's correlation). Details on ERP data of patients and controls are given in figure 1 and in table 2. N1 amplitudes increased with stimulus intensity ($F[3.3;202.4] = 28.8$, $p<.001$). Amplitudes differed between electrode positions ($F[1.7;202.4] = 15.1$, $p<.001$) and there was an interaction between the intensity dependent amplitude increase and electrode position ($F[5.2;202.4] = 2.7$, $p=.020$). Amplitude slopes differed between electrodes with $F[2.1;177.0] = 10.3$, $p<.001$ for the N1, with $F[2.1;174.0] = 11.4$, $p<.001$ for the P1/N1 and with $F[2.3;194.0] = 20.8$, $p<.001$ for the N1/P2 component.

The IDAP within the control group remained stable over 4 weeks (N1 amplitude slope retest ANOVA $p = .79$).

Following a mean treatment period of 25 days with citalopram or 24 days with reboxetine, respectively, N1 amplitude slopes correlated no longer with clinically observed depression (HDRS total score).

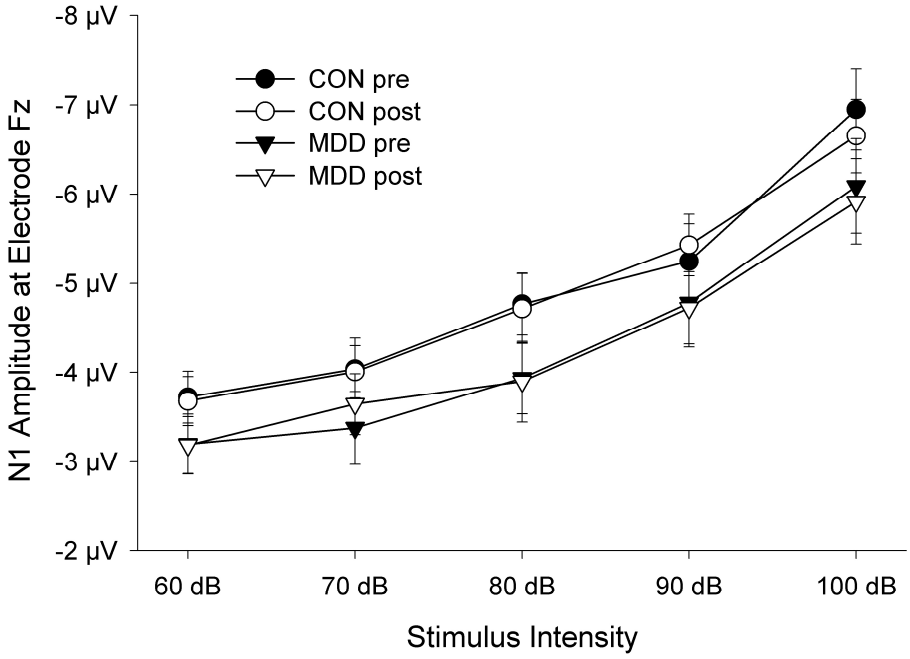

Figure 1
The N1 amplitude at electrode Fz before (pre) and after (post) antidepressant treatment with either citalopram or reboxetine (MDD only). Group differences between MDD patients and controls are not statistically significant.

ERP results within the citalopram treatment group: pre-treatment intensity slopes of the N1 amplitudes correlated significantly with HDRS reduction at Fz (r=0.56, p=.025) at FCz (r=0.55, p=.00.29) and at Cz (r=0.50, p=0.048). No correlations with HDRS reduction were found for N1 amplitude slopes from C3 to C4. N1 amplitude intensity slopes were not affected by sex, age, duration of illness, frequency of episodes of depression, smoking habits (Pearson's correlation). No correlation emerged for N1 intensity slopes with BDI and CGI scores. Additionally, no correlations with psychiatric ratings were found for P1, P1/N1, P2 and N1/P2 amplitude slopes. After a mean of 25 days of pharmacologic treatment with citalopram, the N1 amplitude slope at Fz correlated no longer with HDRS reduction (r = -0.19, p = 0.56). We found no group main effect or interactions involving the

group factor when comparing citalopram treated patients with the control group over time.

ERP results within the reboxetine treatment group: we found highly significant correlations of low intensity slopes of the N1 and high HDRS reduction at Fz (r=.86, p<.001) at FCz (r=.91, p<.001), at Cz (r=.93, p<.001), C3 (r=.81, p<.001) and C4 (r=.75, p<.001). Lower intensity slopes of the N1 amplitude were associated with better outcome as indicated by reduction of HDRS scores after treatment. N1 amplitude intensity slopes were not affected by sex, age, and duration of illness, frequency of depression episodes or smoking habits (Pearson's correlation). Significant correlations (Pearson's) with HDRS reduction were found for P1/N1 peak-to-peak amplitude slopes at Fz (r=.68, p<.001) at FCz (r=.63, p=.015), at Cz (r=.56, p=.038) and C3 (r=.63, p=.017) and N1/P2 amplitude slopes at Fz (r=.70, p<.001) and at FCz (r=.56, p=.036). No correlations emerged from the assessment of P2 amplitude slopes or from ERP intensity slopes and BDI or CGI scores. After a mean of 24 days of pharmacologic treatment with reboxetine N1 amplitude slope at Cz no longer correlated with HDRS (r = -0.27, p = 0.40). We found no group main effect or interactions involving the group factor when comparing reboxetine treated patients with the control group over time.

In the present study, we evaluated the intensity dependence of different auditory ERP components in MDD before and after a mean period of 25 days and 24 days, respectively, of pharmacologic treatment with either the selective serotonin reuptake inhibitor citalopram or the selective noradrenaline reuptake inhibitor reboxetine and compared the results with that of a healthy control group.

Based on several clinical studies, we assumed that patients with a high pre-treatment IDAP might belong to a pathophysiological subtype of MDD, which might be characterized by a low central nervous serotonergic metabolism, and therefore is likely to show a favourable response to SSRI treatment [13, 14]. This assumption led to our hypothesis that the successful treatment with an SSRI antidepressant might bring about a normalization of a pathologically low pre-treatment central nervous serotonergic activity in MDD.

Table 2
N1 amplitudes and N1, P1/N1, N1/P2 amplitude slopes in major depressive disorder before and after antidepressant treatment with either citalopram or reboxetine.

	MDD pre-treatment mean (SD)	MDD post-treatment mean (SD)
citalopram treatment group (n=14)		
N1 amplitude 60 dB / 100 dB (µV) [a]		
Fz	–2.80 (±2.0) / –6.13 (±3.8)	–3.14 (±1.9) / –5.50 (±2.9)
Fcz	–2.85 (±2.1) / –6.26 (±3.0)	–3.19 (±1.9) / –6.21 (±2.2)
Cz	–2.77 (±2.2) / –5.73 (±2.8)	–3.10 (±2.1) / –5.8 (±2.2)
N1 amplitude slope (µV/10 dB) [b]		
Fz	0.83 (±0.5)	0.58 (±0.4)
Fcz	0.85 (±0.5)	0.75 (±0.4)
Cz	0.76 (±0.4)	0.70 (±0.4)
P1/N1 amplitude slope (µV/10 dB) [b]		
Fz	1.02 (±0.6)	0.98 (±0.6)
Fcz	0.91 (±0.6)	1.14 (±0.6)
Cz	0.74 (±0.6)	1.17 (±0.5)
N1 / P2 amplitude slope (µV/10 dB) [b]		
Fz	0.68 (±0.7)	0.93 (±0.4)
Fcz	0.88 (±0.8)	1.15 (±0.4)
Cz	0.87 (±0.8)	1.17 (±0.5)
reboxetine treatment group (n=12)		
N1 amplitude 60 dB/100 dB (µV) [a]		
Fz	–3.38 (±1.8) / –5.74 (±3.6)	–3.28 (±1.8) / –6.10 (±2.8)
Fcz	–3.57 (±1.8) / –5.94 (±3.3)	–3.50 (±1.8) / –6.55 (±2.8)
Cz	–3.48 (±1.7) / –5.78 (±3.3)	–3.39 (±1.7) / –6.22 (±2.9)

	reboxetine treatment group (n=12)	
N1 amplitude slope (µV/10 dB)[b]		
Fz	0.57 (±0.6)	0.67 (±0.4)
Fcz	0.58 (±0.5)	0.75 (±0.5)
Cz	0.57 (±0.5)	0.71 (±0.5)
P1/N1 amplitude slope (µV/10 dB)[b]		
Fz	0.60 (±0.5)	0.91 (±0.6)
Fcz	0.64 (±0.5)	1.01 (±0.6)
Cz	0.68 (±0.6)	0.97 (±0.6)
N1 / P2 amplitude slope (µV/10 dB)[b]		
Fz	0.59 (±0.6)	0.66 (±0.7)
Fcz	0.72 (±0.6)	0.78 (±0.7)
Cz	0.80 (±0.6)	0.74 (±0.7)

[a]Evoked response (ERP) amplitude data are given for the lowest (60 dB) and the highest (100 dB) auditory stimulus intensities at electrode positions Fz, Cz, Fcz in µV.

