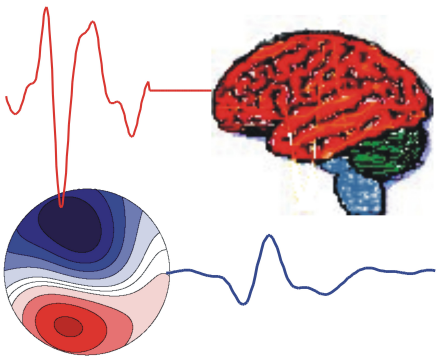
KOGNITIVE NEUROPHYSIOLOGIE DES MENSCHEN

HUMAN COGNITIVE NEUROPHYSIOLOGY



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Kognitive Neurophysiologie des Menschen wurde im Jahr 2008 gegründet. Hier sollen wissenschaftliche Artikel zu Themen der kognitiven Neurophysiologie des Menschen erscheinen Sowohl Beiträge über Methoden als auch Ergebnisse der Grundlagen- und klinischen Forschung werden akzeptiert. Jedes Manuskript wird von 3 unabhängigen Gutachtern beurteilt und so rasch wie möglich publiziert werden.
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Examples of reference format

Johnson, K., Hsiao, S., & Twombly, L. (1995). Neural mechanisms of tactile form recognition. In M. Gazzaniga (Ed.), *The Cognitive Neurosciences* (p. 253-267). Cambridge, Mass.: MIT Press.

Pascual-Marqui, R., Michel, C., & Lehmann, D. (1994). Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *International Journal of Psychophysiology*, *18*, 49-65.

Zani, A., & Proverbio, A. (Eds.). (2002). *The Cognitive Electrophysiology of Mind and Brain*. Academic Press, San Diego: Elsevier USA: Academic Press San Diego.

Inhalt — Contents

Abstracts of the 17 thGerman EEG/EP Mapping Meeting, Giessen, October 31 - November 2, 2008

"Imaging Genetics" with endophenotypic measures of attention-deficit hyperactivity disorder. A. J. Fallgatter, M. M. Plichta, C. Baehne, M. M. Richter, M. M. Schecklmann, K.-P. Lesch & A.-C. Ehlis, *Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany.*
Deficits in response inhibition are, amongst others, considered as candidate endophenotypes of altered prefrontal brain function in ADHD. Based on their superior time resolution, electrophysiological methods like Event-Related Potentials (ERPs) are adequate for the measurement of such endophenotypes, i.e. abnormalities in brain functions underlying psychiatric diseases like ADHD. Moreover, ERPs seem to be particular suited to measure effects of functionally relevant genetic variants directly affecting neurotransmission systems and brain function. This principle of imaging genetics with ERPs has been demonstrated as early as 1999 for the serotonin transporter promoter polymorphism affecting prefrontal brain function (Fallgatter et al., International Journal of Neuropsychopharmacology, 1999). We employed a multi-channel EEG during performance of a Go-NoGo task to assess the electrophysiological basis of the endophenotype response inhibition in healthy subjects as well as in patients with ADHD. The ERP-measure derived from this protocol was termed NoGo-Anteriorisation (NGA) and is characterized by a high interindividual stability, high short- and long-term test-retest reliability and, moreover, is independent from age and gender. In patients with ADHD the NGA was diminished as compared to age- and sexmatched healthy controls. Furthermore, a three-dimensional source location analysis with Low Resolution Electromagnetic Tomography (LORETA) indicated an electrical dysfunction of the medial prefrontal cortex comprising the anterior cingulate cortex (ACC) in ADHD patients in childhood as well as in adulthood. Recent studies showed a significant influence of variants of dopaminergic as well as serotonergic genes on this measure of prefrontal brain function. These results exemplify the imaging genetics approach by measurement of disease related disturbances in brain function with ERPs. Future studies will show whether such electrophysiological endophenotypes may contribute to the diagnosis of subgroups of ADHD and whether they may serve as endophenotypes to further clarify genetic contributions to the disease.

Frontal brain function in schizophrenias: Topographical ERP measures in the diagnosis and treatment of psychotic disorders. A.-C. Ehlis (1), P. Pauli (2), M. J. Herrmann (1) & A. J. Fallgatter (1), *(1) Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany (2) Department of Psychology I, University of Würzburg, Würzburg, Germany.*
Schizophrenic illnesses have been associated with a wide range of neurophysiological abnormalities, one of the most consistent findings concerning a reduced metabolism and diminished functional activation of the frontal cortex ("cerebral hypofrontality"). We conducted

a series of experiments on prefrontal dysfunction in different subgroups of psychotic disorders, investigating its diagnostic and prognostic meaning as well as the influence of antipsychotic drugs on measures of frontal lobe function. We used the NoGo-Anteriorization (NGA) - that quantifies the frontalization of the brain electrical field during processes of inhibitory control and has been associated with increased prefrontal activation - as a topographical ERP measure of frontal lobe function. We observed a) diminished prefrontal activation in schizophrenic patients during tasks of executive control; b) more pronounced abnormalities in patients with a chronic progression than in subgroups with a phasic course of the disease; c) a more positive impact of atypical than typical antipsychotics on prefrontal brain function; and d) prognostic properties of the NGA in predicting the treatment response to different kinds of antipsychotic medication. The results are in line with previous findings and with assumed antipsychotic drug actions, and confirm the usefulness of topographical ERP measures in neuro-psychiatric research.

Neural correlates of executive functions in Attention-Deficit/Hyperactivity Disorder (ADHD). N. Wild-Wall (2), R. D. Oades (1), M. Schmidt-Wessels (1), H. Christiansen (1) & M. Falkenstein (2), *(1) Biopsychology Group, University Clinic for Child and Adolescent Psychiatry and Psychotherapy, Essen, Germany (2) Leibniz Research Centre for Working Environment and Human Factors, Institute of Occupational Physiology, University of Dortmund, Dortmund, Germany.*

The present study is aimed at assessing changes of different executive functions and their neural correlates in children with ADHD and their unaffected siblings compared to healthy control children. Specifically, the processing of irrelevant stimuli, the control over inappropriate responses, and the detection of errors, is analysed, using a modified flanker task. Event-related potentials are used to directly measure these processes. While the behavioral data showed no group differences, the ERPs did. The post-stimulus ERPs mainly showed an attenuation of flanker processing (P1) and of late inhibitory processes (N2, P3a) in ADHD. The post-response ERPs showed a general enhancement of the post-response negativity in the siblings. In particular there was no significant attenuation of error processing, as reflected in Ne/ERN and Pe, in the patients. Finally, preparatory processes were attenuated in siblings and more so in the patients. The pattern of results reveals specific changes of various cognitive control processes in ADHD which are not reflected in overt behaviour. The larger post-response potentials in the unaffected siblings may reflect compensatory enhancement of response monitoring. The study shows that ERPs have an additive value for assessing subtle cognitive changes in ADHD.

Monoamine challenge tests in psychiatry research: results of neurophysiological studies. C. Norra, *Department of Psychiatry, LWL University Hospital, Ruhr University, Bochum, Germany.*

Monoaminergic challenge tests allow investigating central nervous changes in humans under acute depletion of specific neurotransmitters (5-HT, DA, NE). In the design of these studies, various biochemical and methodological aspects have to be taken into account. Here, the tryptophan depletion test (TDT) rep-

resents the currently most established human challenge tool for the assessment of brain serotonin functioning and alterations in various psychiatric disorders. With respect to one proposed electrophysiological marker of the serotonergic system, the stimulus intensity of auditory evoked potentials, TDT in animal and clinical tudies suggests an inverse influence on the 5-HT neurotransmission. However, similar effects of TDT in healthy humans remained mostly unconfirmed including own studies showing only a slight and non-significant increase of the loudness dependence. As opposed to other selective challenges with e.g. SSRI, interactions of TDT with further transmitter systems are worth discussing. Regarding auditory sensory gating and processing, TDT led to reduced acoustic startle amplitudes, but no change of prepulse inhibition. Further results of monoamine depletion in electrophysiological studies (i.e. electroencephalography, magnetoencephalography, polysomnography, evoked potentials) will be presented. All in all, depletion techniques offer a potential non-invasive and reliable biological marker of human monoaminergic vulnerability or dysfunction to investigate changes of neurophysiological parameters.

Electrophysiological correlates of executive functions in psychiatric patients. M. Ruchsow (1), M. Spitzer (2), M. Kiefer (2), G. Grön (2), M. Falkenstein (3) & L. Hermle (1), *(1) Dept. of Psychiatry Christophsbad, Göppingen, Germany (2) Dept. of Psychiatry, University of Ulm, Germany (3) Leibniz Research Centre for Working Environment and Human Factors (IfADo), Dortmund, Germany.*

Dysfunctions of prefrontal and anterior cingulate cortex have been found in a variety of psychiatric diseases like major depression (MDD), obsessive-compulsive disorder (OCD), and borderline personality disorder (BPD) resulting in impaired executive functions which encompass - among others - error monitoring and response inhibition. The Ne/ERN is a negative going ERP component associated with erroneous responses, whereas Nogo-N2 and Nogo-P3 are closely related to response inhibition processes. Several ERP studies were performed in order to investigate whether Ne/ERN, Nogo-N2 and Nogo-P3 are useful tools for the assessment of depressiveness, impulsivity, and compulsiveness. Participants performed a hybrid flanker-Go/Nogo paradigm while a 64-channel EEG was recorded. BPD patients had reduced and OCD patients had enhanced Ne/ERN amplitudes in relation to their respective control groups. With regard to response inhibition patients with MDD and BPD had reduced Nogo-P3 amplitudes and patients with OCD had enhanced Nogo-N2 amplitudes compared to their respective control groups. Three ERP components were found to mirror the psychopathological state of psychiatric patients. It remains an open question whether these ERP parameters are able to predict the clinical outcome, as well.

Tomographic neurofeedback in healthy adults - implications for ADHD treatment. M. Liechti (1,2), P. Ianiro (1,2), M. Mächler (1), M. Döhnert (1,3), L. Jäncke (2), D. Brandeis (1) & R. Drechsler (1), *(1) Department of Child and Adolescent Psychiatry, University of Zürich, Zürich,Switzerland (2) Department of Neuropsychology, Institute for Psychology, University of Zürich, Zürich, Switzerland (3) Department of Child and Adolescent Psychiatry, University of Leipzig, Leipzig, Germany.*

Tomographic neurofeedback (NFB) based on multichannel scalp electroencephalographic (EEG) aims to control intracerebral activity in specific brain regions. In the context of improving NFB for treatment of Attention-Deficit-/Hyperactivity-Disorder (ADHD), ten healthy adults (age: 23-33 years) were trained to increase their beta/theta ratios in two consecutive counterbalanced blocks targeting different prefrontal regions (Anterior cingulate cortex = ACC and right dorsolateral prefrontal cortex = DLPFC). Pre- and post-tests included resting EEG, and tests of attention (TAP). EEG power in different frequency bands was analyzed. We hypothesized that successful region specific NFB has corresponding effects on resting EEG, neuropsychological tests and subjective ratings. Subjects partly learned to control their prefrontal activity, given subjective feelings of control, but significant objective improvement was limited to the ACC training. Objective control of ACC and DLPFC activity was uncorrelated. ACC training improved TAP measures of flexibility, DLPFC training measures of sustained attention and inhibition. Resting EEG with eyes closed was unaffected. The results provide first evidence that tomographic ACC NFB has specific cognitive effects. Its clinical relevance remains to be evaluated with subjects suffering from ADHD. (*Supported by the SBF COST B27 ENOC and by a Grant to the GD of the Kanton of Zurich.*)

Diagnostic EEG mapping in children with ADHD - a failure to replicate. D. Brandeis (1), M. Liechti (1,2), L. Valko (1), U. Müller (1), S. Maurizio (1), H.-C. Steinhausen (1), R. Drechsler (1) & M. Döhnert (1,3), *(1) Department of Child and Adolescent Psychiatry, University of Zürich, Zürich, Switzerland (2) Department of Neuropsychology, Institute for Psychology, University of Zürich, Zürich, Switzerland (3) Department of Child and Adolescent Psychiatry, University of Leipzig, Leipzig, Germany.*
Recent work suggests that resting EEG theta and theta/beta ratios at Cz are so consistently elevated in ADHD that they can serve as diagnostic markers. We attempted a replication in a typical child psychiatric EEG research setting and explored the topography of these presumed markers of ADHD. Resting EEG (46 EEG, 2 EOG electrodes) was mapped for 3 min each with eyes closed and eyes open. Children (8.5-13y) with ADHD combined (N=44) and without ADHD symptoms (N=20 normal controls) were compared. Standard FFT of the EEG (256Hz/ 2s epochs) using average and mean ear reference followed manual plus automatic artefact rejection. Increases of absolute theta, relative theta, and theta/beta ratio in the ADHD group were tested on 12 measures (2 conditions x 2 references x 3 markers at Cz). Topographies of group differences were explored with t-maps. For none of these 12 measures, increases in ADHD could be replicated (at $p<.05$ uncorrected), and no consistent increases were found at other electrodes. Instead, some measures even tended to reduced (e.g., relative theta /eyes closed /average reference). These results demonstrate that "classical" quantitative EEG markers can not be used for ADHD diagnostics in typical child psychiatry settings. (*Supported by the SNF project "MFAA" (32-109591)*)

Clinical neuro-monitoring by visual evoked potentials - New ways for useful performance. P. Christophis, M. Preuss, F. Wanis & V. Schreiber, *Department of Neurosurgery, University of Giessen, Giessen, Germany.*

Intraoperative monitoring via acoustic and somato-sensory evoked potentials is suitable to protect brain stem functions during surgery and is routinely used. Conflicting reports of the usefulness of intra-operative monitoring via visual evoked potentials (VEP) and also of the VEP derivation in patients of the intensive care unit, were the cause for this study. Most interesting for the neurosurgeon is the monitoring via flash-VEP (f-VEP) during operations along the visual pathways for detect of imminent lesions and minimise the risk of lesions of visual system respectively. Own pilot study in 6 cases and last reports show a possibility to realise an intraoperative f-VEP-monitoring in intravenous anaesthesia in about 50% of the cases. In the present follow-study we derive the steady-stay f-VEP and use frequency analytic methods for clear identification of the P100 and of previous f-VEP-waves in healthy persons additionally. In a second step we will derive f-VEP in brain-healthy persons under intravenous narcosis to find the best combination of the used drugs, which allow a clear identification of P100 and also of the previous f-VEP-waves. The third and last step will be the use of f-VEP-monitoring in neurosurgical operations along the visual pathways.

EEG correlates of fMRI resting state networks. T. Koenig (1), K. Jann (1), M. Kottlow (1), C. Boesch (2) & T. Dierks (1), *(1) Dept. of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, Bern, Switzerland (2) Dept. of Clinical Research (AMSM), University of Bern, Bern, Switzerland.*

Functional synchronization of brain areas is a main concept of how information processing in the brain is performed. Synchronous oscillations have been observed and investigated in EEG during the past decades and more recently such oscillations, however in a different timescale, have been discussed in fMRI. Oscillations occur over a wide frequency range. In EEG, one prominent oscillation is the alpha rhythm, present when a subject is relaxed keeping the eyes closed. The spectral power of the alpha rhythm has recently been investigated in simultaneous EEG/fMRI considering the relationship between neuronal activity and BOLD fluctuations. Even more recently, spontaneous fluctuations of the BOLD signal in fMRI measurements have been observed establishing the notion of so called resting state networks (RSN). The similarity of the networks delineated by either method is surprising considering their different temporal dynamics. Hence, their relationship is presently investigated. One hypothesis is that the subunits assembling a specific RSN might be coordinated by different EEG rhythms. Simultaneous EEG/fMRI recordings were performed in 10 healthy subjects. Time-frequency analysis on the EEG data and Independent Component Analysis (ICA) on the fMRI BOLD signal were performed to reveal relationships between EEG features and RSNs. Correlations could be found between different RSNs and EEG rhythms on individual data sets, evidencing the hypothesis that BOLD oscillations are linked to EEG oscillations. The understanding of relations between BOLD signal fluctuations and associated EEG rhythms may also play a role in pathology, since several psychiatric disorders show changes in BOLD signals and/or EEG oscillations.

