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Visual mismatch negativity reveals automatic detection of sequential regularity violation

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In the absence of focal attention even large visual changes may remain unnoticed (Simons and Levin, 1997). However, an increased body of studies shows that the human brain is capable of detecting even small visual changes, especially if such changes violate established environmental regularities. An indicator of the automatic change detection is the visual mismatch negativity (vMMN) component of the event-related potentials (ERPs). VMMN is a counterpart of the auditory mismatch negativity (for reviews see Näätänen and Winkler, 1999; Näätänen et al., 2007), and typically elicited by stimuli with infrequent (deviant) features embedded in streams of identical (standard) stimuli. VMMN is elicited by deviant color (Czigler et al., 2002), orientation (Aistikainen et al., 2004; Kimura et al., 2010a), movement (Pazo-Alvarez et al., 2004), spatial frequency (Heslenfeld, 2003), contrast (Stagg et al., 2004, for reviews see Pazo-Alvarez et al., 2003; Czigler, 2007, 2010). In the current study we investigated the ability of the system underlying vMMN to register conditional rules. Acquisition of such rules implicates memory for predictive relationships, i.e., expectation of a stimulus "A" if this stimulus was preceded by a stimulus "B" with certain characteristics. Prior results showed that vMMN is elicited by stimuli violating sequential rules. Czigler et al. (2006) presented colored patterns in AABBAABB... order, where A and B refers to red-black and green-black checkerboard patterns, respectively. Infrequently, a third pattern identical to the previous two (AABBB) was presented. Such deviant repetitions elicited a vMMN-like posterior negativity. Violation of stimulus alternation rule also elicited vMMN (Kimura et al., 2010a). In these studies sequential regularities were defined by a particular pattern of short duration. It is possible, that vMMN appeared as result of mismatch between the stored and presented patterns. This possibility is supported by the results of the study by Kimura et al. (2010b) showing that regularly repeating patterns (e.g., SSSSDDSSSSSS...D...) were automatically registered only if the duration of a pattern was no longer than approximately 1 s. Furthermore, attention to the non-sequential aspects of the visual stimuli may prevent the automatic detection of regularity violation (Kimura et al., 2010c).

The sequential rule tested in the present study cannot be represented as a single repeating pattern of sequential features. In our study two colored patterns consisting of either red or green disks were presented with equal probability. As a rule, stimuli within a pair had identical color, and this rule was violated by infrequent pairs with different colors. Accordingly, the regularity was based on the repetition of a particular feature within a pair, but this feature was not identical between all the pairs in the stimulus stream. We expected emergence of vMMN to the second member of deviant pairs with non-repeating colors. Detection of the sequential
were 100 ms. The within-pair inter-stimulus interval (ISI) was set to 300 ms, the between-pair ISI was 800 ms. The subjects were asked to detect unpredictable changes in the length of arms of a white fixation cross, presented in the center of the visual field. From time to time, the cross became wider or longer, with the average frequency of 10 changes per minute, and 3–10 s range. The task was a speeded button-press to the changes of the cross. Participants were instructed that the disk patterns were irrelevant, and the function of this pattern was "to produce a more vivid display."

Automatic detection of visual changes is also reflected by a posterior positive component, the so-called change-related positivity (Fu et al., 2003; Wang et al., 2003; Kimura et al., 2005, 2006a). In our first experiment we expected the emergence of change-related positivity to the second members of pairs with different colors in sequences without conditional rules, i.e., in paired stimulation with identical probability of identical and different members of the pairs. In the present study we contrasted this situation to the effect of within-pair identity rule. Our second experiment served as a control to test whether the stimuli used in Experiment 1 was feasible to elicit a typical vMMN response.

**EXPERIMENT 1: RANDOM SEQUENCE**

**METHODS**

**Participants**

We recorded ERP responses from 15 healthy subjects in this experiment. Two subjects’ data were excluded from the final analysis due to low trial number or lack of canonical ERP responses. The final sample comprised 13 subjects (mean age = 21.9 years, SD = 2.5 years, six females). Both experimental protocols were approved by the Institutional Review Board of the Institute for Psychology, Hungarian Academy of Sciences. All subjects gave their written informed consent after the nature of the experiments had been fully explained. All subjects had normal or corrected-to-normal vision.

