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TEMPORAL PROCESSING OF SENSORY INFORMATION IN DEVELOPMENTAL DYSLEXIA: NEUROMAGNETIC AND PSYCHOPHYSICAL STUDIES

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ACADEMIC DISSERTATION

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LIST OF PUBLICATIONS

This thesis is based on the following publications which are referred to in the text by Roman numerals I – VI.

I Loveless N and **Koivikko H**. Sluggish auditory processing in dyslexics is not due to persistence in sensory memory. *NeuroReport* 2000, 11: 1903–1906.

II **Renvall H** and Hari R. Auditory cortical responses to speech-like stimuli in dyslexic adults. *Journal of Cognitive Neuroscience* 2002, 14: 757–768.

III **Renvall H** and Hari R. Diminished auditory mismatch fields in dyslexic adults. *Annals of Neurology* 2003, 53: 551–557.

IV **Renvall H**, Lehtonen R and Hari R. Abnormal response recovery in the right somatosensory cortex of dyslexic adults. Submitted, 2003.

V Hari R, **Renvall H** and Tanskanen T. Left minineglect in dyslexic adults. *Brain* 2001, 124: 1373–1380.

VI Saarelma K, **Renvall H**, Jousmäki V, Kovala T and Hari R. Facilitation of the spinal H-reflex by auditory stimulation in dyslexic adults. *Neuroscience Letters* 2002, 327: 213–215.

ABSTRACT

Developmental dyslexia is a disorder affecting the ability to learn to read despite normal intelligence and adequate tutoring. However, the problems of dyslexics extend beyond the skills directly needed for reading: for example, language-learning-impaired children are slow in processing sounds presented in rapid succession or containing fast frequency transitions. These auditory deficits, at a time scale of up to a few hundreds of milliseconds, have been shown to persist to adult age. Recent behavioral studies imply that dyslexic subjects have defects in temporal processing in other sensory modalities as well; altogether these findings have encouraged a wide search for a general underlying explanation. This thesis characterized the temporal impairment in auditory, tactile, visual, and motor domains in dyslexic adults by utilizing the good temporal resolution of magnetoencephalography (MEG), and also by applying psychophysical approaches.

Studies I–III demonstrated that dyslexic adults are deficient in processing sounds and acoustic changes presented in rapid succession within tens to hundreds of milliseconds. The observed abnormalities could be related to insufficient triggering of auditory stimulus-driven attention, possibly reflecting a deficiency of the magnocellular system. In line with this view, Study III showed that infrequent deviant sounds in an otherwise monotonous stimulus sequence elicit smaller mismatch responses in dyslexic than normal-reading subjects. Study IV revealed abnormal response recovery in the right somatosensory cortex of dyslexic individuals, in agreement with earlier proposals of a pansensory processing deficit. In the visual psychophysical tasks of Study V, dyslexic adults processed stimuli about 15 ms more slowly in the left than right visual hemifield, suggestive of a left-sided "minineglect". Furthermore, abrupt stimuli captured attention in both visual hemifields less effectively in dyslexics than in normal readers. Study VI indicated normal, although slightly prolonged, auditory alerting via cerebrospinal pathways in dyslexic subjects.

On the basis of these and earlier findings we have proposed that limitations of both modality-specific and of more global attentional capacities could prolong sensory input chunks and thus result in anomalous cortical representations in dyslexic individuals.

ABBREVIATIONS

ANOVA	Analysis of variance
ECD	Equivalent current dipole
EEG	Electroencephalography
EMG	Electromyography
EOG	Electro-oculography
FM	Frequency modulation
FMRI	Functional magnetic resonance imaging
HG	Heschl's gyrus
ISI	Interstimulus interval
IQ	Intelligence quotient
LGN	Lateral geniculate nucleus
LI	Lateralization index
M	Magnocellular
MCE	Minimum current estimate
MGN	Medial geniculate nucleus
MEG	Magnetoencephalography
MMF	Mismatch field
MMN	Mismatch negativity
MRI	Magnetic resonance imaging
P	Parvocellular
PAC	Primary auditory cortex
PET	Positron emission tomography
PPC	Posterior parietal cortex
PT	Planum temporale
RT	Reaction time
SEF	Somatosensory evoked field
SEM	Standard error of mean
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SLI	Specific language impairment
SOA	Stimulus onset asynchrony
SPL	Sound pressure level
SQUID	Superconducting quantum interference device
VEP	Visual evoked potential
V1, V2, V4, MT/V5	Visual cortical areas
WAIS	Wechsler adult intelligence scale

1 INTRODUCTION

"*Time is three things for most people, but for you, for us, just one. A singularity. One moment. This moment. Like you're the center of the clock, the axis on which the hands turn. Time moves about you but never moves you. ... Time is an absurdity. An abstraction.*"

from *Memento Mori*, by Jonathan Nolan

Time, the most abstract of dimensions, has often played the role of a bystander in theories of perception and motor control (Ivry 1996) even though timing is essential for all proper brain functions. We have to continuously extract sensory information presented in time, and form sequences of precisely timed motor behaviors. Lately, the relevance of proper timing has been strongly advocated in relation to linguistic processes (Werani and Kegel 2001). Speech as a physical signal contains many chronologically ordered elements, like phonemes, syllables, and words. Disturbing the temporal synchronization of a speech signal at different levels distorts the perception, and deficiencies in the perceptional mechanisms can degrade the analysis of a proper signal. Similarly, reading as a complex task requires sensory, phonological, and attentional skills – all of which depend on fast and accurate temporal processing mechanisms.

Developmental dyslexia, or specific reading impairment, has been in the scientific spotlight during the last decades, and not least because of the numerous behavioral studies that have revealed non-linguistic sensory processing deficits in reading-impaired subjects. Many of these findings have been unrelated to reading acquisition as such, and have specifically pointed to impaired temporal processing as a possible causal or confounding factor in the genesis of dyslexia. Consequently, several "sensory" theories on the development of dyslexia have been formed: for example, phonological deficits in dyslexic subjects have been suggested to stem from a more general auditory dysfunction, manifested as impaired temporal processing of sounds (Tallal 1980), and findings in the visual modality have pointed to a general deficit of rapidly-conducting magnocellular pathways (Stein and Walsh 1997).

Imaging of dyslexic brains has given new insight into understanding the disorder. However, the imaging studies have mainly concentrated on the reading

process itself, and studies on non-linguistic processing in reading-impaired subjects have been scarce. Nevertheless, knowledge of non-linguistic auditory functions in dyslexic subjects could serve as a relevant background for understanding the successive steps and problems in processing phonemes and words. Only electroencephalography (EEG) and magnetoencephalography (MEG) can, non-invasively and with millisecond time scale, target the different relevant time windows of sensory processing. However, whereas electric inhomogeneities outside the brain affect EEG, the magnetic field patterns are not distorted, and MEG can thus provide additional spatial information on the reactivity of specific cortical areas.

Studies I–III of this thesis concentrated on different aspects of non-linguistic auditory cortical processing in Finnish dyslexic adults. Although auditory deficits have been frequently reported in dyslexic individuals, these subjects are impaired in perceptual processing of rapidly presented visual and tactile stimuli as well. Study IV was therefore designed to test the pansensory deficit in dyslexic subjects at the brain-signal level, by assessing the neuromagnetic signals generated in response to rapidly presented tactile stimuli. On the basis of the suggested general magnocellular deficit in dyslexics, we tested in Study VI, whether dyslexic subjects would be alerted less efficiently than normal readers by external stimuli. Earlier behavioral studies have suggested similarities between dyslexic subjects and patients suffering from visuospatial neglect after right-hemisphere lesions. In Study V, we tried to further illuminate this aspect; on the basis of the results we suggested that dyslexic adults suffer from a visual “minineglect”.

2 BACKGROUND

This section starts with an introduction to developmental dyslexia, and then reviews the anatomy and physiology of auditory, tactile, and visual domains in sufficient detail for the present studies. Finally, it provides a brief review of the MEG method and its applications.

2.1 Developmental dyslexia

This disorder, which was initially termed *congenital word blindness* and later *developmental dyslexia*, has been defined by World Federation of Neurology as ”a disorder manifested by difficulty in learning to read despite conventional instruction, adequate intelligence, and sociocultural opportunity” (Critchley 1970, p. 268). In practice, dyslexia typically means a discrepancy between reading achievement and intelligence quotient (IQ), or discrepancy between actual reading skills and those predicted by age or IQ (Dykman and Ackerman 1992; Fletcher *et al.* 1992; Pennington *et al.* 1992; Katusic *et al.* 2001). Writing and spelling difficulties often accompany dyslexia. Depending on the research method and the population under study (Duane 2001; Katusic *et al.* 2001), the prevalence of dyslexia has been estimated to range from 4% (Hulme 1987) to 15% (Stein and Walsh 1997). In Finland, the prevalence roughly corresponds to the international values (Poussu-Olli 1993; Lyytinen *et al.* 1995). There is a longstanding controversy about whether the prevalence of dyslexia differs between sexes: Whereas some studies have indicated similar incidence rates for boys and girls (Shaywitz *et al.* 1990; Wadsworth *et al.* 1992), a recent longitudinal study of 5718 American children suggested that boys would be 2 to 3 times more likely to be affected (Katusic *et al.* 2001). Dyslexia has been suggested to simply represent the lower tail of a normal distribution of reading abilities (Shaywitz *et al.* 1992).

2.1.1 Phonological core deficit

The most robust finding among dyslexic children is a deficit in the phonological processing of spoken and written language. Phonological processing can be divided into three subcategories: *phonological awareness*, *phonological recoding*

in lexical access, and *phonetic recoding in working memory* (Wagner and Torgesen 1987). A deficit in phonological awareness is believed to impair the mapping of written letters into the corresponding phonemes, and to impair the subject's ability to manipulate the constituent sounds of the words. These abilities can be tested, for example, with rhyme detection or phoneme deletion. Children's reading skills correlate well with their pre-school phonological awareness (Lundberg *et al.* 1980; Bradley and Bryant 1983; Liberman and Shankweiler 1985; Muter *et al.* 1998). For instance, in a longitudinal study of 133 Swedish children (Lundberg *et al.* 1980), the ability to segment three-phoneme words into their constituent phonemes and the reversal of phonemes predicted reading skills during the first years at school. Likewise, American children who were born to dyslexic parents and were later diagnosed as reading impaired, had deficits in phonological awareness at the age of 5 years (Scarborough 1990). Reading-impaired children have problems also in identifying and discriminating consonant-vowel syllables (Godfrey *et al.* 1981; Reed 1989), which suggests a disorder in the phonemic representation itself.

Phonological recoding in lexical access refers to the efficiency in recoding written symbols into phonemes, and it can be assessed by pseudoword reading, as well as rapid naming of objects, colors, or other symbols (Wagner and Torgesen 1987). German dyslexic children are slower and more error-prone than age-matched normal readers in nonword reading (Wimmer 1996), but they are relatively faster and more accurate than English-speaking dyslexic children who have more difficult grapheme-to-phoneme correspondence (Landerl *et al.* 1997). Both dyslexic children and adults are slower than normal readers in rapid naming tasks (Denckla and Rudel 1976; Korhonen 1995; Vellutino *et al.* 1995), and object naming in pre-literate children predicts later reading problems (Scarborough 1990).

Written symbols have to be translated into phonemes and maintained in working memory for short time periods during ongoing cognitive processing (Wagner and Torgesen 1987). The capacity of this phonological store can be assessed with memory span tasks: Dyslexic adults and children are significantly worse than control subjects in digit and word repetition tasks (Korhonen 1995; Leinonen *et al.* 2001; Plaza *et al.* 2002), and word-string spans in pre-school children predict their reading skills one year later (Mann and Liberman 1984).

Phonological awareness probably develops independently of the underlying orthography: phonological skills and reading are related in shallow orthographies like

Finnish and German, as well as in deep (English) and logographic orthographies (Goswami 1997). Moreover, phonological processing deficits in dyslexia seem universal (Paulesu *et al.* 2001). However, learning to read is easier in languages with shallow orthography where letters are uniquely mapped into speech sounds. Consequently, dyslexic individuals in these languages perform better in reading tasks than dyslexics using deep orthographies because the orthography itself can aggravate the existing impairment (Paulesu *et al.* 2001). Many dyslexic adults who eventually compensate for their reading difficulties still continue to have deficient phonological processing skills (Pennington *et al.* 1990). At the brain-signal level, phonological problems have been suggested to arise from congenital dysfunction of temporoparietal regions involved in phonology and reading (Galaburda *et al.* 1985; Paulesu *et al.* 2001; Temple *et al.* 2001).

In the Finnish language the grapheme-to-phoneme correspondence is nearly perfect. Thus slowness of reading is a better marker of dyslexia than poor accuracy, and this pattern continues up to adult age (Leinonen *et al.* 2001). Phoneme durations are commonly used to differentiate between Finnish word meanings; for example, *tiili* (brick), *tili* (account), and *tilli* (dill). Such distinctions are especially difficult for Finnish dyslexic subjects (Lyytinen *et al.* 1995).

2.1.2 Sensory deficits

Although the fundamental role of a phonological deficit in dyslexia has been widely accepted among researchers, several studies have emphasized the role of more general deficits of auditory, visual, and motor systems (for a review, see Habib 2000). For example, speech perception requires well-developed auditory capabilities for extracting the spectral shape of the signal, for detecting and discriminating rapid amplitude and frequency modulations, and for segregating the relevant speech from background noise (Bailey and Snowling 2002). Some of these capabilities are probably present already *in utero*; for example, fundamental frequency characteristics of motherese speech are highly salient to 4-month-old infants (Fernald and Kuhl 1987), and newborn infants can segregate sound streams (Winkler *et al.* 2003).

2.1.2.1 Auditory processing

In 1970's, studies of children with specific language impairment (SLI) started a new era in dyslexia research (Tallal *et al.* 1998). The results challenged the specificity of the phonological deficit and suggested that the phonological problems encountered in dyslexic subjects could derive, at least in part, from a non-verbal auditory processing deficit, manifested as impaired temporal processing of sounds. SLI children fail to develop normal oral language and thus differ from dyslexic subjects in whom the failure is limited to reading development. As many children have problems in both oral language and reading, SLI and dyslexia have been suggested to be just two faces of the same disorder (Tallal *et al.* 1997).

Processing of rapidly presented stimuli

Tallal and Piercy (1973a, 1973b) were the first to demonstrate that SLI children are impaired in the processing of rapidly presented stimuli: The children were impaired in discriminating and sequencing two tones of 100-Hz and 305-Hz frequency when the tones were presented with interstimulus intervals (ISIs) of less than 400 ms. Furthermore, the same children had problems in discriminating speech sounds /ba/ and /da/ containing rapid 40-ms formant transitions (Tallal and Piercy 1974), whereas they performed similarly to control children when the duration of the transition was prolonged to 80 ms (Tallal and Piercy 1975). Later on, the problems at rapid stimulus presentation rates were shown to extend to dyslexic children, and they correlated with performance in a phonological task (Tallal 1980). Recently, similar relationship between auditory temporal judgments and phonological measures has been demonstrated in average and above-average readers (Au and Lovegrove 2001). Training of rapidly changing acoustic cues, combined with training of phonological and language processing with acoustically modified speech, has been shown both to improve language skills in SLI children (Merzenich *et al.* 1996; Tallal *et al.* 1996, 1998), and to induce changes in the cortical representation of sounds (Hayes *et al.* 2003).

The processing of fast frequency transitions and sounds presented in rapid succession occurs at different time scales, the neural bases of which are thus likely to differ. Dyslexics have been suggested to have a longer than usual time window within which successive stimuli may interfere (Cutting and Pisoni 1978). Recent studies on

illusory directional hearing and on auditory stream segregation in dyslexic adults (Hari and Kiesilä 1996; Helenius *et al.* 1999b) are in line with this proposal. In the auditory saltation illusion (Hari 1995), 4 left-ear leading binaural clicks were followed by 4 right-ear leading ones; interaural time differences of 0.8 ms were used to produce the lateralized percepts of the single clicks. When presented at long ISIs, the binaural clicks were perceived as 4 left-sided clicks followed by 4 right-sided clicks. However, when the ISI was shortened below 150 ms, a saltatory percept emerged, with the sounds appearing to jump from left to right at equidistant steps. Hari and Kiesilä (1996) demonstrated that dyslexic adults perceive the saltation at significantly longer ISIs than do the normal readers.

Further evidence for the prolonged processing window was obtained from an auditory stream segregation experiment (Helenius *et al.* 1999b), in which high and low tones were presented alternately. When such a sequence is presented with a long ISI, a continuous sequence of high-low-high-low… tones is heard. When the ISI is shortened, the streams segregate and two separate streams, high-high-high… and low-low-low…, are simultaneously perceived. Helenius *et al*. (1999b) observed that the ISI leading to segregation was almost double in dyslexic adults compared with control subjects. The results from these two studies suggest sluggish processing of rapid stimulus sequences in dyslexics, indicating that the difficulties in perceiving sounds presented at rapid rates persist to adult age.

The relationship of the auditory and phonological deficits is not settled; the problems of dyslexics in discriminating tones and speech sounds have also been claimed to reflect independent deficits (Studdert-Kennedy and Mody 1995). Moreover, the problems in differentiating, for example, /ba/-/da/ syllables have been suggested to reflect perceptual confusion between phonetically similar syllables rather than a difficulty in perceiving rapid spectral changes (Mody *et al.* 1997).

Other auditory perceptual tasks

Dyslexic adults are also impaired in tasks that involve spectral pitch discrimination without any temporal constraints (Hari *et al.* 1999a; Ahissar *et al.* 2000), and they are less sensitive than normal readers in detecting slow (2 Hz and 40 Hz) frequency modulations (FMs) of tones (Witton *et al.* 1998). During the crucial time period when infants are refining their phonological representations, ~50% higher

thresholds of dyslexics for 2-Hz FM (Witton *et al.* 1998) might be sufficient to degrade speech perception for those at risk for dyslexia (Bailey and Snowling 2002). In addition, the 2-Hz FM detection predicts phonological skills in both dyslexic adults and normal-reading children (Witton *et al.* 1998; Talcott *et al.* 1999).

Tallal and Stark (1981) already suggested that the impaired nonverbal and speech processing abilities of SLI children might be attributed to abnormalities in mechanisms involved in auditory masking. Auditory masking refers to a change in the perception of target stimulus because of a simultaneous, preceding, or following auditory stimulus. Indeed, Wright *et al.* (1997b) observed that some SLI children are deficient in detecting 20-ms, but not 200-ms tones that are immediately followed by noise; the impairment was particularly clear when the noise contained the tone frequency. This finding was replicated in later studies (McArthur and Hogben 2001; Rosen and Manganari 2001), and it was suggested to be specific to children with concomitant oral language and reading impairments (McArthur and Hogben 2001). In addition, adult dyslexics have been reported to be impaired in detecting long binaural 1-kHz tones embedded in noise when the tones are in opposite phase (McAnally and Stein 1996), suggesting reduced binaural masking level differences; these results were, however, not replicated in recent studies using 0.2-kHz (Hill *et al.* 1999) and 0.5-kHz tones (Amitay *et al.* 2002).

