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Motion-onset VEPs: Characteristics, methods, and diagnostic use

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Abstract

This review article summarises the research on the motion-onset visual evoked potentials (VEPs) and important motion stimulus parameters which have been clarified. For activation of the visual motion processing system and evocation of the motion-onset specific N2 peak (with latency of 160–200 ms) from the extra-striate temporo-occipital and/or parietal cortex, the following stimulus parameters can be recently recommended: low luminance (<ca. 20 cd/m^2) and low contrast (<ca. 10%—sinusoidally modulated) of a moving structure with low velocity and temporal frequency (<ca. 6 Hz). A short (up to 200 ms) duration of motion and a long (at least 1 s) inter-stimulus interval reduce adaptation to motion and predominance of a pattern-related P1 peak. Radial motion (with increasing velocity and decreasing spatial frequency towards the periphery) produces larger reactions as compared to a unidirectional translation. In view of the slow maturation (up to the age of 18 years) and early ageing of the visual motion processing system, the use of age-dependent latency norms may be necessary. Since early or selective involvement of the motion processing system is suspected in some CNS disorders, we suggest an evaluation of the utility of motion-onset VEPs as part of the electrophysiological CNS examination since this method may recognise motion processing involvement better than other methods. Motion-onset VEPs might increase the sensitivity of this examination for diagnosing CNS diseases including Multiple Sclerosis, Neuroborreliosis, Glaucoma, Dyslexia and Encephalopathies.

Keywords: Visual evoked potentials; Motion-onset VEPs; Magnocellular system/dorsal stream; Visual motion stimuli; Radial motion; Clinical applications of motion-onset VEPs; Multiple Sclerosis; Glaucoma; Dyslexia

1. Introduction

Despite the relatively long history of visual evoked potentials (VEPs), their diagnostic use has so far been limited almost exclusively to flash or pattern (mainly pattern-reversal) related responses of the primary visual cortex (see IFCN standards—Celesia et al., 1993; ISCEV standards—Odom et al., 2004; Misulis & Head, 2003; Fahle & Bach, 2006) following the recommended stimulus conditions (high contrast and/or quite high spatial frequency), mainly via prevailing activation of the parvocellular system of the visual pathway (e.g., Livingstone, Rosen, Drislane, & Galaburda, 1991; Ellemberg, Hammarrenger, Lepore, Roy, & Guillemot, 2001). The requirement for standard VEP examinations for clinical diagnosis seems to be reduced since the introduction of new brain imaging techniques (mainly MRI), and the method is considered obsolete in some cases. Although VEP is a completely non-invasive, objective, and inexpensive investigation, which provides information about early functional changes of the visual pathway and visual brain cortex (which are sometimes recognisable prior to any detectable morphological changes observed by imaging techniques), it is surprising that efforts to extend it to more complex testing of visual and brain functions are quite rare.

An examination of the motion processing system (magnocellular system and dorsal stream) of the visual pathway is a necessary extension of VEP (Braddick, Atkinson, & Wattam-Bell, 2003). Some attempts to record various motion-related responses of the visual cortex were made

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many years ago (e.g., Clarke, 1973a, 1973b; Yokoyama, Matsunaga, Yonekura, & Shinzato, 1979; Gallichio & Andreassi, 1982; Göpfert, Müller, Markwardt, & Schlykowa, 1983; Spekreijse, Dagnelie, Maier, & Regan, 1985; Dagnelie, De Vries, Maier, & Spekreijse, 1986). However, these papers reported variable and controversial results which were not applicable to clinical diagnosis. Nevertheless, the majority of the important methodological factors which play a decisive role in the character of motion-related VEPs have been described, and some significant and promising diagnostic applications (mainly those which selectively involve the magnocellular system or the dorsal stream) have been developed.

However, the difficulty of generating the stimulation and the utilization of different recording and evaluation methods hampered the development of motion-related VEPs into routine neuro-ophthalmological diagnostics. Moreover, since the methods differ from those of a standard VEP examination, there is still doubt and scepticism about the reliability and diagnostic significance of motion related VEPs. In this article we try to summarise recent knowledge about the most commonly investigated type of motion related VEP, the *motion-onset VEP*, in an effort to promote the use of this method and to increase interest in the inclusion of an extended VEP examination in functional neuro-ophthalmological diagnostics. The clinical applications of motion-onset VEP that are described in this article are mainly based upon pilot studies from a few labs. Verification of their diagnostic value by evaluation of their specificity in clinical labs is suggested before their introduction into standard examinations.

2. Types of motion-related VEPs

Among all visual motion-related VEPs tested to date, *motion-onset VEPs* display the largest amplitudes and the lowest inter- and intra-subject variability (Göpfert et al., 1983; Kuba & Kubová, 1992; Kuba, Toyonaga, & Kubová, 1992; Bach & Ullrich, 1994; Skrandies, Jedynak, & Kleiser, 1998; Heinrich & Bach, 2003). Therefore, they seem to be the most promising modality for diagnostic purposes (e.g., Kubová & Kuba, 1992; Kubová & Kuba, 1995; Kubová, Kuba, Peregrin, & Nováková, 1995b; Kuba, Kremláček, Hůlek, Kubová, & Vít, 1996; Kubová, Kuba, Hrochová, & Svěrák, 1996b; Korth, Kohl, Martus, & Sembritzki, 2000). The much smaller amplitude of *motion-offset VEPs* require a longer duration of motion causing adaptation of the motion-processing visual cortex, which leads to inclusion of pattern related (most likely *pattern-on*) components (Clarke, 1973a, 1973b). To our knowledge, no diagnostic applications of *motion-offset* VEPs have been reported.

Motion-reversal VEPs represent responses to motion direction changes. They display large inter-subject variability of their shape (including also *pattern-on/off* components), which prevents clear identification of corresponding peaks (Kuba et al., 1992). The continuous motion stimulation, usually with changing directions in only one axis, causes motion adaptation and may provoke a dominance of pattern-related components (dependent on the temporal frequency and other parameters of a moving pattern—see below) (Odom, De Smedt, Van Malderen, & Spileers, 1999).

To date, *steady-state motion-related* VEPs using continuously moving stimuli have rarely been tested (e.g., Clarke, 1974; Tyler & Kaitz, 1977; Snowden, Ullrich, & Bach, 1995). Moreover, they do not seem to be a useful diagnostic variant of motion-related VEPs because of their variability (Heinrich & Bach, 2003).

So far, motion related VEP studies have used mostly *first-order* visual motion stimuli (defined by spatio-temporal luminance variations), although the V5 area (homologous to the area MT of the monkey) is also strongly activated by *second-order motion*, defined by differences in contrast or texture (Smith, Greenlee, Singh, Kraemer, & Hennig, 1998). However, the responses from *second-order* motion are dependent on a different neural mechanism with a slower response and higher variability (Ellemberg et al., 2003).

Chromatic moving stimuli have only been used rarely. It was reported that *motion-onset* responses have low chromatic sensitivity at higher motion velocities (>5 deg/s) (Mc Keefry, 2002).

