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Category-selective Attention Modulates Unconscious Processing: Evidence from ERP

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Authors' contributions

This work was carried out in collaboration between all authors. Authors CL and ZS contributed equally to this work. Authors CL, ZS, QZ and ST designed the study. Authors JQ and ST wrote the protocol and supervised the work. Authors CL and ZS carried out the experiment. Authors CL, ZS and QY performed the data analysis. Authors CL and ZS wrote the first draft of the manuscript. Authors JJ, UM and ST edited the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Recently, using the fMRI method in a paradigm in which visible word cues were followed by masked faces at a completely unconscious level or masked tools at a partially conscious level, Tu, Qiu, Martens, & Zhang [31] showed that the top-down modulation effects were in opposite directions for the two conditions. Because five different pictures of masked faces/tools were displayed in a trial, the authors proposed that the modulation effects could further interact with the

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conscious component of the partial awareness processing (i.e., awareness of the global contour change). In the present event-related potential study, we employed a paradigm similar to that of Tu et al.'s [31] except that the masked stimulus was displayed only once to test the effect of category-selective attention on unconscious processing of picture identity and to try to investigate the above hypothesis.

Study Design: Two semantic category cues ("face" or "tool") and two types of subliminal stimuli (face or tool images) were crossed to generate four conditions: a face cue followed by a masked face picture, a face cue followed by a masked tool picture, a tool cue followed by a masked face picture, and a tool cue followed by a masked tool picture.

Place and Duration of Study: Department of psychology, Institute of education, China West Normal University, between September 2013 and April 2014.

Methodology: The technique of event-related potentials (ERP) was used.

Results: Processing of masked face and tool images both elicited the ERP components of C1, P1, N1, and P2. In addition, C1 component between 25 ms and 55 ms was smaller in the valid category cue-word condition (face cue-word followed by masked face image & tool cue-word followed by masked tool image) than in the invalid cue-words (face cue-word followed by masked tool image & tool cue-word followed by masked face image). The other three waves, P1, N1, and P2, were found to be unaffected by the top-down modulation.

Conclusion: Category-selective attention can modulate unconscious processes at an early stage of visual processing supporting the interaction hypothesis.

Keywords: *Top-down attention; category-selective attention; unconscious processes; partial awareness; ERP.*

1. INTRODUCTION

Some classic theories and approaches show that sensory processing is a bottom-up process [1-3], and the brain is viewed as a stimulus-driven, passive device [4]. However, other studies have revealed that perceptual processing heavily depends on expectations derived from experience and generalized knowledge [4], and that visual and perceptual processing is an active process sensitive to top-down influence of attention and expectation [5]. This top-down modulation could allow us to focus our attention selectively on relevant stimuli and ignore distracting stimuli [6]. Consistent with the top-down modulation view, numerous studies showed that early visual processing in the visual cortex could be modulated by top-down processing. For example, animal experimentation indicated that the top-down process could influence the early cortical activation of sensory processing [7,8]. Likewise, human studies revealed that attention load could modify visual cortex activity [9,10]. Moreover, even in the absence of visual stimulation, extrastriate cortex activation could be modulated by attention [11].

Unconscious processing is obscure and fleeting [12], and the question arises whether subliminal processing could also be modulated by top-down attention. Firstly, the global neuronal workspace hypothesis postulates that subliminal

stimuli are mainly processed in the posterior areas of the brain [13]. In accordance with this model, single-cell recording studies revealed occipital cortex activation [14,15] and temporal cortex activation both caused by heavily masked stimuli in backward masking paradigms [16,17]. Studies with fMRI demonstrated that early visual activation could be elicited by subliminal stimuli [18-20], and moreover there was evidence that the early visual activation elicited by the subliminal stimuli could be modulated by top-down attentional processes such as attention load [21], and task contexts [22,23]. Many other behavioral studies also demonstrated that the top-down attention, such as spatial attention, [24,25], temporal attention [26] and attention to different stimulus dimensions [27] could modulate subliminal processes. ERP evidence also suggested that temporal attention [28] and task sets [29] could modulate the masked semantic priming.