**Stimuli and procedure**

The stimuli consisted of eight circles at peripheral locations (3.3° upper, lower, left, and right, and 4.7° upper-left, upper-right, lower-left, and lower-right) that were either green or red on a dark gray background presented on a computer screen. Figure 1A shows a schematic illustration of the stimuli. The duration of the stimuli were 100 ms. The within-pair inter-stimulus interval (ISI) was set to 300 ms, the between-pair ISI was 800 ms. The subjects were asked to detect unpredictable changes in the length of arms of a white fixation cross, presented in the center of the visual field. From time to time, the cross became wider or longer, with the average frequency of 10 changes per minute, and 3–10 s range. The task was a speeded button-press to the changes of the cross. Participants were instructed that the disk patterns were irrelevant, and the function of this pattern was "to produce a more vivid display."

Three stimulus conditions were used. In the 50:50 condition the probability of single-color and double-color pairs were equal, in the 30:70 condition 30%, and in the 10:90 condition 10% of the pairs had different colors. Two-hundred stimuli (100 pairs) were presented in a block. The probability of red and green stimuli was equal within the sequences. To collect a sufficient number of artifact-free trials, three blocks of the 50:50 condition, five blocks of the 30:70 condition and ten blocks of the 10:90 condition were run. A total of 18 blocks were presented. The order of these blocks (i.e., probability conditions) was randomized between the subjects. Figure 1B shows the schemata of the experimental conditions and protocol.

**ERP recording**

EEG was recorded from 62 electrodes (A1, AF7, Fp1, Fpz, Fp2, AF8, AF3, AFz, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FC2, FC4, FC6, FT8, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO7, PO3, POz, PO4, PO8, O1, Oz, O2) covering the whole scalp (modified international 10–20 system) referred to the right mastoid and off-line re-referenced to the common average. EEG was recorded with a low-pass filter at 100 Hz. The ground electrode was placed on the nose-tip. Eye movements were monitored by two horizontal and two vertical bipolar EOG electrodes. Data were digitized at 32 bit resolution and a sampling rate of 500 Hz (Neuroscan Synamp). EEG was filtered off-line between 0.1 and 30 Hz (24 dB/octave). All subsequent data analyses were off-line on PC using built-in and self-developed functions as well as the freeware EEGLAB toolbox (Delorme and Makeig, 2004) in the Matlab (MathWorks, Natick, MA) development environment.
Analysis and comparisons
For standard and deviant stimuli, epochs of 600 ms including a 100 ms pre-stimulus period were extracted from further analysis. Epochs were baseline-corrected for the -100-0 ms period and averaged separately for standards and deviants (Figure 2A). Trials occurring within an 800 ms interval after a change in the fixation cross were automatically excluded from the analysis. To avoid potential artifacts, epochs with a voltage change below 0.1 or voltage exceeding ±75 μV on any EEG or EOG channel were rejected from the analysis.

FIGURE 2 | Visual mismatch negativity waveforms and ERP responses to standard and deviant stimuli. (A) Responses from Experiment 1 (upper panel). (B) Responses from Experiment 2 (lower panel). Shaded areas mark the intervals where significant differences were found between deviant and standards (indicated by point-by-point t-tests).
Difference waveforms were created by subtracting the ERPs to the second member of the pairs with identical colors from ERPs to the second member of the pairs with different colors (Figure 3A). Visual inspection of the topographic maps of the difference waveforms confirmed the change-related positivity component in the 50:50 condition and vMMN responses in the 30:70 and 10:90 conditions at parieto-occipital electrodes (Figure 4A). To find the exact intervals where ERPs to standard and deviant stimuli differed in the post-stimulus 100–400 ms time window where change-related effects were expected, we compared ERPs' amplitude values by point-by-point t-tests (see e.g., Guthrie and Buchwald, 1991) at parieto-occipital electrodes. Mean amplitude were measured within the intervals where the difference between standard and deviant responses was marked as significant on five consecutive point-by-point t-tests at the O1 site for the 50:50 condition and the Oz site for the 30:70 and 10:90 conditions. The change-related positivity component was analyzed using a matrix of six electrodes (PO3, POz, PO4, O1, Oz, O2), whereas vMMN responses were analyzed using a matrix of nine electrodes (P3, Pz, P4, PO3, POz, PO4, O1, Oz, O2). These sets of electrodes corresponded to the expected and observed activity differences elicited by the second member of the pairs with different colors. The effects of stimulus-type on the ERP responses were analyzed with a three-way repeated-measures analysis of variance [ANOVA; stimulus-type (standard vs. deviant) × anteriority (parietal vs. parieto-occipital vs. occipital) × hemisphere (left vs. midline vs. right)]. Greenhouse–Geisser correction of the degrees of freedom was applied where appropriate. Significant interactions were further specified by Tukey HSD post-hoc tests. VMMN peak latencies were defined as the time points of most negative values in the 134–254 ms time window, which included both intervals marked as significantly different for deviants and standards by point-by-point t-tests for the 30:70 and 10:90 conditions.