With the use of a motion discrimination task also *motion event related potentials* (ERP—wave P300) can be recorded (Kuba, Kremláček, & Kubová, 1998; Kubová, Kremláček, Szanyi, Chlubnová, & Kuba, 2002).

Since this article is oriented toward the description of clinically useful motion-onset VEPs, it does not include many reports describing the theoretical physiological aspects of the motion-processing system.

3. Characteristics of motion-onset VEPs and their dependence on motion stimuli parameters

Motion-onset VEPs are typically composed of three main peaks—P1, N2 and P2. From Fig. 1 it is evident that there are basically two variants of the motion-onset VEP shape differing in their predominance of either a motion-specific N2 peak or pattern-specific P1 peak. The P2 peak rarely dominates and its increase is dependent on the recording site and type of motion (see below).

Although some early studies that used convenient stimulus parameters correctly reported (with respect to the current knowledge) the late *negative peak N2 with a latency of about 160–200 ms* as the *motion-onset specific component* (Yokoyama et al., 1979; Gallichio & Andreassi, 1982; Göpfert et al., 1983), the majority of the initial papers describing *motion-onset* VEPs (e.g., Clarke, 1973a, 1973b; Spekreijse et al., 1985; Dagnelie et al., 1986; De Vries, Van Dijk, & Spekreijse, 1989) concluded that the earlier positive peak P1 with a latency of about 130 ms represented the main *motion-onset* related potential. However, it is now evident that in these studies inadequate parameters of motion stimuli were used for the activation of the motion processing system.

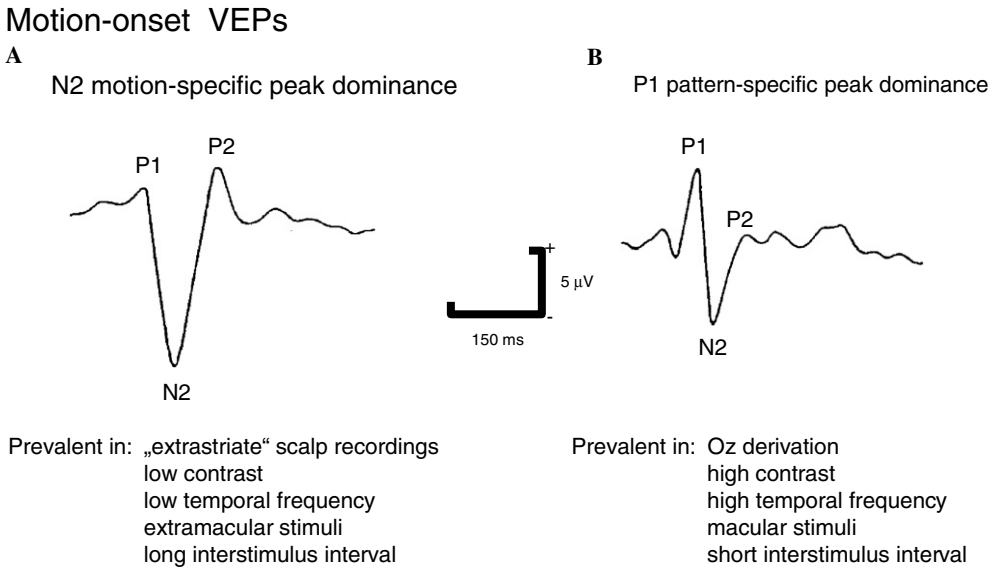

Fig. 1. Typical variants of motion-onset VEPs. (A) Dominance of N2 peak—motion specific. (B) Dominance of P1 peak—pattern specific (see the text for an explanation).

The *dominance of the P1 peak* (which most probably represents pattern-related activity of the parvo-cellular subsystem) seems to be caused by two factors:

1. The first one is a *pattern-off effect* (high contrast pattern-disappearance due to its blurring at the beginning of motion—see Clarke, 1973b) which is dependent on the high *temporal frequency* (multiple of spatial frequency and velocity) of a periodic moving pattern. In order to decrease a significant blur effect at the beginning of motion (evoking the pattern-offset dependent peak with a latency of ca. 110–130 ms Kuba et al., 1992), a *pattern of low spatial frequency*, or an *irregular (aperiodic) pattern* (e.g., random dots) with a lower number of superimposed pattern elements during motion (influencing perception of the pattern) is preferable. The temporal frequency should be kept below about 6 Hz (the spatial frequency range of 0.2–1.0 c/deg and the velocity range of 5–25 deg/s are recommended for generating the temporal frequency of 5 Hz—according to Kuba & Kubová, 1992; Kremláček, Kuba, Kubová, & Chlubnová, 2004b) to minimise "contamination" of the motion-onset VEPs with the *pattern-offset* dependent positive peak. The blur effect seems to be particularly effective in combination with high contrast patterns (contrast dependence—see below) and it mainly influences the character of recordings from vicinitiy to the striate area (Oz derivation) (Kuba & Kubová, 1992).
2. The second important factor is the *timing* of the motion stimuli. Long motion stimuli or short stationary phases between two motions (inter-stimulus intervals) cause adaptation of the motion sensitive cortical areas and decrease the size of N2 peak. Thus, a predominance of the P1 peak can appear in such a stimulus arrangement (this was probably the case in the study of De Vries et al. (1989) with 400 ms duration of both moving and stationary phases). The ratio of the motion duration and inter-stimulus interval should not exceed about 0.2 (see Kuba & Kubová, 1992), otherwise it leads to motion adaptation and P2 peak dominance. "*Duty cycles*" (duty cycle (%) = time of motion/total cycle time × 100) were used by Bach and Ullrich in 1994 to describe this crucial motion stimulation parameter. They recommended that the duty cycle should be kept below 20% to achieve N2 motion specific peak dominance in *motion-onset* VEPs.

A *stimulus field* that is restricted to the central (about the macular area) part of the visual field, and scalp *recordings closely to the striate area* (Oz derivation) also support the predominance of the pattern-related P1 peak in the resulting VEPs (Kuba & Kubová, 1992; Bach & Ullrich, 1994; Hoffmann, Dorn, & Bach, 1999).

The *N2 peak*, which probably represents motion processing system activity, seems to be generated from the *extrastriate temporo-occipital and associate parietal cortical areas* and dominates usually in the right hemisphere (Göpfert, Schlykowa, & Müller, 1988; Kubová, Kuba, Hubáček, & Vít, 1990; Kuba & Kubová, 1992; Probst, Plendl, Paulus, Wist, & Scherg, 1993; Bach & Ullrich, 1997; Skrandies et al., 1998; Nakamura & Ohtsuka, 1999).

The specificity of the N2 peak to motion-processing (activity of the magnocellular system) is supported with studies comparing reactions of various VEP components to a decrease in contrast (Kubová, Kuba, Spekreijse, & Blakemore, 1995a; Bach & Ullrich, 1997). It was reported that the N2 peak of motion-onset VEPs can be recorded at very low contrast levels of ca. 0.4% (Bach & Ullrich, 1997), dependent on the spatial frequency of the moving pattern (Kuba, 2006). On the contrary, the P100 peak of the pattern-reversal VEPs disappears at about 2% contrast (Kubová et al., 1995a; Bach & Ullrich, 1997).

