INTRODUCTION

Dyslexic subjects suffer from a selective impairment of reading skills, which cannot be attributed to low intelligence, to motivational or behavioral problems or to a lack of reading opportunities. The origin of the condition is not known. Traditionally, the disorder has been attributed to deficits in linguistic abilities, and research has focused on the identification of abnormalities in the underlying anatomical structures. Reduced asymmetry of the planum temporale has been the most consistent finding (1-3) but was questioned in one study, in which
the effects of sex and age were carefully controlled (4).

Event-related brain potential research has confirmed the following cerebral electrical activity abnormalities related to language-processing: increased N2 and P3 latencies in reading-related tasks (5); reversed right/left cortical direct current (DC) negativity distribution during linguistic tasks (6); reduced and abnormally lateralized P300 in difficult paradigms (7).

As far as vision is concerned, the classical view is that this function is normal in dyslexia (8). Indeed, both visual acuity and other elementary visual functions are generally found to be within normal limits in these subjects. However, psychophysical research has shown that some temporal aspects of the visual processing both of unpatterned and of patterned stimuli are involved in dyslexia. These studies showed altered flicker fusion thresholds (9), difficulties in temporal order judgements (10), increases in visual persistence (11), and alterations in visual masking effects (12). These alterations fit Breitmeyer's theory of visual processing (13). It is known that reading involves a sequence of fixations that are separated by saccadic eye movements. The aim of these movements is to bring the next part of the text into foveal vision. According to Breitmeyer's theory this sequential process is accompanied by dynamic interaction between two main afferent systems, which remain segregated until the primary visual cortex. These systems are called magnocellular and parvocellular on the basis of the histological aspect of cell nuclei in lateral geniculate body layers. The theory developed by Breitmeyer et al. (13) assumes that a saccade-evoked transient/magnocellular input inhibits the sustained/parvocellular input, which prevails during fixation periods. The theory proposes that dyslexics have a selective magnocellular deficit, which could interfere with saccadic suppression, and thus determine the persistence of the visual image throughout the saccade and the subsequent fixation periods (14).

Neurophysiological studies have used visual evoked potentials (VEPs) in attempts to validate the hypothesis of a selective magnocellular deficit in dyslexia (15-21). These authors manipulated specific stimulus parameters in order to achieve a predominant activation of either the magnocellular or the parvocellular subsystem. The results of these studies are conflicting: five (15,17-20) found differences between dyslexics and controls, and two (16,21) did not. These results will be analytically reported and compared with our own in the discussion section. For now, it is worth mentioning the anatomical data that Livingstone et al. (18) obtained from five patients, in whom cell disorganization and reduced cell body areas were found in the lateral geniculate body magnocellular, but not parvocellular, layers.

The present study used a variety of VEP paradigms to evaluate nine carefully selected dyslexic children and nine age- and sex-matched controls. The VEP paradigms were chosen on the grounds of their capacity to activate the two subsystems preferentially; specifically, high spatial frequency and low stimulus rate to enhance the parvocellular subsystem, and low spatial frequency and high stimulus rate to enhance the magnocellular subsystem. We avoided extreme stimulus parameters because although they may be more specific, they often give unreliable responses. In view of their potential clinical relevance, we chose stimulation and recording procedures that can be performed in all neurophysiological laboratories.

MATERIALS AND METHODS

Subjects

The study enrolled nine children and adolescents (8 boys and 1 girl) aged 10-17 years, all presenting a specific reading disability. All
of them had been diagnosed at least one year prior to enrollment by our institute’s pediatric neurology staff as having a specific developmental reading disability. Inclusion criteria were as follows:

– a normal neurological examination and no history of central nervous system disease;
– no significant behavioral problems;
– normal educational opportunities;
– a normal I.Q. (WISC > 100); the lowest score was in fact 109;
– normal verbal production, as evaluated clinically and in structured tests, and normal verbal comprehension, as evaluated clinically and by means of the Token test (22);
– abnormalities in reading performance objectively assessed (23) according to correctness of reading and speed of reading parameters;
– normal (10/10) corrected visual acuity.

The nine control subjects were age- and sex-matched normal readers, who fulfilled all inclusion criteria, except those relating to reading abilities.