Recently, in a fMRI study, it was found that category-selective attention, elicited by a category cue word (e.g., face or tool), could modulate masked tool processing at a partial awareness level [30] and masked face processing at a completely unconscious level in the middle occipital gyrus (MOG) [31]. However, the modulation effects in MOG were in opposite directions. That is, the MOG activation decreased in the masked faces condition but

increased in the masked tools condition under the consistent (the masked pictures in a trial matched the category cue at the beginning of a trial, e.g., Face cue followed by masked Face picture or FF for short, and Tool cue followed by masked Tool picture, or TT) compared with the inconsistent cue-selective-attentional condition (TF and FT). In that study, five different masked tools or faces were presented successively in a trial. According to the predictive coding model proposed by Rao and Ballard [32], the unconscious components of the partially conscious tool processing and of the completely unconscious face processing could be modulated by the category-selective attention in the earlier visual cortex, which should both lead to decreased activity in the MOG under the consistent relative to the inconsistent condition. However, Tu, Qiu, Martens, & Zhang, (2013) suggested that the above modulation effects could further interact with the conscious component of partial awareness of the global contour change in the masked tool condition (the interaction hypothesis, as we called it in present paper). It was the detectable global contour change of the five successively presented different tools (in contrast to different faces that had the similar contour) that must have led to the increased activity in the MOG. Further research even demonstrated that the interaction effect could be continuous [33].

However, there is a need to investigate more directly the above interaction hypothesis, which was the main purpose of the present study. In the present event-related potential (ERP) study, we used a paradigm same as that in the Tu et al. [31] study, in that category-selective attention was elicited by a category cue word (e.g., face or tool), except that the masked face or tool appeared only once instead of five times. If the opposite MOG effect of modulation (see the detail in the last paragraph) in the Tu et al. [31] fMRI study resulted from the global contour change of the five successively presented different tools, then when the masked stimulus appeared only once as in the present ERP study, the modulation results measured in ERP components should be in the same direction, i.e., the ERP results should be similar for both the masked tool at the partially conscious level and the masked face at the completely unconscious level condition. The expected results will be the same because both conditions involve only the selective-attentional modulation on the unconscious identity processing of the masked stimuli and not the detectable global contour change. There is

evidence that only the detectable global contour feature of the masked tool at the partial awareness level did not contribute to the opposite MOG effect of modulation. That is, when the five successively presented tools were the same and therefore there was no contour change, the MOG activation decreased under the consistent compared with the inconsistent condition [33].

In ERP studies about subliminal processing, there is evidence that a subliminal stimulus can activate P1 and N1 in the early visual cortex [34,35]. Moreover, under the visible stimulus condition, P1 and N1 are larger for the attended stimuli than the unattended stimuli [36]. Another ERP component associated with the top-down effect is the C1 component, which is the earliest ERP component triggered by the stimulus and is about 50 ms post-stimulus. Some studies revealed that C1 evoked by visual stimuli can be modulated by spatial attention [37], emotional content [38], and perceptual learning [39]. Therefore, in the present ERP study, we hypothesized that the early ERP components (C1, P1, and N1), which might be elicited by subliminal stimuli (e.g., masked face or tool pictures) in the early visual cortex, could be modulated by top-down influences of different category cues (i.e., the word “face” or “tool”). Moreover, according to the view stated in the last paragraph, the modulation reflected in these ERP components could be similar for both the masked tool at the partial awareness level and the masked face at the completely unconscious level.

2. MATERIALS AND METHODS

2.1 Participants

A total of 14 Chinese undergraduates (6 women and 8 men between 18 and 26 years of age; mean age = 21.5) were paid to participate in this study voluntarily. All participants were right-handed and had normal or corrected-to-normal vision. No history of neuralgic or psychiatric disorder was reported. This study has been approved by the IRB at China West Normal University.

2.2 Stimuli

The stimuli included three types of pictures: 40 images of neutral faces (20 male, 20 female) from the Chinese Facial Affective Picture System [40], 40 images of tools (e.g., scissors, flashlight,

telephone), and 20 images of things of other categories (e.g., animals, fruits) from the Internet. The mean valence and arousal value of the neutral faces, which were adopted from the Chinese Facial Affective Picture Norms, were 4.31 (SD = 0.58) and 3.61 (SD = 0.51), respectively, on a 9-point scale. The criterion for selecting tools and things of other categories was that they be common, familiar objects in our daily life. And all the pictures were transformed into grey pictures for presentation in the experiment. In the formal experiment, the stimuli were presented centrally on a computer screen with a uniform grey background (RGB = 175, 175, 175) and subtended 4.3° (height) × 3.8° (width) of visual angle. The refresh rate of the computer screen was 60 Hz and the screen resolution was 1024 × 768. Picture presentation was synchronized with the refresh rate of the computer screen.