[b] Amplitude slopes give the absolute value of the mean increase in ERP amplitudes within the five (60, 70, 80, 90 and 100 dB) stimulus intensities in µV per 10 dB.

Moreover, patients with MDD who show a low pre-treatment IDAP in comparison to a healthy control group have been found to respond favourably to non-serotonergic, e.g. noradrenergic antidepressants [15]. Considering the pathophysiological concepts of MDD comprise a presumed imbalance of central nervous noradrenergic and serotonergic activity, any successful treatment is likely to be accompanied by or result from a normalization of a presumably disturbed central nervous serotonergic and noradrenergic balance. Thus, we assumed that a low IDAP within the subgroup of MDD patients who favourably respond to reboxetine should also show increasing similarity with the healthy control group in the course of treatment.

The results of our investigations did not confirm our hypotheses, because they suggest that neither serotonergic medication with citalopram itself nor treatment effects as measured by an increase in HDRS total score in the reboxetine treatment subgroup had a significant effect on the IDAP in the course of treatment.

Considering methodological aspects of our ERP data analysis, we may say that the intensity dependent amplitude slopes of the subjects in our study are comparable with those obtained in previous studies using similar procedures and measures. While our inter-stimulus interval is at the lower end of what has been used by other groups, stimulus intensities, electrode positions and stimulus intensity slope calculation are in keeping with previously employed methods [4]. The resulting N1/P2 amplitude slopes of our study are similar to the results reported by Sandor et al. [21]. In line with our earlier studies, we investigated auditory stimulus intensity with regard to raw data ERP amplitude slopes as did many previous studies (N1 [9], N1/P2 [9, 23], P2 [21]). Our relatively small patient samples are an important limitation of our study. However, applying raw data analysis of single electrodes, a high test-retest reliability retest-stability of the IDAP after about 3 weeks of .71, .77 and .59 at Cz, C3, C4, respectively, in a sample including 8 men and 16 women (mean age = 47, SD = 11) has been demonstrated [4]. Nevertheless, the detection of statistically smaller treatment effects on the IDAP might require larger samples.

Further limitations result from the open-label and treatment-as-usual design of our study due to the ethical problems a double-blind randomized design with fixed doses of the applied antidepressants bring about in the research with patients, who suffer from clinically relevant depressive disorders. Furthermore, we did not control the female subjects of our samples for menstrual cycle and associated hormonal fluctuations, which have been shown to affect auditory ERP components [24] and did not perform any control procedure for possible attention effects on the IDAP [26].

The lack of treatment effects on the IDAP in the course of our evaluation indicates that the IDAP is not significantly associated with the current depressive state in MDD. This conclusion is in line with several studies which demonstrated a considerable degree of heritability of the IDAP [21] and reported an association of the IDAP with 5-HTTLPR, a genetic polymorphism of the revealed serotonin transporter coding gene [9, 10, 25]. Moreover, our results harmonize with recent studies by Guille et al. [17], who found no effects of acute treatment with various

SSRI on the IDAP, and by Norra et al. [12], who found no correlation of the IDAP with acute tryptophan depletion and with states of mood in healthy subjects.

The results of our study revealed that serotonergic as well as noradrenergic antidepressant treatment over more than 3 weeks were not associated with significant change in the IDAP in MDD. This finding does not contradict the concept of the IDAP as a pre-treatment indicator of treatment-response to serotonergic versus non-serotonergic antidepressants, but suggests that the IDAP may not reflect the individual depressive state. The latter assumption implies that treatment-success in MDD does not go along with a 'normalization' of the IDAP. However, further studies with a larger sample and with control for the above mentioned methodological aspects are needed to give more evidence on this question.

Acknowledgements

The authors are grateful to S. Bender, R. Franzke, A. Hesse, O. Ligneth-Dahm, N. Löbbecke, R. Windelschmidt for their help in data collection.

References

[1] M.H. Trivedi, A.J. Rush, S.R. Wisniewski, A.A. Nierenberg, D. Warden, L. Ritz, G. Norquist, R.H. Howland, B. Lebowitz, P.J. McGrath, K. Shores-Wilson, M.M. Biggs, G.K. Balasubramani, M. Fava, STAR*D Study Team, Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry.163 (2006) 28-40.

[2] M.J. Owens, Selectivity of antidepressants: from the monoamine hypothesis of depression to the SSRI revolution and beyond. Journal of Clinical Psychiatry 65 Suppl 4 (2004) 5-10.

[3] U. Hegerl, J. Gallinat, G. Juckel, Event-related potentials. Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? Journal of Affective Disorders 62 (2001) 93-100.

[4] A. Beauducel, S. Debener, B. Brocke, J. Kayser, On the reliability of augmenting / reducing. Peak amplitudes and principal component analysis of auditory evoked potentials. Journal of Psychophysiology 14 (2000) 226-240.

[5] M. Buchsbaum, J. Silverman, Stimulus intensity control and the cortical evoked response. Psychosomatic Medicine 30 (1968) 12-22.

[6] U. Hegerl, R. Bottlender, J. Gallinat, H.J. Kuss, M. Ackenheil, H.J. Möller, The serotonin syndrome scale: first results on validity. European Archives of Psychiatry and Clinical Neuroscience 248 (1998) 96-103.

[7] G. Juckel, U. Hegerl, M. Molnar, V. Csepe, G. Karmos, Auditory evoked potentials reflect serotonergic neuronal activity--a study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus. Neuropsychopharmacology 21 (1999) 710-716.

[8] A. Wutzler, C. Winter, W. Kitzrow, I. Uhl, R.J. Wolf, A. Heinz, G. Juckel, Loudness dependence of auditory evoked potentials as indicator of central serotonergic neurotransmission: simultaneous electrophysiological recordings and in vivo microdialysis in the rat primary auditory cortex. Neuropsychopharmacology. 33 (2008) 3176-81.

[9] Strobel, S. Debener, D. Schmidt, R. Hunnerkopf, K.P. Lesch, B. Brocke, Allelic variation in serotonin transporter function associated with the intensity dependence of the auditory evoked potential. American Journal of Medical Genetics 118B (2003) 41-47.

[10] T. Hensch, H.L. Wargelius, U. Herold, A. Strobel, L. Oreland, B. Brocke, Electrophysiological and behavioral correlates of polymorphisms in the transcription factor AP-2ß coding gene. Neuroscience Letters 440 (2008) 331-335.

[11] Uhl, I. Gorynia, J. Gallinat, C. Mulert, A. Wutzler, A. Heinz, G. Juckel, Is the loudness dependence of auditory evoked potentials modulated by the selective serotonin reuptake inhibitor citalopram in healthy subjects? Hum Psychopharmacol. 21(2006) 463-71.

[12] Norra, S. Becker, A. Bröcheler, W. Kawohl, H.J. Kunert, H. Buchner, Loudness dependence of evoked dipole source activity during acute serotonin challenge in females. Hum Psychopharmacol. 23 (2008), 31-42.

[13] J. Gallinat, R. Bottlender, G. Juckel, A. Munke-Puchner, G. Stotz, H.J. Kuss, P. Mavrogiorgou, U. Hegerl, The loudness dependency of the auditory evoked N1/P2-component as a predictor of the acute SSRI response in depression. Psychopharmacology (Berl) 148 (2000) 404-411.

[14] T. Linka, B.W. Müller, S. Bender, G. Sartory, The intensity dependence of the auditory evoked N1 component as a predictor of response to citalopram treatment in patients with major depression. Neuroscience Letters 367 (2004) 375-378.

[15] T. Linka, B.W. Müller, S. Bender, G. Sartory, M. Gastpar, The intensity dependence of auditory evoked ERP components predicts responsiveness to reboxetine treatment in major depression. Pharmacopsychiatry 38 (2005) 139-143.

[16] G. Juckel, O. Pogarell, H. Augustin, C. Mulert, F. Muller-Siecheneder, T. Frodl, P. Mavrogiorgou, U. Hegerl, Differential prediction of first clinical response to serotonergic and noradrenergic antidepressants using the loudness dependence of auditory evoked potentials in patients with major depressive disorder. Journal of Clinical Psychiatry 68 (2007) 1206-1212.

