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RESEARCH ARTICLE

Paired-pulse behavior of visually evoked potentials recorded in human visual cortex using patterned paired-pulse stimulation

Oliver Höffken · Torsten Grehl · Hubert R. Dinse · Martin Tegenthoff · Michael Bach

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Abstract Paired-pulse stimulation techniques are used as common tools to investigate cortical excitability and cortical plastic changes. Similar to investigations in the somatosensory and motor system here we applied a new paired-pulse paradigm to study the paired-pulse behavior of visually evoked potentials (VEPs) in 25 healthy subjects. VEPs were recorded and the responses to the first and the second P100 peak were analyzed at different SOAs [stimulus onset asynchrony (SOA) = interstimulus interval (ISI) + pulse duration (13 ms)]. Two measures describe the paired pulse interaction: the "amplitude ratio", the ratio of the second to the first amplitude, and the "latency shift", the difference of the inter-peak interval between the P100 peaks and the respective SOA. To separate alterations in the amplitude of the second VEP response due to changes in paired-pulse inhibition from those originating from superposition of the two waveforms, particularly at short SOAs, we created a waveform template from recordings made at SOAs of 1 s, where interaction can be assumed to be negligible. Superposed traces of VEP recordings were then created by adding two templates at delays corresponding to the SOAs used. The original recordings were then digitally subtracted from the traces obtained by superposition. Analysis of the subtracted traces revealed evidence that at short SOAs the second VEP response is substantially suppressed, a finding comparable to the paired-pulse inhibition described for motor and somatosensory cortex following paired-pulse stimulation. However, paired-pulse inhibition seen in V1 varied considerably from subject to subject, both in respect to amplitude, and to time of maximal inhibition. We found paired-pulse inhibition ranging from 12 to 76% (mean 34%) at SOAs between 80 (shortest discriminable SOA) and 320 ms (mean 128 ms). At intermediate SOAs between 80 and 720 ms (mean 215 ms) the amplitude ratios were between 94 and 145% (mean 116%) indicative of slight paired-pulse facilitation. Comparable to recovery studies by means of paired-pulse median nerve stimulation in somatosensory cortex, at shorter SOAs we found a delayed second VEP response. Combined together, our findings suggest that VEPs are characterized by significant paired-pulse inhibition at short SOAs, a phenomenon reminiscent of findings reported in other modalities. Possible mechanisms and pharmacological properties of the described paired-pulse behavior in visual cortex remain to be explored.

Keywords Paired-pulse · Excitability · Plasticity · Visual evoked potentials

O. Höffken · T. Grehl · M. Tegenthoff
Department of Neurology, Ruhr-University Bochum, BG-Kliniken Bergmannsheil, Bochum, Germany

H. R. Dinse
Neural Plasticity Lab,
Institute for Neuroinformatics,
Department of Theoretical Biology,
Ruhr-University Bochum, Bochum, Germany

M. Bach (✉)
Univ.-Augenklinik Freiburg, Killianstr. 5,
79106 Freiburg, Germany
e-mail: michael.bach@uni-freiburg.de

Introduction

Paired-pulse techniques are used as common tools to investigate cortical excitability and cortical plasticity in the motor and somatosensory systems. In the human motor cortex paired-pulse transcranial magnetic stimulation (TMS) was used to demonstrate intracortical inhibition and facilitation (Kujirai et al. 1993; Ziemann et al. 1996): in healthy

subjects, a motor-evoked potential (MEP) was inhibited by a conditioning subthreshold stimulus at shorter interstimulus intervals (ISI) of 1–5 ms, but facilitated at longer ISIs of 8–15 ms. Consequently, activation of separate inhibitory and excitatory interneuron populations within motor cortex at different ISIs was postulated. This paired-pulse TMS protocol was subsequently used in healthy subjects performing different tasks (Liepert et al. 1998) as well as in patients with various neurological deficits, e.g., post-stroke or dystonia, to study motor intracortical circuits (Cohen et al. 1998; Liepert et al. 2000; Ziemann et al. 1998). Paired-pulse studies of the somatosensory system, using paired-pulse somatosensory-evoked potentials (SSEP), found different effects on peripheral and central recovery functions (Klostermann et al. 2000; Schwartz and Shagass 1964). More recently, a strong paired-pulse inhibition was described for SEPs recorded in human somatosensory cortex after electrical median nerve stimulation for ISIs of 30 ms, which was reduced for a period of up to 1 h after application of 5 Hz TMS (Ragert et al. 2004). Hoshiyama and Kakigi (2001, 2003) used somatosensory-evoked magnetic cortical fields (SEF) to investigate the recovery function in the primary somatosensory cortex. They found a progressive recovery of the first component of the SEF with increasing ISI. Furthermore latencies at ISIs less than 20 ms were significantly longer as compared to higher ISIs. In general, paired-pulse stimulation offers a unique possibility to evaluate cortical excitability and plastic changes through learning or pathologies of various forms.