2.3 Procedure

Task programming, stimulus delivery, and behavioral response recording were performed using the E-prime 2.0 Software (Psychology Software Tools Inc. <http://www.pstnet.com>).

2.3.1 Experiment 1 (ERP test)

Two kinds of materials, a face and a tool, were used to test top-down modulation on subliminal stimulus perception. Two semantic category cues ("face" or "tool") and two types of subliminal stimuli (face or tool images) were crossed to generate four conditions: a face cue followed by a masked face picture (FF), a face cue followed by a masked tool picture (FT), a tool cue followed by a masked face picture (TF), and a tool cue followed by a masked tool picture (TT). The masked face pictures in the FF and TF conditions were the same and appeared in both conditions an equal number of times as were the masked tools in the TT and FT conditions to eliminate any difference in the low-level features, so that the top-down effects on the masked stimulus (see ERP Data Analysis) cannot be attributed to stimulus differences between the conditions.

Each of the four conditions was repeatedly tested 100 times. The test was conducted in four blocks. Each block had 100 trials, with various conditions mixed randomly in each block. The stimulus sequence in the trial is shown in Fig. 1. After a 2000 ms fixation point display, a cue word ("face" or "tool") was displayed for 500 ms followed by a blank screen for a duration varying from 250 ms

to 500 ms. A backward-masked image (face or tool) was then presented centrally for 16 ms followed by a 400 ms backward mask. After a 400 ms blank screen, the last picture (a face, tool, animal or fruit) was presented supraliminally for 1600 ms. The participants were informed that the stimuli between the cue word and the last picture were distractors. The participants were asked to judge as quickly and as accurately as possible whether or not the last suprathreshold photo matched the category word cue by pressing "1" or "2" on the button box with "1" indicating a match, and "2" otherwise. This approach insured that the participants use the cues and keep their spatial attention on the time window. The responses of "1" and "2" were counterbalanced between the participants. For the 100 trials of each condition (FF, FT, TT, TF), 70% (70 trials) were cue/final-picture congruent (the last supraliminally presented picture was consistent with the cue word) and 30% (30 trials) were incongruent (the last supraliminally presented picture was not consistent with the cue word). There were 4 blocks of 100 trials each, with 25 trials for each condition in a block. The different conditions in each block were presented randomly. Between blocks, subjects could take a rest. Subjects were seated in a quiet room facing a screen placed at an approximate 70 cm distance from the eyes and were asked to try to avoid eye movements and blinks as much as possible.

2.3.2 Experiment 2 (behavioral test)

Following the ERP experiment, an objective two-alternative-forced-choice test was given on the masked faces and tools in separate blocks to determine whether the participants could perceive the masked images. The trial outline is presented in Fig. 2. After a 2000 ms fixation, a masked picture appeared for 16 ms, followed by a backward mask for 400 ms. The subliminal pictures used in this experiment were the same as those used in Experiment 1. Following a 400 ms blank screen, two supraliminal images of the same kind (two faces of different people or two different samples of the same tool type) subsequently appeared, one of which was the masked picture. The participants were asked to decide which of the two pictures had been presented in the subliminal display.

In this test, the two supraliminal images in the forced choice task were either two faces or two tools with similar contours but variations in detailed features. However, it was possible that in the subliminal display phase, the participants

could only sense the contours and know what the stimulus was without being able to discern the details of the stimuli [31]. To test this possibility, another version of two-alternate-forced-choice test was given later using the same participants in the ERP study, in which the two choices were displayed in two words rather than in two pictures of the same kind, for example, "flashlight"- "chair" in the masked tool condition, and "telephone"- "face" in the masked face condition. This test would determine whether the participants were aware of the type of the stimuli in the subliminal display phase.

In the word-version-forced-choice test for the masked tool, the two words were all of the tool type. In theory, participants might be able to categorize the masked stimulus as a tool but could not tell what the tool was. Therefore, we tested 16 additional participants, with another two-alternate-forced-choice test in which one of the words was a tool type of the masked picture and the other word not a tool type ("telephone"- "hand").