Table 1
Parameters of the motion-onset related N2 peak in different types of motion (according to Kremláček et al., 2004b)

	Latency (ms)	Var. coeff. (%)	Amplitude (μV)	Var. coeff. (%)	*e* (μV/ms)
Radial motion	158.1 ± 6.0	3.8	14.2 ± 7.0	49.2	2.4
Spiral motion	159.0 ± 10.3	6.5	13.8 ± 5.5	39.6	1.3
Rotation	147.7 ± 11.0	7.5	10.1 ± 1.8	18.1	0.9
Translating motion	169.9 ± 17.1	10.1	9.2 ± 3.6	39.2	0.5

N2 peak motion specificity was also demonstrated in a set of experiments with adaptation to visual motion (Müller, Göpfert, & Hartwig, 1986; Kuba & Kubová, 1992; Bach & Ullrich, 1994; Hoffmann et al., 1999; Bach & Hoffmann, 2000; Hoffmann, Unsold, & Bach, 2001; Maurer & Bach, 2003) in which a significant reduction of the N2 peak (related mainly to the same direction of adapting and test motion) was reported.

The *P2 peak* with latency of about 240 ms has larger inter-subject variability compared to the N2 peak and seems to depend on the type of motion. This peak increases with more complex visual moving stimuli (expanding/contracting radial motion), perhaps because it represents a higher order of visual processing of biologically important stimuli (our unpublished data). Its largest amplitude is usually recorded by the parietal (up to central) electrodes (Hoffmann & Bach, 2002; Kremláček, Kuba, Chlubnová, & Kubová, 2004a) and it is not sensitive to motion direction (Hoffmann et al., 2001).

The above-mentioned systematic studies on motion-onset VEPs led to the conclusion that the N2 (N200) peak of a motion-onset VEP is the main motion specific component produced in the extrastriate temporo-occipital or parietal cortex, and that its dominance and parameters are dependent on the main stimulus and recording conditions as specified below. This opinion was confirmed by localisation of the cortical dipoles (e.g., Probst et al., 1993; Skrandies et al., 1998; Nakamura & Ohtsuka, 1999) by MRI and MEG studies (Ahlfors et al., 1999; Bundo et al., 2000; Hollants-Gilhuijs, De Munck, Kubová, van Royen, & Spekreijse, 2000; Schellart, Trindade, Reits, Verbunt, & Spekreijse, 2004; Henning, Merboldt, & Frahm, 2005) and by testing of functional deficits of the visual pathway (Benson, Gou, & Hardiman, 1999; Korth et al., 2000). There is the continuing problem that some decisive factors (for the magnocellular system activation) are ignored, omitted, or underestimated in the selection of important stimulus and recording parameters. This leads to confusion about the character of the recorded motion related VEPs (doubts about the motion specificity of their components). For example, a study by Spileers, Mangelschots, Maes, and Orban (1996) uses high luminance (105 cd/m^2), a very high temporal frequency (41.6 Hz) and records only from Oz. Separate manipulation of any stimulus parameter could not significantly change the N2 peak when the other conditions were unsuitable.

It should also be noted that there is larger variability among subjects in the shape of the motion-onset VEPs related to different sensitivity to motion stimuli (Kuba & Kubová, 1992) and also in their parameters compared to the quite constant responses to pattern-reversal (see Langrová, Kuba, Kremláček, Kubová, & Vít, 2006—e.g., in the age group 19–60 years, the 25–75 percentiles of the pattern-reversal VEPs (40′ check size) are 108–114 ms and, in the radial motion-onset VEPs, the appropriate values are 156–172 ms). Thus, studies of only a few subjects may only obtain a correct overview of the typical responses by chance. This is also complicated by distinct variability in topography of motion-processing cortical areas (Bundo et al., 2000) which requires a larger set of derivations (at least four—see their specification below) to be used in motion-onset VEP studies.

4. Motion-onset VEP (N2 peak) dependence on motion stimulation parameters

4.1. Type of motion

Kremláček et al. (2004b) reported that the largest amplitudes with the lowest inter-subject variability of motion-onset VEP latencies providing the best clinical applicability (expressed by a criterion "*e*"—see below) can be achieved with a *radial motion* (randomly changing expansion/contraction—used also by Bach & Hoffmann, 2000) of concentric circular rings with *sinusoidally modulated luminance* (to eliminate high spatial frequencies present in patterns with rectangular luminance changes which are not suitable for magnocellular system activation Shapley & Lennie, 1985). The selective criterion "*e*" used by Kremláček et al. (2004b) (*e* = N2 peak amplitude/SD of N2 peak latency (μV/ms)) for the tested types of motion stimuli is displayed in Table 1.

Decreasing spatial frequency towards the periphery and *increasing motion velocity towards the periphery of the stimulus field* seem to be preferable. This is in agreement with the physiological properties of the visual system—the increasing size of receptive fields in the retinal periphery and better sensitivity to higher motion velocity in the periphery of the visual field (McKee & Nakayama, 1984; Orban, Kennedy, & Bullier, 1986). The arrangement described by Kremláček, Kuba, Kubová, and Vít (1999) and Kremláček et al. (2004b) keeps temporal frequency constant in all parts of the stimulus field and ensures recording of recognisable motion-onset VEPs up to about 50° of eccentricity. Compared to linear unidirectional (translational) motion with randomly changed directions of motion (to decrease motion adaptation), expansion/contraction evokes significantly larger (by 54%) VEP amplitudes (Kremláček et al., 2004b)—see Fig. 2. This might be explained by simultaneous activation of a

