

Research profile



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- 1989 M.D., Hannover Medical School and University of NSW, Newcastle, Australia
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Objects of research

Affective disorders belong to the most common psychiatric disorders, in contrast, the knowledge about the etiopathology and the availability of highly effective treatment strategies is still limited. The major scientific interest and research experience of our group are possible etiopathogenetic factors [1,2] and new treatment strategies of affective disorders [3,4], their influence on neurocognitive aspects, especially attentional and memory processing [1,2] as well as emotion/cognition-coupling processes within this field. Electrophysiological methods (event related potentials = ERPs) are the main tools to investigate these processes in our ERP-lab which provide information especially on the time course of certain steps of the information processing as well as sources of neuronal activity (LORETA-analysis). In cooperation with the Department of Neuroradiology of the Hannover Medical School (MHH) MRI-techniques are used to gain information about morphological as well as functional aspects.

Our current research focusses on:

1. Neurobiological factors of psychiatric disorders

Biological and genetic factors have been shown to be involved in the complex etiology of depression. Leading hypotheses concerning the pathophysiology of affective disorders suggest disturbances of neurotransmitter-circuits and second as well as third messenger systems. Moreover, several studies describe chromosomal regions containing genes that are supposed to play a role in determining the susceptibility to depressive disorders and associations between certain genetic polymorphisms and structural changes of the hippocampus in patients with major depression. Unfortunately, it is difficult to discern the functional relevance of these results and existing treatment strategies have only limited efficacy. There is need for further treatment options which may even influence etiopathogenetic factors.

a) BDV

Currently Borna disease virus (BDV) was suggested to represent a co-factor in the etiopathogenesis of affective disorders: BDV has been classified as a member of the family *Bornaviridae* within the order *Mononegavirales* and is known to cause persistent infections of the brain in animal species. Like other related RNA viruses with a nonsegmented and single strand genome of negative polarity, BDV exhibits selective affinity to specific brain areas. Preferentially infected sites of limbic structures and

the basal ganglia seem to play a role in the neuropathogenesis of BDV infections, the likely mechanism of which is a functional interference of viral components with neurotransmitter circuits. The detection of BDV-specific antibodies in neuropsychiatric patients, the discovery of specific viral components (proteins, RNA) in PBMCs and isolation of infectious virus from PBMCs and brain of psychiatric patients has suggested a role of Borna virus in the etiology of psychiatric disorders. Although there seems to be no doubt about a higher BDV prevalence in depressed and schizophrenic patients compared to healthy control subjects, the impact of BDV in these patients, however, is currently subject of a highly controversial debate. Whereas Bode et al. (2001) found a very high prevalence of BDV-specific circulating immune complexes (CICs) others questioned the specificity of these parameters and could not replicate these data (compare Ikuta et al. 2002). Our group tries to shed light on this controversy by using electrophysiological methods (ERPs) and modern imaging techniques (voxel-based morphometry; diffusion tensor imaging) to investigate possible correlations of virological and immunological parameters in patients with BDV-infection, e.g., patients with obsessive-compulsive disorder (OCD), affective disorder in the remitted state, Tourette syndrome. One major finding was the detection of an enhanced N1 ERP-component only in the OCD-patients with a high amount of BDV-CICs (group H, high) compared to the other OCD-patients (group L, low) and a control group suggesting a pathophysiological impact of BDV regarding cognitive disturbances in these patients [1] (compare **Fig. 1**). Further studies (in submission) suggest similar correlations also for other BDV-parameters than CICs, e.g. BDV-antibodies measured with ELISA.