[17] V. Guille, R.J. Croft, B.V. O'Neill, S. Illic, K.L Phan, P.J. Nathan, An examination of acute changes in serotonergic neurotransmission using the loudness dependence measure of auditory cortex evoked activity: effects of citalopram, escitalopram and sertraline. Hum Psychopharmacol. 23(2008) 231-41.

[18] NIMH, CGI. Clinical global impressions. In: R. Bonato (Ed.), Manual for the EDCEU assessment battery, 2nd edition (1976) Vol. 12. Chevy Chase: NIMH.

[19] M. Hamilton, A rating scale for depression. J Neurology, Neurosurgery and Psychiatry 23 (1960) 56-62.

[20] A.T. Beck, C.H. Ward, M. Mendelson, J. Mock, J. Erbaugh, An inventory for measuring depression. Archives of General Psychiatry 4 (1961) 561-571.

[21] P.S. Sandor, K.I. Roon, M.D. Ferrari, J.G. van Dijk, J. Schoenen, Repeatability of the intensity dependence of cortical auditory evoked potentials in the assessment of cortical information processing. Cephalalgia 19 (1999) 873-879.

[22] A. Proietti-Cecchini, J. Afra, J. Schoenen, Intensity dependence of the cortical auditory evoked potentials as a surrogate marker of central nervous system serotonin transmission in man: demonstration of a central effect for the 5HT1B/1D agonist zolmitriptan (311C90, Zomig). Cephalalgia 17 (1997) 849-854.

[23] T. Dierks, S. Barta, L. Demisch, K. Schmeck, E. Englert, A. Kewitz, Intensity dependence of auditory evoked potentials (AEPs) as biological marker for cerebral serotonin levels: effects of tryptophandepletion in healthy subjects. Psychopharmacology (Berl) 146 (1999) 101–7.

[24] V. Walpurger, R. Pietrowsky C. Kirschbaum OT. Wolf, Effects of the menstrual cycle on auditory event-related potentials. Hormones and Behavior 46 (2004) 600-6.

[25] J. Gallinat, D. Senkowski, C. Wernicke, G. Juckel, I. Becker, T. Sander, Allelic variants of the functional promoter polymorphism of the human serotonin transporter gene is associated with auditory cortical stimulus processing. Neuropsychopharmacology, 28 (2003) 530–2.

[26] MT Carrillo-de-la-Peña. Effects of intensity and order of stimuli presentation on AEPs: an analysis of the consistency of EP augmenting/reducing in the auditory modality. Clinical Neurophysiology 110 (1999) 924-32.

CHAPTER 7

GENERAL DISCUSSION

1. Introduction

In this research project, the stimulus intensity dependence of auditory evoked potentials (IDAP) of several ERP components in patients suffering from major depressive disorder (MDD) and in healthy control subjects was investigated. We assessed the predictive value of the IDAP for treatment with the SSRI citalopram (Chapter 2), as well as for treatment with the selective norepinephrine re-uptake inhibitor (SNRI) reboxetine in MDD (Chapter 3). We compared the IDAP of auditory ERP components in unmedicated patients with MDD with the results from healthy controls (Chapter 4) and evaluated treatment effects of serotonergic and noradrenergic antidepressants in MDD on the IDAP itself (Chapter 6). Furthermore, we studied associations of certain clinical symptoms of MDD with auditory ERP components (Chapter 5).

2. The IDAP as a predictor of response to citalopram and reboxetine treatment in patients with MDD

The results of the study evaluating the IDAP in 16 in-patients with MDD during the course of treatment with the SSRI citalopram revealed a significant correlation between the intensity slopes of the N1 amplitude prior to citalopram-treatment and treatment-response: patients with higher intensity slopes of N1 amplitude showed a significantly stronger decrease of HDRS-Score after citalopram-treatment than patients within the lower intensity slope ranges. A second study comprising 14 in-patients with MDD during treatment with the SNRI reboxetine demonstrated a highly significant correlation between lower pre-treatment intensity dependent N1 amplitude slopes and stronger decrease of HDRS total score.

In both treatment conditions, we investigated auditory stimulus intensity with regard to raw data of P1, P1/N1, P2, N1 and N1/P2 amplitude slopes, although according to the theory of Hegerl et al. (1993), the IDAP should be ideally assessed in the primary auditory cortex. In human studies, the latter can indirectly be done by using multichannel-EEG combined with source analysis techniques such as Brain Electrical Source Analysis (BESA; Scherg and Von Cramon, 1986) or Low Resolution Electromagnetic Source Analysis (LORETA; Pascual-Marqui et al., 1994). However,

many previous studies applied scalp analysis with regard to N1 (Brocke et al., 2000, Strobel et al., 2003), N1/P2 (Strobel et al., 2003, Croft et al., 2001) or P2 (Paige et al., 1994) amplitude slopes.

In both efficacy prediction studies, highly significant associations of ERP amplitude slopes with treatment outcome were found, predominantly for the N1 amplitude and to a lesser extent for P1/N1 and the N1/P2 component as well, but not for the P2 component. This result contrasts with a study by Paige et al. (1994), who found a significant correlation of P2 amplitude intensity dependence with SSRI treatment outcome and with Beauducel et al. (2000), who suggested that the P2 amplitude slopes may reflect stimulus intensity changes more precisely than other ERP component slopes.

The negative results of the IDAP derived from the P2 amplitude slope in our studies might be due to the relatively small samples. Considering the high split-half coefficients in our studies, indicating high internal consistency of ERP data and intensity slopes, comparable to previously reported studies, it seems unlikely that our studies might lack from data quality. Methodological studies of the IDAP, using raw data analysis from single electrodes, detected reliabilities between r =.7 and .8 (Beauducel et al., 2000). A study by Dierks et al. (1999) using an acute tryptophan depletion paradigm, revealed a high correlation of the IDAP of tangential dipoles with the IDAP at Cz. Recently, Guille et al. (2008), who used a double-blind, placebo-controlled cross-over design in which healthy subjects were tested under acute treatment with pharmacologically equivalent single doses of placebo, escitalopram, citalopram and sertraline and applied two methods of ERP analysis (dipole source analysis and scalp analysis), revealed similar results for both assessment strategies(dit is wel een erg lange zin). In conclusion, the IDAP has been shown to be a clinically relevant indicator a central nervous serotonergic activity, that can be reliably assessed by the easily applicable, conventional scalp analysis of ERP.

3. Treatment effects of antidepressants on the IDAP in major depression

We postulated that patients with a high pre-treatment IDAP might belong to a pathophysiological subtype of MDD characterized by a low central nervous serotonergic metabolism, and therefore are likely to show a favourable response to SSRI treatment (Gallinat et al., 2000, Linka et al., 2004). This assumption led to the hypothesis that a successful treatment with an SSRI might bring about a normalization of a pathologically low pre-treatment central nervous serotonergic activity in MDD. Thus, we expected that treatment with citalopram should lead to a decrease of a heightened pre-treatment IDAP. Furthermore, we postulated that a low IDAP within the subgroup of MDD patients who favorably respond to reboxetine, should also show increasing similarity with the healthy control group during the course of treatment, i.e., that an increase of a low pre-treatment IDAP under pharmacotherapy with reboxetine should be due to an improvement of the depressive state rather than to pharmacological effects of reboxetine itself on central nervous serotonergic metabolism.

We evaluated the intensity dependence of various auditory ERP components in MDD before and after a mean period of 25 days and 24 days of treatment, respectively, with either the selective serotonin reuptake inhibitor citalopram or the selective norepinephrine reuptake inhibitor reboxetine, and compared these results with that of a healthy control group.

The results of our investigations did not confirm our hypotheses, because they suggest that neither serotonergic medication with citalopram nor treatment effects as measured by an increase in the HDRS total score in the reboxetine treatment subgroup had a significant effect on the IDAP derived from the N1, P1/N1 and N1/P2 ERP components during the course of treatment. However, we found significant 3-way (treatment group x time x intensity) interaction effects at electrodes Cz and C3 with regard to the P2 component. These were due mainly to a decrease in P2 intensity slopes over time in the reboxetine group. Considering that our group did not find the P2 component of relevance in the prediction of antidepressant treatment efficacy, this result was unexpected. There are, however, previous reports on P2 effects (Paige, 1994), showing higher pre-treatment P2 intensity slopes to be associated with positive treatment responses

to SSRIs. With regard to the small sample sizes in the treatment subgroups, our P2 results should be replicated in a larger sample of patients. Our data indicate that during the course of treatment, the N1 component seems to be more stable than the P2. In our data, the N1 amplitude slope at electrode Fz was significantly correlated with the N1/P2 ($r=.57$, $p<.001$), with the P1/N1 ($r=.65$, $p>.001$), but to a much lower degree with the P2 ($r=.32$, $p=.043$) slopes. We suggest that in our experimental set-up the N1 is the most sensitive variable. This is in line with our previous reports using the same experimental protocol (Linka et al., 2004; Linka et al., 2005).