Imaging studies

Imaging studies on auditory processing in dyslexia have been relatively scarce and mainly concentrated on the processing of speech stimuli. Metabolism is higher in the medial temporal areas of dyslexic than control adults during an auditory syllable discrimination task (Hagman *et al.* 1992). Auditory rhyme detection failed to activate the left temporal and inferior parietal cortex in dyslexic men (Rumsey *et al.* 1992), and a tonal memory task activated less strongly temporal and frontal regions in dyslexic than control men (Rumsey *et al.* 1994). Whereas left prefrontal activity was stronger to rapidly than slowly changing non-linguistic stimuli in control subjects, such activity was essentially absent in dyslexic adults (Temple *et al.* 2000).

Techniques relying on electrophysiological measures can better target the different relevant time windows of auditory processing. In SLI children, brainstem auditory evoked potentials display prolonged latencies and interwave transmission

times (Piggott and Anderson 1983), and they are diminished in amplitude (Mason and Mellor 1984). At the cortical level, abnormal hemispheric balance or reduced 100-ms response amplitudes, as well as prolonged 50-ms response latencies have been detected in children with reading or spelling difficulties (Mason and Mellor 1984; Byring and Järvilehto 1985; Pinkerton *et al.* 1989; Brunswick and Rippon 1994).

The magnetic 100-ms response to the second sound of a tone pair is, at short stimulus onset asynchronies (SOAs), smaller in dyslexic than normal-reading adults (Nagarajan *et al.* 1999). Recent studies in our laboratory have demonstrated that dyslexic adults have abnormally strong 100-ms responses in their left auditory cortex to onsets of speech sounds, and that the responses are delayed to speech sounds containing rapid frequency transitions (Helenius *et al.* 2002).

Diminished electric mismatch responses to infrequent sound deviances are associated with impaired behavioral discrimination of /da/ *vs.* /ga/ syllables in SLI children (Kraus *et al.* 1996). Results from dyslexic subjects are somewhat contradictory: diminished mismatch responses have been found either only to speech sounds (Schulte-Körne *et al.* 1998, 2001), or to non-speech stimuli as well (Baldeweg *et al.* 1999; Kujala *et al.* 2000, 2003).

2.1.2.2 Visual processing

Classically the visual system has been considered the most probable candidate for anatomical or sensory deficits in dyslexia, due to the need for identification of letter shape and order during reading. Only quite recently dyslexic subjects have been suggested to be specifically impaired in visual tasks involving magnocellular (M), or the “transient”, visual system that is primarily involved in analyzing stimuli with low spatial and high temporal frequencies. Lovegrove and co-workers (1980) were first to demonstrate that dyslexic children’s contrast sensitivity for static gratings is reduced at low (2–4 cycles/deg) spatial frequencies but not at higher (12–16 cycles/deg) frequencies at mesopic luminance levels. Even more marked deficiencies were found for flickering gratings, especially at high temporal frequencies (Lovegrove *et al.* 1986). Dyslexic children are behaviorally impaired also in detection of visual motion (Cornelissen *et al.* 1995), and motion-detection thresholds can explain letter position errors during reading even in normal-reading children (Cornelissen *et al.* 1998).

Livingstone and co-workers (1991) found in dyslexic adults delayed transient visual evoked potentials (VEPs) and diminished steady-state VEPs to transient pattern reversals at low contrast conditions that rely mainly on the M system. These results were, however, not replicated by Victor *et al.* (1993) who used similar paradigms but a larger subject group and more rigorous statistical criteria. In line with the proposed M deficit, the 60-ms and 150-ms deflections of transient VEPs for low (0.5 cycles/deg) spatial frequencies were delayed in dyslexic children (Lehmkuhle *et al.* 1993). In a functional magnetic resonance imaging (fMRI) study of Eden and co-workers (1996), dyslexic adults had essentially no activity in the motion-sensitive area MT/V5 to the presentation of moving dots. The complete absence of MT activity was not supported by further studies, which reported slightly (by about 11 ms) delayed MEG responses from the MT area (Vanni *et al.* 1997) and reduced fMRI activity at V1 and several extrastriate areas, including MT, in response to low-luminance, moving gratings in dyslexic adults (Demb *et al.* 1998).

The findings of possible M deficits in dyslexic subjects have given rise to a hypothesis suggesting that the basic disorder is a neurodevelopmental abnormality in the magnocellular system (Lovegrove *et al.* 1980; Livingstone *et al.* 1991; Galaburda *et al.* 1994; Stein and Walsh 1997). However, many physiological and psychophysical studies have yielded incompatible results with the M deficit theory (Gross-Glenn *et al.* 1995; Skottun 2000). This has resulted in constant debate regarding the significance of visual processing deficits in dyslexia. Moreover, the reduced contrast sensitivity in dyslexic individuals seems to be restricted to mesopic luminance levels; at higher (photopic) luminance levels usually encountered during reading, dyslexics perform normally (Cornelissen *et al.* 1995). Defective contrast sensitivity is thus unlikely to significantly contribute to reading problems. Consequently, the M system has been suggested to be more involved in integrating information across successive fixations during reading (Lovegrove *et al.* 1986), and – due to a deficient input to the cerebellum and the parietal cortex – in saccade and vergence control, as well as in visuospatial attention (Stein and Talcott 1999).

2.1.2.3 Tactile processing

Only few studies have concentrated on tactile processing in dyslexic or language-impaired subjects. SLI children have difficulties in identifying which two

fingers of the same hand were touched simultaneously (Johnston *et al.* 1981; Tallal *et al.* 1985). Dyslexic adults are impaired in detecting 3-Hz, but not 30-Hz or 300-Hz, vibratory stimuli in the index finger of the writing hand (Stoodley *et al.* 2000), and their tactile discrimination thresholds for the orientation and ridge-width of gratings are enhanced in both hands (Grant *et al.* 1999); detection thresholds for orientation discrimination are especially high in the dominant right hand of dyslexic subjects. Laasonen and colleagues (2000, 2001, 2002b) observed in dyslexic children and adults impaired segregation of rapidly presented auditory, visual, and tactile stimuli; crossmodal segregation times were also prolonged.

2.1.2.4 Balance and motor system

Dyslexic children often suffer from motor impairments, such as clumsiness, poor balance and coordination (Wolff *et al.* 1984; Moore *et al.* 1995). It has been proposed that dyslexic individuals have a general deficit in automatization for skills – for motor as well as for cognitive – and that these symptoms would reflect mild cerebellar dysfunction. In addition, as the cerebellum plays a role in motor control and thus in speech articulation, dyslexics' phonological skills would be impaired via deficient articulatory fluency. This proposal is supported by a series of studies on a dyslexic population demonstrating impairments in standard motor tests for cerebellar impairment (Fawcett *et al.* 1996), in time estimation, a non-motor cerebellar task (Nicolson *et al.* 1995), and in eye-blinking conditioning (Nicolson *et al.* 2002). Brain imaging studies have also demonstrated metabolic, functional, and anatomical abnormalities in the cerebellum of dyslexic subjects (Rae *et al.* 1998; Nicolson *et al.* 1999; Leonard *et al.* 2001).

Although recent studies confirm the presence of motor deficits among dyslexic children (Ramus *et al.* 2003a), it is still questionable whether these deficits are restricted to dyslexic individuals or rather are more common in subjects with concomitant attention deficit disorder (Denckla *et al.* 1985; Raberger and Wimmer 2003; Ramus *et al.* 2003a). On the other hand, the cerebellum has also been considered one part of a deficiently functioning M system in dyslexic subjects (Stein and Talcott 1999; Stein 2001). In macaque monkeys, the magnocellular divisions of the red nucleus receive their main input from the cerebellar deep nuclei (Darian-Smith *et al.*

1999), and they form the starting point of the rubrospinal tract which is important for the control of distal limb muscles.

2.1.3 Abnormalities of brain anatomy

Dyslexia was originally characterized as a disorder of anomalous cerebral asymmetry and lateralization (Orton 1937). Later, the idea of diagnosing dyslexia on the basis of neuroanatomy was abandoned, although additional evidence has been found of anomalous asymmetries and brain structures in dyslexia.

Reading disability has been suggested to be associated with anomalous symmetry of temporal lobe structures, in particular of the planum temporale (PT). In a postmortem study of 100 normal brains, the left PT was larger than the right in 65 brains (Geschwind and Levitsky 1968), and this asymmetry was hypothesized to correlate with the well-known left-hemisphere language dominance. Indeed, the first computerized tomography study (Hier *et al.* 1978), as well as postmortem studies (Galaburda and Kemper 1979; Galaburda *et al.* 1985; Galaburda 1989) of dyslexic brains reported abnormal symmetry of parieto-occipital regions. However, while early MRI experiments still supported this view (Hynd *et al.* 1990), recent MRI studies have consistently demonstrated normal planar asymmetry in dyslexia (Leonard *et al.* 1993; Best and Demb 1999; Eckert and Leonard 2000), and even anomalously larger asymmetry of PT has been reported (Leonard *et al.* 2001). The current view supports the idea that PT asymmetry might rather be related to language skills and verbal IQ (Heiervang *et al.* 2000; Eckert *et al.* 2001, 2003) and as such would not predict reading disability.

Lately, the focus of anatomical studies has changed, and other asymmetrical or otherwise atypical brain areas have been considered as new candidate structures for the neural basis of dyslexia. Several studies have shown lack or even reversed asymmetry in the visual and auditory areas outside PT in dyslexic brains (Galaburda *et al.* 1985; Hynd *et al.* 1990; Jenner *et al.* 1999; Heiervang *et al.* 2000), and reduction of gray matter within the left temporal lobe has been reported (Brown *et al.* 2001). In addition, abnormalities have been found in the cerebellum and the inferior frontal gyrus (Brown *et al.* 2001; Leonard *et al.* 2001; Rae *et al.* 2002; Eckert *et al.* 2003), and these measures may predict subject's phonological and naming performance (Eckert *et al.* 2003). A frequently proposed mechanism of abnormal

interhemispheric transfer in dyslexia has pointed to involvement of the corpus callosum, but results on its size and shape have been contradictory (von Plessen *et al.* 2002; Eckert and Leonard 2003).

A series of postmortem studies (Galaburda and Kemper 1979; Galaburda *et al.* 1985; Galaburda 1989) has suggested anomalous cortical development in dyslexic individuals. These studies revealed several cortical malformations: neuronal ectopias in the inferior frontal and superior temporal regions, predominantly in the left hemisphere, dysplasias, and occasionally vascular micro-malformations. From the perspective of dyslexia's etiology, probably the most important post-mortem findings were obtained from altogether five dyslexic subjects; their brains showed abnormal magnocellular layers in the lateral geniculate nuclei (LGN) and in the medial geniculate nuclei (MGN) of thalamus (Livingstone *et al.* 1991; Galaburda *et al.* 1994). In the LGN, the magnocellular neurons were, on the average, 30% smaller in the brains of dyslexic than control individuals. The left MGN showed an excessive number of small neurons and diminished number of large neurons. These anomalies in the visual and auditory pathways are in line with many of the observed behavioral deficits in dyslexics, and have often been taken as the most convincing evidence of the magnocellular deficit in dyslexia.

Unfortunately, these findings have not been replicated nor expanded to a larger population beyond the five subjects. Recently, Jenner *et al.* (1999) demonstrated that the thalamic changes in these five brains were not associated with any changes in the layers with magnocellular input at the primary visual cortex. In the same study, the normal hemispheric asymmetry of primary visual cortices was absent in dyslexic subjects, indicating some kind of morphological abnormality.

MRI studies have also revealed atypical pattern of gyrification in the temporal and parietal perisylvian cortices of both hemispheres (Leonard *et al.* 1993). Moreover, diffusion tensor imaging showed bilateral differences in temporo-parietal white matter microstructure between dyslexics and fluent readers (Klingberg *et al.* 2000); the white matter disturbances of the left hemisphere correlated with reading scores within both subject groups.

2.1.4 Genetic basis

Although the phenotypic definitions of dyslexia vary greatly, the disorder has been shown to be highly familial and heritable (Fisher and DeFries 2002). The risk for reading problems is greatly elevated for relatives of dyslexic probands (Finucci *et al.* 1976; Pennington *et al.* 1991), and the diagnosis of dyslexia is much higher in monozygotic than in dizygotic twins (DeFries *et al.* 1987), thereby demonstrating the significance of contributing genetic factors.

In addition to the constraints on phenotypic definitions, the genetic studies have been complicated by the genetic complexity of the disorder itself. Reading as a complex cognitive process is likely to be affected by several genes, even genes with relatively small effects (Gayán *et al.* 1999). Different etiologies for different dyslexic phenotypes have also been suggested (Grigorenko *et al.* 1997; Castles *et al.* 1999). So far, several chromosomes, including chromosomes 15 (Smith *et al.* 1983), 1 (Rabin *et al.* 1993), 6 (Cardon *et al.* 1994), 2 (Fagerheim *et al.* 1999), 3 (Nopola-Hemmi *et al.* 2001), 18 (Fisher *et al.* 2002), and 7 (Kaminen *et al.* 2003) have all been linked to dyslexia. Interestingly, chromosome 6 has also been linked to attention deficit disorder (Warren *et al.* 1995) with which dyslexia shows considerable overlap (Willcutt *et al.* 2000). In Finnish dyslexic families, linkages have been found to chromosomes 15, 3, 2, and 7 (Nopola-Hemmi *et al.* 2000, 2001; Kaminen *et al.* 2003), and recently the first candidate gene for developmental dyslexia was demonstrated in chromosome 15 in Finnish dyslexics (Taipale *et al.* 2003). These results imply again large heterogeneity within the disorder, and also raise the question of how well these genetic effects, found within families and within different nationalities, will ever be generalized to a wider population (Fisher and DeFries 2002).

2.2 Sensory systems

2.2.1 Auditory processing and auditory evoked responses

After amplification and filtering in the external and middle ear, the sonic air pressure waves are transmitted to vibrations of the inner ear fluids and the basilar membrane of the cochlea, and transformed into neural signals. Sensory cells and their afferent fibers are at the cochlear base maximally tuned to high frequencies and at the apex to low frequencies. This tonotopical organization is preserved at each following level of the auditory pathway. Auditory nerve fibers synapse at the ipsilateral cochlear nuclei, and second-order neurons ascend to the contralateral inferior colliculus and the superior olivary nuclei bilaterally; acoustic information is already at this stage organized in a highly parallel fashion. The pathway continues via the inferior colliculus and the MGN of thalamus to the auditory cortex in the temporal lobe.

The main human cortical auditory areas are located bilaterally in the superior temporal region, corresponding to Broadmann's areas 41, 42, and 22. Current view of the functional organization of human auditory areas is still largely based on animal data. In both nonprimates and primates, primary auditory areas contain multiple fields with distinct tonotopic maps (Merzenich and Brugge 1973; Merzenich *et al.* 1975; Reale and Imig 1980; Aitkin *et al.* 1986). Primate superior temporal regions have been suggested to consist of three specific and parallel architectonic areas (Kaas *et al.* 1999; Kaas and Hackett 2000): *core*, *belt* and *parabelt* areas. Figure 1 (left) depicts schematically this organization. The central core area has koniocellular architecture and other histological features of a primary sensory cortex, and constitutes two or three separate primary-like fields that can be distinguished from each other by having different systematic presentations of the cochlea. The core is surrounded by a narrow belt region, which still shows tonotopical organization and may contain up to eight separate fields. The parabelt region lies adjacent to the lateral belt and comprises at least two subdivisions. The core receives dense input from the ventral division of the MGN, and it projects to the belt region, which receives strong input also from the dorsal and medial divisions of the MGN. The belt area sends afferents to the parabelt which receives its thalamic input from medial and dorsal MGN, as wells as from the suprageniculate and limitans nuclei. Auditory processing extends beyond auditory

cortex via connections of the parabelt, especially to adjacent areas of the temporal cortex and the prefrontal cortex.

Cross-species comparisons of auditory cortex architectonics suggest that this model may apply to humans as well (Hackett *et al.* 2001). The human primary auditory cortex (PAC; Broadmann area 41) resides in the Heschl's gyrus (HG) in the depth of Sylvian fissure, and it has recently been suggested to comprise three distinct koniocortical areas along the mediolateral axis of HG (Morosan *et al.* 2001; see Fig. 1, right). MEG and EEG (Romani *et al.* 1982; Pantev *et al.* 1995), together with intracranial recordings (Howard *et al.* 1996) have suggested tonotopic organization within PAC. However, macroanatomic landmarks for PAC do not necessarily correspond to the cytoarchitectonically defined areal borders (Morosan *et al.* 2001; Rademacher *et al.* 2001), and thus the functional-anatomical interpretations are not straightforward.

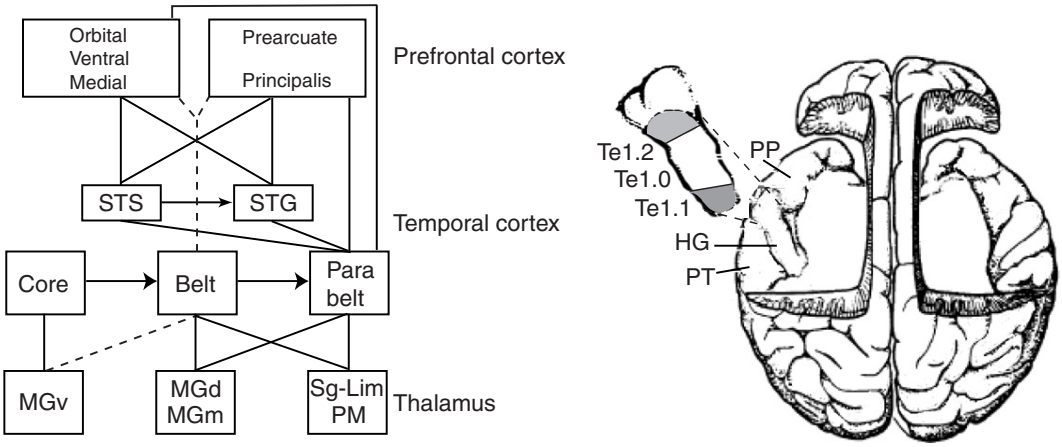

Figure 1. Left: Levels and connections in the primate auditory cortex. Solid lines refer to main connections, and dashed lines to minor connections. MGv/d/m = ventral/dorsal/medial divisions of the medial geniculate nucleus; Sg-Lim = suprageniculate and limitans nuclei; PM = medial pulvinar nucleus; STS = superior temporal sulcus; STG = superior temporal gyrus. Adapted from Kaas *et al.* (1999). Right: Anatomy of human auditory areas. PP = planum polare; PT = planum temporale. Areas Te1.0, Te1.1, and Te1.2 refer to the distinct cytoarchitectonic areas in PAC. Adapted from Morosan (2001) and Rademacher (2001).

