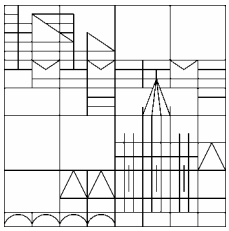

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Cortical and behavioural characteristics of children with developmental disorders – does treatment change the picture?

Dissertationsschrift
Vorgelegt im April 2005 von

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Zur Erlangung des akademischen Grades *Doktor der Naturwissenschaften*

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Zweitgutachterin: Professor Brigitte Rockstroh
Termin der mündlichen Doktorprüfung: 29. Juli, 2005

Für Marie

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Danke.

Christof Bott
Ohne Christof gäbe es diese Arbeit nicht. Abgesehen von seiner hohen Professionalität und Verlässlichkeit, die eine unübertrefflich gute Teamarbeit ermöglicht hat, war die Zeit dank seiner großartigen Persönlichkeit auch noch ausgesprochen schön! Ich hätte mit keinem anderen dieses Projekt umsetzen wollen, einen besseren Kollegen kann man sich nicht wünschen… Das Arbeiten ohne Christof wäre nur halb so motivierend gewesen und hätte nicht annähernd so viel Spaß gemacht. Und vermutlich hätte ich niemals so viele verschiedene Instant-Kaffeesorten kennenlernen dürfen…

Thomas Elbert
Ich danke Thomas dafür, dass er über viele Jahre Vertrauen in mich hatte und mir die Möglichkeit gegeben hat, in unserer großartigen Arbeitsgruppe zu promovieren. Ich danke ihm für das scheinbar selbstverständliche Zur-Verfügung-Stellen aller Mittel und Möglichkeiten – die alles andere als selbstverständlich sind. Ganz besonders danke ich ihm für die Übernahme der Betreuung und Begutachtung meiner Dissertation.

Brigitte Rockstroh
Ohne Brigitte wäre keiner von uns hier. Mit unermüdlichem Engagement hält unsere Chefin diese große Gruppe an Mitarbeitern am Laufen. Darüber hinaus danke ich ihr ganz besonders für viel tatkräftige Unterstützung bei der Entwicklung von Zukunftsperspektiven. Nicht nur das, Brigitte stand immer mit Rat und Tat an meiner Seite. Ich möchte ihr außerdem herzlich für die Übernahme der Zweitbegutachtung dieser Arbeit danken.

Christian Wienbruch
Christian zu danken ist schwierig, da ich gar nicht mehr differenzieren kann, wo ich ihm überall zu danken hätte. Eines ist sicher: Mein Interesse an MEG und Gehirnforschung ist seinem Engagement zu verdanken. Christian ist immer jemand gewesen, den ich wegen allerlei Dinge fragen und um Hilfe bitten konnte, der immer dann zur Stelle war, wenn er gebraucht wurde. Ohne seine Expertise und seine praktische Unterstützung wäre die Auswertung der vielen Kinderdatensätze nicht so problemlos vonstatten gegangen. Kurzum: Alle Worte wären nicht genug, ihm für das zu danken, wofür er Dank verdient.

Ramin Assadollahi
Ramin möchte ich ganz besonders für die tolle Zusammenarbeit an Studie IV danken!

Sabine Heim
Sabine hat viel Vorarbeit geleistet und uns dadurch erst ermöglichst, so effektiv und zügig unsere Studie mit den legasthenischen Kindern durchzuführen. Vielen Dank hierfür und für die vielen wertvollen Ratschläge.

Hermann Kivelitz
Ich danke Herrn Kivelitz für die Anregung der ADHS-Studie und für die Zusammenarbeit.

Claudia, Claudia, Stephan, Sandra, Jonas, Tanja, Johanna
Dank der vielen lieben Kollegen war das Labor nicht nur eine Arbeitsstelle, sondern ein Zuhause (wie man an der immer größer werdenden Ansammlung an Hausrat in unserem Büro erkennen kann...). Mit ihnen zu arbeiten hat Spaß gemacht. Und nicht nur das. Unzählige Kaffeekränzchen, Mittagessen, Ausflüge in die Cafete, sachliche und vor allem unsachliche Gespräche, Musik-Sessions und vieles mehr haben unersetzlichen Freundschaften entstehen lassen.

Ursel, Bärbel, Christiane
Unsere „technischen Assistentinnen“ sind mit dieser Beschreibung nicht ganz treffend bezeichnet. Sie sind nämlich viel mehr als das. Vielen Dank für unzählige Stunden handfester Unterstützung und Hilfe bei kniffligen Problemchen, die nur dank jahrelanger Erfahrung gelöst werden konnten.

...last und ganz bestimmt nicht least...
Vielen Dank all unseren Versuchspersonen, deren Bereitschaft, sich an dieser aufwändigen und zeitintensiven Studie zu beteiligen die Grundvoraussetzung für das Gelingen unserer Untersuchungen war. Natürlich gilt der Dank auch deren Eltern, die ihre Kinder und uns dabei unterstützt haben. Insbesondere möchte ich auch den Schulleitern und Lehrern danken, die durch ihre Aufgeschlossenheit und Kooperation maßgeblich zu der Studie beigetragen haben.

Abstract

This dissertation was motivated by two questions: 1) Do children with developmental disorders have reliable cortical characteristics that distinguish them from control children or that are unique for different disorder-subtypes? 2) Do these cortical characteristics reflect behavioural changes effectuated by an intervention?

Five studies that contribute to answering these questions will be presented and discussed in detail. Study I was dedicated to source localisation of auditory syllable-processing in children with developmental dyslexia and control children. Study II investigated the influence of different training programs on a cortical measure of auditory sensitivity in dyslexia. Study III investigated visual word processing differences between dyslexic and control children. For more detailed insight, study IV investigated the same set of words in skilled adult readers. Study V examined the effect of a stimulant medication on cortical measures of attentional deficit hyperactivity disorder (ADHD) – a disorder that often occurs comorbid with dyslexia.

The results indicate that dyslexia is characterised by (a) more posterior source localisations of speech sounds in right temporal regions possibly resulting from more symmetrical plana temporali and (b) reduced activation and enhanced spectral frequencies following words that require sublexical processing in occipital regions possibly reflecting reduced phonological awareness in dyslexia. Dyslexic children did not differ from control children in their sensitivity for sound changes. Nevertheless, the auditory sensitivity measure was differentially influenced by different intervention programs. It was found that a training of phonological awareness had most effects on cortical and behavioural measures. These findings favour a phonological awareness deficit as general aetiological factor in dyslexia rather than a more basic auditory perceptual deficit.

The results on ADHD suggest different cortical profiles of ADHD subtypes. Children with ADHD of the combined type not only differed from children with ADHD of the predominantly inattentive type, they also responded differently to stimulant medication. The results further propose that good and poor medication responders have differing cortical characteristics. The overall medication effect supports fronto-cortical hypoarousal as a relevant aetiological factor in ADHD.

Zusammenfassung

Diese Dissertation war maßgeblich von 2 Fragestellungen motiviert: 1) Unterscheiden sich Kinder mit einer Entwicklungsstörung in Bezug auf kortikale Charakteristiken verlässlich von Kontroll-Kindern, bzw. unterscheiden sich verschiedene Sub-Typen einer Störung auf kortikaler Ebene voneinander? 2) Bilden sich die Effekte verschiedener Interventionen in einer Veränderung der kortikalen Maße ab? Zur Beantwortung dieser Fragen werden fünf Studien vorgestellt und im Detail diskutiert.

Studie I berichtet die Unterschiede in der Quelllokalisation auditorischer Silbenverarbeitung zwischen legasthenischen und Kontroll-Kindern. In Studie II wird der Einfluss verschiedener Trainingsverfahren auf ein kortikales Maß auditorischer Sensitivität untersucht. Studie III berichtet Unterschiede bei der visuellen Wortverarbeitung zwischen legasthenischen und Kontroll-Kindern. Für ein genaueres Verständnis dieser Mechanismen untersucht Studie IV dasselbe Wortmaterial bei erwachsenen, geübten Lesern. In Studie V wird der Einfluss von Stimulanzmedikation auf kortikale Maße bei Kindern mit einer Aufmerksamkeits-Defizit-Hyperaktivitäts-Ströung (ADHS) untersucht.

Die Ergebnisse weisen darauf hin, dass Legasthenie charakterisiert ist durch (a) rechts temporal weiter posterior gelegene Quelllokalisationen von Sprachreizen, die möglicherweise von einer symmetrischeren Organisation der Plana Temporali herrührt und (b) eine reduzierte Aktiverung und erhöhte Spektralfrequenz-Werte nach visueller Präsentation von Worten, die sublexikalische Verarbeitung erfordern. Dies könnte mit einer reduzierten phonologischen Bewusstheit bei legasthenischen Probanden zusammenhängen. Legasthenische und Kontroll-Kinder unterschieden sich nicht in dem Maß für auditorische Sensitivität. Nichtsdestotrotz wurde dieses Maß von verschiedenen Trainingsverfahren differentiell beeinflusst. Die Ergebnisse deuten darauf hin, dass ein Training phonologischer Bewusstheit die meisten Effekte auf kortikaler und behavioraler Ebene erzielt. Insgesamt favorisieren die Ergebnisse die Hypothese eines phonologischen Verarbeitungsdefizits als allgemeinen ätiologischen Faktor. Sie sprechen eher nicht für eine basalere auditorische Wahrnehmungsschwäche.

Die Ergebnisse bezüglich ADHS deuten auf kortikale Unterschiede zwischen den ADHS Subtypen hin. Kinder mit *ADHS kombinierter Typus* zeigen nicht nur

andere kortikale Charakteristiken als Kinder mit *ADHS vornehmlich unaufmerksamer Typus,* sie reagieren auch in unterschiedlicher Weise auf die Stimulanz-Medikation. Darüber hinaus weisen die Ergebnisse in die Richtung, dass sich auch diejenigen Kinder, die besonders gut auf Medikation ansprechen sich in ihren kortikalen Charakteristiken von den Kindern unterscheiden, die weniger gut auf Mediaktion ansprechen. Der allgemeine fronto-kortikal auftretende Medikamenteneffekt unterstützt die ätiologische Hypothese einer frontalen Unteraktivierung bei ADHS.

Abbreviations

A	alpha
ADHD	attention deficit hyperactivity disorder
AP	training of auditory perception
B	beta
CNS	central nervous system
CPT	continuous performance test
CV	consonant-vowel
D	delta
D2	test of short-term attention
DAT	dopamine transporter
DRT	diagnostischer Rechtschreibtest
DSM IV	diagnostic and statistical manual of mental disorders, 4th edition
ECD	equivalent current dipole
ECG	electrocardiogram
EEG	electroencephalography, electroencephalographic, electroencephalogram
EOG	electrooculogram
ERF	event-related field
ERP	event-related potential
FBA	time-frequency-band analysis
fMRI	functional magnetic resonance imaging
GL	global power
GMA	global mean amplitude
GPC	grapheme-phoneme correspondences
HF	high frequent
ICD 10	international classification of diseases, 10th edition
ISI	inter-stimulus interval
LF	low frequent
LGN	lateral geniculate nucleus
MEG	magnetoencephalography, magnetoencephalographic, magnetoencephalogram
MGN	medial geniculate nucleus
MMN	mismatch negativity
MNE	minimum norm estimate
MPH	methylphenidate
MRI	magnetic resonance imaging
PA	training of phonological awareness
PET	positron emission tomography
PS	pseudo
PT	planum temporale
REML	restricted maximum likelihood
RMS	root mean square
RP	recognition potential
RSVP	rapid serial visual presentation
SLI	specific language impairment
SOA	stimulus onset asynchrony
SPECT	single photon emission computed tomography
SPM	standard progressive matrices
SR	training of spelling rules
T	theta
VWFA	visual wordform area
WCST	Wisconsin card sorting test
ZLT	Zürcher Lesetest

1. General Introduction

This dissertation was motivated by two questions:

1) Do children with developmental disorders have reliable cortical characteristics that distinguish them from control children or that are unique for different disorder-subtypes?
2) Do these cortical characteristics reflect behavioural changes effectuated by an intervention?

Five studies that contribute to answering these questions will be presented and discussed in detail. Study I was dedicated to source localisation of auditory syllable-processing in dyslexic and control children. Study II investigated the influence of different training programs on a cortical measure of auditory sensitivity in dyslexia. Study III investigated visual word processing differences between dyslexic and control children. For more detailed insight, study IV investigated the same set of words in skilled adult readers. Study V examined the effect of a stimulant medication on cortical measures of attentional deficit hyperactivity disorder (ADHD) – a disorder that often occurs comorbid with dyslexia (9-48%, [1]; 40% in males, 20% in females, [2]).

The first question is especially relevant for both dyslexia and ADHD. They share the difficulty of most psychological disorders that diagnostics are solely based on observations of distinctive behavioural features. These distinctive features (e.g. spelling difficulties or inattention) also occur in healthy children – the difference lies in the intensity and appropriateness for the developmental stage a child is in. Diagnostics based on behavioural ratings increase the chance that a child might become falsely diagnosed with a developmental disorder. On the other hand, it is also possible that a child will not be diagnosed despite indication, because the symptoms are considered as “normal” and difficulties are explained by a child´s personality. Therefore, it is necessary to formulate a better understanding of the cortical mechanisms behind developmental disorders. Identification of cortical characteristics might not only be useful for more complementary diagnostics. It also helps to gain better insight in aetiological factors of a disorder. This in turn is critical

for the development of valuable training or remediation programs that focus not only on the symptoms but also the causes.

The second question is relevant for three reasons. First, intervention-induced changes of cortical parameters can be correlated with behavioural improvements. Thus, it can be determined which cortical dynamics are relevant for behavioural changes. Second, intervention-induced cortical changes might also serve as a more objective control of intervention progression than behavioural changes. Finally, varying the focus of intervention and observing the effects on both behavioural and cortical levels can also be an applicative resource for gaining insight in aetiological determinants of a disorder (The latter will be discussed in more detail in chapter 2.2.).

1.1. Dyslexia

1.1.1. Phenotype and diagnostics

Dyslexia is a specific learning disability that is neurological in origin. It is characterized by difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities. These difficulties typically result from a deficit in the phonological component of language that is often unexpected in relation to other cognitive abilities and the provision of effective classroom instruction. Secondary consequences may include problems in reading comprehension and reduced reading experience that can impede the growth of vocabulary and background knowledge (definition taken from the *International Dyslexia Association, USA*). Dyslexia is coded as reading disorder (315.00) and/or disorder of written expressions (315.20) in the DSM IV (Diagnostic and statistical manual of mental disorders, [3]) and as reading disorder with spelling problems (F81.0) or isolated spelling disorder (F81.1) in the ICD 10 (International classification of diseases, [4]). Prevalence estimates range between 2 and 5.6% in Germany [5] and between 6 and 9% the USA [6]. Rutter and colleagues [7] reported results from 4 large-scale epidemiological studies in New Zealand and the UK. Prevalence estimates varied between 8 and 22%, boys being more affected than girls (1.4-3:1). It should be noted, however, that the latter results were only based on reading tests as critical measure. Nevertheless, prevalence estimates in English-speaking countries appear to be higher than in Germany (or Italy [8]). This is very likely the consequence of a more transparent phonology in German

or Italian compared to English, i.e. the letters of the alphabet, alone or in combination, are in most instances clearly mapped to each of the speech sounds occurring in German or Italian, while this is not the case for English [9]. As an example the letter bigram /au/ in the German words *Haus, Maus, Brauch, Auto, Mauer,* etc. is always pronounced as [au], while the letter-string /ough/ in the English words *bough, tough, although, through,* etc. is pronounced differently in each case ([au], [af], [ou], [u:]). Prevalence differences between languages with differing transparancy of phonology already indicate to phonology as a crucial factor for the development of a functioning reading and spelling ability.

1.1.2. Cortical measures of dyslexia

Dyslexic children and adults have been found to differ in cortical measures from control subjects (see [10] for a recent review). First, reduced activity has been found in regions of a ventral reading pathway (left inferior temporal / occipito-temporal). This was the case during letter perception in the MEG, as well as during implicit and explicit word and pseudoword reading in PET studies. Second, reduced activity has been found during rhyming, pronunciation, reading and decision making tasks in PET studies, as well as during phonological processing in the fMRI in left parietal/temporal regions that are part of a dorsal reading path. Finally, decreased activation was revealed in left inferior frontal regions during memory tasks in a PET study. Additionally, increased activation was reported in the same region during phonological processing in the fMRI, as well as implicit and explicit word and pseudoword reading.

More detailed findings from studies investigating cortical mechanisms in dyslexia will be discussed in the chapters 2.1., 2.2. and 2.3. Nevertheless, it already becomes apparent that dyslexia is linked with cortical processing differences in a variety of tasks and regions. Again, the majority of differences seem to be found during tasks that involve phonological processing in one or another way (e.g. pseudoword reading, rhyming).

1.1.3. Aetiology of dyslexia – phonological awareness

By now, it is undisputed that lacking phonological awareness is one of the core deficits in dyslexia [11-13]. Learning to read and write involves the awareness that each grapheme corresponds to a phoneme and vice versa [11]. This is only possible,

if there is explicit knowledge that the sound-stream of spoken language can be sub-divided into distinct units [14, 15], such as phonemes. Phonological awareness therefore denotes the ability to perceive and manipulate the sounds of spoken words [16]. Phonological awareness is not only crucial when reading and spelling is being instructed for the first time in first grade children, it is also necessary in skilled readers when it comes to decoding low frequent words (words that do not occur often in written language). According to dual route models of reading (e.g. [17]), the pronunciation of words can be retrieved in two different ways, depending on the frequency and regularity of a word. High frequent words are more familiar to the reader, as they appear more often in spoken and written language. It is likely that the visual forms of high frequent words are directly associated with their meaning in the same way as images are [18]. Therefore it is possible to read a word at a glance, if it is well-known enough. In contrast, other strategies may be used to decode low frequent words or pseudowords. If a word is not familiar to the reader, it is necessary to phonologically assemble the word from sublexical parts following grapheme-to-phoneme correspondences in order to read and retrieve the meaning correctly.

Tests (and training) of phonological awareness can involve counting or repeating phonemes within a word ("name each sound in *drink*"); the "deletion" of distinct phonemes ("what does /toeb/ sound like without the /b/?"); naming of words with the same initial or last letter; pseudoword repetition; syllable segmentation ("name all syllables in the word *television*"); rhyme tasks ("does *bat* rhyme with *hat*?) or the combination of several scrambled phonemes to form one or more existing words ("make as many words of /r/ /e/ /a/ /d/ as you can"). Muter and colleagues [19] investigated 90 children between 4 and 6 years on tests of letter knowledge, word recognition and phonological awareness in a longitudinal study. Phoneme awareness and letter knowledge were found to be early predictors of word recognition at age 6. The authors interpreted, that children who come to school knowing letters and being able to segment spoken words into speech sounds do better when it comes to reading. In a recent review about phonological awareness [16] it was argued that the nature of that awareness is most likely the ability to perceive and manipulate phonemes (with lower impact of syllabic or rhyme awareness).

Snowling et al. [20] followed the development of at-risk children for dyslexia (children with a family history of dyslexia). Those children, who were going to be classified as dyslexic at age 8 were already impaired on measures pf phonological

awareness and letter knowledge at age 6. Marshall and colleagues [21] tested 17 dyslexic children on tasks of phonological awareness (phoneme deletion, pseudoword repetition) and found them to perform significantly worse than the control group matched for chronological age and even the younger control group matched for reading age. This strongly supports the notion that phonological awareness is not only delayed, but also deficient in dyslexia.

Difficulties with phonological awareness seem to persist into adulthood. Ramus and colleagues [22] tested 16 adult dyslexics with a large test battery including tests of phonological awareness. The authors found that despite individual performance profiles and deficits varied to a great extent, all subjects were impaired at tests of phonological awareness. More evidence comes from a recent study on event related potentials (ERPs) in dyslexic adults [23] and controls. Subjects participated in an auditory lexical decision task with spoken stimuli of which 80% started with a standard phoneme and 20% with a deviant phoneme. A P300 modulation was revealed for deviants in control adults, indicating that the phonological change had been detected. This effect was absent in dyslexic adults. This result suggests that dyslexic adults still fail to detect phonological cues in the same way that normal adult readers do.

There have been many studies showing that phonological awareness training has positive effects on later reading skills in preschool-children and school children (see [24] and [16] for review). However, not so many studies have investigated phonological awareness training in dyslexic children. Schneider and colleagues [25] examined the effects of a phonological awareness training on reading and spelling performance in grades 1 and 2. Training was performed with kindergarten children at risk for developing dyslexia. They found that the trained children at risk showed better reading and spelling performance than a randomly selected control group and that the training program substantially reduced the risk of becoming dyslexic in school. Torgesen and colleagues [26] investigated sixty children with severe reading disabilities who were assigned to instructional programs that incorporated instruction in phonemic awareness and phonemic decoding skills. Although the children only received two 50-minute sessions per day for 8 weeks, large improvements in generalized reading skills that were stable over a 2-year follow-up period could be achieved (effect sizes of 4.4 for one of the interventions and 3.9 for the other).

Effectiveness of phonological awareness training could even be shown in adults [27]. Phonological training led to improved performance at single word decoding and secondary reading skills (reading accuracy) for trained dyslexics compared to un-trained dyslexics. Behavioural improvements were accompanied by signal increases in bilateral parietal and right perisylvian cortices – those left-hemisphere regions being normally activated in skilled readers.

Taken together, it has been shown that dyslexic children and adults have lesser phonological awareness than control children and adults and training this ability seems to positively influence reading skills. This strongly supports the idea of lacking phonological awareness being the major underlying factor in dyslexia. Nevertheless, there is still debate about whether deficient phonological awareness is the consequence of yet another, more basic deficit of auditory perception – a deficit in auditory temporal processing.

1.1.4. Aetiology of dyslexia – auditory temporal processing

Children with dyslexia have been found to show poorer performance than control children categorizing speech sounds [28-31] or distinguishing consonant-vowel (CV) syllables [31]. This might be a result of their deficiency processing stop-consonants [31, 32]. While vowels are constituted of relatively stable, changeless formants, the formants of stop-consonants are characterised by fast frequency changes. These formant transition periods contain all the information needed to identify a stop-consonant and last only for a very short time. I.e. the time range that distinguishes the syllables /ba/ and /da/, for example, only lasts about 40 ms. The idea that something might be wrong in the ability of dyslexic children to process short auditory information has been formulated in the 70ies. Tallal and Piercy [33] found that children with specific language impairments (SLI) have difficulties judging two stimuli as being same or different when the inter-stimulus interval (ISI) was short. While control children were still able to perform the task when stimuli were only about 10 ms apart, SLI children failed at ISIs below ~400 ms. In another study discrimination of vowels and syllables was investigated [34]. Syllables and vowels were 250 ms long. The vowels differed from each other over the whole time range of 250 ms, while the syllables only differed within the first 43 ms. Both, control and SLI children were able to perform the same/different judgement for vowels, i.e. stimuli not being characterised by a short formant transition period. However, SLI children were

impaired judging the syllables. These results were interpreted in the sense that SLI children are selectively impaired processing rapid auditory information. A similar result was obtained for a sample of dyslexic children [35].

Support for these findings was obtained by electrophysiological measures of auditory sensitivity for sound changes (mismatch negativity, MMN [36]). Schulte-Körne and colleagues found both, dyslexic children and adults to have diminished MMN amplitudes after stimulation with syllables [37, 38]. Interestingly, no attenuated MMN amplitudes were found after stimulation with sine tones [37]. However, when a sequence of 4 sine tones was used as standard and deviant stimulus, the two tone sequences only differing in the position of the second and last tone (which had the same frequency), an attenuated MMN was found for dyslexic subjects. Since the only difference between standard and deviant stimuli lay in the temporal structure of the tone-pattern, the authors concluded that temporal auditory processing might be deficient in dyslexia.

Assuming that an auditory perceptual deficit might be the underlying deficit in dyslexia, a training program was developed by Merzenich and Tallal [39, 40], that aimed at improving the perception of rapidly changing auditory information. The training consisted of audio-visual “games” that involved identification and ordering frequency modulated tones and CV syllables. One important aspect of the training was that its adaptiveness to the children´s performance. I.e. the tasks became more difficult when children reacted correctly in three consecutive trials and became more difficult when children made mistakes. Difficulty was modulated by increasing or decreasing ISIs or shortening/lengthening the formant transition period of syllables, and respectively the frequency modulation duration of tone sweeps. After completion of the training, SLI children had improved significantly on the tasks within the training, as well as a test of speech comprehension and phoneme discrimination.

Based on these results, Temple and co-workers [41] measured the magnetic resonance images (MRIs) of 20 children with dyslexia during phonological processing before and after a remediation program analogue to the one described above. The authors found behavioural improvements of oral language and reading performance. Physiologically, children with dyslexia showed increased activity in left temporo-parietal regions and left inferior frontal gyrus, bringing brain activation in these regions closer to that seen in normal-reading children. Further, a correlation between

the magnitude of increased activation in left temporo-parietal cortex and improvement in oral language ability was reported.

Taken together, the findings above speak in favour of an even more basic deficit than impaired phonological awareness in dyslexia. Improving the children´s ability to perceive subtle auditory changes also seemed to improve other language-relevant abilities beyond auditory processing of the trained stimuli. However, based on results described in the following, this view has become more and more challenged.

Another study on the effectiveness of a training program that aimed to improve the ability to detect and identify rapidly changing auditory stimuli was performed by Agnew and colleagues [42]. Children showed improved accuracy on a test of auditory duration judgement following the intervention. However, these improvements did not generalize to reading skills, as assessed by measures of phonological awareness and non-word reading. Mody and colleagues [30] investigated performance of dyslexic children on several tasks requiring auditory judgement. They found that dyslexic children were not impaired on either temporal order judgement or identification of the syllables /ba/ and /sa/ and respectively /da/ and /ʃa/ even at the shortest ISIs of 10 ms. Neither were the dyslexic children impaired to discriminate or identify two complex sounds that had been designed to resemble the structure of the syllables /ba/ and /da/. The authors interpreted that dyslexic children do not generally have an impaired auditory perception. They argued that *"all the supposed difficulties in 'auditory temporal perception' or actual difficulties in perceiving rapidly presented information, so far reported for both reading-impaired and specifically language-impaired children, can be traced to difficulties in stimulus identification."* From this point of view, one might not expect differences in electrophysiological measures of sound *changes*, such as MMN, that do not involve identification of the stimuli. However, attenuated MMN amplitudes have been found in dyslexic samples [37, 38, 43-45]. How can this caveat be explained?

Share and colleagues [46] investigated a large unselected sample of over 500 children over subsequent years. Most importantly, a subgroup of reading disabled children with evidence of temporal deficits did not perform lower on later phonological or reading measures than children with no evidence of early temporal impairment. The authors concluded that although there seemed to be a *concurrent* correlation between temporal deficits and phonological awareness at school entry, early

temporal deficits did not *predict* later phonological impairment, pseudoword processing difficulties, or specific reading disability. Bretherton and co-workers [47] examined forty-two children with developmental reading disability. They were subdivided by their performance on a tone-order task. Average and poor tone-order subgroups were then compared on their ability to process speech sounds and visual symbols, and on phonological awareness and reading. The authors did not find a relationship between performance on the order processing of speech sounds with phonological awareness or more severe reading difficulties. Further, they did not find evidence of a group by interstimulus interval interaction, and thus little support for a general auditory temporal processing difficulty as an underlying problem in poor readers. They concluded that deficient order judgement on a nonverbal auditory temporal order task did not underlie phonological awareness or reading difficulties. Ramus and co-workers [13] investigated 16 adult dyslexics with an extensive test-battery focussing on phonological, auditory, visual and cerebellar deficits. Besides the fact that the profile of performance and individual deficits varied to a great extent across the subjects, they found that all of the dyslexics had problems with phonology, while only 10 of 16 had deficits with auditory processing. They even consider this as a high incidence compared to other studies that typically find 1/3 of dyslexics affected on auditory processing [22]. In accord, Amitay and colleagues [48] investigated 30 reading disabled adults and found that only 6 had difficulties on tasks with high demand on temporal processing while all of them had difficulties with other auditory and visual tasks with no special demand on temporal processing.

It thus appears that given the selectivity of the dyslexic sample investigated, a greater or smaller subset of the subjects will be found being impaired on auditory temporal processing - in agreement with the view that dyslexia is a highly heterogeneous disorder that varies to a great extent in strength and expression [10, 49]. Further, there does not seem to be a causal relationship between deficient auditory temporal processing and phonological skills, even in the children who do show auditory perceptual deficits. It therefore might be concluded that deficient audition *can* lead to poor phonology, but poor phonology is not a consequence of deficient audition.

1.1.5. Aetiology of dyslexia – multimodal temporal processing

The attempt has been made to link dyslexia with an even more basal deficit that is not restricted to the auditory domain [50]. The theory is based on the assumption that there are two types of cells in the visual system forming parvo- and magnocellular paths (e.g. [51]). While the magnocellular system is sensitive for stimuli with a high temporal but a low spatial resolution, the parvocellular system is sensitive for stimuli with high spatial and low temporal resolution. Since the magnocellular system is thought to predominantly process stimuli with high *temporal* resolution, this system was thought to be deficient in dyslexia [50, 52].

Given the findings described above that profoundly question the role of a general auditory perceptual deficit as the underlying cause of dyslexia, it is not surprising, that the magnocellular theory could not be confirmed in dyslexia. Skottun and colleagues [53] reviewed results from studies investigating the magnocellular system in dyslexia. 4 of 22 studies found support for a deficient magnocellular system in dyslexia. However, these results were outnumbered both by studies that found no loss of sensitivity and by studies that found contrast sensitivity reductions that are inconsistent with a magnocellular deficit. The authors thus concluded that the majority of studies on contrast sensitivity was highly conflicting with regard to the magnocellular system deficit theory of dyslexia.

1.1.6. Aetiology of dyslexia – genetics

It seems that the risk for developing dyslexia is higher in families with one or more dyslexic members (see [54] for overview). This might be a hint towards a genetic contribution, but it could also foster the view that the environment has a strong influence on the development of dyslexia. Thus, it is advisable to investigate differences between monozygotic and dizygotic twins. Two studies with large samples following this purpose were the Colorado Twin Project (e.g. [55, 56]) and the London twin study [57]. Heritability of spelling difficulties was reported between .53 and .75%, heritability for word reading difficulties around .50%. Phonological coding was reported to have a heritability of .36 - .86% (see [54]).

Linkage of dyslexia to several chromosomes was found, yet chromosome 6 and 15 seem to be the most likely candidates [58-60]. It still remains unclear, however, which components of the dyslexic phenotype are linked to which chromosome. It also remains unclear, what the mechanisms of heritability might be

[61]. In accordance to its heterogeneous phenotype, dyslexia appears to be a genetically heterogeneous and complex trait that cannot be inherited in the classical mendelian way [10, 62].

Taken together, there seems to be a substantial genetic factor in dyslexia. Nevertheless, there is no “dyslexia-gene”, that will determine if a child develops a reading and spelling disorder. It also remains unclear, what influence on development is eventually exerted by chromosomal anomalies.

1.1.7. Conclusion

From the current literature it seems that lacking phonological awareness plays a major role in the development of dyslexia. An auditory temporal processing deficit cannot be assumed as the general underlying cause, yet it does seem to be present in a subsample of dyslexic children and adults. Ramus [63] proposed an aetiological model of dyslexia (see fig. 1.1.1, modified following [63]). He proposes that in the majority of children (left side, solid ellipses) genetic influences cause anomalies in left hemispheric perisylvian regions. These anomalies in turn are assumed to cause poor phonological awareness, grapheme-phoneme matching, verbal short term memory and slow lexical retrieval being manifested in slow automatic naming, a poor digit span, poor performance at spoonerism tasks (exchanging letters of words) and distorted reading ability on the behavioural level.

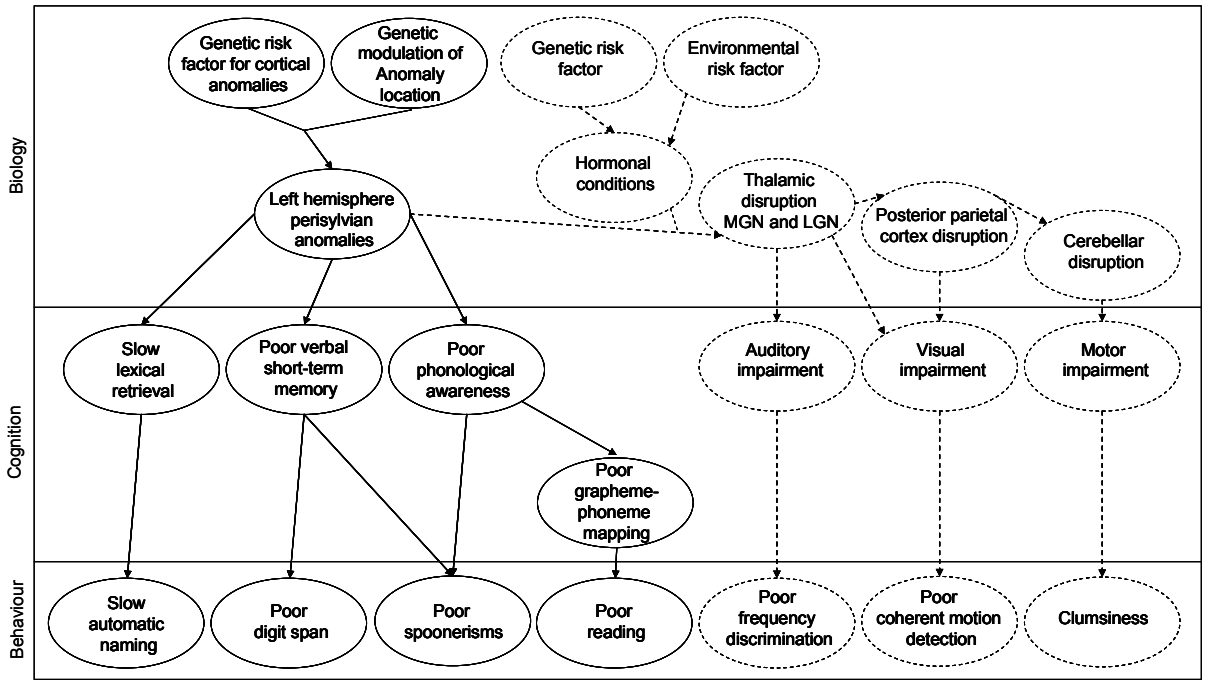

Fig. 1.1.1: Aetiological model of dyslexia proposed by Ramus, 2004

In some children (right side, dashed ellipses) genetical factors are assumed to influence hormonal conditions which in turn might lead to a disruption of the thalamic lateral geniculate (LGN) and medial geniculate (MGN) nuclei. The latter nucleus projects to auditory cortical areas and has been found to be morphologically anomalous in dyslexia [64]. The LGN projects to visual cortical fields and has also been reported to show anomalies in cell structures [65]. Ramus proposes that disruption of LGN and MGN functioning leads to impaired auditory, visual and motor processing manifested in poor frequency discrimination, coherent motion detection and clumsiness on the behavioural level.