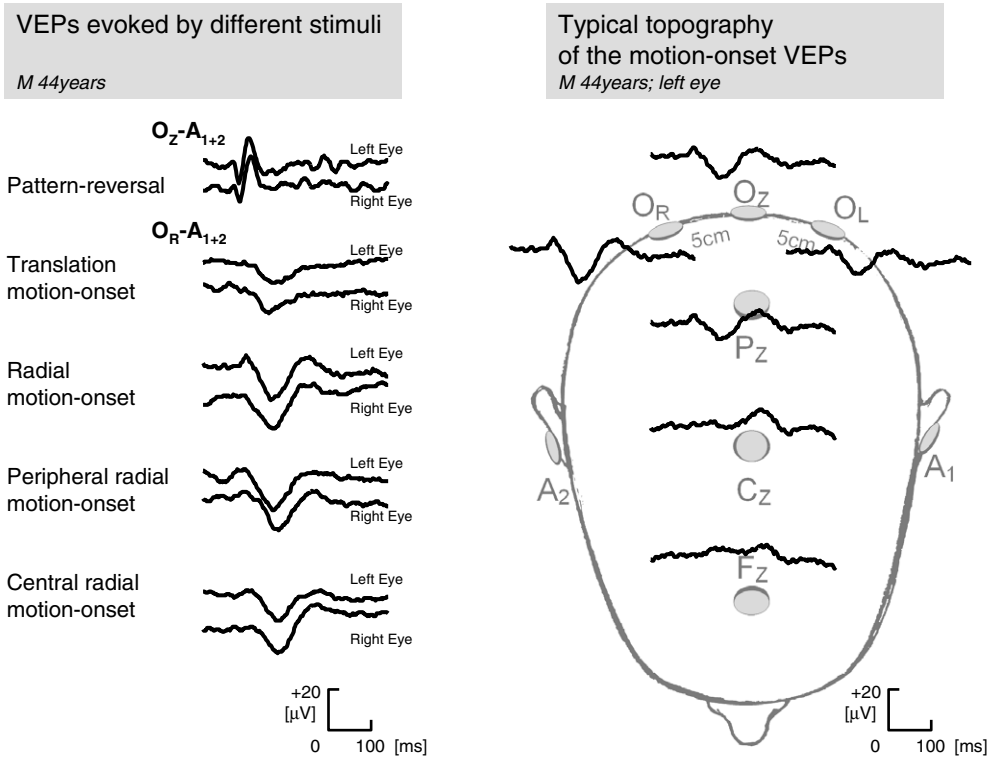

Fig. 2. Set of individual motion-onset VEP recordings. (Left) Comparison of typical reactions to various motion stimuli (peripheral stimulus is outside the central 20° of the stimulus field 32° × 40°; central stimulus covers central 8° of the stimulus field) from the right occipital derivation (5 cm from Oz) and to the pattern-reversal (Oz derivation). (Right) Comparison of the topographical distribution of motion-onset VEPs to the full-field radial (expanding/contracting) motion.

higher number of cortical direction sensitive neurones by multidirectional radial motion or by the higher sensitivity of expansion/contraction selective cells in the MST cortical area (Grzywacz & Merwine, 2003). This stimulus might represent more biologically important information—the expansion evokes an illusion that something moves towards the examined subject. Although we observed higher reactivity to translational motion than to radial motion in only a few subjects,. our standard set of stimuli for VEP examination (see Langrová et al., 2006) still include both of these motion variants.

Another convenient stimulus for motion-onset VEP acquisition is a random-dot kinematogram (Nakamura & Ohtsuka, 1999). This was improved with a limited dot lifetime application, which reduces the positive pattern-related component of motion-onset VEPs (Maurer & Bach, 2003).

4.2. Time course of motion stimulation

Since the *timing* of the motion stimuli is a critical stimulus parameter that influences the character of the motion-onset VEPs through adaptation of the motion processing system, a *short duration of motion is necessary*. However, to prevent a mixture of *motion-on* and *motion-off* components (although this is not significant in a majority of subjects because of the very small motion-offset response), at least a 200 ms duration of motion is needed. A minimum of a 1 s inter-stimulus interval is recommended to prevent adaptation and the decrease of N2 amplitude (Kuba & Kubová, 1992). The first description of the motion adaptation effect on motion-onset VEPs was provided by Göpfert, Müller, and Hartwig (1984). Detailed adaptation experiments that fully prove the prevailing motion specificity of the N2 peak in the motion-onset VEPs were performed by Bach and Ullrich (1994), Hoffmann et al. (1999), Hoffmann et al. (2001), Maurer and Bach (2003), Müller, Göpfert, Leineweber, and Greenlee (2004), Heinrich, van der Smagt, Bach, and Hoffmann (2004). Two adaptation effects were observed for the N2 peak by Hoffmann et al. (2001)—a global amplitude reduction of 47% (also inducible by pattern-reversal or pattern-onset adaptation) and a direction-specific reduction of 28%.

4.3. Duration of motion-onset VEP examination

According to our experience (Kremláček, Kuba, Kubová, Langrová, & Vít, 2006), the *number of recorded sweeps* (number of motion stimuli), and the total duration of the recording play important roles in adaptation processes. Compared to pattern-reversal VEPs, which are rather resistant to adaptation (Heinrich & Bach, 2001), a prolonged stimulation increases adaptation and decreases amplitudes of the motion-onset VEPs. Even in the described proportion of the motion duration and inter-stimulus interval 1:5 (duty cycle of 16.7%), it is evident that the amplitude of the N2 peak is significantly reduced after

20 s (Hoffmann et al., 1999). This "short term adaptation" is followed by a "long term adaptation" with an adaptation time constant of 1.5–2.5 min (for a direction selective process in cats—Giaschi, Douglas, Marlin, & Cynader, 1993). Although human motion-onset VEP results (Kremláček et al., 2006) may not be fully comparable, they show similar adaptation time dependence—for up to about 20 s stimulation, the amplitude is reduced by 40%, and after further 20 s the N2 peak amplitude of the motion-onset VEPs still exhibits additional 30% reduction. Thus, not more than about 40 sweeps (max. 60 s long recordings—with the above specified motion and inter-stimulus interval duration) are recommended for averaging. Approximately 20 sweeps might be preferable (when the signal-to-noise ratio is sufficient) in individuals with low voltage EEG.

4.4. Stimulus luminance and contrast

Motion-onset VEP parameters seem to be rather resistant to *luminance and contrast decreases* (Kuba & Kubová, 1992; Dodt & Kuba, 1995). It is recognisable in the article by Kubová, Kremláček, Kuba, Chlubnová, and Svěrák (2004) that the pattern-reversal P100 peak disappears from the response when the luminance is below ca. 0.5 cd/m^2 (probably due to a depression of the parvocellular activity) and that the N2 peak of the motion-onset VEPs (but partially also N2 peak in the pattern-reversal VEPs) is recordable up to a luminance of about 0.001 cd/m^2(scotopic conditions). At luminance levels below ca. 0.5 cd/m^2, the motion-onset VEPs (N2 amplitude) can be larger in some subjects, but N2 latency is more variable. Despite basic experience with the luminance influence which leads to the conclusion that its optimum for the motion-onset VEPs (related to N2 peak latency and amplitude changes) is in the interval of about 3–20 cd/m^2 (Dodt & Kuba, 1995), more detailed quantitative studies of its effects on motion-onset VEPs are needed (a consequence of the very few labs that are studying motion-onset VEPs).

Contrary to the pattern-reversal P100 peak, the N2 peak of the motion-onset VEPs is recordable down to a Michelson contrast of about 0.3%, dependent on the spatial frequency. This confirms its dominating magnocellular origin (Kubová et al., 1995a; Bach & Ullrich, 1997).