The human auditory association areas are located anterior, posterior, and medial to HG in the superior temporal gyrus, containing the planum polare and temporale areas (see Fig. 1, right); at least six putative auditory areas have been reported (Rivier and Clarke 1997). At these areas, tonotopic organization is probably less precise or even absent (Clarey *et al.* 1992) and they may play an important role in the processing of more complex stimuli, such as speech (Vouloumanos *et al.* 2001), pitch sequences

and melodies (Griffiths *et al.* 1998; Patterson *et al.* 2002) and spatial properties of sounds (Warren and Griffiths 2003). The intrinsic connectivity differs between human auditory areas: whereas connections in PAC involve mainly nearby units, the association areas have larger spread of connections which may play a role in integrating auditory features (Tardif and Clarke 2001).

In both human and non-human primate auditory cortices, auditory information is processed in parallel systems that are tied together to form a highly ordered network. Substantial controversy still surrounds the functional organization of the histologically defined auditory pathways. In primates, ventral and dorsal parts of the belt area project to largely different areas in the prefrontal cortex, and distinct dorsal and ventral processing streams have recently been suggested (Rauschecker 1998; Kaas and Hackett 1999; Romanski *et al.* 1999; Rauschecker and Tian 2000). Electrophysiological as well as functional imaging data in humans (Alain *et al.* 2001; Maeder *et al.* 2001) support such a division, but it is still unclear as to the extent to which these would be organized to "what" and "where" pathways, analogous to the visual cortical processing streams (Kaas and Hackett 1999; Romanski *et al.* 1999; Belin and Zatorre 2000; Maeder *et al.* 2001; Zatorre and Belin 2001).

Auditory evoked responses can be classified on the basis of their latency to early (< 10 ms from the stimulus onset), middle (10–50 ms), and late (> 50 ms) responses (Kraus and McGee 1992). The early responses originate in the cochlea, auditory nerve, and brain stem nuclei. The neural generators of the earliest middle-latency responses probably receive subcortical contribution (Picton *et al.* 1974; Woods *et al.* 1987; McGee *et al.* 1992), whereas the later ones have a cortical origin (Pelizzone *et al.* 1987; Mäkelä *et al.* 1994; Lütkenhöner *et al.* 2003a). Late responses are generated at the auditory cortex (for a review, see Hari 1990).

2.2.1.1 Transient responses to sound onset

The 100-ms response is the most conspicuous deflection of the auditory evoked response, and it is called N100 (EEG) or N100m (MEG; Hari *et al*. 1980). The source location of N100m suggests a main contribution from areas in the supratemporal auditory cortex immediately posterior to the primary auditory cortex in HG, thereby including the PT (Hari *et al.* 1987; Pelizzone *et al.* 1987; Pantev *et al.* 1995; Lütkenhöner and Steinsträter 1998; Godey *et al.* 2001); intracranial recordings

agree with this view (Liégeois-Chauvel *et al.* 1994). Contralateral hemispheric dominance is evident in N100m distribution: responses are larger and 4–10 ms earlier for contra- than ipsilateral stimuli (Reite *et al.* 1981; Elberling *et al.* 1982; Pantev *et al.* 1986; Hari and Mäkelä 1988).

Electric N100 consists of at least three subcomponents (Näätänen and Picton 1987); one in the supratemporal plane, one in the auditory association cortex in the superior temporal gyrus, and the third one probably in the motor and premotor cortices. Comparisons between the ISI dependencies of electric and magnetic responses has indicated that the source configurations of these signals differ (Hari *et al.* 1982; Tuomisto *et al.* 1983). N100m has also been comprised into two different components, an early posterior component and a later anterior component that have different recovery times and probably reflect different aspects of auditory sensory memory (Sams *et al.* 1993; Loveless *et al.* 1996).

N100m can be evoked by various kinds of changes in the auditory environment, but it also reflects stimulus-specific neural activity, and the stimulus-specificity increases at short ISIs (Hari 1990). Amplitopic and tonotopic organization (Pantev *et al.* 1989a, 1989b) of the N100m sources have been suggested, although these issues are still controversial (Vasama *et al.* 1995; Lütkenhöner *et al.* 2003b).

The N100m amplitude is affected by the trace left by previous stimuli: the response decreases if the stimulus is repeated within a short interval. The neuronal mechanisms underlying ISI dependence are not known, but the amplitude decrement has been suggested to reflect a temporary loss of neuronal excitability or increased active inhibition (Loveless *et al.* 1989). Näätänen and Picton (1987) suggested that the (electric) N100-type responses could be related to non-specific attention-triggering processes in the auditory cortices. The relationship of N100m to the triggering of stimulus-driven attention is in line with its ISI dependence: The amplitude of N100m "recovers" up to ISIs of 8–16 s (Hari *et al.* 1982, 1987). The recovery function agrees with behavioral measures of remembered loudness of tones (Lu *et al.* 1992).

2.2.1.2 Responses to infrequent stimulus changes

Infrequent deviant sounds, occurring randomly among otherwise monotonous auditory stimulation, elicit mismatch responses in EEG and MEG recordings (Näätänen *et al.* 1978; Hari *et al.* 1984; Näätänen 1992). Mismatch responses have

been reported to various deviations of the physical parameters of the sounds (Alho 1995; Näätänen 2003), as well as to more complex changes in phonetic stimuli (Aulanko *et al.* 1993; Näätänen *et al.* 1997). Mismatch responses are elicited without the subject's attention to the auditory stimuli, even though the response amplitudes can be modulated by voluntary attention. When the subject is strongly attending to one ear, the mismatch responses are attenuated to intensity deviants in the other, unattended ear (Woldorff *et al.* 1991); however, the amplitudes of responses to attended, unattended or ignored frequency deviants may be similar (Näätänen *et al.* 1993).

The magnetic mismatch fields (MMFs) are generated in the supratemporal auditory cortices (Hari *et al.* 1984; Sams *et al.* 1985, 1991; Hari *et al.* 1992), but additional parietal-lobe sources have been reported as well (Levänen *et al.* 1996). The electric mismatch negativity (MMN) also receives contribution from frontal-lobe activity (Giard *et al.* 1990).

2.2.2 Somatosensory processing

The somatic senses can be classified into three physiological categories: The mechanoreceptive somatic senses that include both tactile and proprioceptive sensations, the thermoreceptive senses for detecting heat and cold, and the sense of pain, activated by tissue damage. The following text concentrates on tactile perception, and is referenced primarily from Guyton and Hall (1996) and Nicholls *et al.* (2001).

The hairless surface of palm and fingers is innervated by ~17 000 cutaneous receptors, and these areas are thus among the most sensitive ones of the body (Johansson and Vallbo 1979). Touch information from the periphery to the somatosensory cortex is mainly carried in the dorsal column–medial lemniscal pathway which consists of large, myelinated fibers specialized in transmitting information with high temporal and spatial fidelity, with only a few synaptic contacts along the path. The afferent nerve fibers enter the dorsal columns of the spinal cord and pass uninterrupted up to the medulla where they synapse in the dorsal column nuclei. The second-order cells cross the midline, and ascend in the medial lemniscus to synapse in the thalamus with third-order neurons projecting to the postcentral gyrus of the cortex. Some fibers mediating tactile information enter the anterolateral system

that crosses to the opposite side already in the spinal cord. This pathway mediates crude touch and pressure sensations with poor localization capability on the surface of the body.

The primary somatosensory cortex (SI) lies immediately behind the central sulcus, and comprises Broadmann's areas 3a, 3b, 1, and 2. In general, SI is somatotopically organized (Foerster 1936); the legs and trunk reside most medially, and are followed by hands and head. The cortical map of the body is distorted: Representation areas of hands, fingers, and lips are much larger than those concerned with the trunk or legs. Cutaneous tactile receptors project mainly to areas 3b and 1. Areas 3a, 3b, 1, and 2 are interconnected, but whereas most thalamic connections terminate at areas 3a and 3b, areas 1 and 2 receive their predominant input from areas 3a and 3b. Although callosal fibers connect the corresponding regions of right and left SI, these connections are very sparse at areas 3b and 1 (Killackey *et al.* 1983).

The secondary somatosensory cortex (SII) is located in the upper bank of the Sylvian fissure and it displays crude somatotopical organization. In contrast to the primary somatosensory cortex, SII is activated bilaterally. The functional significance of SII in humans is not well understood, but it probably plays a role in integrating somatosensory and motor actions (Huttunen *et al.* 1996; Forss and Jousmäki 1998) as well as information from the two body halves (Simões and Hari 1999; Simões *et al.* 2001). The posterior parietal cortex (PPC) integrates tactile and proprioceptive input from the two hands and participates in tactile object exploration and recognition (Binkofski *et al.* 2001). The PPC also combines somatosensory and visual information, and plays a role in movement guidance and monitoring, in saccade control, and in visuospatial attention. Lesions to PPC frequently impair the patients' ability to react to and process visual, tactile, or auditory stimuli presented to the contralesional hemispace. In addition, mesial walls of parietal and frontal lobes contribute to somatosensory processing.

2.2.3 Magno- and parvocellular visual streams

The visual input system comprises two highly interconnected but anatomically segregated pathways that mediate different features of the visual world. In primates, ~90% of the retinal ganglion cells consist of M and P cells that project to magnocellular and parvocellular divisions of LGN in thalamus, respectively; less than

10% of the cells are M cells and the rest are P cells (Silveira and Perry 1991). The M cells have larger cell bodies and more thickly myelinated axons than P cells, corresponding to their larger receptive fields and faster conduction velocities. M and P cells terminate in different layers of LGN that can also be distinguished on the basis of cell size.

M cells respond vigorously to transient stimuli, adapt quickly, and are sensitive even at low light levels and to low contrasts: these properties make them ideal for visual change detection. P cells respond in a sustained manner, adapt slowly, and have high spatial resolution: they can provide information about fine details at high contrast (Kaplan and Shapley 1986). M cells respond weakly to color changes at isoluminance, whereas P cells can convey color information regardless of the relative luminance of colors.

From the LGN, the M and P pathways project to different sublayers of layer 4 of the primary visual cortex V1 and then to different stripes of V2; after that, the signals get largely intermingled.

Dorsal pathway is dominated by magnocellular input, and projects from V1 and V2 to MT/V5 and to the PPC (Merigan and Maunsell 1993); this stream is considered important for assessing motion and spatial and visuomotor relationships (Ungerleider and Mishkin 1982). *Ventral pathway* receives both magno- and parvocellular input (Ferrera *et al.* 1992, 1994) and projects through V1, V2, and V4 to the inferotemporal cortex (Merigan and Maunsell 1993); lesions to this stream interfere with object, color, and fine-detail identification (Ungerleider and Mishkin 1982). Imaging studies support separate cortical processing streams also in humans (Watson *et al.* 1993; Haxby *et al.* 1994; Martin *et al.* 1995; Tootell *et al.* 1995).

2.3 Magnetoencephalography (MEG)

2.3.1 Neural current sources

Neurons use electrical and chemical signals to transmit information to other neurons. The electrical signals are similar in all neurons, whether they carry information on auditory events or send motor commands; the complexity needed for accomplishing the diversity of tasks comes from the $>10^{14}$ connections between the 10^{10} to 10^{12} neurons in the human brain (Nicholls *et al.* 2001).

The electrical signals of the neurons are generated primarily by changes in the permeability of the cell membrane to ions such as sodium (Na^+) and potassium (K^+). Nerve cells have high intracellular K^+ concentration, whereas Na^+ concentration is higher outside the cell. The differences between intra- and extracellular ion concentrations are maintained with active ion pumps; the concentration gradients result in a negative resting potential of about –70 mV (inside with respect to outside).

When an electric signal arrives at a synapse, chemical transmitters are released into the synaptic cleft. These transmitters change the permeability of the postsynaptic cell membrane to Na^+, K^+, and Cl^- ions, thus generating a current inward or outward in the postsynaptic cell. Consequently, the cell's membrane potential increases or decreases; if the potential at the axon hillock exceeds a certain threshold, a transient increase in Na^+ conductance results, and a traveling action potential along the axon is initiated.

The apical dendrites of cortical pyramidal cells lie parallel to each other and approximately perpendicular to the cortical surface. The simultaneous postsynaptic currents in thousands of close-by pyramidal cells produce a measurable magnetic field that decreases as $1/r^2$ with the distance r. The postsynaptic potentials can last for tens of milliseconds, which enables effective temporal summation of currents in neighboring cells. In contrast, the traveling action potential along a straight axon segment forms a quadrupolar source configuration with a more rapidly decaying $1/r^3$-dependent field. Moreover, the brief (~1 ms) duration of action potentials reduces the probability of their temporal overlap: MEG is thus believed to mainly measure postsynaptic currents, similarly to EEG (Creutzfeldt 1983). On the basis of measured intracortical current densities, a typical evoked response signal has been estimated to correspond to an active cortical area of 25–250 mm^2 (Hari 1990; Hämäläinen and Hari 2002).

2.3.2 Neuromagnetic fields

The following discussion is largely based on the reviews by Hämäläinen *et al*. (1993) and Hämäläinen and Hari (2002).

Laws of electromagnetism form the link between the neuronal activity within the brain and the electromagnetic field outside the head. Neuronal currents generate

electric and magnetic fields, governed by Maxwell's equations. When the conductivity σ of brain tissue and the electric current generators are known, the electric field **E** and magnetic field **B** can be calculated from the total electric current density **J**. As the bioelectromagnetic fields vary slowly (< 1 kHz), the contributions of time-dependent terms can be neglected, and the quasistatic approximation of the field equations can be used. Therefore, the Maxwell's equations are written

$$\nabla \cdot \mathbf{E} = \frac{\rho}{\varepsilon_0} \tag{1}$$

$$\nabla \cdot \mathbf{B} = 0 \tag{2}$$

$$\nabla \times \mathbf{E} = 0 \tag{3}$$

$$\nabla \times \mathbf{B} = \mu_0 \mathbf{J} \tag{4}$$

where ρ is the charge density, and ε_0 and μ_0 are the permittivity and permeability of vacuum, respectively.

As can be seen from equation (4), **B** can be calculated from the known current density **J**; this is called the forward problem of neuromagnetism. A solution for the induced magnetic field that obeys Maxwell's equations and the condition that **B** vanishes at infinity, is given by the Ampere-Laplace's law

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int \frac{\mathbf{J}(\mathbf{r}') \times \mathbf{R}}{R^3} dV' \tag{5}$$

where $\mathbf{R} = \mathbf{r} - \mathbf{r}'$ is the vector connecting the current element at $\mathbf{r}'$ to point $\mathbf{r}$ where the magnetic field is calculated. It is suitable to divide **J** as follows:

$$\mathbf{J}_{\text{total}} = \mathbf{J}^{\text{p}} + \mathbf{J}^{\text{v}} \tag{6}$$

where $\mathbf{J}^{\text{p}}$ is the primary current, and $\mathbf{J}^{\text{v}} = \sigma(\mathbf{r})\mathbf{E}(\mathbf{r}) = -\sigma(\mathbf{r})\nabla V(\mathbf{r})$ the passive volume current resulting from the macroscopic electric field on charge carriers in the conducting medium; here V is the scalar potential. It is important to note that σ refers to the macroscopic conductivity; the cell-membrane level phenomena are discarded from the model, and the whole brain is modeled as a homogenous conductor. Division

of $\mathbf{J}_{\mathbf{total}}$ to $\mathbf{J}^{\mathbf{p}}$ and $\mathbf{J}^{\mathbf{v}}$ is also neurophysiologically meaningful, as the neuronal activity generates $\mathbf{J}^{\mathbf{p}}$ primarily in the cell and its close proximity, whereas $\mathbf{J}^{\mathbf{v}}$ flows passively everywhere in the conducting media according to Ohm's law. Therefore, finding $\mathbf{J}^{\mathbf{p}}$ corresponds to locating active brain areas. From equations (1)–(6), one obtains

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi}\int \left(\mathbf{J}^{\mathbf{p}} + V\nabla'\sigma\right)\frac{\mathbf{R}}{R^3}dV' \qquad (7)$$

and

$$\nabla \cdot (\sigma \nabla V) = \nabla \cdot \mathbf{J}^{\mathbf{p}}, \qquad (8)$$

which solve the forward problem of MEG and EEG when σ and $\mathbf{J}^{\mathbf{p}}$ are known.

2.3.3 Source modeling

MEG measurements aim at determining the primary current distribution that produces the measured magnetic field. Helmholtz (1853) showed exactly 150 years ago that such an inverse problem does not have a unique solution, *i.e.* infinite numbers of current distributions inside the conductor can produce similar electromagnetic fields outside the head. Thus it is necessary to find constraints to source configurations and to define goodness-of-fit criterions to the model.

The head is typically modeled as a spherically symmetric volume conductor. In this model, radial primary currents do not, for symmetry reasons, produce magnetic fields outside the sphere, and volume currents do not contribute to **B** outside the sphere. MEG is thus greatly selective to tangential currents. Sphere model in its simplicity is computationally fast and typically an accurate enough estimate for many brain areas, such as auditory, visual, and sensorimotor areas (Hämäläinen and Sarvas 1989; Tarkiainen *et al.* 2003b). More realistic models, which take into account the exact shape of the brain, can be constructed, but the benefits seem to be largely masked by the noise present in any real MEG measurement (Tarkiainen *et al.* 2003b). Only thin strips of the convexial cortex are within 15° of radial orientation (Hillebrand and Barnes 2002), suggesting that signal-to-noise ratio limits detectability much more than source orientation.

One generally applied model for interpreting the neuromagnetic fields is the current dipole model (Williamson and Kaufman 1981). This model is both

physiologically and physically plausible if the activated brain area is small compared with the distance to the sensors. The best-fitting dipole, called an equivalent current dipole (ECD), is typically found by a least-squares search (Tuomisto *et al.* 1983). A generalization of the single-dipole model is to assume multiple sources that can be separated first either temporally or spatially; thereafter, their orientations and locations are fixed but their amplitudes are allowed to vary with time (Scherg *et al.* 1989, 1990). An alternative approach is to assume that the source currents are distributed within a volume or surface, with no or only minor restrictions to the source configuration (Hämäläinen and Ilmoniemi 1984; Ioannides *et al.* 1990; Dale and Sereno 1993; Matsuura and Okabe 1995; Uutela *et al.* 1999). These minimum-norm or minimum-current techniques offer a more user-independent approach for complex source patterns, and they allow a combination of positron emission tomography (PET) and fMRI as *a priori* information (Dale and Sereno 1993).