This model might apply to explain different phenotypes of dyslexia and is also able to explain the existence of auditory and/or visual deficits in some children but not in others. Nevertheless, it is necessary to gain more insight into the mechanisms that determine the phenotype of a child as well as into the interactions between the different aetiological factors. It should be further determined, how to better identify children with deficits in auditory perception and other pan-sensory deficits. This is of interest, since children with “pure” phonological dyslexia and those with more basic deficits are possibly in need of differential interventions in order to be helped optimally in the long run.

1.2. ADHD

1.2.1. Phenotype and diagnostics

Children and adults with ADHD have symptoms like restlessness, inattention or impulsivity. They cannot sit still, wait their turn and often interrupt other people. It is difficult for them to stay attentive over a longer period of time or to focus attention on the information being most relevant. Both, DSM IV and ICD 10 distinguish between three types of the disorder: a predominantly hyperactive type (codes 314.0 and F98.8), a predominantly hyperactive type (codes 314.01 and F90.1) and a combined type (codes 314.01 and F90.0). ADHD often is comorbid with other disorders like dyslexia (9-48%, see above) or depression (31.6% in children and 63% in adults [66]). The prevalence of ADHD is estimated between 4 and 12% among elementary school children [67] with the majority of children meeting criteria for the combined or

predominantly inattentive type [68]. Boys are more affected than girls (ca. 3:1, see [69] for review). It is noteworthy, however, that in a study examining DSM IV criteria for ADHD [68], *16%* of the sample qualified for a diagnosis when functional impairment was *not* incorporated in the diagnostics in comparison with *6.8%* when impairment was accounted for. Likewise, Scahill and Schwab-Stone [70] reviewed results of 13 prevalence studies between 1985 and 2000 and found prevalence estimates between 2 and 14.9% being particularly high when DSM IV criteria without impairment measures were used.

Children with ADHD have been reported to perform worse on several neuropsychological measures (see [71] for an overview). Besides the obvious difficulty in sustaining attention at tasks like the Continuous Performance Test (CPT), children with ADHD have been found to perform particularly bad at tests of response inhibition such as stop tasks (a response has to be made following a stimulus unless there is a signal indicating to stop the response for 1 trial) [72, 73] or the stroop task [74]. They also seem to be impaired at tasks involving set-shifting such as the Wisconsin Card Sorting Test (WCST) [75]. Most reliable differences between ADHD and control children have been found for the CPT, stop tasks and choice-delay tasks (children repeatedly choose between a large delayed reward and a smaller immediate reward) [71].

These findings support the idea that one underlying aetiological factor in ADHD might be a dysfunctional inhibitory [76] and executive [77] system, likely localised in frontal cortical regions [69, 78].

1.2.2. Cortical measures of ADHD

As revealed by SPECT studies, ADHD seems to be related to an increased number of dopamine reuptake receptors leading to a decreased level of dopamine in the synaptic cleft [79, 80]. In accordance, Zametkin and colleagues [81] found decreased bloodflow in prefrontal and premotor areas in a sample of ADHD adults. Several EEG studies [82-84] have shown that ADHD children are characterised by increased slow-wave activity (Delta 1.5-3.5 Hz and Theta 3.5-7 Hz), which is also interpreted as cortical underarousal (see [85, 86] for reviews on EEG measures of ADHD). This hypoarousal has particular meaning in connection with frontocortical inhibitory mechanisms. Inhibition is essential for stopping planned or initiated actions, to protect a processing mechanism from internal or external interference, or to delay a reaction

[87]. Response inhibition has been measured in stop designs (see above). The frontally dominant N2 component in the event related EEG potential (ERP) is normally larger for stimuli where a behavioural response (like a button press) is supposed to be suppressed in comparison with stimuli, where a behavioural reaction is supposed to be shown. This is especially the case in subjects with good response inhibition [88]. In ADHD subjects, N2 amplitude has been found to be reduced, which consequently has been interpreted as disrupted inhibitory control [89, 90]. In line with these results, frontal and prefrontal areas have been found to be underactivated during inhibition tasks in an fMRI study with ADHD subjects [87]. Another ERP component – the P2 – also seems to distinguish control and ADHD subjects. P2 can be evoked in oddball paradigms (a *standard* stimulus constitutes 80-85% of all stimuli, a *deviant* stimulus 15-20%). It has been found that deviant stimuli [91-93] and respectively standard *and* deviant stimuli [94] are related to higher P2 amplitudes in ADHD subjects compared to controls. Elevated P2 amplitudes have been explained by atypical inhibition of sensory stimuli. An increased P2 for standard stimuli in ADHD might reflect that standard stimuli - being relatively unimportant compared to deviant stimuli – are processed without competition. The P3 component (evoked in oddball paradigms with selective inhibition) has found to be reduced in ADHD. This was interpreted as abnormal allocation of processing capacity [95], deficient memory mechanisms [91] or an attentional deficit [92].

1.2.3. Aetiology

It has already become clear that a disturbance of inhibitory and executive functions play a major role in ADHD. This disturbance is reflected on both, behavioural and cortical levels. ADHD symptoms can be effectively decreased by the psychostimulant drug *methylphenidate* (MPH) [96]. MPH is known to be a potent blocker of the dopamine receptor DAT [79] that seems to act primarily in the fronto-striatal system [80]. Given the greater density of DAT receptors (see [97] for review) resulting in lower dopamine levels, it appears that ADHD is characterised by a form of dopamine deficiency despite efficient dopamine production. MPH remediates this state by blocking dopamine reuptake.

Lou and colleagues [98] showed in their SPECT pioneer study that unmedicated ADHD subjects had reduced bloodflow in frontal regions as well as enhanced bloodflow in motor areas. After application of MPH, this pattern normalized.

Niedermeyer [99, 100] interpreted these findings as support of the “lazy frontal lobe” hypothesis underlying ADHD. He argues that the prefrontal cortex – being hypoactive in ADHD - is not only involved in allocation and sustaining attention (e.g. [101, 102]), but also in inhibiting motor activity. Support for this idea comes from Langleben and colleagues [103]. They performed a SPECT study with ADHD children who were on and off MPH. When the subjects were not taking MPH, bloodflow was higher in motor, premotor, and the anterior cingulate cortices. The authors concluded that brief discontinuation of MPH treatment is associated with increased motor and anterior cingulate cortical activity. Thus, it appears that if the prefrontal cortex is underactivated, both attentional processes and the inhibition of the motor cortex will be diminished.

Based on the findings that EEG activity is slowed in ADHD, a hypoarousal theory of ADHD has already been formulated in the 1970ies [104]. In line with this, several studies have shown that slow wave activity diminishes with application of MPH [84, 105, 106], P3 amplitudes (reflecting attentional processing) increase [107, 108] and N2 amplitudes (reflecting inhibitory processes) increase [109].

Twin studies have revealed very high heritability estimates for ADHD ranging between 75 and 98% (see review [69]). Nevertheless - as in dyslexia - the mode of inheritance remains unclear. Candidates for genetic influence might be the 10-repeat allele on chromosome 5 [110] and the 7-repeat allele on chromosome 11 [111]. The first locus was found to be related to the dopamine reuptake receptor DAT, the latter locus has been linked with the dopamine sensitive receptor D4. Similar to the DAT receptor, D4 was located primarily in the frontal cortex [112].

Given the results described above, a model for ADHD could look like figure 1.2.1: a strong genetic factor influences development of dopamine receptors (increased number of DAT receptors, reduced sensitivity of D4 receptors). This leads to a frontocortical dopaminergic dysfunction resulting in hypoarousal of the cortex which in turn results in a malfunctioning executive and inhibitory system.

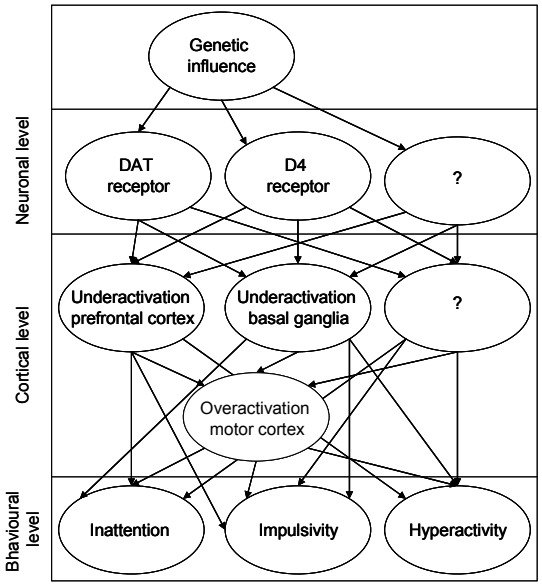

Fig. 1.2.1: Aetiological model of ADHD

The model proposed above would only hold true for ADHD children of the combined type. Parts of it might also hold true for the other subtypes. Yet, it is difficult to further elucidate this question from the current state of literature.

It still remains unclear, if the three ADHD subtypes are different expressions of the same disorder, or if they are different in nature. Given that some children do not show signs of hyperactivity (predominantly inattentive type) or signs of inattention (predominantly hyperactive type), it seems plausible that they do not have the same underlying deficits. Before the background of vast literature on ADHD in general, very little research has dealt with this question. Clark and colleagues [113] found that predominantly inattentive ADHD children are more similar to control children than combined ADHD children in terms of their EEG power spectrum characteristics. The authors thus conclude that predominantly inattentive ADHD children are less affected than ADHD combined children. This rather unspecific finding does not add information to the question of subtype-aetiology, however.

2. Studies[1]

2.1. Study I: *Reduced hemispheric asymmetry of the auditory N260m in dyslexia*

2.1.1. Background Study I

Dyslexia has been related to an atypical organisation of auditory cortical areas. Heim and colleagues [114] measured event related fields (ERFs) after auditory speech stimulation and found more posterior source localisations of the N100m in the right hemisphere for dyslexic adults and the P100m in children [115] compared to control subjects.

Typically, right hemispheric sources of auditory processing are found to localise more anterior to sources in the left hemisphere in normally literate subjects [116-119]. This has generally been explained with morphology differences of the planum temporale (PT) between the two hemispheres. The PT is located in the supratemporal cortex, posterior to Heschl´s gyrus within the Sylvian fissure. The left planum is larger than the right planum in adults (see [120, 121] for reviews) and children [122, 123]. This asymmetry increases during adolescence [124] and has therefore been linked to hemispheric differences in white matter maturation [125].

Although questioned by some authors [126, 127], PT asymmetry was found to be reduced or even reversed in dyslexic populations [128-132]. Eckert et al. [133] showed that PT asymmetry was correlated with phonological and verbal skills, i.e. children with more symmetrical PT performed lower in verbal tests. The authors note that mainly the size of the *right* PT predicted task performance: right PT size was negatively correlated with phonological skills. A lack of PT asymmetry has also been reported for children with specific language impairment [134, 135], which is considered to widely overlap with dyslexia in phenotype and aetiology [136].

The planum temporale is part of Wernicke´s area and is considered to be dedicated mainly to language processing [137]. Yet, it has also shown to be active during stimulation with non-speech sounds [138, 139]. Jäncke et al. [140] point out that the PT might not be solely sensitivity to speech but rather to any kind of sounds

[1] Studies I to III are based on the same sample of children. Due to better understanding and due to differing artefact-exclusion criteria, the composition of the sample is described in each individual chapter. The same data set was used for other analyses in the dissertation “Differentielle Effekte verscheidener Trainingsverfahren auf behaviorale und neurophysiologische Parameter bei Kindern mit LRS“ by Christof Bott, 2005.

containing fast frequency changes. Several functional imaging studies (using fMRI or PET) have revealed activation differences between dyslexic and control subjects in the PT and adjacent areas. Brunswick and colleagues [141] reported reduced activity in the Wernicke area for their dyslexic sample during loud and silent reading. Further, dyslexic subjects had a lower level of activation in temporo-parietal and other perisylvian areas during phonological tasks [126, 142, 143]. Shaywitz and colleagues [144] measured cortical activation during 5 tasks with increasing demand on phonological decoding. Control subjects showed an activity increase in Wernicke area, angular gyrus and striate cortex corresponding to phonological demand. This activation increase was not found for the dyslexic subjects. Thus, while dyslexics and controls did not differ in activation during visual, non-phonological tasks, they did differ during phonological tasks.

Group differences in the studies described above were mainly found in left hemispheric regions. However, the right hemisphere has also been reported to be deviant in dyslexia. McCrory et al. [145] found reduced activity in right superior temporal and post central regions for dyslexic subjects during repetition of words and pseudowords. The authors explain this right hemispheric underactivation as a decreased processing of non-phonetic speech aspects thus allowing the allocation of more processing capacitiy towards (left hemispheric) phonological language aspects.

To summarise, dyslexia seems to be related to a lack of PT asymmetry that is accompanied by functional differences to control subjects in both left and right hemispheric temporal regions during language tasks.

There is little research on localisation of auditory ERFs or event related potentials (ERPs) making use the more timing-sensitive measures of MEG or EEG. To our knowledge Heim et al´s experiments [114, 115] have been the only ones so far investigating differences in source localisation after speech stimuli between dyslexic and control children. They found localisation differences for the N100m component in adults, the P100m component as well as the M210 response in children. These results have been interpreted as a reflection of atypical PT symmetry or the recruitment of other structures than the PT for speech processing.

The aim of ***study I*** was to replicate and extend these findings by using a larger sample of dyslexic (n=64) and control children (n=22) within a narrower age range (8-10 years). The latter aspect is of importance, since the morphology of ERPs and ERFs is subject to developmental changes throughout childhood [146-150]. We

measured cortical activity during an auditory oddball-paradigm in the MEG and localised ERF sources evoked by the standard stimulus /ba/. Our results suggest that localisation of ERF components is indeed an applicative tool for investigating cortical deviances in dyslexia.

2.1.2. Methods Study I

Generation of the sample and behavioural tests

The participating children were contacted through 14 primary schools in or around Konstanz, Germany, and attended either 3rd or 4th grade. Schools were asked to name children with massive problems reading and spelling, as well as children without any such difficulties. In order to objectively classify the children to be dyslexic, all children underwent a test-battery that was designed to assess a variety of abilities ranging from spelling and reading to phonological abilities (*DRT* (Diagnostischer Rechtschreibtest 3rd grade [151]; 4th grade [152]): Standardized spelling test; *ZLT* (Zürcher Lesetest [153]): Standardized reading test; *SPM* (Standard Progressive Matrices, German version [154]): non-verbal IQ-test; non-standardised *Word reading*: List of words with increasing difficulty to be read aloud; non-standardised *Pseudoword reading*: List of pseudo-words with increasing difficulty to be read aloud; *Mottier-Test* [155]: Pseudowords with increasing difficulty are read aloud by the experimenter and are to be repeated by the child; *Dictation* [156]: only words were used that are spelled as one “hears” them, i.e. no knowledge about spelling rules or exceptions is necessary; *Categorical perception* [157]: judgement, if a syllable sounds more than “ba” or “da”, when the formant transition period of the syllable is varied on a ten-item continuum[2]). If a child, who was suggested to be dyslexic by the teacher, was not significantly worse than the norm-sample in the standardized spelling test, he/she was excluded from the study. Control children who performed significantly worse than the norm sample in the spelling test were either excluded or classified as dyslexic.

[2] Item 1 on the 10-item continuum represents a clear /ba/, item 10 a clear /da/. Categorical perception performance is quantified by the following formula with ai representing the number of responses for /ba/ and bi the number of responses for /da/. A high categorical perception index indicates reliable and correct categorisation of /ba/ and /da/.

$$f = \sqrt{\sum_{i=1}^{10}(a_i - b_i)^2}$$

Subjects

Altogether, 64 children with dyslexia and 22 children without any reading or spelling deficits participated in the study. Table 2.1.1 shows the number of subjects per group, handedness and gender distributions.

Table 2.1.1: Demographic information

Group	N	Age in years	Handedness l=left, r=right	% Right-Handers	Gender f=female, r=male	% Male
Dyslexic	64	9:5	9 l, 55 r	85	19 f, 45 m	70
Control	22	9:6	1 l, 21 r	96	8 f, 14 m	64

Table 2.1.2 depicts that test performance of the dyslexic children was below test performance of the control children in all measures.

Table 2.1.2: One way ANOVAs of dependent variables SPM, DRT (T-values); ZLT Correctness, Word Reading Correctness, Pseudoword Reading Correctness, Mottier Test, Dictation (% correct); Word Reading Time, Pseudoword Reading Time (seconds); ZLT Reading Time (seconds/no words); Categorical Perception (Index) and GROUP (control, dyslexic) as between group factor

	SPM	DRT	ZLT Correctness	ZLT Reading time	Word Reading Corectness	Word Reading Time	Pseudoword Reading Correctness	Pseudoword Reading Time	Mottier Test	Dictation	Categorical Perception
Control	62.2	57.8	96	0.67	90	72.5	75	115.4	83	93	30.7
Dyslexic	51.4	36.8	87	1.41	74	166.7	52	216.3	66	75	24.6
F (1,84)	14.65	213.14	23.58	24.58	33.60	33.40	38.79	15.13	22.51	40.50	16.15
p	0.0002	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0002	<0.0001	<0.0001	<0.0001

Stimulation in the MEG

Two synthesized consonant-vowel (CV) syllables /ba/ and /da/ were used for auditory stimulation in an oddball task. Both syllables were 250 ms long with a 40 ms formant transition period in the beginning that encoded the consonant information and thereby distinguished the syllables. For both syllables the fundamental frequency of formant F0 was 128 Hz with a linear decline to 109 Hz towards the end of the stimulus. The formant frequencies for the vowel /a/ (which was also the same for both syllables) were 770, 1340 and 2400 Hz for F1, F2 and F3, respectively. Starting frequencies for the formants F2 and F3 were 1365 and 2337 Hz for /ba/, 1567 and 2515 Hz for /da/. Therefore, the only acoustical difference between the syllables was between formants F2 and F3 within the first 40ms. Syllable /ba/ was used as standard stimulus, /da/ was used as deviant. All in all 500 stimuli were presented with

a constant ISI of 500 ms. Occurrence rates were 85% and 15% for /ba/ and /da/, respectively. Stimuli were presented pseudo-randomly. Deviant stimuli were not analysed, neither were data epochs with standard stimuli occurring directly after a deviant. Stimuli were presented 60 dB/SPL above the individual hearing threshold.

MEG Recordings

Recording was done with a 148-channel magnetometer (MAGNES™ 2500 WH, 4D Neuroimaging, San Diego, USA). Subjects were lying supine in a comfortable position in the magnetically shielded room (Vakuumschmelze Hanau). Auditory stimuli were presented through ear tubes 60 dB/SPL over the individual hearing level. For artefact control, eye movements (EOG) were recorded from four electrodes attached to the left and right outer canthus and above and below the right eye, as well as cardiac activity (ECG) via two electrodes, one on each forearm. A SynAmps amplifier (NEUROSCAN) served for the recording of EOG and ECG. A video camera installed inside the chamber allowed monitoring the subject's behaviour and compliance at any time throughout the experiment.

Subjects were instructed to not pay any attention to the syllables they would here. To distract attention, a silent video was screened onto a white projection field at the ceiling of the chamber using a video beamer (JVC™, DLA-G11E) and a mirror system. Data were recorded with an online high-pass filter of 0.1 Hz and a sampling rate of 508.63 Hz (bandwidth 100Hz). Recording was continuous.

Data Analysis

Data were noise-reduced and corrected for cardiac activity. For each subject data epochs with a 200 ms baseline and a post-trigger window of 800 ms were analysed. Epochs containing artefacts (signals > 120 µV in the EOG and signals > 5pT in the MEG-channels) were rejected. Epochs containing the deviant stimulus as well as epochs following the deviant stimulus were not analysed. The remaining epochs were averaged. The resulting average files were 20 Hz low-pass-filtered and baseline corrected. Single equivalent dipoles (ECDs) were fitted for the average-files, one per sampling-point in each hemisphere (using software provided by 4D Neuroimaging, San Diego, USA). ECDs were free in location and orientation (moving dipoles). Following channel groups were used for analysis (Fig. 2.1.1): Standard left and right

channel groups were chosen, since they are considered to cover most temporal activity.

left and right temporal

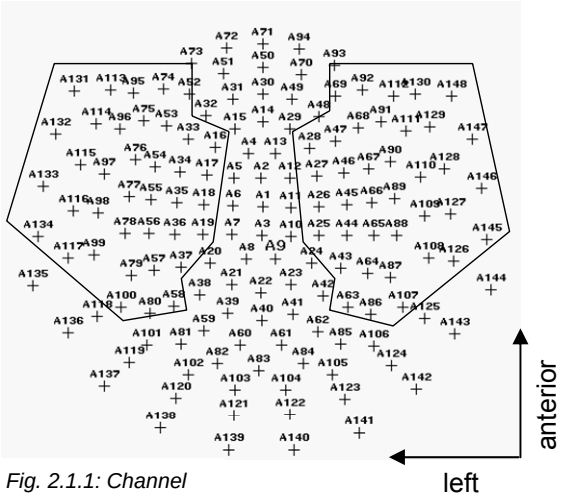

Fig. 2.1.1: Channel

The following ECD-parameters were analysed at the RMS peak-latency in two different time-windows (Component 1: 50-160 ms, Component 2: 170-350 ms): (1) three-dimensional ECD location (x-axis position: posterior-anterior; y-axis position: medial-lateral, z-axis position: inferior-superior); (2) dipole strength; (3) RMS peak-latency. ECDs, that did not match the following criteria, were excluded from further analysis: (1) x-axis position: -1 cm < X < 4 cm; (2) y-axis position: X > 2 cm; (3) goodness of Fit > 0.9. Statistical analysis was done with mixed models using the PROC MIXED module of SAS^{TM}. Covariance parameters were estimated with the restricted maximum likelihood method (REML). The ECD-parameters described above were analysed per person, and per component. GROUP (control, dyslexic) and HEMIPSHERE (left, right) were fixed effects; PAT (subject) nested within GROUP was used as random factor. The variance structure used was variance components (VC). Least square means were estimated with the restricted maximum likelihood method (REML), plots show standard errors. Post hoc testing was done using the test of Tukey-Kramer. For investigation of possible relationships between ECD localisation and behavioural performance, an asymmetry index was calculated (x-axis position (right) – x-axis position (left)) for subjects, where ECD fits met inclusion criteria for both hemispheres (20 controls, 49 dyslexics). Correlations were calculated between the asymmetry index and test performance. Only significant results are reported.

2.1.3. Results Study I

Figure 2.1.2a shows the grand mean signal of all MEG channels for the control children. An early component around 100 ms and a later component around 260 ms are clearly identifiable. Figure 2b indicates a reversal of field topography around 140 ms, i.e. two separate sources with different orientations. The early source is oriented positively, the later source is oriented negatively.

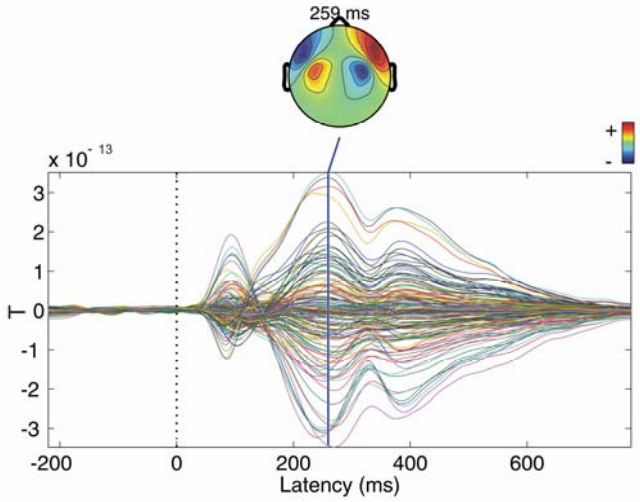

Fig. 2.1.2a: Grand mean of the standard condition (control children). The butterfly plot shows all MEG channels.

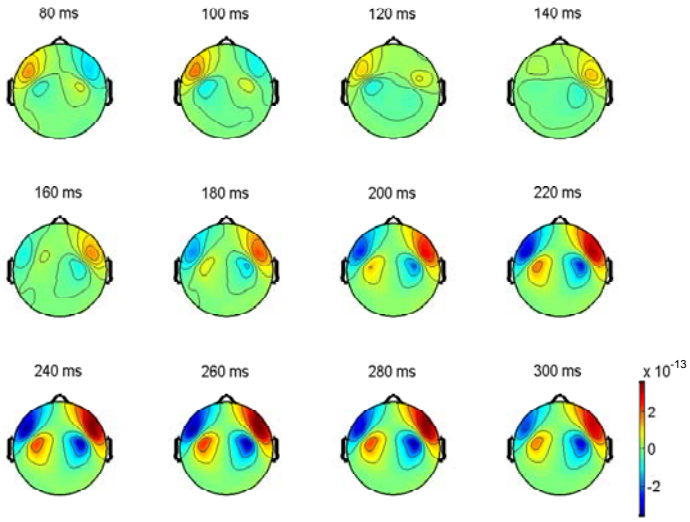

Fig. 2.1.2b: Topography maps of the grand mean in the standard condition.

Early positive component

ECD fits for the early component were not consistently stable and in many cases did not meet criteria (see methods section) for statistical analysis. High quality ECDs in the right hemisphere could only be obtained for 4 control children. Thus, we decided not to analyse the early component.

Late negative component

ECD fits of 21 control children met criteria for statistical analysis for both the left and the right hemisphere. For the dyslexic children, 54 data sets of left hemispheric ECDs and 55 data sets of right hemispheric ECDs could be used[3].

[3] The groups did not differ in age ($F(1,74)=0.03$, $p=0.87$), handedness ($X^2(1,74)=1.02$, $p=0.31$) or gender distribution ($X^2(1,74)=0.27$, $p=0.6$).

Posterior-anterior axis position

The interaction GROUP*HEMISPHERE (F(1,70)=4.12, p=0.046) was found. ECDs in the right hemisphere were localised more anterior than in the left hemisphere for the control children (p=0.002). This hemispheric asymmetry was not present for the dyslexic children (see fig. 2.1.3). ECDs for the control group were located more anterior than ECDs for the dyslexic group in the right hemisphere (p=0.07).

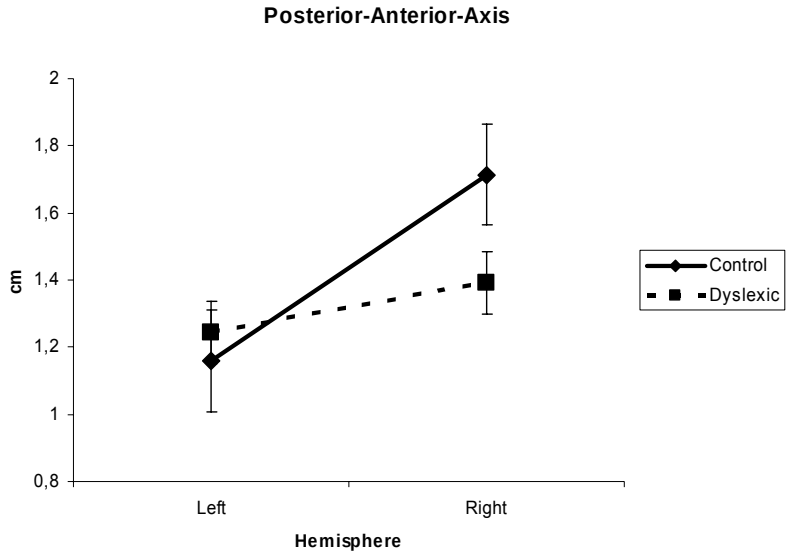

*Fig. 2.1.3: Interaction GROUP*HEMISPHERE.*

Dipole strength

No main effects or interactions were obtained for the dependent variable *dipole strength*.

Latency

The main effect HEMISPHERE (F(1,70)=7.17, p<0.005) was revealed. The RMS peak occurred later after stimulus presentation in the right hemisphere (261 ms) than in the left hemisphere (252 ms). Further, a strong trend towards the main effect GROUP (F(1,70)=3.30, p=0,07) was found. The RMS peak occurred earlier for the control group (252 ms) than for the dyslexic children (260 ms).

Correlations

A moderate but significant correlation was found between the asymmetry index and performance in the DRT (r=0.3, p<0.05). Figure 2.1.4 displays that a greater hemispheric asymmetry was related to better spelling test performance.

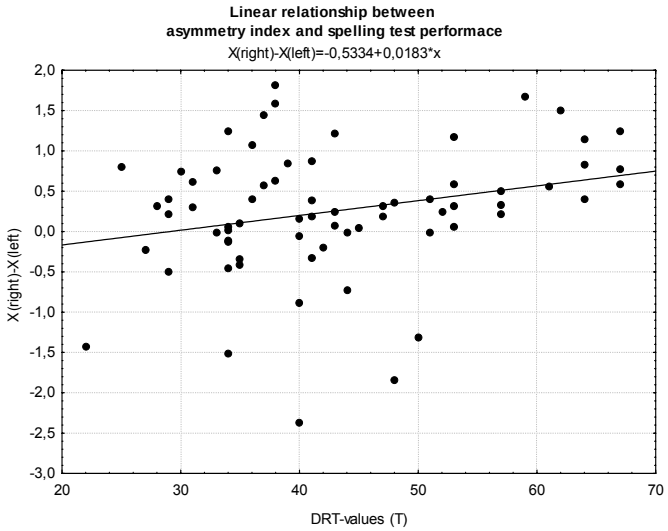

Fig.2.1. 4: Linear relationship between asymmetry index and performance in the standardised spelling test (DRT)

2.1.4. Discussion Study I

In accord to several other studies [114-119], we found right hemispheric ECD-localisations of the syllable /ba/ to be more anterior than left hemispheric ECDs in our sample of normally literate children. This asymmetry was not present for the dyslexic children. Our finding replicates results of Heim et al. [114, 115], who also found more symmetrical ECD localisations for their dyslexic samples – an effect, that was mainly driven by group differences in the right hemisphere. However, Heim [114] found ECD differences on the N100m component in adults and the P100m component in children [115]. In the present study, asymmetry differences were found for the N260m component. This difference might be explained by varying sample sizes (n=14 for [115]; n=55 in the present study) and age distributions (8-16 years for [115]; 8-10 years in the present study). A generally high heterogeneity in the phenotype of dyslexia [10, 49] might also contribute to differences in sample characteristics.

The N260m source was the earliest negatively oriented source derived from the ERFs in our sample. It was preceded by a positively oriented source at around 100ms. A P1/N1 complex with latencies very similar to ours has repeatedly been reported for auditory ERP/ERF data in children [114, 115, 147, 150, 158-160]. An adult-like N1/P2 complex seems to reliably occur not until adolescence [116, 147-150]. Different ERP/ERF morphologies of children are thought to reflect maturational aspects like enhanced refractory periods [146] or development of cortical layers [148].

It is unclear, whether and which of the adult components correspond to the ones of children [160]. Some authors argue that the child N250 is commensurate with the adult N100 [159, 161], while other authors think of it as a counterpart of the adult N2. Paetau et al. [116] noticed that an adult-like N1m response occurred in children when longer ISIs were used (1.2-2.4s). Ceponiene and colleagues [162] discovered 2 additional negative components (N160 and 460) besides the N250 in their sample of children when ISIs were longer than 2 seconds. The authors interpreted the fronto-centrally distributed N160 as a correlate of the adult N1. In their 2002 study [150] an adult-like N1 could be detected in the ERP data of 9-year olds after the slow N2 activity was filtered out.

Albrecht et al. [147] found no differences between children and adults when localising N250, N1 and N2. Ceponiene and colleagues [150] localised N1 and N2 sources of both adults and children in supratemporal areas with N2 sources being close by but more anterior. Takeshita et al. [149] also localised the N250m anterior to the N100m.

To sum up, it appears that longer ISIs are necessary to elicit adult-like auditory ERP/ERF components in children. With short ISIs, the negative component complex found around 250ms in children might constitute of overlapping N1 and N2 responses. It nevertheless seems that the N250m – despite lying anterior to the N1 – originates in supratemporal areas.

In contrast to control children we found rather symmetrical ECD localisations for dyslexic children. This might be an effect of a more symmetrical PT formation in dyslexia [128-133]. PT asymmetry has been found to increase throughout childhood [124]. Therefore, symmetrical auditory ECD localisations in dyslexia might be interpreted as an indication of a maturational lag. This view is supported by our findings concerning N260m latency. Although left hemispheric latencies were shorter than right hemispheric latencies (in accord to left hemispheric specialisation for language) for both groups, control children showed an earlier activation peak (252ms) post stimulus than dyslexic children (260ms). Latencies of late auditory evoked potentials are longer in children than in adults (e.g. [148]). Albrecht et al. [147] showed that a latency decrease occurs until adolescence. Thus, prolonged latencies in dyslexia might reflect a maturational delay. Other authors also found increased ERP/ERF latencies for their dyslexic samples. This was explained by an abnormal auditory processing pattern in dyslexia [163], slower processing of auditory

pathways due to delayed maturation [164] and subtle difficulties in the perception of consonants [165]. Helenius et al´s [165] view is of relevance to our results as well, since we presented the CV syllable /ba/, the consonant taking up the first 40ms.

While ECD localisations were very similar between dyslexic and control children in the left hemisphere, they differed in the right hemisphere. It is possible that right hemispheric areas involved in speech processing for the dyslexic subjects are less efficient than the ones active in control subjects. This interpretation is backed by the correlation between the asymmetry index and spelling test performance in the present study. If the involvement of aberrant right temporal regions is the origin or the consequence of dyslexic symptoms remains unclear, however. Right hemispheric deviances have also been reported by McCrory et al. [145], who found a right hemispheric underactivation in their dyslexic sample during repetition of words and pseudowords. In contrast, Corina and colleagues [166] reported an increased right hemispheric activation in the right PT during a phonological judgement task in dyslexic subjects. These controversial results might be explained by the use of different methods (PET and fMRI), different tasks and samples (children and adults). Nevertheless, it seems that not only the language-specific left hemisphere is deviant in dyslexics (e.g. [126, 142, 143]), but also the right hemisphere.

2.1.5. Conclusion Study I

In conclusion, our results support the notion of a deviating cortical organisation in dyslexia. Reduced hemispheric asymmetry in the localisation of auditory ERF components in dyslexia appears to be a robust finding across different samples of dyslexic children and adults. It appears that different cortical areas are involved in auditory (language) processing. This might be the consequence of a more symmetrical PT formation, which in turn might be the result of maturational delay.