2.4 ERP Recording and Analysis

Brain electrical activity was recorded from 64 scalp sites by using Ag/AgCl electrodes mounted

in an elastic cap (Brain Products), with the left and right mastoids as references. The vertical electrooculogram was recorded with electrodes placed above and below the left eye, and the horizontal electrooculogram with electrodes placed by right side of right eye and left side of left eye. All interelectrode impedance was maintained below 5 k Ω . The electroencephalogram and the EOG were amplified using a bandpass in the range of 0.05 Hz to 80 Hz and were continuously sampled at 500 Hz/channel for offline analysis. Trials with EOG artifacts (mean EOG voltage exceeding ± 100 μ V) and trials contaminated with artifacts due to amplifier clipping, bursts of electromyography activity, or peak-to-peak deflection exceeding ± 100 μ V were excluded from analysis.

The ERP waves were time-locked to the onset of the masked face or tool pictures. The averaged epoch for ERP, including a 200-ms pre-pictures baseline, was 700 ms. EEG of each condition (FF/FT/TT/TF) were separately averaged, and at least 70 trials were available for each condition of each subject. On the basis of the ERPs grand averaged potentials (Figs. 3 and 4) and previous studies about subliminal processing, we analyzed the C1, P1, N1, and P2 waves evoked

Fig. 1. Stimulus sequence of a single trial in ERP experiment

Fig. 2. Example of a single trial in two-alternate-forced-choice task

by valid cues (congruent condition) versus invalid cues (incongruent condition) for masked face or tool pictures, respectively. These comparisons allowed us to assess the category-selective attentional modulation on unconscious processes. Specifically, the mean amplitudes are exported in the time course between ± 15 ms around the peak of each averaged component: C1 (25 to 55 ms), P1 (90 to 120 ms), N1 (128 to 158 ms), and P2 (220 to 250 ms). Statistical analysis of the C1, P1, N1, and P2 mean amplitudes was conducted using two repeated-measures ANOVA with the conditions (FF versus TF, TT versus FT) and electrodes in parietal-occipital area (Oz, O1, O2, POz, PO3, PO4, PO7, PO8) as factors. In addition, because the face pictures were used, the N1 should be the N170 component which was sensitive to face processing. The N170' positive counterpart VPP (vertex positive potential) [41] was also observed at the middle electrodes in present study. Therefore, we also analyzed the VPP at Cz and Fz electrodes.

3. RESULTS

3.1 Visibility Test

In the first forced choice task, participants reported that they could recognize neither the masked faces nor the tools but could sense some contours in the tool block. All participants performed at chance level in the recognition of the masked face condition, with a mean percentage of correct recognition being 47.80%, $SD = 7.839$, $t(13) = -1.087$, $p = 0.295$. However in the masked tool condition, the mean percentage of correct recognition was 44.53%, $SD = 9.553$, $t(13) = -2.216$, $p = 0.044 < 0.050$. The less than chance level mean percentage of correct recognition suggested the possibility that the sensed contour might have misled participants.

In the second forced choice task, participants also reported that they could recognize neither the masked faces nor tools but could sense some contours in the tool block. Meanwhile, discrimination performance did not deviate from chance level in both conditions: mean percentage of correct recognition for face was 49.93%, $SD = 8.316$, $t(13) = -0.032$, $p = 0.975$; and mean percentage of correct recognition for tool was 50.43%, $SD = 8.847$, $t(13) = 0.181$, $p = 0.859$. In addition, in the two words test condition where one word was a tool type and the other was not, the results were similar to those of previous forced choice task: mean percentage of

correct recognition was 49.75%, $SD = 9.191$, $t(15) = -0.109$, $p = 0.915$. The combined results suggested that the participants could not perceive the masked stimuli, although they could sense some contours of the tools. Moreover, the d' values were not significantly different from zero in all the three two-words-version forced choice tasks, $ps > 0.844$.