Common non-invasive methods to examine cortical plasticity of the visual system are phosphene-inducing single- and paired-TMS (Boroojerdi et al. 2000; Gerwig et al. 2005; Kammer 1999; Sparing et al. 2005) as well as the analysis of single, visually evoked potentials (VEP) (Bohotin et al. 2002; Kong et al. 2000).

Because the detection and evaluation of TMS-induced phosphenes includes subjective factors and depends on the compliance of the respective subject, the aim of the present study was to introduce in healthy subjects a new paired-pulse stimulation protocol, which allows assessing with high reliability the paired-pulse behavior of visual cortex VEPs in order to obtain a marker of visual cortex excitability and to compare it to the paired-pulse behavior typically observed in somatosensory cortex.

Methods

Subjects

We tested 25 healthy subjects (16 female, mean age 29 years, range 20–40 years). All subjects had to be free from neurological diseases, especially free from headaches and seizure disorders. Before participation, they all gave their written informed consent. The study was approved by the Ethics Committee of the Ruhr-University of Bochum.

Stimulation

The stimuli were displayed on a CRT spanning 23° × 17° of visual angle at the observation distance of 80 cm. The CRT was driven at a frame rate of 75 Hz and a pixel resolution of 800 × 600. When presenting the pattern with a CRT screen, one is bound by its temporal properties, especially the frame rate. The shortest pattern pulse possible is presentation of one frame (Bach et al. 1997), which, here, with a 75-frame rate lasts 13.3 ms. Although the CRT image is sequentially scanned from top to bottom in about 10 ms, the pattern apparently appears and vanishes in full, probably because the frame rate is above the critical flicker fusion frequency.

Two types of stimuli were employed for (a) initial check-up and (b) the experimental paradigm.

(a) Initial check-up. A sequence of checkerboard patterns, phase-reversing two times per second, with either 0.25° or 1.0° check size, at 95% contrast and a luminance of 16 cd/m^2. This is the standard VEP stimulus suggested by the Visually Evoked Potentials standard (Odom et al. 2004).
(b) Paired-pulse paradigm. Checkerboard patterns with 36% contrast appeared for one frame (13.3 ms) from a homogenous gray background without a change in the mean luminance of 16 cd/m^2. After one such pulse the next pattern appeared after an ISI ranging from 40 ms (3 frames) to 1,000 ms in 22 steps [all multiples of the frame interval of 13.3 ms to avoid temporal aliasing (Bach et al. 1997)]. The respective SOAs are ISI plus the pulse duration time of 13.3 ms. Each SOA value was presented ten times, then the next value followed. After the last SOA value the entire cycle repeated for a total of 40 sweeps per SOA step (Fig. 1).

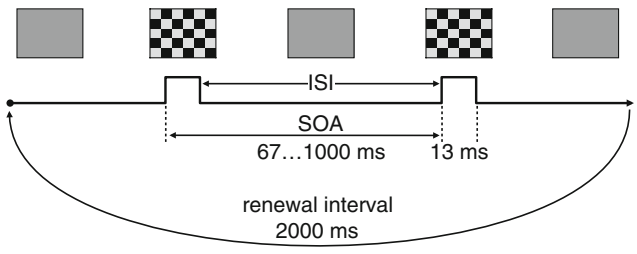

Fig. 1 The paired-pulse stimulation paradigm. Because of the finite stimulus pulse duration of 13.3 ms, one needs to discern between stimulus onset asynchrony (*SOA*) and interstimulus interval (*ISI*); SOA = ISI + pulse duration

The stimuli were produced by the EP2000 system (Bach 2000), which also recorded the EEG and averaged and displayed the responses on-line.

Recording

Gold-cup electrodes were attached to Oz and Cz (American Encephalographic Society 1994). Signals were amplified and filtered (1–100 Hz, first order band-pass) using conventional Neuropack 8 equipment (Nihan Kohden), and digitized to 16-bit resolution at 1 kHz sampling frequency in a Macintosh G4 computer running EP2000. Signals exceeding 140 μV were rejected as artifacts and not counted in the stimulation sequence.

During the recording sessions subjects sat in a comfortable chair in a shaded room at a distance of 80 cm from the stimulus screen. Two electrodes (Oz and Cz) were positioned according to the International 10–20 system. A reference electrode was placed at the Fpz-position. Subjects were instructed to relax and to focus binocularly on the dot in the center of the display. The testing paradigm consisted of two sessions with seven different SOAs each.