2.2. Study II: *Training-induced alterations of the mismatch field (MMF) in dyslexic children*

2.2.1. Background Study II

Reduced phonological awareness (the reduced ability to discriminate speech-sounds in spoken words) is considered to be a core-deficit in dyslexia [22, 167-169]. Phonological awareness is not only assumed to be a pre-requisite for speech-perception, but also for learning the correspondence between graphemes and phonemes which again is crucial for reading and writing [22, 170-173]. Children with dyslexia have been found to show poorer performance than control children categorizing speech sounds [28-30]. Most dyslexic children have problems distinguishing CV-syllables [31]. This seems to be related to their deficiency processing stop-consonants [31, 32]. Stop consonants are characterised by *fast frequency changes* within a timeframe of milliseconds. Therefore some authors argue that the processing deficiencies in dyslexia might not be purely phonological, but a result of an underlying temporal (auditory) processing deficit [35, 40, 143, 174, 175].

Mismatch negativity (MMN) and field (MMF) recorded during language-specific speech sound traces may help to clarify this question. Usually, MMN is reported to peak between 100 and 300 ms after a deviant stimulus that is embedded in a stream of standard sounds. Later MMN peaks (300-600 ms) have been found [37, 38, 43, 176] in children. At least 2 generators are assumed to underlie the MMN: a temporal generator detecting pre-attentive sound-changes and a frontal generator associated with attention switch [177].

MMN after auditory stimulation has been investigated in dyslexic populations. Schulte-Körne and his co-workers [37] found an attenuated MMN for a dyslexic sample compared to controls after stimulation with CV-syllables (standard /da/, deviant /ba/), but not after stimulation with sine-tones (standard 1000 Hz, deviant 1050 Hz). This was interpreted as evidence for dyslexia being a speech-related phenomenon that does not extend to other domains of auditory processing. In Schulte-Körne et al´s 1999 study [43], a sequence of 4 tones differing in frequency and length was presented as standard stimulus. Deviants only differed in the position of the second and last tone (which had the same frequency). Using this paradigm, the dyslexic subjects did show an attenuated MMN also for non-speech sounds. Since the only difference between standard and deviant stimuli lay in the temporal

structure of the tone-pattern, the authors concluded that temporal auditory processing might be deficient in dyslexia. Baldeweg and colleagues [44] found no MMN differences between controls and dyslexics when stimuli differed in duration (standard always being 200 ms long). They did find attenuated MMN when standard and deviant stimuli were short in duration (50 ms) and differed in pitch. The attenuation was the larger the smaller the pitch-difference was between standard and deviant. The results of Schulte-Körne et al. and Baldeweg et al. suggest, that dyslexia is related to processing difficulties of *speech*-sounds as well as temporally complex and short duration *non-speech* sounds. This implies that the processing deficit in dyslexia is not only phonological in nature.

Another possibility to find out about the nature of the underlying deficit in dyslexia is to investigate the effect of training programs on dyslexic symptoms and/or cortical correlates. Tallal and colleagues [40] developed a computer-based adaptive training-program consisting of two tasks or "games" for language learning impaired children. One task required the children to reproduce the sequence of two frequency-modulated tones via button-presses. In the other task they were presented with a CV-syllable as a sample and had to decide between 2 adjacent syllables, which of them was identical with the sample. The games were adaptive, i.e. the better the children got, the shorter the ISIs, the frequency-modulations of the tones, or the formant transitions of the syllables became. That is, only the temporal aspects of the stimuli were manipulated. Interestingly, the children showed improved performance after the training not only at the tasks within the training-program, but also at a test for speech-comprehension (Token-Test) and at a test for phoneme discrimination (Goldman Fistoe Woodcock Test of Auditory Discrimination). This finding illustrates that a training-program, that focused on improving temporal processing also had an effect on other language-related tasks. Temple and colleagues [41] investigated dyslexic children in the fMRI before and after they underwent an adaptive training that was focussing on auditory and language processing using non-linguistic and acoustically modified speech. Before the training, dyslexic children showed less activation than controls in the left-hemispheric temporo-parietal cortex, as well as the inferior frontal gyrus during a phonological task. After the training, activity in these cortical areas increased for the dyslexic children. The children also improved in reading ability (word and pseudo-word reading), as well as passage comprehension, oral language ability and rapid naming. The improvement in oral language ability was positively

correlated with the increase in activity in left temporo-parietal regions. Both, behavioural performance and cortical activity was comparable to controls after the training. Kujala and colleagues [45] measured the MMN of dyslexic children before and after an audio-visual training. The training involved sound elements that varied in pitch, duration and intensity. The sounds were visually represented as rectangles that respectively varied in position, length and thickness. Subjects could change SOA and sound duration during the training. The task was to either identify an auditory pattern in one of two visually presented sequences of rectangles, or to follow the pattern while it was played and press the space-bar at the moment when the last element of the pattern was played. MMN was elicited by using a tone-pair (first tone 500 Hz, second tone 750 Hz) as standard and the same tone-pair reversed as deviant. Before the training, the two dyslexic groups did not differ in MMN amplitude and morphology. After the training, MMN amplitude was increased for the training group but not for the control group. Behaviourally, there were no differences in reading skill between the dyslexic groups before the training. After the training, the training-group read more words correctly than the control group. Additionally, a positive correlation was found between MMN amplitude-increase and the change in reading performance. Comprising, another training using non-linguistic stimuli improved reading skills in dyslexic children and enhanced the ability to distinguish sounds. This supports the view that the underlying deficit in dyslexia is not only restricted to phonology, but is a more general auditory perceptual deficit.

The findings described above demonstrate that training studies accompanied by the measurement of brain activity are not only suitable for pinpointing cortical correlates of behavioural improvements, but also help answering questions about the aetiology of dyslexia. In the present study we tried to utilize this by comparing 3 groups of dyslexic children, who participated in training programs focussing on different aspects of dyslexia. One training was developed following Tallal et al. [40] and was aimed to improve auditory temporal processing (*Training of Auditory Perception (AP*)). Another training program aimed at improving phonological awareness by teaching the children to syllabify words (*Training of phonological awareness (PA*)). The last program set focus on cognitive compensation and mainly involved learning spelling rules (*Training of Spelling Rules (SR*)). Dyslexic children were compared to a non-dyslexic control group. We were interested in the differential influence of the trainings on reading and spelling performance, as well as categorical

perception. Additionally, we measured the MMF (/ba/ standard, /da/ deviant) before and after a 5-week training period. If the principal underlying deficit in dyslexia was an auditory perceptual deficit, we expected to find the largest improvements on behavioural performance and the greatest enhancement of the MMF after the AP training. If there was no general auditory perceptual deficit, but only a lack of phonological awareness, we expected to find most improvements after the PA training. After the SR training, we only expected to find behavioural improvements and no changes in the MMF, since the training did not aim at auditory processing.

2.2.2. Methods Study II

Generation of the sample, tests and trainings

The participating children were contacted through 14 primary schools in or around Konstanz, Germany, and attended either 3rd or 4th grade. Schools were asked to name children with massive problems reading and spelling, as well as children without any such difficulties. Children and their care-takers gave informed consent to participate in tests and examinations to diagnose their reading problems. The test-battery that was designed to assess a variety of abilities ranging from spelling and reading to phonological abilities (*DRT* (Diagnostischer Rechtschreibtest, 3rd grade: [151]; 4th grade [152]): Standardized spelling test; *ZLT* (Zürcher Lesetest, [153]): Standardized reading test; *SPM* (Standard Progressive Matrices, German Version: [154]): non-verbal IQ-test; *Word reading* [157]: List of words with increasing difficulty to be read aloud; *Pseudoword reading* [157]: List of pseudo-words with increasing difficulty to be read aloud; *Mottier-Test* [155]: Pseudowords with increasing difficulty are read aloud by the experimenter and are to be repeated by the child; *Dictation* [156]: only words were used that are spelled as one “hears” them, i.e. no knowledge about spelling rules or exceptions is neccessary ; *Categorical perception* [157]: judgement, if a syllable sounds more than “ba” or “da”, when the formant transition period of the syllable is varied on a ten-item continuum). Only children who were 1 ½ standard-deviatons below the norm-sample in the standardized spelling test, were invited to participate in the study. Control children who performed significantly worse than the norm sample in the spelling test were excluded in 2 instances or classified as dyslexic in 3 cases. Dyslexic children were randomly assigned to 1 of 3 trainings that focused on different aspects of dyslexia: Training of auditory perception (AP, by

means of a computer game), training of cognitive compensation (SR, elements of the "Marburger" training by *Schulte-Körne & Mathwig, 2001 [178]*) and training of phonological awareness (PA, following *Buschmann*, *1988* [179] and respectively *Hofmann, 1998 [180]*) (see below for more detailed descriptions).

Subjects

Altogether, 64 children with dyslexia and 22 children without any reading or spelling deficits participated in the study. Dyslexic children were randomly assigned to one of three treatment groups. Table 2.2.1 shows the number of subjects per group, handedness and gender distributions. Groups were comparable in age ($F(3,82)=0.66$, $p=0.58$), handedness ($X^2(3,82)=4,4$; $p=0,22$) or gender ($X^2(3,82)= 0,75$, $p=0.86$).

Table 2.2.1: Demographic information

Group	N	Age in years	Handedness l=left, r=right	% Right-Handers	Gender f=female, r=male	% Male
SR	20	9:3	5 l 15 r	75	7 f 13 m	65
PA	23	9:6	2 l 21 r	91	6 f 17 m	74
AP	21	9:7	2 l 19 r	91	6 f 15 m	71
Control	22	9:6	1 l 21 r	96	8 f 14 m	64

Trainings[4]

The AP training (following in parts Tallal et al., 1996 [40], Merzenich et al., 1996 [39]) was realised through an adaptive computer program specifically designed to enhance temporal auditory processing. The program consisted of two auditory "games". In the first game, two frequency-modulated tones were presented auditorily via headphones. Tones could either sweep upwards or downwards. Four different tone-pair combinations were possible: up/up, down/down, up/down, down/up. Two arrows were visible on the screen, one arrow pointing upwards, the other one downwards. The task was to reproduce the sequence of the tone-pair by mouse-clicking the corresponding arrows. I.e. if an up-sweep was followed by a down-sweep, the child was to first click on the arrow pointing upwards, then on the arrow pointing downwards. If a child responded correctly 3 times in a row, difficulty increased by

[4] For a more detailed description of the trainings see "Differentielle Effekte verscheidener Trainingsverfahren auf behaviorale und neurophysiologische Parameter bei Kindern mit LRS" by Christof Bott, 2005.

either shortening the frequency-modulation-duration of the tone sweeps, or the inter-trial-interval between the two tones. If a child responded incorrectly twice in a row, difficulty decreased. In the second game, a target syllable (/ba/, /da/ or /ga/) was played, uttered by an animal on the screen. In consecution, two different animals appeared on the screen subsequently, each uttering another syllable. A decision was to be made by the child, which animal had said the same syllable as the first animal by clicking on the correct animal. Difficulty (depending on the child´s performance) was modulated as described above by either varying formant-transition-duration of the syllables or the inter-trial-interval between the 2 syllables that were to be compared with the first one.

The SR training (following Schulte-Körne & Mathwig, 2001 [178]) aimed at improving spelling problems by teaching the children the application of rules. In contrast to the AP training that focussed on perceptional aspects of sounds without reference to spelling rules, the SR training focussed on teaching spelling rules without any reference to perceptional aspects. Thus, the training was cognitive in nature (in order to polarize SR and AP-Training, only rule-based chapters were used, phonological aspects were neglected although they are a part of the original training package). The first 7 sessions of the training were dedicated to the refreshment and consolidation of general basics (i.e. distinction between vowels and consonants; wordclasses; word-stems, prefixes and suffixes; capitalisation of nouns (in German)). In session 8-18, spelling rules concerning *Umlaute* and word endings were practised. Rules were printed on plastic cards and handed out to each child. Only one rule was given at a time, followed by an intense practising period.

In the *PA training (following Buschmann*, *1988* [179] and respectively *Hofmann, 1998 [180])*, children were taught to listen to the syllable-structure of a word and to physically display it by making an arm-movement per syllable while moving one step aside. Practising this somatosensory coupling, children were thought to “hear” how a word is spelled. Later on in the training, children started writing words and sentences while drawing little bows under each syllable to transfer the “auditory” structure. “Tricks” (rules) were taught, how difficult words can be transformed, so the syllable structure can be heard. The main focus of the training was set on finding out, when consonants are doubled in a word (a common source of mistakes for dyslexic children in German) and how word endings are spelled (i.e. *g* or *k*; *d* or *t*).

Study Design

Each child underwent the test-battery that was split into three sessions/days. Following the behavioural tests, a magnetoencephalogram (MEG) was recorded for each child. Ensuing, training was provided for five weeks at the individual schools for all the dyslexic children by the same two experimenters. The amount of training varied for the different training programs. AP training and SR training were performed 4 times a week for 45 minutes, PA training was performed twice a week for 45 minutes, since this amount of training been shown to be effective in a pilot study [181]. Control children did not receive any training apart from their usual schooling. After the training period, another MEG was recorded for each child. Finally, the test battery was performed again. B-forms of the tests were used where available (DRT, word reading, pseudoword reading). A schematic display of the design can be seen in figure 2.2.1.

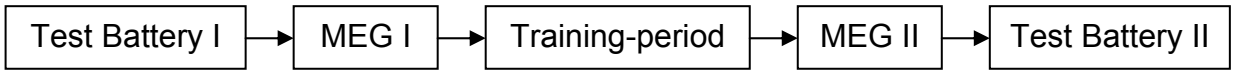

Figure 2.2.1: Study Design

Data were recorded in three blocks over the period of 1 ½ years.

Stimulation in the MEG

Two synthesized syllables /ba/ and /da/ were used for auditory stimulation in an oddball task. Both syllables were 250 ms long with a 40 ms formant transition period in the beginning that encoded the consonant information and thereby distinguished the syllables. For both syllables the fundamental frequency of formant F0 was 128 Hz with a linear decline to 109 Hz towards the end of the stimulus. The formant frequencies for the vowel /a/ (which was also the same for both syllables) were 770, 1340 and 2400 Hz for F1, F2 and F3, respectively. Starting frequencies for the formants F2 and F3 were 1365 and 2337 Hz for /ba/, 1567 and 2515 Hz for /da/. Therefore, the only acoustical difference between the syllables was between formants F2 and F3 within the first 40 ms.

Syllable /ba/ was used as standard stimulus, /da/ was used as deviant. All in all 500 stimuli were presented with a constant ISI of 500 ms. Occurrence rates were 85% and 15% for /ba/ and /da/, respectively. Stimuli were presented pseudo-randomly. Data epochs with standard stimuli occurring directly after a deviant were not analysed.

MEG Recordings

Recording was done with a 148-channel magnetometer (MAGNES™ 2500 WH, 4D Neuroimaging, San Diego, USA). Subjects were lying supine in a comfortable position in the magnetically shielded room (Vakuumschmelze Hanau). Auditory stimuli were presented through ear tubes 60 dB/SPL over the individual hearing level. For artefact control, eye movements (EOG) were recorded from four electrodes attached to the left and right outer canthus and above and below the right eye, as well as cardiac activity (ECG) via two electrodes, one on each forearm. A SynAmps amplifier (NEUROSCAN) served for the recording of EOG and ECG. A video camera installed inside the chamber allowed monitoring the subject's behaviour and compliance at any time throughout the experiment.

Subjects were instructed to not pay any attention to the syllables they would here. To distract attention, a silent video was screened onto a white projection field at the ceiling of the chamber using a video beamer (JVC™, DLA-G11E) and a mirror system. Data were recorded with an online high-pass filter of 0.1 Hz and a sampling rate of 508.63 Hz (bandwidth 100Hz). Recording was continuous.

Data Analysis

Data were noise-reduced and corrected for cardiac activity. For each subject data epochs with a 200 ms baseline and a post-trigger window of 800 ms were generated. Epochs containing artefacts (signals > 120 µV in the EOG and signals > 5pT in the MEG-channels) were rejected. The remaining epochs were averaged separately for the standard condition and the deviant condition. The resulting average files were 20 Hz low-pass-filtered and baseline corrected. Following formula was used for calculating the root mean square (RMS) *for each time point* in different channel groups:

$$\frac{\sqrt{\sum_{\text{channels}} \text{Amplitude Value}^2}}{\text{Number of channels}}$$

Following channel groups were used for analysis:

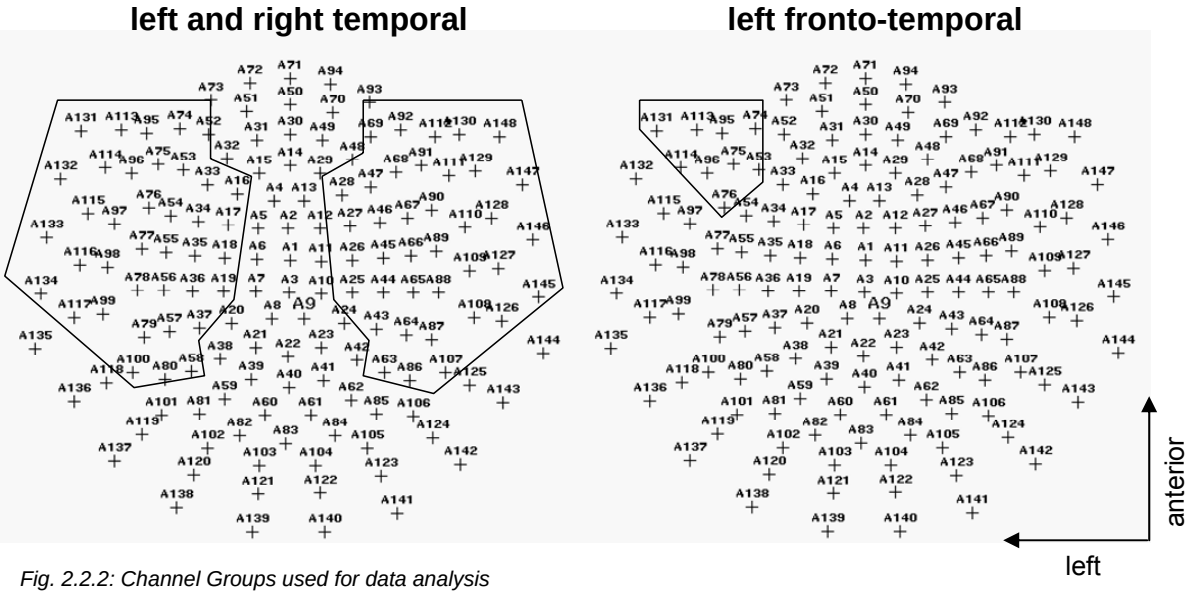

Fig. 2.2.2: Channel Groups used for data analysis

Standard left and right channel groups (fig. 2.2.2) were chosen, since they are considered to cover most activity generated in temporal regions. The left fronto-temporal group was chosen, because it showed the clearest amplitude differences between standards and deviants. Mean amplitudes for the standard and deviant condition were calculated by averaging the RMS-values in 3 different time-windows (W1 = 180-230 ms; W2 = 230-280 ms; W3 = 280-330 ms (see results section)). Mean amplitudes of the standard condition were subtracted from the mean amplitudes of the deviant condition yielding a measure of amplitude difference (Mismatch Field, MMF) between deviant and standard condition. Difference values per person, per time window, before and after training were statistically analysed using the PROC MIXED module of SAS^{TM}. Covariance parameters were estimated with the restricted maximum likelihood method (REML). MMF was used as dependent variable. TRAINING (Control, PA, AP, SR), TIME (pre, post) and WINDOW (W1, W2, W3) were fixed effects; PAT (subject) nested within TRAINING was used as random factor. Plots show standard errors. Data before the training period were analysed separately. Here, statistical analysis was the same, except TIME was not used as a fixed effect and GROUP (Dyslexic, Control) was used as fixed effect instead of TRAINING. Statistical analysis was done with mixed models, since in some cases data had to be excluded due to artefacts. Table 2.2.2 shows the sample sizes in the different conditions.

Table 2.2.2: Sample sizes before and after the training period.

Time	Group	N
PRE	Control	21
	PA	21
	AP	17
	SR	20
POST	Control	18
	PA	20
	AP	16
	SR	18

Instead of weighted means, *least square means* (LS-means) are reported. LS-means of fixed effects are *predicted population margins* - that is, they estimate the marginal means over a balanced population. In a sense, LS-means are to *unbalanced* designs as class and subclass arithmetic means are to balanced designs. The standard errors are adjusted for the covariance parameters in the model. Post-hoc testing was done with planned contrasts.

Behavioural Data

Behavioural performance in the SPM, DRT, ZLT, Word and Pseudoword Reading Test, Mottier-Test and Categorical Perception before and after the training period was analysed. Data of children, whose MEG-data had to be rejected due to artefacts were not analysed. Statistical analysis was done with mixed models. Scores of the individual tests (DRT: T-Values, ZLT Correctness: Percent correct, ZLT Reading Time: seconds/number of words, SPM: T-Values, Word Reading Correctness: Percent correct, Word Reading Time: seconds, Pseudoword Reading Correctness: % correct, Pseudoword Reading Time: seconds, Mottier-Test: Percent correct, Dictation: Percent correct, Categorical Perception: Index) were dependent variables, TRAINING (Control, PA, AP, SR), TIME (pre, post) were fixed effects. PAT (subject) nested within TRAINING was used as random factor. Data before the training period were analysed separately. Here, statistical analysis was the same, except TIME was not used as a fixed effect and GROUP (Dyslexic, Control) was used as fixed effect

instead of TRAINING. Plots show standard errors. Post-hoc testing was done with planned contrasts.

In order to find out about the relationship between improvement in the behavioural tests and MMF amplitude change before and after the training period, difference values (post-pre) were calculated for all test-scores and MMF amplitude for the subjects with both pre and post data (17 control, 15 AP, 16 SR, 18 PA). In cases where MMF amplitude was significantly different after the training than before the training (significant TIME*TRAINING interaction and post-hoc tests), correlations were calculated between MMF differences and differences in the behavioural tests.

Behavioural description of the sample before the training period

The main effect TRAINING was found for all tests. Performance of the control children was better than performance of the dyslexic children on all measures. Table 2.2.3 shows the test scores and F statistics.

Table 2.2.3: Test Values before the training period (SPM, DRT: T-values*; ZLT Correctness, Word Reading Correctness, Pseudoword Reading Correctness, Mottier Test, Dictation:* % correct*; Word Reading Time, Pseudoword Reading Time:* seconds*; ZLT Reading Time:* seconds/no words*; Categorical Perception:* Index)

	SPM	DRT	ZLT Correctness	ZLT Reading time	Word Reading Corectness	Word Reading Time	Pseudoword Reading Correctness	Pseudoword Reading Time	Mottier Test	Dictation	Categorical Perception
Control	61.8	57.8	96	0.68	90	71.2	76	116.7	84	92	30.7
Dyslexic	51.4	36.8	87	1.43	74	169.4	52	217.7	66	75	24.7
F (1,77)	12.17	195.49	22.82	23.65	32.81	30.95	37.14	13.91	22.66	37.09	17.13
p	0.0008	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0004	<0.0001	<0.0001	<0.0001

2.2.3. Results Study II

Behavioural improvement after training

The main effect TIME was found for all test measures except *pseudoword reading correctness* and *categorical perception*. Children of all groups profited from the training period on different aspects of reading and spelling abilities. Differential effects were found for the SPM, DRT, ZLT reading time (trend), word reading correctness, pseudoword reading time (trend) and the dictation. Table 2.2.4 depicts the amount of improvement for all tests (post – pre training), as well as F-statistics for the interactions TRAINING*TIME.

Table 2.2.4: Test improvement (post training – pre training), bold differences were statistically significant (planned comparisons. SPM, DRT: T-values*; ZLT Correctness, Word Reading Correctness, Pseudoword Reading Correctness, Mottier Test, Dictation:* % correct*; Word Reading Time, Pseudoword Reading Time:* seconds*; ZLT Reading Time:* seconds/no words*; Categorical Perception:* Index*).*

	SPM	DRT	ZLT Correctness	ZLT Reading Time	Word Reading Correctness	Word Reading Time	Pseudoword Reading Correctness	Pseudoword Reading Time	Mottier Test	Dictation	Categorical Perception
Control	-1.1	-0.2	0.06	-0.05	**0.05**	-5	-0.4	0.4	0.7	0.02	0.1
PA	**6.7**	**5.0**	2	**-0.2**	**0.04**	-24.4	3.6	-47.1	2.4	0.01	-1
AP	**5.3**	**4.3**	3	**-0.23**	0.005	-12.8	2.5	-7.7	8.4	0.04	-0.1
SR	3.4	**5.5**	3	**-0.27**	**0.08**	-21.3	3.6	-39	3.4	**0.1**	2
F (3,62)	2.98	5.59	1.67	2.47	3.62	1.51	0.42	2.25	1.22	4.73	0.62
p	0.04	0.002	0.18	0.07	0.05	0.22	0.74	0.09	0.91	0.005	0.6

Only children in the AP group (p=0.02) and PA (p=0.0009) improved in non-verbal intelligence (SPM) during the training period. All dyslexic children improved their spelling performance in the DRT (AP p=0.0007; SR p<0.0001; PA p<0.0001) and their reading speed in the ZLT during training (AP p=0.001; SR p<0.0001; PA p=0.0007). Word reading correctness improved for the control children (p=0.01), PA (p=0.02) and SR group (p<0.0001) after the training period. Pseudoword reading time increased for children in the PA (p=0.003) and SR group (p=0.01), while spelling performance in the dictation only improved for the children in the SR group (p<0.0001).

Results MMF

Figure 2.2.3a displays the grand mean butterfly plot of all MEG channels in the standard condition for the control children. As can be seen in figure 2.2.3b, an earlier, mainly left hemispheric bipolar field is followed by a later bilateral field pattern with

reversed polarity. The earlier component is oriented positively, the later component (starting ~ 180 ms) is oriented negatively.

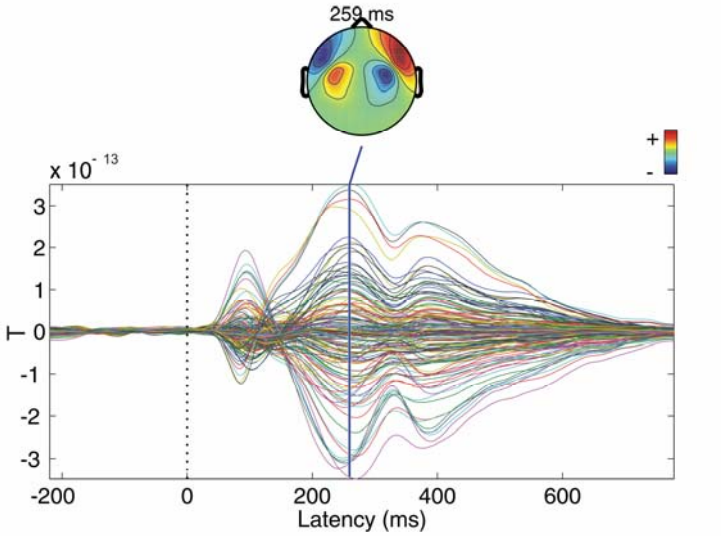

Fig. 2.2.3a: Grand mean of the standard condition (control children). The butterfly plot shows all MEG channels.

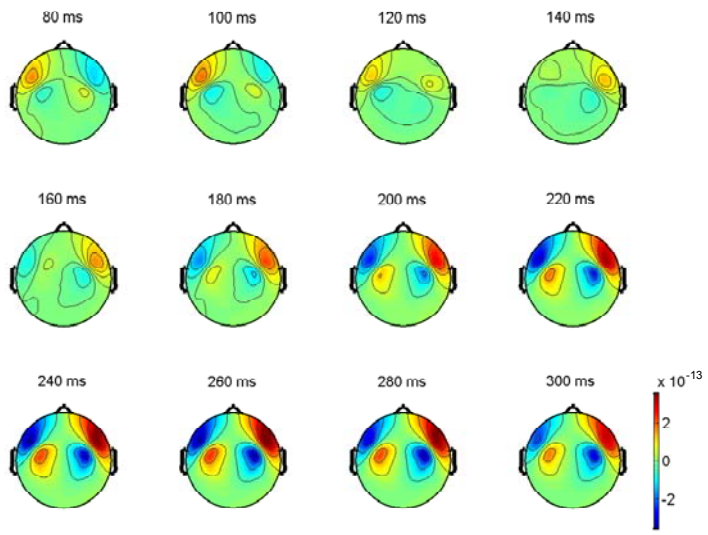

Fig. 2.2.3b: Topography maps of the grand mean in the standard condition.

Figure 2.2.4 displays standard and deviant waveforms recorded at a left fronto-temporal channel group for all children.

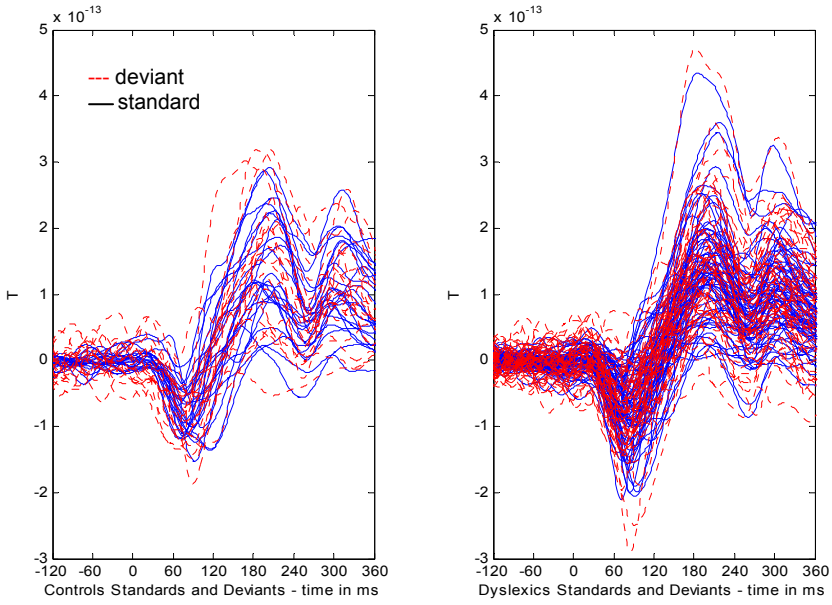

Fig. 2.2.4: Standard and deviant waveforms of control and dyslexic children

Figure 2.2.5a shows the RMS curves recorded at the same left fronto-temporal channel group by a control and a dyslexic child. A clear difference can be seen between standard and deviant conditions starting around 180 ms for the control child.

The difference is less pronounced for the dyslexic child. Figure 2.2.5b shows the RMS-waveforms of the standard and deviant condition for all control and dyslexic children at the left fronto-temporal channel group between 80 and 330 ms.

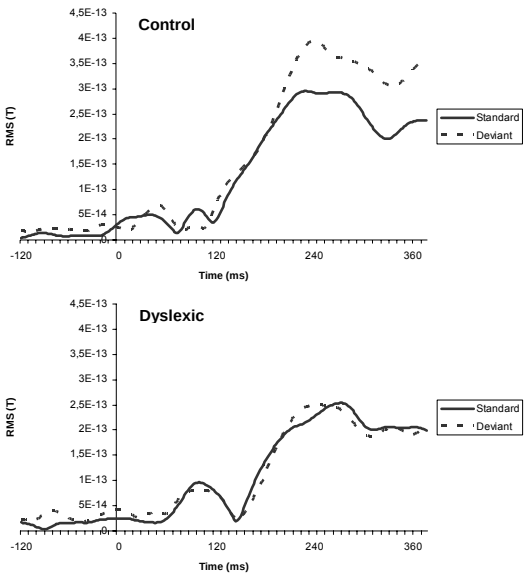

Fig. 2.2.5a: RMS course at the left fronto-temporal channel group in the standard and deviant condition for a control and a dyslexic child.

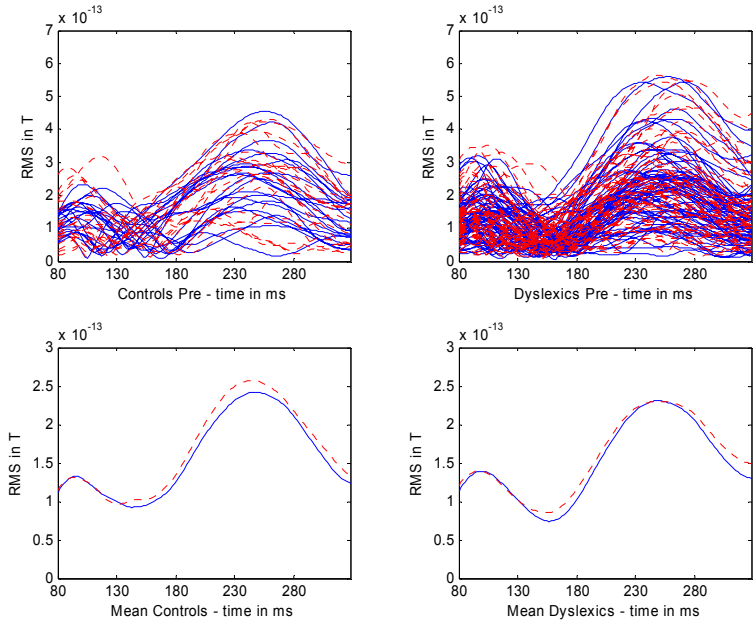

Fig. 2.2.5b: RMS course of standards and deviants for control and dyslexic children. Bottom graphs display group means.

Statistical analysis was performed for the component starting at 180 ms, because it was clearly identifiable in most of the cases (see fig. 5b). Analysis was done in 50 ms time-windows, the first window covering the rising slope of the component (180-230 ms), the second window covering the peak (230-280 ms), the third window covering the falling slope (280-330ms). Results for the three different channel groups (left and right temporal, left fronto-temporal) were as follows:

<u>Before training</u>

MMF amplitudes were not significantly different between control and dyslexic children (fig. 2.2.6). Means of controls were somewhat larger indicating that only a subgroup of dyslexic children may actually show a reduced MMF.

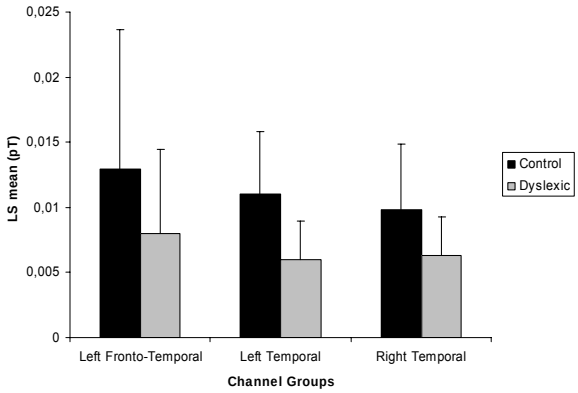

Fig. 2.2.6: Group differences in MMF amplitude before training

MMF changes after training

The interaction TRAINING*TIME was found for all three channel groups (Left Fronto Temporal F(3,62)=5.55, p=0.002; Left Temporal F(3,62)=2.82, p=0.046; Right Temporal F(3,62)=2.79, p=0.04), indicating that MMF amplitude changed differentially for the different training groups. Figure 2.2.7 depicts the MMF change values (post – pre training).