Our relatively small patient samples are an important limitation of our studies. Further limitations result from the open-label and treatment-as-usual design of our studies. These limitations were due to the ethical problems that a double-blind randomized design with fixed doses of the applied antidepressants brings about in the research with patients, who suffer from clinically relevant depressive disorders.

The observed lack of treatment effects on the IDAP might indicate that the IDAP is a rather trait than a state parameter of central nervous serotonergic transmission. This conclusion is in line with several studies which demonstrated a considerable degree of heritability of the IDAP (Sandor et al., 1999) and reported an association of the IDAP with 5-HTTLPR, a genetic polymorphism of the serotonin transporter coding gene (Gallinat et al., 2003;Hensch et al., 2006; Strobel et al., 2003). Moreover, our results are in accordance with those obtained in recent studies by Guille et al. (2008), who found no effects of acute treatment with various SSRIs on the IDAP, and by Norra et al. (2008), who found no correlation of the IDAP with acute tryptophan depletion and with states of mood in healthy subjects.

4. The IDAP in unmedicated patients with MDD and in healthy controls

The presented study was designed to compare the IDAP in unmedicated depressed patients with that of healthy control subjects, in order to answer the question whether there is a general abnormality of the IDAP in MDD. We therefore

evaluated the change of auditory evoked P1, N1, P2, as well as P1/N1 and N1/P2 peak to peak amplitudes, in 34 in-patients with MDD prior to antidepressant treatment, and in 44 healthy control subjects. In multivariate analyses of variance, no group differences in the IDAP of the P1, N1, P2 and of the P1/N1 and N1/P2 peak to peak amplitudes between patients and controls were detected.

Although, compared to patients, controls showed a slightly higher intensity dependent amplitude increase at Cz, in an overall analysis of electrodes Fz, FCz, Cz, C3, C4, we found no significant group differences. Given the sample size and compared to the highly significant predictive power of the IDAP with regard to treatment outcome (Gallinat et al., 2000; Lee et al., 2005; Linka et al., 2004; Linka et al., 2005), the IDAP baseline differences between patients and controls at Cz were small and after adjustment for multiple testing (Bonferoni) turned out to be non-significant.

We performed analyses based on five commonly used methods in the calculation of amplitudes (P1/baseline, N1/baseline, P2/baseline, P1/N1, N1/P2). The intensity dependent amplitude slopes of the subjects in our study can be compared to those obtained in previous studies using similar procedures and measures. Therefore, it can be concluded that results from our experimental setup are comparable to previously reported results assessing healthy subjects with similar methods and that the lack of significant differences in auditory evoked potentials between patients with major depression and matched healthy control subjects is unlikely to be related to methodological factors.

Our data revealed no general abnormality of the IDAP in patients with major depression in comparison to healthy control subjects. The lack of such a difference between patients and controls in our study, seems to be contradictory to the studies that support the significance of the IDAP as a clinically relevant indicator of the central nervous serotonergic dysfunction in depressive disorders. In our study, variances of the IDAP were only slightly larger in patients than in controls. It can be assumed that a subgroup of controls as well as MDD patients show some kind of dysregulation of the serotonergic system. Considering the results from Methylen-Diethyl-Metamfetamine (MDMA, ecstasy)-users (Croft et al., 2001; Tuchtenhagen et al., 2000) and the inverse association between IDAP and the serotonin syndrome (Hegerl et al., 1998), it is very likely that the IDAP reflects the sensitivity of the central serotonergic system. On the other hand, the IDAP allows indirect

conclusions as to the sensitivity to noradrenergic antidepressants considering an assumed imbalance of NE- and 5-HT neurotransmitter systems as a relevant pathophysiological factor in MDD. The results of our study do not necessarily contradict the assumed role of the IDAP as an indicator a central nervous serotonergic sensitivity in MDD and other psychiatric disorders, but suggests that specific alterations of the IDAP are not to be expected in MDD in general. Such differences may be confined to subgroups of depressed patients. The phenomenon that only a subgroup of depressed individuals shows associations with a biological factor that is assumed to reflect serotonergic sensitivity is also known from genetic approaches, e.g. such as from serotonin transporter polymorphism studies.

These finding indicate that in the clinical practice, the IDAP might be useful to identify patients suffering from MDD who are more likely to respond to SSRI treatment.

5. Clinical symptoms of major depression are associated with the intensity dependence of auditory ERP components

The purpose of this study was to investigate whether the IDAP is associated with certain patterns of psychometrically assessed symptoms of depression. The study aimed to identify, describe and discuss those psychometric syndromes, which might thus indirectly be associated with a favourable outcome to SSRI treatment as predicted by a strong IDAP.

We assessed 40 in-patients with MDD prior to antidepressant treatment. Psychometric characteristics of depression were assessed by means of broadly accepted psychiatric rating scales (HDRS, BDI, HAMA, STAI and CGI) and the results were subsequently evaluated for associations with auditory evoked P1, N1, P2, as well as P1/N1 and N1/P2 peak to peak amplitude slopes.

Seven rating scale items (HAMA “Depressed Mood”, BDI “Lack of interest in sex“, HDRS “insomnia, early“ and “decreased libido or menstrual disturbance”, BDI “hopelessness” and “decreased appetite”, and the HDRS item “weight loss”) correlated with more than r = 0.2 with the IDAP. The correlation coefficient of the

composite score of these 7 items was statistically highly significant with r = .64. The composite score can be viewed at as a construction of a kind of questionnaire derived from the pool of questions obtained in our study. The fact, that the correlation of the composite score with the N1 amplitude slope was considerably higher than each of the correlations with the single items, may be considered as indirect evidence for the relevance of the selected items. The first four of these single items (HAMA "Depressed Mood", BDI "Lack of interest in sex", HDRS "insomnia, early" and "decreased libido or menstrual disturbance") correlated significantly with the IDAP whereas the remaining three (BDI "hopelessness" and "decreased appetite", and the HDRS item "weight loss") showed a statistical trend towards significance only. Of special relevance were the items that identified congruent symptom severity on both the external rating (HDRS) as well as the patient's self-rating (BDI). It concerned the HDRS item "decreased libido or menstrual disturbance" and BDI item "lack of interest in sex" , as well as the HDRS item "weight loss" and BDI item "decreased appetite".

Of special clinical interest is the finding that a high score of sexual disturbance on the BDI, as well as on the HDRS, was associated with a high IDAP, considering that a high IDAP correlates with a favourable response to SSRI-treatment (Gallinat et al., 2000; Paige et al., 1994). The presence of sexual dysfunction associated with depression has so far not been described as a criterion for pharmacotherapy with an SSRI. However, these observations seem to be in contrast to a study suggesting a beneficial treatment effect of reboxetine in depressive patients with sexual dysfunction (Clayton et al., 2003). In line with the latter result, many clinicians tend to avoid SSRIs in the treatment of major depression associated with sexual disturbances. On the other hand, Cyranowksi et al. (2004) found that SSRI-induced sexual dysfunction in a group of 68 women treated for recurrent MDD, was restricted to orgasmic difficulties only, whereas libido and sexual interest were related to depression itself. As a consequence of our findings, future studies might evaluate the hypothesis that the existence of sexual dysfunction (apart from orgasmic difficulty) in MDD may be an additional criterion that favours the treatment with SSRIs.

6. Conclusions

In two clinical studies we were able to demonstrate the predictive value of the IDAP in differentiating antidepressant treatment: A high pre-treatment IDAP was shown to be associated with a favourable treatment outcome to the SSRI citalopram, whereas a low pre-treatment IDAP appeared to coincide with an increased treatment effect to the SNRI reboxetine in MDD. These results corroborated the concept of the IDAP as a non-invasive, clinically applicable pre-treatment indicator of central nervous serotonergic neurotransmission. Moreover, the association between IDAP and reboxetine response suggested that the IDAP may also reflect a disturbed serotonin/norepinephrine balance in the central nervous system.