Simultaneous EEG-fMRI during a working memory task. L. Michels (1,4), K. Bucher

(2,4), E. Martin (2,4) , D. Jeanmonod (1,4) & D. Brandeis (3,4), *(1) Functional Neurosurgery, University Hospital Zürich, Zürich, Switzerland (2) MR-Center University Children's Hospital, Zürich, Switzerland (3) Department of Child and Adolescent Psychiatry, University of Zürich, Zürich, Switzerland (4) Zürich Center for Integrative Human Physiology (ZIHP), Zürich, Switzerland.*

Increased EEG alpha power is often reported during resting states. However, the role of alpha during cognitive tasks is still unclear. For theta it has been reported that the spectral power increases with working memory load at frontal electrodes. Furthermore, negative correlations between frontal theta and the fMRI (BOLD) signal have been found within the default network (DFN) during rest. In this study, we used time-frequency analyses to investigate correlations between task-dependent fluctuations in theta and alpha power and the BOLD signal. Brain activity was measured by simultaneous EEG-fMRI in 16 healthy adults. During the task, sets of either 2 or 5 letters were presented for 2s. Subjects had to retain them in memory to deciding whether a probe letter shown after 3.5s was part of the set. Occipital alpha power negatively correlated with BOLD activity in parietal and lateral prefrontal areas. The same cortical network was observed by the fMRI contrast 'task vs. rest'. Our findings demonstrate that alpha is not only a marker for resting state activity but further modulates cognitive processing. Frontal theta power at AFz increased with memory load and these theta load effects were correlated with BOLD load effects in prefrontal regions and the angular gyrus. Frontal theta activity was negatively correlated with the BOLD signal in fronto-parietal areas. A comparison of these regions with the DFN revealed a strong overlap. We propose that resting state activity in the DFN is at least partially controlled by a desynchronization of frontal theta EEG.

Dimensions of meaning in multi-sensory perception: Comparison of early and late components of evoked potentials. A. Hiessl, S. Hörner & W. Skrandies, *Institute of Physiology, Justus Liebig University, Giessen, Germany.*

The semantic differential is used to define connotative dimensions of meaning, and the processing of words by the brain depends on such dimensions. Earlier studies demonstrated that stimuli of the different semantic classes lead to differences in neuronal processing. We investigated the influence of connotative meaning on multi-sensory processing (words strongly related to odour, taste, vision or texture). A group of 795 subjects rated 197 food words on the basis of 11 pairs of opposed adjectives. Factor analysis revealed three dimensions (Evaluation, Potency and Texture). Words with high positive or negative scores and low scores on the other dimensions were used as stimuli in an ERP experiment with 40 adults. EEG was recorded from 30 channels, and averaged according to semantic stimulus class. Component latency, global field power and topography were influenced by semantic meaning. We found differences between early (between 80 and 200 ms) and late (around 500 ms) ERP components. Major differences were seen when the polarity of stimulus classes was compared: GFP evoked by positive word classes was smaller than that evoked by negative classes with early components. This effect was reversed with late components. Similar ef-

fects were observed with component latency. In summary, semantic dimensions influence neuronal processing of words related to multisensory perception. The semantic dimensions found were similar to those described earlier. Instead of ”activity” we found ”texture” which reflects the ”mouthfeel” of food items. In addition, we describe early effects on ERP components, and the influence of semantic meaning was different with late cognitive components.

Dimensions of meaning in multi-sensory perception: Gender-specific differences of evoked potentials. S. Hörner, A. Hiessl & W. Skrandies, *Institute of Physiology, Justus Liebig University, Giessen, Germany.*
According of Osgood every word is placed in a 3D space of connotative meaning that is defined by the factors ”evaluation”, ”potency”, and ”activity”. One aim of our study was to investigate whether there are additional factors which represent sensory modality. A total of 197 food words were rated by 795 subjects, and in addition to ”evaluation” and ”potency” the dimension ”texture” emerged which is related to the consistency and surface of food items. Females had a larger awareness of ”healthy” and ”unhealthy” food, and they differentiated more exactly among different food categories. These results provided the basis for an ERP study in which unambiguous food words were presented to 40 healthy subjects (20 males, 20 females). Each stimulus belonged to one of six classes (E+, E-, P+, P-, T+, T-.). EEG was recorded from 30 channels, and averaged according to semantic stimulus class. Peaks of Global Field Power (GFP) defined 11 components which were then compared between males and females. With all components GFP was significantly higher in females than in males. In addition, there were gender-specific differences in scalp topography revealed by the scalp location of centroids: as early as at 107 ms the location of the positive centroids was close to the midline with females while in male subjects there was a significant lateralization towards the right hemisphere. A number of other effects with late components support the notion that there were differences between males and females in electrophysiological parameters. In summary, we could show that there are gender-specific differences in the evaluation of food items as well as in neurophysiological processing of multi-sensory stimuli belonging to different semantic classes.

Eye dominance and nasal-temporal retinal differences are reflected by the scalp topography of visual evoked brain activity. W. Skrandies, *Institute of Physiology, Justus Liebig University, Giessen, Germany.*
There are anatomical and neurophysiological differences between nasal and temproal areas of the human retina. Thus, we expect that eye dominance affects cortical activity. In a group of 23 healthy adults with different eye dominance checkerboard reversal activity was measured from 30 channels (binocular stimulation; 2 reversals / sec; 21° x 15° test field; 50’ check size; 97% contrast). Stimulation occurred either in the center, or in the left or right half-field. Latency, global field power (GFP), and topography were compared between experimental conditions. Mean latency (110.75 ms) and GFP were not affected while topography of the P100 component displayed the well known paradoxical lateralization. Analysis of the scalp location of the positive centroids revealed small but significant differences

between left or right eye dominant subjects: with central fixation, the centroids of subjects with right eye dominance showed a stronger lateralization over the right hemisphere while subjects with left eye dominance displayed the opposite pattern (more extreme lateralization over the left hemisphere). This was significant ($F(1,21) = 6.62$; $p = 0.017$). Similar effects were seen with lateralized stimuli. Since the human pattern ERG demonstrates differences between nasal and temporal retinal areas (Skrandies & Leipert, Int. J. Neuroscie., 1988, 39, 137-146), our present results might reflect basic functional differences extending from the retina to the visual cortex of man.

Resting EEG-based intracortical functional connectivity in Alzheimer's disease and frontotemporal degeneration. F. M. Dahinden (1,2), L. R. R. Gianotti (1), G. Künig (3), R. D. Pascual-Marqui (1), P. L. Faber, (1), D. Lehmann (1), K. Kochi (1) & U. Schreiter-Gasser (4), *(1) The KEY Institute for Brain-Mind Research, University Hospital of Psychiatry, Zürich, Switzerland (2) Department of Neuropsychology, University of Zürich, Zürich, Switzerland (3) Department of Geriatric Psychiatry, University Hospital of Psychiatry, Zürich, Switzerland (4) Praxis für Psychiatrie Rehalp, Zürich, Switzerland.*

We recorded resting-state EEG (19 channels) from two groups of mild-to-moderate AD (n=21) and FTD (n=16) patients and a group of age-matched healthy controls (n=17). sLORETA (Pascual-Marqui, Methods Find Exp Clin Pharmacol, 2002, 24, Suppl. D, 5-12) was applied to calculate the source strength of the intracortical generators in nine regions of interest (ROI, frontal left/right, temporal left/right, central, parietal left/right, occipital left/right) and in the seven classical frequency bands. A 3-way ANOVA with group as between-subject factor and ROI and frequency bands as within-subject factors revealed a significant interaction between group x frequency bands x ROI ($F=1.7$, $p<0.0001$). Post-hoc analyses (t-statistics) confirmed a significantly decreased connectivity in AD relative to healthy controls in the alpha1 band (8.5-10Hz). Also, AD showed a significantly decreased connectivity compared to FTD in the alpha1 and the theta (6.5-8Hz) frequency bands. The decreased connectivity in AD relative to the two groups concerned the whole brain, suggesting a generalized loss of functional interactions between different brain regions in AD. In line with previous reports (e.g., Pijnenburg et al., Clin Neurophysiol, 2008) which found no detectable deviations of EEG parameters in FTD in spite of widespread neuronal degeneration, our study's EEG intracerebral connectivity remained in the normal range during mild-to-moderate stages of the disease.

Scalp EEG connectivity and intracerebral electrical connectivity (sLORETA lagged coherence) during resting and five meditation traditions. P. L. Faber (1), S. Tei (2), R. D. Pascual-Marqui (1), L. R. R. Gianotti (1), H. Kumano (2), K. Kochi (1) & D. Lehmann (1), *(1) The KEY Institute for Brain-Mind Research, University Hospital of Psychiatry, Zürich, Switzerland (2) Department of Stress Science and Psychosomatic Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.*

Brain electric functional connectivity was studied in experienced meditators of five traditions (13 Tibetan Buddhists 'TB', 15 QiGong 'QG',

14 Sahaja Yoga 'SY', 14 Ananda Marga Yoga 'AY', 15 Soto Zen 'Zen') during tradition-specific meditation (self-dissolution, QiGong, Samadhi, Satori) and during wakeful resting before ('rest1') and after ('rest2') meditation. EEG (19-56 electrodes) was computed (via sLORETA, current density in 6239 voxels) into intracerebral waveshapes of 19 intracerebral regions (ROIs) that correspond to cortex underlying the 10/20 electrode positions. Functional connectivity was computed from scalp-recorded data as conventional coherence between 19 locations, and from sLORETA waveshapes as 'lagged coherence' between 19 ROI's; lagged coherence only measures connections with time delay; these are interpretable as true functional connectivity. - For each meditator group, t tests identified significant coherence differences between rest1 vs meditation and rest2 vs meditation in each of 8 EEG frequency bands (delta to gamma). Between 19 locations or ROIs, there are 171 connections. For each subject and frequency band, the percentage of connections were counted that reached significant different coherence between rest1 vs meditation and rest2 vs meditation; from these two values, mean was computed, and averaged across all 8 bands for each tradition separately. For scalp coherences, in the 5 traditions, between 1% to 4% of the connections were significant higher in meditation than rest, between 6% to 36% lower; for intracerebral lagged coherence, 0% were higher, between 26% to 68% were lower. On average across the 5 traditions, scalp coherence decreased most strongly in alpha1&2 and beta1&2, while intracerebral lagged coherence decreased most strongly in delta, theta, beta1&2. For the gamma frequency band alone, scalp coherences were higher between 1% to 13%, lower between 1% to 27%; intracerebral lagged coherences were higher in 0%, lower between 2% to 75% of cases. In sum, all 5 traditions clearly showed more significant decreases than increases in scalp coherence, and only significant decreases, no increases in intracerebral lagged coherence that avoids distorting volume conduction. Contrary to published reports of strongly increased gamma band coherence in meditation, our 5 traditions on average in scalp coherence increased significantly only 4% of the gamma band coherences while 9% decreased; in intracerebral lagged coherence none increased but 44% decreased. (*Partial support by Bial Grant No. 44 2006/2007*).

Active intracerebral areas (EEG LORETA) in non-meditators and experienced meditators differ during resting. P. L. Faber (1), S. Tei (2), D. Lehmann (1), L. R. R. Gianotti (1), T. Tsujiuchi (3), H. Kumano (2) & K. Kochi (1), *(1) The KEY Institute for Brain-Mind Research, University Hospital of Psychiatry, Zürich, Switzerland (2) Department of Stress Science and Psychosomatic Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan (3) Department of Health Science and Social Welfare, Faculty of Human Sciences, Waseda University, Tokorozawa, Saitama, Japan.*

Do experienced meditators and meditation-naïve people have different brain functional states during no-task resting 19 channel EEG was recorded (versus average reference) from 8 QiGong meditators with 3 30 years experience (mean 11.5+/-8.8) and 9 meditation-naïve controls (mean ages 41+/-10 years (3 males), and 37+/-6 years (3

males), respectively) during eyes closed rest (sitting; meditators did not meditate). All artifact-free 2-second EEG epochs (mean 33.9+/-8.5/subject) were recomputed into intracortical 3 dimensional generator distributions using LORETA (2394 voxels) for each subject and each of the 8 EEG frequency bands. Results were normalized per frequency band and subject (total current density across all LORETA voxels scaled to 1). Current density of all voxels was tested (t tests) for differences between groups for each frequency band. An exceedance proportion test correcting for multiple testing identified voxels at $p<0.05$. Only differences in delta frequency band (1.5-6 Hz) were significant (355 voxels): 229 were stronger, 126 weaker in meditators than controls. All but 4 stronger voxels were in anterior areas (BA 9, 10, 11, 44, 45, 46, 47), 81 of them left, 144 right; all weaker voxels were in central-posterior areas (BA 4, 6, 7, 18, 19, 22, 30, 31, 32, 37, 39, 40), 107 of them left, 19 right. - In sum: during task-free resting, experienced meditators had different brain states compared to non-meditators. Meditators had stronger delta EEG activity than non-meditators in frontal cortex (64% right hemisphere voxels), and weaker delta activity in central-posterior cortex (85% left hemisphere voxels). In view of the general assumption that EEG delta activity represents inhibition, experienced meditators have stronger inhibitory activity than controls anterior right-preponderant, and less inhibitory activity central-posterior predominantly left. These results suggest that meditators reduce internal information processing while enhancing input and output processing, an interpretation that agrees with the meditators' subjective experience of disengaging from perceived information. (*Partial support by Bial Grant No. 44 2006/2007.*)

Unconscious processing of words and non-words. M. Hollenstein (1), T. Koenig (2), W. J. Perrig (1) & M. Kubat (1), *(1) Institute of Psychology, University of Bern, Bern, Switzerland (2) Dept. of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, Bern, Switzerland.*

A well debated issue in cognitive psychology and neuropsychology is the question to which level an unconsciously perceived linguistic input is processed. This has often been investigated with subliminal pattern masking techniques that reduce the stimuli's sensory activation strength, which has implied problems to define an objective threshold of awareness. In this event-related-potential-(ERP-) study, a new mirror-masking technique was used that does not reduce sensory activation, but assumingly reduces top-down attentional activation. Stimuli were words and non-words written in a quadratic font that were merged with their inverted counterpart mirrored at the baseline of the letters (mirror-masking). The visual result of such mirrored letter strings were unfamiliar, abstract patterns that prevented subjective awareness of the linguistic information hidden in the seemingly meaningless patterns. Significant differences in ERPs between mirror-masked words and non-words were found in a time range from 112-160ms after stimulus-onset above right posterior areas. A Low Resolution Electromagnetic Tomography (LORETA) model localised neuronal generators of these differences between masked words and non-words in right supramarginal gyrus (BA 40) and posterior temporal lobe,

suggesting that at least an automatic differentiation occurred at a sublexical, phonological level of processing. Our results strongly indicate that subjects unconsciously and automatically extracted some linguistic information from masked words.

Localization by norm. E. Januts (1), A. Klein (2) & T. Sauer (2), *(1) Medical Optics, Institute of Medical Physics, Friedrich-Alexander University, Erlangen, Germany (2) Numerical Mathematics, Justus-Liebig University, Gießen, Germany.*

Underdetermined inverse problems which usually appear in the context of source localization are usually regularized by choosing a solution that is minimized with respect to a quadratic energy norm. However, this approach is more of traditional nature and motivated by the fact that equality constrained quadratic minimization problems are easy to solve. Unfortunately, the quality of such a location often leaves a lot to be desired, which, nevertheless, is not necessarily a measurement artifact but a purely mathematical one stemming from the underlying algorithm. Already the simple change of passing to the 1-norm which has a smaller, better localized unit ball, often leads to significantly better results that can be computed quickly and efficiently due to the wide availability of good software for linear programming. We will illustrate this phenomenon with some examples from optical tomography.

Continuous wavelet transformation and EEG analysis. A. Klein & T. Sauer, *Numerical Mathematics, Justus-Liebig University, Gießen, Germany.*

Wavelets transforms have become a standard tool for the decomposition of signals in the time-frequency-domain. Much effort has been put into algorithms for discrete wavelet transforms (DWT) which allow for very fast implementations. Along with their inverse transforms, DWTs serve very well as bandpass-filters and as tools for data compression, but despite their representing all information contained in the signal, the results of DWTs are often lacking in terms of interpretability, especially when it comes to giving visuals cues about the data being analysed. On the other hand, continuous wavelet transforms (CWT) have been used for a long time as a means of data analysis, because they give very many visual cues, but due to their cumbersome inversion their use for any kind of real data processing beyond sheer analysis has been very limited. In order to overcome these problems, we have developed a set of tools allowing for analysis as well as synthesis of data at a somewhat slower but still competitive speed as compared to DWTs.