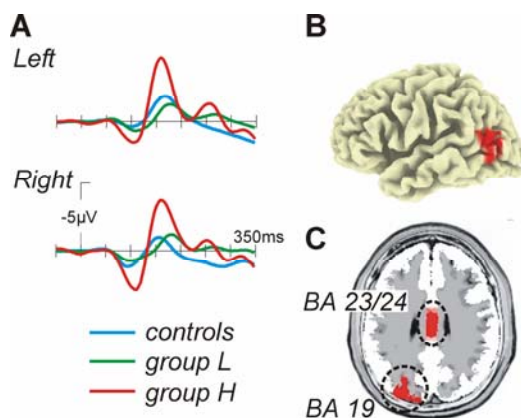


Figure 1 **A:** Grand-average ERPs from left and right temporoparietal sites (P7/P8) showing a marked increase of N1 amplitude for group H. Mean amplitude (160-180 ms) at this electrode pair showed an overall group difference ($F(2,21)=6.98$; $P<0.005$) with post-hoc tests (Scheffé) indicating differences between group H and controls ($P<0.01$), group H and group L ($P<0.01$), but no difference between group L and controls. **B:** Source analysis (LORETA) for the grand average showed a prominent left temporoparietal source at 152 ms for group H subjects corresponding to Brodmann areas 19/37/39. Voxels in the region marked in black showed activity higher than $0.01\mu A/mm^2$. **C:** A statistical comparison of the individual source solutions (LORETA, time window 140-180 ms) of group H and control subjects revealed group differences in medial frontal and lateral temporo-occipital regions. The darker zones (encircled) represent those voxels for which t-values exceeded the threshold of significance (corrected for multiple comparisons).

b) S100B

The neuroplasticity marker S100B, a calcium-binding protein produced mainly by astrocytes, evolves paracrine as well as autocrine effects on neurons and glia. It balances proliferation and differentiation of brain cells. With regard to depression, S100B has been shown to be increased in the CSF of patients with mild or moderate severity of the disease and in the serum of patients with the melancholic subtype of major depression. Patients with increased S100B concentration have also shown a better therapeutic response than those with normal S100B levels. So far it has been unknown whether an elevation of S100B in patients suffering from depression is limited to a depressed state or remains after recovery.

Therefore (and to exclude state dependent effects), we investigated a group of patients with a currently remitted affective disorder in a pilot study [2]. Using a descriptive approach a visual Go/Nogo-reaction time paradigm was used to elicit the parietal P3 and frontal N2 as indicators of target selection / response inhibition processes. Concomitantly serum levels of the neuroplasticity marker S100B were measured. Patients with increased S100B serum levels ($n=6$; group H) showed a normal N2- and P3-amplitude in contrast to a reduced N2- and P3-amplitude in patients with normal

S100B levels (n=6; group N). These findings provide evidence of a correlation between S100B levels and attentional processes in patients with recurrent depression and further substantiate S100B's role as a marker in the course of affective disorders.

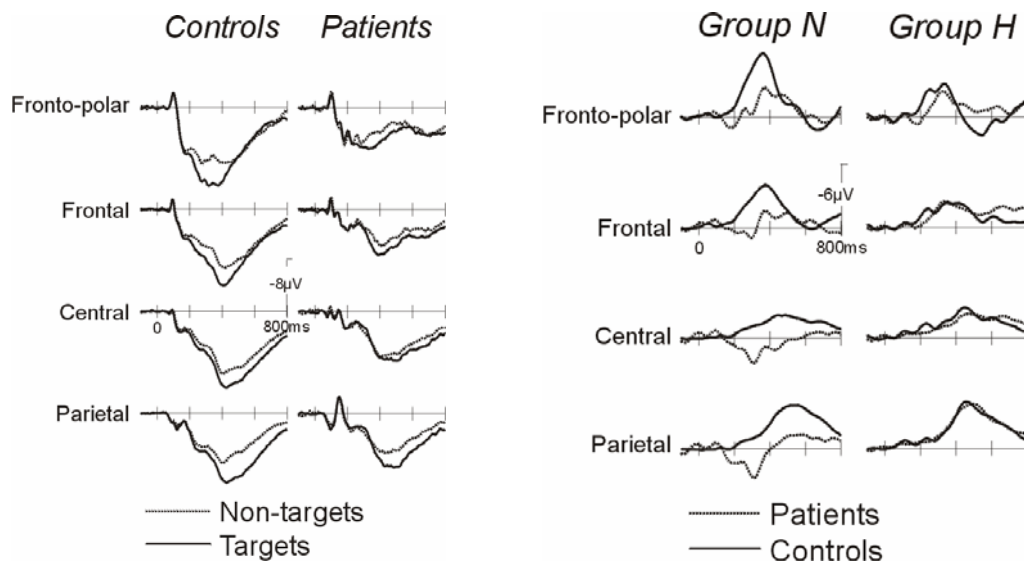


Fig. 2 A: Grand-average ERPs for the non-targets and the correctly detected targets for the patients (n=12) and the control group (n=12) for the right parasagittal electrodes Fp2, F4, C4, and P4. **B:** Difference waves (non-target minus target) of the ERPs comparing the group H patients (higher S100B level; n=6) with the control group H (n=6) and the group N patients (normal S100B level; n=6) with the control group N (n=6) over the right parasagittal electrodes Fp2, F4, C4, and P4.