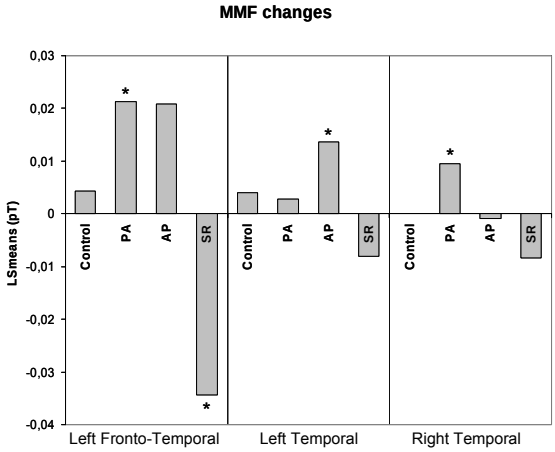

Fig. 2.2.7: MMF amplitude changes (post training – pre training)

MMF amplitude did not change over the five-week training period for the control children, while MMF amplitude increased for the children in the PA group in left fronto-temporal (p=0.05) and right temporal (p=0.03) channel groups. MMF amplitude also grew for the AP children over left temporal channels (p=0.02), while it decreased for children in the SR over left fronto-temporal channels (p=0.003). The increase in MMF amplitude for the PA group in the left fronto-temporal channel group correlated with an improvement in dictation performance (r=0.51, p<0.05, see fig. 2.2.8).

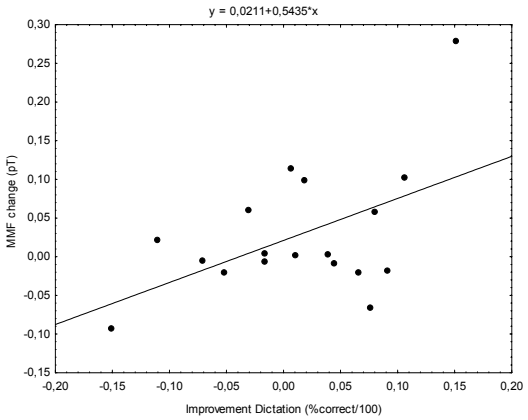

Fig. 2.2.8: Linear relationship between dictation improvement and MMF amplitude increase over left fronto-temporal channels for the PA children

2.2.4. Discussion Study II

Group differences before training

The MMF of dyslexic children and control children were not statistically different. This finding was surprising, since others reported a significantly reduced MMN for dyslexic samples [37, 43-45]. However, no differences between the dyslexic sample and control group were found, when relatively long sine tones were used for stimulation [37, 44], i.e. simply structured stimuli that were neither speech-related, nor morphologically complex. The stimulation used in this study, however, was both speech-related (synthesized syllables /ba/ and /da/) and demanding in terms of processing short-duration information (the only distinction between the syllables was encoded in the initial 40 ms formant transition period). Since dyslexics are reported to be deficient categorising speech sounds [28-30] and distinguishing CV-syllables [31], and since the dyslexic children in our sample had significantly lower scores in categorical perception than the control children, we expected to find smaller MMF amplitudes for the dyslexic children compared to controls using the stimulation described. The results obtained here suggest that not all children, who have pronounced problems with reading and spelling, as well as categorical perception, have a reduced sensitivity to sound changes that is reflected by an attenuated MMF. One possibility to explain this finding is, that sound changes are indeed detected in the sense that a stimulus is recognised as being “different”, but that in an ensuing processing stage the nature of the “difference” cannot be clearly categorised. If this

was the case, one might assume that dyslexia may generally not result from a general auditory perceptual deficit. It seems more likely that decoding difficulties occur later in the processing stream when phonemes are categorised by segmenting a stream of incoming sounds. Mody and colleagues [30] point out the need for a clear terminology when speaking of temporal perception. On the one hand there is the perception of temporal properties such as duration, sequence, relative timing or rhythm; this includes segmentation. On the other hand there is rapid identification and discrimination between very brief events, e.g. differentiating the formant transitions between ba and da. They argue further that *"all the supposed difficulties in "auditory temporal perception" or actual difficulties in perceiving rapidly presented information, so far reported for both reading-impaired and specifically language-impaired children, can be traced to difficulties in stimulus identification."* If this was the case, however, a deviant MMF should be expected.

Given a greater sensitivity of magnetic measurements of MMF than for MMN and the fact that the present sample of dyslexic children (n=58) was considerably larger than the samples in other studies examining MMF or MMN, it is unlikely that our finding is a result of an insufficient signal to noise ratio.

One possibility to explain the lack of MMF attenuation in the experimental groups might lie in the definition of diagnostic criteria for dyslexia. Dyslexia is a specific disability with reading and spelling despite appropriate schooling, normal intelligence and without any other sensory or neurological deficits (DSM IV, APA, 1994). These diagnostic criteria do not involve any etiological premises. Therefore, a variety of children might be diagnosed to be dyslexic, without having the same underlying deficit. Dyslexia has been viewed as a heterogeneous disorder that varies to a great extent in strength and expression [10, 49]. Amitay and colleagues [48] investigated 30 reading disabled adults and found that only 6 had difficulties on tasks with high demand on temporal processing while all of them had difficulties with other auditory and visual tasks with no special demand on temporal processing. Heim et al. [182] found that children with auditory deficits usually show relatively less visual impairments and vice versa. It is likely that some but not all children have difficulties with temporal processing in an unselective sample of dyslexics. But there will also be children, whose phonological awareness is reduced without parallel deficient temporal processing. For the present study, we did not pre-screen the dyslexic children for their temporal processing abilities. We only followed diagnostic criteria as

defined in the DSM IV. Thus, our sample may have been more representative but also more heterogeneous than the ones of other studies. Ramus and colleagues [22] investigated 16 adult dyslexics with an extensive test-battery focussing on phonological, auditory, visual and cerebellar deficits. Besides the fact that the profile of performance and individual deficits varied to a great extent across the subjects, they found that all of the dyslexics had problems with phonology, while only 10 of 16 had deficits with auditory processing. They even consider this as a high incidence compared to other studies that typically find 1/3 of dyslexics affected on auditory processing [22]. It is also stressed that the auditory problems found cannot be characterized as being the consequence of a rapid auditory processing deficit, since the dyslexic subjects did not perform worse on tasks involving rapid auditory processing compared to other auditory tasks. Another important conclusion was that deficient audition leads to poor phonology, but not vice versa. In the light of Ramus et al´s results, our finding of a "dissociation" between poor performance in categorical perception (phonology) and control-like MMF amplitudes (audition) seems plausible. The children perceive the difference between syllables, yet they cannot categorize them.

Training-induced changes

Children of all groups profited from the training. This finding replicates and extends results from other studies investigating the efficacy of the PA- [183], SR- [184, 185] and a comparable version of the AP-training [41]. In the present study, differential effects were found for word reading correctness, where only children in the PA- and SR-group improved. Since the children in the control group performed better after 5 weeks as well, improvement of the dyslexic children may not be accredited to the training they took part in. At the dictation, only children in the SR group improved. This was somewhat astonishing, since only words were used that did not *necessarily* require rule-knowledge in order to spell them correctly. It is possible, however, that the children in the SR group could make use of the rules they were taught and thereby circumvented the reliance on possibly deficient phoneme-grapheme correspondences. Interestingly, the children in the AP- and PA- group improved at the non-verbal intelligence test SPM after the training. We had not expected any effects on the SPM, since none of the trainings was designed to improve intelligence. It is imaginable, however, that the AP training promoted the ability to concentrate and

focus attention, which are crucial premises to solve the demanding tasks of an intelligence test [186, 187]. Since giving the correct responses required the children to be extraordinarily attentive during the AP training, and since the training was applied 45 minutes a day, four times a week over a period of five weeks, it is possible, that the ability to concentrate was trained as well. This can, however, not explain the improvement of the PA group. Therefore it may be possible that improved segmentation and categorisation abilities provided these children with better tools to process information, improving their overall performance in school (which indeed was the case), their self-confidence and consequently their performance also in non-verbal intelligence tests.

We did record differential training-induced changes in MMF amplitude. The AP group showed a distinct increase in MMF amplitude after training at left temporal channels, Children in the PA group had increased MMF amplitudes over the left fronto-temporal and right temporal regions. These findings fit to the areas that are eloquent for the respective tasks (pre-attentive auditory perception of language sounds in left temporal regions; phonological awareness and attention switching in left frontal regions and simultaneously sound to movement – foxtrot in the right hemisphere).

It might not be surprising to find an MMF amplitude increase after the AP training, since it was designed to improve auditory temporal processing and in consequence the ability to discriminate sounds. This result is in line with the results of Kujala and colleagues [45], who also found an increased MMN for the group of dyslexic children, who participated in an audio-visual Computer training.

It is interesting, that the PA training, that aimed at improving phonological awareness and basically taught the children how to make the syllable structure of a word listenable in order to spell it correctly, also increased the sensitivity to sound changes. This finding is novel and has not been reported before. The MMF increase in the PA group was correlated with an improvement in the dictation. These findings support the hypothesis that the PA training improved auditory perceptual precision and the sensitivity to sound changes without aiming at an underlying temporal processing deficit.

In contrast to results of AP and PA, children in the SR group produced decreased MMF amplitudes with a significant attenuation in left-temporal channels. Given that controls showed little changes from test to re-test, habituation may not be

a likely explanation. We had not expected the SR training to have an effect on the MMF, since it focused on cognitive, rule-based learning. An explanation for the MMF decrease after training might be that the children learned to use the rules very effectively and thereby had a functional compensatory tool that enabled them to spell words correctly without having to rely on their deficient phoneme-to-grapheme representation. Possibly, the children were "focussed away" from audition by intensely practising and applying spelling rules. The MMF amplitude decrease did not seem to correspond to changes in behavioural test performance, however.

Given the results described above and the hypotheses we formulated in the introduction, we can make inferences about possible etiological factors of dyslexia. We found most training-induced effects on the cortical measure MMF for the PA training. After training, the MMF increased in left fronto-temporal and right hemispheric channel groups. This increase was correlated with an improvement in dictation performance. We also found an increase in MMF amplitude after the AP training. The SR training led to a decrease in MMF amplitude that did not correlate with any qualitative behavioural change. Since the PA training produced the greatest effects, we can assume that the underlying deficit – at least in our sample – may be related to a lack of phonological awareness rather than a more general auditory perceptual deficit.

2.2.5. Conclusion Study II

We found dyslexic children to show poor performance in categorical perception (*phonology*). Nonetheless, they had control-like MMF amplitudes (*audition*). Thus, it seems that dyslexic children do perceive the difference between syllables, yet they cannot categorize them reliably. This supports the view that deficient *audition* leads to poor *phonology*, but not necessarily vice versa. It is likely that some but not all children have difficulties with temporal processing in an unselective sample of dyslexics.

We also found MMF amplitude to be a measure of training effects. Most effects were found for the PA training of phonological awareness that improved the sensitivity to sound changes at left fronto-temporal and right temporal sites without aiming at an underlying temporal processing deficit. The MMF increase in the PA group was correlated with an improvement in the dictation.

From these results we infer that a lack of phonological awareness rather than a more general auditory perceptual deficit may be the most relevant underlying cause of dyslexia.

2.3. Study III: *Word processing differences between dyslexic and control children*

2.3.1. Background Study III

It is widely agreed that a core deficit of dyslexia is reduced phonological awareness (the reduced ability to discriminate speech-sounds in spoken words; [22, 43, 48, 167-169]. Phonological awareness is not only assumed to be a pre-requisite for speech-perception, but also for learning the correspondence between graphemes and phonemes which again is crucial for reading and writing [22, 170-173]. According to dual route models of reading (e.g. [17]), the pronunciation of words can be retrieved in two different ways, depending on the frequency and regularity of a word. High frequent (HF) words are more familiar to the reader, as they appear more often in spoken and written language. It is likely that the visual forms of HF words are directly associated with their meaning in the same way as images are [18]. Therefore it is possible to read a word at a glance, if it is well-known enough. This way of reading is often termed “direct route” or “lexicosemantic route”. In contrast, other strategies may be used to decode low frequent (LF) words or pseudowords (PS). If a word is not familiar to the reader, it is necessary to phonologically assemble the word from sublexical parts following grapheme-to-phoneme correspondences in order to read and retrieve the meaning correctly. This route is called “graphophonological route”, “indirect route” or “sublexical route”.

Due to their lack of phonological awareness, it appears reasoned that dyslexics should be most impaired reading novel or unfamiliar words, where successful decoding relies on the application of the graphophonological route. Castles and Coltheart [188] investigated the reading performance of 53 dyslexic and 56 age matched control children. Children were to read aloud regular, irregular and PS words. They found that the majority (72%) of the dyslexic children were below the confidence limit for pseudoword reading, i.e. they had difficulties reading via the graphophonological route. Only 19% of the dyslexic children were exclusively impaired reading irregular words with a control like performance reading PS words. I.e. these children were able to successfully apply grapheme-phoneme-conversion rules necessary for pseudoword reading while being impaired using the direct route.

Visual word processing differences between high and LF words have been revealed in several studies measuring electrical or magnetic brain activity. Sereno et

al. [189] reported higher amplitudes for LF words in comparison to HF words in anterior parietal and occipital regions between 132 and 164ms. Assadollahi and Pulvermüller [190, 191] found that LF words led to stronger brain responses than HF words starting as early as 120 ms post stimulus. Calculating source localisations of the effects, they found that the frequency effects were strongest over a left occipito-temporal area. Hauk and Pulvermüller [192] also reported higher amplitudes for LF words in an early timeframe from 150-190ms (most pronounced at left occipital electrodes), as well as in a later timeframe between 320 and 360ms for parietal leads. Interestingly, Proverbio et al. [193] found similar P150 amplitudes for both PS words and words when their lexical frequency was low. The authors concluded that highly familiar words are recognized as unitary objects at early processing stages, while this is not the case for unfamiliar words. Rudell [194] visually presented HF and LF words using the rapid stream paradigm [195]. The component elicited using this paradigm is called recognition potential (RP). A target word (HF or LF) was presented for 200 ms and then immediately followed by three different letter-strings. Data were recorded at two occipital electrodes. They reported a frequency effect with HF words having a shorter RP peak latency than LF words (266 vs. 292 ms).

All these findings reflect distinct cortical processing of HF and LF words at relatively early processing stages (between 100 and 360 ms), possibly reflecting different reading strategies. Hauk and Pulvermüller [192] postulate that the synaptic connections representing a word become more and more efficient, the more often a word is encountered. As a consequence less activation is necessary to activate the corresponding word. Thus, it appears reasoned that the graphophonological route will draw more processing resources than the direct route.

Not many studies have investigated word reading varying word frequency in dyslexia. The studies that did, however, found rather unexpected results. Johannes et al. [196] visually presented HF and LF words to 6 dyslexic adults and control subjects while measuring EEG. Each word was presented twice. In both groups they found LF words to elicit higher N400 amplitudes than HF words. While control subjects showed an amplitude decrease for both word types in the repeat condition, this decrease was only present for LF words in dyslexics. The authors inferred that N400 amplitude for HF words is already reduced on the first encounter in dyslexics. Johannes and colleagues interpreted this as a result of enhanced semantic integration of HF words, having compensatory function. The finding is surprising

since one would have expected to find differences between dyslexic and control subjects processing LF words (only LF words require graphophonological reading). It should be noted, however, that the sample size in this study was very small and the dyslexics were recruited at a university, implicating that they were well compensated dyslexics.

Rüsseler and colleagues [197] investigated recognition memory for HF and LF words in 12 adult dyslexics and 12 adult controls in the EEG. Again, no specific processing differences for LF words were found between the groups. Recognition memory for both HF and LF words was reduced in dyslexics. Additionally, an old/new effect for the P600 component (that was stronger for LF words) was only present for control subjects. The authors explained this by a reduced recognition memory in dyslexic subjects, regardless of word type. Like in the study by Johannes et al. [196], it should be mentioned, however, that the dyslexic sample consisted of highly compensated university students, thus raising the question if the results can be generalised.

Hyönä and Olson [198] examined eye fixation patterns of 21 dyslexic and 21 younger, reading-age matched control children during reading of HF and LF words. They did not find the two groups to differ in number and length of fixations. The more “difficult” LF words attracted more and longer fixations than HF words. The authors interpreted their finding as support for a maturational lag hypothesis in dyslexia, since performance of the younger control group (mean age 10 years) resembled performance of the older dyslexic group (mean age 14 years). However, reading correctness did differ between the groups. Dyslexic children made twice as many word substitution errors (e.g. *travelled* instead of *traversed*) and 50% more nonword substitution errors (e.g. *compendent* instead of *competent*) than control children, with 95% of the latter and 76% of the word substitutions occurring on LF words.

In summary, the lack of group differences for processing LF words might be a consequence of the dyslexic samples being highly compensated university students [196, 197] or of the dependent measure (eye fixations) not being sensitive enough to mirror the pattern found in the behavioural data [198].

The aim of the present study was to investigate cortical processing of HF, LF, and PS words in a representative dyslexic sample and a matched control group. We were not interested in semantic processing of different word types, but in automatic processes triggered by a visual word stimulus - like the initiation of different reading

strategies depending on the familiarity of the stimulus. Thus, we chose to visually present different word types in a rapid serial visual presentation (RSVP) design (1 stimulus per 350 ms) while measuring cortical activity in the MEG. Since processing differences between HF and LF words have been found on early components (as early as 120 ms) probably reflecting pre-semantic processes of different reading strategies, we thought it possible to detect such differences when faster presentation rates than 1 stimulus per 800 ms – 1 stimulus per 2000 ms are used. The assumption that early word processing differences can be found using higher presentation rates than the ones generally used in electrophysiological word reading studies is supported by the work of Rubin and Turano [199]. They visually presented words as a conventional text passage (PAGE) or in a rapid serial fashion (RSVP) and found that subjects were able to read (and comprehend) 1100 words/min (one word per 54 ms) when reading words in RSVP while only 300 words/min in the PAGE condition. The authors argue that saccadic eye-movements (being more prominent in the PAGE condition) impose an upper limit on reading speed.

We assumed RSVP to be an appropriate tool to investigate word processing in dyslexia, since it allows setting focus on early, more *automatic* aspects of word processing induced by visual word stimuli. Control and dyslexic subjects were not expected to differ processing HF words, since the majority of dyslexics is not impaired reading highly familiar words. We did expect to find group differences for low frequent words: Skilled readers should be able to successfully decode low frequent words, while dyslexic readers should have difficulties doing so (due to their reduced ability to apply grapheme-phoneme correspondences). No specific hypotheses were formulated for PS word processing. We chose to analyse the stimulus-evoked cortical activity by the means of wavelet transformation, since it offers additional information about the spectral frequency of the effects.

2.3.2. Methods Study III

Generation of the sample and behavioural tests

The participating children were contacted through 14 primary schools in or around Konstanz, Germany, and attended either 3rd or 4th grade. Schools were asked to name children with massive problems reading and spelling, as well as children without any such difficulties. In order to objectively classify the children to be dyslexic,

all children underwent a test-battery that was designed to assess a variety of abilities ranging from spelling and reading to phonological abilities (*DRT* (Diagnostischer Rechtschreibtest 3rd grade [151]; 4th grade [152]): Standardized spelling test; *ZLT* (Zürcher Lesetest [153]): Standardized reading test; *SPM* (Standard Progressive Matrices, German version [154]): non-verbal IQ-test; Non-standardised *Word reading*: List of words with increasing difficulty to be read aloud; Non-standardised *Pseudoword reading*: List of pseudo-words with increasing difficulty to be read aloud; *Mottier-Test* [155]: Pseudowords with increasing difficulty are read aloud by the experimenter and are to be repeated by the child; *Dictation* [156]: only words were used that are spelled as one "hears" them, i.e. no knowledge about spelling rules or exceptions is necessary; *Categorical perception*: judgement, if a syllable sounds more than "ba" or "da", when the formant transition period of the syllable is varied on a ten-item continuum with 1 representing a clear /ba/ and 10 representing a clear /da/). If a child, who was classified as being dyslexic by the teacher, was not significantly worse than the norm-sample in the standardized spelling test, he/she was excluded from the study. Control children who performed significantly worse than the norm sample in the spelling test were either excluded or classified as dyslexic.

Subjects

20 control children and 55 dyslexic children participated in the study. The two groups did not differ statistically in age ($F(1,73)=0.24$; $p=0.6$, range 8-10 years), handedness ($X^2(1,73)=1.3$; $p=0.3$) or gender distribution ($X^2(1,73)=0.01$; $p=0.9$). Table 2.3.1 displays the group mean results of the behavioural tests.

Table 2.3.1: One way ANOVAs of dependent variables SPM, DRT (T-values); ZLT Correctness, Word Reading Correctness, Pseudoword Reading Correctness, Mottier Test, Dictation (% correct); Word Reading Time, Pseudoword Reading Time (seconds); ZLT Reading Time (seconds/no words); Categorical perception (Index) and GROUP (control, dyslexic) as between group factor

	SPM	DRT	ZLT Correctness	ZLT Reading time	Word Reading Corectness	Word Reading Time	Pseudoword Reading Correctness	Pseudoword Reading Time	Mottier Test	Dictation	Categorical Perception
Control	63.0	58.1	97	0.67	90	71.7	76	117.1	85	92	30.7
Dyslexic	51.4	36.9	87	1.45	74	170.1	52	218.7	65	75	24.8
F (1,73)	15.2	194.7	22.4	22.5	33.3	28.8	34.9	12.6	25.1	36.5	16.3
p	0.0002	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0002	<0.0001	<0.0001	0.0001

Stimulation

Three different types of words were presented: 1) high frequent content words, 2) low frequent content words, and 3) PS words. Content words were selected from the German version of the standardized word-database CELEX [200]. HF words were selected to be as high frequent as possible (1091-104 per million words text), LF words were supposed to be as low frequent as possible (1-9 per million words text). All words were nouns. PS words were generated by shuffling letters of actual words so that they were still pronounceable, orthographically legal but non-existing German words. All words and PS words were 5 to 7 letters long, written in capital black letters on a white background.

100 HF, 100 LF and 100 PS words were selected. Together they formed a block of 300 words being presented in a randomised fashion. Each block was presented twice at a presentation rate of 1/350 ms. There was no temporal gap between successively presented words.

Words were generated in bitmap-format; “Presentation” software (Neurobehavioral Systems, Inc. (NBS)) was used for stimulation. Words were screened onto a white projection field (max. word size: 20-32cmx9 cm, 1.4 m away from the subject´s eyes) at the ceiling of the chamber using a video beamer (JVC™, DLA-G11E) and a system of mirrors.

Subjects were told that they would see different words and PS words on the screen and were instructed to read them as carefully as possible. They were also told that words might flash so fast that reading would be difficult, but that they should still try as hard as they can. Children were also asked to name some of the words they saw after the experiment.

MEG Recording

MEG was recorded using a 148-channel whole-head magnetometer (MAGNES™ 2500 WH, 4D Neuroimaging, San Diego, USA). Subjects were lying supine in a comfortable position in the magnetically shielded room (Vakuumschmelze Hanau). Data were recorded with an online high-pass filter of 0.1 Hz and a sampling rate of 508.63 Hz (bandwidth 100Hz), as well as standard noise reduction procedures. Recording was continuous.

For artefact control, eye movements (EOG) were recorded from four electrodes attached to the left and right outer canthus and above and below the right eye, as well as cardiac activity (ECG) via two electrodes, one on each forearm. A Synamps amplifier (NEUROSCAN) served for the recording of EOG and ECG. A video camera installed inside the chamber allowed monitoring the subject's behaviour and compliance at any time throughout the experiment.

Data Analysis

Data were noise-reduced and corrected for cardiac activity. For each subject data epochs with a 350 ms baseline and a post-trigger window of 350 ms were generated. Epochs containing artefacts (signals > 120 µV in the EOG and signals > 5pT in the MEG-channels) were rejected. The remaining epochs were averaged separately for the three word conditions. As the next step, a time-frequency-band analysis (FBA) with a complex Gabor wavelet [201] and a f_0/σ_f ratio of 7 was computed for all MEG-channels. Power spectra were retrieved from the FBA for each time point and frequencies between 10 and 100 Hz. In order to reduce the amount of information, selected channels above frontal, temporal and occipital regions in both hemispheres were averaged to form 6 channel groups (left and right frontal, left and right temporal, left and right occipital). Frontal and temporal channel groups consisted of 20 channels, occipital channel groups consisted of 15 channels.

Channel groups were selected individually based on pickup coil positions. The centre and neighbouring pickup coils were estimated as being closest in terms of angle to predefined positions (all positions (x, y, z, see Fig. 3.2.1) in cm: left frontal (8, 4, 5), right frontal (8, -4, 5), left-temporal (0, 7, 5), right-temporal (0, 7, 5), left-occipital (-8, 4, 5), right-occipital (-8,-4, 5)). This assured that channels over the same brain regions were averaged for all the subjects.

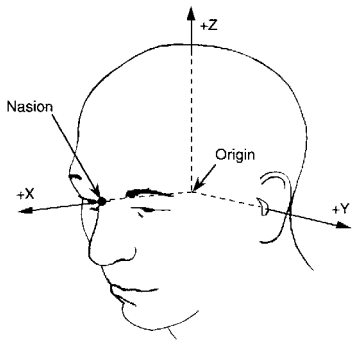

Fig. 2.3.1: Headcoordinate system

Statistical analysis

Since the exact timing of maximum activity, as well as the spectral frequency of activation peaks varies considerably between subjects, it was decided to investigate maximum evoked power amplitudes as dependent variable rather than mean amplitude in a selected time-frequency bin (see results section). Using mean activity in a time-frequency window might have led to blurred results.

Statistical analysis was done with mixed models using the PROC MIXED module of SAS^{TM}. Covariance parameters were estimated with the restricted maximum likelihood method (REML). Maximum amplitude of evoked power (MAX) in the time-frequency bin 80-150 ms and 20-35 Hz (see results section) was dependent variable, HEMISPHERE (left, right), WORDCLASS (HF, LF, PS) and GROUP (control, dyslexic) were fixed effects. PATIENT nested in GROUP was used as random factor. Variance structure was *variance components (VC)*. Least square means were estimated with the restricted maximum likelihood method (REML). Tukey-Kramer test was used for post-hoc investigations of significant differences. In cases of significant differences, spectral frequency (Hz) and latency (ms) of the maximum amplitudes were analyzed as dependent variable. Fixed effects and random effect were the same as described above. *Only significant main effects, interactions and post hoc tests are reported*.

Where significant group effects were found, correlations were calculated between the correspondent dependent variable (MAX amplitude, spectral frequency or latency) and performance at the behavioural tests.

2.3.3. Results Study III

Figure 2.3.2 shows the *average power* evoked by the three word conditions for the control children in occipital regions. Evoked power is expressed in z-values. Most activity can be seen between 15 and 35 Hz in a time window from 80 to 150 ms. Thus, further analysis was performed in this time-frequency bin. *MAX amplitudes* were determined and statistically analysed in the time-frequency bin per condition, hemisphere and person.

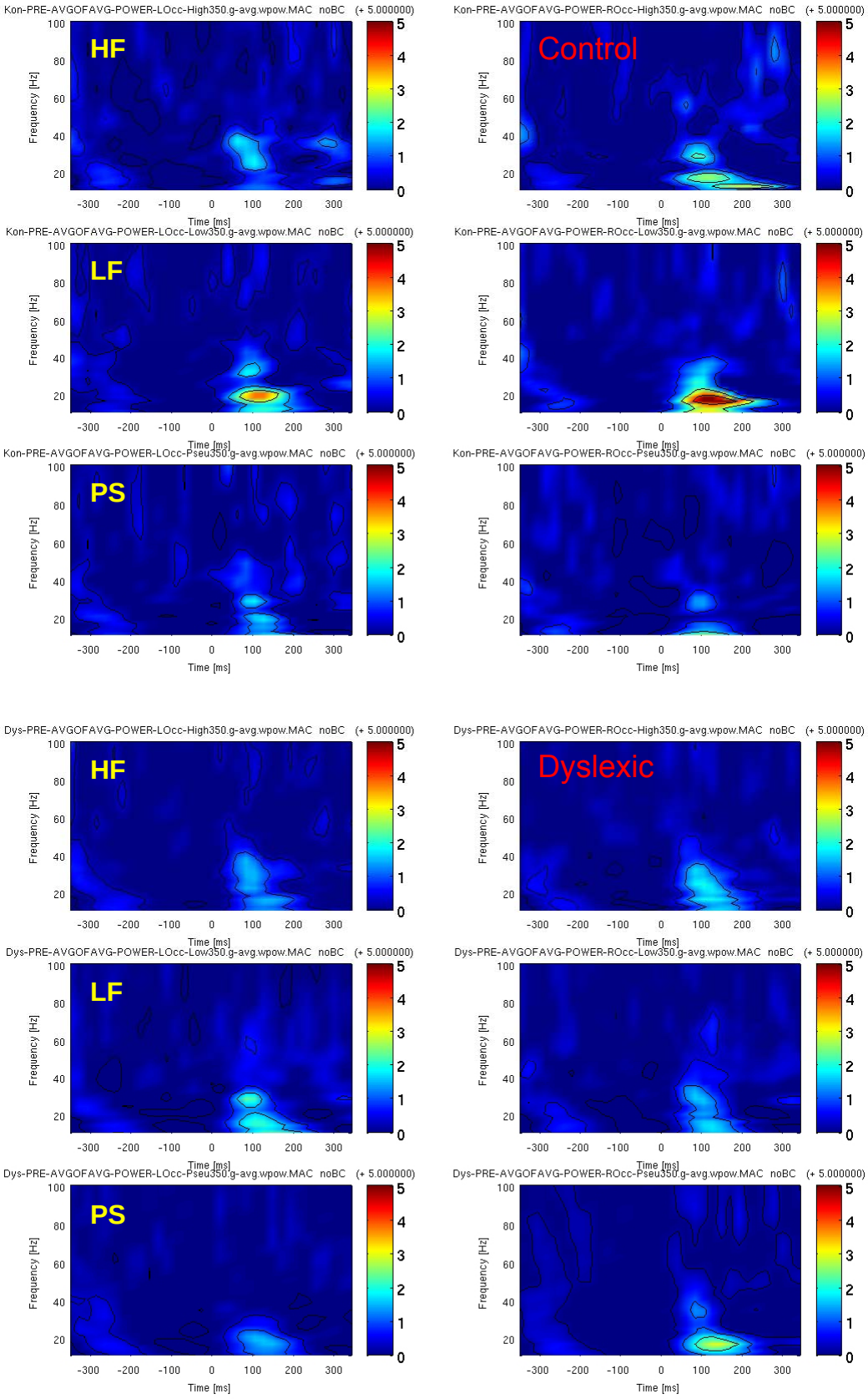

Fig. 2.3.2: Average evoked power for high, low frequent and pseudo words in both hemispheres. Most activity was found between 80 and 150ms and between 15 and 35Hz.

Results statistical analysis

Frontal and temporal channels

No differences between the groups or interactions between GROUP and WORDCLASS were found for frontal and temporal channels.

Occipital channels

MAX amplitude

The interaction GROUP*WORDCLASS (F(2,146)=4.62, p=0.01) was found. Figure 2.3.3 displays the LS means of GROUP*WORDCLASS. As can be seen, clear amplitude differences between the wordclasses were found for the control children, whereas no such clear differences were apparent for the dyslexic children. Post hoc testing revealed that within the group of control children, LF words led to higher amplitudes than HF words (p=0.01) and PS words (p=0.001). The two groups differed in amplitude of LF words. Amplitudes in the group of control children were higher than amplitudes in the group of dyslexic children (p=0.005).

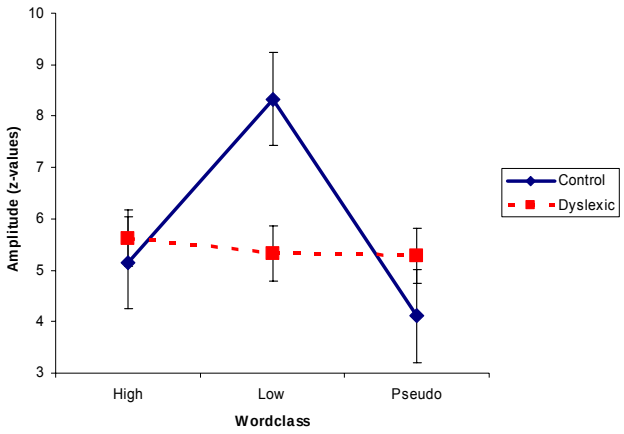

*Fig. 2.3.3: Interaction GROUP*WORDCLASS. LF words were related with higher amplitudes only for the control children.*

MAX spectral frequency

The interaction GROUP*HEMISPHERE (F(1,73)=4.48, p=0.038) was found. Whereas MAX frequency was higher in the left hemisphere compared to the right hemisphere in the group of control children, the opposite pattern could be seen for the group of dyslexic children. However, the only statistically significant post-hoc

difference was found between left and right hemispheric spectral frequencies for the dyslexic children (p=0.047, see figure 2.3.4a).

Finally, the interaction GROUP*WORDCLASS (F(2,146)=3.07, p=0.049) was revealed. While MAX frequency differed between the wordclasses within the group of control children, this was not the case for the dyslexic children. In the control group, LF words were associated with lower spectral frequencies than HF (p=0.01) and PS words (p=0.009). Furthermore, spectral frequency of LF words was lower for the control children than for dyslexic children (p=0.04, see figure 2.3.4b).

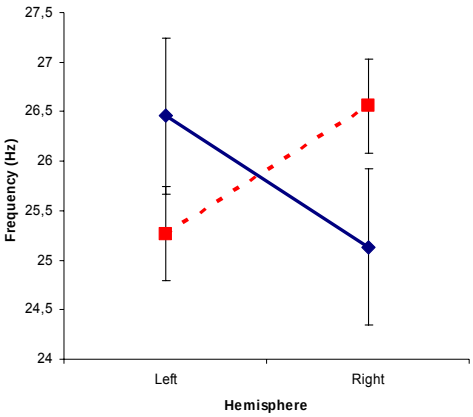

*Fig. 2.3.4a: Interaction GROUP*HEMISPHERE. Right hemispheric activity was related with higher spectral frequencies only for dyslexic children.*

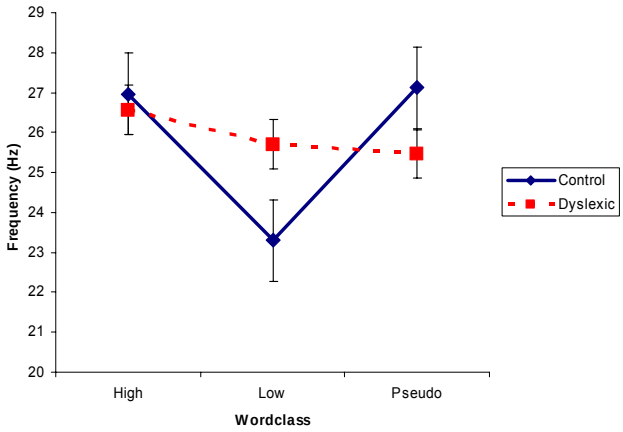

*Fig. 2.3.4b: Interaction GROUP*WORDCLASS. LF words were related to lower spectral frequencies only for the control children.*

Latency of MAX

No significant group differences were found for MAX latency. Latencies for the different word types were 100.2 ms (HF words), 102.3 ms (LF words) and 87.57 ms (PS words).