Neither serotonergic nor non-serotonergic antidepressants were found to induce significant alterations in the IDAP. Furthermore, the IDAP did not significantly change during the course of treatment of MDD and, as such, was not influenced by clinically observed changes of depressive symptoms. These results indicated that the IDAP does not reflect depressive states but is more likely a trait indicator of central serotonergic neurotransmission. The latter conclusion implies that treatment-success in MDD is unlikely to bring about a “normalization” of the IDAP.

Although we expected a lower central nervous serotonergic neurotransmission in depression, we were not able to detect a general abnormality of the IDAP in MDD. Therefore, we concluded that a pre-treatment abnormality of the IDAP might be confined to a specific subgroup of MDD. In line with this hypothesis, we found associations of a strong libido decrease, sexual dysfunction, loss of appetite and weight with a strong IDAP.

STIMULUS INTENSITY DEPENDENT ERP COMPONENTS IN THE PHARMACOTHERAPY OF MAJOR DEPRESSIVE DISORDER

SUMMARY

SAMENVATTING

STIMULUS INTENSITY DEPENDENT ERP COMPONENTS IN THE PHARMACOTHERAPY OF MAJOR DEPRESSIVE DISORDER

Major depressive disorder (MDD) belongs to the most common mental diseases in Europe and in the United States. The multifactorial etiology of depression is widely accepted, but the contributional value of psychosocial, neurobiological and genetic factors remains unclear. Heritability of major depression probably ranges from 31% to 41%. Disturbances in various neuroendocrine and neurotransmitter systems have been associated with the pathophysiological mechanisms, which are assumed to contribute to the origin of depressive disorders. Particularly the discussion of the role of the monoaminergic system and the hypothalamic-pituitary-adrenal axis has a long tradition. The etiologic impact of stressful life events, economic status, social relationships and personality on depressive disorders has been investigated extensively, but there are hardly theoretic concepts which have been widely accepted.

Despite significant advances in the pharmacological treatment of depressive disorders over the past 20 years, many patients (28 - 55%) fail to respond sufficiently to the treatment with the newer serotonin re-uptake inhibitor (SSRI) antidepressants. That is why reliable prediction methods of treatment response to serotonergic versus non-serotonergic antidepressants could be of considerable clinical value.

Electroencephalography (EEG) is a diagnostic method based on the measurement of electrical activity produced by the brain as recorded from electrodes placed on the scalp. Cognitive research conducted with the EEG frequently uses the event-related potential (ERP) technique. Preclinical and clinical studies indicate that a high intensity (loudness) dependent amplitude increase (“high intensity dependence”, “high IDAP”) of auditory evoked potentials seems to reflect a low central nervous serotonergic neurotransmission and vice versa. This hypothesis has been confirmed in animal and human studies.

The major aims of this thesis were to evaluate the predictive value of pre-treatment IDAP in MDD under treatment with either the SSRI citalopram or with the SNRI reboxetine, to investigate whether the IDAP is mainly a state or a trait indicator of central serotonergic neurotransmission. In addition, it was studied whether serotonergic and non-serotonergic antidepressants differently influence

the IDAP and whether the IDAP changes during the course of treatment of MDD. Furthermore, the hypothesis was addressed that unmedicated individuals suffering from major depression exhibit a higher IDAP compared to healthy control subjects and that this is associated with certain patterns of psychometrically assessed symptoms of depression.

In **chapter 2,** we report the results of a study evaluating the IDAP in 16 in-patients fulfilling the DSM-IV criteria for major depressive episode during treatment with the SSRI citalopram. Our data revealed a significant correlation between the intensity slopes of the N1 amplitude prior to citalopram-treatment and treatment-response: patients with higher intensity slopes of N1 amplitude showed a significantly stronger decrease of HDRS-Score after citalopram-treatment than patients within the lower intensity slope ranges.

In **chapter 3,** we present the first study to assess the predictive value of the IDAP in SNRI treatment. We evaluated the pre-treatment intensity dependent change of auditory evoked P1, N1, P2, as well as P1/N1 and N1/P2 peak to peak amplitudes, in 14 in-patients with major depressive episode (DSM IV criteria) during the course of 24 days of treatment with the SNRI reboxetine (6 to 12 mg/d). Our data revealed a highly significant correlation between lower intensity dependent N1 amplitude slopes prior to reboxetine treatment and a stronger decrease of the HDRS total score at Fz ($r=.86$, $p<.001$), FCz ($r=.91$, $p<.001$) and Cz ($r=.93$, $p<.001$).

In **chapter 4,** we describe a study that aimed to compare the IDAP in unmedicated depressed patients with that of healthy control subjects. We evaluated the change of auditory evoked P1, N1, P2, as well as P1/N1 and N1/P2 peak to peak amplitudes, in 34 in-patients with a major depressive episode (DSM-IV criteria) prior to antidepressant treatment, and 44 healthy control subjects. In multivariate analyses of variance, we found no group differences in the intensity dependent increase, neither of the P1, N1, and P2, nor of the P1/N1 and N1/P2 peak to peak amplitudes, between patients and controls.

In **chapter 5,** we present a study that aimed to evaluate associations between clinical symptoms of major depression and the IDAP as an indirect indicator of serotonergic function in the cortex. We assessed 40 in-patients suffering from a major depressive episode (DSM-IV criteria) prior to antidepressant treatment. Psychometric characteristics of depression were assessed by means of psychiatric

rating scales (HDRS, BDI, HAMA, STAI and CGI) and evaluated for associations with auditory evoked P1, N1, P2, as well as P1/N1 and N1/P2 peak to peak amplitude slopes. Our data revealed a positive correlation of the intensity dependent N1 amplitude slope with the degree of certain somatic symptoms of depression: libido decrease and sexual dysfunction, loss of appetite and weight and insomnia.

Chapter 6 deals with a study that measured the IDAP in major depressive disorder (MDD) before and after treatment with either a selective serotonin reuptake inhibitor or a selective norepinephrine reuptake inhibitor antidepressant and compared the results with that of a healthy control group. Auditory evoked P1, N1, P2, P1/N1 and N1/P2 peak to peak amplitudes were evaluated in 26 in-patients with MDD prior to and after antidepressant treatment with citalopram (24 days, n=14) or reboxetine (25 days, n=12), and 43 healthy control subjects. Neither antidepressants nor decrease in the HDRS total score had a significant effect on the IDAP. These results suggested that the IDAP is rather a trait than a state indicator of serotonergic neurotransmission in MDD.

In **chapter 7** we discuss the results and present the final conclusions of this thesis. Our results indicate an association of N1 amplitude intensity dependence with response to antidepressant treatment with citalopram and reboxetine: a high IDAP predicts better treatment outcome with SSRIs like citalopram, whereas a low IDAP is associated with better outcome to reboxetine treatment. Our data revealed no general abnormality of the IDAP in patients with major depression in comparison to healthy control subjects. This result suggested that specific alterations of the IDAP are not to be expected in major depression in general, but that these may be confined to subgroups of depressed patients. Our data revealed a positive correlation of the intensity dependent N1 amplitude slope with the degree of certain somatic symptoms of depression. As neither antidepressants nor decrease in the HDRS total score had a significant effect on the IDAP, we conclude that the IDAP is rather a trait than a state indicator of serotonergic neurotransmission in MDD.

STIMULUS INTENSITY DEPENDENT ERP COMPONENTS IN THE PHARMACOTHERAPY OF MAJOR DEPRESSIVE DISORDER

SAMENVATTING

STIMULUS INTENSITEIT AFHANKELIJKE ERP COMPONENTEN BIJ DE BEHANDELING VAN DEPRESSIEVE STOORNISSEN

Depressieve stoornissen (Major Depressive Disorder; MDD) behoren tot de meest voorkomende psychiatrische ziekten in Europa en de Verenigde Staten. De multifactoriële etiologie van depressie is algemeen aanvaard, maar de etiologische waarde van psychosociale, neurobiologische en genetische factoren, blijft onduidelijk. De erfelijke component van depressies varieert waarschijnlijk van 31% tot 41%. Verstoringen in verschillende neuroendocriene en neurotransmitter systemen zijn geassocieerd met de pathofysiologische mechanismen, die geacht worden bij te dragen aan de oorsprong van depressieve stoornissen. Vooral de bespreking van de rol van het monoaminerge systeem en de hypothalamus-hypofyse-bijnier as heeft een lange traditie. De etiologische gevolgen van stressvolle gebeurtenissen in het leven, economische situatie, sociale relaties en persoonlijkheid op depressieve stoornissen zijn uitvoerig onderzocht, maar er zijn nauwelijks theoretische concepten die algemeen aanvaard zijn.