2.3.4 Instrumentation

The neuromagnetic fields are extremely weak, typically 50–500 fT, *i.e.* one part in 10^9 or 10^8 of the geomagnetic field. The only devices of sufficient sensitivity to measure these tiny signals are Superconducting Quantum Intereference Devices (SQUIDs; Zimmerman and Silver 1966; Ryhänen *et al.* 1989), immersed in liquid helium at 4 K. The SQUID is a superconducting loop, interrupted by one (rf SQUID) or two (dc SQUID) weak links, called Josephson junctions. The weak links constrict the supercurrent flow, and they are characterized by the critical current I_c, up to which the current can flow in the loop without resistance. In practice, a suitable bias current is fed through the SQUID, and the voltage that varies periodically as a function of the magnetic flux across the SQUID is measured. To obtain a linear relationship between the voltage and external magnetic flux, the flux threading the SQUID is kept constant by means of feedback current. The changes in the external magnetic field are thus indirectly measured by monitoring the required feedback current.

The magnetic signals are brought to the SQUID by flux transformers consisting of a pick-up coil that senses the brain's magnetic field, and a signal coil coupled to the SQUID. A magnetometer has only one loop in the pickup coil, which makes it beneficial in detecting deep sources but also sensitive to environmental noise. Gradiometers consist of two or more loops that are wound in opposite

directions, in either axial or planar designs, to make them effective for measuring inhomogeneous fields from near-by sources, and insensitive to homogenous fields typically produced by far-away noise sources.

The studies presented in this thesis were conducted with 122-channel Neuromag-122™ device (Ahonen *et al.* 1993) and 306-channel Vectorview™ system (see Fig. 2). Neuromag-122™ consists of 122 first-order planar gradiometers covering the whole scalp. The 61 sensor units measure the two orthogonal tangential derivatives $\frac{\partial B_z}{\partial x}$ and $\frac{\partial B_z}{\partial y}$ of the magnetic field component B_z normal to the helmet surface. Vectorview™ system contains 102 identical triple sensors, each comprising two orthogonal first-order planar gradiometers and one magnetometer.

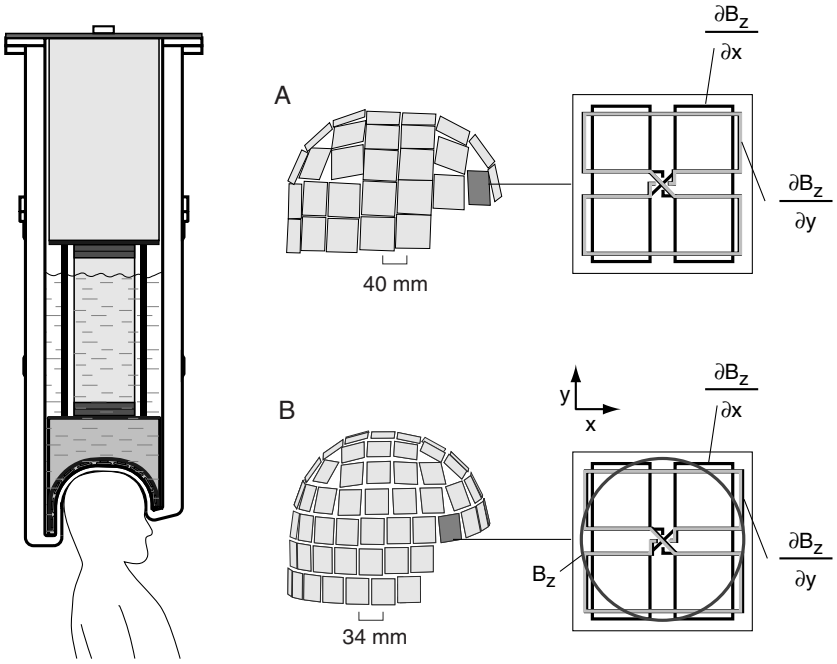

Figure 2. Schematic view of the Neuromag-122™ neuromagnetometer (left), and the helmet-shaped sensor arrays of Neuromag-122™ (right, A) and Vectorview™ (right, B). Adapted from Ahonen *et al*. (1993) and Vectorview™ Users Guide.

For additional rejection of external noise, measurements are usually performed in a magnetically shielded room consisting of layers of μ-metal and aluminum. The present room in the Low Temperature Laboratory provides additional active shielding: The external magnetic field is continuously measured in three orthogonal directions with coils embedded in the walls of the shielded room, and compensating currents are generated in the coils outside the shielded room.

2.3.5 Applications of MEG

The MEG technique is relatively new: The first SQUID measurements of brain signals were conducted by David Cohen (1972) who measured spontaneous alpha activity in a healthy and an epileptic subject. Since then, MEG has evolved from laborious measurements with one-channel devices to whole-head-coverage sensor arrays, and established its role in noninvasive studies of temporal aspects of human cortical processing.

MEG has been widely used to investigate basic functions in all major senses, such as vision (Brenner *et al.* 1975; Teyler *et al.* 1975), somatosensation (Brenner *et al.* 1978; Hari *et al.* 1983a), audition (Reite *et al.* 1978; Elberling *et al.* 1980; Hari *et al.* 1980), as well as pain (Hari *et al.* 1983b) and olfaction (Kettenmann *et al.* 1996). Compared with EEG recordings at the scalp or on exposed cortex, MEG can more easily distinguish, for example, between signals at various somatosensory cortices (for a review, see Hari and Forss 1999).

Development of whole-head neuromagnetometers has enabled studies of specific cognitive brain functions. Language perception and production are examples of such applications. Studies in our laboratory have demonstrated that MEG can be used to follow the processing stages from perception to speech production during picture naming (Salmelin *et al.* 1994), and to distinguish distinct subprocesses of reading in both fluent and dyslexic subjects (Salmelin *et al.* 1996; Helenius *et al.* 1999a). Action observation and imitation are relevant for human social communication: Recent MEG studies have confirmed the existence of a human "mirror-neuron system" that is activated both during subject's own movements and observation of similar movements made by other person (Hari *et al.* 1998), as well as during observation and imitation of lip forms (Nishitani and Hari 2002).

Different cortical areas exhibit spontaneous rhythmical activity with characteristic frequency ranges. MEG has been employed to study these rhythms and their changes (Tiihonen *et al.* 1989b; Williamson *et al.* 1989; Hari and Salmelin 1997). For example, MEG measurements of sensorimotor rhythmical activity with simultaneous recordings of surface electromyogram (EMG) have demonstrated coherence between the motor cortex and contracting muscles (Salenius *et al.* 1997).

The extensive studies in healthy subjects have provided a sound basis to apply MEG to different neurological patient groups. So far, the most important clinical

applications have been localization of epileptic foci (Barth *et al.* 1982; Tiihonen *et al.* 1990) and presurgical mapping of sensory and motor areas (Gallen *et al.* 1993; Mäkelä *et al.* 2001). MEG studies carried out in our laboratory have been reviewed in several papers (*e.g.,* Hari 1990; Salmelin and Mäkelä 1995; Hari and Salmelin 1997; Hari 1998; Salmelin *et al.* 2000; Hari *et al.* 2003).

3 AIMS OF THE STUDY

This thesis compared processing in auditory, visual, tactile, and motor domains between dyslexic and normal-reading adults. The specific aims were

1) To characterize auditory temporal processing in dyslexic subjects by exploring
   - the temporal characteristics of auditory sensory memory (Study I)
   - the dynamics of processing non-linguistic auditory stimuli (Study II)
   - hemispheric differences in auditory change detection (Study III)

2) To investigate the proposed pansensory deficit in dyslexic individuals by studying cortical tactile processing (Study IV)

3) To illuminate the neuronal mechanisms of dyslexia by quantifying the strength and lateralization of visual attentional capture (Study V)

4) To study auditory alerting in dyslexic adults by quantifying the strength of sound-induced spinal facilitation (Study VI)

4 MATERIALS AND MAIN METHODS

4.1 Subjects

The 23 dyslexic subjects (15 females, 8 males; 19–44 years) who participated in the studies were selected on the basis of their own report of definite childhood history of difficulties in learning to read. Nineteen subjects had participated in special tutoring at school age, and all except one subject had a stated diagnosis of dyslexia by a special teacher, speech therapist, or psychologist. In Finland, the diagnosis of dyslexia consists of a large test battery assessing different aspects of reading, writing, auditory and visual memory, *etc*. Indication of a family history of dyslexia was present in 20 individuals (affected parent, sibling, or child). Nine dyslexic subjects were studying at university, or had completed their degree, and 3 subjects had an academic-level professional degree. Three individuals participated in five studies, 7 individuals in two to four studies, and 13 individuals in one study.

Altogether 31 non-reading-impaired subjects, mainly laboratory personnel, served as control subjects (16 females, 15 males; 20–47 years) and 11 of them participated in at least three studies.

Therefore, given that some subjects participated in more than one experiment, the total amount of individual data collected on dyslexic subjects was 51, and 67 on the control subjects.

Table 1. The experiments: overview.

Study	**Number of Subjects**		**Mean Age (yrs)**		**Method**
	Controls	Dyslexics	Controls	Dyslexics	
I	15	10	28	32	Auditory MEG: 50-ms noise bursts, SOA 70–500 ms
II	11	9	29	31	Auditory MEG: bursts of white noise (0, 50, 100, or 200 ms) followed by a 400-ms, 250-Hz square-wave
III	11	8	29	30	Auditory MEG: 1000-Hz 50-ms standard (86% probability) and 920-Hz & 1080-Hz deviant (7% probability each) tones
IV	8	8	29	28	Tactile MEG: 3 stimuli (thumb –> index finger –> thumb) at SOAs of 100 ms and 200 ms
V	14	9	31	32	Visual psychophysics: temporal order judgment and line motion illusion tasks
VI	8	7	29	31	H-reflex: electric stimulation of tibial nerve, preceded by 1-kHz, 100-dB (SPL) square-wave sounds at 0–320 ms

4.1.1 Reading-related tests

All dyslexic and control subjects were tested in our laboratory with a concise battery of tests previously shown to be sensitive to dyslexia. In the oral reading task, the subject had to quickly read aloud a Finnish story, and the reading speed was measured during 1 min in the middle of reading. In a computerized word recognition task, the subject had to decide, as fast as possible, whether a word presented on a computer screen was a real Finnish word or an orthographically legal pseudoword. Correctly recognized words were used for calculating the word recognition speed. Naming speed was measured with a 5 x 10 matrix consisting of numbers, letters, and colors. Working memory was tested with digit spans forwards and backwards by using the standard Wechsler Adult Intelligence Scale (WAIS) procedure. In Study IV, the dyslexic subjects were also tested for general linguistic abilities using a subset of the WAIS-R tests (Comprehension, Similarities; Wechsler 1981).

Figure 3 depicts the average times to recognize *vs.* read aloud one Finnish word in our dyslexic and control subjects, and in 19 other non-reading-impaired subjects (mean ± SEM age of 26 ± 1 yrs, range 20–41 yrs; P. Helenius and T. Parviainen, personal communication). The dyslexic subjects clearly differed from the other two groups in terms of their reading and word recognition speed.

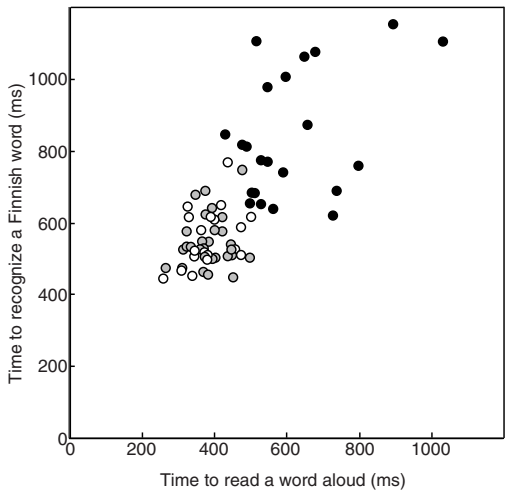

Figure 3. The time to recognize *vs*. to read aloud a Finnish word in dyslexic and control individuals, and in 19 other non-reading-impaired subjects (black circles = dyslexics, gray circles = controls, white circles = 19 other non-reading-impaired subjects).

4.2 MEG recordings (Studies I–IV)

4.2.1 Stimulation

In Studies I–III, the auditory stimuli were presented to the subject binaurally through plastic tubes and earpieces. In Study IV, the tactile stimuli (rise time 30 ms, peak pressure duration 100 ms, fall time 150 ms) were delivered to the palmar skin of thumb and index finger, about 1.5 cm from the fingertip, with balloon diaphragms driven by compressed air (Mertens and Lütkenhöner 2000). The pressure was the same for all subjects, and the stimulus resulted in the percept of a clear local touch at an area of approximately 0.8 cm^2.

4.2.2 Recordings

The recordings were carried out in the magnetically shielded room of the Low Temperature Laboratory. In Studies I–III, MEG signals were measured with the 122-channel Neuromag-122™ device (Ahonen *et al.* 1993), and in Study IV, with the 306-channnel Vectorview™ system. During the recordings, the subject was sitting with the head supported against the helmet-shaped bottom of the neuromagnetometer. The head position with respect to the sensor array was determined by feeding currents to four head-position-indicator coils. These coils were attached to the scalp, and their positions with respect to two periauricular points and the nasion were measured with a three-dimensional digitizer (Isotrak 3S1002, Polhemus Navigation Sciences, Colchester, Vermont, USA) to allow the alignment of functional MEG and anatomical magnetic resonance imaging (MRI) data. MRIs were recorded at the Department of Radiology, Helsinki University Central Hospital, with 1.5 T Siemens Magnetom™ device.

The recording passbands were 0.03–100 Hz and 0.03–172 Hz, and the sampling rates 300 and 600 Hz, respectively, in Studies I–III and IV. To discard data contaminated by eye movements and blinks, vertical (Studies I–IV) and horizontal (Study IV) electro-oculograms (EOGs) were recorded. A minimum of 100 (Studies I–III) or 140 (Study IV) artifact-free responses was averaged for each stimulus category.

4.2.3 Data analysis

For statistical analysis, two-tailed *t* tests, Mann-Whitney *U* test, and analysis of variance (ANOVA) were employed. The hemispheric lateralization of responses was quantified by calculating the lateralization index (LI) of response amplitudes between the right (R) and left (L) hemispheres: LI = (R–L)/(R + L). LI value ranges from –1 (left-hemisphere activation only) to 1 (right-hemisphere activation only); the 0-value refers to hemispheric symmetry.

4.2.3.1 Evoked responses

In the statistical analysis of Study I and in a part of Study II, response amplitudes were measured from the vector sum $\sqrt{\left(\frac{\partial B_z}{\partial x}\right)^2 + \left(\frac{\partial B_z}{\partial y}\right)^2}$ of the two orthogonal gradients in a channel pair showing the maximum signal. In signal strength comparisons, the vector sums simplify the analysis when the orientation of the neural current changes drastically as a function of time, with minor accompanying changes in the source location. In such a case, the amplitude measurements from a single channel could be misleading. In Study IV, areal vector sums at the site of the maximum signal were calculated, by first computing vector sums for each channel pair, and then averaging signals across 6–9 channel pairs.

4.2.3.2 Cerebral sources

To locate the cerebral sources of the responses, in Studies II–IV ECDs were searched by a least-squares fit to the data (Hämäläinen *et al.* 1993) for each subject. An ECD represents the location, orientation, and strength of current flow in the activated brain area. Only ECDs explaining more than 80–85% of the field variance during the response peak in 10–32 channels were accepted for further analysis. In Studies II–III, the analysis was extended to the entire time period, and all channels were taken into account: the previously found ECDs were kept fixed in orientation and location while their strengths were allowed to change. The adequacy of the model was checked by comparing the predicted signals computed from the model with the original measured signals.

For source analysis, the head was modeled as a homogeneous sphere. In Studies II and III, average head models were used for all subjects. In Study IV, the model parameters were optimized for the intracranial space obtained from MR images that were available for all 8 control subjects and for 2 dyslexic subjects; the average of these 10 subjects' head models was used for the analysis of the remaining six dyslexic subjects.

In Study III, the results were also visualized by using the L1 minimum current estimate (L1 MCE) method. MCE presents the current distribution in which the total sum of current amplitudes is as small as possible (Uutela *et al.* 1999). The method does not require any explicit *a priori* information about the number of active brain areas (Uutela *et al.* 1999), and the results have been shown to agree with those obtained by multidipole modeling (Uutela *et al.* 1999; Stenbacka *et al.* 2002).

4.3 Psychophysical measurements (Study V)

4.3.1 Stimulation

Subjects participated in two visual psychophysical experiments, which were presented on a screen controlled by a Macintosh Quadra 840AV computer. The viewing distance was ~65 cm, and the stimuli were gray (7.9 cd/m^2) on a black background (2.0 cd/m^2). The main stimulus parameters were chosen on the basis of the original descriptions of the tasks (line motion illusion task by Hikosaka *et al.* 1993; temporal order judgment task by Robertson *et al.* 1998) and adapted for local viewing conditions; low luminance levels were used to increase the proportion of magnocellular *vs.* parvocellular visual processing.

4.3.2 Procedure

The subjects answered without any time pressure, and their verbal responses were coded to the computer by the experimenter’s key press. The experiments were preceded by a short training period of 5–7 trials on each task to ensure that the subject had fully understood the instructions.

4.3.3 Data analysis

The individual response frequencies were converted to response probabilities, and a cumulative normal distribution was fitted to the data of each subject using the least-squares criterion. The widths of the distributions were quantified by calculating the difference between the 75% and 25% points of the cumulative normal distributions. Two-tailed *t* tests were used in statistical comparison of the results.

4.4 Spinal facilitation (H-reflex; Study VI)

The H-reflex was recorded from the gastrocnemius muscle with surface electrodes (spaced by about 5 cm) by applying 0.2-ms electric stimuli to the tibial nerve in the popliteal fossa while the subject was lying supine and relaxed on a bed. The stimulus intensities were adjusted so that the direct muscular responses were essentially absent. The test of each subject was repeated once or twice, and the set with the most stable baseline responses was used in analysis. The deviance of the H-reflex mean amplitude from baseline was computed against zero with two-tailed *t* tests, and the group differences in the H-reflex amplitudes were analyzed with mixed-model ANOVA.

5 EXPERIMENTS: BACKGROUNDS, SETUPS, RESULTS, AND BRIEF DISCUSSIONS

5.1 Sluggish auditory processing in dyslexics is not due to persistence in sensory memory (Study I)

In the auditory saltation illusion (Hari 1995), auditory perception in normal readers is affected by preceding and following sounds within a time-window of up to 500 ms. Hari and Loveless (1997) related this finding to their observation that N100m is enhanced in response to the 2nd tone of a pair when the pair interval is less than 300 ms, in contrast to the normal (~8 s) recovery cycle of N100m. This "enhancement" was attributed to persistence in a temporal integration process.