Correlation between MAX amplitude, frequency and behavioural tests (p<0.05)

MAX amplitude

For **LF words**, a significant correlation was found between test performance in the DRT and MAX amplitude (r=0.25), as well as between performance in the dictation and MAX amplitude (r=0.24). I.e. higher spelling ability seemed to be associated with higher MAX amplitudes.

MAX spectral frequency

For **HF words**, a linear relationship was found between word reading performance and MAX frequency (r=0.24). A negative correlation was revealed between word reading time and MAX frequency (r=-0.27). I.e. a small amount of errors and high reading speed at the word reading test was related with higher MAX spectral frequencies.

For **LF words**, negative correlations were found between performance in categorical perception and MAX spectral frequency (r=-0.30), performance in the Mottier test (r=-0.37) and MAX spectral frequency as well as between performance in the SPM and MAX spectral frequency (r=-0.35). I.e. both, good performance in tests of phonological awareness and good performance at the nonverbal IQ test were associated with a lower MAX spectral frequency.

2.3.4. Discussion Study III

While control children displayed a typical pattern of higher activity following LF words than HF words, this word frequency effect was not present for dyslexic children. A word frequency might reflect different strategies reading HF and LF words. HF words are possibly recognised as a unitary pattern [18], whereas LF words have to be phonologically assembled from sublexical parts following grapheme-to-phoneme correspondences [17]. The latter procedure is likely to draw more processing resources and thus results in higher amplitudes in the EEG or MEG signal [192]. Our finding of a word frequency effect in healthy control children is in line with several studies on visual word processing (e.g. [189-192]). The absence of a word frequency effect in dyslexic children might result from a specific difficulty encoding LF words. As formulated in our hypotheses, control and dyslexic children did not differ processing HF words. We assume this might be the case, since dyslexics are generally not impaired reading highly familiar words. Neither did the groups differ processing PS words. One possible explanation is that processing (in terms of wordform recognition) succeeds for HF words in both groups and LF words in the control group (with more effort due to phonological assembly) but not for PS words due to lacking word representation. Similar amplitudes of HF and PS words thus might reflect different underlying processes. It is imaginable that highly tuned neural cell assemblies respond to the visual pattern of HF words resulting in a relatively low amplitude [192],

whereas a similarly low amplitude for PS words may result from a lacking wordform representation for PS words.

We had expected group differences for LF words. Reduced amplitudes in the dyslexic children are possibly a consequence of their reduced ability to read via the graphophonological route which in turn might result from reduced phonological awareness. Whereas control children manage to successfully apply grapheme-phoneme matching, dyslexic children might not be able to do so resulting in lower amplitudes for LF words compared to control children. Interestingly, we found significant correlations between MAX amplitude for LF words and performance in the dictation as well as the standardised spelling test. This supports the idea that good spelling performance is related to the ability to apply grapheme-phoneme correspondences (reflected in higher amplitudes for LF words).

One might argue that dyslexic children were simply not able to read LF words at a presentation speed of 1 word per 350 ms. It should be noted, however, that we were not interested in *reading capability* at a relatively high presentation rate, but in *automatic reading processes* triggered by a rapid serial visual stimulation with different wordtypes. Under this premise, we interpret that the graphophonological reading route is automatically activated for words that are not represented as unitary objects in control children, whereas this process is not activated in dyslexic children. It should also be noted that reading and even retrieval of *word meaning* is possible at much higher presentation rates (1 word per 54 ms, [199]) using RSVP.

In the present study, interactions between GROUP and WORDCLASS occurred at occipital channels. The occipital cortex has been repeatedly found to be relevant for linguistic processing. Polk and colleagues [202] found a left occipitotemporal region being more sensitive to letters than to digits. Bokde et al. [203] revealed functional connectivity between left inferior frontal and occipital areas only for words, pseudowords and letter strings, but not for false font strings. Patients with lesions to the left temporo-occipital cortex have difficulties reading and spelling comparable to dyslexic symptoms. These patients are especially impaired at spelling irregular and LF words [204]. It has been claimed that extrastriate regions in the left hemisphere might be crucial in the acquisition of orthographic word representations [205].

Assadollahi & Pulvermüller [191] found their word frequency effect at left occipitotemporal regions. The authors state that this region might correspond to the

visual word form area (VWFA, [206]), which has – although not undisputed [207] - generally been found to be activated stronger by visual words and pseudowords than by other visual stimuli (see [208]). The VWFA seems to be modality-specific, insensitive to semantic modulation [209] and can be activated without awareness. Interestingly, it has been shown that dyslexic adults activate the VWFA less than controls in response to visual words and pseudowords [9, 144, 210, 211]. It thus appears that left occipitotemporal regions are crucial for fluent and automatised word recognition.

Jobard et al., [18] performed a metaanalysis of 35 neuroimaging studies on reading and found an activation cluster around the occipitotemporal sulcus thus supporting the existence of a VWFA. The authors conclude that prelexical processing of words and pseudowords might take place in this area, i.e. segmentation, classification and the relay of visual word information to other cortical regions for further analysis. This view is supported by Coultheart and Rastle [17], who already stated in the original description of their reading model that initial processing stages are shared between the two reading routes (direct and graphophonological).

From our results of course, we cannot claim to show activation of the VWFA, since our channel selection covered more cortical areas than the VWFA. Neither did we find left lateralised results. Nevertheless, it is likely, that VWFA activation is strongly *contained* in our effects, especially since the effects were found rather early (~100 ms) – probably reflecting prelexical processing. If Jobard et al´s [18] view is correct that occipitotemporal regions might be involved in prelexical processing and the relay of visual word information to other cortical areas, it might be assumed that there is a specific deficit in dyslexic children concerning LF words. Control children showed stronger activation for LF words compared to HF or PS words (see above). Dyslexic children did not. LF words can only be successfully decoded applying grapheme-phoneme correspondences – the reading requisite where dyslexics seem to be most impaired.

The word frequency effect for amplitudes was accompanied by a word frequency effect for spectral frequencies. LF words were related to lower spectral frequencies (~23 Hz) than HF and PS words (~27 Hz) only in control children. Maximal activity for LF words thus peaked in a high beta-band range, while HF and PS words peaked in a low gamma-band range. Xiang et al., [212] also investigated neuromagnetic spectral distribution during word and non-word stimulation and found

frequency changes between 15 to 30 Hz to be crucial for word and non-word processing at occipital sites. The authors related these frequency changes to spatiovisual information processing. They interpreted that implicit word processing is automatically activated as soon as words are present in the visual field, even if reading is not intended. Another study on power changes during various cognitive tasks was performed by Fitzgibbon et al. [213]. They reported an increase in gamma activity in the posterior cortex especially during reading.

Wrobel [214] found increased beta activity (15-25 Hz) during visual attention in primary and higher order visual areas. The author proposes that beta band activity might have the general role of an attention carrier comparable to the role of alpha activity in idle arousal, or gamma activity in feature integration processes. Support for the meaning of beta activity in attention also comes from the field of attentional disorders. It has generally been found that children with attentional deficit hyperactivity disorder (ADHD) show decreased levels of beta activity in posterior regions compared to healthy control children (for review see [85]). Finally, Gross et al., [215] also reported beta activity to play an important role in attentional processes by mediating interactions of a widely distributed attentional network. The authors argue that changes in synchronisation might reflect changes in attentional demand of a task. In this view, we might interpret selective beta band activity for LF words in control children to stem from an increase in attention. It is possible that unfamiliar LF words draw more attention than highly familiar HF words or pseudowords (that do not have any ascribed meaning) in skilled readers. Although speculative, it might be assumed that an increased attentional level is necessary for the more demanding processing of LF words. It appears as if the whole cascade of processing steps necessary for decoding LF words is dysfunctional in dyslexic children.

In the present study, significant negative correlations were revealed between the spectral frequency of LF words and performance in the SPM, Mottier test as well as categorical perception. The latter two correlations are of particular relevance, since both Mottier test performance and categorical perception ability reflect phonological awareness. In the Mottier test, children are only required to repeat back pseudowords the experimenter reads out to them. I.e. the ability is measured, if children perceive phonemes correctly. In the test of categorical perception, the children had to categorise if a syllable sounds more like /ba/ or /da/ (when the formant transition period of the syllable is varied on a ten-item continuum with 1

representing a clear /ba/ and 10 representing a clear /da/). Thus, this test is also a measure of phonological awareness. Dyslexic children performed worse in both tests, i.e. they made more errors repeating back pseudowords and were less certain if they heard /ba/ or /da/. They also did not show lower spectral frequencies for LF words compared to HF and pseudowords as control children did. Thus it appears that there is a relationship between phonological awareness and spectral frequencies for LF words. Lower spectral frequency for LF words seems to correspond to higher phonological awareness. Additionally, high spectral frequency values for HF words were correlated with good reading performance and short reading time. Interestingly, there were no correlations between spectral frequency and PS words. This might also strengthen the view that the seemingly similar processing of HF and pseudowords are different in nature.

Besides the lacking word frequency effect in dyslexic children, the interaction GROUP*HEMISPHERE was revealed in the present study. In control children, left occipital activity peaked at 26.5 Hz and right occipital activity peaked at 25 Hz. This was exactly reversed for the dyslexic children. Nevertheless, the meaning of this interaction is hard to interpret, since the differences in spectral frequency are very small (1.5 Hz). It is likely that the reversed pattern in dyslexia is related to a functional meaning. Our exact knowledge about single frequencies so close together is unfirm, however.

2.3.5. Conclusion Study III

The aim of the study III was to investigate *automatic* reading processes triggered by different wordclasses in dyslexic and control children. For this purpose we utilised a RSVP design and performed wavelet analysis on the evoked activity. We had hypothesised that dyslexic children should mainly differ from controls processing LF words due to their lacking ability to read via the graphophonological route. This was confirmed at the level of evoked power amplitude and its corresponding spectral frequency. Our results support the hypothesis that dyslexic children are selectively impaired reading words that require sublexical processing. This might be another manifestation of lacking phonological awareness in dyslexia.

2.4. Study IV: *Reading words at different presentation rates produces differential effects*

2.4.1. Background Study IV

Study IV was designed to investigate processing of HF, LF and PS words at different presentation rates in skilled readers. This was of interest for three reasons: First, if it was possible to find processing differences with a high speed-presentation, it would open doors for more efficient experimental designs. A larger amount of stimuli could be used leading to a better signal-to-noise ratio with at the same time shorter investigation-times. Second, stimulus-presentation in a rapid stream would allow us to set focus on early, automatic aspects of word-processing. Third, this study was conveyed to explore how a limitation of processing time would affect visual word processing in the brain. We investigated the well known aspects word frequency and wordness and varied the presentation rate. We hypothesized that the brain must have a minimal processing time to produce these effects.

The emotional content of a picture can be recognised even if pictures are presented at high rates. In an EEG study Junghöfer and colleagues [216] found a stronger negativity for affective pictures compared to neutral pictures at temporo-occipital sites at presentation rates of 1/333 ms and 1/200 ms starting around 150 ms post stimulus. A similar finding was reported by Schupp and coworkers [217], who additionally found a later increased positivity for affective pictures at centro-parietal sites, when pictures were presented at a rate of 1/120 ms. They argued that “a quick glimpse of emotionally relevant stimuli appears sufficient to tune the brain for selective perceptual processing”.

If the human brain is able to process complex visual stimuli at such a high rate and even differentiate between emotional contents, is it able to distinguish different word types (i.e. high and low frequent words, words and pseudowords) when written words are visually presented?

The frequency of a word (frequency meaning the incidence of a word in written language) determines the response latency (e.g. [218, 219]): In Lexical Decision Tasks (is the presented letter string a word or not?), reaction times to high frequent words are shorter than to low frequent words. This could be because lexical access is faster when reading high frequent words in comparison to low frequent words.

Differences between word-types have also been found in psychophysiological studies (see study III), when moderate presentation rates (between 1 stimulus/800 ms and 1 stimulus/2000 ms) were used: Tarkiainen and colleagues [211] localised early visual word processing and found activation in left occipito-temporal regions being stronger for real words than for symbol strings around 140ms. Sereno *et al*. [189] observed a similar difference in the 100 and 132 ms time bin at posterior parietal sites. A variation of word frequency then led to stronger activation for low frequent words in comparison to high frequent words in anterior parietal and occipital regions between 132 and 164ms. Compton and coworkers [220] reported that real-word/non-word distinction starts as early as 125ms after stimulus onset with stronger responses to words at left posterior temporal and parieto-temporal electrodes. Assadollahi and Pulvermüller [190, 191] investigated visual word processing found that low frequent words led to stronger brain responses than high frequent words starting as early as 120 ms post stimulus. Calculating source localisations of the effects, they found that the frequency effects were strongest over a left occipito-temporal area. This area is often referred to as the Visual Word Form Area [221, 222].

All these findings reflect distinct cortical processing of different word-types at relatively early processing stages (between 100 and 300 ms). Thus, it may be possible to detect such differences when faster presentation rates than 1/800 ms – 1/2000 ms are used.

The assumption that early word processing differences can be found using higher presentation rates than the ones generally used in electrophysiological word reading studies is supported by the work of Rubin and Turano [199]. They visually presented words as a conventional text passage (PAGE) or in a rapid serial fashion (RSVP) and found that subjects were able to read (and comprehend) 1100 words/min when reading words in RSVP while only 300 words/min in the PAGE condition. The authors argue that saccadic eye-movements (being more prominent in the PAGE condition) impose an upper limit on reading speed.

2.4.2. Methods Study IV

Subjects

19 adults (10 female) gave written informed consent to participate in this study. Mean age was 24.5 years (range 20-32 years). All subjects were right handed (mean value 93%, range 80-100% according to the questionnaire of Oldfield, 1971). Subjects were healthy with no history of neurological impairment.

Stimulation

Three different types of words were presented: 1) HF words, 2) LF words, and 3) PS words. Words were selected from the German version of the standardized word-database CELEX [200]. HF words were selected to be as high frequent as possible (1091-104 per million words text), LF words were supposed to be as low frequent as possible (1-9 per million words text). All words were nouns. PS words were generated by shuffling letters of actual words so that they were still pronounceable, orthographically legal but non-existing German words. All words and pseudo-words were 5 to 7 letters long, written in capital black letters on a white background.
100 HF, 100 LF and 100 PS words were selected. Together they formed a block of 300 words being presented in a randomised fashion. Each block was presented twice with a given presentation rate. Three different RATES were used: 2.86 Hz (each word was visible for 350ms), 4 Hz (250ms), and 6.7 Hz (150ms) with no temporal gap between successively presented words. Every subject received the same sequence of conditions:

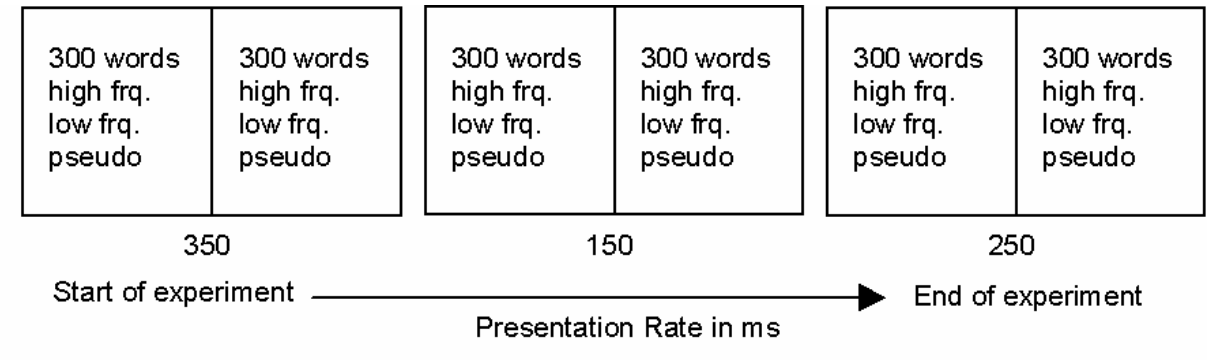

Fig. 2.4.1: Presentation design

Words were generated in bitmap-format; “Presentation” software (Neurobehavioral Systems, Inc. (NBS)) was used for stimulation. Words were screened onto a white

projection field (max. word size: 20-32cmx9 cm, 1.4m away from the subject´s eyes) at the ceiling of the chamber using a video beamer (JVC™, DLA-G11E) and a system of mirrors.

Subjects were told that they would see different words and pseudo-words on the screen and were instructed to read them as carefully as possible. They were also told that some words would flash so fast that reading would be almost impossible, but that they should still try as much as they can.

MEG Recording

MEG was recorded using a 148-channel whole-head magnetometer (MAGNES™ 2500 WH, 4D Neuroimaging, San Diego, USA). Subjects were lying supine in a comfortable position in the magnetically shielded room (Vakuumschmelze Hanau). Continuous data sets were recorded with a real high-pass filter of 0.1Hz and a sampling rate of 678.17Hz (bandwidth 200Hz), as well as standard noise reduction procedures.

For artefact control, eye movements (EOG) were recorded from four electrodes attached to the left and right outer canthus and above and below the right eye. A Synamps amplifier (NEUROSCAN) served for the recording of the EOG. A video camera installed inside the chamber allowed monitoring the subject's behaviour and compliance at any time throughout the experiment.

Data Analysis

Global noise was filtered from the MEG data by subtracting external, non-biological noise recorded by 11 MEG reference channels. The data was then split into epochs of 1400ms length discarding all epochs with an EOG level > 100μV, or an MEG level > 5pT between the minimum and maximum on one or more MEG channels. A maximum of 200 MEG-traces was obtained for each of the three WORD sets per RATE condition and subject. For each subject and for each of the nine conditions (3 RATE x 3 WORD), stimulus-triggered evoked magnetic fields were calculated relative to a baseline of one whole presentation time window. Therefore, the baselines for the three RATE conditions were different (baseline for 1/150ms condition: 150ms, 1/250ms: 250ms, 1/350ms: 350ms). We favoured different baselines over a fixed baseline interval, in order to be able to subtract the complete information of the

preceding word in the individual RATE conditions. As the word presentations were randomised, word class effects will be eliminated in the baseline. This strategy worked quite well as can be seen in Fig. 1.

Cortical sources of the average responses were approximated using the minimum norm estimate (MNE), an inverse modelling to reconstruct the distribution of the primary current that has generated the measured magnetic field distribution: Following Hauk et al. [223, 224], we approximated cortical activity in a three-dimensional spherical source space of radius 10 cm fitted individually to the head-shape of the subjects (4-D Neuroimaging software). On this sphere 197 equidistant dipoles were assumed of which the upper 121 locations were selected (excluding neck, jaw etc.). MNE amplitudes of these locations were submitted to the statistically robust global mean of all dipoles. In some cases, we also analysed focal activity by computing the mean activity of dipoles covering a focus (i.e. only dipoles were selected that as a group showed a clearly higher activation than surrounding dipoles). To illustrate the difference between WORD conditions, difference maps of the MNE were also calculated.

For statistical analyses, average values of the global mean over time were calculated in pre-selected time windows. We selected the time windows around maxima of the global power averaged across subjects. In cases of focal activity, we analysed the peak amplitude in the according time window.

Two-way repeated measures Analyses of Variance (design: RATE (3 levels) x WORDS (3 levels)) were calculated to assess significance of between-category differences. Corrections of the degrees of freedom were made following Greenhouse-Geisser, since there were more than 2 factor levels. All reported p-values are corrected values. Newman-Keuls tests were used to further investigate significant main effects or interactions. In the following, only significant main effects, interactions and post-hoc tests are reported.

2.4.3. Results study IV

The global mean of activity suggested that the main effects were to be found between 100 and 200ms post trigger (see fig. 2.4.2).

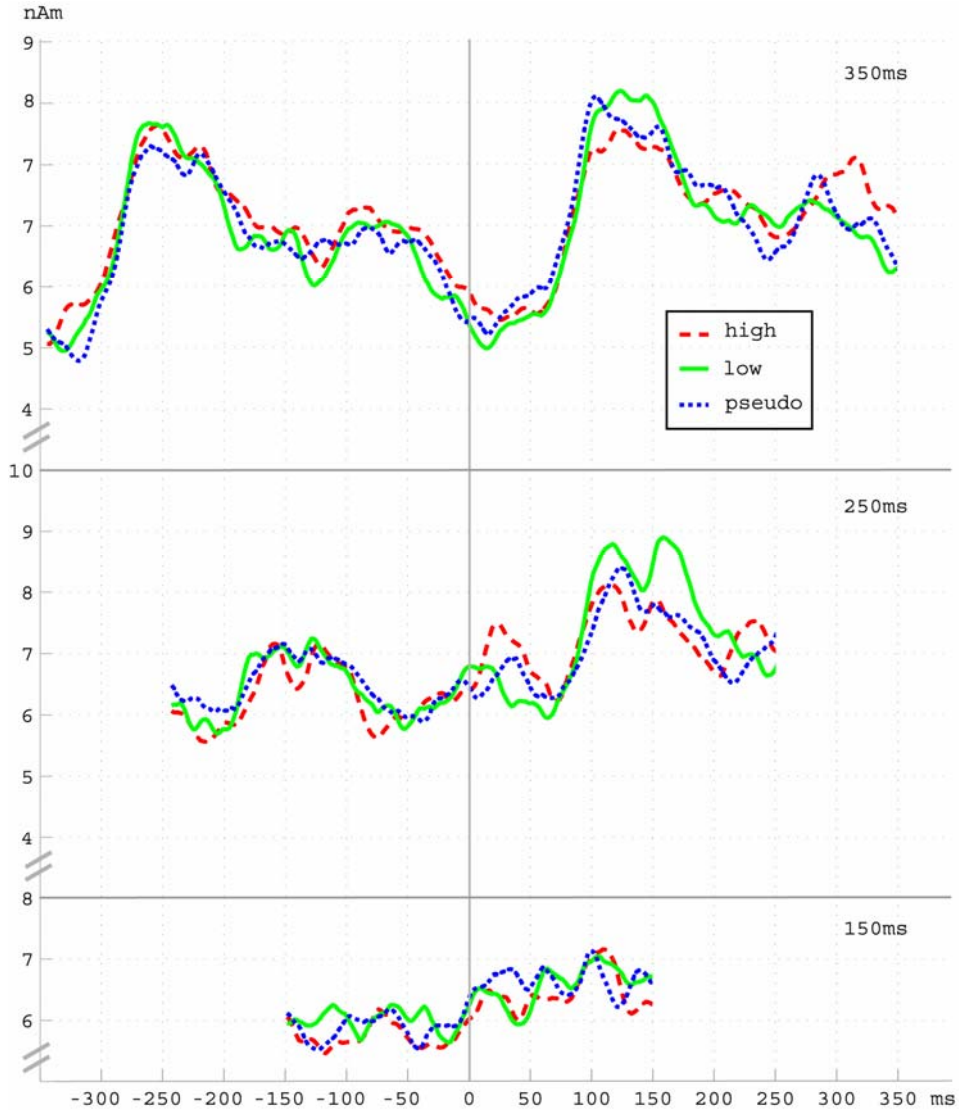

Fig. 2.4.2: Global mean amplitude plots at three different presentation rates (1/350ms, 1/250ms, 1/150ms). Stimulus onset was at time point 0.

While results for the 350ms presentation time suggest that there is only one peak for low frequency words, it is evident that there are two peaks for the 250ms presentation time. Notably, the 150ms presentation time does not suggest any differences. We thus decided to first analyse the entire window from 100 to 200ms and then to analyse the window around the first peak (100-150ms) and the second peak (150-200ms) as suggested by the 250ms condition.

100-200ms

An analysis of variance (ANOVA) was computed in this time window. Global mean amplitude (GMA) was the dependent variable with WORD (HF, LF, PS) and RATE (1/150ms, 1/250ms, 1/350ms) as repeated measures. Significant main effects were

found for WORD (F(2,36)=5.93; p<.01; ε=0.96) and RATE (F(2,36)=11.84; p<.001; ε=0.76). For the WORD effect, post-hoc testing revealed no significant differences between the word types. Post hoc testing of the RATE effect confirmed the impression that the 1/150ms RATE condition had a significantly smaller amplitude than the 1/250ms condition (p=.04) and the 1/350ms condition (p=.02), as shown in Fig. 2.4.3. Amplitude means for RATE were 0.0068nAm, 0.0080nAm, and 0.0083nAm for 1/150ms, 1/250ms, and 1/350ms, respectively.

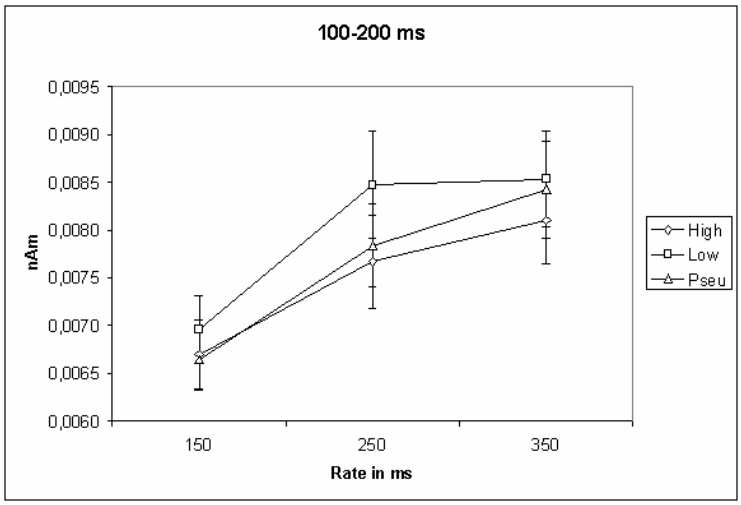

Fig. 2.4.3: ANOVA plot for global mean amplitudes at three different presentation rates (1/350ms, 1/250ms, 1/150ms) between 100 and 200ms.

In the next step separate ANOVAs were computed for the individual presentation RATE-conditions with global mean amplitude as dependent variable. WORD (HF, LF, PS) was repeated measure. No significant WORD effect was found for the 1/150ms RATE condition. For the 1/250ms condition, the WORD effect almost reached significance (F(2,36)=3.23; p=.06; ε=0.94). A significant WORD effect was found for the 1/350ms condition (F(2,36)=3.68; p<.05; ε=0.85). Post hoc testing showed that high frequent content words led to significantly smaller amplitudes than low frequent content words (p=.03). Amplitude means for high and low frequent content words as well as pseudo-words were 0.0081nAm, 0.0085nAm, and 0.0084nAm, respectively.

In order to separately account for two peaks of the global mean amplitude the time range from 100-200ms was split into two segments (100-150ms and 150-200ms). ANOVAs were calculated for the global mean amplitude for the individual RATE conditions with GMA as dependent variable and WORD (HF, LF, PS) as repeated measure. In the earlier latency range (100-150ms) the only main effect for WORD was found for the 1/350ms RATE condition (F(2,36)=3.91; p=0.04; ε=0.84). The only

main effect for WORD found for the later time window (150-200ms) was revealed for the 1/250ms condition ($F(2,36)=3.43$; $p=0.05$; $\varepsilon=0.81$). Therefore, more detailed analysis in the early time segment was performed only for the 1/350ms presentation rate and analysis in the later time segment was restricted to the 1/250ms condition.

100-150ms

Minimum norm maps for the 1/350ms RATE condition in the earlier time window indicated a left occipital focus (Fig. 2.4.4) that was analysed statistically.

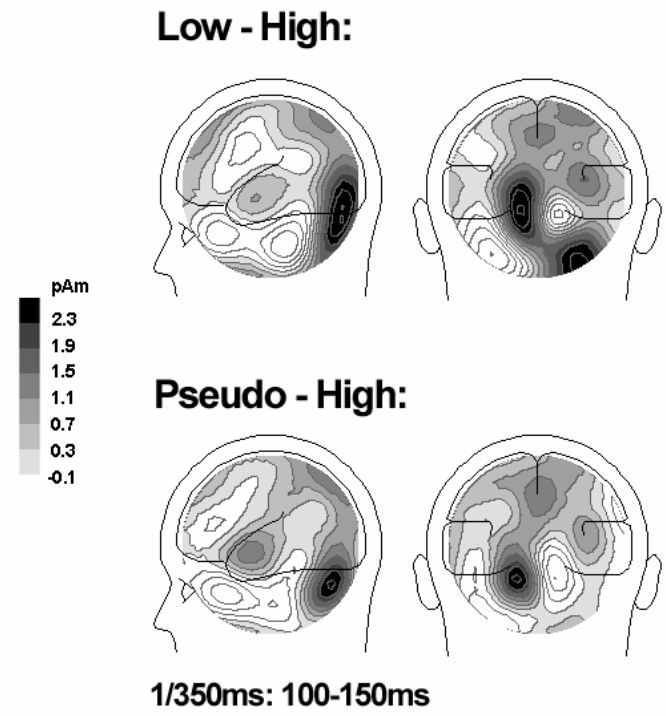

Fig. 2.4.4: Minimum norm difference maps averaged across 100 to 150ms after stimulus onset for the presentation rate 1/350ms. A strong difference can be observed between words that occur at a high and those that appear at a rather low frequency in written language: Low frequent and pseudo words lead to stronger signals than high frequent words at a left occipital focus.

A selection of five MNE dipoles was made, that covered the occipital focus over the visual cortex as illustrated in Figure 4. An ANOVA was calculated for the selected locations using the peak amplitude as dependent variable. A WORD main effect ($F(2,36)=7.91$; $p=.001$; $\varepsilon=.99$) indicated that LF words had larger amplitude values than HF words ($p=.002$). PS words also had larger amplitude values than HF words

(p=.007) (see Fig. 2.4.5). Peak amplitude values for HF and LF words, as well as PS words were 0.022nAm, 0.027nAm, and 0.026nAm, respectively.

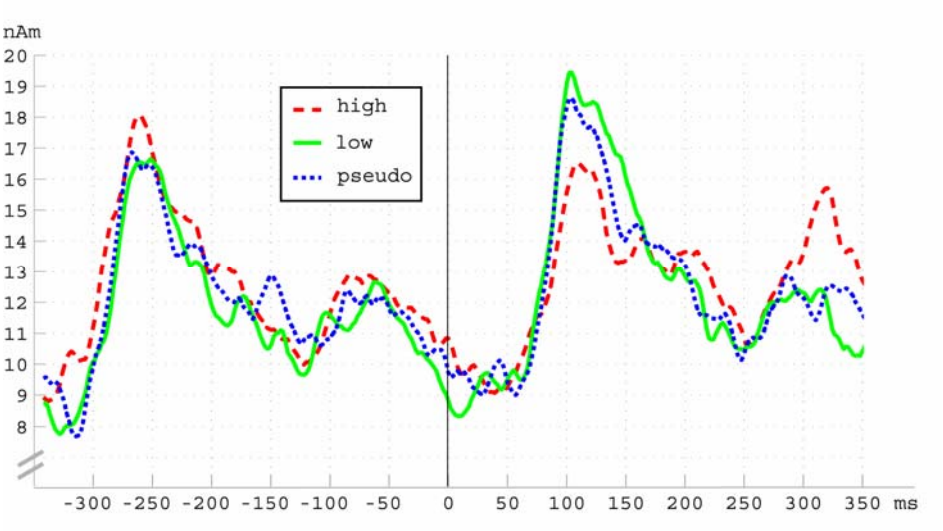

Fig. 2.4.5: Amplitude plots between 100 and 150ms at the left occipital focus.

150-200ms

Inspection of the time window between 150 and 200ms minimum norm maps revealed a left occipito-temporal focus for the 1/250ms presentation rate (Fig. 2.4.6).

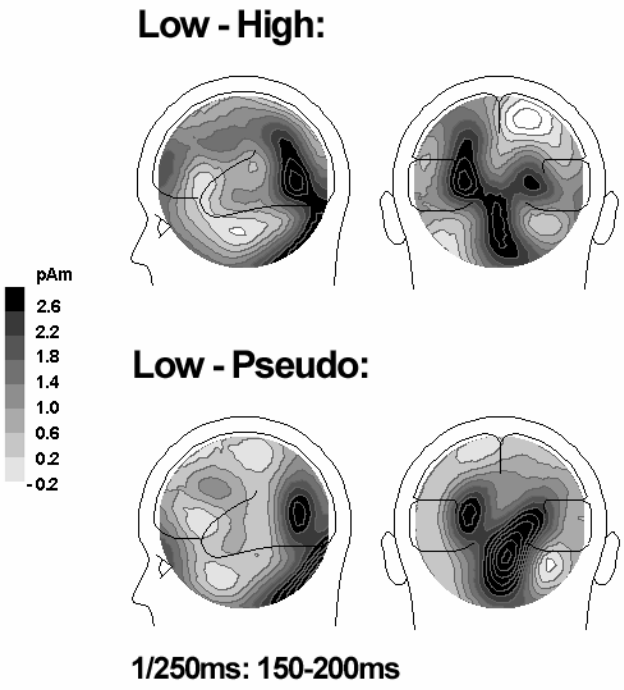

Fig.2.4. 6: Minimum norm difference maps between 100 and 150ms at the presentation rate 1/250ms. Low frequent words lead to stronger signals than high frequent words and pseudo words at a left occipito-temporal focus.

A selection of four minimum norm dipoles covered this temporal focus. An ANOVA was calculated for the selected channels using the peak amplitude as dependent variable and WORD (HF, LF, PS) as repeated measure. A WORD main effect ($F(2,36)=4.51$; $p=.03$; $\varepsilon=.70$) indicated that LF words had larger amplitude values than HF words ($p=0.02$) and PS words ($p=0.02$) (see Fig. 2.4.7). Peak amplitude values for HF and LF words, as well as PS words were 0.016nAm, 0.020nAm, and 0.016nAm.

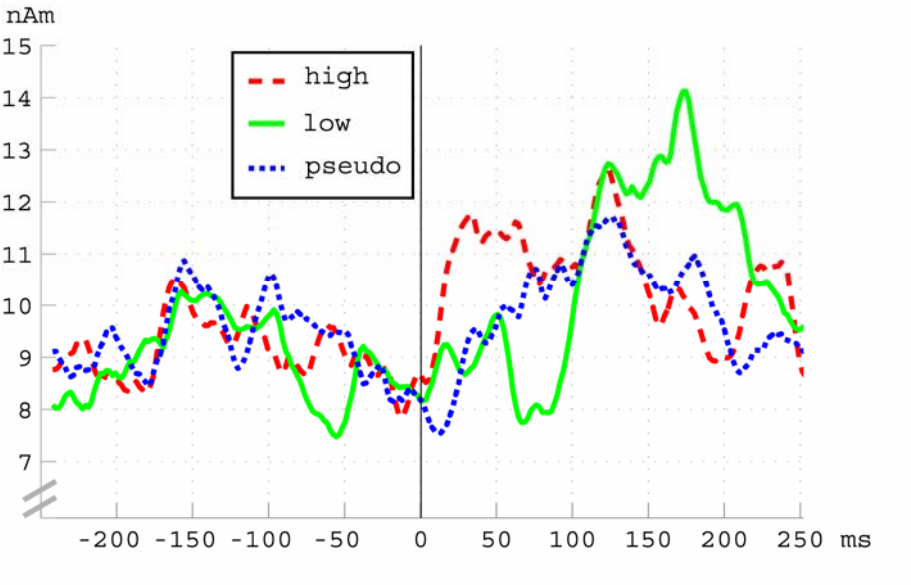

Fig. 2.4.7: Amplitude plots between 150 and 200ms at the left occipito-temporal focus.