Congruent music and affective attitude influence the anticipation and perception of emotional events - a sLORETA study on healthy subjects with low depression scores. M. Kottlow (1), R. Willi (2), T. Baumgartner (3), G. Tanner (4), T. Koenig (1) & L. Jaencke (2), *(1) Department of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, Bern, Switzerland (2) Department of Neuropsychology, Institute of Psychology, University of Zürich, , Zürch, Switzerland (3) Institute for Empirical Research in Economics, University of Zürich, Zürich, Switzerland (4) Institute of Human Movement Sciences, ETH, Zürich, Switzerland.*

Recent studies have shown the influence of

music on the experience of emotion intensity. In this study, we replicated the results, additionally analyzing the cued expectation of the emotional stimuli. 17 female subjects with low depressiveness scores participated in this EEG study expecting and afterwards processing blocks of sad or happy pictures with or without congruent music. Peripheral psychophysiology and psychometrical ratings were collected. Alpha frequency band power, inversely related to neural activity, was analyzed with sLORETA (standardized low resolution brain electromagnetic tomography). A significant increase in brain activity was visible during the announced expectation of happy emotional pictures with music vs. without music in anterior cingulate and inferior parietal regions. During the presentation of conditions with vs. without music, we found significantly higher activations in emotion relevant brain regions, supported by increased empathy ratings and HR during happy conditions with music. Happy compared with sad conditions resulted in activity within emotion relevant areas, whereas sad conditions activated rather visual and auditory perception areas. Our results show intensity related anticipation and processing of emotional events, presumably influenced by the positive affective attitude of subjects. Definitive argumentations require the outstanding comparison with healthy subjects with high depressiveness scores.

Influence of COMT-genotype on sensory gating in patients with ADHD and healthy controls. J. Langer, A.-C. Ehlis, T. Daubitz, C. Bähne & A. J. Fallgatter, *Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany.* Catechol-O-Methyltransferase (COMT) is an enzyme involved in the degradation of dopamine (DA) in the synaptic cleft mainly in the prefrontal cortex. In humans the COMT gene shows a functional polymorphism (AA158/AA108, Val158Met) resulting in three phenotypes (Met/Met, Val/Met, Val/Val) differing in the availability of DA in the brain (highest Met/Met, lowest Val/Val). Mainly enervated by dopaminergic neurons, the dorso-lateral prefrontal cortex (DLPFC) is especially affected by this polymorphism. The DLPFC is crucially involved in working memory and attention and therefore often investigated in ADHD. One electrophysiological construct associated with long term attention and the DLPFC is sensory gating (SG). It is supposed to represent a protective neuronal mechanism filtering irrelevant stimuli to prevent informational ”overload” in the brain. We assessed genotype and SG via the P50 double-click paradigm in 23 ADHD patients (18 to 35 years) and 25 age and gender matched healthy controls. Using a 21-channel EEG event-related potentials were recorded at Cz. ADHD patients overall showed deficient SG. In controls subjects with Val/Val genotype showed the worse SG as dopamine is degraded most quickly in this subgroup. No influence of the COMT-Genotype on SG was found in ADHD-patients which could be confounded by medication influencing the DA-level.

EEG in Tibetan Buddhist meditators during rest and meditation, and effects of meditation experience. D. Lehmann (1), S. Tei (2), P. L. Faber (1), H. Kumano (2), L. R. R. Gianotti (1) & K. Kochi (1), *(1) The KEY Institute for Brain-Mind Research, University Hospital of Psychiatry, Zürich, Switzerland (2) Department of Stress Science and Psycho-*

somatic Medicine, The University of Tokyo, Tokyo, Japan.

Nineteen-channel EEG from 13 Tibetan Buddhist meditators (27-58 years old, mean 39+/-8) with 2 to 25 years experience in meditation was recorded during task-free resting while not meditating, and during meditation aiming at the condition of self-dissolution. The sequence 'rest - meditation - rest' was recorded twice. 286 artifact-free seconds EEG during rest (1084 seconds during meditation) were available on average/subject. EEG was analyzed into power spectra (1.5 to 44 Hz, versus average reference). Spectra were averaged for each subject, separately for the 2 meditation and the 4 rest conditions. From mean spectra across the 19 channels we computed 1) centroid spectral frequency for the full 1.5-44 Hz band, and 2) integrated power for each of the 8 EEG frequency sub-bands (delta to gamma). From the 19 channel spectra, we computed 3) the location of the gravity center of band power distribution over the 19 scalp recording locations. Results were A) compared between meditation and rest, and B) correlated with years of meditation experience controlled for age. Significant results were: A) Comparing meditation versus rest, full-band spectral centroid frequency was higher during meditation, power in theta and alpha 1 frequency bands was lower during meditation, and location of gravity center of band power distribution on the scalp was more left for delta, and more posterior for beta bands during meditation. B) With increasing meditation experience, full-band spectral centroid frequency decreased in meditation, theta and alpha1 frequency band power increased but beta2 and beta3 band power decreased in meditation (theta power increased also in rest), and gravity center location of band power distribution of alpha1 and of all higher frequency bands moved posterior during rest and meditation. - These results are in agreement with concentration-related changes from rest to meditation, and suggest lessening of these differences with increasing experience in meditation. (*Supported by Bial Grant No. 44 2006/2007*).

The neurophysiological signature of habitual prospective memory processes. S. Matter (1), T. Koenig (2) & B. Meier (1), *(1) Institute of Psychology, University of Bern, Bern, Switzerland (2) Dept. of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, Bern, Switzerland.*

Tasks that require remembering to realize delayed intentions at the appropriate occasion are defined as prospective memory tasks. Realizing the same prospective memory task repeatedly transfers an episodic into a habitual prospective memory task. Using event-related potentials (ERPs) the goal of the present study was to investigate whether characteristic neurophysiological episodic to habitual transition effects emerge when a prospective memory task is repeated. ERPs evoked by correctly answered prospective memory cues in the first part of the experiment were contrasted with those of the second part of the experiment under the assumption that the former rather represents episodic and the latter habitual prospective memory. Results revealed a significant episodic to habitual transition effect expressed by enhanced frontal negativity and parietal positivity in the ERP 400 - 600 ms post-stimulus, a time-window interpreted as critical for retrieval of the intention and post-retrieval processes. Additionally, source local-

ization using LORETA attributed the transition to a significantly lower activation in the anterior frontal regions while posterior parietal and occipital regions showed higher activation in the second compared to the first part of the experiment. The findings indicate that episodic and habitual prospective memory tasks require different processes. While episodic prospective memory is supported by controlled retrieval processes guided by frontal structures, habitual prospective memory was found to be supported by automatic retrieval processes. The present study adverts to the importance of a conceptual distinction between episodic and habitual prospective memory tasks.

Neural activity before stimulus presentation predicts the success of stimulus retrieval. T. Padovani (1) , T. Koenig (1,2), D. Brandeis (3) & W. J. Perrig (1), *(1) Institute of Psychology, University of Bern, Switzerland (2) University Hospital of Psychiatry, University of Bern, Bern, Switzerland (3) Department of Child and Adolescent Psychiatry, University of Zürich, Zürich, Switzerland.*

The brain's information processing is state dependent. In this context, previous research has shown that pre-stimulus ERP activity predicts later recollection (subsequent memory effect). In this experiment, we attempted to systematically manipulate the pre-stimulus state by giving the subjects a) a semantic decision task and b) an emotional decision task and after that testing the incidental encoding of each single item presented in the study phase with a recognition memory test. We recorded and analyzed 65 channel ERPs in 21 healthy volunteers. We found a significant interactions of task and later memory performance using a TANOVA in two different intervals preceding the words onset (-800 to -400 ms, -400 to 0 ms). When the cue indicated to execute a semantic decision, ERPs of subsequently remembered and forgotten words differed in an interval from -800 to -400 ms. When the cue indicated to execute a emotional decision ERPs of subsequently remembered and forgotten words differed from -400 to 0 ms. This indicates that the neural networks necessary for a successful incidental encoding depend on the task that the subject is preparing. When searching for those networks, Loreta analyses suggested that for the semantic condition, the maximal difference between remembered and forgotten words was in the left middle frontal gyrus that is known to be related to semantic processes. In the emotional condition, the maximal difference was estimated to be in the left middle temporal gyrus. This structure has been related to memory encoding and processing of emotional stimuli. These effects may also reflect latency differences between semantic and emotional preparatory processes important for efficient encoding into episodic memory. This study supports the idea that the formation of lasting memories involves the role of neural activity that both precedes and follows the presentation of a stimulus event.

Early topographical differences elicited by color and food words. N. Reuther & W. Skrandies, *Institute of Physiology, Justus Liebig University, Giessen, Germany*

We investigated the relationship between color, food, odor and taste stimuli. Subjects were studied with questionnaires and in electrophysiological experiments. First, a total of 144 word pairs were rated by 660 subjects who determined whether the second stimuli

(a food or color word) matched the first stimulus (taste or odor word). Clearly matching or non-matching word pairs were used in an EEG experiment. Activity was recorded from 30 electrodes in 24 healthy adults while single words were randomly presented on a monitor. Evoked potentials were computed for different stimulus classes (matching and non-matching combinations of color or food words with odor or taste words). Six components were identified and topography was compared between conditions. Most location differences occurred in the left-right-direction. We observed significant cognitive effects as early as 100-150 ms after stimulus presentation: the locations of the positive centroids differed when food/color stimuli were paired with taste/odor stimuli ($F(1,23)=4.92$, $p<0.05$). Odor and taste words yielded different lateralization over the right hemisphere, depending whether taste or odor words were processed by the subjects. Between 400-500 ms color and food words affected the locations of negative centroids (significant interaction between stimulus modality and target type $F(1,23)=4.44$, $p<0.05$). These findings suggest rapid cognitive processing of semantic differences between color, food, odor and taste in the visual cortex. The topographical effects indicate that different underlying neural populations are activated by different semantic classes.

Nogo-N2 and Nogo-P3 in psychiatric patients. M. Ruchsow (1), M. Spitzer (2), M. Kiefer (2), G. Grön (2), M. Falkenstein (3) & L. Hermle (1), *(1) Dept. of Psychiatry Christophsbad, Göppingen, Germany (2) Dept. of Psychiatry, University of Ulm, Ulm, Germany (3) Leibniz Research Centre for Working Environment and Human Factors (IfADo), Dortmund, Germany.*

Nogo-N2 and Nogo-P3 were measured in patients with major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and borderline personality disorder (BPD) and in three independent sex-, age-, and education-matched control groups. In a fourth study, RT residuals were calculated in a group of healthy subjects ($n = 26$) in order to split the entire group in a high impulsiveness subgroup (HI, $n = 13$) and a low impulsiveness subgroup (LI, $n = 13$) according to the method of Pailing et al. (2002). Participants performed a hybrid flanker-Go/Nogo paradigm while a 64-channel EEG was recorded. MDD patients, BPD patients, and HI subjects showed reduced Nogo-P3 amplitudes compared to their respective control groups. OCD patients had enhanced Nogo-N2 components in relation to control subjects. Possibly, Nogo-N2 and Nogo-P3 are affected by impulsiveness, compulsivity, and depressiveness in a different manner. Further studies are needed to exactly determine the underlying neuropsychological and neurobiological mechanisms resulting in altered Nogo-P3 and Nogo-N2 amplitudes in psychiatric patients.

Ne/ERN in obsessive-compulsive spectrum disorders. M. Ruchsow (1), M. Spitzer (2), M. Kiefer (2), G. Grön (2), M. Falkenstein (3) & L. Hermle (1), *(1) Dep. of Psychiatry Christophsbad, Göppingen, Germany (2) Dep. of Psychiatry, University of Ulm, Ulm, Germany (3) Leibniz Research Centre for Working Environment and Human Factors (IfADo), Dortmund, Germany.*

The error negativity (Ne) or error-related negativity (ERN) was investigated in patients with obsessive-compulsive disorder (OCD) and

borderline personality disorder (BPD) and in two independent sex-, age-, and education-matched control groups. In a third study, RT residuals were calculated in a group of healthy subjects (n = 32) in order to split the entire group in a high impulsiveness subgroup (HI, n = 16) and a low impulsiveness subgroup (LI, n = 16) according to the method of Pailing et al. (2002). Participants performed a hybrid flanker-Go/Nogo paradigm while a 64-channel EEG was recorded. Both, BPD patients and HI subjects showed reduced Ne/ERN amplitudes compared to their respective control groups, whereas OCD patients and LI subjects had enhanced Ne/ERN amplitudes. The Ne/ERN seems to reflect a continuum of compulsiveness (OCD patients and LI subjects) and impulsiveness (BPD patients and HI subjects) in a spectrum of obsessive-compulsive disorders. It seems a reasonable target for further studies whether Ne/ERN amplitudes in psychiatric patients change with successful pharmacological and/or psychotherapeutic treatment.

Effects of working memory load and methylphenidate in healthy adults during a visual working memory task. P. Studer (1), S. Wangler (1), M. Diruf (1), O. Kratz (1), G. H. Moll (1) & H. Heinrich (1,2), *(1) Child and Adolescent Psychiatry, University of Erlangen, Erlangen, Germany, (2) Heckscher-Klinikum, Munich, Germany.*

In the present study, we investigated how working memory load affects the neuronal processing during the encoding, retention and retrieval phases of a visual working memory task and how processing is modulated by methylphenidate. Eleven adults participated in a placebo-controlled, double-blind, crossover study. They performed the task in which they memorized the order of four, five or six pictures under methylphenidate (20 mg) and under placebo. Brain electrical activity was recorded, eye movement artefacts were corrected using independent component analysis and repeated-measurement ANOVAs were calculated. The number of correct responses decreased with incremental working memory load. In the encoding phase the P3 amplitudes became smaller with increasing numbers of pictures shown within one trial. Over the midline electrodes P3 amplitudes increased with increasing memory load. In the retention period a slow negative wave occurred with a fronto-central distribution. The retrieval phase was characterized by a slow negative wave with a posterior topography. Medication neither influenced performance nor the different processing stages in our small sample. Increasing working memory load was associated with P3 effects during encoding. Methylphenidate does not seem to modulate processing during a visual working memory task in healthy adults significantly.

sLORETA, eLORETA, and SWARM in the presence of noise and multiple sources. M. Wagner, M. Fuchs & J. Kastner, *Compumedics Neuroscan, Hamburg, Germany.*

Standardized low resolution brain electromagnetic tomography (sLORETA) retrieves the sources of EEG and MEG data with low localization error. Its outcome, however, is not a distribution of currents modeling brain activity but a statistical map thereof. As a consequence, like EEG/MEG beamformers or fMRI images, it is not a solution to the underlying inverse problem. Two new methods promise to solve the inverse problem

by computing neuronal current flow instead of statistical maps, also with low localization error for point sources: sLORETA-weighted accurate minimum-norm (SWARM) and exact low resolution brain electromagnetic tomography (eLORETA). In this contribution, we evaluate the performance of these methods under the presence of noise and with multiple, simultaneously active sources. The same simulation setup and data as in [1] and [2] are used.

[1] M. Wagner, M. Fuchs, J. Kastner. 2004. Evaluation of sLORETA in the presence of noise and multiple sources, Brain Topography 16:277-280.

[2] M. Wagner, M. Fuchs, J. Kastner. 2004. Evaluation of sLORETA for MEG data in the presence of noise and multiple sources, in: Biomag 2004, Eds. Halgren E, Ahlfors S, Hämäläinen M, Cohen D. Boston, Biomag 2004 Ltd., p. 611.