Analysis

Off-line, all traces were processed by a phase-neutral digital low-pass filter with a corner frequency of 40 Hz and trace features were interactively identified. To characterize the paired-pulse response, the amplitude difference of the C1 [positive peak about 100 ms after stimulus onset (Odom et al. 2004)] and the C2 (negative peak following C1) was measured. The same measures ($C1_2$, $C2_2$) were obtained for the second pulse, and could unequivocally be identified for all SOAs of 80 ms and higher (see Fig. 2). In 12 of 25 cases, the second cortical response partly merged into the first one at an SOA of 67 ms, so that the complete extent of the first amplitude could not clearly be determined. At SOAs of 53 ms all and at SOAs of 67 ms most of the responses fused into a complex. All those cases were excluded. To factor out interindividual amplitude variability, the amplitude ratio = $(C1_2 - C2_2)/(C1_1 - C2_1)$ was calculated.

VEP responses extend to several hundred milliseconds after the stimulus. Thus, in addition to any possible modulation of the second response by paired-pulse interaction, the response to the second pulse will "ride" on the ongoing response to the first pulse. To separate alterations in the amplitude of the second VEP response due to changes in paired-pulse inhibition from those originating from superposition the two waveforms, particularly at short SOAs, we created a waveform template from recordings made at SOAs of 1 s, where interaction was assumed to be negligible. Linear-model traces of VEP recordings were created by adding two templates at delays corresponding to the SOAs used (Fig. 3). The original recordings were then digitally subtracted from the linear-model traces. When the actual paired-pulse VEP response is subtracted from the waveform

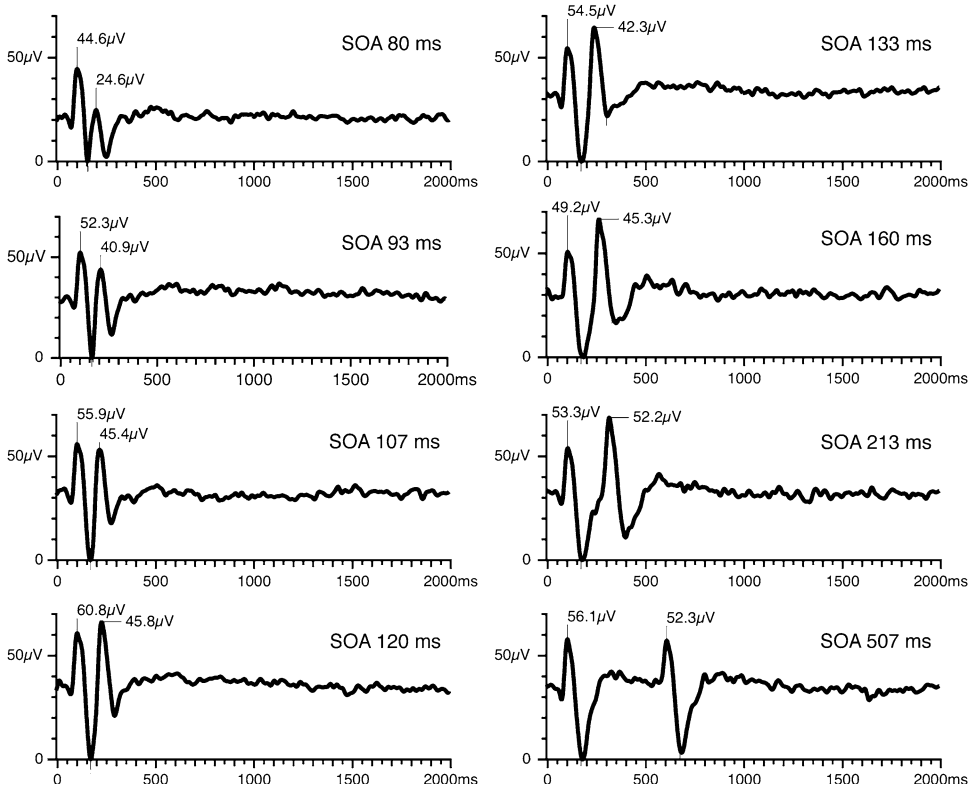

Fig. 2 Cortical responses to paired-pulse stimulation of one subject at different SOAs, positive is upwards. At large SOAs (*bottom right*), the first pulse does not markedly influence the second one. For brief SOAs (*top left*), the second pulse evokes a smaller response with a slightly higher latency