2.4.4. Discussion study IV

We investigated brain responses to visually presented HF, LF and PS words at different presentation rates and found the following effects:

1) Differences in word-evoked brain responses became apparent at presentation rates faster than the ones previously reported.
2) There seems to be a minimal processing time: Amplitude differences between the three stimulus types were found at presentation rates of 1/350 ms and 1/250 ms. The 1/150 ms condition yielded no differences.
3) Differential effects were found in different time bins for the two slower presentation rates.

a. Between *100 and 150 ms* post stimulus onset at a presentation rate of 1/350 ms: HF words led to smaller amplitudes than LF words and PS words – "graphophonological effect"
b. Between *150 and 200 ms* post stimulus at a presentation rate of 1/250 ms and between *100 and 200 ms* at a presentation rate of 1/350 ms: LF words led to higher amplitudes than HF words and PS words – "word frequency effect"

4) Effects were related to differential topography.
   a. The "graphophonological effect" was found over left occipital regions.
   b. The "word frequency effect" was found at left occipito-temporal sites in the 1/250 ms condition as well as in the global mean amplitude in the 1/350 ms condition.

Ad 1) and 2) Given the results by Rubin and Turano [199], as well as the early word processing differences found in various psychophysiological studies, we expected to find word processing differences using a RSVP design with higher presentation rates than the ones commonly used in psychophysiological experiments on word processing. Thus, it does seem to be possible to investigate word processing with a more efficient experimental design using a larger amount of stimuli with at the same time shorter investigation-times.

However, the fastest presentation rate (1/150 ms) did not yield clear amplitude differences between the word types as those found for the 1/350 and 1/250 ms presentation rates. Moreover, the global mean amplitude in the fastest condition was significantly smaller than for the more moderate presentation rates. This suggests that a 1 word/150 ms presentation rate might imply too great a load to sufficiently process each word. Rubin and Turano´s findings would have led to the assumption to also find word processing differences at 1/150 ms. As described above, their subjects were able to read 1100 words/min, which corresponds to 18.3 words per second or 1 word/54.5 ms. Yet, there was an important difference between our study and Rubin and Turano's design. They used words in context. Reading words in a context enables the reader to build expectations about the following words (e.g. [225, 226]). This could lead to increased reading speed. In contrast, we presented HF, LF and PS words in a random fashion. Therefore, no expectation about the following stimulus could build, so that words had to be processed "one by one".

Ad 3) We found two qualitatively different word processing effects, the earlier effect termed “graphophonological effect”, the later effect called “word frequency effect”. Our results are in line with dual route models of reading. Thus, we will discuss our findings in this light.

Dual route models of reading (e.g. [17]) are based on the assumption that the pronunciation of words can be retrieved in two different ways, depending on the frequency and regularity of a word. HF words are more familiar to the reader, as they appear more often in spoken and written language. It is likely that the visual forms of high frequent words are directly associated with their meaning in the same way as images are [18]. Therefore it is possible to read a word “at a glance”, if it is well-known enough. This way of reading is often termed “direct route” or “lexicosemantic route”. In contrast, other strategies may be used to decode LF words or PS words. If a word is not familiar to the reader, it is necessary to phonologically assemble the word from sublexical parts following grapheme-to-phoneme correspondences (GPC) in order to read and retrieve the meaning correctly. This route is called “graphophonological route”, “indirect route” or “sublexical route”. Thus, it is likely that the graphophonological route will draw more processing resources than the direct route.

In the present study, the words we used for our set of low frequent words were as rare as possible (1-9 per million words). It can be assumed that the association between the words as a pattern and their meanings is not as strong as it is for high frequent words, since subjects most likely have not *visually* encountered the words often before the study (frequency meaning the incidence of a word in *written* language). As pseudowords do not exist in written or spoken language, it is clear that their pattern is not automatically associated with any meaning or pronunciation. Thus, in order to read them correctly, they must be processed after phonetic rules. Reading with the direct route is less functional for low frequent content words and pseudowords.

We found significant amplitude differences between the word types between 100 and 150 ms at a 1/350 ms presentation rate: HF words led to smaller amplitudes than LF words. Moreover, HF words led to smaller amplitudes than PS words, but PS and LF words did not differ in this time range. These results might mirror the graphophonological and direct routes of reading. Reading PS and LF words involves

the application of sublexical GPCs, while the direct route can be used for retrieving the meaning of HF words. Increased processing resources of the graphophonological route compared to the direct route might be represented in higher amplitudes for LF and PS words. Our results are in line with the work of Ischebeck and colleagues [227]. They performed a study on word processing in Japanese Kana orthography. Kana with its two phonologically equivalent, but visually different syllabaries offers the opportunity to present the same word in two ways, one being orthographically familiar, the other being unfamiliar. The authors presented visually familiar and unfamiliar words, as well as PS words while measuring the fMRI. As a result they found PS words and visually unfamiliar word forms causing an increase in brain activity compared to visually familiar words. The authors take their results as support of dual route reading models, since visually unfamiliar and PS words have to be assembled after GPC rules and thus require more processing resources.

Between 150 and 200 ms, significant amplitude differences were found between the word types at a 1/250 ms presentation rate. LF words led to higher amplitudes compared to both, HF and PS words. The difference to the effect in the earlier time window (100-150 ms) lies in the amplitude of the PS words. While it was as high as the amplitude of LF words in the earlier time window, it dropped to the level of HF words in the later time window (150-200 ms). Thus, the word frequency effect with LF words leading to higher amplitudes than FH words remained, only the role of the PS words changed. The finding of larger amplitudes to words with lower frequencies is well established (e.g. [189, 190, 228]). A word frequency effect in a similar time range (between 132 and 192 ms) was reported by Sereno and colleagues [189]. They also found greater amplitudes to LF than to HF words and interpreted this finding as a greater difficulty processing LF words. Since the (global) mean amplitude represents the strength of brain activation we agree with the interpretation that the word frequency effect in our data might reflect greater processing difficulty for LF words. It is also reported in the literature that gaze durations are longer for LF words than HF words [229, 230], knowing that the ease or difficulty associated with processing a fixated word influences the initiation of eye-movements [231].

Why are the amplitudes of LF and PS words similar in an earlier time window, and why do PS words then seem to “drop” in amplitude later on? According to dual route models, strings of letters that are uncommon or novel are processed using the

graphophonological route. The graphophonological process will succeed (in terms of retrieval of word meaning) for LF words, but will fail for PS words, since there is no meaning to retrieve. The low amplitude for PS words in the later time range from 150 to 200 ms may result from a lacking whole-word (word form) representation for PS words.

A word frequency effect as described above for the 1/250 ms condition was found in the whole range from 100 to 200 ms at a 1/350 ms presentation rate: LF words again led to higher global mean amplitudes than HF words. I.e. the word frequency effect in the 1/350 ms condition was stable over a longer time period than in the 1/250 ms condition. Furthermore, a *graphophonological* and a *word frequency effect* were found in the 1/350 ms condition, whereas only a *word frequency effect* was found in the 1/250 ms condition. We therefore assume that the brain employs different processing strategies depending on the time elapsing between the individual stimuli. Our data thus suggest that processing in the 1/350 ms condition is more detailed and thorough than in the 1/250 ms condition, which is in turn more thorough than in the 1/150 ms condition. It is known from eye movement studies that eye fixations last about 200 to 250 ms during reading (normal text) and that fixation time primarily reflects depth of word processing (the more time, the deeper the processing) [232]. This may explain why different effects are found depending on the amount of time one has to fixate a word. The brain might allocate different amounts of processing resources depending on the presentation rate. This is suggested by the fact, that we did find effects in the time range between 100 and 200 ms for the more moderate presentation rates, but not for the 1/150 ms presentation rate.

Ad 4) We obtained information about the localization of the effects. The graphophonological effect was found at left occipital sites, whereas the word frequency effect was located at slightly more anterior, left temporo-occipital sites. The results suggest that graphophonological and word frequency effects on word processing not only become apparent in different time windows after stimulus onset, but also are to some degree processed in different cortical regions. The word frequency effect related to whole words was exactly located at the same cortical region as in Assadollahi and Pulvermüller´s study [191] investigating word frequency effects. Together, the data corroborate the view, that an area responsible for the representation of visual word forms (the so-called Visual Word Form Area [221, 222])

may reflect the frequency of visual word forms. In contrast, the more posterior area responsible for graphophonological processing may reflect the probabilities at which letters can follow each other. As pointed out by Broadbent & Gregory [233], a word made up by an improbable sequence of letters has a low chance of being a probable word itself. Thus it is clear, that the word frequency effect was comparable at both cortical areas: low frequency items led to larger amplitudes than high frequency items. A further study varying sequential probabilities of letters and word frequencies orthogonally and localising these effects would be able to investigate this hypothesis.

2.4.5. Conclusion study IV

The RSVP design seems to be a useful tool for investigating early automatic effects of word processing. The present data replicate the finding that word properties such as frequency are differentially reflected in the brain response as early as 100 ms. We found evidence for a word processing scheme that comprises two mechanisms, the whole-word/word-form representation and the graphophonological route. We were not only able to obtain information about the time course of cortical word processing mechanisms - we were also able to link different processing stages to separate cortical sites. The graphophonological route is located at left occipital sites whereas the Visual Word Form Area is located at relatively more anterior sites.

It also appears that within a RSVP design, processing becomes more and more detailed the “slower” the presentation rate. No effects were found at the rate of 1 word/150ms. “Only” a frequency effect was found at the rate of 1 word/250ms. Finally, evidence for a frequency effect and a graphophonological effect was found at the “slowest” rate of 1 word/350ms.

2.5. Study V: *The influence of Methylphenidate on the power spectrum in ADHD*

2.5.1. Background study V

Attention Deficit Hyperactivity Disorder (ADHD) is characterized by difficulties concentrating, completing assigned tasks, keeping track of things, waiting one´s turn or sitting still. Three subtypes are classified in the DSM IV (APA, 1994) ADHD of the predominantly inattentive type, ADHD of the predominantly hyperactive type and a combined type. The prevalence of ADHD is estimated to lie between 3 and 5% of all school children with a stronger tendency for boys to be diagnosed (APA, 1994). However, Scahill and Schwab-Stone [70] investigated data from 13 studies and found prevalence to vary between 2 and 14.9%, depending on diagnostic tools and community sample. An increase in prevalence has been observed throughout the last years, which might be related to a change in diagnostic criteria and the introduction of ADHD predominantly hyperactive type in the DSM IV. All ADHD subtypes are generally treated the same way, the prescription of Methylphenidate (MPH) (NIH consensus statement, 1998). MPH has shown to be effective in 75-90% of ADHD children (Mental Health Report of the Surgeon General, 1999). In line with increasing prevalence estimates, the usage of MPH has increased several fold during the last years in the USA (United Nations International Narcotics Control Board, 1995) as well as in Germany [234].

It has been stated by several authors, that ADHD is related to cortical hypoarousal [85, 99, 100, 104]. The mechanism behind this possible hypoarousal is not yet clarified. However, evidence from SPECT studies [98, 103] and the mere fact that MPH – a psychostimulant - is an effective treatment of ADHD symptoms suggest there is a deficit in the dopaminergic neurotransmitter system. As SPECT studies (e.g. [80]) have shown, ADHD patients seem to have a higher number of DAT receptors, which are responsible for dopamine re-uptake, and in consequence have less dopamine available in the synaptic gap. MPH is a potent blocker of DAT receptors.

It has previously been shown that some children respond more to MPH than others, or that children with different sub-diagnoses react differentially. Clarke and colleagues [113, 235] compared EEG power in different frequency bands of good and poor responders to MPH and found a cortical activation profile suggesting that good responders are more cortically hypoaroused than poor responders. The authors

assume that MPH is most effective for children who are cortically hypoaroused. Loo and co-workers [110] conclude from their results that there are different electrophysiological correlates to MPH for responders and nonresponders. They also compared EEG power in different frequency bands and found that reponders showed a decrease in Theta and Alpha activity, as well as an increase in Beta activity, while nonresponders showed the opposite pattern. Clarke and colleagues [113, 236, 237] investigated cortical differences between ADHD children of the combined type (ADHDcom) and the predominantly inattentive type (ADHDin). Generally, they found ADHDcom children having higher slow wave activity than ADHDin children. The authors concluded from their results that children with ADHDcom are more cortically hypoaroused than children with ADHDin. They hypothesized that ADHDcom might be related to frontal lobe dysfunctions, while children with ADHDin may have other forms of CNS functioning.

Due to the findings that MPH is more effective for some children than for others and since the cortical profiles of ADHD subtypes seem to differ, it is advisable to study the effects of MPH on cortical processing more closely. One desirable outcome of these studies might be to identify cortical indicators in order to differentiate between children who are responders and those who are nonresponders *before* they are treated with amphetamines. Another value lies in elucidating etiological factors of ADHD. Differential effects for the different subtypes can help understanding the underlying cause of the disorder.

The present study was dedicated to investigate the influence of MPH on cortical processing. All of the previous studies investigating power differences in different frequency bands have been using EEG, mostly with a relatively small number of electrodes. Our aim was to obtain new aspects using high density magnetoencephalography (MEG). MEG comprises several advantages over EEG. First of all, the magnetic fields measured are not as biased by low skull conductivity as electrical potentials. Second, MEG is reference-free. Unless EEG analysis is done using average reference (which only is reliable if the recording of the reference electrode is flawless), there will always be an influence on cortical effects produced by the reference type chosen. Third, MEG using magnetometers by definition mostly reflects cortical activity. Subcortical activity is too weak to be detected. Thus, the complexity of the detected signals is reduced. Fourth, MEG mainly reflects radial

components of cortical activity, which are primarily produced by intracellular currents in sulci. Thus, the activity measured stems from circumscribed focal activation, whereas potential differences measured by EEG can originate from various sources.

2.5.2. Methods Study V

Subjects

35 children (6 female, 29 male) participated in this study. Mean age was 11.7 years (±1.92 years). 17 children were diagnosed of having an Attention-Deficit/Hyperactivity Disorder of the combined type (ADHDcom, DSM IV code 314.01); the other 18 were diagnosed for ADHD of the predominantly inattentive type (ADHDin, DSM IV code 314.0). Diagnoses were made by a paediatrician specialized in child psychiatry. All children and parents gave their written informed consent to participate according to the World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (www.wma.net).

Procedure

We measured the effect of Methylphenidate (MPH) on the MEG during a 5 minute resting period (subjects being relaxed but awake). The behavioural performance with and without medication was measured by a highly demanding attention test (D2 test of attention, [238]). Dosage of methylphenidate was based on the body weight of the child (0.1-0.5 mg/kg/day). To ensure that medication and not the mere administration of a pill had an effect, we chose a placebo design. Placebo and methylphenidate were applied by a pediatrician in form of pills that looked identical (placebo dosage was matched with MPH dosage).

The overall-design was the following (Fig. 2.5.1):

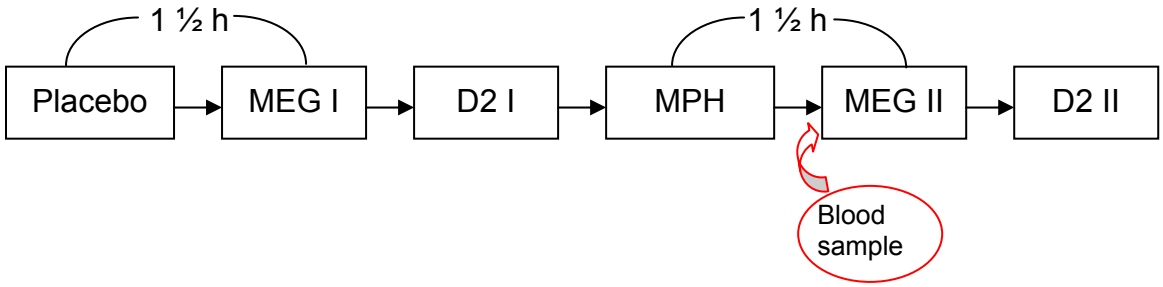

Fig. 2.5.1: Study Design

Due to feasibility it was decided to run the whole procedure within one day. Therefore it was not possible to counterbalance the application time of placebo and MPH, since MPH takes several days to be untraceable in the blood. In order to have an objective measure of the concentration of MPH in the blood serum, blood samples were taken from the children an hour after drug administration. The blood serum was separated right after being taken and was then deep frozen. MPH serum concentrations were measured in an external professional laboratory.

MEG Recording

Recording was done with a 148-channel magnetometer (MAGNES™ 2500 WH, 4D Neuroimaging, San Diego, USA). The children were lying supine in a comfortable position in a magnetically shielded room (Vakuumschmelze Hanau). They were instructed to lie still for 5 minutes and to fixate a point at the ceiling in order to keep eye movements minimal. Continuous data sets were recorded with a real high-pass filter of 0.1 Hz and a sampling rate of 678.17 Hz (bandwidth 200 Hz), as well as real time noise reduction procedures.

For artifact control, eye movements (EOG) were recorded from four electrodes attached to the left and right outer canthus and above and below the right eye. A Synamps amplifier (NEUROSCAN™) served for the recording of the EOG. A video camera installed inside the chamber allowed monitoring the children´s behaviour and compliance at any time throughout the experiment.

D2 Test

Immediately after the MEG recording, each child performed the D2 test in a quiet room. The test involves finding and marking the letter “d” within a string of letters (“d” and “p”), only when 2 dashes are arranged either individually or in pairs above and below “d”. A high amount of attention is necessary to perform the task successfully, since not only the letter “d” is orthographically similar to the letter “p”, but because there are many distractor letters “d” with more than 2 dashes. Additionally, a time limit is set for finding as many D2s with as little errors as possible.

Data Analysis MEG

Global noise was filtered from the MEG data by subtracting external, non-biological noise recorded by 11 MEG reference channels. The data was then split into epochs of 2500 ms length and was corrected for eye and cardiac artefacts by subtracting the moving average cardiac and vertical EOG signal from the data. All epochs with an MEG level > 3.5 pT between the minimum and maximum on one or more MEG channels after artefact correction were rejected. A fast fourier transformation (FFT) was computed for all epochs.

For each subject the average power was calculated across channels for 6 cortical regions (frontal, temporal and occipital; left and right, respectively). In order to ensure that the same cortical regions were covered by the channel-groups for all children, we defined 6 fixed positions in a headframe-based coordinate system. In the second step, we selected 6 centre channels (one per region) that were closest to the fixed headframe-position. In the third step, either 15 (occipital) or 20 (frontal, temporal) channels were selected that were nearest neighbours to the centre channel of the according channel group. Within these channel-groups the power values were averaged for 5 bands (see Fig. 2.5.2) and normalized to the size of the frequency bin: Delta (D, 1.5-3.5Hz), Theta (T, 3.5-7.5Hz), Alpha (A, 7.5-12.5Hz), Beta (B, 12.5-25Hz) and Global (GL, 1.5-25Hz).

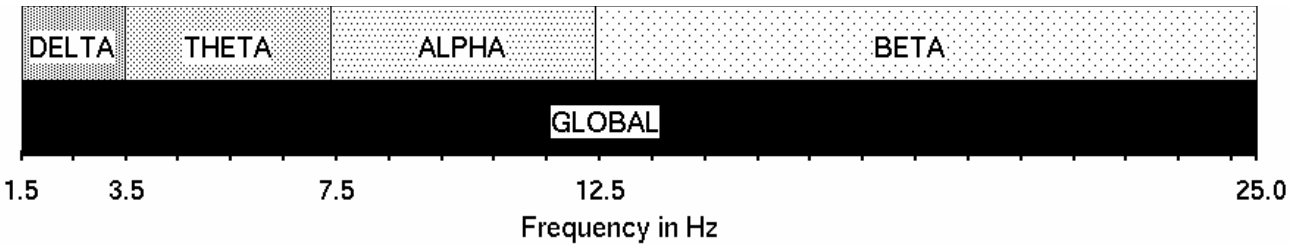

Fig. 2.5.2: power bands

The power values of the Delta, Theta, Alpha, and Beta frequency bands were normalized to the global power yielding relative power values. Additionally, T/A and T/B ratios were calculated.

Data Analysis D2 test

The total number of correctly marked items was used to determine the individual child´s attention level. Raw values were expressed in percentiles (derived from age-

matched norm samples), in order to achieve age-independent test scores. Improvement of attention was determined by subtracting the test score after placebo application from the test score after MPH application. Further, the subjects were divided into good responders (ADHDg) and poor responders (ADHDp): a child was classified as a ADHDg, if the improvement was larger than 30 percentiles (this was slightly more than 1 standard deviation).

Statistical analysis

To see if D2 test performance improved after medication, a one-way repeated measure ANOVA (analysis of variance) was calculated. D2 test score was dependent variable, TIME (pre, post) was repeated measure.

To quantify the influence of medication on the power bands in the different cortical regions, a mixed model analysis was computed using the statistical package SAS®9. Covariance parameters were estimated with the restricted maximum likelihood method (REML). Relative power values (D, T, A, B, T/A, T/B) as well as the global power (GL), were defined as dependent variables. TIME (pre, post), HEMISPHERE (left, right), REGION (fontal, temporal, occipital) and either DSMtype (combined, inattentive) or Response (responders, non-responders) were fixed effects. Depending on which fixed effect was used in the analysis, the factor *Patient* either nested in *DSMtype* or *Response* was used as random factor. Variance structure was *variance components* (VC). Post-hoc testing was performed following Tukey-Kramer. In cases of non-significant post-hoc tests, uncorrected p-values are reported.

Finally, all power values (all bands and all regions) after placebo were subtracted from the respective power values after MPH application. This gave us a measure of MPH induced power changes. Correlations were calculated between the power changes, MPH blood serum concentration, age in months and D2 test improvement.

Only significant main effects, interactions and post-hoc tests are reported. For the mixed model analysis, *only significant interactions with D2-response or DSM-type are reported*, since the aim was to reveal cortical differences between the different DSM-subtypes and children, who respond well to MPH compared to those who do not profit as much. All plots show standard errors.

2.5.3. Results Study V

D2-Test

A main effect for TIME was found ($F(1,34)=86.87$, $p < 0.001$). D2-test performance was significantly higher after the application of MPH (73.1 percentiles) than before MPH (41.2 percentiles).

In order to investigate, which cortical region would be most affected by MPH application, an analysis over all ADHD children was performed, no matter what subtype they were diagnosed. The analysis yielded the significant interaction TIME*REGION ($F(1,33)=4.46$, $p=0.015$) for the dependent variable Global Power. As can be seen in figure 2.5.3, MPH effects were only found in frontal regions ($p=0.05$) with higher amplitudes after MPH than before MPH. No differences were observed in temporal or occipital regions. Thus, further analysis was restricted to frontal channel groups.

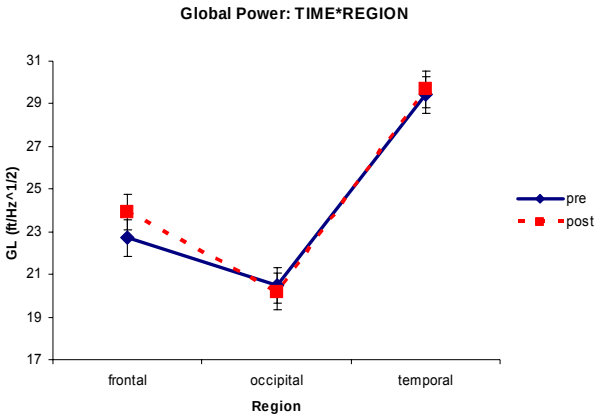

*Fig. 2.5.3: Interaction TIME*REGION for GL*

Results frontal channels

Global Power

The main effect TIME ($F(1,33)=7.53$, $p=0.0098$) was found. Global power amplitude was higher after MPH (23.9 ft/Hz^1/2) than before MPH (22.7 ft/Hz^1/2).

The interaction DSMtype*HEMISPHERE ($F(1,33)=7.79$, $p=0.009$) was revealed. Figure 2.5.4 displays that ADHDin children showed a hemispheric asymmetry with higher global power amplitudes in the left hemisphere compared to the right

hemisphere (p=0.04). They also had higher global power amplitudes left hemispheric than ADHDcom children (p=0.07).

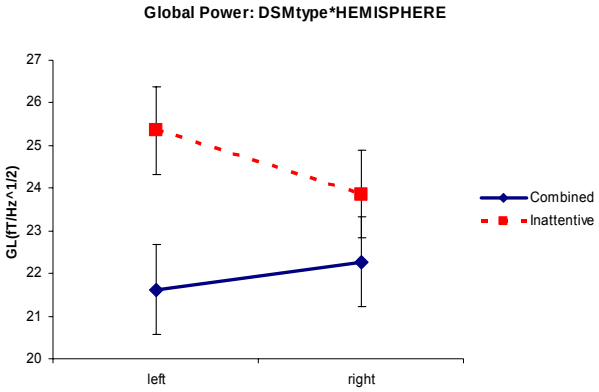

*Fig. 2.5.4: Interaction DSMtype*HEMISPHERE for GL*

Relative Delta

The interaction DSMtype*HEMISPHERE (F(1,33)=4.61, p=0.039) was revealed. However, no differences were found in the post hoc analysis when p-values were adjusted following Tukey-Kramer. Looking at unadjusted p-values (p=0.04), it was found that ADHDin children had lower relative delta band amplitudes in the right hemisphere (1.64) compared to the left hemisphere (1.66). No hemispheric differences were found for ADHDcom children.

Relative Theta

The interaction TIME*HEMISPHERE (F(1,33)=6.15, p=0.018) was found. Figure 2.5.5a shows that in the left hemisphere relative Theta band amplitudes were higher after MPH than before MPH (p=0.04).

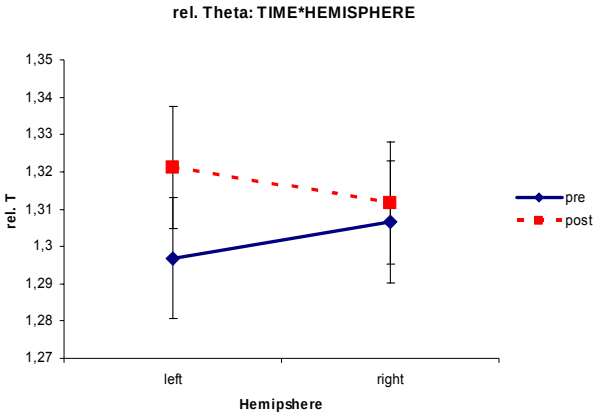

*Fig. 2.5.5a: Interaction TIME*HEMISPHERE for rel. Theta*

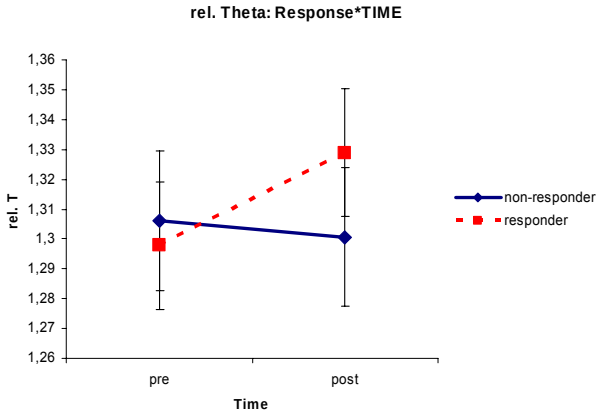

*Fig. 2.5.5b: Interaction Response*TIME for rel. Theta*

The interaction Response*TIME (F(1,33)=6.16, p=0.018) was revealed. As can be seen in figure 2.5.5b, ADHDg children had higher amplitudes in the relative Theta band after MPH than before MPH (p=0.02).

Relative Alpha

The main effect TIME (F(1,33)=7.09, p=0.012) was found. Amplitudes in the relative Alpha band were lower after MPH (1.01) than before MPH (1.03).

The interaction DSMtype*TIME (F(1,33)=4.9, p=0.03) was revealed. ADHDcom children had lower amplitudes in the relative Alpha band after MPH than before MPH (p=0.009, see fig. 2.5.6).

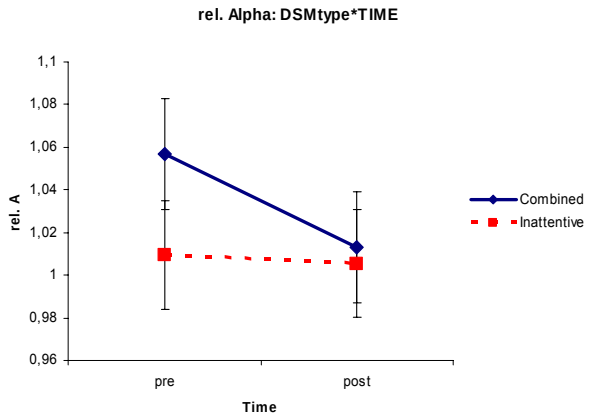

*Fig. 2.5.6: Interaction DSMtype*TIME for rel. Alpha*

The main effect Response (F(1,33)=6.27, p=0.017) was found. ADHDg children (1.06) had higher relative Alpha amplitudes than ADHDp children (0.98).

Relative Beta

The interaction TIME*HEMISPHERE (F(1,33)=4.77, p=0.036) was revealed. However, no differences were found in the post-hoc analysis.

The interaction Response*TIME (F(1,33)=5.18, p=0.029) was found. Again, effects did not prove to be significant in the post-hoc analysis.

Theta/Alpha ratio

The main effect TIME (F(1,33)=7.24, p=0.01) was revealed. The Theta/Alpha ratio was higher after MPH (1.32) than before MPH (1.28).

The main effect Response (F(1,33)=4.58, p=0.0399) was revealed. The Theta/Alpha ratio was lower for ADHDg children (1.24) than for ADHDp children (1.37).

Theta/Beta ratio

The interaction TIME*HEMISPHERE (F(1,33)=6.74, p=0.014) was found. However, no differences were found in the post hoc analysis when p-values were adjusted following Tukey-Kramer. Looking at unadjusted p-values, it was revealed that the Theta/Beta ration was higher after MPH than before MPH in the left hemisphere (p=0.02, see fig. 2.5.7a).

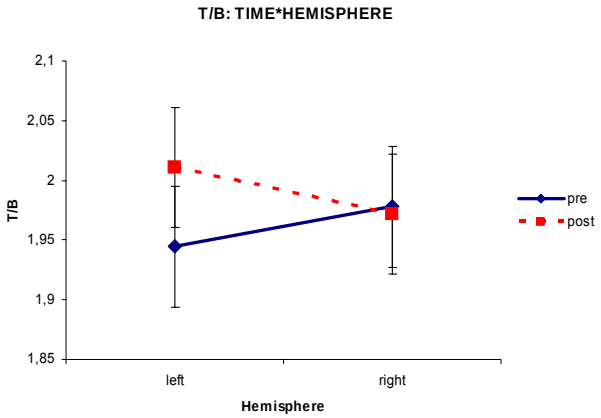

*Fig. 2.5.7a: Interaction TIME*HEMISPHERE for T/B ratio*

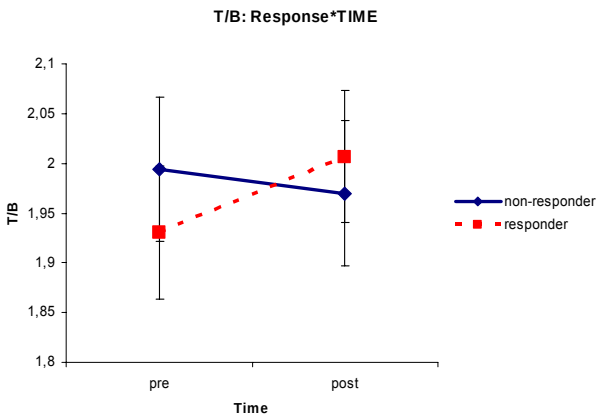

*Fig. 2.5.7b: Interaction Response*TIME for T/B ratio*

The interaction Response*TIME (F(1,33)=4.75, p=0.037) was revealed. Again, no differences were found in the post hoc analysis when p-values were adjusted following Tukey-Kramer. Looking at unadjusted p-values, it was found that ADHDg

children had a higher Theta/Beta ratio after MPH than before MPH (p=0.02, see fig. 2.5.7b).

Correlations and linear regressions

A correlation was found between D2 test improvement and MPH-induced power changes in the relative Theta band left frontal (r=.37, p<.05). A linear regression was computed and confirmed that the larger the improvement in D2 test performance was, the larger was the increase in T after MPH application (t=2.27, p=0.03) , see fig. 2.5.8. No other correlations were found between any MPH-induced power band changes, MPH blood serum concentration and D2 test improvement.

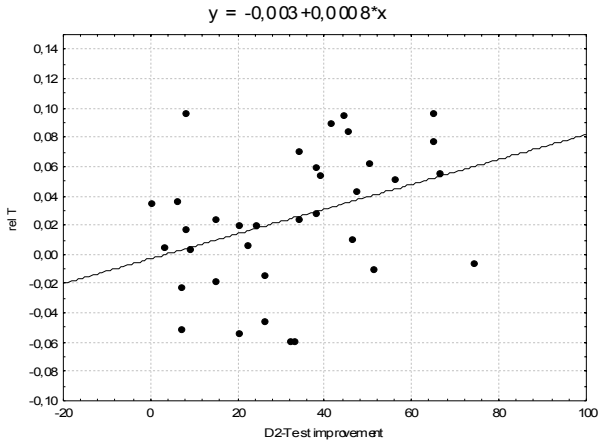

Fig. 2.5.8: Relationship between D2 test improvement and rel. Theta power increase

2.5.4. Discussion Study V

In the present study, main effects induced by medication were found in frontal regions. This result is consistent with etiological hypotheses of ADHD, as well as the working mechanism of MPH. MPH-influence on frontal lobe acitivation in ADHD subjects was also found in a SPECT study by Lou and colleagues [98]. They found ADHD subjects having reduced bloodflow in frontal regions as well as enhanced bloodflow in motor areas. After application of MPH, this pattern normalized. Niedermeyer [99, 100] interprets these findings as support of the “lazy frontal lobe” hypothesis underlying ADHD. He argues that the prefrontal cortex is not only involved in allocation and sustaining attention (e.g. [101, 102]), but also in inhibiting motor activity (augmented motor activity being characteristic for ADHD). Langleben and

colleagues [103] performed a SPECT study with ADHD children who were on and off MPH. When the subjects were not taking MPH, bloodflow was higher in the motor, premotor, and the anterior cingulate cortices. The authors concluded that brief discontinuation of MPH treatment is associated with increased motor and anterior cingulate cortical activity. Thus, it appears that if the prefrontal cortex is underactivated, both attentional processes and the inhibition of the motor cortex will be diminished.