Because dyslexic adults perceived the saltation illusion at three times longer ISIs than controls (Hari and Kiesilä 1996), we envisaged that the enhancement of N100m could be displaced to longer intervals in dyslexic individuals, as a sign of persistence in auditory sensory memory.

5.1.1 Stimuli

Pairs of 50-ms noise bursts were presented with SOAs of 70, 150, 230, 300, 370, or 500 ms within the pair, similarly to Loveless *et al.* (1989, 1996). The pairs were presented randomly within the same sequence, with the restriction that no SOA could occur more than twice in succession. The interval between onsets of stimulus pairs varied from 1.2 to 1.4 s.

5.1.2 Results

Figure 4 shows the responses of one control subject at SOA of 230 ms.

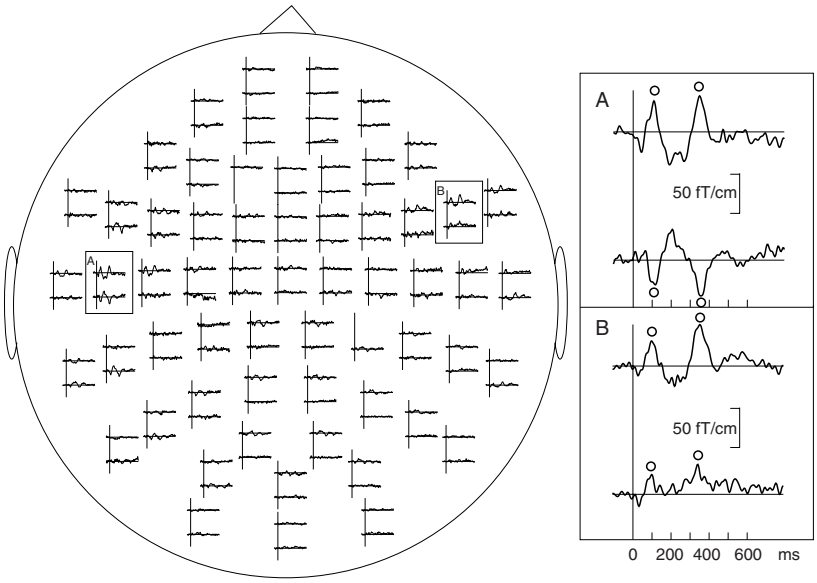

Figure 4. Responses of one subject at SOA of 230 ms. The head is viewed from above and, in each response pair, the upper trace illustrates the field derivative along the latitude and the lower trace along the longitude. The inserts show enlarged responses recorded over the left and right auditory cortices.

Both sounds evoked prominent responses at a latency of ~100 ms (dots in the insert of Fig. 4). The responses were largest over the temporal lobes, reflecting activation of the auditory cortices.

The waveform of the second response at short SOAs overlaps the first response. To obtain a better estimate of N100m, we subtracted the response recorded at the 500 ms SOA from responses obtained at all the other SOAs. Figure 5 shows the N100m amplitudes for both hemispheres and for both subject groups as a function of SOA.

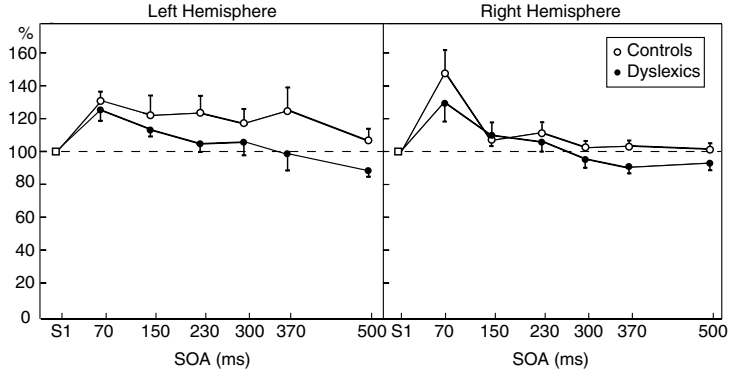

Figure 5. N100m amplitudes to second sounds of the pairs in both hemispheres and for both groups as a function of SOA. The responses were individually normalized according to the N100m response to the first stimulus. The N100m amplitudes were measured from the maximum channel as vector sums of the gradients, and all responses were high-pass filtered at 3 Hz to discard sustained fields produced by the stimuli. S1 refers to the first stimulus.

In the control group, the normalized N100m responses were significantly ($p < 0.05$) stronger to the second than to the first sound at SOAs of 70 ms and 230 ms in the left hemisphere, and at 70, 150, and 230 ms in the right hemisphere. The average of the second N100m across the four longest SOAs (230, 300, 370, and 500 ms) was 18 ± 8% ($p < 0.05$) stronger than the first response in the left hemisphere and 5 ± 3% (n.s.) stronger in the right hemisphere.

In the dyslexic group, the normalized N100m to the second sound was significantly ($p < 0.05$) stronger than the first N100m at SOAs of 70 and 150 ms in the left hemisphere, and at 70 ms in the right hemisphere; the enhancement was not displaced to longer SOAs. However, the normalized N100m was significantly ($p < 0.05$) weaker than the first response at SOA of 500 ms in the left hemisphere, and at 370 ms in the right hemisphere. At the longest SOAs (300, 370, and 500 ms), N100m was significantly smaller in dyslexics than in controls in the right hemisphere ($p < 0.03$), with a similar trend in the left hemisphere ($p < 0.09$).

5.1.3 Discussion

The results confirmed that enhancement of N100m evoked by the 2nd sound of a pair separated by a short interval holds for binaural presentation in both hemispheres and for both groups of subjects (Loveless *et al.* 1989, 1996). The enhancement function was not displaced to longer SOAs in dyslexics; instead, in dyslexics, the function fell away at SOAs greater than 230 ms, *i.e.* significantly earlier than in controls. Thus the sluggish auditory processing of dyslexics might not be attributed to prolonged persistence in sensory memory. Rather, the less prominent responses evoked by the second sounds at SOAs of 230–500 ms in dyslexics could be related to difficulties in modality-specific attention-triggering mechanisms (Näätänen and Picton 1987) as reflected in N100m response.

5.2 Auditory cortices are less reactive to acoustical changes in dyslexic than normal-reading adults (Study II)

Speech sounds typically contain acoustic transitions at approximately 100 ms intervals. The onset of the Finnish word /hei/ (pronounced [hay]) elicits N100m

response, followed by N100m' triggered by the transition from the fricative consonant to the vowel (Kaukoranta *et al.* 1987). A similar N100m–N100m' sequence is elicited by a stimulus in which a noise burst is followed by a square-wave. These responses seem to be related to non-speech acoustic parameters common to both stimuli (Mäkelä *et al.* 1988). Although the N100m' response therefore is elicited by purely acoustic features of the stimuli, it may reflect mechanisms of transient detection that are essential for proper acoustic analysis of speech sounds (Kaukoranta *et al.* 1987). This study was set to determine how the auditory system of dyslexic adults processes speech-like, non-linguistic stimuli.

5.2.1 Stimuli

Noise/square-wave sequences, mimicking transitions from a fricative consonant to a vowel, were presented binaurally once every 1.1 s. The stimuli consisted of a burst of white noise (0, 50, 100, or 200 ms in duration), followed immediately by a 400-ms square-wave of 250 Hz. The rms values of the noise and square-wave bursts were equal.

5.2.2 Results

Figure 6 shows the responses of control subjects C1 and C6 and of dyslexic subjects D3 and D6 to all stimuli at one channel over the left hemisphere.

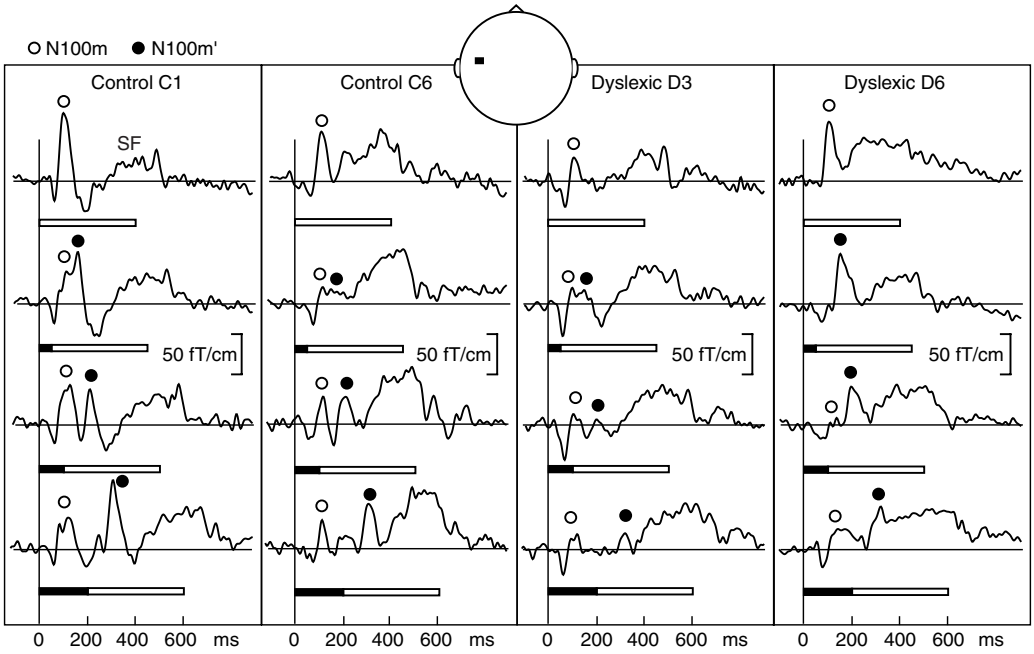

Figure 6. Evoked responses at one channel in the left hemisphere for two control and two dyslexic subjects. Open circles indicate the N100m responses, filled circles the N100m' responses, and SF refers to sustained field. In the horizontal bars below the traces, black parts refer to noise and white parts to square-wave stimuli.

Onsets of the square-waves presented alone (top traces) evoked a prominent N100m at 103 ± 2 ms in both control and dyslexic subjects. The noise/square-wave transitions elicited an additional response, N100m', 107 ± 2 ms after the transition of noise to square-wave. In both control subjects, all stimulus onsets elicited clear N100m and N100m' responses. Duration of the noise had a clear effect on the transition-triggered response in subjects C1 and C6: the N100m' response increased when the noise duration increased from 50 to 200 ms. In contrast, the responses of dyslexic subjects behaved differently: Subject D3 exhibited small N100m and N100m' to all noise/square-wave combinations, and in subject D6, N100m' decreased along with the increasing noise duration.

Figure 7 illustrates the current dipoles for the square-waves presented alone in control subject C10, superimposed on his MR images, and the corresponding N100m source waveforms. The sources of both N100m and N100m' responses were located bilaterally in the supratemporal auditory cortices. In the control subjects, the N100m' sources were located on average 6 mm more anterior than the N100m sources ($p < 0.05$); a similar tendency was seen in the right hemisphere of the dyslexic subjects ($p < 0.07$).

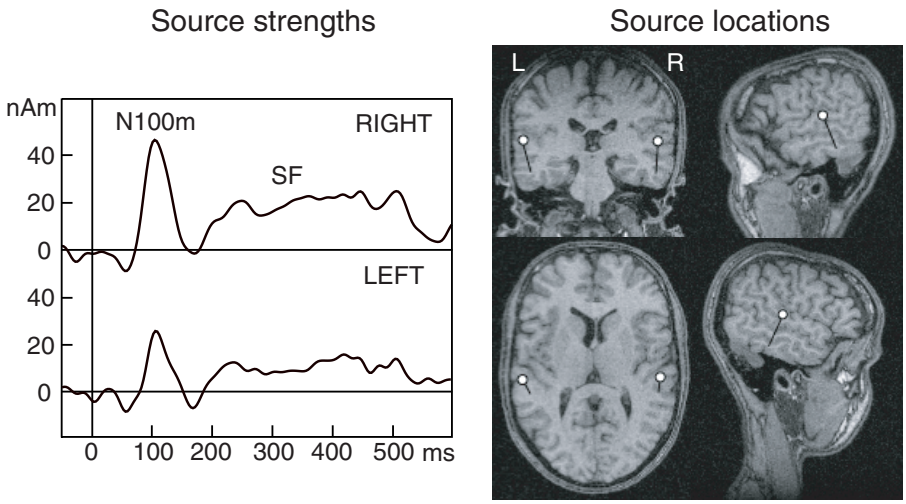

Figure 7. N100m source strengths as a function of time in control subject C10 for square waves presented alone, and the locations (dots) and the orientations (bar) of the current dipoles used to model the responses superimposed on subject's MR images.

The largest N100m responses were elicited by square-waves presented alone, with no amplitude differences between the groups or hemispheres. For the noise/square-wave stimuli, N100m increased with increasing noise duration, apparently due to the associated prolonged mean-ISI preceding the stimulus; the responses at the longest noise durations were significantly smaller in both hemispheres of dyslexic than control subjects.

Figure 8 shows the individual N100m' source strengths as a function of noise duration. The results showed a significant Subject Group × Noise Duration interaction ($p < 0.004$). In controls, noise duration had a significant effect on N100m' amplitudes in both hemispheres (left hemisphere: $p < 0.001$; right hemisphere: $p < 0.001$): N100m' amplitude increased with increasing noise duration and was significantly larger at 200-ms than at 50-ms noise in both hemispheres ($p < 0.001$). In dyslexics, noise duration had no significant effect on N100m' amplitude in the left hemisphere ($p = 0.77$); in the right hemisphere, the responses tended to increase from 100-ms to 200-ms noise duration, but this effect did not reach statistical significance ($p = 0.07$).

The effect of Subject Group on N100m' amplitudes across both Hemispheres and Noise Durations was statistically significant ($p < 0.05$): the responses were smaller in dyslexic than control subjects at 200-ms noise in the left hemisphere ($p < 0.03$), and at 100-ms ($p < 0.04$) and 200-ms noise ($p < 0.02$) in the right hemisphere.

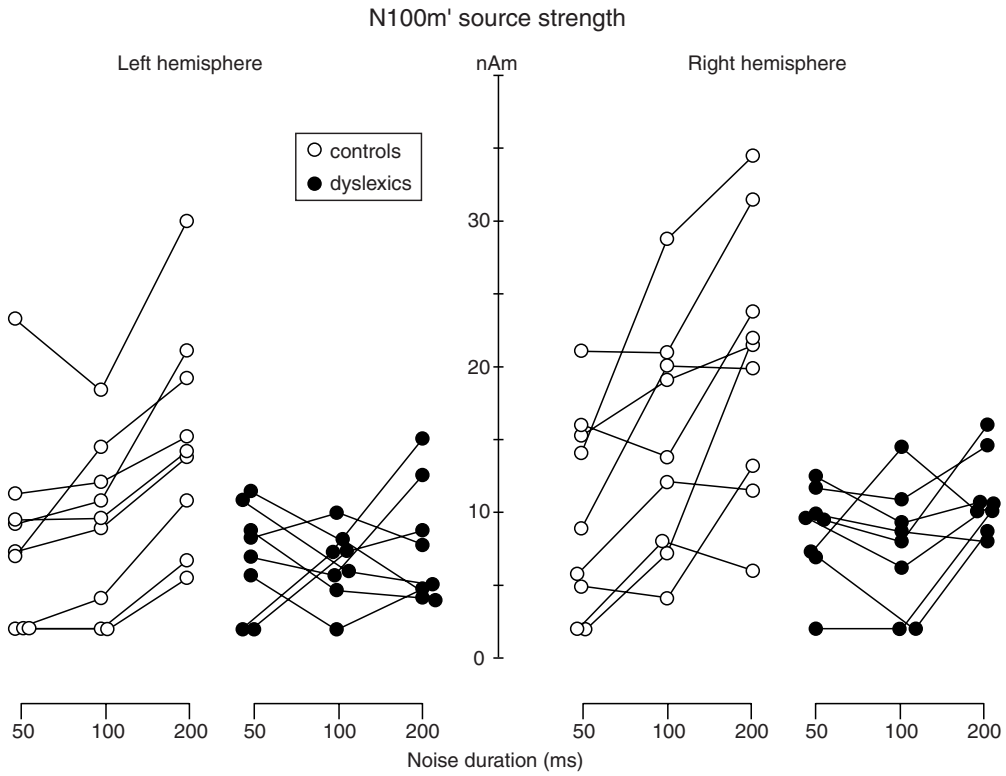

Figure 8. The absolute changes in N100m' source strengths of all subjects in both hemispheres when the noise of the stimuli was 50, 100, and 200 ms. Each individual's data points are connected with lines.

5.2.3 Discussion

In control subjects, the transition-triggered N100m' increased as a function of increasing noise duration, similarly as happens when the duration of the fricative consonant is increased in fricative/vowel combinations (Kaukoranta *et al.* 1987). In dyslexic subjects, however, no enhancement was observed in the left hemisphere; in the right hemisphere, a subtle enhancement occurred from 100-ms to 200-ms noise stimuli but the increase from 50-ms to 200-ms noise was significantly weaker than in the control subjects. The results demonstrate that dyslexic adults are deficient in processing acoustic changes presented in rapid succession within at least a couple of hundreds of milliseconds.

The recovery cycle of N100m is probably mediated by two mechanisms, one affecting the number of activated neurons and their synchrony (Hari 1990), and the other affecting their reactivity via active inhibition (Loveless *et al.* 1989). In the present study, the N100m and N100m' responses were diminished in amplitude in dyslexics, whereas the response latencies were not delayed. Therefore increased active inhibition, rather than a decrease in neuronal synchrony, might account for the

observed effects. This view agrees with results by Nagarajan and collaborators (1999) who found that at short SOAs, N100m to the second sound of a pair is smaller in dyslexic than normal-reading adults. N100-type responses have been related to non-specific attention-triggering processes in the auditory cortices (Näätänen and Picton 1987), and the smaller transition-related N100m' responses in dyslexics might thus reflect weakened stimulus-driven attentional capture by the auditory changes, as a result of increased inhibition in the corresponding neuronal pool.

SLI children perform below controls in a dichotic listening task that requires selective attention to either ear (Asbjørnsen and Bryden 1998), and automatic orienting of auditory spatial attention is impaired in dyslexic children (Facoetti *et al.* 2003). However, in general, very little is known about auditory attention in dyslexic subjects. In the visual modality, the magnocellular pathway is relevant for attention capturing and focusing (Steinman *et al.* 1997; Vidyasagar and Pammer 1999). Although similar magno/parvo distinctions are not typically made in the auditory system, 'magno' cells exist also in the MGN of the auditory thalamus and they are smaller and more disorganized in dyslexic than normal-reading subjects (Galaburda *et al.* 1994). Thus our results could stem from a generally deficient function of magnocellular system.