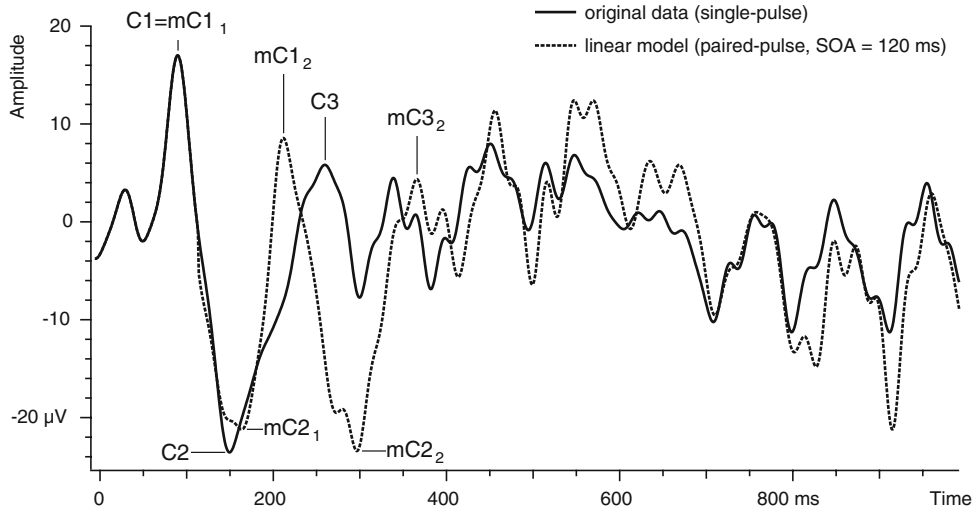

Fig. 3 Linear model of a paired-pulse response. *Continuous trace* pattern-onset VEP to a single pulse, C1/C2/C3 indicate the typical onset-VEP peaks. *Dashed trace* linear model of a paired-pulse response (SOA = 120 ms) by adding two single-pulse responses with a time shift of 120 ms, peaks are indicated with a leading "m". The modeled C1 from the second pulse ($mC1_2$) has a lower peak value than the $C1 = mC1_1$, due to the fact that it rides partially on the C2 trough. The figure demonstrates that to assess "true" paired-pulse interaction such linear superposition effects need to be factored out

template, the result of the subtraction of the actual paired-pulse VEP response from the linear-model template will be close to zero, if no paired-pulse interaction takes place, but will be significantly different from zero in case of the presence of a paired-pulse interaction.

Additionally, a so-called latency shift was calculated, which was defined as the difference between the latency of the first response peak (stimulus onset to the first response peak) and the latency of the second response peak (stimulus onset to the second response peak minus the respective SOA).

For quantitative statistics, the effect of SOA was tested with repeated-measures ANOVAs on the measures "amplitude ratio" and "latency shift" (after subtraction of the linear-model from the original recordings).

Results

The amplitude ratio of cortical responses to paired-pattern-pulse stimulation was calculated and analyzed with respect to SOA. Amplitude ratios at an SOA of 80 ms ranged from 0.3 to 0.88 with a mean of 0.65. With increasing interstimulus intervals, the amplitude ratios increased systematically in all subjects. On average, the amplitude-ratio peaked at 1.04 at an SOA of 160 ms. At longer SOAs, the amplitudes of the second peak initially declined with the lowest values found at 213 ms, and then increased again showing an asymptotical behavior (one example subject Fig. 4, grand mean Fig. 5).

At an SOA of 80 ms we found maximum inhibition for all subjects tested. At SOAs shorter than 80 ms the second cortical response partly merged into the first one in approximately half of the subjects, therefore analysis of amplitude behavior was restricted to SOAs $\geq$80 ms, while latency behavior could be reliably analyzed down to SOAs of 67 ms.

The influence of SOA was statistically tested on the difference between the recording and the linear model (thus on the difference between the continuous and the dashed lines of Figs. 4, 5 and 6). It was found to be significant both

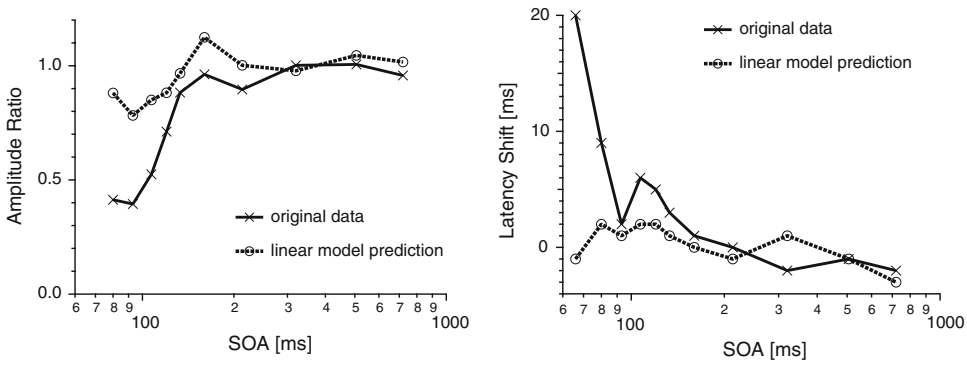

Fig. 4 *Left* amplitude ratio, *right* latency shift of one subject at different SOAs. Analysis based on the original recording is shown in *continuous lines*, *dashed lines* represents the linear model prediction, the difference revealing the "true" paired-pulse interaction