2. The use of anticonvulsants in psychiatry

The anticonvulsants carbamazepine and valproate have successfully been used in pharmacopsychiatry after their therapeutic value in affective and schizoaffective disorders was documented in several clinical trials. Meanwhile, different anticonvulsant compounds have been investigated regarding their use in affective and other psychiatric disorders. Based on the sound experiences of the head of the department (Prof. Dr. Dr. H.M. Emrich) different pilot studies where/are performed (lamotrigine in confusion psychosis, lamotrigine and gabapentin in behavioral disturbances based on dementia) and manuscripts published [e.g., 3].

3. Amantadine in affective disorders

The possible role of BDV in affective disorders is corroborated by treatment effects of the antiviral drug amantadine. This compound has led to a reduction of both clinical symptoms and viral activity in BDV infected patients with bipolar or recurrent depression [4]. The paralleled clinical improvement supported the possibility of amantadine's antidepressive action partially being linked with its antiviral effect. However, these findings are also subject to the ongoing controversy on the role of BDV (see above) and placebo-controlled as well as long-term investigations were lacking. Therefore, aims of current studies of our group are (1) to investigate the antidepressive and antiviral effects of amantadine in BDV-infected depressive patients in a randomized, placebo-controlled, and double-blind cross-over study followed by an open investigation period of 12 months (2) to investigate the clinical use of amantadine in manic bipolar patients.

Future projects

We aim to expand our knowledge on the possible role of neurobiological markers and the use of amantadine in psychiatric disorders by using different directions: (1) to investigate interactions of immunological (e.g., IL-1b, IL-6 und TNF- α) and neuromodulatory proteins (BDNF, S100B) and virological parameters and their possible correlations with brain morphological (voxel-based

morphometry, diffusion tensor imaging) and neurophysiological (ERPs, fMRI) changes, (2) to correlate virological markers to the imaging of possible neuroinflammatory changes in the brain using the peripheral benzodiazepine receptor ligand PK11195 that binds to activated microglia (in cooperation with Prof. Dr. Berding, ZSN), and (3) to investigate the role of telomere shortening - measured in lymphocytes (T-cells/B-cells) – for the clinical course and outcome of affective disorders (PhD-project, in cooperation with Prof. Dr. Rudolph, Ulm).

Further goals of our group are the development of new computer-based neuropsychophysiological experiments to detect higher cognitive functions which are relevant for the understanding of affective disorders and schizophrenia. For example, a binocular depth inversion paradigm will be used to detect top-down (versus bottom-up) processes with fMRI and ERP-techniques (PhD-project).

Selected publications

1. Dietrich DE, Zhang Y, Bode L, Münte TF, Hauser U, Schmorl P, Richter-Witte C, Gödecke-Koch T, Feutl S, Schramm J, Ludwig H, Johannes S, Emrich HM: Brain potential amplitude varies as a function of Borna disease virus-specific immune complexes in obsessive-compulsive disorder. *Molecular Psychiatry* 2005; 10: 519-520, 515 (Image)
2. Dietrich DE, Hauser U, Peters M, Zhang Y, Wiesmann M, Hasselmann M, Rudolf S, Jüngling O, Kirchner H, Münte TF, Arolt V, Emrich HM, Johannes S, Rothermundt M: Target evaluation processing correlates with serum levels of nerve tissue protein S100B in patients with remitted major depression. *Neuroscience Letters* 2004; 354: 69-73
3. Dietrich DE, Gödecke-Koch T, Richter-Witte C, Emrich HM: Lamotrigine in the treatment of confusion psychosis: A case report. *Pharmacopsychiatry* 2004; 37: 88-90
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5. Johannes S, Wieringa BM, Nager W, Rada D, Dengler R, Emrich HM, Münte TF, Dietrich DE: Discrepant target detection and action monitoring in obsessive-compulsive disorder. *Psychiatry Research: Neuroimaging* 2001; 108: 101-110

Group structure

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