Ondanks de aanzienlijke vooruitgang in de farmacologische behandeling van depressieve stoornissen in de afgelopen 20 jaar, reageren veel patiënten (28 - 55%) niet voldoende op de behandeling met de nieuwere serotonine heropname remmer (SSRI) antidepressiva. Dat is de reden waarom een betrouwbare voorspelling van de effectiviteit van de behandeling, met serotonerge versus niet-serotonerge antidepressiva, van aanzienlijke klinische waarde zou kunnen zijn.

Electroencephalografie (EEG) is een diagnostische methode gebaseerd op het meten van de elektrische activiteit die ontstaat in de hersenen en wordt afgeleid via elektroden op de hoofdhuid. Cognitief onderzoek uitgevoerd met deze EEG methode maakt vaak gebruik van de gebeurtenis gerelateerde potentialen (Event Related Potentials; ERP) techniek. Uit preklinische en klinische studies blijkt dat een hoge intensiteit (volume) afhankelijke amplitude stijging ("hoge intensiteit afhankelijkheid", "hoge IDAP") van auditief opgewekte potentialen een lage neurotransmissie van serotonine in het centrale zenuwstelsel lijkt te weerspiegelen en vice versa. Deze hypothese werd bevestigd in dierexperimenteel onderzoek en in humane studies.

De belangrijkste doelstellingen van dit proefschrift waren: a. wat is de voorspellende waarde van de IDAP in het kader van de behandeling met de SSRI

citalopram of met de selectieve noradrenaline heropname remmer (SNRI) reboxetine bij patiënten met een MDD en b. is de IDAP vooral een state of een trait-indicator van de centrale serotonerge neurotransmissie. Daarnaast werd onderzocht of serotonerge en niet-serotonerge antidepressiva verschillend van invloed zijn op de IDAP en of de IDAP veranderingen ondergaat in de loop van de behandeling van de MDD. Tenslotte werd de hypothese getoetst of niet medicamenteus behandelde personen die lijden aan een ernstige depressie een hogere IDAP vertonen in vergelijking met gezonde controle personen en of dit dit in verband gebracht kan worden met bepaalde patronen van psychometrisch beoordeelde symptomen van depressie.

In **hoofdstuk 2** worden de resultaten van een studie ter evaluatie van de IDAP met 16 opgenomen patiënten die voldoen aan de DSM-IV criteria voor ernstige depressieve episode tijdens de behandeling met de SSRI citalopram beschreven. Uit onze gegevens bleek een significante correlatie te bestaan tussen de intensiteit afhankelijke stijging van de N1 amplitude voorafgaand aan citalopram behandeling en behandelrespons: patiënten met een hogere intensiteit afhankelijke stijging van de N1 amplitude vertoonden een significant sterkere daling van de ernst van de depressie (HDRS-Score) na citalopram behandeling dan patiënten met lagere intensiteit afhankelijke toename van de N1 amplitude.

In **hoofdstuk 3** presenteren wij de eerste studie naar de voorspellende waarde van de IDAP bij SNRI behandeling met reboxetine. Hiertoe werden de intensiteit afhankelijke veranderingen van voorafgaand aan de medicatie auditief opgewekte P1, N1, P2, evenals P1/N1 en N1/P2 piek tot piek amplituden, bij 14 opgenomen patiënten met een ernstige depressieve episode (DSM-IV criteria) geëvalueerd in de loop van 24 dagen van een behandeling met de SNRI reboxetine (6 tot 12 mg / d). Uit onze gegevens bleek een hoog significante correlatie te bestaan tussen een lagere intensiteit afhankelijke toename van de N1 amplitude [Fz (r =. 86, p <.001), FCz (r =. 91, p < .001) en CZ (r =. 93, p <.001)] voorafgaand aan de behandeling met reboxetine en een sterkere daling van de totale score op HDRS.

In **hoofdstuk 4** beschrijven wij een studie die gericht is op een vergelijking van de IDAP bij niet medicamenteus behandelde depressieve patiënten met die bij gezonde controlepersonen. De verandering van auditief opgewekte P1, N1, P2, evenals P1/N1 en N1/P2 piek tot piek amplituden, werd geëvalueerd bij 34 in-patiënten met een ernstige depressieve episode (DSM-IV criteria) voorafgaand aan

de behandeling met een antidepressivum, en 44 gezonde controlepersonen. In de multivariate analyses van de variantie, vonden wij geen enkel groepverschil tussen de patiënten en de controles in de intensiteit afhankelijke stijgingen, noch van de P1, N1, en P2, noch van de P1/N1 en N1/P2 piek tot piek amplituden.

In **hoofdstuk 5** presenteren wij een onderzoek dat gericht is op het evalueren van associaties tussen klinische symptomen van een depressie en de IDAP als een indirecte indicator van serotonerge functie in de cortex. Veertig patiënten met een ernstige depressieve episode (DSM-IV criteria) werden onderzocht voorafgaand aan behandeling met een antidepressivum. Psychometrische kenmerken van de depressie werden beoordeeld aan de hand van gestandaardiseerde beoordelingsschalen (HDRS, BDI, HAMA, STAI en CGI) en geëvalueerd voor associaties met auditief opgewekte P1, N1, P2, evenals P1/N1 en N1/P2 piek tot piek amplitude stijgingen. Uit onze gegevens bleek een positieve correlatie tussen de intensiteit afhankelijke N1 amplitude stijging met de graad van bepaalde somatische symptomen van depressie: daling van libido en seksuele disfunctie, verlies van eetlust en gewicht en slapeloosheid.

Hoofdstuk 6 beschrijft een onderzoek naar de gemeten IDAP bij depressieve stoornissen (MDD) vóór en na behandeling met een selectieve serotonine heropname remmer of een selectieve noradrenaline heropname remmer en vergelijkt de resultaten met die verkregen van een gezonde controle groep. Auditief opgewekte P1, N1, P2, P1/N1 en N1/P2 piek tot piek amplituden werden geëvalueerd bij 26 patiënten met MDD voorafgaand aan en na de behandeling met de antidepressiva citalopram (24 dagen, n = 14) of reboxetine (25 dagen, n = 12), en 43 gezonde controlepersonen. Geen van beide behandelstrategieën, noch een afname van de totale score op de HDRS, had een significant effect op de IDAP. Deze resultaten suggereren dat de IDAP eerder als een trait dan als een state indicator van serotonerge neurotransmissie kan worden beschouwd bij patiënten met MDD.

In **hoofdstuk 7** bespreken wij de resultaten en worden samenvattende conclusies geformuleerd. Onze resultaten wijzen op een associatie van N1 amplitude intensiteit afhankelijkheid met de respons op een behandeling met de antidepressiva citalopram of reboxetine: een hoge IDAP voorspelt betere behandelresultaten met SSRI's, zoals citalopram, terwijl een lage IDAP geassocieerd is met een beter resultaat met reboxetine behandeling. Uit onze

gegevens bleek geen algemene afwijking van de IDAP bij patiënten met depressie in vergelijking met gezonde controlepersonen. Dit resultaat wijst erop dat specifieke wijzigingen van de IDAP bij een depressie in het algemeen niet zijn te verwachten, maar dat deze beperkt zijn tot bepaalde subgroepen van depressieve patiënten. Uit onze gegevens bleek namelijk een positieve correlatie tussen de intensiteit afhankelijke N1 amplitude stijging met de ernst van bepaalde somatische symptomen van een depressie. Aangezien noch antidepressiva, noch een daling van de totale score op de HDRS een significant effect had op de IDAP, concluderen wij dat de IDAP eerder als een trait dan als een state indicator van serotonerge neurotransmissie in MDD moet worden beschouwd.

STIMULUS INTENSITY DEPENDENT ERP COMPONENTS IN THE PHARMACOTHERAPY OF MAJOR DEPRESSIVE DISORDER

ZUSAMMENFASSUNG

LAUTSTÄRKEABHÄNGIGE ERP KOMPONENTEN IN DER PHARMAKOTHERAPIE DEPRESSIVER STÖRUNGEN

Depressive Störungen (Major Depressive Disorder, MDD) gehören zu den häufigsten psychischen Erkrankungen in Europa und den Vereinigten Staaten. Die multifaktorielle Ätiologie depressiver Störungen ist weithin anerkannt, aber die genaue ätiologische Bedeutung von psychosozialen, neurobiologischen und genetischen Faktoren nach wie vor unklar. Der Einfluss genetischer Faktoren wird auf 31% bis 41% geschätzt. Vor allem Störungen in neuroendokrinen und Neurotransmitter-Systemen werden im Zusammenhang mit den pathophysiologischen Mechanismen, die zur Entstehung depressiver Erkrankungen beitragen, diskutiert. Vor allem die Diskussion über die Rolle der Monoamine und der Hypothalamus-Hypophysen-Nebennieren-Achse hat eine lange Tradition. Die Auswirkungen von belastenden Lebensereignissen, der wirtschaftliche Situation, sozialer Beziehungen und von Persönlichkeitsfaktoren auf die Entstehung und Manifestation depressiver Störungen wurden vielfach untersucht, aber es gibt diesbezüglich nur wenig allgemein akzeptierte theoretische Konzepte.