Methods

Visual evoked potentials by checkerboard pattern reversal stimulation were performed with a Nicolet NIC 1015 stimulator and a Nicolet Pathfinder Plus system. The subjects binocularly fixated the center of a display subtending 18° x 14°. Mean luminance (60 cd/m²) and contrast (50%) were kept constant throughout the recording procedures, whereas check size and reversal frequency were changed; the procedure thus consisted of two transient VEP paradigms [1.05 Hz (2.1 reversal/sec): VEP-tr], one with 60' checks (or, in cycles per degree units: 0.5 cpd) and the other with 15' checks (2 cpd), along with two steady-state VEP paradigms [4 Hz (8 reversal/sec): VEP-ss], with the same check sizes as those previously reported. The order of presentation of the four paradigms was randomized across subjects.

Surface electrodes were filled with electrode paste and fixed at Oz and Cz. The reference electrode was A1 and the ground A2. Impedance was kept below 3 kOhms. The signal was filtered (1-100 Hz), and epochs of 250 ms and 2000 ms (512 points per trace) were averaged in the VEP-tr and VEP-ss paradigms respectively. Two replications of 100 artifact-free (i.e., with no point beyond the first 2.5 ms of the sweep less than 96% of the full scale, which was set at 100 µV) averaged responses were obtained for the VEP-tr and 50 for the VEP-ss paradigms.

Parameters. Only the Oz-A1 derivation was considered, as highly reproducible tracings with little noise were obtained in all subjects, with easily identifiable peaks in the VEP-tr paradigms. For the VEP-tr paradigms, we considered the latencies and the amplitudes (from a baseline defined as the mean value of the first 25 ms) of the first negative (N70) and positive (P100) peaks. The scorer was blind to the diagnosis.

The VEP-ss tracings were submitted to Fast Fourier Transform. The amplitudes and phases of the harmonics at 8, 16 and 24 Hz (here called 2nd, 4th and 6th harmonics, on the basis that the whole stimulation “cycle” consisted of two reversals) were measured automatically.

Statistical analysis

The distributions of parameter values were checked for deviation from normality by means of inspection and the Kolmogorow-Smirnow test. Amplitude values for VEP-ss were logarithmically transformed so that they approached normal distribution. The parameters were submitted to analysis of variance for repeated measures (MANOVA), which considered one between-subject factor (group: 2 levels: control/dyslexic) and one within-subject factor (check size: 2 levels: 60'/15') and their interaction. Parameters that significantly differed between groups were submitted to a step-
wise discriminant analysis. All calculations were performed by SPSS/PC+.

RESULTS

Figure 1 shows a representative example of VEP-tr and VEP-ss obtained in one control and in one dyslexic subject.

1. VEP-tr. Both components were easily identifiable in each subject. The results of MANOVA on VEP-tr parameters are reported in Table I and Fig. 2.

We did not find group-related differences as regards the P100 measures, whereas we did find differences both in amplitude and in latency for N70. These differences were entirely attributable to the low spatial frequency condition (60'): at this spatial frequency, N70 showed both a lower amplitude and a shorter latency in dyslexics. We further analysed these findings, which could seem contradictory, by checking each subject’s traces. We observed that the dyslexics who had a shorter N70 latency also had a low N70 amplitude. Figure 3 shows the grand average of normal subjects, of the 6 dyslexic subjects showing a

<table>
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<th>Group</th>
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<tr>
<td></td>
<td>(F_{(1,16)})</td>
<td>p</td>
<td>(F_{(1,16)})</td>
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<td>N70 lat.</td>
<td>4.4</td>
<td>0.05</td>
<td>152.4</td>
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<td>N70 amp.</td>
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<td>0.03</td>
<td>14.5</td>
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<td>P100 lat.</td>
<td>0.6</td>
<td>n.s.</td>
<td>22.1</td>
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<tr>
<td>P100 amp.</td>
<td>1.3</td>
<td>n.s.</td>
<td>25.5</td>
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Abbreviations: lat. = latency; amp. = amplitude; n.s. = not significant
clearly ascending N70 slope, and of the 3 dyslexics without or with only a minimal ascending phase.

The apparent reduction in latency is actually attributable to a loss of a negative component, whose latency does not differ from that of control subjects (see the lower traces in Fig. 3).

To demonstrate that this loss of negative activity, without a “real” latency shift, may indeed result in an “apparent” latency reduction, we built a simple mathematical model (24). This model is based on superimposed Gaussian functions. Figure 4 (see over) shows a function obtained by the sum of two slightly shifted Gaussian curves of opposite sign. It can be observed that the reduction in amplitude of one component also results in a shift in the peak, which resembles our “paradoxical” latency reduction.

Fig. 2 - Mean values for VEP-tr N70 latency and amplitude (60’ and 15’ checks) of controls and of dyslexic subjects. Amplitude is significantly lower and latency shorter in dyslexics exclusively with 60’ checks.