4.5. Stimulus position

Motion-onset VEPs are recordable up to about 50° in the periphery of the visual field (Kremláček et al., 2004a) and they have a much lower amplitude decrease with retinal eccentricity compared to pattern-reversal (Schlykowa, Van Dijk, & Ehrenstein, 1993). This holds for appropriate stimulus conditions—mainly that the "temporal frequency" should be kept relatively constant over the whole stimulus field (Müller, Göpfert, Schlykowa, & Anke, 1990; Kremláček et al., 2004b). Thus, motion-onset VEPs seem to be more suitable for objective perimetry compared to other types of VEP (Kremláček, Kuba, & Kubová, 1996; Kremláček et al., 2004a). They also have quite a low dependence on the stimulus field size (Göpfert, Müller, & Simon, 1990), with the exception of the above mentioned selective central stimuli that can cause a predominance of the P1 peak in the Oz derivation, probably due to rather intense parvocellular system activation (dependent on the temporal frequency and contrast of the stimulus). Hence, masking of the central area (approximately the macular area) can help to make the motion-specific N2 peak dominant in subjects who are rather "pattern-sensitive" (Kuba & Kubová, 1992—Fig. 4).

Motion-onset VEPs display similar differences relative to the pattern-reversal VEPs when horizontal half fields of the stimulus field are used (shorter latencies and larger amplitudes for the lower half field stimulation—Kremláček et al., 2004a). However, they also display parameter changes related to right and left hemifield stimuli (motion-onset VEPs for the left stimulus hemifield exhibited larger amplitudes and shorter latencies in general) which are not fully understood (Kremláček et al., 2004a).

5. Recommended stimulus parameters for motion-onset VEPs

(According to the cited literature data and our own experience)

- *Stimulus field*—A large (at least 20°) stimulus field is preferable since a motion in the more peripheral parts of the visual field produces a larger (dominant) motion specific N2 peak as compared to stimuli that are restricted to the central part which may cause a predominance of the pattern related P1 peak (see Kuba & Kubová, 1992). A 21" monitor with a high (100 Hz) frame frequency provides a sufficient stimulus filed size (observing distance of ca. 0.6 m) and acceptable quality of motion (a lower frame frequency may result in the "apparent" motion causing a "stroboscopic effect").
- *Mean luminance*—Luminance in the range of about 3–20 cd/m^2 produces a large N2 peak amplitude and short N2 peak latencies with low variability (Dodt & Kuba, 1995; Kubová et al., 2004). (More detailed studies on luminance effect are needed.)
- *Contrast*—Low Michelson contrast of about 10% with sinusoidal modulation (Kremláček et al., 2004b) is recommended for a dominance of the motion-specific N2 peak (Bach & Ullrich, 1997). (While in a lower contrast amplitude size is maintained, prolonged latencies have increased variability—Kubová et al., 1995a).
- *Moving pattern characteristic*—Either randomly expanding/contracting concentric rings with decreasing spatial frequency (about 1–0.2 c/deg) and increasing velocity of the radial motion towards the periphery (about 5–25 deg/s—to keep the temporal frequency of about 5 Hz constant over the whole stimulus field—Kremláček et al., 2004b) or random-dot kinematograms (see e.g., Maurer & Bach, 2003) seem to be the best structures for

evoking the N2 peak (predominant activation of the magnocellular pathway).
- *Motion duration*—A duration of 100–200 ms motion and inter-stimulus interval (stationary pattern presentation) of about 1000 ms ("duty cycle" $\leqslant 20\%$—according to Bach & Ullrich, 1994) are recommended to prevent adaptation to motion (reduction of the N2 peak).

(Demonstration of some stimuli for the motion-onset VEPs and their downloading is possible at http://www.lfhk.cuni.cz/elf.)

6. Recording conditions

In motion-onset VEP recording it is necessary to be aware that the distribution over the scalp is quite different compared to the pattern-reversal VEPs generated by the primary visual area (Di Russo et al., 2005), and also that inter-subject variability exists (Bundo et al., 2000). Because they represent the activity of the extra-striate and associated visual cortical areas (Schellart et al., 2004; Henning et al., 2005), the necessary set of recording electrodes must include the lateral temporo-occipital and parietal areas in addition to Oz. From the above cited topographical studies it is evident that in the majority of subjects temporo-occipital regions 5 cm to the left and right from Oz position represent optimal electrode placement (in the middle between O_1, O_3 and O_2, O_4 derivations). With respect to the "upper" parietal localisation of responses in the case of more complex variants of motion stimuli (mainly radial motions—see above—types of motion) or in peripheral stimulation, the use of parietal or central electrodes is also recommended (Langrová et al., 2006).

Motion-onset related negativity is widely distributed over the scalp and therefore, the suggested placement of the reference electrode differs from the recommended ISCEV (International Society for Clinical Electrophysiology of Vision) standard (Odom et al., 2004). Instead of an Fz reference (where the existing motion-onset related negativity in some subjects can significantly reduce the recorded bipolar signals), earlobe references (either single or linked earlobes) are preferable, since they do not display any significant signal during motion stimulation (Kuba, Kubová, & Kremláček, 1996; Kuba, 2006).

Compared to the other variants of VEPs, there are many more stimulus and recording factors that influence the resulting parameters in motion-onset VEPs. Each laboratory must form its own norms for all stimulus conditions. Because of the inter-subject variability of maximal motion-onset VEP location and individual latency differences among derivations, the selection of VEP parameters from the chosen "optimal" derivation (with shortest latencies and/or largest amplitudes) in each subject is preferable to reduce their variability (Langrová et al., 2006). Table 2 summarises a comparison of motion-onset VEP parameters (group mean values from 45 subjects in the age span 19–60 years) from Oz, Ol, Or (5 cm left and right from Oz), Pz and the selected "optimal" derivation. In addition to larger amplitudes and shorter latencies, the "optimal" derivation displays a significant reduction of variability. Similar selection of the lateral occipital derivation (based only on an amplitude criterion) has also been performed by the research group of M. Bach (see e.g., Hoffmann et al., 1999).

Table 2
Latencies and amplitudes (median and 25–75 percentiles) of the motion-onset VEPs in a group of adult subjects—comparison of values in different derivations

Age 18–60 years ($n = 48$)	Motion-onset VEPs—radial motion	
	L (ms)	A (μV)
Derivation		
Oz	172 (164–180)	9.1 (6.7–12.0)
Ol	172 (164–180)	9.2 (7.5–12.2)
Or	168 (162–178)	9.8 (6.9–13.4)
Pz	166 (158–176)	10.9 (8.0–13.4)
Optimal	164 (156–172)	12.4 (9.5–15.8)

The shortening of latencies towards the parietal (associate visual) cortex is not present in all subjects. However, it is quite distinct in some subjects (compared to occipito-temporal derivations the group mean latency in Pz is about 6 ms shorter; $p < 0.001$—Langrová et al., 2006). This corresponds to the hypothesised parallel arrangement of visual motion processing which allows fast input into the extrastriate and visual associate areas with by-passing of V1 (ffytche, Guy, & Zeki, 1995). The principle of a "network function of the brain areas responsive to visual motion" (Ahlfors et al., 1999) might explain different temporal patterns of motion information processing.