Trotz der erheblichen Fortschritte in der pharmakologischen Behandlung von depressiven Erkrankungen in den letzten 20 Jahren respondieren viele Patienten (28 bis 55%) nicht oder nicht ausreichend auf die Behandlung mit den neueren Serotonin-Wiederaufnahmeaufnahme-Hemmstoffen (SSRI). Das ist der Grund, weshalb zuverlässige Vorhersagemethoden der individuell anzunehmenden Effektivität serotonerger und nicht-serotonerger Antidepressiva wesentliche klinische Bedeutung zukommen kann.

Die Elektroenzephalografie (EEG) ist eine diagnostische Methode, bei der die elektrische Aktivität im Gehirn über Elektroden auf der Kopfhaut abgeleitet und gemessen wird. Kognitive Forschungsansätze unter Einsatz des EEGs machen häufig Gebrauch von sogenannten Ereigniskorrelierten Potentialen (Event Related Potentials, ERP). Präklinische und klinische Studien haben ergeben, dass ein verstärkter lautstärkeabhängiger Amplitudenanstieg (= hohe Intensitäts-abhängigkeit, hohe IDAP) von akustisch (auditorisch) evozierten Potentialen mit einer relativ geringen Transmission von Serotonin im zentralen Nervensystem assoziiert ist. Diese Assoziation gilt offenbar auch umgekehrt (niedriger,

lautstärkeabhängiger Amplitudenanstieg entspricht hoher zentralnervöser Serotoninaktivität). Diese Hypothese wurde in Tierversuchen und in Studien am Menschen belegt.

Die wichtigsten Fragestellungen der vorliegenden Untersuchungen lauteten: a. Welcher klinische Vorhersagewert kommt der IDAP in der Differentialindikation des SSRI Citalopram und des NRI Reboxetin bei Patienten mit depressiven Störungen zu? und b. Ist die IDAP vor allem ein State- oder eher ein Trait-Indikator der zentralnervösen serotonergen Transmission bei MDD? Auch wurde untersucht, ob serotonerge und nicht-serotonerge Antidepressiva signifikant unterschiedliche Auswirkungen auf die IDAP haben und ob die IDAP während der Behandlung der MDD Veränderungen unterliegt. Darüber hinaus wurde die Hypothese geprüft, dass nicht medikamentös behandelte Personen mit MDD eine höhere IDAP im Vergleich zu gesunden Kontrollpersonen aufweisen. Schließlich wurde der Zusammenhang zwischen bestimmten Gruppen psychometrisch bewerteter Symptome der Depression und der IDAP evaluiert.

In **Kapitel 2** werden die Ergebnisse einer Studie zur Beurteilung der IDAP bei 16 Patienten, die die DSM-IV-Kriterien für eine MDD-Episode erfüllten, in der Behandlung mit dem SSRI Citalopram beschrieben. Unsere Daten zeigen eine signifikante Korrelation zwischen dem lautstärkeabhängigen Anstieg der N1-Amplitude vor Beginn der Citalopram-Behandlung und der klinischen Response: Patienten mit einem höheren lautstärkeabhängigen Anstieg der N1 Amplitude zeigten eine signifikant stärkere Abnahme der Schwere der Depression (HDRS -- Ergebnis) nach Citalopram-Behandlung als Patienten mit geringerem lautstärkeabhängigem Anstieg der N1-Amplitude.

In **Kapitel 3** haben wir die erste Studie zur prädiktiven Aussagekraft der IDAP in der Behandlung mit einem SNRI-Antidepressivum dargestellt. Die Intensitäts-abhängigkeit der auditorisch evozierten P1-, N1-, P2-, und P1/N1- und N1/P2-Amplituden (peak-to-peak) wurde bei 14 Patienten einer MDD-Episode (DSM-IV-Kriterien) vor und nach der durchschnittlich 24-tägigen Behandlung mit dem SNRI Reboxetin (6-12 mg / d) erfasst. Es ergab sich eine signifikante Korrelation zwischen einem geringeren lautstärkeabhängigen Anstieg der N1-Amplitude [Fz (r =. 86, p <.001), FCz (r =. 91, p <.001) und Cz (r =. 93, p <.001)] vor

Behandlungsbeginn und einer deutlicheren Minderung des HDRS-Gesamtwertes nach erfolgter Behandlung mit Reboxetin.

In **Kapitel 4** beschreiben wir eine Studie, die die IDAP bei nicht medikamentös behandelten Patienten mit MDD mit der IDAP bei gesunden Kontrollpersonen vergleicht. Es wurden auditorisch evozierte P1-, N1-, P2-, und P1/N1- und N1/P2-Amplituden (peak-to-peak) bei 34 Patienten mit einer MDD-Episode (DSM-IV-Kriterien) vor Behandlungsbeginn mit einem Antidepressivum und bei 44 gesunden Kontrollpersonen miteinander verglichen. In der multivariaten Varianzanalyse, fanden sich keine Gruppenunterschied zwischen Patienten und Kontrollen weder im Hinblick auf die Intensitätsabhängigkeit der P1-, N1- und P2-, noch auf die IDAP der P1/N1- und N1/P2- Amplitude.

In **Kapitel 5** stellen wir eine Studie zur Bewertung der Zusammenhänge zwischen den klinischen Symptomen der Depression und der IDAP als indirektem Indikator der zentralnervösen serotonergen Transmission vor. Vierzig Patienten mit einer MDD-Episode (DSM-IV-Kriterien) wurden vor der Behandlung mit einem Antidepressivum untersucht. Psychometrische Merkmale der Depression wurden mit standardisierten Rating-Skalen (HDRS, BDI, HAMA, STAI und CGI) bewertet und im Hinblick auf Assoziationen mit Lautstärkeabhängigkeit von auditorisch evozierten P1-, N1-, P2-, P1/N1- und N1/P2-Amplitude (peak-to-peak) evaluiert. Die Ergebnisse weisen auf eine positive Korrelation zwischen der Intensitätsabhängigkeit der N1-Amplitude und dem Ausprägungsgrad bestimmter somatischer Symptome der Depression hin: Libidoverlust und sexuelle Dysfunktion, Appetitmangel und Gewichtsverlust sowie Schlaflosigkeit.

Kapitel 6 beschreibt eine Studie, die die IDAP bei depressiven Störungen (MDD) vor und nach der Behandlung entweder mit einem SSRI oder einem SNRI erfasste und die Ergebnisse mit denen einer gesunden Kontrollgruppe verglich. Auditiv evozierte P1-, N1-, P2, P1/N1- und N1/P2- Amplituden wurden bei 26 Patienten mit MDD vor und nach der Behandlung mit den Antidepressiva Citalopram (24 Tage, n = 14) oder Reboxetin (25 Tage, n = 12) und bei 43 gesunden Kontrollpersonen gemessen. Weder die verabreichten Antidepressiva noch eine Verminderung der HDRS-Gesamtwertes hatten signifikante Auswirkungen auf die Höhe der IDAP. Diese Ergebnisse deuten darauf hin, dass die IDAP eher ein Trait-

als State-Indikator der serotonergen Neurotransmission bei Patienten mit MDD sein könnte.

In **Kapitel 7** diskutieren wir die Ergebnisse und zusammenfassenden Schlussfolgerungen dieser Dissertation. Unsere Ergebnisse legen eine Assoziation der Intensitätsabhängigkeit vor allem der N1-Amplitude mit der Therapieresponse auf eine Behandlung mit den Antidepressiva Citalopram und Reboxetin nahe: eine hohe IDAP prognostiziert bessere Behandlungsergebnisse mit SSRI wie Citalopram, während eine niedrige IDAP mit einem günstigeren Effekt bei Reboxetin-Behandlung assoziiert ist. Unsere Daten zeigten insgesamt keine signifikanten Unterschiede der IDAP bei Patienten mit depressiven Störungen (MDD) im Vergleich mit gesunden Kontrollpersonen. Dieses Ergebnis deutet darauf hin, dass eine pathologische Abweichung der IDAP bei depressiven Störungen im Allgemeinen nicht besteht. Möglicherweise spezifische Veränderungen IDAP sind allenfalls bei gegebenenfalls pathophysiologisch definierbaren Untergruppen depressiver Störungen zu erwarten. Unsere Ergebnisse weisen außerdem auf eine positive Korrelation zwischen der Intensitätsabhängigkeit der N1-Amplitude und der Schwere einiger somatischer Symptome bei MDD hin. Da bei unseren Untersuchungen weder die verabreichten Antidepressiva noch eine Reduktion des HDRS-Gesamtwertes eine signifikante Auswirkung auf die Höhe der IDAP hatte, kommen wir zu dem Schluss, dass die IDAP vornehmlich als Trait- nicht jedoch als State-Indikator der serotonergen Neurotransmission bei MDD betrachtet werden kann.