3.2 Behavioral RT Results

Because the combined inconsistent and consistent trials (in 30% of the trials, the supraliminally presented picture at the end of a trial did not match the cue word and in 70% of the trials, it did) could mask the RT effects in the behavioral analysis (the RT to the conscious target might be influenced by the object type of targets, the cues, the masked picture and the relationship between the cue and masked picture), the RTs analysis included only the correct trials in the consistent condition to focus on the relationship between cues and masked stimuli. The mean RTs and the 95% confidence intervals were: 580.53 ms and 539.25~621.82 ms for the FT, 566.62 ms and 526.66~606.59 ms for the FF, 672.48 ms and 630.75~714.20 ms for the TT, and 645.19 ms and 604.29~686.08 ms for the TF condition, respectively. A two-way repeated-measures ANOVA, using cue (tool vs. face) and masked stimulus (tool vs. face) as factors, revealed a main effect of cue, $F(1, 13) = 57.93$, $p < .05$, $\eta^2 = .82$, demonstrating that participants exhibited significantly faster RTs to face than to tool cues. Moreover, the main effect of masked stimulus was also significant, $F(1, 13) = 12.74$, $p < .05$, $\eta^2 = .50$, demonstrating that participants exhibited significantly faster RTs in masked face condition compared to masked tool condition. The interaction between the two factors was not significant, $F(1, 13) = 1.36$, $p > .05$, $\eta^2 = .10$. The main effect of masked stimulus across the two cue conditions might indicate the different conscious states between the masked tool and the masked face, in which partial awareness of the masked tool led to a slower RT.

3.3 ERP Results

The amplitude difference of C1, P1, N1/VPP and P2 were analyzed for the top-down modulation on the unconscious face and tool processing, respectively (Figs. 3 and 4).

Firstly, for the masked face condition (Fig. 3), the ANOVA results showed that FF activated a

Fig. 3. Grand average of ERPs at Oz, POz, O1, and O2 for congruent and incongruent responses in masked face condition

Fig. 4. Grand average of ERPs at Oz, POz, O1, and O2 for congruent and incongruent responses in masked tool condition

significantly smaller C1 compared with the TF, $F(1, 13) = 6.257$, $p = 0.027$. The interaction between condition (FF vs. TF) and electrode was

not significant, $F(7, 91) = 0.342$, $p = 0.932$. In addition, the differences in P1, N1, and P2 between FF and TF conditions did not reach

significance: P1 [$F(1, 13) = 0.980, p = 0.340$], N1 [$F(1, 13) = 0.366, p = 0.556$], and P2 [$F(1, 13) = 1.866, p = 0.195$]. None of the interactions between condition and electrode was significant, all $ps > 0.154$.

Secondly, for the masked tool condition (Fig. 4), the results were similar to that of the masked face condition. TT elicited a significantly smaller C1 compared with FT, $F(1, 13) = 5.488, p = 0.036$. The interaction between condition (TT vs. FT) and electrode was not significant, $F(7, 91) = 0.973, p = 0.456$. But again, there was no significant effect of the cue word on the P1, N1, and P2 components: P1 [$F(1, 13) = 1.297, p = 0.275$], N1 [$F(1, 13) = 0.155, p = 0.700$], and P2 [$F(1, 13) = 3.372, p = 0.089$]. None of the interactions between condition and electrode was significant, all $ps > 0.282$.

In addition, at Cz and Fz electrodes, it showed no significant effect of VPP in both masked face and masked tool conditions, $ps > 0.121$.

In short, the masked face and tool conditions showed similar results: the amplitude of C1 was significantly smaller under the valid cues compared with under the invalid cues condition, whereas the other components (P1, N1/VPP, and P2) showed no significant effect. The implications of the results are discussed below.

4. DISCUSSION

In the present ERP study, we employed a modified paradigm with visible cues followed by masked images of faces and tools to test the category-selective attentional modulation on subliminal processes. Comparing the FF with the TF condition, we were able to assess the top-down modulation effect evoked by valid cues versus invalid cues on the processing of the masked face pictures at completely unconscious level: this effect was indicated in the prominent C1 waves in the parietal-occipital area. The same analysis of the top-down modulation on the processing of the masked tool images at the partial awareness level indicated a significant C1 difference between TT and FT. The C1 effect was the same for the masked face and tool conditions: the incongruent trials elicited larger C1 waves compared with the congruent trials. In contrast, P1, N1, and P2 showed no difference between the congruent and incongruent conditions in both masked face and tool conditions. The results support the interaction hypothesis in Tu et al.'s [31] study. We believe that the C1 reflects the

early neural activity of top-down modulation on unconscious processing. The findings will be discussed in detail below.