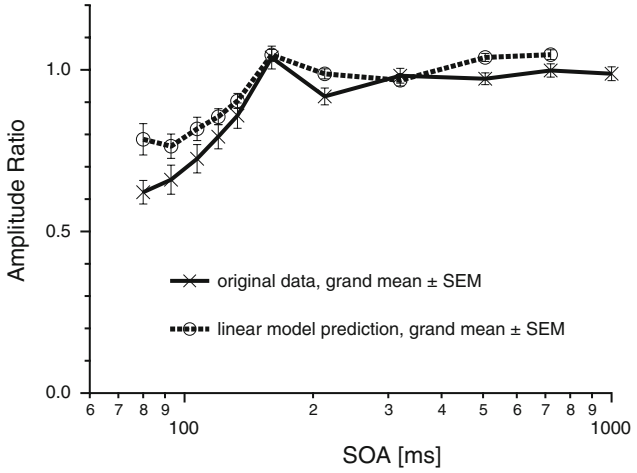

Fig. 5 Amplitude ratio of the original recordings and the linear model prediction, as a function of SOAs, grand mean ± SEM of all 25 subjects

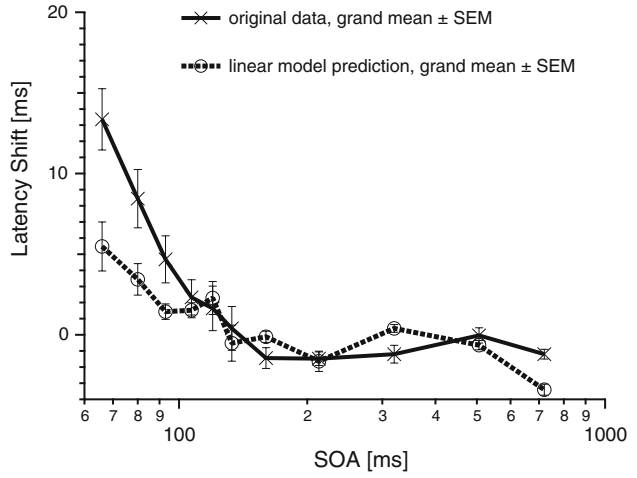

Fig. 6 Latency shift of the original recordings and the linear model prediction, as a function of SOA, grand mean ± SEM of all 25 subjects

for the amplitude ratio [$P = 0.015$, $F(9; 24) = 2.34$] and for the latency shift [$P < 0.0001$, $F(9; 24) = 4.138$], thus remaining significant after Bonferroni adjustment to correct for testing twice.

On average, the latency shift was maximal at short SOAs: At 67 ms it ranged from −1 to 31 ms (mean 13.4 ms), and then declined to a mean value of −1.48 ms at SOA = 213 ms (Fig. 6).

As illustrated in Fig. 5, the averaged superposed amplitude ratios show that paired-pulse inhibition is on average only 21% at an SOA of 80 ms. On the other hand, inspecting single subject data revealed the existence of substantial paired-pulse inhibition of more than 70%. We therefore analyzed the individual scatter of the paired-pulse inhibition and facilitation for both amplitude ratio and latency shift after subtraction of the original data from the superposed traces. Figure 7 illustrates the scatter of the maximal

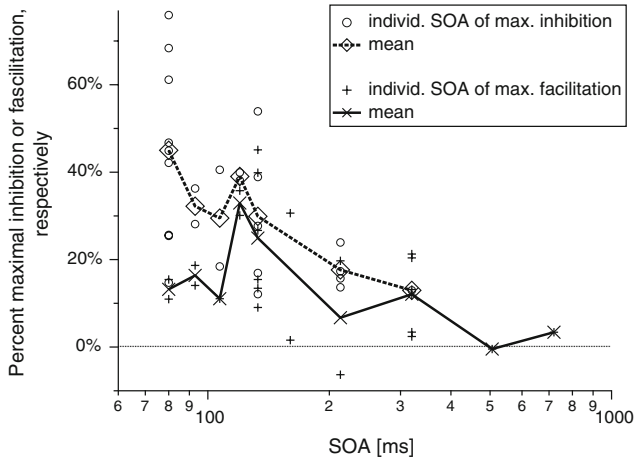

Fig. 7 Distribution of the SOA-dependent occurrence of maximal inhibition and facilitation of amplitude ratios of the difference between recordings and linear model prediction, for all 25 subjects