Acknowledgements

I am very grateful to the numerous people who contributed to the presented studies and made this thesis possible. Completing a Dutch PhD thesis was a challenging as well as an enjoyable task.

First of all, I owe my deepest gratitude to those patients of the Clinics for Psychiatry and Psychotherapy of the University of Essen who were idealistic enough to voluntarily participate in our research project despite suffering from a severe affective disorder.

This work would not have been possible without the support and encouragement of my colleague and promoter Prof. Dr. Willem Verhoeven, under whose supervision I began and finished the thesis. Dear Willem, I am very grateful for your suggestions and guidance.

I would like to thank Dr. Joke Tulen for being my copromotor. Dear Joke, your very precise and effective review style enormously helped to improve the manuscript of this thesis.

Prof. Dr. M.W. Hengeveld, Prof. Dr. F. Verhey and Prof. Dr. G. Sartory, members of the small commission, I am grateful for your time and for thoroughly reading through my manuscript.

I am especially grateful to my dear colleague Dr. Bernhard Müller, who taught me the methodology of EEG and ERP, very much helped me to apply this method in clinical psychiatric research and has also been abundantly helpful with the analysis of our extensive data. Dear Bernhard, thank you very much for the many hours we spent together with brainstorming, data analysis, statistical analysis, and writing.

Special thanks go to Arndt Hesse, who took care of the study patients and was of great help with the collection of our clinical data.

I will not end without thanking my family, on whose constant encouragement and love I could always rely. I am very happy that my wife Julia always appreciated my work and showed very much understanding for the numerous hours I had to spend in front of my computer. I am very proud of my daughter Pauline and of my son Jonathan, who did their very best to support my work by being not too noisy and by not disturbing their father too often. I am grateful to my parents for their sense and sensibility. Last but not least I want to thank my brother Christian and my sister Katharina for practical and emotional support in numerous ways.

Curriculum Vitae

Thomas Linka was born on January 24, 1971 in Bochum, Germany. He attended grammar school at Dorsten, Germany, where he graduated with the Abitur in 1990. After finishing military service in Coesfeld in 1991, he moved to Essen for his medical studies. In 1998 he finished his medical studies at the University of Duisburg-Essen and began his clinical education in psychiatry and psychotherapy. In 2000 he finished his medical thesis ("Dr. med.") on the autonomic diabetic neuropathy with degree cum laude from the University of Duisburg-Essen. In 2004, after residencies at the Clinics for Psychiatry and Psychotherapy of the University of Bochum, the Clinics for Psychiatry and Psychotherapy of the University of Duisburg-Essen and at the Clinic of Neurology and Neurophysiology of the Evangelic Hospital in Gelsenkirchen, he received his registration as psychiatrist and psychotherapist in Germany. In 2005 he decided to work as a psychiatrist in the Netherlands and received BIC and MSRC registration.

Since April 2005 Thomas Linka is working as a psychiatrist for the GGZ Noord- en Middenlimburg in Venray, since November 2007 he works fulltime as a psychiatrist and medical head of the Clinic for Addictive Disorders Paschalis, Oostrum, the Netherlands.

List of publications

Papers

- Linka T., Sartory G., Gastpar M., Jens Wiltfang, Müller B.W. (2009) Treatment effects of serotonergic and noradrenergic antidepressants on the intensity dependence of auditory ERP components in major depression. Neurosci Lett. 2009 Sep 29; 463(1):26-30.
- Linka T., Sartory G., Gastpar M., Jens Wiltfang, Müller B.W. (2009) Clinical symptoms of major depression are associated with the intensity dependence of auditory ERP components. Psychiatry Research (in press)
- Linka T., Bender S., Sartory G., Gastpar M., Müller B.W. (2007) The intensity dependence of auditory ERP components in unmedicated patients with major depression and healthy controls. An analysis of group differences. J Affect Disord. 2007 Nov;103(1-3):139-45.
- Linka T., Müller B.W., Bender S., Sartory G., Gastpar M. (2005) The intensity dependence of auditory evoked ERP components predicts responsiveness to Reboxetine treatment in major depression. Pharmacopsychiatry. 2005 May;38(3):139-43.
- Linka T., Müller B.W., Hesse A., Bender S., Sartory G.(2004).The intensity dependence of the auditory evoked N1 component as a predictor of reponse to Citalopram treatment in patients with major depression. Neurosci Lett. 2004 Sep 9;367(3):375-8.
- Bender, S., Linka, T., Wolstein, J., Gehendges, S., Paulus, H.-J., Schall, U., Gastpar, M. (2004). Safety and efficacy of combined clozapine-lithium pharmacotherapy. Int J Neuropsychopharmacol. 2004 March;7(1):59-63.
- Linka T., Bender S.(2002) Halluzinationen sind ein Warnzeichen. Notfallmedizin 2002;28:298-302.
- Agelink M.W., Majewski T., Wurthmann C., Postert T., Linka T., Rotterdam S, Klieser E.(2001) Autonomic neurocardiac function in patients with major depression and effects of anti-depressive treatment with nefazodone. J Affect Disord. 2001 Feb; 62(3):187-98.
- Agelink M.W., Majewski T., Wurthmann C., Lukas K., Ullrich H., Linka T., Klieser E.(2001) Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpride, olanzapine, sertindole, and Clozapine. J Clin Psychopharmacol 2001 Feb;21(1): 8-13.

Abstracts

- Linka T., Wiltfang, J., Sartory G., Müller B.W. (2008). Effects of antidepressant treatment on the intensity dependence of auditory evoked potential components. European Neuropsychopharmacology, Volume 18 Supplement 4, Page S321
- Linka T., Sartory G., Hesse A., Gastpar, M., Müller B.W. (2007). The intensity dependence of auditory Event Related Potential (ERP) components in unmedicated major depression and healthy controls. European Neuropsychopharmacology, Volume 17 Supplement 4, Page S369.
- Linka T., Müller B.W., Sartory G. (2006).Clinical Symptoms of major depression are associated with intensity dependence of auditory evoked ERP components. European Neuropsychopharmacology 16, Supplement 4, S312.
- Linka T., Müller B.W., Hesse A., Bender S., Sartory G.(2004).The intensity dependence of the auditory evoked N1-amplitude as a predictor of response to citalopram-treatment in major depression European Neuropsychopharmacology 14, Supplement 1, S58.
- Linka T., Müller B.W., Hesse A., Bender S., Sartory G.(2003).The intensity dependence of the auditory evoked N1/P2-ERP-component increases in pharmacotherapy of major depression with citalopram. Pharmacopsychiatry 36, 246.
- Bender S., Linka T., Grohmann R., Engel R., Degner D., Rüther E. (2003) Severe adverse drug reactions of typical and atypical neuroleptics in routine clinical treatment: results from the AMSP drug safety program. Pharmacopsychiatry 36, 214.
- Bender S., Müller B.W., Linka T., Sartory G. (2002). Neuropsychological deficits in patients with major depression during treatment. Eur Arch Psychiatry Clin Neurosci 252, Suppl. 1, P233, 2002.
- Linka T., Müller B.W., Bender S., Sartory G.(2002) The intensity dependence of the auditory evoked N1-ERP-component in major depression. Eur Arch Psychiatry Clin Neurosci 252, Suppl.1, P225.
- Linka T., Müller B.W., Bender S., Wolstein J., Condrads H., Banger M.(2001). The intensity dependence of the auditory evoked potential in major depression: Short term stability and first results of a controlled treatment study. The World Journal of Biological Psychiatry 2 (Suppl. 1)
- Agelink M.W., Linka T., Lemmer W., Klieser E.(1999). Cardiovascular Effects of Neuroleptic Medication Assessed by Standardized Investigations of Heart Rate Variability (HRV): A Comparison of Clozapine, Olanzapine and Sertindole. Pharmacopsychiatry, Abstracts of the 21st Symposium of AGNP, Oct 1999.