5.3 Change detection is impaired in the left auditory cortex of dyslexic adults (Study III)

The results of Studies I and II suggested that deficits in stimulus-driven auditory attention could play a significant role in the problems that dyslexics encounter in processing rapidly presented stimuli in the auditory domain. Auditory mismatch responses are elicited without subject's attention to the stimuli (Alho 1995). Earlier studies have demonstrated diminished electric MMN responses to frequency deviants in dysphasic children (Korpilahti and Lang 1994) and in dyslexic adults (Baldeweg *et al.* 1999). As MEG can provide additional information on interhemispheric differences in cortical reactivity to stimulus changes, we set out to study processing of frequency deviants in dyslexic adults.

5.3.1 Stimuli

The oddball sequence consisted of three tones of 50-ms duration (with 10 ms rise and fall times) with ISI (from onset to onset) of 0.5 s. The standard stimuli, 86% of all, were 1000 Hz in frequency and the two deviant stimuli, each with probability of 7%, were of 920 Hz and of 1080 Hz.

5.3.2 Results

The magnetic mismatch fields were examined by subtracting the responses to standard sounds from those to deviants. MMFs were adequately explained by two equivalent current dipoles, one in the left and the other in the right supratemporal auditory cortex. The responses were also modeled with MCEs, and Figure 9 demonstrates the MCE results for one dyslexic and one control subject. In the time window of 145–165 ms, the activation in the right hemisphere is evident in both subjects, whereas left-hemispheric activation is visible only in the control subject.

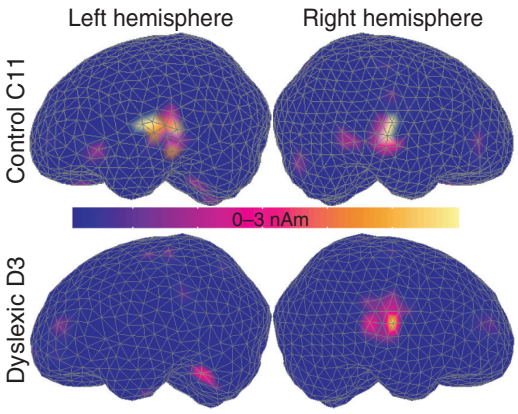

Figure 9. Minimum current estimates for MMFs to 920-Hz deviant stimuli in one control subject (top) and one dyslexic subject (bottom) in the time window of 145–165 ms.

Figure 10 (left) depicts the mean (+ SEM) source strengths of MMFs in both groups. In control subjects, the source strengths did not differ between the hemispheres ($p = 0.22$) but in the dyslexic group the sources were significantly weaker in the left than in the right hemisphere ($p < 0.01$). In 5 out of 8 dyslexic subjects, the left-hemispheric responses were so small that no dipole could be fitted. Figure 10 (right) demonstrates the individual lateralization indices: The LIs of controls subjects were symmetrically distributed along the left–right axis ($p = 0.24$

compared with zero), whereas in dyslexics, the LIs were clustered closer to the right side of the axis ($p < 0.004$). The P50m response strengths, latencies, and the MMF latencies did not differ between groups.

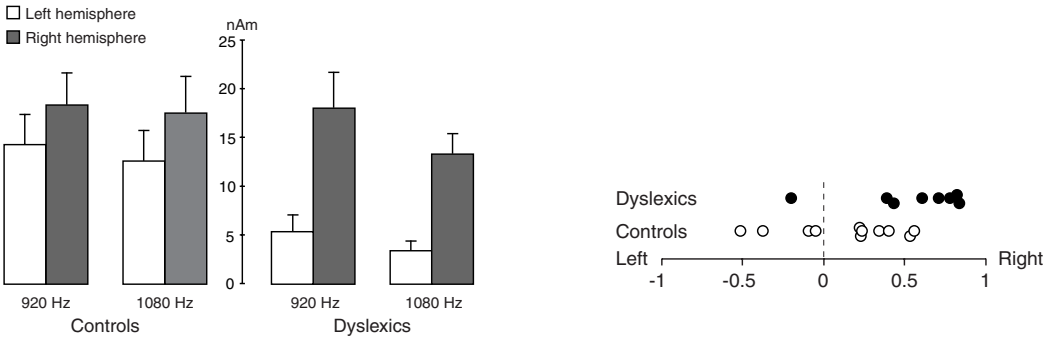

Figure 10. The MMF source strengths to both deviant stimuli (left) and the individual lateralization indices (right). The responses to the two deviants were averaged before LI calculation.

5.3.3 Discussion

The recordings revealed markedly weaker reactivity of the left auditory cortex of dyslexic than normal-reading adults to infrequent changes in tone pitch. The results are in line with data from infants with genetically elevated risk for dyslexia who have smaller MMN responses in the left than the right hemisphere to duration changes within speech sounds (Leppänen and Lyytinen 1997). Abnormal hemispheric balance itself is not without prerequisites, either; for example, auditory MGN is anomalous in a left-hemisphere-dominant manner in dyslexic subjects (Galaburda *et al.* 1994), and the reduction of gray matter (Eliez *et al.* 2000) as well as developmental anomalies in inferior frontal and superior temporal regions (Galaburda *et al.* 1985) are predominant in the left hemisphere.

Typically the N100m responses increase and MMFs decrease when the ISI is prolonged (Sams *et al.* 1993). The smaller N100m responses to the second sound of a pair at short SOAs in dyslexic than in normal-reading adults (Nagarajan *et al.* 1999) suggest prolonged post-stimulus suppression and lengthening of the auditory recovery cycle. Similarly, the smaller MMFs in dyslexic subjects could be related to a deficient build-up or a more rapid fading of the sensory memory trace. This view is also in line with Study I in which the enhancement of N100m to the second sound of a pair fell away at significantly shorter SOAs in dyslexic than control subjects.

5.4 Response recovery cycle is abnormal in the right somatosensory cortex of dyslexic adults (Study IV)

Several studies have indicated problems in dyslexic adults in processing rapidly presented non-speech auditory stimuli, and similar kinds of problems seem to exist in other senses. Recent psychophysical data demonstrated that dyslexics are impaired in perceptual processing of rapidly presented visual and tactile stimuli (Laasonen *et al.* 2000, 2001). As no previous imaging data exist on somatosensory processing in dyslexic subjects, we applied MEG to study in dyslexic adults cortical processing of repetitive tactile stimuli.

5.4.1 Stimuli

Tactile stimuli were delivered to the palmar skin of the distal phalanges of thumb and index finger in trains of three. The stimuli were delivered in a sequence of thumb –> index finger –> thumb, alternatingly to the left and right hands with an intertrain interval (from the beginning of the 3rd stimulus to the beginning of the next 1st stimulus) of 1 s. The SOAs within each train were 100 ms and 200 ms in separate runs. During the measurement, the subject was watching a video without any further task.

5.4.2 Results

Figure 11 illustrates the spatial distribution of somatosensory evoked fields (SEFs) of one control subject to left-sided stimulus trains presented at the 200-ms SOA. The strongest responses occurred over the right sensorimotor cortex and consisted of three prominent transient deflections, each peaking about 50–90 ms after the onset of a finger stimulus; this triplet was followed by a smaller fourth response. The responses were high-pass filtered at 2 Hz (see insert B), and for statistical analysis, areal vector sums at the site of the maximum signal were calculated (insert C).

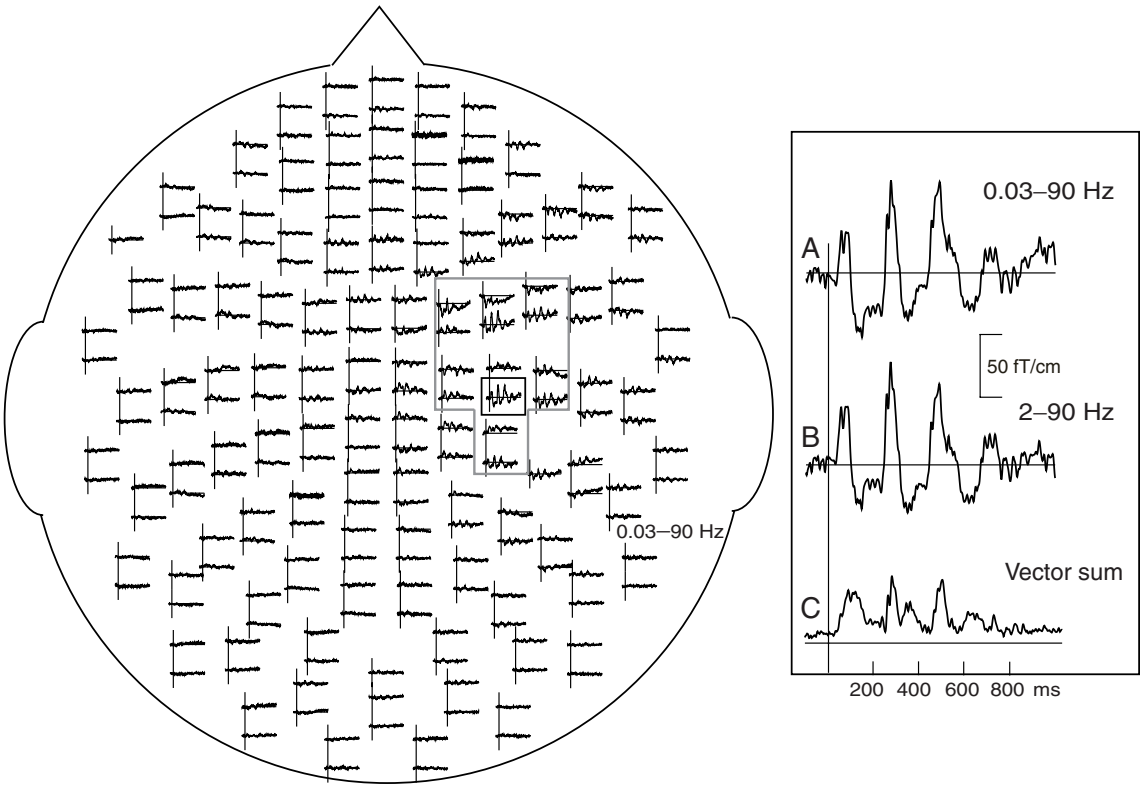

Figure 11. Evoked responses of a normal-reading control subject to left-hand stimulation at the 200-ms SOA. The inserts show enlarged responses from the maximum channel over the right hemisphere before (A) and after (B) 2-Hz high-pass filtering. Insert C depicts the areal vector sum of a subset of 14 channels encircled with the gray line.

Figure 12 depicts the channels showing the largest responses in 3 control and 3 dyslexic subjects at the 200-ms SOA. In control subjects, the 2nd response (shaded) tended to be larger than the 1st response in both hemispheres. However, in the dyslexic subjects, the corresponding 2nd to 1st response ratios were smaller in the right than the left hemisphere.

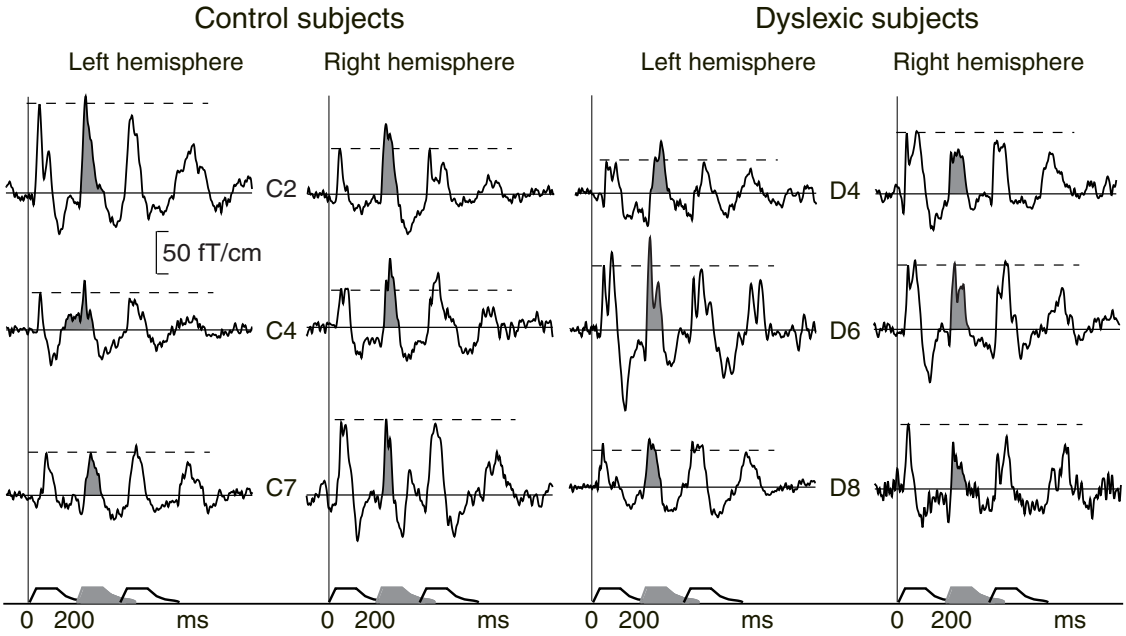

Figure 12. Evoked responses from the maximum channels for three control and three dyslexic subjects at the 200-ms SOA. The dashed lines mark for each subject the level of the first response peak; the responses to 2nd stimuli are shaded. The horizontal white and gray envelopes below the traces refer to stimulus timing.

Figure 13 shows the mean (± SEM) response amplitudes and latencies across all subjects at both SOAs. In control subjects (open symbols), the response amplitudes behaved in a similar way in both hemispheres: The 1st and 2nd responses were practically equal at the 100-ms SOA, and the 2nd response was larger than the 1st ($p < 0.05$) at the 200-ms SOA (upper panels). In the right hemisphere, the responses to the 2nd stimuli were at both SOAs smaller in dyslexic (filled symbols) than in control subjects (100-ms SOA: mean difference 41%, $p < 0.01$; 200-ms SOA: 27%, $p < 0.03$). At the 200-ms SOA, the 2nd response was larger than the 1st response in the left ($p < 0.02$) but not in the right hemisphere of dyslexic subjects. The latencies did not differ between the groups.

At the 200-ms SOA, an additional 4th response was seen in all subjects, of similar strength and latency in both subject groups. At the 100-ms SOA, two additional responses (4th and 5th transients) were detected in most subjects in both groups.

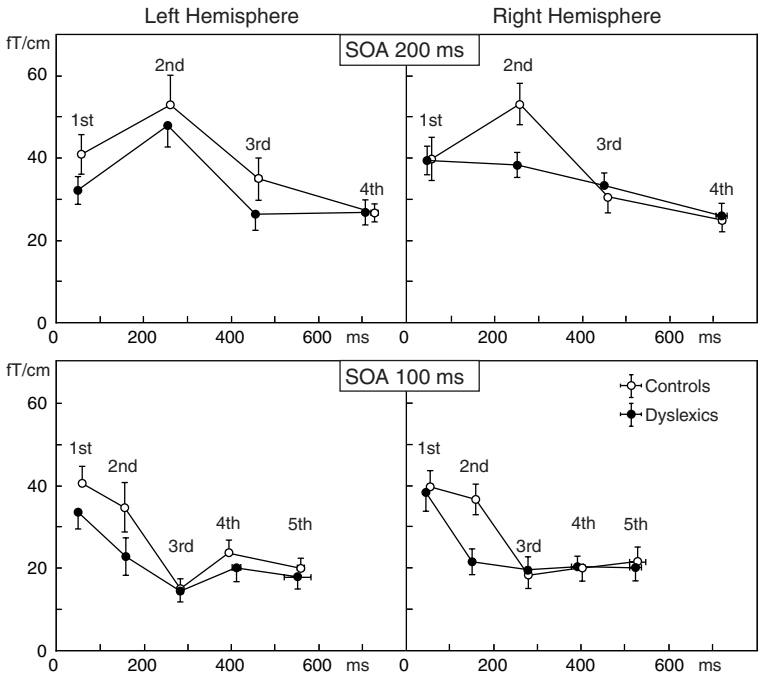

Figure 13. The mean (± SEM) response amplitudes and latencies for all subjects at both SOAs measured from the areal vector sums. Note that the error bars for latencies are typically so small that they are covered by the symbols.

In a control experiment with one normal-reading and one dyslexic subject, only the thumb was stimulated at the 200-ms SOA. The $2^{nd}/1^{st}$ response ratios behaved again in a left-hemisphere-dominant manner in the dyslexic but not in the control subject, therefore agreeing with the results of the main experiment.

5.4.3 Discussion

This study revealed statistically significant differences between dyslexic and normal-reading subjects in the reactivity of their right somatosensory cortex to repetitive tactile stimuli. The results suggest slower recovery of the 50-ms tactile responses in the right than the left SI cortex in dyslexic individuals, in contrast to the symmetric recovery cycle in normal readers.

The diminished SEFs in the right SI cortex to rapidly presented tactile stimuli are in line with the proposed pansensory nature of the processing deficit in dyslexics. The first responses of the train were of similar strength between groups and hemispheres, implying that the observed effect was specific to rapid stimulus presentation rate.

5.5 Dyslexic adults suffer from a visuospatial "mininеglect" (Study V)

Although the magnocellular theory of dyslexia still remains highly debated, several behavioral, histological, and electrophysiological studies have demonstrated deficits in the magnocellular pathways in dyslexic subjects. Activation of the magnocellular system is important for efficient capturing of automatic attention (Steinman *et al.* 1997); accordingly, dyslexic subjects often suffer from minor attentional problems (Asbjørnsen and Bryden 1998; Casco *et al.* 1998; Facoetti and Turatto 2000).

Right-hemisphere-damaged neglect patients are significantly impaired in visual "attentional blink" task (Husain *et al.* 1997). In this task, subjects are presented a rapid sequence of letters, and they have two targets, the first one to be identified and the second to be detected. The task requires attentional shift between the two targets, and even in healthy subjects, identification of the second target is impaired during 400–600 ms after the first stimulus. In neglect patients, the attentional blink is prolonged up to three times that of control subjects (Husain *et al.* 1997), and interestingly, it is also prolonged in dyslexic adults, although only ~30% (Hari *et al.* 1999b).

On the basis of these similarities between neglect patients and dyslexics, we wondered whether dyslexic subjects would resemble neglect patients also in other aspects. We tested adult dyslexics in a temporal-order judgment task (Fig. 14, left), in which neglect patients have demonstrated abnormal right-hemifield preference (Robertson *et al.* 1998). We also applied a line motion illusion task (Hikosaka *et al.* 1993; Fig. 14, right) to test whether dyslexics would have difficulties in their automatic attentional capture by visual cues (Steinman *et al.* 1997).