Spatio-temporal organisation of quadratic phase- couplings in tracé alternant EEG pattern in full-term newborns. K. Schwab, P. Putsche, M. Eiselt & H. Witte, *Institute of Medical Statistics, Computer Sciences and Documentation, Friedrich Schiller University Jena, Jena, Germany.*

The aim of this work was the investigation of the spatio-temporal organisation of quadratic phase-couplings (QPC) in the electroencephalographic 'trace alternant' pattern during quiet sleep. The investigation was carried out in a group of 6 clinically and neurologically normal, full-term newborns (8-channel-EEG: Fp1, Fp2, C3, C4, T3, T4, O1, O2). The quiet sleep EEG was segmented by a trained physician into 4 sec periods of burst and interburst patterns. The Gabor expansion, a fast Fourier transformation based method, was adapted to examine the time-course of biamplitude, bicoherence and phase-bicoherence of both burst and inter-burst patterns in the region of interest [1-1.5 Hz, 3.5-4.5 Hz]. The burst and the interburst patterns are characterised by temporally and topographically different QPC profiles. All differences are dominant at Fp1 followed by Fp2. There is a significant difference (combined multiple and global tests) in the QPC characteristics between both patterns within the time period from 0.75 to 1.5 s after the pattern onset at Fp1. The maximal QPC in burst patterns can be observed during this time period. In contrast to this finding, maximal QPC in interburst patterns are reached immediately after the onset and at 3 s. Additionally, a time-variant, parametric bispectral approach resulting in a so-called mean biamplitude (mBA) in the region of interest was adapted to investigate the time-course of QPC within the continuous EEG recordings (total length of recordings 320 to 830 sec). The rhythmicity of the time course of the mBA is dominated by the sequential alteration of burst and interburst patterns. The mBA course rises during the occurrence of a burst pattern. Within all newborns, a periodicity of QPC of about 8-10 s can be calculated. A comparison of the QPC events and of the burst-interburst-pattern segmented by the trained physician shows that the periodicity of the QPC alteration persists in EEG epochs in which no burst patterns can be detected (visually, according to the amplitude criteria). In conclusion, it can be assumed that the QPC rhythm of the TA is generated by a pattern-spanning time-variant phase-locking process, and there are indications for a correspondence between the QPC rhythm and vegetative rhythms. This study showed that advanced, time-variant analysis methods quantifying QPC rhythms are able to add new

scientific information to the understanding of nature, characteristics and significance of TA in the neonatal EEG.

Decomposition of multivariate time series by state space modelling. A. Galka (1,2,3), K. F. K. Wong (3), T. Ozaki (3), H. Muhle (4), U. Stephani (4) & M. Siniatchkin (4), *(1) Department of Neurology, University of Kiel, Kiel, Germany (2) Institute of Experimental and Applied Physics, University of Kiel, Kiel, Germany (3) Institute of Statistical Mathematics (ISM), Tokyo, Japan (4) Department of Neuropediatrics, University of Kiel, Kiel, Germany.*

In many situations, decomposition of multivariate time series data into a set of source components represents a useful and important step for preprocessing and analysis of time-resolved data in neuroscience. As a prior constraint, the components may be assumed to be mutually independent, which leads to Independent Component Analysis (ICA). In this contribution we propose to employ linear state space modelling for the purpose of time series decomposition, as an alternative to currently available algorithms for ICA. State space modelling, a generalisation of classical ARMA modelling, is well suited for exploiting the dynamical information encoded in the temporal ordering of time series data, while this information remains inaccessible to most ICA algorithms. Within the state space framework, the assumptions of mutual independence of components, of stationarity and of normality (gaussianity) can be relaxed. Using a Kalman Filter, linear state space models can be employed even for detecting strongly nonlinear dynamical processes. As a result, much more detailed decompositions become possible, and both components with sharp power spectrum, such as alpha components, sinusoidal artifacts or sleep spindles, and with broad power spectrum, such as FMRI scanner artifacts or epileptic spiking components, can be separated. Results from simulations and from practical EEG processing tasks are presented.

Randomization techniques specific for the analysis of ERP data. T. Koenig & T. Dierks, *Department of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, Bern, Switzerland.*

ERP data is redundant in many ways. Channels are intrinsically correlated across the scalp, similar scalp distributions are observed across prolonged time intervals, and the measurements are typically repeated within and across subjects. This redundancy is problematic for statistics, because it obscures the real degrees of freedom of the data, which in return increases the possibility of false conclusions due to repeated testing or overly conservative corrections for multiple testing. These problems can be overcome by randomization statistics. Randomization statistics allow the user to invent a suitable measure of effect size and then test the effect size in the measured data against the null-hypothesis. The problem of redundancy of ERP data can thus be overcome by choosing specific effect size measures that are global across the dimension where the redundancy is expected. We present a series of techniques that apply global measures of effect size to ERP data. One series of tests investigates whether there is evidence that at one moment in time, one or several ERP topographies are systematically related to the experimental design or to some continuous predictor. Another series of tests investigates whether the distribution

of statistical effect sizes across the analysis period is likely to have occurred by chance, thus dealing with redundancy across time. Finally, a method is proposed that allows to determine periods of consistent topography across repetitions (trials or subjects).

Abstract

M. Doppelmayr, E. Weber, K. Hoedlmoser & W. Klimesch (Salzburg) — Effects of SMR Feedback on the EEG Amplitude Neurofeedback (NF) is a method to learn how to voluntarily produce and modulate specific brain rhythms, as assessed by the electroencephalogram (EEG). It is used both, in the treatment of a variety of disorders, such as epilepsy or attention deficit (hyperactivity) disorder (AD(H)D), as well as in healthy subjects to increase performance in a specific type of task. However, especially for healthy subjects, there is a lack of empirical data focusing on the effects of NF on the EEG. While there are some reports indicating that subjects are able to learn to increase the amplitude within the sensorimotor rhythm frequency range (SMR; 12 - 15 Hz) by neurofeedback training (NFT), there are almost no studies describing the concomitant effects on a resting EEG preceding and/or following NFT. In our study 20 healthy subjects participated in 25 NF sessions. The experimental group (SMR n=12) was instructed to increase the SMR amplitude, while the control group (n=8) received a pseudo-NF (PNF). EEG was recorded at C3 and C4 during the training as well as in resting conditions preceding and following each NF session.

With respect to amplitude changes, we found that, during training, SMR amplitude significantly increased in the experimental group, whereas it remained unchanged over time in the PNF-training. Our results indicate that a significant increase in SMR amplitude is present only during the training. However, there was a clear tendency that in a resting condition with eyes open SMR amplitude was also increased. This leads to the assumption that possibly after more than 25 sessions, SMR NFT might exert effects on resting EEG parameters. As there was no difference between experimental and control group concerning the motivation (measured by visual analogue scales), it can be ruled out that the training-related increase is due to a placebo effect.

Effects of SMR Feedback on the EEG Amplitude

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Introduction

The roots of neurofeedback (NF) reach back to the 1970s. In 1969 Joe Kamiya was the first to propose that the alpha rhythm of the human electroencephalogram (EEG) can be self-regulated. This was followed by a study from Sterman, Howe, and Macdonald (1970), who reported that cats are able to learn to increase specific frequencies of their electroencephalogram (EEG). In a later experiment by

Sterman and Friar (1972), it was found that these cats showed a decreased sensitivity to epileptic seizures as induced by monomethylhydrazine. Although NF has not been the focus of neuroscience for a long time, scientific interest in different aspects of NF has been reestablished in the last decade.

In general, it is assumed that NF is a type of operant conditioning procedure used to modulate EEG parameters such as amplitude, power and coherence (Sterman & Egner, 2006). Subjects are connected to the EEG device and receive visual and/or acoustic feedback of the EEG parameter of interest. This feedback may be a circle, a bar, or more sophisticated displays such as video games. An increase or decrease in the relevant EEG parameter leads to changes in this feedback. Participants are supposed to alter their individual EEG guided by the presented feedback (e.g. increase or decrease a bar), which, in turn, should lead to changes in brain rhythmicity by operant conditioning.

Meanwhile, there is a series of well published manuscripts that analyzed behavioural changes after a neurofeedback-intervention. Effectiveness of neurofeedback training (NFT) has been demonstrated in the treatment of epilepsy (Kotchoubey et al., 1999, 2001; Strehl, Kotchoubey, Trevorrow, & Birbaumer, 2005; Strehl, Trevorrow, et al., 2006; Sterman & Egner, 2006) and attention deficit (hyperactivity) disorder (AD(H)D) (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Monastra et al., 2006; Lubar, Swartwood, Swartwood, & O'Donnell, 1995; Strehl, Leins, et al., 2006). In addition, it is documented that sigma NFT can increase spindle power during sleep (Berner, Schabus, Wienerroither, & Klimesch, 2006) and that NFT exerts positive effects on sleep and memory (Hoedlmoser et al., 2008). Other studies reported the more or less successful treatment of migraine (Kropp, Siniatchkin, & Gerber, 2002), tinnitus (Dohrmann, Weisz, Schlee, Hartmann, & Elbert, 2007), emotional dysfunctions (Hammond, 2005; Raymond, Sajid, Parkinson, & Gruzelier, 2005) and stroke rehabilitation (Doppelmayr, Nosko, Pecherstorfer, & Fink, 2007). Furthermore, several NFT investigations have been conducted demonstrating the modification of cognitive (Hanslmayr, Sauseng, Doppelmayr, Schabus, & Klimesch, 2005; Egner & Gruzelier, 2001; Gruzelier, Egner, & Vernon, 2006) and creative (Gruzelier & Egner, 2005; Raymond et al., 2005) performance. Last but not least, modification of brain rhythms by means of NF is used for brain computer interface technology (Birbaumer, 2006; Birbaumer et al., 2006).

Studies investigating the treatment of disorders focus on participants that are cognitively or emotionally impaired, while research focusing on the enhancement of cognitive or creative processes is based on healthy subjects. Depending on the type of treatment, different frequency bands are used for training: sensorimotor rhythm SMR (approximately 12 - 15 Hz) (Sterman & Egner, 2006) or slow cortical potentials (SCPs) for epilepsy (Kotchoubey et al., 2001) and AD(H)D or theta/beta ratio for AD(H)D (Leins et al., 2007), to give some examples.

Although many investigations have focussed on the behavioural efficiency of NFT, there is less literature reporting the respective changes in the EEG. However, there are some studies showing changes in the powerspectra af-

ter NFT in patients suffering from AD(H)D or epilepsy (Fernández et al., 2007; Grin-Yatsenko, Kropotov, Ponomarev, Chutko, & Yakovenko, 2001; Kropotov, Ponomarev, & Grin-Yatsenko, 2001; Pineda et al., 2008). In contrast to clinical populations, there is little, if any literature concerning changes in the EEG after NFT in healthy subjects. Therefore, it is an interesting question whether NFT changes EEG-characteristics only during the training or whether the effects are longer lasting. Under the assumption that the EEG reflects, at least in part and indirectly, cognitive processes it is of outstanding importance to know whether NFT modifies these processes only for short (Hanslmayr et al., 2005) time periods or in a more general and longer lasting way (Pineda et al., 2008).

Vernon et al. (2003) demonstrated that subjects were able to increase their SMR (or at least the SMR/theta and SMR/beta ratio) after 8 sessions of NFT. A second group had to learn to enhance theta activity and failed to change the EEG in any aspect. Unfortunately neither SMR amplitude or power values (only ratios) nor data relating to the accompanying resting conditions were reported.

Further research concerning changes in EEG after NFT was published by Egner, Zech, and Gruzelier (2004) who used healthy subjects in two experiments. In Experiment 1 the participants received two different beta trainings followed by an alpha/theta training. The results, however, yielded no clear evidence that those frequency bands that had been trained demonstrated altered spectral properties.

In Experiment 2, subjects were assigned to either alpha/theta, low beta, or beta training. For absolute power analyses, none of the hypotheses concerning the modification of the respective frequency bands could be confirmed. In addition, relative power analyses only yielded an effect on the alpha/theta training in the low beta band at prefrontal areas. Therfore, as the authors conclude, the straightforward assumption that training in a specific frequency band would alter the EEG respectively could not be proven.

Cannon et al. (2007) used a new approach of low resolution brain electromagnetic tomography (LORETA) - NF. Eight subjects had to increase 14 – 18 Hz beta power in the area of the anterior cingulate cortex (ACC) [for details of LORETA-NF see Congedo, Lubar, & Joffe, 2004]. The results indicated that the subjects were able to increase beta power in the ACC as well as adjacent areas, but no increase was detected in more distant locations.

As outlined above, little data exist relating to the impact of NFT on amplitude and power in healthy subjects; there is only one report concerning the effect of NFT on the resting EEG of healthy participants. Cho et al. (2008) analyzed effects of alpha (8 - 12 Hz) NFT in 9 subjects during 16 sessions of NFT including preceding resting conditions. They found a significant increase in alpha amplitude after 9 sessions, in both the training and in the resting condition with eyes open.

Taken together, the effect of NFT on the EEG of healthy subjects has not been investigated in depth. Therefore, from our point of view, it is necessary and highly important for the future application of NFT to address these basic issues, especially if NFT is used in healthy subjects. Due to the fact that SMR is the most commonly used frequency of interest in NF studies, we decided to concentrate on this

rhythm. The main focus of this study, therefore, was to investigate a) whether healthy subjects increase their SMR-amplitude over the course of 25 SMR-NFT sessions, and b) if thereby any changes in SMR-amplitude are detectable during the resting periods preceding and following each NFT.

Methods

Subjects and Design

23 healthy subjects were carefully instructed, signed written informed consent and received 250.- Euro for their participation. The experiment was conducted in line with the declaration of Helsinki. Subjects had to perform 25 sessions of NFT (one each day for five weeks, excluding weekends). Each of these sessions consisted of 2 min rest with eyes open, 2 min rest with eyes closed, 8 3-min blocks of NFT, followed by 2 resting conditions such as at the beginning.

Due to missing or bad data, 3 subjects had to be excluded, so resulting in a sample of 20 participants (11 male), with a mean age of 29.3 years (SD 10.5).

Subjects were randomly assigned to either an experimental group (n =12, SMR) or to a control group (n = 8, pseudoneurofeedback PNF). Participants in the experimental group were supposed to increase SMR (12 – 15 Hz, referred to as low beta by several authors) amplitude during the NFT. The PNF group, on the other hand, was instructed to increase amplitude in different frequency bands in a pseudorandomized way (delta 2 – 3 Hz, theta 6 – 7 Hz, beta 1 18 – 20, gamma 1 30 – 35 Hz and gamma 2 40 – 45 Hz). In the PNF group, the respective frequency bands were changed after each 3 min. block so no learning effects within a specific frequency range were expected.

Data were recorded by BioGraph Infinity-ProComp (Thought Technology ®) using a sample rate of 256 Hz. Electrodes were located at C3 and C4 with reference on the left earlobe. Ground electrode was placed on the right earlobe.

Neurofeedback training

Subjects were seated in front of a computer monitor displaying a green background, a white counter on the top, the main feedback in the centre, and bars representing the inhibit bands on the right hand side (see Figure 1). The main feedback in the centre consisted of an orange circle, indicating the reward threshold, including a white filled circle representing the actual amplitude of the respective frequency band. Increases in the amplitude lead to an increase of the filled circle until the reward threshold was reached. If the reward threshold was exceeded for more than 250 ms one point was added on the counter. After a reward, no further reward was given for the next 3 seconds. On the right hand side of the monitor three bars were depicted representing the inhibit bands. Inhibit bands are used to prevent subjects from manipulating EEG amplitude by eye blinks or modulating amplitude estimates by voluntary muscle contraction (e.g. m. masseter or temporalis). The frequency bands for these inhibit bands were adjusted from 3 – 5 Hz (eye blinks), 22 – 30 Hz and 45 – 60 Hz (muscle artefacts). If the amplitude in one of these bands was increased no positive feedback was provided. In general the ongoing EEG was band-pass

filtered to continuously extract the average amplitude within the respective frequency bands. The average amplitude of C3 and C4 was transformed into visual feedback (circle and bars).

The reward threshold was set individually for each of the training blocks. The idea was to provide sufficient rewards within a 3 minute period to keep the subjects motivated. We therefore decided to change the reward threshold if less than 20 or more than 30 rewards were given within a 3 minute block. For the first training block each day the last threshold value of the previous day was used. The reward threshold for the PNF was set similarly in such a way that the subject received approximately the same amount of positive feedback, independently of which frequency band they trained.

Motivation

To evaluate whether motivational aspects are similar, we used a visual analogue rating scale, 5 cm in length, indicating low motivation on the left and high motivation on the right hand side. Motivation was evaluated each day after NFT by subjects marking that point on the scale which represented how motivated they were. The distance was measured and the respective value [cm] was used for analysis.