To compare vMMN responses in the 30:70 and 10:90 conditions, a difference waveform was calculated by subtracting the vMMN waveform obtained in the 30:70 condition from the vMMN waveform obtained in the 10:90. Visual inspection of the topographical map of this difference waveform indicated larger negativities in the 10:90 condition at parietal sites (Figure 4C), therefore the effects of deviant probability on the vMMN amplitude were analyzed at parietal electrodes with a two-way repeated-measures ANOVA [condition (70 vs. 90%) × electrode (P3 vs. Pz vs. P4)]. Greenhouse–Geisser correction of the degrees of freedom was applied where appropriate. Significant interactions were further specified by Tukey HSD post-hoc tests.
The effects of stimulus-type on the ERP responses were analyzed with a four-way repeated-measures ANOVA [stimulus-type (standard vs. deviant) × position (first vs. second) × anteriority (parietal vs. parieto-occipital vs. occipital) × hemisphere (left vs. midline vs. right)]. Greenhouse–Geisser correction of the degrees of freedom was applied where appropriate and \( \varepsilon \) values are reported in the results. Significant interactions were further specified by Tukey HSD post-hoc tests.

Deviant-minus-standard waveforms were calculated (Figure 3B) and mean amplitudes of the observed MMN peaks were also analyzed in a three-way ANOVA with repeated-measures factors of position (first vs. second) × anteriority (parietal vs. parieto-occipital vs. occipital) × hemisphere (left vs. midline vs. right).

**Results – Experiment 1**

**Behavioral performance**

A one-way ANOVA of reaction times showed no significant differences between the conditions [401 ms (SD = 52), 418 ms (SD = 86), and 409 ms (SD = 97) for the 50:50, 30:70, and 10:90 conditions, respectively]. Hit rate was above 95% in each condition, i.e., there were no significant differences between conditions.

**Event-related potentials**

Figure 2A shows grand-averaged ERPs elicited by deviant and standard stimuli at the O1, Oz, and O2 electrode locations. Both stimuli evoked the canonical P1, N1, P2, and N2 components. We found a positive-going deflection in the difference wave for color changes in the 50:50 condition marked as significant by point-by-point \( t \)-tests in the 176–198 ms range (Figure 2A). Negative-going peaks of the difference waves were marked as significant in the 134–160 and 232–254 ms intervals for the 30:70 and 10:90 conditions, respectively (Figure 2A). Topographic maps of scalp potential distributions within these intervals are shown in Figure 4A. Mean interval amplitude values used for statistical comparisons are presented in Table 1.
The ANOVA of the amplitude values in the 50:50 condition with repeated-measures factors of stimulus-type (standard vs. deviant) × anteriority (parieto-occipital vs. occipital) × hemisphere (left vs. midline vs. right) yielded a significant stimulus-type × anteriority interaction \( [F(1, 12) = 5.20, p < 0.05, \eta^2 = 0.30] \), which was due to the more positive responses to changing compared to non-changing stimuli at occipital sites \( (p < 0.001, \text{Tukey HSD}) \).

The ANOVA of the amplitude values in the 30:70 condition with repeated-measures factors of stimulus-type (standard vs. deviant) × anteriority (parietal vs. parieto-occipital vs. occipital) × hemisphere (left vs. midline vs. right) yielded a significant main effect of stimulus-type \( [F(1, 12) = 5.8354, p < 0.05, \eta^2 = 0.33] \) caused by more negative responses to deviants compared to standards. A significant stimulus-type × anteriority interaction was also observed \( [F(2, 24) = 5.5456, p < 0.05, \eta^2 = 0.32, \epsilon = 0.62] \), which was caused by significantly less positive responses to deviants compared to standards at parieto-occipital and occipital sites \( (p < 0.01 \text{ and } p < 0.0001, \text{respectively}) \), whereas standard and deviant responses were not significantly different at parietal electrodes.