The visual P1, N1, and P2 were sensitive to specific visual features. The posterior P1 was associated with attention, and it was enhanced by the attended unilateral stimuli in left or right visual fields [42]. Moreover, N1 and P2 were affected by the orientation and location of stimuli; in particular, P2 was sensitive to selective attention to different attributes of stimuli [43]. However, in our study, there was no indication of significant differences in these components between the masked tool and masked face conditions, the reason of which might be that the stimulus contents were processed subliminally. This suggested that the top-down effect cannot reach these later stages. Moreover, the N1 might be the N170 sensitive to face processing. Previous studies found that N170 was a negative component at occipito-temporal scalp sites between 130 and 200 ms. N170 was larger when elicited by faces than by other object categories [44] which was obvious from pictures 3 and 4 in present study. Therefore, the N1 could be the N170. In addition, N170's positive counterpart VPP (vertex positive potential) [41] was also observed at the middle electrodes in present study, which also had no category-selective attentional modulation effect.

The C1 wave is the earliest component of the visually evoked potential (onset around 50 ms post-stimuli), and its polarity reverses between the upper and the lower visual fields [45,46]. However, the foveally presented stimulus could also trigger a modest C1 [47,48], with an amplitude weaker than the one from an unusual location [49]. In this study, we presented the masked stimuli in the central visual field, which also elicited a small C1 in the 25 ms to 55 ms time window. This observation indicated that masked stimuli could also trigger an earlier C1 regardless of whether at the partial awareness level or completely unconscious level.

An early view proposed that C1 was not susceptible to the influence of top-down attention [37,50-52]. However, recent studies challenged this view. It was found that C1 was modulated by spatial attention [53] and attentional load [10]. In addition, the C1 was found to originate from V1 cortex, and there was evidence that human V1 activation to subliminal stimuli could be modulated by top-down attention (e.g., attentional load) [21]. In the present ERP

study, the C1 effect showed that the processing of unconscious contents at both the partial awareness level and the completely unconscious level could be modulated by category-selective attention at a very early stage.

The results were also consistent with those of Tu et al.'s [31] fMRI experiment in which the masked tool at the partial awareness level and masked face at the completely unconscious level were found to be modulated by the category-selective attention in the MOG. However, the modulation results in MOG were in the opposite directions in the masked face and tool conditions (see the detail in the introduction). In that study, five different masked tools or faces were presented successively in order to get a better BOLD signal. The opposite modulation effects were supposed to reflect not only that the unconscious component (unawareness of the identity of the tool) of the partial awareness of the tool stimulus and the complete unawareness of the identity of the face could be modulated by the category-selective attention in the earlier visual cortex but that the modulation effects could further interact with the conscious component of partial awareness of the global contour change of different tools. However, in the present ERP study in which the masked face or tool appeared only once, the C1 effect was the same for the masked face at the completely unconscious level and the masked tool at the partial awareness level. They both showed that the incongruent trials elicited larger C1 waves than the congruent trials. Therefore, the similar C1 effects support the interaction hypothesis proposed by the Tu et al. [31].

Conceptually, the results of the present study are in accordance with the expectation-driven processing model and the predictive coding model [32]. Grossberg [54] has proposed that the brain can learn to generate a top-down prediction by estimating the visual input according to contextual information from the past and to match these predictions against bottom-up processes. These processes improve the effectiveness of our perceptive processes and hence our adaptation to the environment. Consistent with this idea, in the present study, we found that category-selective attentional modulation may activate an expectation which directs / modulates subliminal processes. In addition, other studies showed that different unconscious processes could interact with or influence each other [55-57]. Considering the fact that most information our brains receive is

processed unconsciously and that unconscious processes could influence the conscious task processing, the relationship between conscious / top-down and unconscious processes might form a cognitive mechanism which serves the function of information integration [58,59].

5. CONCLUSION

In summary, the present results showed that category-selective attention could modulate unconscious processing in the visual areas at a very early stage. Furthermore, the similar C1 effects observed in the masked face and tool conditions support the interaction hypothesis proposed by the Tu et al. [31]. However, the present ERP study did not include a condition with contour changes, therefore, the effects of such changes could be further investigated in future ERP studies.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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