Data Analyses

EEG data were exported for analysis to Scan 4.3.3. (Neuroscan Inc.) software and visually inspected for artefacts. For each 3 min training block as well as for the resting conditions powerspectra were calculated to extract the mean power of Alpha (8 - 11 Hz), SMR (12 - 15 Hz), Beta (16 - 25 Hz) and the Total frequency band (2 - 40 Hz). Root values of the powerspectra, representing amplitudes were calculated and the respective values averaged across C3 and C4. Relative SMR amplitude was calculated by dividing SMR amplitude by the Total amplitude.

The original dataset comprised 8 NFT blocks plus 4 resting sessions for 25 days, i.e. 300 datasets per person. To reduce the amount of data, we decided to compare the EEG values from the beginning, t1 (average of day 1, 2 and 3), with those from the middle of the training, t2 (average of day 12, 13, and 14), and those from the end of the training t3 (average of day 23, 24, and 25). The values for three days were averaged to reduce the substantial intraindividual variance.

To evaluate the effects of NFT on Alpha, SMR, Beta and relative SMR amplitude, 2-factorial ANOVAs with the factors TIME (t1, t2, t3) and GROUP (SMR, PNF) were calculated. In addition, an ANOVA comprising the factors TIME-ALL (day 1 to day 25) and GROUP (SMR, PNF) was conducted. To compare SMR amplitude changes in the resting condition with eyes open before/after the training, a 3-factorial ANOVA including the factors PRE/POST (before the training, after the training), TIME (t1, t2, t3) and GROUP (SMR, PNF) was calculated. The same process was performed for the eyes closed condition.

To compare motivation between subjects and across the training sessions, the motivation rating values provided after the first, second and third training were averaged for t1; after the 12^{th}, 13^{th}, and 14^{th} session for t2 and after the 23^{rd}, 24^{th} and 25^{th} for t3. Again, these values were contrasted using a 2-way ANOVA with the factors TIME (t1, t2, t3) and GROUP

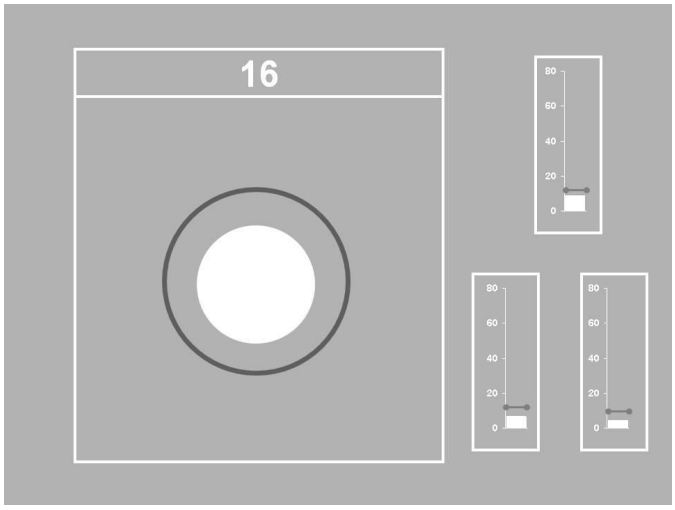

Figure 1: *The counter on the top increased every time the reward threshold, represented by an orange circle in the middle of the green screen was exceeded for more than 250 ms. The amplitude of the relevant EEG frequency was represented by the white circle within the threshold circle. This white circle increased or decreased in response to amplitude changes of the selected frequency. On the right hand side, three bars represented amplitude of the three inhibit frequency bands (3 - 5 Hz, 22 – 30 Hz, and 45 – 60 Hz).*

(SMR, PNF).

Results

Kolmogorov-Smirnov tests were applied to test for the normality of the distribution of the data, which was given in all cases. In addition, Greenhouse-Geisser corrected p-values are presented if the sphericity assumption was violated. The ANOVA for the SMR band addressing the differences between the groups and the changes during the course of the training sessions revealed a significant main effect for TIME $F(2,36) = 8.776$, $p = 0.003$ and a significant interaction between TIME and GROUP $F(2,36) = 3.703$, $p = 0.050$. The main factor GROUP did not reach significance. These results indicate that there is a general increase of SMR amplitude during the training, steadily increasing from t1 to t3. As depicted in Figure 2, only the experimental group increased SMR amplitude, whereas the control group remained at a relatively constant amplitude.

Pairwise comparisons revealed a significant increase in SMR amplitude for the experimental group from t1 to t2 ($T=-3.787$, df 11, $p = 0.003$) and from t1 to t3 ($T=-3.452$, df 11, $p = 0.005$) but no significant difference between t2 and t3. For the PNF group, no significant differences could be observed.

Using relative SMR amplitude as dependent variable revealed no significant results, merely a marginal not significant interaction of TIME and GROUP $F(2,36) = 2.981$, $p = 0.076$ with increased relative SMR amplitude with TIME for the SMR group only.

For the Alpha frequency range, the ANOVA resulted in a significant main effect for TIME $F(2,36) = 8.44$, $p = 0.003$, indicating a steady increase in amplitude from t1, to t2 and t3, but

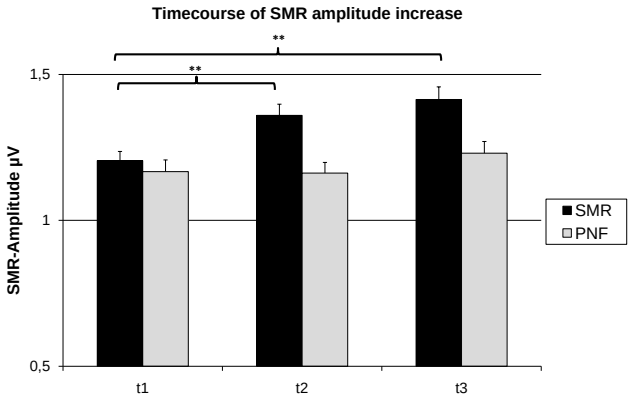

Figure 2: *Significant interaction between TIME and GROUP, indicating that SMR amplitude selectively increased in the SMR-training group, but not in the pseudo-neurofeedback group (PNF). The increase in SMR amplitude in the SMR group is more pronounced for the time interval t1 to t2 as compared to t2 to t3. The PNF group did not show any significant changes in the SMR amplitude. Error bars indicate the standard error of means and asterisks indicate significant increases of SMR amplitude, with respect to t1 at 1% (**) level of significance.*

no main effect for GROUP or interaction has been found. Similarly, the ANOVA for the Beta band revealed only a significant main effect for TIME $F(2,36) = 18.69$, $p <= 0.001$, again indicating a steady amplitude increase from t1, to t2 and t3.

The ANOVA addressing specific changes in the amplitude values for each day between the groups revealed a significant main effect for TIME $F(24,423) = 2.57$, $p = 0.017$, but neither a significant effect for GROUP nor a significant interaction. Figure 3 depicts all the amplitude values for both groups throughout the whole training process.

The 2 ANOVAs focussing on the differences concerning resting amplitude PRE/POST X TIME X GROUP yielded neither a significant main effect for any of the factors nor a significant interaction. However, for eyes open a strong tendency for TIME and GROUP $F(2,36) = 3.219$, $p = 0.060$ could be observed. The result indicates, that in general, the SMR amplitude in the eyes open condition increases only for the training group, but not for the PNF. For eyes closed, no effects were observed.

The ANOVA with the dependent measure MOTIVATION indicated no differences between groups or sessions. The average value of both groups for motivation was 3.73 cm on the visual analogue rating scale indicating a relatively high motivation throughout NFT.

Discussion

As outlined in the introduction, changes in the EEG spectrum in response to a specific NFT are assumed to lead to behavioural changes. In NFT, it is assumed that the relationship be-

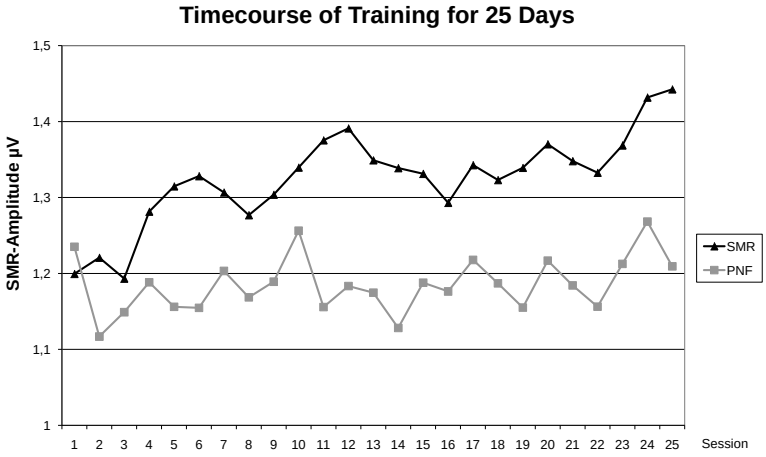

Figure 3: *SMR amplitude for all 25 training sessions is depicted for both groups. Although there is no significant TIME X GROUP interaction, this figure is shown for better presentation of the single day results.*

tween EEG pattern and cognitive processes is causal rather than correlative. Using rTMS to manipulate alpha power preceding a cognitive task Klimesch, Sauseng, and Gerloff (2003) were able to demonstrate this causal relation experimentally. The highly interesting finding was that enhancement of alpha amplitude by the means of rTMS at Fz or P6 lead to increased performance in the requested cube rotation task. These findings clearly demonstrate a functional relation between EEG amplitude and behaviour (at least for the alpha band and cognitive performance).

Given this functional relationship, effective NFT should lead to an alteration in EEG-activity and thereby to behavioural modifications. Similar to the results reported by Hoedlmoser et al. (2008) our results clearly indicate that healthy subjects are able to increase SMR amplitude during training in a rather linear way. The increase of SMR amplitude was more pronounced from t1 to t2, as compared to the time interval t2 to t3. This indicates that the strongest effects of training can be achieved in approximately 12 to 15 sessions, although further training continuously improves the performance. Cho et al. (2008) recently investigated the effects of NFT in the alpha band and reported, well in line with our findings, a significant increase already after the 9^{th} and 11^{th} session.

Analyzing the relative SMR amplitude yielded similar, but marginal non significant results, indicating a clear tendency in the same direction, namely an increase in relative SMR amplitude with training, but only for the SMR-NFT group. The increase of SMR and relative SMR amplitude in our study is not due to any type of placebo effect or other variables, because the PNF group did not show this increase. In ad-

dition this result corresponds to reports from AD(H)D studies documenting a modification of the trained EEG parameters or the ability to learn to modulate SCPs (Kotchoubey et al., 1999; Strehl et al., 2005). Similarly Cannon et al. (2007) found a learning effect in the beta band when subjects had to increase the power in the ACC.

The results for the Alpha and Beta band indicated no group related effects. In both frequency bands, amplitude increased with the number of the trainings. For the Alpha band, this may be interpreted in a way that the subjects were more relaxed, and therefore exhibited higher amplitudes.

However, the question is whether these changes in brain rhythms are stable or disappear within a very short time after the actual training. The analysis of the resting EEG indicated that there is no clear, highly significant change in SMR amplitude over time. However for the resting condition with eyes open, a strong tendency emerged demonstrating an amplitude increase for the SMR group only. This can be interpreted in two ways. Either there is a long lasting effect of the SMR training resulting in generally increased SMR amplitude or this increase in SMR amplitude is situation-specific and occurs only in preparation for (during) and after the training. The fact that this effect was only observed for eyes open, but not for eyes closed, leads us to the assumption that it might be situation-specific. The fact that these findings only reached the 6% level of significance, causes the question whether using more than 25 sessions might show more clear cut results.

The reported tendency of increased resting SMR amplitudes in the SMR group is well in line with reports from clinical samples, where NFT related power changes have been demonstrated to remain for a longer time (Kropotov et al., 2007; Vernon, Frick, & Gruzelier, 2004). Similar to our results, Cho et al. (2008) reported a significant increase in alpha amplitude during a resting condition with eyes open (recorded before each training session).

The main goal of our study was to investigate whether SMR-NFT in healthy subjects is capable of increasing SMR amplitude during the training as well as in resting situations preceding or following the training. We used a control group design to account for placebo effects and compared subjects instructed to increase SMR amplitude with participants who had to increase different frequency bands (PNF). The results clearly indicated that, during the actual training, SMR amplitude steadily increased only in the SMR group, but not in the control group. Therefore, we can conclude that healthy subjects are very capable of learning to increase SMR amplitude in the course of 25 training sessions. For changes in the concomitant resting EEG, the results were less clear. While there was no increase in SMR amplitude for the resting condition with eyes closed, there was a strong tendency for group-specific increases in the eyes open condition.

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Abstract

A. J. Fallgatter, Ch. G. Baehne, A.-Ch. Ehlis, M. M. Plichta, M. M. Richter, M. J. Herrmann, A. Conzelmann, P. Pauli, Ch. Jacob, & K.-P. Lesch (Würzburg) — Impact of COMT Genotype on Prefrontal Brain Functioning in Adult ADHD

The enzyme catechol-O-methyltransferase (COMT) is involved in the degradation of dopamine and has been shown to modulate prefrontal brain function. The *COMT* Met variant displays decreased COMT enzyme activity corresponding to higher concentrations of synaptic dopamine in prefrontal regions of the brain as compared to the Val variant. 200 adult ADHD patients and 115 healthy volunteers were assessed with a 21 channel EEG while performing a response inhibition task. Topographical event-related potential (ERP) measures (centroids) in the P300 time range as well as the NoGo-anteriorisation (NGA), an electrophysiological marker of prefrontal brain function, were determined and checked for an association with *COMT* genotypes. The study aimed at uncovering the impact of *COMT* genotype on prefrontal brain function in ADHD patients and healthy controls. We obtained very different results in a preliminary analysis of 50 ADHD patients vs. 50 healthy controls and in the final analysis of the whole sample: While for the preliminary sample, ADHD patients with assumed low prefrontal dopamine levels displayed a significantly lower NGA as compared to those with a presumably strong prefrontal dopaminergic tone ("gene-dose effect"; Val/Val $<$ Met/Met, p $<$0.01; Val/Met $<$ Met/Met, p $<$0.05), which was in accordance with our a-priori hypotheses, we could not replicate a significant impact of *COMT* genotype on the NGA in the final ADHD sample. In conclusion, the findings obtained from the preliminary study must be considered to reflect a type-I error. This, however, is not likely to result from the smaller sample size per se, since cell-size was sufficient to meet the criteria of the applied statistical tests. Results from studies on the impact of *COMT* genotype (and other polymorphisms) on neural and behavioral measures need independent replication before strong conclusion can be drawn.

Impact of COMT Genotype on Prefrontal Brain Functioning in Adult ADHD

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Introduction

A catecholaminergic dysregulation hypothesis is proposed in at least some neurobiological subtypes of ADHD (Castellanos & Tannock, 2002). But how are the etiology and/or the symptomatology of ADHD affected by variations in catecholaminergic genes? The link between genes and symptoms is not necessarily a direct one, thus endophenotypes may be an adequate concept to uncover the influence of genes in a disorder, as they are correlated with the disease and may be more directly linked to the genetic disposition of an individual than the phenotypic behavior (Almasy & Blangero, 2001). One of the proposed endophenotypes for ADHD is a deficit in response control (Castellanos & Tannock, 2002; Sonuga-Barke, 2002).

Go/NoGo tasks are suited to measure the endophenotype of response control as they require the preparation and execution of responses to predefined target-stimuli (Go) and the inhibition of the anticipated motor response in the non-target condition (NoGo). The NoGo anteriorisation (NGA) is an electrophysiological measure of response control based on Go- and NoGo event-related potentials (ERPs) elicited during a Continuous Performance Test (CPT) (Bokura, Yamaguchi, & Kobayashi, 2001; Fallgatter, Brandeis, & Strik, 1997; Fallgatter et al., 2000; Fallgatter & Strik, 1999). This topographical ERP-parameter (NGA) has been shown to be stable (Fallgatter et al., 1997; Fallgatter, Mueller, & Strik, 1999), highly reliable (short- and long-term test-retest reliability; Fallgatter, Aranda, Bartsch, & Herrmann, 2002; Fallgatter et al., 2001) and to be independent of age and gender (Fallgatter et al., 1999). Topographical ERP measures such as the NGA are suitable to detect effects of genetic variants affecting neurotransmitters, as has already been shown for the serotonin transporter (Fallgatter, Ehlis, et al., 2004) and dysbindin (Fallgatter et al., 2006) gene variants in healthy subjects. Moreover, NGA patterns seem to be altered in ADHD patients. The NGA was found to be reduced in adult patients with personality disorders and ADHD during childhood, whereas patients with personality disorders only did not differ from the healthy control group (Fallgatter et al., 2005).