The ANOVA of the amplitude values in the 10:90 condition yielded a significant main effect of stimulus-type \( [F(1, 12) = 10.819, p < 0.01, \eta^2 = 0.47] \) caused by less positive responses to deviants compared to standards. A significant main effect of anteriority \( [F(2, 24) = 6.5458, p < 0.05, \eta^2 = 0.35, \epsilon = 0.52] \) was also observed, which was due to an anterior-posterior positivity gradient, i.e., larger responses at occipital compared to parietal electrodes \( (p < 0.01, \text{Tukey HSD}) \).
DIFFERENCE POTENTIALS – COMPARISON OF vMMN IN THE 30:70 AND 10:90 CONDITIONS

Distribution of vMMN responses in the 30:70 and 10:90 conditions were compared by subtracting the former from the latter one (see Methods). Difference map of the two vMMN responses indicated larger negativity in the 10:90 condition at parietal sites (Figure 4C). The ANOVA of the vMMN amplitude values in the 30:70 and 10:90 conditions, measured within the 134–160 and 232–254 ms intervals, respectively, with factors of condition (70 vs. 90%) × electrode (P3 vs. Pz vs. P4) yielded a main effect of condition [F(1, 12) = 5.4772, p < 0.05, η² = 0.31] which was due to a larger negativity at parietal electrodes in the 10:90 condition.

Comparison of vMMN peak latencies in the 30:70 and 10:90 conditions was carried out by an ANOVA with factors of condition (30:70 vs. 10:90), anteriority (parietal vs. parieto-occipital vs. occipital) and hemisphere (left vs. midline vs. right). A main effect of condition was found [F(1, 12) = 4.8018, p < 0.05, η² = 0.29], caused by significantly later vMMN peaks in the 10:90 compared to the 30:70 condition. A significant condition × hemisphere interaction [F(2, 24) = 7.6417, p < 0.01, η² = 0.39, ε = 0.81] was due to the earlier MMN peaks at the midline and right compared to the left electrodes in the 30:70 condition (all p < 0.01, Tukey HSD). VMMN peak latency values used for statistical comparisons are presented in Table 1.

RESULTS – EXPERIMENT 2

BEHAVIORAL PERFORMANCE

The mean reaction time in Experiment 2 was 458 ms (SD = 116). The mean hit rate was 97%.

EVENT-RELATED POTENTIALS

Figure 2B shows grand-averaged ERPs elicited by deviant and standard stimuli at the O1, Oz, and O2 electrode locations. Both stimuli evoked the canonical P1, N1, P2, and N2 components. Deviant-minus-standard difference waveforms showed negative-going peaks for both members of the stimulus pair. The difference between deviants and standards were marked as significant by point-by-point t-tests in the 154–230 and 262–280 ms intervals for the first member within the pair, whereas for the second member a continuous interval of 142–286 ms was marked (Figure 2B). As the vMMN waveforms for the first and second members showed a high overall similarity (Figure 3B), amplitude measurements were done in the time window of 142–286 ms for both members of the stimulus pairs1 for the ERP and vMMN analyses. Topographic maps of scalp potential distributions within this interval are shown in Figure 4B. Mean interval amplitude values used for statistical comparisons are presented in Table 1.

The ANOVA of the ERP amplitude with factors of stimulus-type (standard vs. deviant) × position (first vs. second) × anteriority (parietal vs. parieto-occipital vs. occipital) × hemisphere (left vs. midline vs. right) yielded a main effect of stimulus-type [F(1, 14) = 8.0207, p < 0.01, η² = 0.36] caused by less positive responses to deviants compared to standards. A main effects of position [F(1, 14) = 56.634, p < 0.00001, η² = 0.80] was observed, originating from more positive response to the first member of the pair compared to that of the second. A topographic map of the difference potential resulting from subtraction of the vMMN waveform to the first member from the vMMN waveform to the second member of the pairs is shown in Figure 4D.

A significant stimulus-type × anteriority interaction, [F(2, 28) = 47.779, p < 0.00001, η² = 0.77, ε = 0.77] was found, which was due to the less positive responses to deviants compared to standards at the parieto-occipital and occipital line of electrodes (all p < 0.01, Tukey HSD). A significant position × anteriority interaction [F(2, 28) = 12.225, p < 0.01 η² = 0.47, ε = 0.63] was caused by less positive responses to the second compared to the first member of the pair at parietal, parieto-occipital and occipital lines of electrodes (all p < 0.001, Tukey HSD; the 1st member at parietal and 2nd at occipital did not differ).

DISCUSSION

As expected, deviant colors elicited vMMN in the oddball sequences of our control experiment, and vMMN was slightly larger for deviant second members of the stimulus pairs. The ISI before the first member was longer than before the second one. These results of our control experiment are in line with prior studies of auditory mismatch negativity (e.g., Czigler et al., 1992; Jääskeläinen et al., 1999). Furthermore, these results fit both to the memory-trace mismatch account (e.g., Näätänen, 1992), and the regularity violation account of the visual (Czigler, 2010; Kimura et al., 2010a) and the auditory MMN (Schröger, 2007; Winkler, 2007). As the oddball results show, our stimuli and the parameters of stimulus presentation (ISI) were feasible to elicit vMMN.