7. Age-dependence of motion-onset VEPs parameters

With respect to significant age-dependent changes in the function of the motion processing system (see age dependent changes in motion-onset VEPs latencies in Fig. 3), it is necessary to use age related norms for motion-onset VEPs. Due to their very slow maturation, besides the latency shortening up to the age of about 18 years (Langrová et al., 2006), age related changes in the shape of motion-onset VEPs (including a more pronounced first positive peak and a significant decrease of amplitudes in low contrast and peripheral stimuli) can also complicate their evaluation in childhood. The longer developmental time course of the motion processing system (reported also from psychophysical studies—e.g., by Fischer & Hartnegg, 2002) might be related to its hypothesised greater plasticity as compared to the parvo-cellular system (ventral stream) (Mitchell & Neville, 2004; Coch, Skendzel, Grossi, & Seville, 2005).

In adulthood the motion-onset VEPs undergo accelerated latency prolongation as compared to pattern-reversal VEPs and they seem to be much more sensitive to ageing factors (Langrová et al., 2006—in agreement with psychophysical tests—e.g., Gilmore, Wenk, Naylor, & Stuve, 1992; Fischer & Hartnegg, 2002). The systematic prolongation of motion-onset VEP latencies, which begins in early adulthood, might be a good indicator of

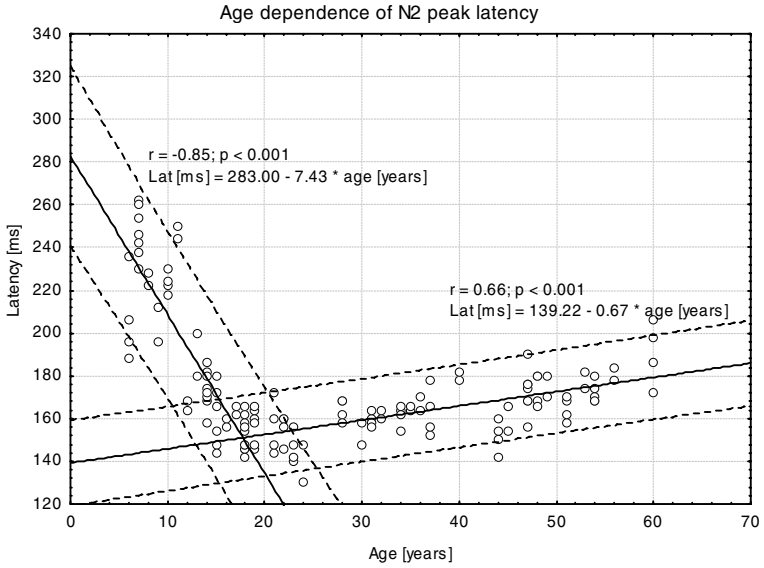

Fig. 3. Dependence of motion-onset VEP (expansion/contraction) latency on the age of subjects (each circle represents one examined eye). The two linear regressions used here to describe the age dependence provide better results compared to other regression fits (e.g., use of continuous polynomial functions of the second and third order). For this analysis, the entire group was split into two intervals—from 6 to 18 and from 19 to 60 years, since the highest correlations were in the resulting subgroups. Correlation coefficients, their significance and regression curve formulas are specified. Solid line—regression curve, dashed lines—95% borders of predicted interval of normal values. (Although the two linear regression curves are depicted in the whole calculated range of ages, their validity (for both younger and older subgroup) is limited by the intersection point at an age of about 18 years.) For more details see Langrová et al. (2006).

individual biological ageing. The large differences in N2 peak latencies (from 160 to 200 ms) reported in the literature may not be completely attributable to different parameters of motion stimuli, but also to differences in the age of subjects.

8. Motion-onset VEPs in neuro-ophthalmological diseases

The above specified characteristics of motion-onset VEPs indicate that they probably represent a different neuronal activity compared to the standard flash or pattern-related VEPs. Although there is some "cross-talk", mainly at the cortical level of the visual system (e.g., Young, 1992), that leads to a mixture of responses mediated by parallel subsystems and despite the new models of visual perception which indicate that the ventral and dorsal (form and motion) pathways co-operate in the recognition of motion stimuli (Giese & Poggio, 2003; Burr & Ross, 2004), motion-onset VEPs seem to be more specific for testing predominant or early magnocellular system/dorsal stream involvement (before manifestations of the parvocellular system/ventral stream dysfunction) than the other standard VEPs. We have tried to provide an overview of existing pilot studies on particular diagnostic applications.

The terminology used to describe the visual motion processing system disorders should still be addressed. As claimed by Skottun and Skoyles (2004), it is not adequate to interpret prolonged motion-related VEPs exclusively as a "magnocellular system deficit" since it is not possible to directly differentiate the level (subcortical, primary cortical, association cortex— "dorsal stream") of motion processing system involvement from these studies.

8.1. Criteria for VEP pathology assessment

The classification of pathological VEPs (in studies from our lab) indicates that latencies that exceed the mean + 2.5 standard deviations of the control group (with age corrected values for the motion-onset VEPs) are considered pathological. This represents ca. 99% confidence of the correct pathology detection with a lower probability of false positive findings as compared to the common use of the 95% confidence interval (mean + 2.0 SD). For the inter-ocular latency differences, 10 ms in pattern-reversal VEPs and 14 ms in motion-onset VEPs (represents again ca. 99% confidence interval) were recognised as significant (Kubová & Kuba, 1992). In VEP amplitudes, evaluation of their systematic interocular differences exceeding ca. 3 μV (in repeated VEP recordings) seems to be significant for the detection of pathology.

Since the specificity of any pathological VEP findings is rather low (when a particular disease and not just a general malfunction of the visual pathway or the CNS is to be proven), their interpretation is only possible if taken together with the case-history and parallel diseases that may influence the VEP results.

8.2. Optic neuritis and multiple sclerosis

It has been reported that motion-onset VEP increases the sensitivity of the VEP examination in Multiple Sclerosis

by about 26% (Kubová & Kuba, 1992, 1995). It seems possible to differentiate electro-physiologically "pure" acute optic neuritis, and changes in the optic nerve function due to the demyelination process in Multiple Sclerosis (Kubová & Kuba, 1995). Whilst the common form of optic neuritis mainly involves the maculo-papillary bundle of the optic nerve (causing a reduction of visual acuity and P100 peak prolongation in the pattern-reversal VEP), the demyelination process sometimes affects the magnocellular system earlier (e.g., Vleugels et al., 2001). In demyelination processes the motion-onset VEPs were prolonged in 68% of patients (either selectively or together with the pattern-reversal VEPs) but their changes were quite rare (28%) in "pure" optic neuritis (Kubová & Kuba, 1995). Thus, the selective motion-onset VEPs delay might indicate a higher probability of demyelination than an optic neuritis process.

In the later study, which compared results of pattern-reversal VEPs and motion-onset VEPs with MRI findings (Szanyi, Kuba, Kremláček, Taláb, & Žižka, 2003), the classification of examined patients was more precise since it was possible to differentiate suspected demyelination due to Neuroborreliosis (see below). Meta-analysis of cases with definite Multiple Sclerosis ($n = 39$) indicated "only" 64% sensitivity of VEPs (compared to 79% in MRI)—in 23 patients the pattern-reversal VEPs were delayed and in 24 cases the motion-onset VEPs latencies were prolonged. However, 10% of pathological findings leading to the diagnosis of Multiple Sclerosis were exclusively observed in the motion-onset VEPs, which might be interpreted as mild selective involvement of the magnocellular system which is invisible by MRI examination. In 5 out of 67 cases with "possible" (not proven) Multiple Sclerosis, pathological motion-onset VEPs were caused by a different pathology (Neuroborreliosis or Glaucoma).