and minimal values for each subject as a function of the SOA at which they occurred (after subtracting the linear model). This analysis demonstrates that the paired-pulse inhibition shows a severe inter-individual variability, both in terms of the magnitude of inhibition and facilitation, and for the SOA at which it develops. For example, maximal paired-pulse inhibition can reach values of 70%, however, the range over which maximal inhibition can occur varies greatly between subjects (Fig. 7). We observed maximal inhibition at SOAs between 80 and 320 ms. On average the maximal inhibition was 34% (range 12–76% observed at SOAs between 80 and 320 ms, mean 128 ms). On average the maximal facilitation was 16% (range −6 to 45% at SOAs between 80 and 720 ms, mean 215 ms). For latency, the maximal relative acceleration was 13 ms (range 3–34 ms at SOAs between 66 and 320 ms, mean 167 ms) and the maximal relative deceleration was −6 ms (range −18 to 1 ms at SOAs between 66 and 320 ms, mean 193 ms). Interestingly, there was a relation between the amount of inhibition and the SOA value: as a rule, maximal inhibition was always found at shortest SOAs, while less inhibition occurred at longer SOA. For paired-pulse facilitation this relation was less clear. Conceivably, the huge interindividual scatter explains that averaging across individuals cancels out most of the effect magnitude.

Discussion

We provide a systematic study addressing paired-pulse behavior of the visual cortex evoked responses using paired-pattern-pulse VEP stimulation. VEPs after paired-pulse stimulation at different interstimulus intervals were recorded and the relations of the first to the second response

were expressed as amplitude ratio and latency shifts. The objective of the present study was to assess whether the pattern of cortical VEP responses to paired visual stimuli is verifiable, reproducible and comparable to the respective paired-pulse behavior reported for motor and somatosensory cortex. We analyzed the responses to the first and second C1/C2 component at different stimulus onset asynchronies (SOA) ranging from 67 to 1,000 ms.

We found paired-pulse inhibition of the second VEP amplitude with marked individual variations, maximal at short SOAs of about 80 ms (at shorter intervals the peaks merged). After that we observed a gradual recovery of the second amplitude reaching first amplitude height at >700 ms. Notably, there was a range of high excitability peaking from 93 to 720 ms. As to the timing of the second response component, response latencies displayed a complementary behavior, where latencies were longer than those of the first component for short SOAs (<120 ms) and shorter for long SOAs (>120 ms).

When contrasting the present results to the relevant literature, the term ISI (inter-stimulus duration) is found more often than SOA (stimulus onset asynchrony). In the case of very brief electric pulses, or auditory clicks, this is not an issue because then ISI equals SOA. When finite pulse lengths are applied (here a necessity of the CRT-based pattern stimulation), SOA becomes the more relevant term, but can be easily transformed via the formula: ISI = SOA − stimulus duration.

Interestingly, more than 40 years ago, Schwartz and Shagass (1964) obtained a recovery function of the visual evoked potential. They used flashes from a strobe stimulator and SOAs of ~5 to 160 ms. However, the VEP response to flash has a highly complex shape with an unwieldy high inter-individual variability. In addition, the shape of the VEP response changed during recovery. Schwartz and Shagass (1964) commented on this problem in their attempt to quantitatively analyze their results. We assume that these problems may be the reason why this line of research was not pursued. With similar rationale as in the present study, for their analysis, Schwartz and Shagass (1964) subtracted the single-pulse response from the one of the paired-pulse responses and described the amplitude dependence on SOA of the difference traces. In consequence, they saw a steep rise from 5 to 30 ms, because during this interval the first and second responses become separable. Subsequent to that, they found a more shallow, but monotonous rise of their ~100 ms component up to their highest SOA of 160 ms. We assume that this part corresponds to the rise of amplitude ratio described in our study (Fig. 5), which saturates above 160 ms.

In another early paired-pulse study of visually evoked potentials, Musselwhite and Jeffreys investigated cortical responses and subjective limits of temporal resolution by changing the luminance of the stimulus at different ISIs in three subjects (Musselwhite and Jeffreys 1983). Their visual patterns were generated by a tachistoscope with levels of luminance up to 500 cd/m^2. They found that the VEPs showed a complicated dependence on the timing and parameter settings of both stimuli.

