When two visual stimuli are presented successively, the first stimulus (cue) has a great influence on the visibility of or the reaction time (RT) to the second stimulus (target). It is known that the interval between the onset of the cue and the target, stimulus onset asynchrony (SOA), is important to determine the effect of paired stimulation on the RT to the target. The target that appears right at the same location as the cue at a short SOA is captured by the attention for the cue. Consequently, the RT to the target becomes shorter at the cued location than an un-cued location\textsuperscript{1-3}. In other words, the cue attracts attention to the cued location and results in a faster RT. However, this influence of the cue reverses at a long SOA and the RT to the target becomes shorter at an un-cued location than the cued location. This biphasic effect on the RT in response to the target occurs usually at a crossover point of around SOA 200-300 ms. The delay in the RT to the cued target at a long SOA is called inhibition of return (IOR) in psychological studies\textsuperscript{1,2}. In studies using a typical IOR paradigm\textsuperscript{1,2}, the IOR phenomenon has been explained as the automatic mechanism of visuo-spatial attention to facilitate the visual search of a novel area by inhibiting already scanned ones\textsuperscript{2,4,5}. Visual attention in daily life plays an important role in the selection of visual information among surroundings. Previous studies on visual attention have proposed at least two hypotheses. One is exogenous or involuntary stimulus-driven attention. For example, a red apple on a white table or fireworks in the night sky automatically
attracts attention. By contrast, endogenous or goal-directed attention represents the conscious cognitive function triggered by the observer’s intentions. For example searching for a red car in a parking lots needs the attentional load for the goal of searching. An attentional load of this type is hard to evaluate as a numerical quantity. Therefore, illuminating automatic processing is useful to comprehend the fundamental mechanism underlying cognitive functions, and IOR research should help us to understand how the mind operates. The IOR phenomenon is mostly studied using behavioral tasks such as button pressing or saccadic eye movement. However, since the perceptual and motor components of IOR seem to contaminate each other, it is difficult to clarify where this inhibitory mechanism is generated and to determine whether the areas responsible for the IOR phenomenon are related to perceptual function, motor function, or both. Moreover, attention to detect a target and to press the button operates based on a participant’s preparation to detect a target. Therefore it is hard to clarify the relation between attentive and pre-attentive processing.

The aim of this study was to clarify whether there are IOR phenomena in the sensory cortex and whether IOR reflects the cortical involuntary response. For this purpose, visual evoked magnetic fields (VEFs) were recorded during the performance of two different tasks with the same visual stimulus (Fig.1).
Results

The target in each condition in both experiments evoked a large deflection (1M) at around 180 ms post-onset. Fig. 2 shows the recorded and RMS (root mean square) waveforms calculated in the RL condition of a representative subject (subject 1) in Experiment 1. The equivalent current dipoles (ECDs) and isocontour maps in response to the target were similar in location and pattern within a subject (Fig.3).

The isocontour maps of 1M showed a one-dipole pattern on the scalp in the occipital area. The ECD responsible for 1M was estimated to lie in the visual area in all the subjects, mainly in the primary visual cortex (V1), but it was estimated to be in the parieto-occipital area, probably V6 area\textsuperscript{11}, in two subjects. Although we tried to add one or two more ECD(s) using a multi-dipole model, no new significant sources, which fulfilled our criteria (see experimental method), were found in any of the conditions.

Experiment 1

Fig. 4a shows the RMS waveform of a representative subject (subject 2) in Experiment 1. The mean peak latency and mean peak amplitude of the main VEF component (1M) in response to the target in the three conditions, LL, RL and L, are listed in Table 1. Results of ANOVAs showed a significant main effect ($F_{1,262, 12.625} = 6.2$, $p = 0.022$ by Greenhouse-Geisser’s modification) on the peak latency of 1M among the
three conditions (LL, RL and L). A post hoc test indicated that peak latency was significantly longer for LL than RL ($p<0.05$), but did not differ between L and the other two conditions. Regarding the peak amplitude of 1M, results of ANOVA showed a significant effect ($F_{2,20} = 4.0$, $p=0.035$) of condition. The post hoc test indicated that amplitude was significantly smaller for LL than for RL, but did not differ between L and the other two conditions. The RT was significantly different among the three conditions ($F_{2,20} = 80.6$, $p = 0.001$). The post hoc multiple comparisons indicated the RT to be significantly shorter for RL, and significantly longer for L than the other two conditions (Table 1).