The main purpose of our study was the investigation of ERPs to occasional sequential deviancy in the visual domain in Experiment 1. In the 50% color change condition there was no regularity in the stimulus sequence. In this condition, the second member of the stimulus pairs with color change elicited a posterior positivity with 192 ms peak latency. Similar positivity emerged in tasks with double-stimulus (S1-S2) paradigms for task-irrelevant changes of stimulus features (Fu et al., 2003; Wang et al. 2003; Kimura et al., 2005, 2006). Emergence of this component (change-related positivity, CRP) is considered as an index of detection of a divergent stimulus feature.

In the 30% within-pair change condition the second member of the pairs elicited a posterior negativity with 140 ms main latency. A posterior negativity with broader distributions over the posterior scalp (Figure 4A) emerged to the second member of the pair in the 10% within-pair condition with 244 ms main latency. Probabilities of the two colors were equal within the 30:70 and 10:90 sequences, therefore color deviancy per se cannot explain the presence of these negativities. Within-pair changes, however, violated a sequential regularity. Unlike in previous studies reported MMN to violation of sequential regularities (Czigler et al., 2006; Kimura et al., 2010a), in the present task deviancy cannot be detected as mismatch to a particular pattern. Instead, the rule can be phrased “if the stimulus green (red) the forthcoming member of the pair is also green (red), i.e., temporally adjacent...
stimuli are of the same color.” Accordingly, sequential deviants were unpredicted stimuli. In this respect the vMMN in the 30 and 10% conditions can be conceived as a sign of prediction error (Rao and Ballard, 1999; Friston and Kiebel, 2009; Garrido et al., 2009; Bubic et al., 2010; Denham et al., 2010).

Apparently paradox result of the present study is the shorter vMMN latency in the 30% condition, in comparison to the 10% condition (140 and 244 ms, respectively; Figure 3A). One may argue that this is counterintuitive because the rule was “stronger” in the latter condition, and violation of a stronger rule is expected to elicit vMMN with shorter latency. It is interesting to note that in previous studies vMMNs were reported in two latency ranges corresponding to the two ranges we obtained (e.g., Tales et al., 1999; Maekawa et al., 2005; Kimura et al., 2009; for a review see Czigler, 2007). Selective refractoriness to the frequent standard stimulus may contribute to the deviant-minus-standard difference in the earlier range (Kimura et al., 2006), and it is well established that memory dependent processes also contribute to the deviance-related negativity in the 120–160 ms range (Czigler et al., 2002; Astikainen et al., 2008). Larger vMMN at the shorter ISI in the present study argue against the selective refractoriness interpretation.

Latency difference between the vMMN in the 30 and 10% conditions can be attributed to two different brain activities. However, the latency difference observed in our first experiment can be interpreted as reflecting the speed of prediction error signal generation in different hierarchical structures. Recent theories attributed the auditory MMN to such errors (Garrido et al., 2009; Winkler et al., 2009; Denham et al., 2010), and vMMN can be interpreted similarly. Predictive models (Friston, 2005; Baldeweg, 2006; Winkler et al., 2009) emphasize the hierarchical organization of the cortical architecture (Felleman and Van Essen, 1991; Garrido et al., 2007; Hegde and Felleman, 2007) extracting regularities from environmental events and brain imaging results (Summerfield and Koechlin, 2008; Alink et al., 2010) indicate that predictive models are represented in a hierarchical way in the visual system. Here we conjecture that any level of the cortical hierarchy that makes correct predictions about its incoming input passes its predictions onto higher levels. In such a functional architecture, more repetitions of a stimulus reinforcing a possible regularity results in a more extended representation of invariance at higher levels of the hierarchy. The higher the level though, the longer might be the onset of the prediction error signal when the actual inputs do not fit the predictions, at least in the visual domain. As a metaphor for this proposition, we suggest that at a lower level the system detects after a few repetitions of a stimulus/regularity that “there is something going on,” whereas several repetitions leads to the formation of predictions at higher levels (i.e., to more abstract representations of regularities). Some hints of different stages of deviant detection is reflected by the different vMMN distribution in the 30 and 10% probability conditions, but it is evident, that further research is needed to explore the applicability of hierarchical predictive models in automatic registration of sequential regularities in vision.

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