MPH acts upon the prefrontal cortex via the neurotransmitter dopamine. Involvement of the dopaminergic system has been suggested in patients suffering from ADHD since the symptoms can be successfully treated with MPH, a potent blocker of the dopamine transporter (DAT) [79]. MPH is known to influence the dopaminergic system by blocking dopamine reuptake and in consequence enhancing the availability of dopamine in the synaptic gap [80]. Dopamine is densely distributed in the prefrontal cortex as well as the striatum and acts mainly on inhibitory neurons. By increasing the availability of dopamine MPH seems to diminish the inhibitory effect on motor activity.

Our aim was to find cortical differences between children who were diagnosed with different subtypes of ADHD as well as children who were good or poor responders to MPH. We were also interested in MPH-induced changes that were common to all ADHD children. First of all, global power (amplitude power of the combined frequency band from 1.5 to 25 Hz) increased with MPH. This may be taken as further evidence of the hypoarousal model of ADHD (e.g. [85, 104]). The hypoarousal model assumes that ADHD results from cortical underarousal (compare “lazy frontal lobe” hypothesis). If MPH increases the amplitude of the global power band, one might hypothesize that it counteracts cortical underarousal. Other studies supporting the hypoarousal model found decreased bloodflow especially in prefrontal areas [81, 98]. In the study performed by Lou and colleagues (see above), this underarousal could be remediated by MPH.

In the present study, Alpha activity decreased in both hemispheres with MPH. Alpha activity has been related to attentional processes (e.g. [239-241]). I.e. synchronized Alpha activity can be found in the EEG when subjects are relaxed and inattentive. Alpha activity lessens when attention is directed towards a stimulus [239, 240, 242, 243]. Klimesch and colleagues [239] argue that during Alpha desynchronization, different neural populations start oscillating with different

frequencies which in consequence leads to the disappearance of the dominant Alpha rhythm. Our results cannot be directly compared to the findings described above, since we did not investigate Alpha activity related to vigilance tasks. However, we found decreased Alpha power after MPH application. Knowing that MPH is used to treat ADHD symptoms like excess motor arousal and inattentiveness, it is not surprising to find decreased Alpha activity after MPH application given that Alpha activity relates to attentiveness. The Alpha effect in the present study is in line with the results of an EEG study by Loo and co-workers [106], who also reported decreased Alpha power after MPH. The authors link this effect to an increase in cortical arousal. A similar effect of decreased Alpha activity recorded over left fonto-central sites in the EEG after MPH was reported by Swartwood et al. [105]. In contrast to these findings, the same group found *increased* Alpha activity after MPH over the left frontal pole in the same study. However, the authors take this contradictory result as “difficult to interpret”. Clarke et al. [84] reported increased Alpha activity after MPH application for children diagnosed with ADHD of the predominantly inattentive type. The authors take this as part of a normalization of the EEG, since unmedicated ADHD children have been reported to have lower levels of Alpha activation compared to controls. The contradictory findings concerning the effect of MPH on Alpha activity are difficult to explain. Yet, knowing from studies on attention (see above) that higher levels of attentiveness are related to a decrease in Alpha activity, an MPH-induced decrease in Alpha power seems more plausible than an Alpha increase.

In the present study, Theta band activity increased left hemispherically after MPH application. This finding contradicts the results of Clarke and co-workers [84], Swartwood and colleagues [105] and Loo et al. [106]. All of them found lower levels of Theta power after MPH application. Generally, higher slow wave activity has been reported in ADHD children compared to controls (e.g. [82, 83]). This was interpreted as an indicator of maturational lag in brain functioning (e.g. [83, 244, 245]), since slow wave activity normally decreases from childhood to adulthood (e.g. [246]). In a study by Chabot and Serfontein [247] EEG measures of ADHD children were compared to a normative database. Their results disagreed with the maturational lag hypothesis, since the EEG profile of ADHD children did not resemble the EEG profile of children of any age. Another possibility to interpret increased slow wave activity is again offered by the hypoarousal model. Bresnahan and colleagues [248]

hypothesized that increased slow wave activity in ADHD subjects might be an effect of decreased dopamine functioning which is in turn the origin of cortical underarousal. In line with this, Clarke and co-workers [84], as well as Loo et al. [106] interpret the MPH-induced decrease of Theta power with an increase in cortical arousal. Swartwood and colleagues [105] assume that MPH blocks slow-wave activity. Interestingly, Loo and colleagues [110] found differential MPH-induced effects on Theta-activity depending on the DAT1 risk allele status of the ADHD children. In an eyes-open resting condition, children who carried the DAT1 10R allele (considered the “risk” allele) showed a focal *increase* in left parietal Theta power. Children, who carried the DAT1 9R allele showed a decrease. Unfortunately, this effect was not discussed by the authors. It seems, however, that Theta activity cannot solely be related to drowsiness and hypoarousal, otherwise MPH should not increase its power as in Loo et al.’s or the present study, especially since Theta increase was positively correlated with D2-test improvement. Theta band activity has also been investigated in connection to working memory processes. For instance, “functional” Theta activity was found in an EEG study investigating visual word encoding [249, 250]. Event-related Theta activity was largest for words that could later be recalled. The authors assume that theta synchronization is selectively related to the encoding of new information. Interestingly, Theta power was largest left hemispheric. This corresponds to our finding of a left hemispheric increase in Theta power after MPH application. Larson and colleagues [251] found that long-term potentiation in the hippocampus is optimal when the stimulation pattern mimics theta rhythm. But also Theta oscillations generated in frontal brain regions play an active role in memory maintenance [252]. Aftanas and colleagues [253] found a relation between Theta synchronization and an emotionally positive state and internalized attention. This effect was particularly prominent in left prefrontal regions. Gevins et al. [254] related the midline theta rhythm to intense concentration.

In conclusion, the results described above suggest that Theta activity does not necessarily mirror cortical underarousal. It can also reflect information processing, consolidation and attention. The subjects in our study did not have to perform any task. They only rested in the MEG with open eyes. Thus, it is unlikely that the Theta increase found corresponds to information encoding or memory processes. However, it is possible, that MPH increases the functional aspect of the Theta rhythm rather than increasing underarousal or drowsiness. Again, the increase in Theta power was

correlated with an increase in behavioural performance in the attention test D2. Since we defined children to be MPH responders or non-responders based on their increase in D2-test performance, it is not surprising that it was only the children who responded well to MPH who showed an increase in Theta power and Theta/Beta ratio.

In the present study, the Theta/Alpha ratio also increased with MPH application (mostly in the left hemisphere), as did the Theta/Beta ratio. The increase in the Theta/Beta ratio is of course a consequence of an increase in relative Theta and a concurrent decrease in relative Alpha power. Thus, it does not reveal any new information. Presumably, the same is true for the increase in the Theta/Beta ratio. Although a significant interaction was found between Beta Power and MPH status, no significant differences were found in the post hoc tests. This implies that Beta power did not change to a great degree with MPH application and the increase in the Theta/Beta ratio is very likely a result of an increase in Theta power alone.

We did find differences between the two ADHD subtypes. Children with ADHD of the predominantly inattentive type had higher global power amplitudes in the left hemisphere than children with ADHD of the combined type. If global power activity reflects cortical arousal in our study (see above), one might hypothesize, that children with ADHD of the combined type are more hypoaroused than children with ADHD of the predominantly inattentive type. Clarke and colleagues [113] found the opposite result (combined > inattentive). They stated that higher levels of global power amplitude reflect cortical underarousal and consequently concluded that children with ADHD of the predominatly inattentive type are less hypoaroused than children with ADHD of the combined type. Yet, as described above, we found an MPH-induced increase in global power activity that was accompanied by an increase in behavioural performance. Thus, in our study, higher global power does not seem to mirror cortical hypoarousal, but in fact the opposite. Therefore, we might also conclude from our data that children with ADHD of the predominantly inattentive type are the ones being less hypoaroused. Another characteristic of children with ADHD of the inattentive type was a hemispheric asymmetry in global power and relative delta activity with more power in the left hemisphere. No asymmetries were found for children with ADHD of the combined type. Characteristic for the latter group was an MPH-induced decrease in Alpha power. Although the decrease in Alpha power became statistically

significant for all ADHD children (see above), the effect seemed mainly to be driven by the children with ADHD of the combined type.

2.5.5. Conclusion study V

The purpose of study V was to investigate differences between good and poor MPH responders, ADHD subtypes, and the influence of medication on their cortical parameters. As in study II it could be shown that it is possible to investigate cortical characteristics of a developmental disorder and monitor the effects of remediation on these characteristics. Again, effects of remediation allowed us to draw conclusion about aetiological hypotheses. In ADHD it appears that MPH reduces *cortical hypoarousal* in frontal areas that might be resulting from a dysfunction in the dopaminergic system. We also were found cortical differences between good and poor MPH responders, as well as ADHD subtypes. The latter is of particular interest, since it is still unclear if different ADHD subtypes are expressions of the same disorder or independent disorders under the same label.

Despite the promising results, it should be pointed out, however that this study can only be seen as a pilot study. There are some methodological issues that limit the significance of the findings. First, it would have been necessary to investigate a healthy control group to draw more meaningful conclusions. Second, the within-design placebo/medication should have been counterbalanced. In an unbalanced design, it is not possible to exclude all influences of a time-position error. Third, there might be more powerful dependent variables than the power spectrum to investigate subtype differences and medication effects. This opens many perspectives for future research.

3. General Discussion

In reference to the questions formulated in the general introduction (chapter 1.):

3.1. Dyslexia

3.1.1. Question 1

We did find cortical characteristics that distinguished dyslexic children from control children. First, dyslexic children showed reduced hemispheric asymmetry of the N260m component following stimulation with speech sounds (study I). While control children showed a typical pattern of more anterior source localisations in the right hemisphere, this was not the case in dyslexic children. We interpret this finding as a cortical characteristic of dyslexia, since the asymmetry index correlated with spelling test performance. It appears that different right temporal cortical areas are involved in auditory (language) processing in dyslexia. This might be the consequence of a more symmetrical formation of the plana temporali in dyslexic subjects, which in turn might be the result of a maturational delay or compensatory cortical plasticity. Our results add information to the aetiological dyslexia model proposed by Ramus [63] that only assumes left temporal anomalies on a biologic level. Our data clearly support the existence of right temporal anomalies.

Second, dyslexic children seem to be selectively impaired reading words that require sublexical processing probably reflecting lacking phonological awareness in dyslexia (study III). Their processing deficit of low frequent words was expressed in reduced amplitudes of evoked power in occipital cortical regions that was accompanied by higher spectral frequencies compared to control children. This might be related to a dysfunction in the visual word form area – a left occipito-temporal region where prelexical processing of words and pseudowords seems to take place in skilled readers. Again, this processing difference can be taken as a cortical characteristic of dyslexia, since the occipital activation following LF words correlated with spelling test and dictation performance and spectral frequency was negatively correlated with measures of phonological awareness.

The significance of the study III findings is enhanced by the results of study IV. The word frequency effect seems to be a highly reliable characteristic of skilled

readers – both children and adults - that can be measured using different presentation rates of visual word stimuli, as well as using different methods of signal analysis (wavelet analysis and minimum norm estimate). From the adult data it appears that skilled readers are characterised by even more subtle word processing mechanisms. We were also able to show cortical activation very likely representing processing of pseudowords. It thus appears that at the presentation rate of 1 word per 350 ms, adult readers process high and low frequent words, as well as pseudowords, control children process high *and* low frequent words, while dyslexic children only seem to process high frequent words. It should be noted, that using this relatively fast presentation rate, we set focus on early, *automatic* reading processes that are triggered by the visual encounter with word stimuli.

Against expectations, dyslexic children did not differ from control children in their sensitivity for sound changes (measured by mismatch field amplitudes, study II). Nevertheless, they were impaired categorising the syllables /ba/ and /da/. I.e. dyslexic children were able to perceive the difference between the syllables /ba/ and /da/, but when it came to identifying the stimuli, they were impaired. We took these findings as further support that deficient auditory processing does not seem to a general underlying cause of dyslexia – concurrently supporting the phonological awareness hypothesis of dyslexia.

3.1.2. Question 2

The only cortical measure that was influenced by the three training programs was MMF amplitude (study II). At the same time, MMF amplitude was the only measure that did not distinguish dyslexic and control children. Nevertheless, training-induced cortical changes correlated with behavioural improvement in the dictation. Interestingly, the two trainings, that had focused on improving auditory perception and phonological awareness led to an increase in MMF amplitude, while the cognitive training that focused on spelling rules had a decreasing effect. This finding is of interest, since improvements on the behavioural level were rather unspecific and comparable for all trainings.

We found most training-induced effects on the cortical measure MMF for the phonological awareness training. After training, MMF increased in left fronto-temporal and right hemispheric channel groups. This increase was correlated with an improvement in dictation performance. We also found an increase in MMF amplitude

in left temporal areas after the training of auditory perception. The training of spelling rule knowledge led to a left fronto-temporal decrease in MMF amplitude that did not correlate with any qualitative behavioural change. Since the phonological awareness training produced the greatest effects (with at the same time half the amount of training time), this can be taken as further support that the underlying deficit – at least in our sample – may be related to a lack of phonological awareness rather than a more general auditory perceptual deficit (the latter would have been suggested if the training of auditory perception had led to most improvements).

From the results of study II we can infer that MMF amplitude might not necessarily be a good measure for distinguishing control and dyslexic children, it nevertheless seems to serve as an indicator for training effects. Especially a left fronto-temporal MMF increase seems to reflect training effectiveness.

3.1.3. Conclusion dyslexia

From our sample of dyslexic children, we can infer that dyslexia is characterised by (a) more posterior source localisations of speech sounds in right temporal regions possibly resulting from more symmetrical plana temporali and (b) reduced activation and enhanced spectral frequencies following words that require sublexical processing in occipital regions.

Nevertheless, neither of the measures could be reliably used to predict if a child is dyslexic or not. Using the asymmetry index (right-left, see study I) and MAX amplitude of low frequent words (see study III) for categorisation of the children (children were classified as dyslexic, if they had an asymmetry index or MAX amplitude value below the 95% confidence interval of the control children) led to 57% correct classifications of the dyslexic children for the asymmetry index and 64% correct classifications of the dyslexic children for MAX amplitude. This again speaks for high heterogeneity within dyslexic samples. Interestingly, comparing the 57% of dyslexic children who were classified correctly using the asymmetry index (i.e. the ones with a very low or negative asymmetry index) with the other 43% that were classified as control children in a univariate ANOVA revealed a strong statistical trend ($F(1, 43)=3.7$, $p=.06$) for the dependent variable *categorical perception*. Those children, who were wrongly classified as control children from their asymmetry index performed better at categorical perception than the dyslexics classified correctly (categorical perception index 27 vs 23, respectively) thus being clearly closer to

control performance (categorical perception index 31). Likewise, comparing the 64% of dyslexic children who were classified correctly using MAX amplitude of low frequent words (i.e. the children with very low MAX amplitudes) with the 36% that were classified as control children in a univariate ANOVA revealed a significant main effect ($F(1, 50)=4.70$, $p=.035$) for the dependent variable *categorical perception*. Those children, who were wrongly classified as control children using MAX amplitudes of low frequent words performed better at categorical perception than the dyslexics classified correctly (categorical perception index 27 vs. 24, respectively), again being clearly closer to control performance (categorical perception index 31).

From these findings, we might infer that using the cortical measures *asymmetry index* and *MAX amplitude* of low frequent words as predictors might not reproduce the sample categorisation that we applied based on the children's spelling test performance. It nevertheless might be useful for identifying those dyslexic children with good and bad phonological awareness as reflected in their ability for categorical perception.

3.2. ADHD (see study V)

3.2.1. Question 1

We did find cortical differences between different ADHD subtypes as well as between good and poor methylphenidate responders. ADHDcom children were characterised by a hemispheric asymmetry in global power that was not present in ADHDin children. Further, ADHDcom children had higher globel power values in the left hemisphere than ADHDin children. Based on the finding that GL increased with MPH, accompanied by a marked rise in D2 test performance, it appears that ADHDin children – with their higher GL amplitudes - are less affected than ADHDcom children. If lower GL amplitudes correspond to fronto-cortical hypoarousal, our results can be taken as support that ADHDin children are less hypoaroused than ADHDcom children.

ADHDg children were characterised by higher relative Alpha power compared to ADHDp children. Alpha activity has been related to attentional processes. I.e. synchronized Alpha activity can be found in the EEG when subjects are relaxed, inattentive or tired. Alpha activity lessens when attention is directed towards a

stimulus. From our results it appears that children with higher Alpha levels are the ones improving most in behavioural performance after MPH application. It might be that the children with higher baseline Alpha levels (reflecting inattentiveness) profit most from a stimulant medication.

3.2.2. Question 2

First of all, medication effects - in form of a global power increase - were predominantly found in fronto-cortical regions. This supports the hypothesis of fronto-cortical hypoarousal as an important underlying factor of ADHD.

We also found differential MPH effects on ADHD subtypes as well as good and poor MPH responders. Alpha power dropped for all children after medication. However, this effect seemed to be mainly driven by ADHDcom children. An MPH-induced decrease of Alpha activity has been related to an increase in cortical arousal. Thus, it appears that ADHDcom children profit especially from a stimulant medication.

Good MPH responders were characterised by an increase in Theta activity after medication. Theta increase was correlated with an improvement in behavioural D2 test performance. It thus appears that higher Theta levels are related to better attention test performance. The children whose Theta levels increased after medication also were the ones who improved most behaviourally.

3.2.3. Conclusion

In reference to the open question if different ADHD subtypes are independent disorders or different expressions of the same disorder (see 1.2.3. general introduction), our data suggest, that ADHDcom children not only differ from ADHDin children in cortical parameters, they also respond differently to medication. ADHDcom children seem to be more cortically hypoaroused and show a stronger medication-induced increase in cortical arousal than ADHDin children. However, using the left fronto-cortical GL difference as predictor (classifying those children as ADHDcom with GL values below the 95% confidence interval of ADHDin children) led to a relatively moderate rate of 63% correct classifications. This indicates that group differences are not clear-cut and that other variables have to be added for better classification.

Nevertheless, based on the different cortical profiles of the different ADHD subtypes, one might assume that ADHD subtypes are different disorders in nature.

However, interpreting the difference is difficult from the results of only one study. Other investigations using different parameters and tasks are necessary for this purpose.

Good medication responders were characterised by higher Alpha activity and had higher Theta levels after medication. Using Alpha values as predictor of medication response (classifying those children as ADHDp who had Alpha values below the 95% confidence interval of ADHDg children) led to 72% correct classifications. This finding strengthens the meaning of Alpha activity for medication responsiveness. Higher levels of Alpha seem to predict positive behavioural medication response.

4. References

1. Rapport MD, Scanlan SW, Denney CB: **Attention-deficit/hyperactivity disorder and scholastic achievement: a model of dual developmental pathways**. *J Child Psychol Psychiatry* 1999, **40**:1169-1183.
2. Willcutt EG, Pennington BF: **Psychiatric comorbidity in children and adolescents with reading disability**. *J Child Psychol Psychiatry* 2000, **41**:1039-1048.
3. **Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV)**. In. Washington D.C.: American Psychiatric Association; 1994.
4. **International classification of diseases, 10th edition (ICD 10)**. In: World Health Organisation; 1994.
5. *Lehrbuch der klinischen Psychologie und Psychotherapie des Kindes- und Jugendalters*. Stuttgart; New York: Thieme; 2002.
6. Shaywitz SE, Shaywitz BA, Fletcher JM, Escobar MD: **Prevalence of reading disability in boys and girls. Results of the Connecticut Longitudinal Study**. *Jama* 1990, **264**:998-1002.
7. Rutter M, Caspi A, Fergusson D, Horwood LJ, Goodman R, Maughan B, Moffitt TE, Meltzer H, Carroll J: **Sex differences in developmental reading disability: new findings from 4 epidemiological studies**. *Jama* 2004, **291**:2007-2012.
8. Lindgren SD, De Renzi E, Richman LC: **Cross-national comparisons of developmental dyslexia in Italy and the United States**. *Child Dev* 1985, **56**:1404-1417.
9. Paulesu E, Demonet JF, Fazio F, McCrory E, Chanoine V, Brunswick N, Cappa SF, Cossu G, Habib M, Frith CD, Frith U: **Dyslexia: cultural diversity and biological unity**. *Science* 2001, **291**:2165-2167.
10. Demonet JF, Taylor MJ, Chaix Y: **Developmental dyslexia**. *Lancet* 2004, **363**:1451-1460.
11. *Phonological processes in literacy: A Tribute to Isabelle Y. Liberman*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1991.
12. Snowling M: *Dyslexia*. Oxford: Blackwell; 2000.
13. Ramus F: **Developmental dyslexia: specific phonological deficit or general sensorimotor dysfunction?** *Curr Opin Neurobiol* 2003, **13**:212-218.

14. Ramus F: **The neural basis of reading acquisition**. In: *The new cognitive neurosciences* Edited by Gazzaniga MS. Cambridge, MA: MIT Press; 2000.
15. Schneider W, Roth E, Ennemoser M: **Training Phonological Skills and Letter Knowledge in Children at Risk for Dyslexia: A Comparison of Three Kindergarten Intervention Programs**. *Journal of Educational Psychology .* 2000, **92**:284-295.
16. Castles A, Coltheart M: **Is there a causal link from phonological awareness to success in learning to read?** *Cognition* 2004, **91**:77-111.
17. Coltheart M, Rastle K: **Seriol processing in reading aloud: Evidence for Dual-Route models in reading**. *J Exp Psych* 1994, **20**:1197-1211.
18. Jobard G, Crivello F, Tzourio-Mazoyer N: **Evaluation of the dual route theory of reading: a metanalysis of 35 neuroimaging studies**. *Neuroimage* 2003, **20**:693-712.
19. Muter V, Hulme C, Snowling MJ, Stevenson J: **Phonemes, rimes, vocabulary, and grammatical skills as foundations of early reading development: evidence from a longitudinal study**. *Dev Psychol* 2004, **40**:665-681.
20. Snowling MJ, Gallagher A, Frith U: **Family risk of dyslexia is continuous: individual differences in the precursors of reading skill**. *Child Dev* 2003, **74**:358-373.
21. Marshall CM, Snowling MJ, Bailey PJ: **Rapid auditory processing and phonological ability in normal readers and readers with dyslexia**. *J Speech Lang Hear Res* 2001, **44**:925-940.
22. Ramus F, Rosen S, Dakin SC, Day BL, Castellote JM, White S, Frith U: **Theories of developmental dyslexia: insights from a multiple case study of dyslexic adults**. *Brain* 2003, **126**:841-865.
23. Fosker T, Thierry G: **P300 investigation of phoneme change detection in dyslexic adults**. *Neurosci Lett* 2004, **357**:171-174.
24. Bus AG, Ijzendorm KH: **Phonological awareness and early reading: a meta-analysis of experimental training studies.** *Journal of Educational Psychology .* 1999, **91**:403-414.
25. Schneider W, Ennemoser M, Roth E, Kuspert P: **Kindergarten prevention of dyslexia: does training in phonological awareness work for everybody?** *J Learn Disabil* 1999, **32**:429-436.

26. Torgesen JK, Alexander AW, Wagner RK, Rashotte CA, Voeller KK, Conway T: **Intensive remedial instruction for children with severe reading disabilities: immediate and long-term outcomes from two instructional approaches**. *J Learn Disabil* 2001, **34**:33-58, 78.
27. Eden GF, Jones KM, Cappell K, Gareau L, Wood FB, Zeffiro TA, Dietz NA, Agnew JA, Flowers DL: **Neural changes following remediation in adult developmental dyslexia**. *Neuron* 2004, **44**:411-422.
28. Serniclaes W, Sprenger-Charolles L, Carre R, Demonet JF: **Perceptual discrimination of speech sounds in developmental dyslexia**. *J Speech Lang Hear Res* 2001, **44**:384-399.
29. Adlard A, Hazan V: **Speech perception in children with specific reading difficulties (dyslexia)**. *Q J Exp Psychol A* 1998, **51**:153-177.
30. Mody M, Studdert-Kennedy M, Brady S: **Speech perception deficits in poor readers: auditory processing or phonological coding?** *J Exp Child Psychol* 1997, **64**:199-231.
31. Manis FR, McBride-Chang C, Seidenberg MS, Keating P, Doi LM, Munson B, Petersen A: **Are speech perception deficits associated with developmental dyslexia?** *J Exp Child Psychol* 1997, **66**:211-235.
32. McAnally KI, Hansen PC, Cornelissen PL, Stein JF: **Effect of time and frequency manipulation on syllable perception in developmental dyslexics**. *J Speech Lang Hear Res* 1997, **40**:912-924.
33. Tallal P, Piercy M: **Defects of non-verbal auditory perception in children with developmental aphasia**. *Nature* 1973, **241**:468-469.
34. Tallal P, Piercy M: **Developmental aphasia: rate of auditory processing and selective impairment of consonant perception**. *Neuropsychologia* 1974, **12**:83-93.
35. Tallal P: **Auditory temporal perception, phonics, and reading disabilities in children**. *Brain Lang* 1980, **9**:182-198.
36. Naatanen R, Pakarinen S, Rinne T, Takegata R: **The mismatch negativity (MMN): towards the optimal paradigm**. *Clin Neurophysiol* 2004, **115**:140-144.
37. Schulte-Körne G, Deimel W, Bartling J, Remschmidt H: **Auditory processing and dyslexia: evidence for a specific speech processing deficit**. *NeuroReport* 1998, **9**:337-340.

38. Schulte-Körne G, Deimel W, Bartling J, Remschmidt H: **Speech perception deficit in dyslexic adults as measured by mismatch negativity (MMN)**. *International Journal of Psychophysiology* 2001, **40**:77-87.
39. Merzenich MM, Jenkins WM, Johnston P, Schreiner C, Miller SL, Tallal P: **Temporal processing deficits of language-learning impaired children ameliorated by training**. *Science* 1996, **271**:77-81.
40. Tallal P, Miller SL, Bedi G, Byma G, Wang X, Nagarajan SS, Schreiner C, Jenkins WM, Merzenich MM: **Language comprehension in language-learning impaired children improved with acoustically modified speech**. *Science* 1996, **271**:81-84.
41. Temple E, Deutsch GK, Poldrack RA, Miller SL, Tallal P, Merzenich MM, Gabrieli JD: **Neural deficits in children with dyslexia ameliorated by behavioral remediation: evidence from functional MRI**. *Proc Natl Acad Sci U S A* 2003, **100**:2860-2865.
42. Agnew JA, Dorn C, Eden GF: **Effect of intensive training on auditory processing and reading skills**. *Brain Lang* 2004, **88**:21-25.
43. Schulte-Körne G, Deimel W, Bartling J, Remschmidt H: **Pre-attentive processing of auditory patterns in dyslexic human subjects**. *Neuroscience Letters* 1999, **276**:41-44.
44. Baldeweg T, Richardson A, Watkins S, Foale C, Gruzelier J: **Impaired auditory frequency discrimination in dyslexia detected with mismatch evoked potentials**. *Ann Neurol* 1999, **45**:495-503.
45. Kujala T, Karma K, Ceponiene R, Belitz S, Turkkila P, Tervaniemi M, Naatanen R: **Plastic neural changes and reading improvement caused by audiovisual training in reading-impaired children**. *Proc Natl Acad Sci U S A* 2001, **98**:10509-10514.
46. Share DL, Jorm AF, Maclean R, Matthews R: **Temporal processing and reading disability, Reading and Writing**. 2002, **15**:151 - 178.
47. Bretherton L, Holmes VM: **The relationship between auditory temporal processing, phonemic awareness, and reading disability**. *J Exp Child Psychol* 2003, **84**:218-243.
48. Amitay S, Ben-Yehudah G, Banai K, Ahissar M: **Disabled readers suffer from visual and auditory impairments but not from a specific magnocellular deficit**. *Brain* 2002, **125**:2272-2285.

49. Frith U: **What framework should we use for understanding developmental disorders?** *Dev Neuropsychol* 2001, **20**:555-563.
50. Lovegrove W, Martin F, Bowling A, Blackwood M, Badcock D, Paxton S: **Contrast sensitivity functions and specific reading disability**. *Neuropsychologia* 1982, **20**:309-315.
51. Livingstone MS, Hubel DH: **Do the relative mapping densities of the magno- and parvocellular systems vary with eccentricity?** *J Neurosci* 1988, **8**:4334-4339.
52. Lovegrove W, Slaghuis W, Bowling A, Nelson P, Geeves E: **Spatial frequency processing and the prediction of reading ability: a preliminary investigation**. *Percept Psychophys* 1986, **40**:440-444.
53. Skottun BC: **The magnocellular deficit theory of dyslexia: the evidence from contrast sensitivity**. *Vision Res* 2000, **40**:111-127.
54. Schulte-Korne G: **Annotation: Genetics of reading and spelling disorder**. *J Child Psychol Psychiatry* 2001, **42**:985-997.
55. DeFries JC, Fulker DW, LaBuda MC: **Evidence for a genetic aetiology in reading disability of twins**. *Nature* 1987, **329**:537-539.
56. Castles A, Datta H, Gayan J, Olson RK: **Varieties of developmental reading disorder: genetic and environmental influences**. *J Exp Child Psychol* 1999, **72**:73-94.
57. Stevenson J, Graham P, Fredman G, McLoughlin V: **A twin study of genetic influences on reading and spelling ability and disability**. *J Child Psychol Psychiatry* 1987, **28**:229-247.
58. Schulte-Korne G, Grimm T, Nothen MM, Muller-Myhsok B, Cichon S, Vogt IR, Propping P, Remschmidt H: **Evidence for linkage of spelling disability to chromosome 15**. *Am J Hum Genet* 1998, **63**:279-282.
59. Smith SD, Kimberling WJ, Pennington BF: **Screening for multiple genes infuencing dyslexia.** *Reading and Writing:An Interdisciplinary Journal* 1991, **3**:285-298.
60. Grigorenko EL, Wood FB, Meyer MS, Hart LA, Speed WC, Shuster A, Pauls DL: **Susceptibility loci for distinct components of developmental dyslexia on chromosomes 6 and 15**. *Am J Hum Genet* 1997, **60**:27-39.
61. Fisher SE, DeFries JC: **Developmental dyslexia: genetic dissection of a complex cognitive trait**. *Nat Rev Neurosci* 2002, **3**:767-780.

62. Grigorenko EL: **Developmental dyslexia: an update on genes, brains, and environments**. *J Child Psychol Psychiatry* 2001, **42**:91-125.
63. Ramus F: **Neurobiology of dyslexia: a reinterpretation of the data**. *Trends Neurosci* 2004, **27**:720-726.
64. Galaburda AM, Menard MT, Rosen GD: **Evidence for aberrant auditory anatomy in developmental dyslexia**. *Proc Natl Acad Sci U S A* 1994, **91**:8010-8013.
65. Livingstone MS, Rosen GD, Drislane FW, Galaburda AM: **Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia**. *Proc Natl Acad Sci U S A* 1991, **88**:7943-7947.
66. Perwien A, Hall J, Swensen A, Swindle R: **Stimulant treatment patterns and compliance in children and adults with newly treated attention-deficit/hyperactivity disorder**. *J Manag Care Pharm* 2004, **10**:122-129.
67. Brown RT, Freeman WS, Perrin JM, Stein MT, Amler RW, Feldman HM, Pierce K, Wolraich ML: **Prevalence and assessment of attention-deficit/hyperactivity disorder in primary care settings**. *Pediatrics* 2001, **107**:E43.
68. Wolraich ML, Hannah JN, Baumgaertel A, Feurer ID: **Examination of DSM-IV criteria for attention deficit/hyperactivity disorder in a county-wide sample**. *J Dev Behav Pediatr* 1998, **19**:162-168.
69. Tannock R: **Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research**. *J Child Psychol Psychiatry* 1998, **39**:65-99.
70. Scahill L, Schwab-Stone M: **Epidemiology of ADHD in school-age children**. *Child Adolesc Psychiatr Clin N Am* 2000, **9**:541-555, vii.
71. Nichols SL, Waschbusch DA: **A review of the validity of laboratory cognitive tasks used to assess symptoms of ADHD**. *Child Psychiatry Hum Dev* 2004, **34**:297-315.
72. Overtoom CC, Kenemans JL, Verbaten MN, Kemner C, van der Molen MW, van Engeland H, Buitelaar JK, Koelega HS: **Inhibition in children with attention-deficit/hyperactivity disorder: a psychophysiological study of the stop task**. *Biol Psychiatry* 2002, **51**:668-676.

73. Dimoska A, Johnstone SJ, Barry RJ, Clarke AR: **Inhibitory motor control in children with attention-deficit/hyperactivity disorder: event-related potentials in the stop-signal paradigm**. *Biol Psychiatry* 2003, **54**:1345-1354.

74. Seidman LJ, Biederman J, Monuteaux MC, Valera E, Doyle AE, Faraone SV: **Impact of gender and age on executive functioning: Do girls and boys with and without attention deficit hyperactivity disorder differ neuropsychologically in preteen and teenage years?** *Developmental Neuropsychology* 2005, **27**:79-105.

75. Houghton S, Douglas G, West J, Whiting K, Wall M, Langsford S, Powell L, Carroll A: **Differential patterns of executive function in children with attention-deficit hyperactivity disorder according to gender and subtype**. *J Child Neurol* 1999, **14**:801-805.

76. Hervey AS, Epstein JN, Curry JF: **Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review**. *Neuropsychology* 2004, **18**:485-503.

77. Banaschewski T, Brandeis D, Heinrich H, Albrecht B, Brunner E, Rothenberger A: **Questioning inhibitory control as the specific deficit of ADHD--evidence from brain electrical activity**. *J Neural Transm* 2004, **111**:841-864.

78. Durston S: **A review of the biological bases of ADHD: what have we learned from imaging studies?** *Ment Retard Dev Disabil Res Rev* 2003, **9**:184-195.

79. Dresel S, Krause J, Krause KH, LaFougere C, Brinkbaumer K, Kung HF, Hahn K, Tatsch K: **Attention deficit hyperactivity disorder: binding of [99mTc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment**. *Eur J Nucl Med* 2000, **27**:1518-1524.

80. Volkow ND, Wang GJ, Fowler JS, Logan J, Franceschi D, Maynard L, Ding YS, Gatley SJ, Gifford A, Zhu W, Swanson JM: **Relationship between blockade of dopamine transporters by oral methylphenidate and the increases in extracellular dopamine: therapeutic implications**. *Synapse* 2002, **43**:181-187.