5.5.1 Stimuli

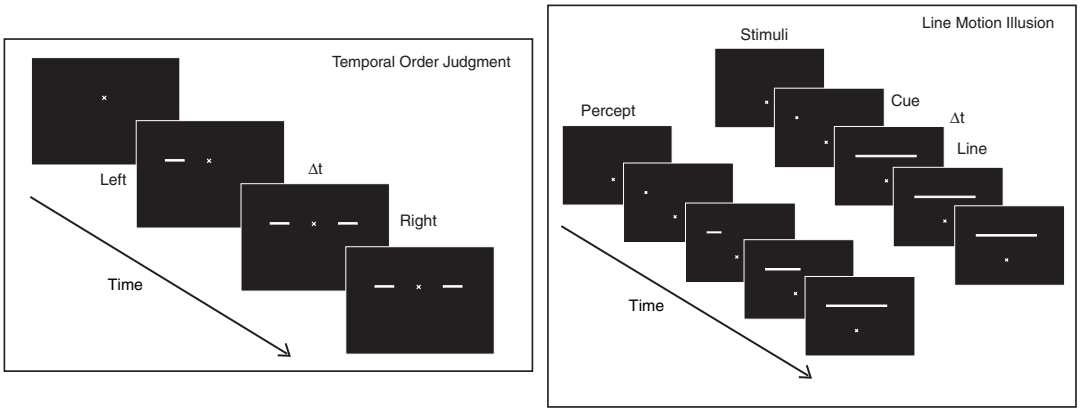

Figure 14. Setup for the temporal-order judgment task (left) and for the line motion illusion task (right; the stimuli are shown on the right and the subject's typical percept on the left).

In *the temporal-order judgment task* (Fig. 14, left), the subjects decided whether a visual bar in the left hemifield preceded or followed a similar bar on the right. A central fixation cross 'X' (height 0.1 deg) was on all the time, two horizontal bars (width 1.4 deg, height 0.1 deg) appeared at symmetrical locations (outer edges 4.2 deg from the fixation cross) in the left and right visual fields. One bar appeared first, randomly either to left or right, and was followed by the other bar after a delay that varied randomly from 0 to 210 ms (in 15 ms steps). Bars were removed 450 ms after the appearance of the second bar. The subjects indicated verbally whether the left or the right bar had appeared first.

In the line motion illusion task (Fig. 14, right), the subject perceives a line growing from a site where a cue stimulus has been presented slightly earlier. The illusion is interpreted to reflect faster processing of stimuli falling into the attended locations (Hikosaka *et al.* 1993). The subject fixated on 'X' (4.4 deg beneath the stimulus level); the cue (a 0.2 x 0.2 deg box) appeared either to the left or right visual field at an eccentricity of 3.7 deg, and was followed after a random 0–210 ms interval (15 ms steps) by a line which connected the two possible cue locations. The subjects perceived illusorily that the line 'grew' from the cue site towards the other end of the line. The subjects indicated verbally whether the line had appeared to move from left to right or from right to left.

In both tasks, each subject viewed 250 stimulus presentations; 40% of the stimuli were randomly scattered across the ISIs and 60% concentrated, again randomly, in the middle half of the interval.

5.5.2 Results

Figure 15 illustrates the results, and Figure 16 the centers of response distributions across subjects in both tasks. The control subjects performed, in both tasks, symmetrically for both stimulus orders (the mean of the distribution did not differ from zero). In contrast, the response distributions of dyslexics centered towards left from zero (temporal-order judgment task: $p < 0.05$; line motion illusion: $p < 0.007$), indicating preference for right visual field. For dyslexic subjects, the left-sided stimuli had to precede the right-sided ones by ~15 ms to allow the subjects to judge the stimuli simultaneous (the temporal-order task), or to perceive the illusion symmetrically. The centers of the distributions differed statistically significantly between the subject groups (temporal-order judgment task: $p = 0.015$; line motion illusion: $p = 0.003$).

In the temporal order judgment task, the 'simultaneity window', derived from the 75%–25% width of the distribution, was significantly prolonged in dyslexics compared with control subjects (94 ms *vs.* 64 ms; $p < 0.04$), indicating increased sluggishness of temporal processing.

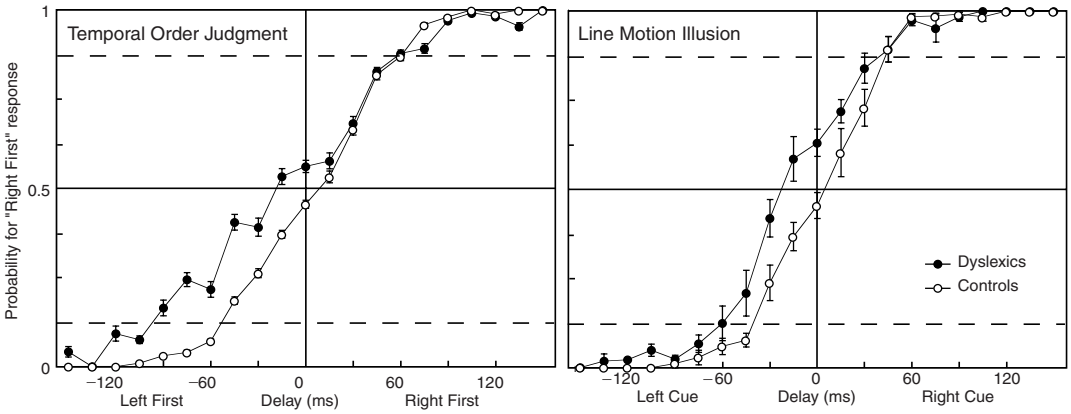

Figure 15. The mean (± SEM) responses of all subjects in the temporal order judgment task (left) and in the line motion illusion task (right). The perceptual judgments, given as the probability of answering 'right first', presented as a function of the time delay between the left- and right-sided bars; the 0.5-level of the perceptual judgment axis refers to equal number of 'left first' and 'right first' responses. The negative and positive time delays refer to left- and right-sided stimulus precedence, respectively.

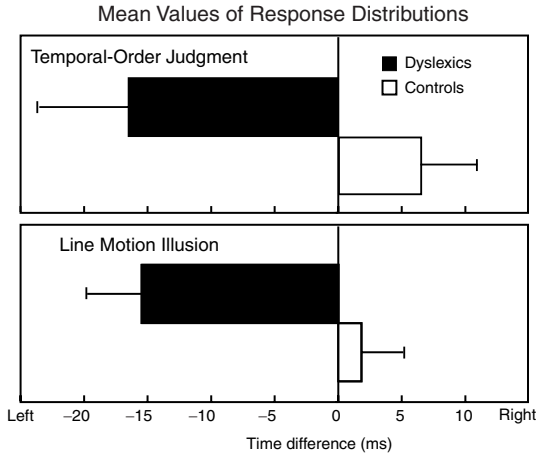

Figure 16. The mean (± SEM) values of response distributions, determined by fitting a cumulative normal distribution to the individual distributions.

5.5.3 Discussion

The present results demonstrated a statistically significant right visual field advantage in dyslexic subjects; the effect was evident in both tasks applied, indicating asymmetric and impaired temporal processing in the left relative to the right visual hemifield. This result suggests a left-sided "minineglect", *i.e.* right-hemispheric dysfunction in selecting and processing visual information. Furthermore, the wider response distributions of the dyslexics in the temporal-order judgment task suggest sluggish attention capture and temporal processing in both visual hemifields.

Dyslexic subjects often suffer from a multitude of minor symptoms that seem to derive from diverse neural systems and to occur variably across individuals. The proposed magnocellular deficit provides one attempt to account for the sensory and motor deficits. It successfully explains several visual abnormalities (Stein and Walsh 1997), and it could also account for sensory deficits in other modalities because magnocellular divisions appear to exist in the auditory, somatosensory, and motor systems (Livingstone *et al.* 1991; Galaburda *et al.* 1994). However, the link from magnocellular deficit to poor reading performance has remained unsettled.

Although the observed minineglect is so mild that it is unlikely to cause any significant direct effects on reading, it may serve as a sign of an underlying attentional problem and thus have important implications. First, it could serve as the link between magnocellular deficit and impaired reading: Too weak a magnocellular input to the dorsal visual stream (Eden *et al.* 1996) might result in hypofunction of the parietal lobe, which in turn would be involved in reading via its role in covert attention and

saccade control. In addition, when children are learning to read, they have to train rapid attentional shifts along the text, to allow accurate targeting of rapid eye movements (Vidyasagar and Pammer 1999). Moreover, weakened and sluggish stimulus-triggered attention could prolong "input chunks" within different sensory modalities, lead into distorted processing of rapid stimulus sequences and impair the proper development of cortical representations needed for reading acquisition.

5.6 Audiospinal facilitation is of normal strength in dyslexic adults but slightly prolonged (Study VI)

Study V demonstrated that dyslexic adults suffer from a left-sided "mininеglect", *i.e.* weakened triggering of automatic attention by visual stimuli in the left hemifield. In the framework of the magnocellular theory, such a disorder could reflect deficient M-input to the parietal lobe and result in sluggish capture of automatic attention. Within the same framework, we wondered whether dyslexic subjects would be alerted less efficiently than normal readers by external stimuli. As the indicator of automatic alerting we used the startle reaction elicited by abrupt loud sounds. The startle reaction involves sound-induced spinal facilitation, transmitted through large-diameter reticulospinal pathways (Gogan 1970). In addition, the spinal facilitation is affected by cortical auditory areas (Liégeois-Chauvel *et al.* 1989), and dyslexic subjects often have deficits in their central auditory pathways (Galaburda *et al.* 1994; Baldeweg *et al.* 1999; Nagarajan *et al.* 1999). We therefore envisioned that the sound-induced spinal facilitation might be abnormal in dyslexic subjects.

5.6.1 Stimuli

We monitored amplitude changes of the monosynaptic H-reflex of the gastrocnemius muscle (Rossignol and Jones 1976). The H-reflex was triggered by 0.2-ms electric stimuli to the tibial nerve in the popliteal fossa with ISI of 14.3 s and recorded with surface electrodes from the gastrocnemius muscle while the subject was lying supine and relaxed on a bed. Binaural square-wave sounds (95–100 dB sound pressure level, 100 ms, 1 kHz) preceded the electric pulse at random intervals of 0–320 ms in 10–40 ms steps.

5.6.2 Results

Figure 17 shows the mean ± SEM amplitudes for the two groups as a function of the sound–electric pulse delay; the 100%-level was determined as the average H-reflex amplitude at the 0 and 20 ms sound–electric pulse delays. Both subject groups showed a significant (200–250%) facilitation of the H-reflex, with maximum around 90–100 ms ($p < 0.02$ for dyslexics, $p < 0.002$ for controls). The mean values were larger in dyslexic than control subjects at all time lags (ANOVA; non-significant difference at $p = 0.38$). Dyslexic subjects showed a tendency for prolonged facilitation, significant still at delays of 160–240 ms ($p < 0.001$; $p = 0.12$ for controls).

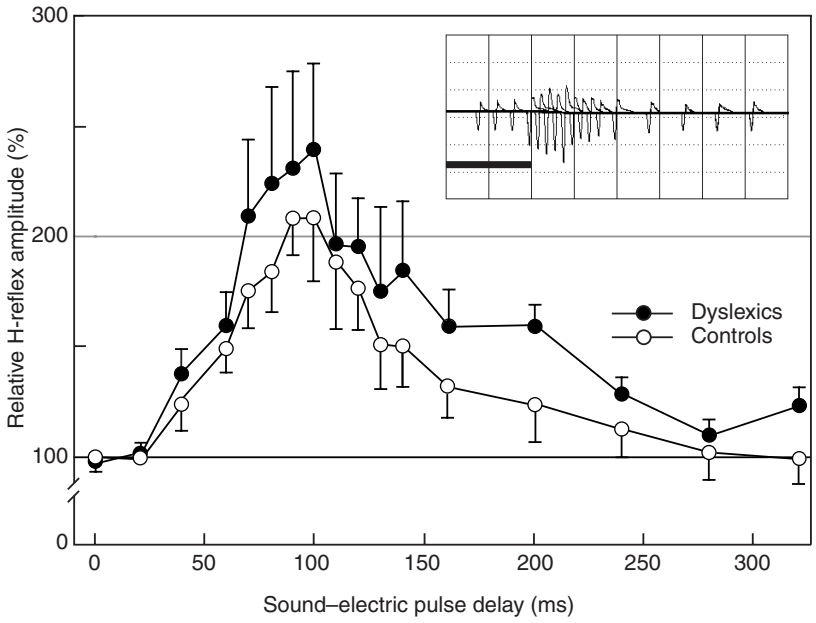

Figure 17. Sound-induced changes in the H-reflex amplitudes as a function of the sound–electric pulse delay. The insert shows original H-reflex recording from one control subject in arbitrary units; the black horizontal bar shows the duration of the 100-ms sound. Due to the conduction time, the first H-reflex (sound–electric pulse delay 0 ms) starts around 30 ms.

5.6.3 Discussion

The strengths and time courses of the observed sound-induced H-reflex changes were in good agreement with previous results on audiospinal facilitation (Rossignol and Jones 1976; Liégeois-Chauvel *et al.* 1989). The facilitation was of similar strength in both groups, indicating normal auditory startle reaction in the dyslexic adults. However, the facilitation tended to last longer in dyslexic than normal-reading individuals. Such a finding would be in line with the frequently observed general sluggishness of sensorimotor processing in dyslexic subjects.

6 GENERAL DISCUSSION

This thesis focused on temporal processing in different senses of developmentally dyslexic adult subjects. The auditory sensory memory of dyslexic subjects was of normal duration (Study I) but the subjects were deficient in processing of sounds and acoustic changes presented in rapid succession within tens to hundreds of milliseconds (Studies I–III). The observed abnormalities could be related to insufficient triggering of auditory stimulus-driven attention. In line with this view, infrequent deviant sounds in an otherwise monotonous stimulus sequence elicited smaller mismatch responses in the left hemispheres of dyslexic than normal-reading adults (Study III). Study IV provided the first MEG data on tactile processing in dyslexics, and revealed abnormal response recovery in the right somatosensory cortex, in agreement with earlier proposals of a pansensory processing deficit. In Study V, abrupt stimuli captured attention in both visual hemifields less effectively in dyslexic than in normal-reading adults. Furthermore, dyslexics showed right visual field advantage in psychophysical temporal-order-judgment and line-motion-illusion tasks, suggestive of a left-sided "minineglect". Study VI suggested normal, although slightly prolonged, auditory alerting via cerebrospinal pathways in dyslexic subjects.

On the basis of these and earlier findings we have recently proposed that limitations in both modality-specific and more global attentional capacities could prolong input chunks for all senses, thereby leading to anomalous cortical representations in dyslexic subjects (Hari and Renvall 2001). This hypothesis envisages problems in all senses, and it could account for deficient motor output as well. These topics are discussed below in more detail.

6.1 Auditory evoked responses and attentional mechanisms

According to Näätänen (1988), sounds are perceived discrete because they activate separate onset-detectors, and the supratemporal N100-type response could reflect such a mechanism. This view is supported by the increasing amplitude of N100m with increasing ISI. The smaller N100m and N100m' responses in dyslexic subjects could thus reflect weakened change detection at SOAs up to hundreds of milliseconds (Study I), as well as during ongoing auditory stimulation (Study II).

The mismatch responses, elicited even without attention to the stimuli, are generally thought to reflect automatic change detection in the auditory cortex (Alho 1995), and thereby they probably depend on neuronal mechanisms that form the prerequisite for stimulus-driven attentional capture. Their role in auditory attentional processes is considerably different from that of N100-type responses: whereas N100 responses are concerned with physical feature extraction, mismatch responses reflect comparison between the neural trace formed by standard stimuli and the input from the incoming deviant stimulus. Consequently, the generator of the mismatch has been suggested to be spatially distinct from the neurons activated by the stimuli (Sams and Hari 1991), in line with the different source locations for magnetic mismatch fields and N100m (Hari *et al.* 1992).

Result similar to that of Study III, impaired reactivity to infrequent pitch changes over the left auditory cortex in dyslexic adults, was obtained in a recent EEG study (Kujala *et al.* 2003) using a rather large difference (500 Hz *vs.* 750 Hz) between the standard and deviant tones. This finding suggests fairly strong deficiency in the left-hemispheric pitch change detection processes. The problems of dyslexic subjects in frequency discrimination have been suggested to reflect the inability to extract temporal structure of auditory stimuli due to impaired phase locking in auditory nerve fibers (McAnally and Stein 1996). This hypothesis would predict dyslexics' performance to be more degraded at stimulus frequencies less than 3–5 kHz where phase locking information is available; however, this seems not to be the case (Hill *et al.* 1999; Bailey and Snowling 2002). Moreover, as dyslexic subjects' performance is not disproportionably worse in a task judging periodicity pitch, relying merely on temporal information, than spectral pitch (Hari *et al.* 1999a), impaired neuronal phase locking does not seem likely. Moreover, dyslexic subjects are as accurate as control subjects in detecting silent gaps in continuous noise (McAnally and Stein 1996).

6.2 Auditory and somatosensory recovery cycles in dyslexia

The strength of an evoked response depends highly on the interstimulus interval; the response recovery differs between cortical areas (Tiihonen *et al.* 1989a; Hari *et al.* 1993; Uusitalo *et al.* 1996), and it is at least in part specific to stimulus characteristics (Picton *et al.* 1970). Response decrease to repeated stimuli occurs at multiple subcortical levels of the sensory pathways. However, at cortical level the

decrease is typically stronger, more stimulus specific, and has a longer recovery time, suggesting existence of intrinsic cortical mechanisms (Chung *et al.* 2002; Nicolelis 2002).

The auditory N100m amplitude probably decreases as a result of either reduced synchrony or the number of activated neurons (Hari 1990), or as a sign of increased active inhibition (Loveless *et al.* 1989). In Studies I and II, the diminished N100m and N100m' amplitudes in dyslexic subjects were not accompanied by delayed latencies, and therefore increased active inhibition seems a plausible explanation. In line with the abnormally slow N100m recovery, the diminished MMFs of dyslexic subjects in Study III could be related to a deficient build-up or a more rapid fading of the sensory memory trace. Auditory N140 responses are diminished and delayed at short ISIs in SLI children who perform poorly in an auditory temporal discrimination task (Neville *et al.* 1993). Interestingly, mice with cortical ectopias display smaller responses to the second tone of a pair at short ISIs (Frenkel *et al.* 2000). As dyslexia is associated both with smaller responses to rapidly presented stimuli and with cortical ectopias (Galaburda *et al.* 1985), these functional and structural abnormalities could be closely connected.

Results from Study IV demonstrated an abnormal recovery cycle in the right somatosensory cortex of dyslexic subjects. The equally strong first responses in both groups and hemispheres suggest that the recovery abnormality was specific to rapid stimulus presentation rate. The present results on interaction of thumb and index finger stimulation could be explained by the inhibitory surround of the activated thumb area, known to persist to ISIs of 600–700 ms (Simões *et al.* 2001).