Fig. 3 - Grande average of (60’ checks) VEP-tr in controls (C), in the 6 dyslexics who showed a substantially negative N70 slope (D1) and in the 3 who did not (D2). The lower traces represent the differences between controls and the two dyslexic subgroups.
2. VEP-ss. The results of MANOVA on VEP-ss parameters are reported in Table II and Fig. 5. All three harmonic amplitudes had lower values in dyslexics, irrespective of check size. No phase-related effects were found. Figure 6 shows the number of times each parameter was altered in dyslexics. Only one dyslexic subject had all parameters within the normal range; most had alterations of more than one parameter. Only one control subject showed a single abnormality (of the 6th harmonic with 15' checks).

3. Discriminant analysis. Including both VEP-tr and VEP-ss measures, discriminant analysis was able to correctly identify all the subjects (chi square: 24.65, 5 d.f.; canonical correlation coefficient: 0.92) The parameters that entered the final equation were: N70 latency (with 60' checks) and amplitude (with 60' checks); (log)amplitude of the 4th harmonic (both with 60' and with 15' checks) and of the 6th harmonic (with 60' checks).

DISCUSSION

Our results confirm previous studies (15,17-20), which found that, under certain stimulation conditions, VEPs differ substantially between dyslexics and controls. Moreover, our data support the conclusion of previous authors, i.e., that the stimulation patterns separating the two groups are those that preferentially activate the magnocellular subsystem. Only one paper (15) reports differences that are not consistent with the magnocellular defect hypothesis. A detailed comparison of our study with previous ones is difficult due to the differences in the methods employed, and to the different ages of

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<th>Group F(1,16)</th>
<th>p</th>
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<th>Group x check F(1,16)</th>
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<td>0.9</td>
<td>n.s.</td>
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<td>n.s.</td>
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Abbreviations: harm = harmonic; amp. = amplitude; n.s. = not significant
the subjects tested. Nevertheless, we here en-
davour to highlight some important points.

First, Livingstone et al. (18) used rectan-
gular checks of 0.16 x 0.12 cpd, and varied
stimulus contrast between 20% and 2%. The
four dyslexic subjects who were submitted to
VEP-tr showed “delay or absence of the first
negative component”, as well as a delay of
P100. However, statistical analysis was not
performed, probably because the case series
was small and because of the type of abnormal-
ities, quantitative in some subjects and qualita-
tive in others. Nevertheless, the absence of the
first negative peak echoes somewhat our find-
ing of reduced N70 amplitude. These authors
also report VEP-ss performed at various con-
trasts (1%; 2%; 15%) at a very high temporal
frequency (30 reversals/s) and, for the low con-
trast condition, at lower temporal frequencies
(20 and 10 reversal/s), too. In all conditions,

Fig. 5 - Mean values for VEP-ss harmonic amplitudes of controls and of dyslexic subjects (60‘ and 15‘ checks). All am-
plitudes are significantly lower in dyslexics.

Fig. 6 - Number of alterations of VEP-tr and VEP-ss parameters in dyslexics.
the fundamental harmonic was lower in dyslexics, but the difference was significant only at 1% and 2% contrast for the fast stimulation. These results were convincingly interpreted by the authors as supporting the magnocellular defect hypothesis of dyslexia.

In the same year, May et al. (19) reported another study of VEPs in ten dyslexics. These authors used different spatial frequencies (0.5 to 8 cpd), which were all higher than those used by Livingstone et al. (18), in a pattern onset-offset paradigm. The main findings were a reduction in the N1-P1 amplitude (measured peak-to-peak) of the offset response, exclusively at the low (0.5 cpd) spatial frequency. It should be noted, however, that the onset amplitude was also reduced at this spatial frequency, at least in one run. In any case, two latencies (N2 and P2) of the offset response were reduced in dyslexics, the difference reaching significance at the 1 cpd spatial frequency. These authors’ conclusions strongly resemble those formed by Livingstone et al., (18) about a transient system deficit in dyslexia. Indeed, low spatial frequency is reported as a stimulus parameter that selectively activates this pathway, as are low contrast and high temporal frequency (25).