81. Zametkin AJ, Nordahl TE, Gross M, King AC, Semple WE, Rumsey J, Hamburger S, Cohen RM: **Cerebral glucose metabolism in adults with hyperactivity of childhood onset**. *N Engl J Med* 1990, **323**:1361-1366.

82. Lazzaro I, Gordon E, Li W, Lim CL, Plahn M, Whitmont S, Clarke S, Barry RJ, Dosen A, Meares R: **Simultaneous EEG and EDA measures in adolescent attention deficit hyperactivity disorder**. *Int J Psychophysiol* 1999, **34**:123-134.

83. Clarke AR, Barry RJ, McCarthy R, Selikowitz M: **EEG analysis in Attention-Deficit/Hyperactivity Disorder: a comparative study of two subtypes**. *Psychiatry Res* 1998, **81**:19-29.

84. Clarke AR, Barry RJ, McCarthy R, Selikowitz M, Brown CR, Croft RJ: **Effects of stimulant medications on the EEG of children with Attention-Deficit/Hyperactivity Disorder Predominantly Inattentive type**. *Int J Psychophysiol* 2003, **47**:129-137.

85. Barry RJ, Clarke AR, Johnstone SJ: **A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography**. *Clin Neurophysiol* 2003, **114**:171-183.

86. Barry RJ, Johnstone SJ, Clarke AR: **A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials**. *Clin Neurophysiol* 2003, **114**:184-198.

87. Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Bullmore ET: **Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI**. *Am J Psychiatry* 1999, **156**:891-896.

88. Falkenstein M, Hoormann J, Hohnsbein J: **ERP components in Go/Nogo tasks and their relation to inhibition**. *Acta Psychol (Amst)* 1999, **101**:267-291.

89. Johnstone SJ, Barry RJ: **Auditory event-related potentials to a two-tone discrimination paradigm in attention deficit hyperactivity disorder**. *Psychiatry Res* 1996, **64**:179-192.

90. Pliszka SR, Liotti M, Woldorff MG: **Inhibitory control in children with attention-deficit/hyperactivity disorder: event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism**. *Biol Psychiatry* 2000, **48**:238-246.

91. Satterfield JH, Schell AM, Nicholas T: **Preferential neural processing of attended stimuli in attention-deficit hyperactivity disorder and normal boys**. *Psychophysiology* 1994, **31**:1-10.

92. Johnstone SJ, Barry RJ, Anderson JW: **Topographic distribution and developmental timecourse of auditory event-related potentials in two subtypes of attention-deficit hyperactivity disorder**. *Int J Psychophysiol* 2001, **42**:73-94.
93. Lazzaro I, Gordon E, Whitmont S, Meares R, Clarke S: **The modulation of late component event related potentials by pre-stimulus EEG theta activity in ADHD**. *Int J Neurosci* 2001, **107**:247-264.
94. Oades RD, Dittmann-Balcar A, Schepker R, Eggers C, Zerbin D: **Auditory event-related potentials (ERPs) and mismatch negativity (MMN) in healthy children and those with attention-deficit or tourette/tic symptoms**. *Biol Psychol* 1996, **43**:163-185.
95. Frank Y, Seiden JA, Napolitano B: **Electrophysiological changes in children with learning and attentional abnormalities as a function of age: event-related potentials to an "oddball" paradigm**. *Clin Electroencephalogr* 1998, **29**:188-193.
96. Mash EJ, Barkley RA: *Child psychopathology*. New York: Guilford Press; 2003.
97. Krause KH, Dresel SH, Krause J, la Fougere C, Ackenheil M: **The dopamine transporter and neuroimaging in attention deficit hyperactivity disorder**. *Neurosci Biobehav Rev* 2003, **27**:605-613.
98. Lou HC, Henriksen L, Bruhn P: **Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder**. *Arch Neurol* 1984, **41**:825-829.
99. Niedermeyer E: **Frontal lobe functions and dysfunctions**. *Clin Electroencephalogr* 1998, **29**:79-90.
100. Niedermeyer E: **Frontal lobe disinhibition, Rett syndrome and attention deficit hyperactivity disorder**. *Clin Electroencephalogr* 2001, **32**:20-23.
101. Posner MI, Petersen SE: **The attention system of the human brain**. *Annu Rev Neurosci* 1990, **13**:25-42.
102. Knight RT, Grabowecky MF, Scabini D: **Role of human prefrontal cortex in attention control**. *Adv Neurol* 1995, **66**:21-34; discussion 34-26.
103. Langleben DD, Acton PD, Austin G, Elman I, Krikorian G, Monterosso JR, Portnoy O, Ridlehuber HW, Strauss HW: **Effects of methylphenidate discontinuation on cerebral blood flow in prepubescent boys with attention deficit hyperactivity disorder**. *J Nucl Med* 2002, **43**:1624-1629.

104. Satterfield JH, Cantwell DP, Satterfield BT: **Pathophysiology of the hyperactive child syndrome**. *Arch Gen Psychiatry* 1974, **31**:839-844.
105. Swartwood MO, Swartwood JN, Lubar JF, Timmermann DL, Zimmerman AW, Muenchen RA: **Methylphenidate effects on EEG, behavior, and performance in boys with ADHD**. *Pediatr Neurol* 1998, **18**:244-250.
106. Loo SK, Teale PD, Reite ML: **EEG correlates of methylphenidate response among children with ADHD: a preliminary report**. *Biol Psychiatry* 1999, **45**:1657-1660.
107. Zillessen KE, Scheuerpflug P, Fallgatter AJ, Strik WK, Warnke A: **Changes of the brain electrical fields during the continuous performance test in attention-deficit hyperactivity disorder-boys depending on methylphenidate medication**. *Clin Neurophysiol* 2001, **112**:1166-1173.
108. Seifert J, Scheuerpflug P, Zillessen KE, Fallgatter A, Warnke A: **Electrophysiological investigation of the effectiveness of methylphenidate in children with and without ADHD**. *J Neural Transm* 2003, **110**:821-829.
109. Verbaten MN, Overtoom CC, Koelega HS, Swaab-Barneveld H, van der Gaag RJ, Buitelaar J, van Engeland H: **Methylphenidate influences on both early and late ERP waves of ADHD children in a continuous performance test**. *J Abnorm Child Psychol* 1994, **22**:561-578.
110. Loo SK, Specter E, Smolen A, Hopfer C, Teale PD, Reite ML: **Functional effects of the DAT1 polymorphism on EEG measures in ADHD**. *J Am Acad Child Adolesc Psychiatry* 2003, **42**:986-993.
111. Langley K, Marshall L, van den Bree M, Thomas H, Owen M, O'Donovan M, Thapar A: **Association of the dopamine D4 receptor gene 7-repeat allele with neuropsychological test performance of children with ADHD**. *Am J Psychiatry* 2004, **161**:133-138.
112. Rubinstein M, Cepeda C, Hurst RS, Flores-Hernandez J, Ariano MA, Falzone TL, Kozell LB, Meshul CK, Bunzow JR, Low MJ, Levine MS, Grandy DK: **Dopamine D4 receptor-deficient mice display cortical hyperexcitability**. *J Neurosci* 2001, **21**:3756-3763.
113. Clarke AR, Barry RJ, Bond D, McCarthy R, Selikowitz M: **Effects of stimulant medications on the EEG of children with attention-deficit/hyperactivity disorder**. *Psychopharmacology (Berl)* 2002, **164**:277-284.

114. Heim S, Eulitz C, Elbert T: **Altered hemispheric asymmetry of auditory N100m in adults with developmental dyslexia**. *Neuroreport* 2003, **14**:501-504.
115. Heim S, Eulitz C, Elbert T: **Altered hemispheric asymmetry of auditory P100m in dyslexia**. *Eur J Neurosci* 2003, **17**:1715-1722.
116. Paetau R, Ahonen A, Salonen O, Sams M: **Auditory evoked magnetic fields to tones and pseudowords in healthy children and adults**. *J Clin Neurophysiol* 1995, **12**:177-185.
117. Eulitz C, Diesch E, Pantev C, Hampson S, Elbert T: **Magnetic and electric brain activity evoked by the processing of tone and vowel stimuli**. *J Neurosci* 1995, **15**:2748-2755.
118. Ohtomo S, Nakasato N, Kanno A, Hatanaka K, Shirane R, Mizoi K, Yoshimoto T: **Hemispheric asymmetry of the auditory evoked N100m response in relation to the crossing point between the central sulcus and Sylvian fissure**. *Electroencephalogr Clin Neurophysiol* 1998, **108**:219-225.
119. Teale P, Sheeder J, Rojas DC, Walker J, Reite M: **Sequential source of the M100 exhibits inter-hemispheric asymmetry**. *Neuroreport* 1998, **9**:2647-2652.
120. Steinmetz H: **Structure, functional and cerebral asymmetry: in vivo morphometry of the planum temporale**. *Neurosci Biobehav Rev* 1996, **20**:587-591.
121. Toga AW, Thompson PM: **Mapping brain asymmetry**. *Nat Rev Neurosci* 2003, **4**:37-48.
122. Galaburda AM, Geschwind N: **Anatomical asymmetries in the adult and developing brain and their implications for function**. *Adv Pediatr* 1981, **28**:271-292.
123. Geschwind N, Galaburda AM: In: *Cerebral Lateralization*. London: MIT Press; 1987.
124. Sowell ER, Thompson PM, Rex D, Kornsand D, Tessner KD, Jernigan TL, Toga AW: **Mapping sulcal pattern asymmetry and local cortical surface gray matter distribution in vivo: maturation in perisylvian cortices**. *Cereb Cortex* 2002, **12**:17-26.

125. Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW: **Growth patterns in the developing brain detected by using continuum mechanical tensor maps**. *Nature* 2000, **404**:190-193.
126. Rumsey JM, Donohue BC, Brady DR, Nace K, Giedd JN, Andreason P: **A magnetic resonance imaging study of planum temporale asymmetry in men with developmental dyslexia**. *Arch Neurol* 1997, **54**:1481-1489.
127. Shapleske J, Rossell SL, Woodruff PW, David AS: **The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance**. *Brain Res Brain Res Rev* 1999, **29**:26-49.
128. Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N: **Developmental dyslexia: four consecutive patients with cortical anomalies**. *Ann Neurol* 1985, **18**:222-233.
129. Humphreys P, Kaufmann WE, Galaburda AM: **Developmental dyslexia in women: neuropathological findings in three patients**. *Ann Neurol* 1990, **28**:727-738.
130. Hynd GW, Semrud-Clikeman M, Lorys AR, Novey ES, Eliopulos D: **Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity**. *Arch Neurol* 1990, **47**:919-926.
131. Larsen JP, Hoien T, Lundberg I, Odegaard H: **MRI evaluation of the size and symmetry of the planum temporale in adolescents with developmental dyslexia**. *Brain Lang* 1990, **39**:289-301.
132. Schultz RT, Cho NK, Staib LH, Kier LE, Fletcher JM, Shaywitz SE, Shankweiler DP, Katz L, Gore JC, Duncan JS, et al.: **Brain morphology in normal and dyslexic children: the influence of sex and age**. *Ann Neurol* 1994, **35**:732-742.
133. Eckert MA, Lombardino LJ, Leonard CM: **Planar asymmetry tips the phonological playground and environment raises the bar**. *Child Dev* 2001, **72**:988-1002.
134. Jernigan TL, Hesselink JR, Sowell E, Tallal PA: **Cerebral structure on magnetic resonance imaging in language- and learning-impaired children**. *Arch Neurol* 1991, **48**:539-545.
135. Gauger LM, Lombardino LJ, Leonard CM: **Brain morphology in children with specific language impairment**. *J Speech Lang Hear Res* 1997, **40**:1272-1284.

136. Bishop DV, Snowling MJ: **Developmental dyslexia and specific language impairment: same or different?** *Psychol Bull* 2004, **130**:858-886.
137. Fiez JA, Raichle ME, Balota DA, Tallal P, Petersen SE: **PET activation of posterior temporal regions during auditory word presentation and verb generation**. *Cereb Cortex* 1996, **6**:1-10.
138. Engelien A, Silbersweig D, Stern E, Huber W, Doring W, Frith C, Frackowiak RS: **The functional anatomy of recovery from auditory agnosia. A PET study of sound categorization in a neurological patient and normal controls**. *Brain* 1995, **118 (Pt 6)**:1395-1409.
139. Tzourio N, Massioui FE, Crivello F, Joliot M, Renault B, Mazoyer B: **Functional anatomy of human auditory attention studied with PET**. *Neuroimage* 1997, **5**:63-77.
140. Jäncke L, Wustenberg T, Scheich H, Heinze HJ: **Phonetic perception and the temporal cortex**. *Neuroimage* 2002, **15**:733-746.
141. Brunswick N, McCrory E, Price CJ, Frith CD, Frith U: **Explicit and implicit processing of words and pseudowords by adult developmental dyslexics: A search for Wernicke's Wortschatz?** *Brain* 1999, **122 (Pt 10)**:1901-1917.
142. Paulesu E, Frith U, Snowling M, Gallagher A, Morton J, Frackowiak RS, Frith CD: **Is developmental dyslexia a disconnection syndrome? Evidence from PET scanning**. *Brain* 1996, **119 (Pt 1)**:143-157.
143. Temple E, Poldrack RA, Salidis J, Deutsch GK, Tallal P, Merzenich MM, Gabrieli JD: **Disrupted neural responses to phonological and orthographic processing in dyslexic children: an fMRI study**. *Neuroreport* 2001, **12**:299-307.
144. Shaywitz SE, Shaywitz BA, Pugh KR, Fulbright RK, Constable RT, Mencl WE, Shankweiler DP, Liberman AM, Skudlarski P, Fletcher JM, Katz L, Marchione KE, Lacadie C, Gatenby C, Gore JC: **Functional disruption in the organization of the brain for reading in dyslexia**. *Proc Natl Acad Sci U S A* 1998, **95**:2636-2641.
145. McCrory E, Frith U, Brunswick N, Price C: **Abnormal functional activation during a simple word repetition task: A PET study of adult dyslexics**. *J Cogn Neurosci* 2000, **12**:753-762.

146. Rojas DC, Walker JR, Sheeder JL, Teale PD, Reite ML: **Developmental changes in refractoriness of the neuromagnetic M100 in children**. *Neuroreport* 1998, **9**:1543-1547.
147. Albrecht R, Suchodoletz W, Uwer R: **The development of auditory evoked dipole source activity from childhood to adulthood**. *Clin Neurophysiol* 2000, **111**:2268-2276.
148. Ponton C, Eggermont JJ, Khosla D, Kwong B, Don M: **Maturation of human central auditory system activity: separating auditory evoked potentials by dipole source modeling**. *Clin Neurophysiol* 2002, **113**:407-420.
149. Takeshita K, Nagamine T, Thuy DH, Satow T, Matsuhashi M, Yamamoto J, Takayama M, Fujiwara N, Shibasaki H: **Maturational change of parallel auditory processing in school-aged children revealed by simultaneous recording of magnetic and electric cortical responses**. *Clin Neurophysiol* 2002, **113**:1470-1484.
150. Ceponiene R, Rinne T, Naatanen R: **Maturation of cortical sound processing as indexed by event-related potentials**. *Clin Neurophysiol* 2002, **113**:870-882.
151. Müller R: *Diagnostischer Rechtschreibtest für 3. Klassen (DRT3)*. Weinheim, Basel: Beltz; 1997.
152. Grund M, Haug G, Naumann C: *Diagnostischer Rechtschreibtest für 4. Klassen (DRT4)*. Weinheim, Basel: Beltz; 1994.
153. Grissemann H: *Zürcher Lesetest (ZLT)*. Bern: Hans Huber; 2000.
154. Heller K, Kratzmeier H, Lengfelder A: *Raven-Matrizen-Test. Standard Progressive Matrices (SPM). Deutsche Version.* Göttingen: Beltz; 1998.
155. Welte V: **Der Mottiertest, ein Prüfungsmittel für die Lautdifferenzierungsfähigkeit und die auditive Merkfähigkeit.** *Sprache-Stimme-Gehör* 1981, **5**:121-125.
156. Findeisen U, Melenk G: *Lauttreue Diktate für die 1. bis 5. Klasse.* Bochum: Winkler; 1991.
157. Heim S: *Auditory processing in dylexia: evidence from psychophysical studies and event-related magnetic fields.* Konstanz: University of Konstanz; 2002.
158. Courchesne E: **Chronology of postnatal human brain development: Event-related potential, positron emission tomography, myelinogenesis, and synaptogenesis studies.** In: *Event-Related Potentials: Basic Issues and*

Applications Edited by Johnson J. pp. 210-241. Oxford: Oxford University Press; 1990: 210-241.

159. Korpilahti P, Lang HA: **Auditory ERP components and mismatch negativity in dysphasic children**. *Electroencephalogr Clin Neurophysiol* 1994, **91**:256-264.
160. Sharma A, Kraus N, McGee TJ, Nicol TG: **Developmental changes in P1 and N1 central auditory responses elicited by consonant-vowel syllables**. *Electroencephalogr Clin Neurophysiol* 1997, **104**:540-545.
161. Kurtzberg D, Vaughan HG, Jr., Kreuzer JA, Fliegler KZ: **Developmental studies and clinical application of mismatch negativity: problems and prospects**. *Ear Hear* 1995, **16**:105-117.
162. Ceponiene R, Cheour M, Naatanen R: **Interstimulus interval and auditory event-related potentials in children: evidence for multiple generators**. *Electroencephalogr Clin Neurophysiol* 1998, **108**:345-354.
163. Neville H, Coffey S, Holcomb P, Tallal P: **The neurobiology of sensory and language processing in language-impaired children**. *J Cogn Neurosci* 1993, **5**:235-253.
164. Tonnquist-Uhlén I: **Topography of auditory evoked cortical potentials in children with severe language impairment**. *Scand Audiol Suppl* 1996, **44**:1-40.
165. Helenius P, Salmelin R, Richardson U, Leinonen S, Lyytinen H: **Abnormal auditory cortical activation in dyslexia 100 msec after speech onset**. *J Cogn Neurosci* 2002, **14**:603-617.
166. Corina DP, Richards TL, Serafini S, Richards AL, Steury K, Abbott RD, Echelard DR, Maravilla KR, Berninger VW: **fMRI auditory language differences between dyslexic and able reading children**. *Neuroreport* 2001, **12**:1195-1201.
167. Swan D, Goswami U: **Phonological awareness deficits in developmental dyslexia and the phonological representations hypothesis**. *J Exp Child Psychol* 1997, **66**:18-41.
168. Elbro C, Rasmussen I, Spelling B: **Teaching reading to disabled readers with language disorders: a controlled evaluation of synthetic speech feedback**. *Scand J Psychol* 1996, **37**:140-155.
169. Vellutino FR: **Dyslexia**. *Sci Am* 1987, **256**:34-41.

170. Shaywitz SE: **Dyslexia**. *Sci Am* 1996, **275**:98-104.
171. Stanovich KE: **The Right and Wrong Places to Look for the Cognitive Locus of Reading Disability**. *Annals of Dyslexia* 1988, **38**:154-177.
172. Rack JP, Snowling MJ, Olson RK: **The nonword reading deficit in developmental dyslexia: A review**. *Reading Reasearch Quarterly* 1992, **27**:29-53.
173. Torgesen JK, Wagner RK, Rashotte CA: **Longitudinal studies of phonological processing and reading**. *J Learn Disabil* 1994, **27**:276-286; discussion 287-291.
174. Farmer M, Klein R: **The evidence for a temporal processing deficit linked to dyslexia: A review**. *Psychonomic Bulletin & Review* 1995, **2**:460-493.
175. Wright BA, Lombardino LJ, King WM, Puranik CS, Leonard CM, Merzenich MM: **Deficits in auditory temporal and spectral resolution in language-impaired children**. *Nature* 1997, **387**:176-178.
176. Kraus N, McGee TJ, Carrell TD, Zecker SG, Nicol TG, Koch DB: **Auditory neurophysiologic responses and discrimination deficits in children with learning problems**. *Science* 1996, **273**:971-973.
177. Alho K: **Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes**. *Ear Hear* 1995, **16**:38-51.
178. Schulte-Körne G, Mathwig F: *Das Marburger Rechtschreibtraining.* Bochum: Winkler; 2001.
179. Buschmann H: *Dynamisch-integrative Förderung von Sprechen, Schreiben, Lesen. Unveröffentlichtes Manuskript.* Waldshut-Tingen: Publisher; 1988.
180. Hofmann B: *Lese-Rechtschreibschwäche - Legasthenie: Erscheinungen, Theorieansätze, Prävention; eine systematische Einführung in die Gesamtproblematik.* München: Oldenbourg; 1998.
181. Heim S, Eulitz C, Wienbruch C, Elbert T: **Effects of syllabic training on literacy skills, phonological processing and cortical organization in children with language impairment.** *Psychophysiology* 2001, **37**:8.
182. Heim S, Freeman RB, Jr., Eulitz C, Elbert T: **Auditory temporal processing deficit in dyslexia is associated with enhanced sensitivity in the visual modality**. *Neuroreport* 2001, **12**:507-510.

183. Tacke G, Brezing H, Schultheiß G: **Rhythmisch-syllabierendes Mitsprechen als Möglichkeit, die Rechtschreibung zu verbessern**. *Lehren und Lernen* 1994, **1**.
184. Schulte-Körne G, Deimel W, Remschmidt H: **Rechtschreibtraining in schulischen Fördergruppen - Ergebnisse einer Evaluationsstudie in der Primarstufe.** *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie* 2003, **31**:85-98.
185. Schulte-Körne G, Deimel W, Hulsmann J, Seidler T, Remschmidt H: **Marburg Spelling Training program--results of a brief intervention**. *Z Kinder Jugendpsychiatr Psychother* 2001, **29**:7-15.
186. Gray JR, Chabris CF, Braver TS: **Neural mechanisms of general fluid intelligence**. *Nat Neurosci* 2003, **6**:316-322.
187. Wiese W, Kroj G: **Studies on the correlation between intelligence (Wechsler) and the ability to concentrate (Brickenkamp's test d2)**. *Z Exp Angew Psychol* 1972, **19**:690-699.
188. Castles A, Coltheart M: **Varieties of developmental dyslexia**. *Cognition* 1993, **47**:149-180.
189. Sereno SC, Rayner K, Posner MI: **Establishing a time-line of word recognition: evidence from eye movements and event-related potentials**. *Neuroreport* 1998, **9**:2195-2200.
190. Assadollahi R, Pulvermuller F: **Neuromagnetic evidence for early access to cognitive representations**. *Neuroreport* 2001, **12**:207-213.
191. Assadollahi R, Pulvermuller F: **Early influences of word length and frequency: a group study using MEG**. *Neuroreport* 2003, **14**:1183-1187.
192. Hauk O, Pulvermuller F: **Neurophysiological distinction of action words in the fronto-central cortex**. *Hum Brain Mapp* 2004, **21**:191-201.
193. Proverbio AM, Vecchi L, Zani A: **From orthography to phonetics: ERP measures of grapheme-to-phoneme conversion mechanisms in reading**. *J Cogn Neurosci* 2004, **16**:301-317.
194. Rudell AP: **The recognition potential and the word frequency effect at a high rate of word presentation**. *Brain Res Cogn Brain Res* 1999, **8**:173-175.
195. Rudell AP: **Rapid stream stimulation and the recognition potential**. *Electroencephalogr Clin Neurophysiol* 1992, **83**:77-82.

196. Johannes S, Mangun GR, Kussmaul CL, Munte TF: **Brain potentials in developmental dyslexia: differential effects of word frequency in human subjects**. *Neurosci Lett* 1995, **195**:183-186.
197. Russeler J, Probst S, Johannes S, Munte T: **Recognition memory for high- and low-frequency words in adult normal and dyslexic readers: an event-related brain potential study**. *J Clin Exp Neuropsychol* 2003, **25**:815-829.
198. Hyona J, Olson RK: **Eye fixation patterns among dyslexic and normal readers: effects of word length and word frequency**. *J Exp Psychol Learn Mem Cogn* 1995, **21**:1430-1440.
199. Rubin GS, Turano K: **Reading without saccadic eye movements**. *Vision Res* 1992, **32**:895-902.
200. Baayen RH, Piepenbrock R, Gulikers L: **The CELEX Lexical Database (CD-ROM)**. In: *Book The CELEX Lexical Database (CD-ROM)* (Editor ed.^eds.). City: Linguistic Data Consortium, University of Pennsylvania; 1995.
201. Tallon-Baudry C, Bertrand O, Delpuech C, Pernier J: **Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human**. *J Neurosci* 1996, **16**:4240-4249.
202. Polk TA, Stallcup M, Aguirre GK, Alsop DC, D'Esposito M, Detre JA, Farah MJ: **Neural specialization for letter recognition**. *J Cogn Neurosci* 2002, **14**:145-159.
203. Bokde AL, Tagamets MA, Friedman RB, Horwitz B: **Functional interactions of the inferior frontal cortex during the processing of words and word-like stimuli**. *Neuron* 2001, **30**:609-617.
204. Rapcsak SZ, Beeson PM: **The role of left posterior inferior temporal cortex in spelling**. *Neurology* 2004, **62**:2221-2229.
205. Samuelsson S: **Converging evidence for the role of occipital regions in orthographic processing: a case of developmental surface dyslexia**. *Neuropsychologia* 2000, **38**:351-362.
206. Cohen L, Dehaene S, Naccache L, Lehericy S, Dehaene-Lambertz G, Henaff MA, Michel F: **The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients**. *Brain* 2000, **123 (Pt 2)**:291-307.

207. Price CJ, Winterburn D, Giraud AL, Moore CJ, Noppeney U: **Cortical localisation of the visual and auditory word form areas: a reconsideration of the evidence**. *Brain Lang* 2003, **86**:272-286.
208. McCandliss BD, Cohen L, Dehaene S: **The visual word form area: expertise for reading in the fusiform gyrus**. *Trends Cogn Sci* 2003, **7**:293-299.
209. Dehaene S, Le Clec HG, Poline JB, Le Bihan D, Cohen L: **The visual word form area: a prelexical representation of visual words in the fusiform gyrus**. *Neuroreport* 2002, **13**:321-325.
210. Salmelin R, Service E, Kiesila P, Uutela K, Salonen O: **Impaired visual word processing in dyslexia revealed with magnetoencephalography**. *Ann Neurol* 1996, **40**:157-162.
211. Tarkiainen A, Helenius P, Hansen PC, Cornelissen PL, Salmelin R: **Dynamics of letter string perception in the human occipitotemporal cortex**. *Brain* 1999, **122 (Pt 11)**:2119-2132.
212. Xiang J, Wilson D, Otsubo H, Ishii R, Chuang S: **Neuromagnetic spectral distribution of implicit processing of words**. *Neuroreport* 2001, **12**:3923-3927.
213. Fitzgibbon SP, Pope KJ, Mackenzie L, Clark CR, Willoughby JO: **Cognitive tasks augment gamma EEG power**. *Clin Neurophysiol* 2004, **115**:1802-1809.
214. Wrobel A: **Beta activity: a carrier for visual attention**. *Acta Neurobiol Exp (Wars)* 2000, **60**:247-260.
215. Gross J, Schmitz F, Schnitzler I, Kessler K, Shapiro K, Hommel B, Schnitzler A: **Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans**. *Proc Natl Acad Sci U S A* 2004, **101**:13050-13055.
216. Junghofer M, Bradley MM, Elbert TR, Lan PJ: **Fleeting images: a new look at early emotion discrimination**. *Psychophysiology* 2001, **38**:175-178.
217. Schupp HT, Junghofer M, Weike AI, Hamm AO: **The selective processing of briefly presented affective pictures: an ERP analysis**. *Psychophysiology* 2004, **41**:441-449.
218. Landauer T, Freedman J: **Information Retrieval from Long-Term Memory: Category Size and Recognition Time**. *Journal of Verbal Learning and Verbal Behavior* 1968, **7**:291-295.

219. Rubenstein H, Garfield L, Milikan J: **Homographic Entries in the Internal Lexicon**. *Journal of Verbal Learning and Verbal Behavior* 1970, **9**:487-494.
220. Compton PE, Grossenbacher P, Posner MI, Tucker DM: **A Cognitive-Anatomical Approach to Attention in Lexical Access**. *J Cogn Neurosci Lett* 1991, **3**:304-312.
221. Shallice T: **From Neuropsychology to Mental Structure**. In. Cambridge: Cambridge University Press; 1988.
222. Petersen SE, Fox PT, Snyder AZ, Raichle ME: **Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli**. *Science* 1990, **249**:1041-1044.
223. Hauk O, Berg P, Wienbruch C, Rockstroh B, Elbert T: **The minimum norm method as an effective mapping tool for MEG analysis**. In: *Recentadvances in biomagnetism* Edited by Yoshimoto T. KM, Kuriki S., Karibe H., Nakasato N., editors. pp. 213-216; 1999: 213-216.
224. Hauk O, Keil A, Elbert T, Muller MM: **Comparison of data transformation procedures to enhance topographical accuracy in time-series analysis of the human EEG**. *J Neurosci Methods* 2002, **113**:111-122.
225. Duffy SA, Henderson JM, Morris RK: **Semantic facilitation of lexical access during sentence processing**. *J Exp Psychol Learn Mem Cogn* 1989, **15**:791-801.
226. Federmeier KD, Kutas M: **Right words and left words: electrophysiological evidence for hemispheric differences in meaning processing**. *Brain Res Cogn Brain Res* 1999, **8**:373-392.
227. Ischebeck A, Indefrey P, Usui N, Nose I, Hellwig F, Taira M: **Reading in a regular orthography: an FMRI study investigating the role of visual familiarity**. *J Cogn Neurosci* 2004, **16**:727-741.
228. Rugg MD: **Event-related brain potentials dissociate repetition effects of high- and low-frequency words**. *Mem Cognit* 1990, **18**:367-379.
229. Altarriba J, Kroll JF, Sholl A, Rayner K: **The influence of lexical and conceptual constraints on reading mixed-language sentences: evidence from eye fixations and naming times**. *Mem Cognit* 1996, **24**:477-492.
230. Henderson JM, Ferreira F: **Effects of foveal processing difficulty on the perceptual span in reading: implications for attention and eye movement control**. *J Exp Psychol Learn Mem Cogn* 1990, **16**:417-429.

231. Rayner K, Sereno SC: **Regressive eye movements and sentence parsing: on the use of regression-contingent analyses**. *Mem Cognit* 1994, **22**:281-285; discussion 286-292.
232. Rayner K: **Eye movements in reading and information processing: 20 years of research**. *Psychol Bull* 1998, **124**:372-422.
233. Broadbent DE, Gregory MH: **Effects on tachistoscopic perception from independent variation of word probability and of letter probability**. *Acta Psychol (Amst)* 1971, **35**:1-14.
234. Schwabe U, Paffrath D: *Arzneiverordnungs-Report 2001*: Springer; 2001.
235. Clarke AR, Barry RJ, McCarthy R, Selikowitz M: **Children with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: an EEG analysis**. *Psychiatry Res* 2002, **111**:181-190.
236. Clarke AR, Barry RJ, McCarthy R, Selikowitz M: **EEG-defined subtypes of children with attention-deficit/hyperactivity disorder**. *Clin Neurophysiol* 2001, **112**:2098-2105.
237. Clarke AR, Barry RJ, McCarthy R, Selikowitz M: **Electroencephalogram differences in two subtypes of attention-deficit/hyperactivity disorder**. *Psychophysiology* 2001, **38**:212-221.
238. Brickenkamp R: *Aufmerksamkeits- Belastungstest d2*. Göttingen: Hogrefe; 1994.
239. Klimesch W, Doppelmayr M, Schimke H, Pachinger T: **Alpha frequency, reaction time, and the speed of processing information**. *J Clin Neurophysiol* 1996, **13**:511-518.
240. Klimesch W, Doppelmayr M, Pachinger T, Ripper B: **Brain oscillations and human memory: EEG correlates in the upper alpha and theta band**. *Neurosci Lett* 1997, **238**:9-12.
241. Babiloni C, Miniussi C, Babiloni F, Carducci F, Cincotti F, Del Percio C, Sirello G, Fracassi C, Nobre AC, Rossini PM: **Sub-second "temporal attention" modulates alpha rhythms. A high-resolution EEG study**. *Brain Res Cogn Brain Res* 2004, **19**:259-268.
242. Vazquez Marrufo M, Vaquero E, Cardoso MJ, Gomez CM: **Temporal evolution of alpha and beta bands during visual spatial attention**. *Brain Res Cogn Brain Res* 2001, **12**:315-320.

243. Fu KM, Foxe JJ, Murray MM, Higgins BA, Javitt DC, Schroeder CE: **Attention-dependent suppression of distracter visual input can be cross-modally cued as indexed by anticipatory parieto-occipital alpha-band oscillations**. *Brain Res Cogn Brain Res* 2001, **12**:145-152.

244. Satterfield JH, Cantwell DP, Saul RE, Lesser LI, Podosin RL: **Response to stimulant drug treatment in hyperactive children: prediction from EEG and neurological findings**. *J Autism Child Schizophr* 1973, **3**:36-48.

245. Matsuura M, Okubo Y, Toru M, Kojima T, He Y, Hou Y, Shen Y, Lee CK: **A cross-national EEG study of children with emotional and behavioral problems: a WHO collaborative study in the Western Pacific Region**. *Biol Psychiatry* 1993, **34**:59-65.

246. Clarke AR, Barry RJ, McCarthy R, Selikowitz M: **Age and sex effects in the EEG: development of the normal child**. *Clin Neurophysiol* 2001, **112**:806-814.

247. Chabot RJ, Serfontein G: **Quantitative electroencephalographic profiles of children with attention deficit disorder**. *Biol Psychiatry* 1996, **40**:951-963.

248. Bresnahan SM, Anderson JW, Barry RJ: **Age-related changes in quantitative EEG in attention-deficit/hyperactivity disorder**. *Biol Psychiatry* 1999, **46**:1690-1697.

249. Klimesch W, Doppelmayr M, Russegger H, Pachinger T: **Theta band power in the human scalp EEG and the encoding of new information**. *Neuroreport* 1996, **7**:1235-1240.

250. Klimesch W, Doppelmayr M, Schimke H, Ripper B: **Theta synchronization and alpha desynchronization in a memory task**. *Psychophysiology* 1997, **34**:169-176.

251. Larson J, Wong D, Lynch G: **Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation**. *Brain Res* 1986, **368**:347-350.

252. Jensen P: **Longer term effects of stimulant treatments for Attention-Deficit/Hyperactivity Disorder**. *J Atten Disord* 2002, **6 Suppl 1**:S45-56.

253. Aftanas LI, Golocheikine SA: **Human anterior and frontal midline theta and lower alpha reflect emotionally positive state and internalized attention: high-resolution EEG investigation of meditation**. *Neurosci Lett* 2001, **310**:57-60.

254. Gevins A, Smith ME, McEvoy L, Yu D: **High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice**. *Cereb Cortex* 1997, **7**:374-385.