**Experiment 2**

Fig. 4b shows the RMS waveform of a representative subject (subject 2) in Experiment 2. The mean peak latency and mean peak amplitude of 1M in response to the target are listed in Table 1. A one way repeated measures ANOVA showed a significant main effect ($F_{2,20} =3.7$, $P=0.042$) on the peak latency. The post hoc test indicated that the peak latency of 1M was significantly shorter for LL than RL, but did not differ between L and either RL or LL. The peak amplitude did not differ significantly among the three conditions ($p = 0.056$), although it tended to be smaller for LL than for the other two conditions.
Comparison between Experiment 1 and Experiment 2

Fig. 5 shows the grand-averaged RMS waveforms and the comparison of each condition between experiments. The peak latency for L did not differ between the experiments while the peak amplitude was significantly larger for Experiment 1 than Experiment 2 ($t_{10} = -4.1$, $p < 0.002$). Results of a two-way ANOVA (Experiment x Condition) showed that Condition ($F_{2, 20} = 9.6$, $p = 0.001$) significantly affected the peak latency but Experiment ($p = 0.54$) and interaction ($p = 0.62$) did not. The post hoc multiple comparison indicated that peak latency was significantly longer for LL than the other two conditions, and did not differ significantly between RL and L. Results of the two-way repeated measure ANOVA showed a significant main effect of Experiment ($F_{1, 10} = 31.0$, $p = 0$) and Condition ($F_{2, 20} = 5.0$, $p = 0.017$) on the peak amplitude. However, there was no significant effect of interaction between Experiment and Condition ($p = 0.97$). Post hoc tests indicated that the peak amplitude was significantly greater for Experiment 1 than Experiment 2 and significantly smaller in LL than RL. The peak amplitude for L did not differ from that for LL or RL (Fig. 4).

Discussion

The peak latency of the major deflection of VEFs (1M) for the target was longer at the cued location (LL) than un-cued location (RL) in both experiments. This delay was similar to the RT delay of IOR. The sensors
selected in the present study corresponded to the occipito-temporal area in each experiment. Therefore, our results suggested that the IOR phenomenon of RT reflects the delay in the sensory cortex at least in part. In addition, the present results indicated that the cortical IOR response is generated under involuntary conditions.

In Experiment 1 of a standard IOR paradigm, the longer latency of 1M at the visual area for LL than RL is the first evidence that the IOR phenomenon involves cortical sensory processing. On the other hand, that the RMS value was smaller for LL than the other two conditions, is consistent with previous findings in psychophysical studies in humans\textsuperscript{12-14} and primates\textsuperscript{7,15}. Although the RT was longer for the control condition (L) than for LL and RL, the peak latency of 1M for L did not differ from that for either of the other two conditions. This effect of the cue to facilitate the motor response (the RT) is called a warning effect\textsuperscript{16,17}. The mean difference between the RT and the peak latency of 1M in each condition of this study was 170 ms for LL, 153 ms for RL, and 300 ms for L, respectively. Therefore, the warning effect was not observed at the stage when 1M appeared. The warning effect must occur at a later stage involved in volitional decision for a motor execution after the sensory information input\textsuperscript{16,18,19}.

Comparison of the latency of 1M between RL and LL suggested that the delay for LL of the RT reflected the delay at 1M. This delay of 1M (9 ms)
could explain part of the delay in the RT (26 ms). In Experiment 2, we tried to clarify whether the delay of 1M for LL included components relating to the attentional task. As a result, we found a delay in the peak latency of 1M in LL as in Experiment 1, suggesting that the delay was not related to attention, in other words, the processing was automatic. Although there have been numerous studies on IOR, such a delay in the cortical response under an IOR paradigm without RT measurements has not been reported previously. Although we could not determine the cortical area responsible for the delay, this finding is compatible with previous psychological studies showing the IOR of the RT to reflect an automatic response\(^1,3,20,21\).