Although very different in their methods, both studies (18,19), like our own, report alterations as mainly occurring in negative components. May et al. (19) report apparently paradoxical latency reductions, as we do for N70. However, we do not think it is possible to compare the two findings directly, as they refer to different components that were evoked by different stimulation methods. A further study (20) compares the pattern onset VEPs (sinusoidal gratings of 0.5 and 4.5 cpd) obtained in two conditions: steady background and Uniform-Field-Flicker (UFF) background. This latter procedure is thought to engage the magnocellular system and thus to isolate the contribution of the slower parvocellular system to the VEP. These authors found differences only with the 0.5 cpd stimulus, which consisted of prolonged N1 and P1 latencies and a reduced P1-N2 amplitude in the steady background condition. Moreover, the effects of UFF on controls confirmed the authors’ expectations, in that it increased the latencies of N1 and P1, and reduced both amplitudes. In dyslexics, the effect was only partial, and consisted solely of an amplitude reduction. The findings were again interpreted as favoring the hypothesis of magnocellular pathway involvement in dyslexia. Kubova et al. (17) developed a more sophisticated motion-onset paradigm to selectively engage the magnocellular system and found consistent alterations in dyslexics. However this stimulation procedure, which undoubtedly provided important research results, is unsuitable for use in a common clinical setting.

A negative study was published by Victor et al. (21). These authors essentially tried to replicate the findings of Livingstone et al. (18), and used slightly different methods on a larger patient sample. They varied both stimulus contrast (between 2% and 20%) and mean luminance (from 4 to 59 cd/m²) for transient VEPs. Check size was very large (3.3 deg: 0.15 cpd). The authors considered P100 alone, even though most previous papers (18-20) had found alterations in the negative peak preceding the major positivity; only two of them (18,20) had found alterations that were clearly attributable to P100. Steady-state responses were analyzed by Victor et al. (21) from the raw EEG and not from averaged epochs, the former route providing “a rigorous criterion” for assessment if a driven signal is present. The authors used a fastest reversal rate of 16.89 Hz. This rate is at substantial variance with the 30 Hz reversal rate, which is the only stimulus frequency at which Livingstone et al. (18) found significant differences. In a second negative study Johannes et al. (16) were not able to obtain reliable VEP-ss at the 30 Hz frequency, and their 4° check pattern-reversal VEP-tr were similar in the 6 dyslexics and in the 6 control subjects.
At this point, a comment on the use of extreme stimulus parameter values (in order to selectively stimulate the magnocellular pathways) is warranted; of particular note are the very low contrasts associated with low spatial frequencies and high stimulation rates, which were employed in the first study by Livingstone et al. (18) and in the two negative studies mentioned earlier (16,21). Such extreme stimulation resulted in disappearance of responses, not only in dyslexics (18), but also in a high percentage of controls (16,21). Moreover, stimulation with check sizes greater than 2°, as employed in these studies (16,18,21), allows the contribution of luminance change effects to dominate (26).

In our patients, VEP-tr were abnormal only with 0.5 cpd checks, the spatial frequency at which alterations were observed by other authors (19,20). Using baseline-to-peak amplitude measurements, we were able to attribute a significant reduction to the N70 component; the same result was seen by other authors for the N70-P100 peak-to-peak amplitudes of VEPs obtained by different stimulation techniques. Unlike Lehmkuhle et al. (20), we were unable to show a latency increase in this component. On the contrary, N70 latency was significantly reduced in our dyslexics. However, we showed that the observed latency reduction may actually arise simply from a “loss” of negative (N70) activity superimposed on the onset of P100, in the absence of real latency changes (24).

VEP-ss amplitudes clearly separated dyslexics from controls in our study. We empirically included amplitudes of two higher harmonics, as they were reliably evident in all subjects. However, the neurophysiological meaning of these frequencies, all of which separated the two groups, is far from fully clear (27). When using the high frequency stimulation, we did not find the spatial frequency effect, as both 0.5 and 2 cpd check VEP-ss differed between the two groups. This finding seems to indicate that, at least at the frequencies used, the temporal frequency effect prevails over the spatial frequency effect.

Our study is the first one to score single patients, and the results seem promising. Indeed, all but one of the dyslexics had VEP abnormalities and all but one of the controls had normal parameters. Using discriminant analysis, we were able to classify all the subjects correctly. One possible clinical application of this finding could be the separation of subjects whose poor reading abilities arise from a possible perceptual dysfunction, from other subjects with differing pathogenesis. Dyslexia therapies based on the magnocellular dysfunction hypothesis, and consisting of colored background illumination or overlays, have been proposed and successfully tested (28). Although further systematic studies are needed, VEPs may contribute to the diagnosis of perceptual dysfunction, and thus predict the response to specific forms of treatment.

Data on perceptual alterations in dyslexia do not imply that this is the only cause of this condition. However, we believe that the evidence of a visual subsystem dysfunction in at least some dyslexic subjects is increasing. Further research, particularly in the field of event-related brain potentials in dyslexia, should consider the possibility of a coexistent peripheral dysfunction that may cause the alterations in higher stages of visual and linguistic processing.

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