To our knowledge there is only one study from outside of our laboratory that evaluated motion-onset VEPs in Multiple Sclerosis. Herbst, Ketabi, Thier, and Dichgans (1997) compared sensitivity of the standard pattern-reversal VEPs, motion-onset VEPs and a battery of psychophysical tests in 30 patients with "definite" Multiple Sclerosis. They evaluated whether "the diagnostic yield is large enough to justify the burden of additional tests put on our patients". It was reported that the pattern-reversal VEPs were pathological in 68.9% of patients and the motion-onset displayed pathology (delayed latencies of the N2 peak) only in 16.6% of patients. In this study the "Motion defined letter test" (MDL-test—Regan & Hong, 1990) was evaluated as the second most sensitive test (beyond the pattern-reversal VEPs)—66.6% of patients displayed pathological measures, which confirmed previous findings that the recognition of motion-defined letters is deficient in Multiple Sclerosis (Giaschi, Regan, Kothe, Hong, & Sharpe, 1992). Herbst and co-workers concluded that motion-onset VEPs reflect activity only in a restricted part of the visual cortex and that "the lack of dependence on the structural integrity of an extensive cortical network might render the motion-onset VEP far less sensitive than the MDL-test (examining "the functional interplay of several areas in very different parts of visual cortex").

In our opinion, the low sensitivity of motion-onset VEPs reported by Herbst et al. (1997) might be explained by quite high variability of their latencies in the control group (standard deviation of 16.9 ms = variation coefficient of 9.7%—in our control group it is only about 5.5%) leading to the very high limit of the norm (217.3 ms). (The mean latency difference between the group of controls and subjects was higher in motion-onset VEPs compared to the pattern-reversal VEPs.) This problem might be caused by two factors:

- Creation of the norm does not take into account the significant age dependence of motion-onset VEP latencies (see above). In our normative study (Langrová et al., 2006), the latency difference between 21 and 60-year-old subjects was 25 ms.
- Latency norm was calculated from the Pz derivation irrespective of the inter-individual topographical differences in latencies, which requires identification of the optimal lead in each subject (with the shortest latencies of the motion-onset VEPs—see above specified methods and Langrová et al., 2006).

Although the majority of electrophysiological, MRI and psychophysical studies on Multiple Sclerosis report prevailing parvocellular pathway involvement by the demyelination process (e.g., Caruana et al., 2000), there are also findings that indicate a more rapid impairment of the magnocellular pathway which is responsible for visuoperceptual disorders (Vleugels et al., 2001). Since there is a large prevalence of visual pathway involvement in patients affected by clinically definite Multiple Sclerosis who lack both a history of optic neuritis and visual symptoms, the performance of multiple tests for its detection is recommended (e.g., Sisto et al., 2005). Although all evoked response modifications observed in Multiple Sclerosis are not disease-specific (Comi et al., 1999), additional investigation of motion-onset VEP (in addition to the standard pattern-reversal VEP) could increase the sensitivity of the electrophysiological diagnostic analyses of Multiple Sclerosis and might even help in the differential diagnosis of sudden vision loss due to optic nerve involvement.

8.3. Neuroborreliosis

Neuroborreliosis represents a special kind of CNS involvement which can result in deterioration of function by a demyelination-like process that is hardly detectable with standard imaging techniques, including MRI. Although it rarely leads to subjective visual disorders, prolongation of VEP latencies was observed in 40% of 81

patients with proven Neuroborreliosis (diagnosis based on cerebro-spinal fluid findings) (Kubová et al., 2006). This was observed more frequently in motion-onset VEPs (27%) than in pattern-reversal VEPs (6%). In 7% of patients with Neuroborreliosis, both types of VEPs were prolonged. Moreover, abnormal motion-onset VEP latency is sometimes the only objective finding that helps to confirm this diagnosis in subjects with a variety of non-specific subjective problems. This might be interpreted as meaning that motion processing system can be the only or the earliest system involved in Neuroborreliosis (Kubová et al., 2006). Not all patients with proven Neuroborreliosis and visual problems displayed abnormal VEPs (only 56% of abnormal VEPs were found in this group) and, on the contrary, not all patients with normal vision had normal VEPs (abnormal VEPs were found in 31%). A similar discrepancy between subjective ophthalmological symptoms and VEP findings is quite common in Multiple Sclerosis and in the recovery phase of acute Optic neuritis (Persson & Wanger, 1984; Frederiksen, Petrera, Larsson, Stigsby, & Olesen, 1996). This indicates that there is not a full correlation between the functional state of the visual pathway (as verified by VEPs) and subjective visual perception of patients.

8.4. Glaucoma

Testing of early changes in visual function in Glaucoma includes a perimeter examination. The standard perimetry is subjective and mfVEPs are useful for objective perimetry in the central about 30° and they are not likely to aid an assessment of more peripheral visual function (see e.g., Hood & Greenstein, 2003). Since motion-onset VEPs can be detected in more peripheral parts of the visual field (up to about 50° of eccentricity), their contribution to the early diagnosis of this disease was tested (Kubová et al., 1996b; Korth et al., 2000).

Despite recently published data that describe non-selective neural abnormalities in early Glaucoma (see McKendrick, Badcock, & Morgan, 2004) and preferential loss of larger ganglion cells irrespective of their magno- or parvocellular classification (Osborne et al., 1999), the cited electrophysiological reports (Kubová et al., 1996b; Korth et al., 2000) support the former hypothesis that earlier/preferential magnocellular system affections exist in Glaucoma or that magnocellular affections are more readily detectable.. They have shown a higher sensitivity of motion-onset VEPs in Glaucoma detection, compared to pattern-reversal VEPs. It is important to note that motion-onset VEPs allow for objective motion perception testing at eccentricities of more than 15°, as is recommended (Shabana, Cornilleau Peres, Carkeet, & Chew, 2003). Quite early magnocellular system involvement has been recently confirmed by various psychophysical tests, mainly by "frequency doubling illusion" (e.g., Maddess, Severt, & Stange, 2001; Jy-Haw Yu et al., 2003).

8.5. Amblyopia

It has been shown that amblyopia mainly represents parvocellular and/or a primary visual cortex deficit (e.g., Hess & Anderson, 1993). This seems to be supported by motion-onset VEP findings (Kubová, Kuba, Juran, & Blakemore, 1996a) which also provide evidence of sparing the magnocellular system in this visual disorder. Thus, motion-onset VEP represents a tool for objective functional testing of amblyopic eyes during other intermittent pathological processes.