The functioning of the prefrontal cortex (PFC) is strongly dependent on dopamine (Seamans & Yang, 2004). The COMT enzyme is critically involved in degrading dopamine (and other catecholamines) in frontal brain areas (Grossman, Emanuel, & Budarf, 1992). A common functional single nucleotide polymorphism (Val158Met) in *COMT* (located at 22q11) affects synaptic breakdown of dopamine in the PFC (Chen et al., 2004; Goldberg & Weinberger, 2004). This *COMT* variation is caused by a single base pair change (G $\rightarrow$ A) at amino acid position 158 (or 108 respectively). Valine (Val) is substituted by methionine (Met) (Lotta et al., 1995). This substitution exerts a significant effect on the enzymatic activity of COMT. The Met variant results in a more thermolabile enzyme which catabolizes dopamine less rapidly than the Val variant (Lachman et al., 1996; Lotta et al., 1995). The variants exert a co-dominant effect (Chen et al., 2004). COMT impacts on dopamine degradation primarily in prefrontal brain areas as there is a paucity of dopamine transporters (DAT) in this region (Chen et al., 2004; Gogos et al., 1998).

High activity *COMT* variants seem to be associated with personality characteristics and

diseases that are associated with ADHD or at least exhibit similar features like a higher degree of extraversion (Reuter & Hennig, 2005) or substance abuse (Vandenbergh, Rodriguez, Miller, Uhl, & Lachman, 1997). Patients with 22q11 microdeletion syndrome (which includes deletion of *COMT*) frequently show ADHD symptoms (Gothelf et al., 2003). While some studies support the hypothesis that *COMT* variants are associated with ADHD (e.g., Eisenberg et al., 1999; Qian et al., 2003), other investigations do not (e.g., Barr et al., 1999; Bellgrove et al., 2005; Bobb et al., 2005; Hawi, Millar, Daly, Fitzgerald, & Gill, 2000; Kirley et al., 2002; Manor et al., 2000; Payton et al., 2001; Turic et al., 2005). Concerning cognition and/or behavior, most studies come to the conclusion that Met alleles are more favorable to prefrontal functioning and prefrontally mediated performance (e.g., Bearden et al., 2004; Bilder et al., 2002; Blasi et al., 2005; Frias et al., 2005; Diamond, Briand, Fossella, & Gehlbach, 2004; Egan et al., 2001; Gallinat et al., 2003; Goldberg et al., 2003; Malhotra et al., 2002), while others report more favorable results for Val allele carriers (Baker, Baldeweg, Sivagnanasundaram, Scambler, & Skuse, 2005; Bellgrove et al., 2005), or cannot find an impact of *COMT* on executive function measures (Ho, Wassink, O'Leary, Sheffield, & Andreasen, 2005; Mills et al., 2004; Taerk et al., 2004). Results seem to be task dependent (Bilder, Volavka, Lachman, & Grace, 2004) and also appear to be influenced by the environmental context like ageing (Gothelf, Furfaro, Penniman, Glover, & Reiss, 2005) and are perhaps dependent on diagnosis. We hypothesized that Met allele and Val allele carriers significantly differ regarding their prefrontal cortex function (as indicated by the NGA) due to the modulating effect of dopamine. Due to the assumed involvement of the dopaminergic system in the pathophysiology of ADHD (Swanson et al., 2007), we furthermore expected the exact impact of *COMT* genotype to differ between diagnostic groups.

Methods

Participants

The investigation was approved by the Ethics Committee of the University of Wuerzburg and was in accordance with the Declaration of Helsinki. Over a data acquisition period of about 4 years, a total of 200 adult ADHD (DSM-IV) in- and outpatients of the Department of Psychiatry of the University of Wuerzburg as well as 115 healthy control participants were included in the study after written informed consent was obtained. Patients and healthy controls were interviewed with the Structured Clinical Interview for DSM-IV (SCID-I) and the Structured Clinical Interview for DSM-IV personality disorders (SCID-II) by an experienced psychiatrist for diagnosis and differential-diagnosis of psychiatric disorders. All adult ADHD patients had a history of ADHD symptomatology during childhood according to self-report and Wender-Utah Rating Scale (short version WURS-k validated for a German population, Retz-Junginger et al., 2002).

Exclusion criteria were age below 18 and above 60 years (actual age ranges of the final sample: ADHD group 18–56 years, control group 18–56 years), current medication with methylphenidate or any other ADHD remedy, as well as serious somatic disorders. In the

ADHD group, only one patient was treated with antidepressants (mirtazapine and maprotiline, i.e. a combination of tetracyclic and serotonergic/noradrenergic medication); three other patients received low doses of a benzodiazepine as PRN medication. Excluding these patients from the data analyses did not significantly affect any of the below reported findings. No further medication affecting the central nervous system was administered. Patients and controls were only included in the final data analysis if their EEG data yielded a sufficient number of artifact-free EEG epochs ($>$ 20) and if the error rates for the Go-NoGo task were acceptable (omission and commission errors $<$ 20).

Due to the rather long data acquisition period ($>$ 4 years), an interim analysis was performed after 2 years, when 50 ADHD patients and 50 controls could be included. Following the end of the data acquisition period, the analyses were repeated for the complete sample of 200 ADHD patients and 115 control participants. The results of both analyses are reported below, and differing findings will be discussed.

Within both ADHD samples (n=50 and n=200, respectively), the genotype distribution was in Hardy-Weinberg equilibrium (χ^2_1=0.35, p=0.55 and χ^2_1=1.61, p =0.20, respectively; with 47 % and 49 % Val alleles, respectively) and genotype groups did not differ significantly for the distribution of gender, handedness, or ADHD subtype composition according to DSM-IV (see Table 1a and Table 1b; all χ^2 values $<$ 2.60, $p >$0.35). Similarly, genotype distribution was in Hardy-Weinberg equilibrium for both healthy control samples (n=50 and n=115, respectively: χ^2_1=0.08, p=0.78 and χ^2_1=0.68, p=0.41, respectively; with 50 % and 52 % Val alleles, respectively), and COMT groups, again, did not differ significantly in gender or handedness distribution (all χ^2values $<$ 2.20; $p >$0.30).

Across diagnostic groups, the genetic subgroups were comparable for age and gender distribution, both for the preliminary (gender: χ^2_2 =0.17, p=0.92; handedness: Fisher's exact test p=0.68) and for the final data analysis (gender: χ^2_2 =0.62; p=0.73; handedness: χ^2_2 =0.39; p=0.82). Overall, healthy controls and ADHD patients also did not differ significantly regarding these variables (gender: χ^2_1 =3.25, p=0.07 and χ^2_1=0.90, p=0.34; handedness: Fisher's exact test p=0.70 and χ^2_1=0.23, p=0.63; for the preliminary and final data analysis, respectively). In an ANOVA analysis of the variable "age", main effects of COMT genotype, diagnosis, or the interaction of genotype and diagnosis did not indicate any significant between-group differences, neither for the preliminary (all F-values $<$ 1.25, p-values $>$ 0.3) nor for the final study sample (F $<$0.70, $p >$0.4). Demographics and genotype composition of both samples are listed in Table 1 (a and b).

The Structured Clinical Interview of DSM-IV (SCID-I) (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) and the Structured Clinical Interview of DSM-IV personality disorders (SCID-II) (Fydrich, Renneberg, Schmitz, & Wittchen, 1997) was administered by an experienced psychiatrist for all participants. Controls were only accepted without any axis I or II morbidities. As assessed by means of SCID I interview, 25 ADHD patients of the preliminary and 91 patients of the final sample were diagnosed with a current axis I disorder (see Table 1 a,b for genotype distribution). Co-

Table 1: Demographic Characteristics

(a) Final sample (age: mean (sd), sd=standard deviation; y=years; n=number; %=percentage)

	ADHD				controls			
	all (n=200)	Val/Val (n=53)	Val/Met (n=91)	Met/Met (n=56)	all (n=115)	Val/Val (n=33)	Val/Met (n=53)	Met/Met (n=29)
age, mean (sd), y	34.6 (9.8)	34 (9.3)	34.6 (9.8)	35.3 (10.3)	35.5 (10.3)	35.1 (10.4)	35.3 (9.5)	36.5 (11.7)
Gender, % male	53	45	55	55	47	55	40	52
left handed, n	16	2	8	6	11	4	5	2
axis I disorder, %	46	45	43	50	0	0	0	0
axis II disorder, %	73	68	69	84	0	0	0	0
Attention problems, n	51	13	22	16	0	0	0	0
Hyperactive problems, n	22	5	13	4	0	0	0	0
Combined problems, n	127	35	56	36	0	0	0	0

(b) Preliminary sample (age: mean (sd), sd=standard deviation; y=years; n=number; %=percentage)

	ADHD				controls			
	all (n=50)	Val/Val (n=10)	Val/Met (n=27)	Met/Met (n=13)	all (n=50)	Val/Val (n=13)	Val/Met (n=24)	Met/Met (n=13)
age, mean (sd), y	33.8 (9.8)	37.8 (11.0)	32.1 (9.4)	34.2 (9.6)	34.3 (10.5)	35.9 (11.1)	33.6 (9.7)	34.0 (12.0)
Gender, % male	56	60	59	46	38	39	29	54
left handed, n	3	0	1	2	4	1	2	1
axis I disorder, %	50	30	56	54	0	0	0	0
axis II disorder, %	74	60	74	85	0	0	0	0
Attention problems, n	17	2	10	5	0	0	0	0
Hyperactive problems, n	4	1	3	0	0	0	0	0
Combined problems, n	29	7	14	8	0	0	0	0

morbid disorders were mood disorders (n=8), anxiety disorders (n=8), and substance abuse or addiction (n=9) in the preliminary sample, and mood disorders (n=31), anxiety disorders (n=27), substance abuse or addiction (n=27), OCD (n=1), post-traumatic stress disorder (n=3) and eating disorders (n=2) in the final ADHD sample. In both samples the most common personality disorder (axis II) was histrionic personality disorder (n=17 and n=60 patients, respectively), followed by narcissistic personality disorder (n=12 vs. n=54). In the preliminary sample, a total of 37 patients were diagnosed with at least one comorbid personality disorder, whereas 146 patients of the final ADHD sample fell into this category.

Electrophysiological investigation

For the electrophysiological investigation the participants sat in an electrically shielded, dimly lit room and performed a CPT, while the ongoing EEG was recorded. 400 letters were presented in a pseudo-randomized order one at a time for 200 ms with an interstimulus interval of 1650 ms. Subjects were instructed to press a response button with their right hand whenever the letter O (primer) was followed by the letter X (Go-condition). Even though the response hand (left, right) was not counterbalanced across participants, left-handed subjects did not differ significantly from right-handed ones for any of the behavioral measures (see below; Mann-Whitney $U \geq$219.0, $Z <$1.5, $p >$0.15). Speed and accuracy were equally emphasized. In the stimulus set of 400 letters (12 different letters: A, B, C, D, E, F, G, H, J, L, O, X) there were 114 primer stimuli (O), 57 Go trials (O followed by X) and 57 NoGo trials (O followed by any other letter than X). 172 distractor letters (other letters, or X without a preceding O) completed the stimulus set. Whenever necessary for understanding, the participants first performed a short training session; this was the case in less than 10% of both patients and controls. This CPT version took about 13 minutes. Responses were registered with ERTS software (Experimental Run Time System, BeriSoft Cooperation, Frankfurt/Main, Germany).

Following the protocol established in our previous studies (e.g., Fallgatter et al., 1997, 2005; Fallgatter, Herrmann, et al., 2004), the EEG was recorded from 21 scalp electrodes placed according to the extended international 10-20 system, with three additional electrodes to monitor eye movements. The recording reference was placed between Fz and Cz. Electrode impedances were below 5 kΩ. Recordings were performed with a 32-channel DC BrainAmp amplifier (Brain Products, Munich, Germany) and the software Brain Vision Recorder (version 1.01 b; Brain Products, Munich, Germany). The A/D rate was 1000 Hz and the hardware filter was set to a bandpass of 0.1–70 Hz.

Data analysis

Behavioral data were the number of correctly executed Go trials, the number of button presses after NoGo trials (commission NoGo) and the number of button presses in other trials (after the primer O or any distractor condition, commission). Furthermore, mean reaction times of correct responses as well as the individual standard deviation of reaction times as a measure of response variability were calculated.

Data analysis was performed offline with the

program Vision Analyzer (Brain Products, Munich, Germany). A low-pass filter of 30 Hz was used. After transforming the data to the average reference, a correction for ocular artifacts (Gratton, Coles, & Donchin, 1983) was executed. The data were then segmented according to the Go and NoGo conditions of the CPT (-100 to 700 ms after stimulus presentation). Only trials with a correct behavioral response were considered. Segments were rejected when amplitudes exceeded $\pm 50\mu$V in any of the EEG channels or if the absolute difference of two values in the segment exceeded 200 μV. The maximal allowed voltage step between two consecutive sampling points was 50μV. The remaining segments were finally averaged to one Go and one NoGo event-related potential per subject if each ERP contained at least 20 epochs.

The anterior-posterior location of the positive centroid (the amplitude-weighted center of gravity of the positive brain-electrical field) (Lehmann, 1987) was calculated for the Go ERPs according to the individual P300 peak latency at Pz and for the NoGo ERPs according to the individual P300 peak latency at Cz in a time frame of 277–434 ms (based on the study of Fallgatter et al., 1997). Visual inspection of the grand average curves indicated that this particular P300 time frame was also adequate for the current data set. The centroid locations were quantified by a coordinate system defined by a two-dimensional delineation of the electrode array, with the digits 1 to 5 indicating the electrode positions in the anterior-posterior and the left-right direction, respectively (see Figure 1). As a measure of NoGo-anteriorisation the difference $y_{go} - y_{nogo}$ was taken, since only the anterior-posterior direction is of interest (1 = prefrontal electrode position Fpz, 5 = occipital electrode position Oz etc.; locations somewhere in between two electrode positions were expressed by respective decimal numbers). The NGA therefore represents the geometrical distance between the Go and NoGo centroid on an anterior-posterior axis (see Figure 1).

Genotyping

Genomic DNA was extracted from ethylene diamine tetraacetic acid (EDTA) blood using the QIAamp Blood Kit (Qiagen, Hilden, Germany). Standard polymerase chain reaction (PCR) procedures modified from a previously published protocol (Egan et al., 2001) were used for genotyping COMT Val158Met. Primers were 5'-GGG GCC TAC TGT GGC TAC TC (forward) and 5'-TTT TTC CAG GTC TGA CAA CG (reverse). PCR reactions were performed in a reaction volume of 25 μl, including approximately 50 ng of genomic DNA, 10 pmol of each primer, 2.5 mM of each dNTP, 0.75 mM $MgCl_2$, and 1 U of Taq DNA Polymerase. Annealing temperature was 58˚C (35 cycles). PCR products were digested with NlaIII (at least 3h at 37˚C; fragment sizes wildtype G1947, 114 bp; 1947A variant, 96bp and 13 bp) and subsequently visualized on a 4% agarose gel. G1947 corresponds to the high-activity Val158 allele, while 1947A codes for the low-activity Met variant. COMT allele frequencies for the ADHD group were 47 % Val alleles vs. 53 % Met alleles (Val/Val n=10, Val/Met n=27, Met/Met n=13) in the preliminary sample and 49 % Val alleles vs. 51 % Met alleles (Val/Val n=53, Val/Met n=91, Met/Met n=56) in the final study sample. The allele frequencies for the healthy control group were 50 % Val vs.

50 % Met alleles (Val/Val n=13, Val/Met n=24, Met/Met n=13) in the preliminary sample and 52 % Val vs. 48 % Met alleles (Val/Val n=33, Val/Met n=53, Met/Met n=29) in the final study sample.

Statistical analysis

The behavioral variables considered were not normally distributed (all Kolmogorov-Smirnov $Z >$1.2, all p-values $<$ 0.2). Therefore, Mann-Whitney-U and Kruskal-Wallis tests were used to test differences between the diagnostic groups and between $COMT$ genotypes in the whole sample and in the different diagnostic or genotypic groups. To correct for multiple testing (35 tests, $p <$0.05), Bonferroni correction was performed ($p <$0.0014). Only significant results will be reported.