In a recent study on priming effects\(^{10}\), we found that the peak latency of 1M for the second stimulus (primed target) was longer than that for the same stimulus presented alone. VEFs were compared between only two conditions, L and LL, using similar tasks in Experiment 2 of the present study, whereby various SOAs were tested in our previous study\(^{10}\). The delay occurred at SOAs longer than 250 ms, which is consistent with the crossover point of the IOR phenomenon. In Experiment 2 of the present study, the cue on the side opposite that of the target had little influence on the peak latency of 1M in RL. Taken together, the change in the peak latency of 1M took place only when the cue was presented at the same location. These results imply that IOR phenomena reflect the delay of
processing of the second (target) stimulus that is presented after the cue at
the same location.
Although the peak latency of 1M for L did not differ between the
experiments, the peak amplitude was larger in Experiment 1 than in
Experiment 2 suggesting that the amplitude difference reflected the
influence of attention. The new paradigm in the present study could
identify this important finding which has not been identified in previous
studies. Therefore, the IOR response of VEFs seems more sensitive to
attention than RT. We suggest that the input of the IOR signal is linked to
the visual and motor area in parallel.

**Methods**

**Subjects**

Eleven healthy volunteers (seven males and four females, 32.6 ± 10.9
years) participated in this study. The subjects had no history of
neurological diseases and had a corrected visual acuity within the normal
range. The objective and the procedure of the study were explained to the
subjects, and their informed consent to participate in the experiment, which
was first approved by the Ethics Committee of the National Institute for
Physiological Sciences, Okazaki, Japan, was obtained prior to the study.

**Visual stimuli**

All stimuli were projected on a screen 198 cm in front of the subject by
a video projector system (Mirage 2000, CHRISTIE digital system Inc; Ontario, Canada). The display stimuli and sequence are illustrated in Fig. 1. The visual stimuli were similar to those used in our previous studies\textsuperscript{9,10}. In brief, the cue was a white figure of a cross (0.38 x 0.38 deg visual angle), while the target was a white circle (0.6 x 0.6 deg) on a gray background. Both stimuli were made of the same pixels. A red fixation point at the center of the screen, the cue and target placed 6.25º left and right of the center, respectively, were presented during both experiments. For each subject, the luminance of the cue and target was 2.99 cd/m\textsuperscript{2} and the luminance of the background was 2.78 cd/m\textsuperscript{2}. In addition to the cue and target, the figure of a heart (REST-1) and face (REST-2) was presented for 2000 ms and 5000 ms, respectively, and the subjects were allowed to blink during REST periods.

Each trial began with REST-2 (5000 ms), then the cue was presented for 50 ms on either the left or right side at an even probability. The target was presented 500 ms after the offset of the cue on either the left or right side at an even probability. The duration of the target was 500 ms. In this study, VFEs in response to the target presented in the left visual field were recorded. Therefore, there were two stimulus conditions, the left cue followed by the left target (LL) and the right cue followed by the left target (RL). In addition to these two conditions, there was a control condition where the target was presented alone (17% of all trials) at either side. Only
trials following the left target alone were recorded (L).

There were two experiments with the same stimulus but with different tasks. The two experiments were carried out on a different day. In the first experiment (Experiment 1), the RT to the target was measured while recording VEFs. The subjects were instructed to press the button with their right hand as quickly as possible when they noticed the target. In the second experiment (Experiment 2), the subjects were instructed to count REST-1 and REST-2 presented at the center and to report the number of them after each session. In both experiments, the subjects looked at the fixation point throughout the experiment. The paired stimulus was presented randomly with an inter-trial interval of 2000-2500 ms in both experiments.

**VEF recording**

The VEF recordings were made in a magnetically shielded room, and the subjects were in a sitting position. VEFs were recorded with a helmet-shaped 306-channel detector array (Vectorview, ELEKTA Neuromag Oy, Helsinki, Finland), which comprised 102 identical triple sensor elements. Each sensor element consisted of two orthogonal planar gradiometers and one magnetometer, and thus provided three independent measurements of the magnetic fields. In this study, we analyzed MEG signals recorded from 204 planar-type gradiometers. These planar
gradiometers are powerful enough to detect the largest signal just over local cerebral sources. Since the target was presented in the left hemi field, we analyzed results recorded from the right hemisphere.

The VEF signals were filtered on-line with a band-pass filter of 0.1-200 Hz and digitized at 900 Hz. We collected epochs from 100 ms prior to the stimulus onset to 1000 ms after the onset. The initial 100 ms was used for adjusting the baseline. Epochs with MEG signals exceeding 3000 fT/cm were rejected. Eye position/movement was monitored with a monitor (ISCAN, Pupil/Corneal reflection Tracking System, Burlington, MA, USA) and epochs with horizontal and/or vertical eye movements of more than 1 degree were rejected.