6.3 Minineglect in dyslexia

Study V suggested that our dyslexic adults suffer from a left minineglect and sluggish attentional capture in both visual hemifields. Our results are in line with reports that children with reading difficulties and unstable vergence control make more errors in locating targets in the left than the right visual hemifield (Stein *et al.* 1989; Riddell *et al.* 1990). Recent support for the minineglect hypothesis comes from a series of studies in dyslexic Italian children. In a visual flanker task, an irrelevant distractor slows down the reaction times (RTs). In dyslexic children, the interference

effect is reduced in the left visual field, indicating left inattention, and is associated with an abnormally strong effect in the right visual field suggesting impaired suppression of distractor information (Facoetti and Turatto 2000). When the children are asked to detect targets appearing at different eccentricities from the foveal focusing-cue, the RTs are slower in the left than right visual field (Facoetti and Molteni 2001); similar results have been obtained in a peripheral cue-target paradigm (Facoetti *et al.* 2001).

Intriguingly, converging phenomena occur in children with attention deficit disorder, a deficit with significant comorbidity with dyslexia: the children react more slowly to uncued targets in the left than right visual field (Nigg *et al.* 1997), and show right-biased line bisection (Sheppard *et al.* 1999). In both tasks, the performance is normalized by application of a stimulant drug, suggestive of underlying right-hemisphere hypoarousal (Sheppard *et al.* 1999).

The left minineglect in dyslexia could result from a minor deficit of the right parietal lobe; the intraparietal sulcus seems to represent the neuronal locus of spatial attention (Bisley and Goldberg 2003a). One route to parietal hypofunction could be via decreased magnocellular input to the dorsal visual stream (Eden *et al.* 1996; Demb *et al.* 1998). Although the magno- and parvocellular inputs are intermingled at the cortical level, the parietal lobe seems to receive mainly magnocellular input (Merigan and Maunsell 1993). Contralesional neglect is more common, more severe, and lasts longer after right than left-hemispheric lesions (Kerkhoff 2001); therefore even a balanced weakening of both parietal lobes could lead to right-hemisphere symptoms. In line with the sluggish attentional capture in both hemifields in dyslexic subjects, many neglect patients have bilateral attentional deficits, although clearly more profound in the left than the right hemifield (Robertson 2001).

The result of Study IV, *i.e.* a right parietal abnormality in somatosensory processing, is appealing in the context of the left-sided visual minineglect in dyslexic adults. Lesions of the right parietal cortex can produce unilateral neglect of tactile stimuli, and right-lateralized engagement of thalamus, posterior parietal cortex, dorsolateral prefrontal cortex, and dorsal frontal cortex during somatosensory processing has recently been demonstrated (Coghill *et al.* 2001). Moreover, some right-hemisphere-damaged neglect patients display stimulus extinction, failing to detect left-sided visual, auditory, or tactile stimuli when they are presented simultaneously with right-sided stimuli (Vallar 1998). Therefore the observed

hemispheric asymmetry in the recovery cycles of somatosensory responses could be interpreted to indicate the existence of a "tactile minineglect". This hypothesis could be tested in the future, as the result predicts decreased relative perceptual salience of left-sided *vs.* right-sided stimuli during rapid bilateral tactile stimulation. Different dyslexic subjects participated in Studies IV and V, preventing us from performing a correlational analysis on the visual and tactile minineglect data.

Interestingly, reduced activation of the right parietotemporal cortex has recently been reported during face perception in dyslexic adults (Tarkiainen *et al.* 2003a); the functional role of this area in face and object processing will, however, need further evaluation.

6.3.1 Supramodal and modality-specific mechanisms of attention

Several researchers have addressed the question of probable supramodal attentional mechanisms that would allow crossmodal cueing of attention shifts; such shifts could be closely related to early sensory processing mechanisms, for example, in stimulus localization. Attentional mechanisms seem to be at least in part modality specific, but also global attentional processes are likely to exist (Farah *et al.* 1989; Ward 1994). Especially the stimulus-driven shifts of auditory attention have been suggested to be under supramodal control (Ward 1994). Lesions of the parietal cortex, known to have crucial effects on visuospatial attention, can produce tactile and auditory neglect as well (Vallar 1998). From this perspective, the elevated thresholds of dyslexic subjects in auditory stream segregation (Helenius *et al.* 1999b) might be related to the speed at which the subject is able to shift attention between successive stimuli. Indeed, patients suffering from right parietal lobe damage are impaired in stream segregation of sounds presented to their left ear (Carlyon *et al.* 2001).

Evidently, attention can critically affect fairly early phases of perception, such as detection of orientation differences between visual stimuli (Joseph *et al.* 1997). Attention can also modulate LGN activity (O'Connor *et al.* 2002). Attention shifts might serve as the prerequisites for proper sensory sampling, and even mild damage to the brain areas that guide the attentional effects might slow down processing of rapidly presented stimuli. In other words, the sensory “input chunks” (Merzenich *et al.* 1993) within which successive stimuli can interfere with each other might get prolonged; this aspect will be discussed in more detail in Paragraph 6.4.

6.3.2 Parietal lobe and reading

We have recently suggested that sluggish attention shifts could slow down processing of rapid stimulus sequences in dyslexic subjects and prolong their input chunks of sensory stimuli (Hari and Renvall 2001). Within this framework, we also discussed the direct role of parietal lobe in reading. For example, covert attention and saccade control involve activation of common areas in the parietal, frontal, and temporal lobes (Corbetta *et al.* 1998; Bisley and Goldberg 2003b), and these two functions seem closely interrelated: One has to shift attention to the target location before a saccade can be made towards it (McPeek *et al.* 1999). Learning to read involves training of rapid attentional shifts, associated with eye movements, along the sequential letters and words (Vidyasagar 1999). Thus the integrity of the parietal lobe seems essential for learning to read**.** Data from robust right parietal dysfunctions agrees with this view: lesions of the posterior parietal lobe may produce 'acquired dyslexia' with letter migration errors (Mayall and Humphreys 2002), and right-hemisphere-damaged neglect patients make letter naming errors and omit letters during reading (Brunn and Farah 1991). Similarly, right hemisphere injections of sodium amobarbital result in reading errors that have been attributed to diminished attentional rather than linguistic mechanisms (Schwartz *et al.* 1997).

6.4 Role of accurate timing in sensory systems

Auditory perception has several relevant time windows with separate underlying neuronal mechanisms. Less than 1 ms interaural time differences are utilized at brainstem level in locating external low-frequency sound sources in space. Sensory integration, reflected as an increase in auditory cortical responses as a function of sound duration, or as backward masking, extends to tens of milliseconds (Cowan 1984). The relevant cues for speech perception and analysis fall typically on time scales from tens to hundreds of milliseconds. Relatively little is know about the neural mechanisms of temporal processing at this time window, but they have been attributed to internal clocks, neural delay-lines, and dynamic networks (Wright *et al.* 1997a; Buonomano and Karmarkar 2002). Finally, a "cognitive integration window" or "input chunk" of up to 500 ms is implied by auditory saltation (Hari 1995) and

stream segregation. Also neuropharmacological intervention affects auditory processing differently at the various time scales (Rammsayer 1999).

Motor and auditory systems are both sequential and thus have much in common, for example chunking occurs in both domains. Similar kinds of chunks do exist in other modalities, as suggested by tactile saltation (Geldard and Sherrick 1972; Kilgard and Merzenich 1995). Many of these results have been interpreted as revealing percepts "backwards in time", or as indicating that "future can affect the past" because later stimuli seem to affect the percepts of the earlier ones within a certain integration window (Hari and Loveless 1997).

How the duration of these chunks is determined has not been resolved. The chunks are probably shaped and shortened in early childhood (Benasich 1998) via plasticity mechanisms (*e.g.,* Merzenich *et al.* 1993). Disturbed shaping of chunks could lead to failure in refining temporal processing capabilities and could, for example, in the auditory modality contribute to problems of temporal order judgments (Merzenich *et al.* 1993, 1998).

Merzenich (1993) suggests two hypotheses to account for the degraded input chunks in dyslexic individuals. On one hand, some infants might adopt more global hearing or looking strategies, with a wider-than-normal field of attention. This would, in turn, lead to temporally less sharpened, *i.e.* less coherent, and noisier inputs that would degrade the organization of cortical maps. The generality of the problems in processing rapidly presented stimuli could be explained by corticocortical couplings via, for example, oscillatory mechanisms between different sensory areas. On the other hand, a genetic or some other physical defect in the "learning machine" could impair shortening of the input chunks; such a mechanism could account for reading difficulties in children with cortical anomalies or degenerative changes in the magnocellular divisions. In addition, noisy input during critical periods, *e.g.* due to chronic middle-ear problems, could delay the organization of adult-like topographic auditory maps as well as the refinement of cortical response selectivity, similarly as in rats who are exposed to pulsed or continuous noise (Zhang *et al.* 2002; Chang and Merzenich 2003).

In view of the present and earlier data on dyslexic subjects, the duration of the time chunks could also be shaped by the speed of attentional shifts and dwell times. Maybe both mechanisms – noisy input and sluggish attentional shifts – are needed to account for different time scales. Tallal *et al.* (1993) suggest that language- and

reading-impaired children, due to their basic auditory temporal processing deficit, are unable to establish stable and invariant phonemic representations. The prolonged input chunks could disturb the phonemic maps and therefore impair the proper development of cortical representations needed for reading acquisition. The prolonged input chunks could also explain many of the pansensory deficits encountered in dyslexics.

Temporal processing deteriorates with age, and more than normally expected if processing is abnormal in the first place due to developmental dyslexia (Laasonen *et al.* 2002a; Virsu *et al.* 2003). Along these lines, some of the apparent age-related decline in cognitive performance during spoken language comprehension has been suggested to be secondary to auditory temporal processing deficit (Pichora-Fuller 2003).

6.4.1 Training of temporal processing

As both human adult subjects and trained monkeys improve in segmenting successive stimuli after intensive behavioral training (Karni and Sagi 1991; Ahissar and Hochstein 1993; Merzenich *et al.* 1993), Merzenich, Tallal, and coworkers hypothesized that the same would apply for SLI children. Indeed, their results demonstrated significant improvement in temporal processing abilities and language comprehension in SLI children after behavioral training (Merzenich *et al.* 1996; Tallal *et al.* 1996, 1998).

In the initial studies, American SLI children were trained 2 hours per day, 5 days a week for 4 weeks with adaptive audiovisual computer games. The games were auditory exercises using nonspeech stimuli, synthetically modified consonant vowel stimuli, and acoustically modified speech. In each exercise, the brief acoustic events were modified by changing their duration or temporal separation, or by amplifying them. Training improved significantly children's performance in tone sequencing task, as well as their phonological and language comprehension abilities; the effect was present in retests at 3 and 6 months. A control group received otherwise similar training, but stimuli were natural speech and without adaptive acoustic modulation; the improvement was significantly greater in the test than the control group (Tallal *et al.* 1996). Later on, more than 500 children were trained successfully with this method (Tallal *et al.* 1998). From three dyslexic adults who underwent a similar training

program (100 min a day, 5 days a week, ~33 days; Temple *et al.* 2000), two improved in tests of rapid auditory processing and auditory language comprehension. Similarly to control subjects, these two individuals showed increased prefrontal fMRI activity for rapidly *vs.* slowly changing acoustic stimuli after training, whereas no such activity was observed before the intervention.

In a following study, remediation of 20 American dyslexic children (100 min a day, 5 days a week, ~28 days) resulted in improved reading scores and increased fMRI activity at several brain areas during a phonological task (Temple *et al.* 2003). The authors suggested that different subcomponents of the remediation program might train different brain regions; for example, some of the changes were attributed to training of attentional mechanisms. This view is intriguing also from the point of the present studies. As concluded by Temple *et al.* (2003), it remains open whether the observed changes were specific to the used remediation program or were associated with remediation in general. With explicit phonological training methods, different approaches can produce very similar outcomes: for example, intensive training with two qualitatively fairly different programs that directly attack phonological awareness and phonological decoding strategies had essentially same long-term effects in SLI children (Torgesen 2001).

The efficacy of auditory training was recently replicated in studies on French dyslexic children (Habib *et al.* 2002): Children's phonological performance improved significantly after shorter (15 min a day, 7 days a week over 6 weeks), but otherwise fairly similar training than that by Merzenich, Tallal, and coworkers. Pre-training performance in temporal-order-judgment task correlated with post-training improvement in phonological measures, leading the authors to suggest the use of this task in finding the children who would gain most from the temporal training.

6.5 "How one may become dyslexic?"

In discussion of Study V, we presented one hypothetical causal chain from M deficit to various sensory disorders encountered in dyslexic subjects. Due to genetic predisposition, some subjects would be more vulnerable to neurodevelopmental disorders. One suggested route could be via congenital immunological attacks to magnocellular neurons (Galaburda and Livingstone 1993; Stein and Richardson 1999; Preuss and Coleman 2002); such suggestions have been based on common surface

antigens, Cat-301+ (McGuire *et al.* 1989) and NPNF+ (Preuss *et al.* 1999), observed in macaque brains, mainly at highly-myelinated "magnocellular" areas. Intriguingly, one of the observed genetic linkages in dyslexia resides within the human major histo-compatibility complex (MHC) in chromosome 6 (Cardon *et al.* 1994), circumstantially supporting the idea of immunological influence in dyslexia (Stein 2001). These effects could also greatly vary between individuals and affected sensory systems.

The M deficit could result both in direct sensory deficits and in slowing down the speed of processing of stimulus sequences in several neural systems, as discussed above. The resulting temporal processing deficits themselves could play an important role in the genesis of the reading disorder (Merzenich *et al.* 1996; Tallal *et al.* 1998; Ahissar *et al.* 2000), and impaired attentional focusing during development could also prevent the genesis of stable phonetic representations, crucial for development of reading ability (Tallal *et al.* 1998).

Although appealing, the M deficit hypothesis has been severely criticized, and its role as the underlying cause of dyslexia is far from clear. Several comprehensive studies have reported findings inconsistent with it (Skottun 2000; Ramus *et al.* 2003b), and some of the M-deficit-supporting results have rather been attributed to inattention or deficits in working memory (Ben-Yehudah *et al.* 2001; Stuart *et al.* 2001; Ramus 2003). Amitay *et al.* (2003) recently suggested an update of the initial M hypothesis to a "parietal-deficit" hypothesis; their proposal was in part stimulated by our "sluggish-attentional-shift" hypothesis (Hari and Renvall 2001). The revised hypothesis was considered consistent with some of the dyslexics' cognitive characteristics, as well as letter position errors (Cornelissen *et al.* 1998), and poor spatial resolution around fixation (Geiger and Lettvin 1987). Parietal deficit might also directly contribute to some of the motor problems encountered in dyslexics; for example, poor bimanual coordination (Moore *et al.* 1995) could be attributed to hypofunction of the left parietal lobe, as seen in patients with lesions at this area (Serrien *et al.* 2001). In line with dyslexics' working memory impairment, the parietal cortex probably mediates short-term storage of verbal information, and it may also be involved in shifting attention from one item to another during the rehearsal process of working memory (Jonides *et al.* 1998).

6.6 Methodological considerations

6.6.1 Subject selection and MEG measurements

Our dyslexic subjects evidently formed a heterogeneous group. However, they were clearly slow in reading (see Background, Fig. 3), which is considered a typical marker of dyslexia in Finnish adult populations (Leinonen *et al.* 2001). In Finnish with easy grapheme-to-phoneme correspondence, sensory impairments might have to be more profound and thus more easily detected than in more complicated orthographies like English.

The excellent temporal resolution of MEG and the-state-of-the-art whole-head devices used in this thesis provided good means to study the aspects of interest. To minimize fatigue in the subject, all MEG measurements were kept fairly short (duration < 20 min). The reproducibility of the measured signals was insured by averaging odd- and even-numbered responses to two different bins in Study IV. In Study I, one control subject was studied in two different sessions separated by 8 days, and in Study III, recordings of one dyslexic subject were repeated after a 10-min break; in both cases, the responses showed good reproducibility.

6.6.2 MEG data analysis

The inverse problem in MEG is always non-unique, but usually "non-ambiguous". In the present studies, the most probable source areas of the auditory and somatosensory activity could be estimated already from the magnetic field patterns measured by the planar gradiometers that detect the maximum signal just above the source. Only one- and two-dipole models were needed in the analyses, and sources explained the measured activity well in both subject groups. In Studies I and III, measured signals were subtracted from each other to reveal stimulus-specific activations. This procedure may be problematic, but also often justified. As planar gradiometers were used, it is probable that the subtracted signals reflected differences in the same underlying source areas. In addition, baselines were set separately for each response, which eliminates possible DC effects.

6.7 Insights to future studies on sensory processing in dyslexia

It is unlikely that any theory would alone ever account for such as heterogeneous disorder as dyslexia. Sensory processing deficits and their severity can differ significantly between subjects and orthographies, and they do not necessarily predict subjects' phonological or reading skills because individual compensatory mechanisms can be influential. However, the results presented in this thesis, together with our model of sluggish attention shifting in dyslexia, do provide several future perspectives.

If N100m were attention-related and dyslexics had problems in attention triggering, masking with intermittent noise or speech (Hari and Mäkelä 1988) should have more distracting effect on N100m in dyslexic than control subjects. So far auditory masking between SLI/dyslexic children and normal readers has been studied only by behavioral measures (Wright *et al.* 1997b; McArthur and Hogben 2001; Rosen and Manganari 2001). The diminished mismatch responses serve as a sign of deficient auditory change detection in dyslexics, but to further illuminate the observed hemispheric imbalance in dyslexics, future studies might be designed to selectively follow the auditory inputs from the two ears up to the auditory cortices of both hemispheres (Fujiki *et al.* 2002). Similarly, the specificity of audiospinal facilitation study might be enhanced by using separate left- and right-ear sounds, and by testing both the short-term and long-term habituation of the H-reflex after conditioning sounds (Maschke *et al.* 2000).

The minineglect in dyslexic individuals is certainly fascinating. An important future challenge is to explore the relationship between the attentional deficit and sensory-specific cortical processing, and to clarify the role of attention in various sensory and reading-related tasks sensitive to dyslexia. We recently made an attempt to study processing of rapidly presented stimuli in healthy subjects during transient neglect, produced by transcranial magnetic stimulation applied to the parietal lobe. Unfortunately, in this preliminary study the results were contaminated by sounds from the stimulator.

Knowledge of temporal and spatial pattern of eye movements in dyslexics would be of outmost relevance, and we have already started such studies. Genetics of dyslexia have recently taken major steps forward: it might soon be possible to study

“genetically selected” dyslexic subject groups, which could give important insight regarding the roles and causal connections of the various deficits encountered in dyslexic children and adults.

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