8.6. Dyslexia

With respect to existing hypotheses that magnocellular system/dorsal stream deficiency exists in some dyslexic subjects (Lovegrove, 1993), we examined whether this could be verified by examination of motion-onset VEPs. It was shown that about 70% of 8- to 10-year-old dyslexic children exhibit significantly prolonged latency of motion-onset VEPs (compared to an age matched group of normal readers) Thus, this can be considered as an objective marker of the reading disability (Kubová et al., 1995b). No effect of dyslexia was visible in the pattern-reversal VEPs. After 4 years, 10 subjects of the same group of dyslexic children were examined again (at age of 14 years). It was found that despite significant shortening of their *motion-onset* VEP latencies, they stayed within pathological values, which corresponded to persistent abnormal reading quotients (ratio between expected (age related) and correctly achieved read words) (Kuba, Szanyi, Gayer, Kremláček, & Kubová, 2001). These results might indicate rather late maturation of temporal processing within the magnocellular pathway (dorsal stream) in dyslexic children.

Although there is controversy about the hypothesised magnocellular deficit in dyslexia in the later years (partially caused by the existence of various types of dyslexia—Borsting et al., 1996), recent electrophysiological findings are consistent with this theory (e.g., Scheuerpflug et al., 2004). However, the majority of these studies rely on the suspected alternative activation of magno- and parvo-system via manipulation with either contrast or spatial frequency of the pattern-reversal stimuli (e.g., Romani et al., 2001). Also, recent psychophysical studies indicated differences in the temporal processing ability between children with dyslexia and children with good reading skills (Edwards et al., 2004). Nevertheless, the latency prolongation of motion-onset VEPs in dyslexia need not be caused by a magnocellular deficit, higher order dysfunctions should also be considered (Skottun & Skoyles, 2004).

8.7. Congenital nyctalopia

Objective functional verification of congenital nyctalopia is usually done by electro-retino-graphy. Additionally there have been some attempts to test visual function in low luminance with pattern-reversal VEP (Benedek, Benedek, Keri, Letoha, & Janáky, 2003). Also, motion-onset VEP has been

used for these purposes since pattern-reversal VEPs are recordable only in mesopic (P100 detectable from about 0.1 cd/m^2) and not in scotopic conditions. Motion-specific N2 was detectable from about 0.003 cd/m^2 in normal subjects. It was shown that there are differences in minimum luminance (in scotopic conditions) requirements for acquisition of reliable motion-onset VEPs in patients with Congenital Nyctalopia (N2 was detectable from about 0.06 cd/m^2—20 times higher luminance compared to normal subjects) (Kubová et al., 2004).

8.8. Encephalopathies

Because motion-onset VEPs are mainly generated in the extrastriate and associate (parietal) visual areas, they might be more sensitive for the detection of various encephalopathies that influence higher order cortical areas (associate sensory and cognitive) than the primary sensory brain cortex. The sensitivity of motion-onset VEP has been tested in hepatic (porto-systemic—after TIPS—artificial porto-systemic shunt) encephalopathy (Kuba, Kremláček et al., 1996). Compared to normal pattern-reversal VEP findings in 93% of patients with suspected encephalopathy (P100 latency of 110.2 ± 5.6 ms in normal age matched subjects versus 112.5 ± 7.1 ms in patients—non-significant difference), motion-onset VEP latencies were significantly prolonged (N2 latency of 160.3 ± 8.8 ms in controls versus 180.7 ± 23.0 ms in patients; $p < 0.001$—pathological latency values were in 38% of patients), and correlated better with the clinical state of patients (classified according to biochemical markers of hepatic failure in plasma) and also with the decreasing dominant frequency of the EEG ($r = -0.55$; $p < 0.01$).

For further studies attempting to detect subtle (sub-clinical) changes in CNS functions via VEP examination, it is important to verify the possibility that VEP results could be influenced by glycemia variations (which cannot be excluded in patients that are subjects of VEP examination). A study of physiological changes of glycemia (after 24 h of fasting or after exertion) did not demonstrate any significant changes in the latencies of pattern-reversal, motion-onset or cognitive VEPs. However, an increased amplitude of motion-onset VEPs (radial motion) could be recognised as an indicator of their higher sensitivity to a moderate decrease of glycemia (from 5.3 to 3.9 mmol/l in average) leading to increased "excitability" of the CNS (Kubová, Chlubnová, Szanyi, Kuba, & Kremláček, 2005).

8.9. Verification of hypothesised compensatory cross-modality processes in deaf subjects

Another attempt to quantify changes (improvement) in the magnocellular pathway and related cortical area functions was performed in deaf subjects in whom some compensatory cross-modality processes were recognised (leading to increased activity of the visual system), in particular of the magnocellular subsystem, and helping to detect events (motion) in the periphery of the visual field (ERP study by Armstrong, Neville, Hillyard, & Mitchell, 2002). However, our study did not confirm the hypothesis of suspected stronger magnocellular visual functions (Chlubnová, Kremláček, Kubová, & Kuba, 2005). On the other hand, normal findings of motion-onset VEPs parameters indicate that deaf subjects may not exhibit more general involvement of the CNS as is sometimes suspected.

9. Conclusions

The proportion of motion-onset and pattern-reversal VEP pathological findings (in parallel pattern-reversal and motion-onset VEPs examinations) in our sample of patients ($n = 500$) with the above reported neuro-ophthalmological diagnoses:

- Only pattern-reversal VEPs pathology 35%
- Only motion-onset VEPs pathology 28%
- Parallel pattern-reversal and motion-onset VEPs pathology 37%

The following comparison of the sensitivity of pattern-reversal VEPs (PREPs) and motion-onset VEPs (M-VEPs) in particular diagnoses is based upon the presented clinical pilot studies:

Diagnosis	Study	*n*	PRVEPs (%)	M-VEPs (%)
Optic neuritis (confirmed)	Kubová and Kuba (1995)	27 patients	100	29
Multiple sclerosis	Kubová and Kuba (1995)			
Definite		15 patients	60	73
Possible		172 patients	35	52
Multiple sclerosis	Szanyi et al. (2003)			
Definite		39 patients	59	44
Glaucoma (confirmed)	Kubová et al. (1996b)	40 eyes	33	73
Glaucoma (conf. + susp.)	Korth et al. (2000)	34 patients	—	77
Dyslexia (confirmed)	Kubová et al. (1995b)	20 patients	0	70
Amblyopia (confirmed)	Kubová et al. (1996a)	37 patients	100	0
Hepatic encephalopathy	Kuba et al. (1996)			
Suspected		69 patients	7	38
Neuroborreliosis (conf.)	Kubová et al. (2006)	81 patients	13	34

The cited reports of diagnostic applications of motion-onset VEPs provide quite promising results; however, these findings should be verified by other laboratories. Moreover, as was mentioned above, it is necessary to gather information concerning the specificity of motion-onset VEPs. Although the specificity of any kind of VEPs is quite low, their contribution to differential diagnostics can be significant if their results are related to the medical anamnesis of the patient. The combination of several variants of VEPs could help to increase their sensitivity and their significance (specificity) to pathological findings. Such an extension of VEP examination need not prolong the total duration or significantly increase the expense of diagnosis if the appropriate stimuli, recordings and evaluation are used.

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