For the NGA, an analysis of covariance (ANCOVA) was performed with $COMT$ genotype (Val/Val vs. Val/Met vs. Met/Met) and diagnosis (ADHD patients vs. healthy controls) as independent variables. We included age and gender as covariates because several studies revealed a sexually dimorphic (Chen et al., 2004; Domschke et al., 2004; Gogos et al., 1998) or age dependent impact of COMT genotypes (Gothelf et al., 2005). As no age and gender effects on NGA could be shown in this ANCOVA, an analysis of variance (ANOVA) on NGA was performed with the same independent variables. To elucidate significant interaction effects, separate ANOVAs were run for the different diagnostic groups with the independent variable $COMT$ genotype. T-tests were used for post hoc testing as well as for calculating the impact of diagnosis in the different $COMT$ genotype groups. Polynomial regression was used to analyze the possible relationships between the number of met-alleles and NGA for the diagnostic groups separately.

For the Go and NoGo centroid localizations, a 2$\times$3 ANCOVA for repeated measurements was conducted with the within-subject factor condition (Go, NoGo) and the between-subject factors diagnosis and $COMT$-genotype. For the same reasons mentioned above we added the covariates age and gender. The ANCOVA showed no significant impact of the factor gender and only a main effect for the factor age with more anterior centroids in elderly subjects irrespective of condition, which is in line with previous findings (Fallgatter et al., 1999; Pfefferbaum, Ford, Wenegrat, Roth, & Kopell, 1984). We, therefore, conducted and report below the results of a 2$\times$3 ANOVA for repeated measurements. As age showed no differences concerning genotypes, diagnosis or their interaction (see above), the ANOVA for repeated measurements without covariates seemed to be justified.

Post hoc analyses were conducted by ANOVAs separated by condition, genotype or diagnostic group. Significant results were specified by means of two-tailed post-hoc t-tests for matched or independent samples. For repeated measurements ANOVAs, Greenhouse-Geisser correction was used whenever necessary. For t-tests, deviations from variance homogeneity were tested by Levene test and corrections were performed when required.

Results

Preliminary analysis (50 ADHD patients vs. 50 healthy controls)

Performance

Overall comparison between groups showed that ADHD patients made significantly more omission errors (U=750.0, p <0.001) and tended to make more commission errors (button presses after an O or a distractor letter; U=842.0, p <0.0018) than healthy controls. No further difference was statistically significant after Bonferroni correction. For details see Table 2.

ERP data

NoGo-Anteriorisation (NGA)

ADHD patients did not differ significantly from healthy controls in NGA ($F_{1,94}$=1.03, p=0.31; Table 3b). However, in six patients and only one healthy control no NGA could be found. This difference was close to a statistical trend (Fisher's exact test p=0.11).

Across all participants independent of diagnosis, genotype had a significant effect on the NGA ($F_{2,94}$=3.55, p <0.05): Val/Val carriers had a significantly smaller NGA than Val/Met (t_{72} = −2.12, p <0.05) and a trend to a smaller NGA as compared to Met/Met carriers (t_{47} = −1.95, p=0.06), with no significant difference between the latter two groups (t_{75} = −0.51, p=0.61). For uncovering the significant interaction effect of genotype and diagnosis ($F_{2,94}$=4.32, p <0.05), the impact of genotype was tested separately for both diagnostic groups. In the ADHD group, *COMT* genotype had a statistically significant impact on the NGA ($F_{2,47}$=5.25, p <0.01), with significantly higher mean values in Met/Met carriers as compared to patients with a Val/Met (t_{38} = −2.06, p <0.05) or Val/Val genotype (t_{21} = −2.95, p <0.01). A trend for a smaller NGA in Val/Val than Val/Met was found (t_{35} = −1.90, p=0.066). In the control group, no effect of genotype on NGA was detected ($F_{2,47}$=1.68, p=0.20). Based on the polynomial regression, the relationship between the number of Met-alleles and the NGA for the ADHD group can be best described as linear (linear model: $F_{1,48}$=10.89; R^2=.185; b=0.43; p <0.01; quadratic model: F-change < 0.01; b = −0.01; p=0.99; change in significance: p=0.99) and for the healthy control group as quadratic (linear model: $F_{1,48}$=0.02; R^2=.002; b = −0.02, p=0.87; quadratic model: F-change = 3.30; R^2=0.07; b = −0.26, p <0.10; change in significance: p <0.10).

When subdividing the study sample into different genotypes to uncover differences between diagnostic groups, significant results could be found for the Val/Met group with a smaller NGA in the ADHD as compared to the control group (t_{49} = −2.19, p <0.05). In the Val/Val group a trend was pointing to a smaller NGA in the ADHD cohort (t_{21} = −1.82, p=0.08). No significant difference between diagnostic groups was found for Met/Met allele carriers (t_{24}=1.53, p=0.14) (for details see Table 3b and Figure 2).

Centroids In additional exploratory analyses, NoGo centroids were found to be more anterior than Go centroids across the whole study sample (main effect "condition": $F_{1,94}$=202.26, p <0.001; Table 3b and Figure 3). The main effect of diagnosis revealed that overall ADHD patients had more anterior centroid locations compared to healthy controls ($F_{1,94}$=8.86, p <0.01). The main effect of genotype was significant as well ($F_{2,94}$=8.17, p <0.001) with

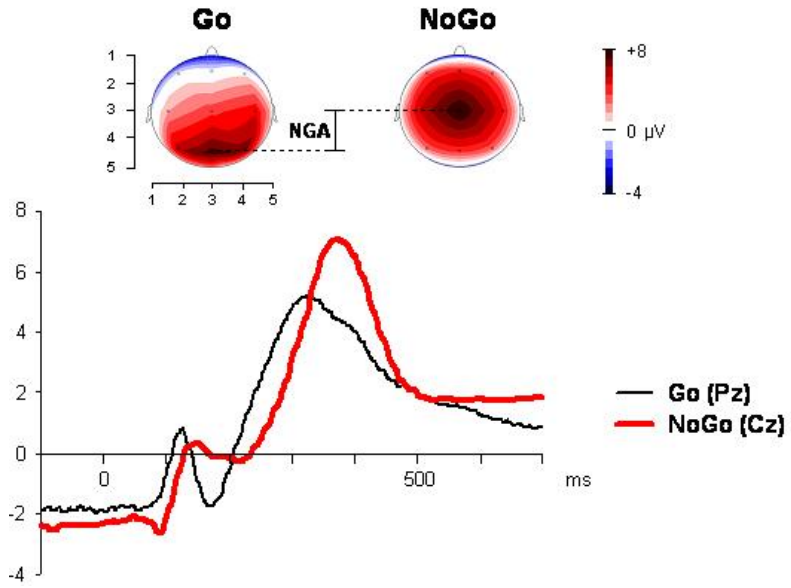

Figure 1: *Grand average curves of the Go (Pz; black line) and Nogo (Cz; red line) condition for the preliminary sample (n=100). Maps illustrate the distribution of the positive brain electrical field at the respective peak of the P300. Schematic illustration of the quantification of the NGA as the geometrical distance between Go and Nogo centroid on the anterior-posterior axis.*

Val/Val allele carriers showing more anterior centroid locations compared to both Val/Met ($t_{72} = -2.56$, $p < 0.05$) and Met/Met allele carriers ($t_{47} = -3.51$, $p < 0.001$).

To further analyze the significant interaction of condition $\times$ genotype $\times$ diagnosis ($F_{2,94}$=4.32, $p < 0.05$), separate post-hoc ANOVAs were conducted for ADHD patients and healthy controls. For the ADHD sample, analyses revealed a significant main effect of *COMT* genotype ($F_{2,47}$=6.68, $p < 0.01$) as well as a significant interaction genotype $\times$ condition ($F_{2,47}$=5.25, $p < 0.01$): Overall, Val/Val allele carriers had significantly more anterior centroid locations compared to both Val/Met ($t_{35} = -2.81$, $p < 0.01$) and Met/Met allele carriers ($t_{21} = -4.65$, $p < 0.001$), but – considering both conditions separately – this genotype effect was found only for the Go centroid ($F_{2,47}$=9.64, $p < 0.001$; NoGo centroid: $F_{2.47}$=1.30, p=0.28). The ADHD Val/Val group had significantly more anterior Go centroids than the Val/Met ($t_{35} = -2.97$, $p < 0.01$) or Met/Met ($t_{12} = -4.66$, $p < 0.001$) group, and patients carrying Val/Met had significantly more anterior Go centroids than Met/Met allele carriers ($t_{38} = -2.32$, $p < 0.05$). Unlike in the patient group, neither the main effect for genotype ($F_{2,47}$=2.09, p=0.14) nor the interaction between condition and genotype ($F_{2,47}$=1.68, p=0.20) led to significant results in healthy controls.

Splitting the sample into different genotype groups and comparing the diagnostic groups for the Go and NoGo condition separately, centroid differences were revealed that appear to

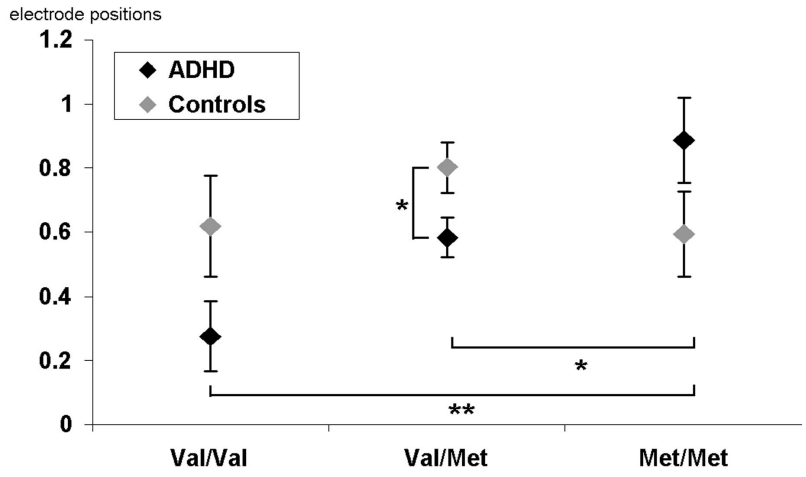

Figure 2: *Effect of COMT genotype on NoGo-Anteriorisation (NGA) separated by diagnostic groups (preliminary sample). NGA is given in electrode positions (y-axis) and error bars represent standard error of the mean. Asterisks represent p-values (*=p <0.05; **=p <0.01). Indicated are the differences between genotypes in the ADHD group and the significant difference between healthy controls and ADHD patients in the Val/Met genotype group.*

underlie the NGA effects reported above: In the Val/Val group, ADHD patients had more anterior Go centroid locations than healthy controls ($t_{21} = -2.59$, p <0.05); in the Val/Met group, this effect was reduced to a statistical trend ($t_{49} = -1.87$, p=0.07). In Met/Met allele carriers the Go centroid did not differ significantly between diagnostic groups (t_{24}=0.11, p=0.92), however, a marginally significant difference was found for the NoGo centroid, with more anterior centroid locations in ADHD patients as compared to healthy controls ($t_{24} = -1.74$, p=0.096).

Final analysis (200 ADHD patients vs. 115 healthy controls)

Performance

Analysis of the final study sample confirmed the finding of a significantly higher number of commission errors (button presses after an O or a distractor letter; U=8554.5, p <0.001) and omission errors (U=8686.0, p <0.001) in ADHD patients as compared to healthy controls. Moreover, the individual reaction times were more variable in ADHD patients than in healthy controls as indicated by significantly larger standard deviations for correct Go responses (U=8062.0, p <0.001). No further difference was statistically significant after Bonferroni correction. For details see Table 2a.

ERP data

NoGo-Anteriorisation (NGA)

In sharp contrast to the above-mentioned preliminary findings, for the final study sample the 2×3 ANOVA conducted to analyze the NGA showed no significant main effects of diagnosis ($F_{1,309}$=1.73, p=0.19) or genotype ($F_{2,309}$=1.11, p=0.33) and no significant interaction between the two factors ($F_{2,309}$=0.19,

Table 2: Performance data

(a) Final sample (all variables: mean (sd), sd=standard deviation, ms=milliseconds, n=number)

	ADHD				controls			
	all (n=200)	Val/Val (n=53)	Val/Met (n=91)	Met/Met (n=56)	all (n=115)	Val/Val (n=33)	Val/Met (n=53)	Met/Met (n=29)
commission errors (O/distractor; n, sd)	1.12 (1.70)	1.17 (1.87)	1.09 (1.40)	1.13 (1.98)	0.47 (0.82)	0.61 (1.03)	0.47 (0.75)	0.31 (0.66)
commission errors (NoGo; n, sd)	0.20 (0.68)	0.09 (0.30)	0.30 (0.80)	0.14 (0.72)	0.13 (0.39)	0.15 (0.36)	0.09 (0.35)	0.17 (0.47)
omission errors (n, sd)	2.02 (3.08)	1.64 (2.73)	2.29 (3.09)	1.93 (3.38)	0.90 (1.59)	1.33 (1.59)	0.53 (1.51)	1.07 (1.62)
reaction time (ms)	494.07 (120.73)	495.12 (113.65)	498.02 (120.23)	486.66 (129.58)	459.27 (111.66)	475.53 (118.66)	448.67 (97.76)	460.14 (128.04)
Sd of reaction times	114.88 (52.15)	114.96 (53.02)	116.06 (52.96)	112.89 (50.85)	89.96 (44.36)	97.79 (53.15)	83.59 (36.60)	92.68 (46.26)

(b) Preliminary sample (all variables: mean (sd), sd=standard deviation, ms=milliseconds, n=number)

	ADHD				controls			
	all (n=50)	Val/Val (n=10)	Val/Met (n=27)	Met/Met (n=13)	all (n=50)	Val/Val (n=13)	Val/Met (n=24)	Met/Met (n=13)
commission errors (O/distractor; n, sd)	1.08 (1.43)	1.70 (1.49)	1.00 (1.52)	0.77 (1.09)	0.36 (0.63)	0.23 (0.44)	0.38 (0.58)	0.46 (0.88)
commission errors (NoGo; n, sd)	0.14 (0.41)	0.00 (0.00)	0.26 (0.53)	0.00 (0.00)	0.06 (0.24)	0.00 (0.00)	0.04 (0.20)	0.15 (0.38)
omission errors (n, sd)	2.56 (3.29)	2.40 (4.03)	2.33 (3.06)	3.15 (3.34)	0.88 (1.73)	0.69 (1.03)	0.83 (1.97)	1.15 (1.91)
reaction time (ms)	488.02 (122.99)	466.12 (127.95)	485.30 (98.17)	510.54 (166.27)	476.87 (116.26)	470.86 (106.61)	460.75 (96.93)	512.63 (154.52)
Sd of reaction times	108.92 (50.90)	99.88 (47.82)	102.14 (43.08)	129.96 (64.75)	89.66 (41.86)	86.41 (50.13)	82.43 (31.50)	106.25 (48.22)

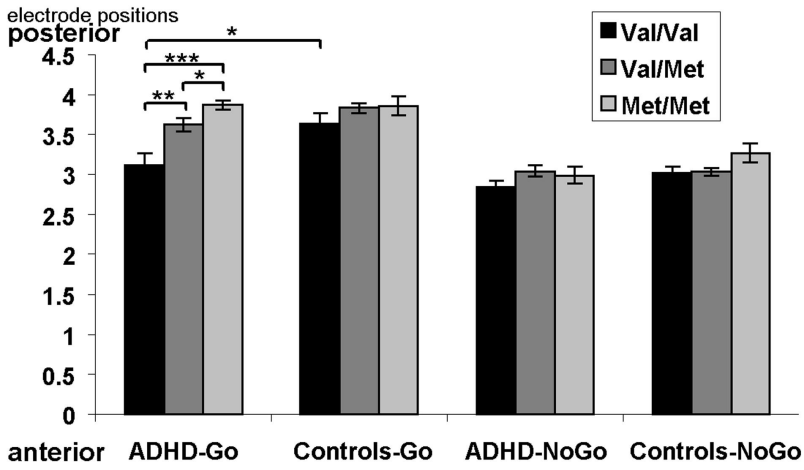

Figure 3: *Effect of COMT genotype on Go and NoGo centroids separated by diagnostic groups (preliminary sample). Centroids are given in electrode positions (y-axis) in anterior posterior direction and error bars represent standard error of the mean. Asterisks represent p-values (*=p <0.05; **=p <0.01; ***=p <0.001). Indicated are the differences in Go centroids between genotypes in the ADHD group and the significant difference between healthy controls and ADHD patients in the Val/Val genotype group.*

p=0.83; see Table 3a). Adding the factors age and gender as covariates did not noticeably change these results (all F-values $<$ 1.70, p $>$ 0.20).