In one recording session, 60 stimuli were presented in a random order, and more than 10 sessions were repeated to obtain 75 noise-free epochs for each condition. One session took 5-7 minutes and the subjects had a short rest between sessions. To keep their eye position constant, the subjects were instructed to gaze at the center.

**VEF data analysis and source localization**

We selected a pair of gradiometers with the largest response in the occipito-temporal area for the control condition (L). These gradiometers were fixed and used for comparison among conditions. Root mean square
(RMS) of the selected pair sensors was calculated, and the peak latency and peak amplitude of the RMS waveform were analyzed (Fig. 2). The mean RMS value during 100 ms before the cue onset was used as the baseline for each condition. We estimated the source responsible for the major component of evoked magnetic fields whose peak latency was about 180 ms for 1M (Fig. 2A). We adopted a spherical head model based on individual MR images. The equivalent current dipole (ECD) at the peak latency of each ERF component was estimated from the magnetic response obtained from 10 to 20 selected channels in the right hemisphere (Fig. 2A). We adopted a reliable single ECD which fulfilled the following criteria. (1) The isocontour map indicated a single ECD pattern, (2) the goodness of fit (GOF) was over 80 %, (3) the confidence volume of ECD was below 3000 mm³, (4) and the ECD was estimated to lie in the visual cortex. Next, we also tried to find a two- or three- dipole model to confirm whether small but significant activities were present in addition to the estimated ECD. (3) and (4) were set as criteria for the new ECD(s).

**Statistical analysis**

Data were expressed as the mean ± standard deviation (SD). For VEFs, the peak latency and peak amplitude were compared among conditions using a repeated analysis of variance (ANOVA) followed by a post hoc test with the Bonferroni correction for multiple comparisons. P values less than
0.05 were considered to be significant.
References


Table 1. Mean peak latency and peak amplitude of the major magnetic component, and reaction time to the target (S.D.)

<table>
<thead>
<tr>
<th></th>
<th>LL condition</th>
<th>RL condition</th>
<th>L condition</th>
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<tbody>
<tr>
<td><strong>Experiment 1</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Latency (ms)</td>
<td>186 (± 23)</td>
<td>177 (±23)</td>
<td>178 (±25)</td>
</tr>
<tr>
<td>Amplitude (RMS, fT/cm)</td>
<td>50.9 (± 18.6)</td>
<td>61.3 (±24.3)</td>
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<tr>
<td>Reaction Time</td>
<td>356 (± 64.3)</td>
<td>330 (±60)</td>
<td>478 (± 51)</td>
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<tr>
<td><strong>Experiment 2</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Latency (ms)</td>
<td>192 (± 29)</td>
<td>183 (±28)</td>
<td>181 (±21)</td>
</tr>
<tr>
<td>Amplitude (RMS, fT/cm)</td>
<td>35.8 (±17.2)</td>
<td>45.2 (±18.8)</td>
<td>47.2 (±22.1)</td>
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Figure Legends

**Figure 1.** Experimental design (A), a cross was the first stimulus (cue) and a circle was the second (target). LL, the cue and target were presented at the same location. RL, the target was presented on the side opposite the cue. L, the target was presented alone on the left side. In Experiment 1, REST 1 and REST 2 were presented for blinking and in Experiment 2, the subjects had to enumerate them. (B), illustration of a trial sequence.

**Figure 2:** Averaged (A) and calculated RMS waveforms (B) of subject 1. Enlarged waveforms were recorded from sensors which showed the largest amplitude of the component.

**Figure 3:** Isocontour maps of 1M and its location overlaid on MRI. The equivalent current dipole (ECD) location (A) estimated at the peak of the large component of Experiment 1 (Fig. 2A) and Experiment 2 (B).

**Figure 4:** Waveforms following the target onset in a representative subject. The upper panel (A) shows the RMS waveforms of subject 2 in Experiment 1 and the lower panel (B), those in Experiment 2. The red, blue and green lines show the waveform in the RL, LL and L condition, respectively. In
both experiments, 1M was significantly larger in amplitude and shorter in latency in RL and L than in LL.

**Figure 5:** Grand-averaged RMS waveforms in each condition in the two experiments aligned on the target onset, and comparison between Experiment 1 and Experiment 2. The RMS value was larger in Experiment 1 than Experiment 2.
A. Recorded waveform

B. RMS waveform
Experiment 1

in RL condition

in LL condition

in L condition

Experiment 2

in RL condition

in LL condition

in L condition