The recovery behavior of the responses in human motor cortex was addressed by Kujirai et al. (1993), who reported that a single subthreshold transcranial magnetic stimulus over the motor cortex suppressed the responses to a later suprathreshold test stimulus. They provided evidence that the first stimulus induces the suppressive effect by activation of intracortical inhibitory neurons. Ziemann et al. (1996) used the same experimental set-up and found a suppressed test response at ISIs of 1–4 ms and a facilitation at ISIs of 6–20 ms. Separate mechanisms of inhibition and facilitation were discussed as synaptic effects, explained by convergence of different inputs or given by repetitive series of I-waves.

Ilic et al. (2002) investigated the effect of stimulus intensity on motor-evoked potentials (MEP) by using paired-pulse transcranial magnetic stimulation. They varied the intensity of the two stimuli at four ISIs from 1.5 to 5.0 ms. These authors found that all four ISIs resulted in inhibitory interaction, when the intensity of the conditioning stimulus was set below the intensity of the resting motor threshold (RMT) and the test stimulus was set above RMT. This is in accordance with other previous paired-pulse experiments (Kujirai et al. 1993).

In the visual system, Sparing et al. (2005) applied short-interval paired-pulses (TMS) to the occipital cortex using phosphenes as a measure of excitability. They examined the observed phosphenes perception in healthy subjects for different ISIs and variation of the first and second stimulus intensity. They described a facilitatory effect of TMS-induced phosphene perception at all measured ISIs from 2 up to 12 ms with a conditioning stimulus (CS) of 90–100% and a test stimulus of 100% of phosphene threshold. This facilitation rapidly declined when the intensity of CS was lowered. An inhibitory effect was not observed in any measured condition. They proposed a different mechanism underlying phosphene induction from those to other paired-pulse techniques, e.g., in the prefrontal and parietal cortices.

The aim of the present study was to introduce a stimulation protocol for the reliable assessment of paired-pulse behavior of VEPs that can be used in upcoming studies as a stable marker of visual excitability and its changes by learning or various pathologies. We, therefore, did not address here how the paired-pulse behavior is subject to further modulation through variation of intensity parameters, e.g., contrast.

For somatosensory-evoked potentials, in a paired-pulse stimulation study of the median nerve, Allison (1962)

found reduced amplitudes to the second pulse response at interstimulus intervals (ISI) of 5–20 ms. Schwartz and Shagass (1964) and Romani et al. (1995) reported similar findings of depressed second responses up to an ISI of 50 ms in somatosensory-evoked potentials. Additionally, Greenwood and Goff (1987) analyzed the development of the SEP response over time: early parts of the SEP (up to 100 ms) showed a complete recovery at ISIs below 100 ms, while late parts of the SEP required ISIs of up to several seconds to recover completely.

Many lines of evidence suggest that the anatomical structure and functional organization of primary sensory and primary motor cortical areas which subserve the input and output system differ substantially. VEP recordings represent the activation of neurons of a sensory area following presentation of a physiological stimulus that stimulates the corresponding receptors, while motor-evoked potentials (MEPs) are generated by an artificial transsynaptic stimulation of pyramidal tract neurons. Accordingly, any comparison of the physiological processes in an afferent somatosensory and an efferent motor system must be done with caution. To discuss similarities and dissimilarities of putative mechanisms of facilitation and inhibition involved in mediating paired-pulse in afferent systems, we compare data from visual cortex obtained here with data available from recordings of SEPs in somatosensory cortex.

In Fig. 8, the dependence of amplitude ratios on SOA is summarized to compare the basic timing properties of the paired-pulse behavior observed in the somatosensory system (Allison 1962) with that described here for the visual cortex. In contrast to the response behavior in the somatosensory cortex the stable C1/C2 component (response about 100 ms after stimulus) of the visually evoked potentials appears considerably later and shows a higher interindividual variance in magnitude and timing. One reason for this difference might be the fact that the visual pathway consists of more synapses and a more complex retinal preprocessing.

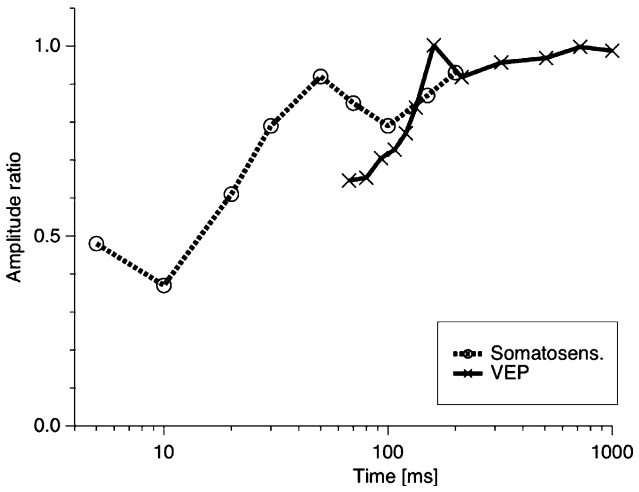

Fig. 8 Relative amplitudes of paired pulse studies in somatosensory (Allison 1962) and visual cortex (VEP, present paper). The course features (initial rise until a saturated region) appear similar across the two modalities assuming a multiplicative time scale expansion from the somatosensory to the visual modality