Centroids

The exploratory analysis of Go and NoGo centroids confirmed the finding of more anterior centroid locations in the NoGo as compared to the Go condition across study groups (main effect "condition": $F_{1,309}$=496.97, p <0.001; see Table 3a). Moreover, the main effect of diagnosis again reached statistical significance indicating an overall more anterior centroid localization in ADHD patients compared to healthy controls ($F_{1,309}$=9.18, p <0.01). However, none of the remaining findings reported above could be replicated in the final study sample: Neither the main effect of genotype ($F_{2,309}$=2.03, p=0.13) nor the interaction between genotype and condition ($F_{2,309}$=1.11, p=0.33) or condition, genotype and diagnosis ($F_{2,309}$=0.19, p=0.83) reached statistical significance. In accordance with the above-mentioned findings, no significant interaction effect of genotype and diagnosis could be found ($F_{2,309}$=0.72, p=0.49).

Comparability

To test whether the obvious differences in results between the preliminary and the final data analysis could be attributed to formal differences between the two study samples, we compared both samples for differences in demographic and clinical variables. We furthermore compared the preliminary sample with the subsample of participants additionally included in the final study sample (in both cases separately for patients and controls). We did not find any significant differ-

ences in age (t <1.15, p >0.25), IQ (t <1.15, p >0.25), gender (χ^2 <1.20, p >0.25; except for the comparison of preliminary control subjects and controls additionally included in the final study sample: χ^2=2.85, p=0.09) or handedness distribution (Fisher's exact test p >0.35), or the distribution of COMT genotypes (χ^2 <2.25, p >0.3) for any of these comparisons. Moreover, the different patient samples did not differ significantly regarding their mean BDI (t <0.85, p >0.4) or WURS score (t <0.35; p >0.7), mean number of personality disorders (t <0.20, p >0.8) or the number of patients diagnosed with comorbid axis I (χ^2 <0.55, p >0.45) or axis II disorders (χ^2 <0.05, p=0.85). They were also well comparable regarding their ADHD subtype compositions (χ^2 <2.80, p >0.25).

Discussion

The aim of this study was to investigate the impact of *COMT* genotype on brain functioning in a response control task in adult ADHD patients as compared to healthy controls. Analysis of the behavioral data revealed significant differences in performance between ADHD patients and control participants with patients performing worse. Differences were found in commission errors when participants directly pressed after an O or a distractor letter (= failed inhibition) and in omission errors, perhaps pointing to a more impulsive or inattentive answering style in ADHD. Furthermore, in the final ADHD sample, reaction times were found to be more variable than in healthy control subjects, possibly indicating fluctuations and lapses in attention (Leth-Steensen, Elbaz, & Douglas, 2000; Molen, Somsen, & Jennings, 1996). *COMT* genotype had no significant influence on any of the behavioral measures.

On a neurophysiological level, we obtained very different results for the preliminary analysis of 50 ADHD patients and 50 healthy controls on the one hand, and the final sample of 200 patients and 115 controls on the other hand. Even though general electrophysiological findings could be demonstrated for both samples (more anterior centroids in NoGo than in Go trials, see Fallgatter et al., 1997; more anterior centroids in ADHD patients particularly for the Go condition, (see Baehne et al., 2008, Fallgatter et al., 2005; Fallgatter & Herrmann, 2001), a significant impact of *COMT* genotype on ERP markers of response control was found in the preliminary analysis, but could not be replicated in the final study sample.

Within the preliminary sample of 50 ADHD patients, a linear, gene dose dependent *COMT* effect on the NGA was uncovered: Patients with the most active COMT enzyme and therefore the presumably lowest dopaminergic tone in prefrontal areas (Val/Val) were characterized by the smallest NGA, those with the least active COMT enzyme and therefore the presumably highest dopaminergic tone (Met/Met) had the highest NGA, the heterozygotes lying in between (see Figures 2 and 4; Figure 4 modified from Fallgatter & Lesch, 2007; Goldman-Rakic, Muly, & Williams, 2000). Patients carrying two copies of the Met allele were also characterized by an NGA that was not significantly different from the values obtained in the healthy control sample, whereas the remaining two ADHD groups (Val/Met, Val/Val) showed at least a statistical trend for reduced NGA values. These findings are immediately plausible, as the very same correlation be-

Table 3: Centroids and NGA

(a) Final sample (all variables: mean (sd); centroids and NGA in electrode positions)

	ADHD				controls		
	all (n=200)	Val/Val (n=53)	Val/Met (n=91)	Met/Met (n=56)	all (n=115)	Val/Val (n=33)	Val/Met (n=53)	Met/Met (n=29)
Centroids Go	3.66 (0.48)	3.54 (0.64)	3.70 (0.41)	3.71 (0.41)	3.80 (0.35)	3.76 (0.39)	3.82 (0.30)	3.83 (0.37)
Centroids NoGo	3.07 (0.37)	3.01 (0.36)	3.08 (0.36)	3.10 (0.39)	3.13 (0.30)	3.13 (0.28)	3.09 (0.25)	3.20 (0.38)
NGA	0.59 (0.50)	0.53 (0.62)	0.62 (0.46)	0.61 (0.45)	0.67 (0.38)	0.62 (0.38)	0.73 (0.35)	0.63 (0.43)

(b) Preliminary sample (all variables: mean (sd); centroids and NGA in electrode positions)

	ADHD				controls			
	all (n=50)	Val/Val (n=10)	Val/Met (n=27)	Met/Met (n=13)	all (n=50)	Val/Val (n=13)	Val/Met (n=24)	Met/Met (n=13)
Centroids Go	3.59 (0.48)	3.11 (0.48)	3.63 (0.46)	3.87 (0.21)	3.79 (0.39)	3.63 (0.48)	3.83 (0.31)	3.86 (0.43)
Centroids NoGo	2.99 (0.35)	2.84 (0.24)	3.04 (0.37)	2.99 (0.37)	3.09 (0.32)	3.02 (0.28)	3.03 (0.23)	3.26 (0.43)
NGA	0.60 (0.48)	0.28 (0.50)	0.58 (0.41)	0.88 (0.47)	0.70 (0.38)	0.62 (0.39)	0.80 (0.30)	0.59 (0.49)

tween *COMT* and NGA values has also been reported in a group of patients with disorders from the schizophrenia spectrum (Ehlis, Reif, Herrmann, Lesch, & Fallgatter, 2007). In this study, patients with a Met/Met genotype had a significantly higher mean NGA than patients with a Val/Met or Val/Val genotype. This finding was accompanied by a trend for prolonged reaction times in the interference condition of the Stroop task in Val/Met as compared to Met/Met carriers, which supports the interpretation of an impact of *COMT* genotype on prefrontal brain function in this group of patients. Since both ADHD and schizophrenia spectrum disorders have been associated with abnormalities in dopaminergic neurotransmission within the prefrontal cortex, a similar influence of *COMT* in both diagnostic groups seems convincing. In the preliminary healthy control sample, no significant impact of *COMT* genotype could be found and the relation between NGA and *COMT* genotypes was numerically best described by an inverted u-shape (Mattay et al., 2003; Meyer-Lindenberg et al., 2005) with both homozygote genotypes displaying smaller values of the NGA than the heterozygote genotype (see Figures 2 and 4), even if these differences did not reach statistical significance.

An exploratory analysis of Go and NoGo centroids indicated that it was the Go ERP that was particularly affected by the COMT effect within the preliminary group of ADHD patients, where Val allele carriers showed a significantly more anterior position of the Go centroid as compared to carriers of the Met allele. Since the Go condition is usually associated with relatively little prefrontal activation, this may be due to an ineffective signal processing during correctly performed Go trials (frontal noise) in the ADHD Val/Val group, possibly due to decreased dopamine levels. In this respect, the frontal P300 may be considered a measure of frontal noise including broadband and unselective oscillatory features, even though some correlated signal-like activity might contribute to the frontal P300-component (Baudena, Halgren, Heit, & Clarke, 1995; Ehlis et al., 2007; Winterer et al., 2004). Based on the assumption that the frontal P300 can be considered as an estimator of "neuronal noise" and that dopamine is in part responsible for the reduction of prefrontal noise, Gallinat et al. (2003) compared the fronto-central P300 amplitude in an auditory oddball task for the three *COMT* genotypes in schizophrenic patients and healthy controls. In line with the frontal noise hypothesis and our own data reported above, the group homozygous for the Met allele was characterized by significantly lower frontal P300 amplitudes as compared to Val/Val allele carriers.

In summary, the impact of *COMT* genotype on ERP measures of response control found in our preliminary sample of ADHD patients is in line with previous findings and the study's a-priori hypotheses. Furthermore, the differential impact of *COMT* in ADHD patients versus healthy controls fits recent models on the assumed relation between dopaminergic tone and prefrontal brain functioning (see Figure 4). Our interim analysis of a reasonably large sample of 50 ADHD patients and 50 control participants, therefore, yielded consistent and plausible results.

However, these results could not be confirmed when analyzing the final study sample of 200 ADHD patients and 115 healthy control sub-

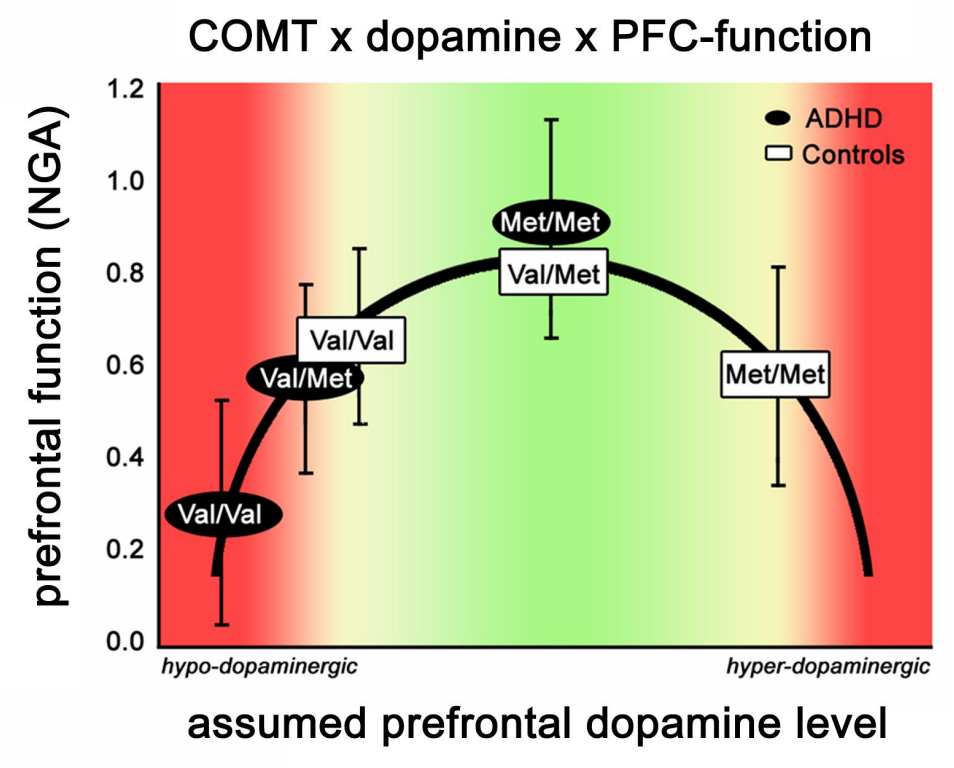

Figure 4: *Hypothetical correlation between prefrontal brain function (as indicated by observed values of the NGA in the preliminary sample; Y-axis) and the hypothesized dopamine concentration (as indicated by COMT genotype; X-axis) in Val/Val, Val/Met, and Met/Met carriers of ADHD patients and healthy controls. Assuming that healthy controls are all located in a normal range of dopamine concentration, it is hypothesized that ADHD Val/Val allele carriers are outside of the optimal range at the lower end of dopamine concentration. ADHD Met/Met allele carriers are presumed to have dopamine concentrations in the normal range.*

jects. In this final analysis, *COMT* genotype was found to have no significant impact on neurophysiological markers of cognitive response control, neither in ADHD patients nor in healthy controls. These very different findings could not be attributed to formal differences between the two samples that were very well comparable regarding numerous demographic and clinical variables (see Results section).

Therefore, it must be concluded that the findings obtained from the preliminary study reflect a type-I error. This, however, is not likely to result from the smaller sample size per se, since cell-size was sufficient for the applied statistical approaches and simulations demonstrated that our statistical analyses were not associated with a type-I-error inflation (data on request). Results from studies on the impact of *COMT* genotype (and other polymorphisms) on neural and behavioral measures need independent replications before strong conclusion can be drawn.

Limitations of our study concern the relatively broad age range that was considered for the present study sample (inclusion criterion: 18-60 years; actual age range of the final sample: 18-56 years) and the high incidence of comorbid disorder. Since the NGA – our primary target parameter – has been shown to be largely independent of the subjects' age (Fallgatter et al., 1999), we do not think that our results were significantly affected by this potential source of variability. Regarding the issue of comorbidity, the frequent occurrence of comorbid disorders is a very common problem in ADHD studies reflecting the actual clinical situation (Kordon & Kahl, 2004; Sobanski, 2006). Nevertheless, it cannot be excluded that our findings were affected by the high incidence of comorbid axis I and axis II disorder. Another critical point concerns the fact that, due to a very strict artifact and error criterion, a total of 30 originally examined ADHD patients could not be included in the data analyses. This might have caused a selection bias since patients with particularly severe symptoms of hyperactivity (prone to cause EEG motion artifacts) and / or inattention (prone to make errors) might have been systematically excluded from the present patient sample, which might have led to a corresponding distortion of the results.

In contrast to our previous study (Fallgatter et al., 2005), we did not find a clear indication of a reduced NGA in ADHD patients. It may be speculated that the clinical symptomatology was more severe in the previous forensic population with severe personality disorders and additional indications for an ADHD symptomatology during childhood (Fallgatter et al., 2005) than in the non-forensic ADHD sample investigated in the current study.

In summary, we did not find any consistent indication of a significant impact of the Val158Met polymorphism of *COMT* on the NGA as a neurophysiological marker of frontal lobe function. A positive finding of a preliminary analysis has to be considered to be the result of a type-I error, which could, however, not be attributed to an excessively small sample size or unequal cell sizes for the three genotype groups. In conclusion, results from imaging genetics studies need independent replication before strong conclusions can be drawn, even with sample sizes that are considered to be reasonably large within imaging genetics literature.

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Ankündigungen – Announcements

- **ISBET Meeting**

  The annual meeting of the *International Society for Brain Electromagnetic Topography (ISBET)* will take place in Kyoto, Japan from September 29 to October 2, 2009.

  Information and Registration at: `http://bfe.kuee.kyoto-u.ac.jp/ISBET2009/index.html`

- **Deutsches EEG/EP Mapping Meeting (DMM)**

  Das *18. Deutsche EEG/EP Mapping Meeting* findet vom 16. bis 18. Oktober 2009 in Schloss Rauischholzhausen statt.

  Angenommen werden freie Beiträge zu Themen der hirnelektrischen Aktivität des Menschen in Form von Vorträgen oder Postern.

  Schwerpunkte

  - Symposium "*Elektrophysiologie kognitiver Veränderungen im Alter*", organisiert von N. Wild-Wall, Dortmund (Sprecher: B. Kopp, Braunschweig, R. Mager, Basel, M. Pietschmann, Berlin, J. Zöllig, Zürich, u.a.).
  - "*ADHD Neurofeedback Research Network Meeting*", organized by D. Brandeis, Zürich/Mannheim and H. Heinrich, Erlangen/München.

  Information und Anmeldung unter: `http://www.med.uni-giessen.de/physio/`