Kujirai et al. (1993) and Ziemann et al. (1996) proposed that the effect of inhibition at shorter ISIs is produced by activation of the intracortical GABAergic inhibitory system. In an experimental study on differences between I waves using paired pulse stimulation of the human motor cortex, Hanajima et al.'s (1998) findings supported the hypothesis of GABAergic influence.

In a paired-pulse study in human motor cortex, Ilic et al. (2002) reported that at lower ISIs (1.5 ms) the GABAA-receptor agonist diazepam increased intracortical inhibition and decreased intracortical facilitation on resting motor-evoked potentials. In the same condition, Diazepam lost its inhibitory effect during isometric contraction. The authors suggested that voluntary contraction is capable of modifying the GABA-A receptor of corticospinal neurons by reducing its sensitivity to regulation by benzodiazepines while its sensitivity to GABA is maintained. The effect of benzodiazepines on the paired-pulse behavior of visually or somatosensory-evoked potentials has to be investigated in further experiments.

Besides GABAergic mechanisms, response depression may be caused by several distinct processes. The term short-term plasticity has been used to describe changes of neural behavior resulting from prior activity (Zucker 1989; Zucker and Regehr 2002). Factors involved include presynaptic depletion of releasable vesicles, postsynaptic receptor desensitization or other presynaptic mechanism depressing vesicle release (Bellingham and Walmsley 1999). Hoshiyama and Kakigi (2003) investigated the role of depletion of synaptic transmitter during high-frequency stimulation of the median nerve. They recorded somatosensory-evoked cortical magnetic fields (SEF) using stimulations in trains at ISIs of 10, 20 and 30 ms. An attenuation of the components of the SEF was recognized after the second stimuli, but there was no significant attenuation with the third or later stimulations. From this observation they concluded that depletion was unlikely to be responsible for the attenuation of the SEF components during repetitive stimulations. They suggested that a transmission failure might occur only at an ISI of less than 10 ms (Stevens and Wang 1995).

While most studies on paired-pulse behavior focus on amplitude behavior, a few studies also took timing into account. For example, in previous studies in somatosensory cortex, the mean latencies, after which the second response occurred, were reported to be prolonged at shorter interstimulus intervals and to be lengthened at higher ISIs (Allison 1962). Schwartz and Shagass (1964) presented similar findings in a recovery study using a paired-pulse

technique. The cerebral latency recovery curves differed from the amplitude curves and were less variable. The second response latency could be prolonged when the second response amplitude were initially recovered and they usually reached the first response level during the period (20–40 ms) when the second response amplitudes were depressed. The authors assumed that latency and amplitude provide different measures of recovery functions for somatosensory cerebral responses.

We found a similar interdependence between amplitude ratio and latency shift. On average, both the amplitude ratio and the latency shift curve peaked in mean at SOAs from 160 to 213 ms, indicating a similar time course of depression and facilitation. At higher SOAs the curve of the amplitude ratio first declined and then asymptotically increased again showing a depression, while the curve of the latency shift remains facilitated below 1. This different behavior of amplitude and latencies in time may be due to the existence of different mechanisms mediating cortical inhibition or facilitation.

All-in-all, we conclude that the second response peaks after paired-pulse stimulation significantly depend on the SOA. However, to separate alterations in the amplitude of the second VEP response due to changes in paired-pulse inhibition from those originating from superposition the two waveforms, a linear model has to be subtracted from the original traces. Because the resulting effects show a huge inter-individual variability of maximal inhibition and facilitation at different SOAs, averaging across individual subjects cancels out most of the effect magnitude. Therefore, significant mean effects of SOA could only be observed at short SOAs. It should be noted that a similar degree of variability has been observed in studies of paired-pulse behavior in somatosensory system in both rats (David-Jurgens and Dinse 2007) and humans (Hoffken et al. 2007). Further studies are required to investigate the underlying nature of amplitude and latency behavior in terms of different inhibitory and excitatory systems, and the nature of the considerably large individual scatter. Besides the analysis of mechanisms, the reliable assessment of paired-pulse behavior of VEPs can be used as a tool to investigate changes of cortical excitability following cortical plastic changes in the visual system.

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