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Piia Laamanen

Pre-attentive Detection of Changes in Serially Presented Stimuli in Rabbits and Humans

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ABSTRACT

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Event-related potentials (ERPs) to changes in serially presented stimuli were recorded from the cortical and subcortical structures in rabbits and from the scalp in humans. The oddball condition, in which frequently presented (standard) stimuli were occasionally replaced by physically different (deviant) stimuli, was applied. In the visual modality, ERPs to an orientation-deviant light bar differed from ERPs to standards in both rabbits (study I) and humans (study IV). In the somatosensory modality (study II), differential ERPs were found to location-deviant air-puff stimuli to the rabbit's muzzle. In study III, the duration of the auditory and visual sensory memory in rabbits was estimated by varying the interval between the stimuli in the oddball condition. Auditory deviants among standards elicited differential ERPs in the hippocampus at 500 ms and 1500 ms intervals. Visual deviants elicited such ERPs only at the 500 ms interval. The differential ERPs found in the auditory, visual and somatosensory modalities in the present studies resemble the mismatch negativity (MMN), which is an ERP component described originally in the auditory modality in humans and is suggested to reflect pre-attentive detection of stimulus change. The MMN-like ERPs found were elicited without voluntary attention and were dependent on the memory trace formed by the previous standards - features also characteristic of MMN. Thus, the present results suggest that the neural mechanism underlying MMN may be multi-modal in the nervous system.

Keywords: rabbit, human, event-related potentials, mismatch negativity, sensory memory

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Jyväskylä, August 2004 Piia Laamanen

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

Astikainen, P., Ruusuvirta, T., & Korhonen, T. (2000). Cortical and subcortical visual event-related potentials to oddball stimuli in rabbits. NeuroReport, 11, 1515–1517.

Astikainen, P., Ruusuvirta, T., & Korhonen, T. (2001). Somatosensory event-related potentials in the rabbit cerebral and cerebellar cortices: a correspondence with mismatch responses in humans. Neuroscience Letters, 298, 222–224.

Astikainen, P., Ruusuvirta, T., & Korhonen, T. Longer storage of auditory than visual information in the rabbit brain: evidence from the dorsal hippocampal electrophysiology. Experimental Brain Research, in press.

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1 INTRODUCTION

The articles constituting this dissertation thesis focus on the brain's ability to detect changes in a series of stimuli. This detection can occur whether stimuli are attended to or not, thus enabling ongoing monitoring of the environment. Mismatch negativity (MMN), a scalp-recorded component of event-related potentials (ERPs), first introduced by Risto Näätänen and his colleagues (Näätänen, Gaillard, & Mäntysalo, 1978), can be used as an indicator the of pre-attentive detection of change. MMN is elicited when a change in a series of stimuli is detected in the brain even when the subject is ignorant of the stimuli or attending to a task which has no relevance to these changes.

MMN was originally thought to reflect detection of change only in the auditory modality and extensive evidence of its elicitation was obtained with scalp recordings in adult humans. Later, the question of its counterpart in other sensory modalities and in non-human species was raised. Hereafter, the term MMN will only be used to refer to the human auditory component recorded in the scalp or cortex. Analogous deflections in animals or possible counterparts in other than the auditory modality will be referred to as MMN-like.

The first evidence of MMN-like processing in animals was obtained in cats with auditory stimuli (Csépe, Karmos, & Molnar, 1987, 1988, 1989). A visual counterpart to auditory MMN was initially looked for in humans, but the results were negative (Nyman et al., 1990). Later, however, data suggesting the existence of visual MMN-like component in both, humans (e.g., Alho, Woods, Algazi, & Näätänen, 1992; Cammann, 1990) and animals (Prechtl & Bullock, 1993), were also presented. In the somatosensory modality, only two studies in humans (Kekoni et al., 1997; Shinozaki, Yabe, Takeyuki, Hiruma, & Kaneko, 1998) have been conducted, but both of these have indicated MMN-like ERPs. Analogous somatosensory ERPs in animals have not, however, been previously reported.

In the articles reported in this dissertation thesis, the first aim was to study whether ERPs analogous to the auditory MMN can be found to visual (study I) or somatosensory (study II) stimuli in rabbits. We hypothesised that a pre-attentive change detection mechanism may be common to several (if not all) modalities, and would thus be found in the visual and somatosensory

modalities as well as the auditory modality. We also presumed that MMN-like processing is an ability of the neuronal system equally found in non-human mammals, and thus may be found also in rabbits. Second, the decay time of the sensory memory as indexed by MMN-like ERPs, which has been studied previously in the auditory modality in humans (e.g., Böttcher-Gandor & Ullsperger, 1992; Mäntysalo & Näätänen, 1987; Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1987; Sams, Hari, Rif, & Knuutila, 1993; Winkler et al., 2002), was estimated by this method in the visual as well as auditory modality in rabbits (study III). The general objective in the animal studies was to examine whether an MMN-like component can be elicited subcortically, as this knowledge has rarely been available in human subjects. Therefore direct recordings from the hippocampus and cerebellar cortex in addition to cortical recordings were made. Finally, because the results from studies I and III suggested that MMN-like ERPs to visual deviants can be elicited in rabbits, and because only a few studies in humans had been reported, we conducted a human experiment (study IV) applying stimulus arrangements very similar to those previously applied in our rabbit study (study I). In this human study we aimed to control the effect of attention carefully, as a possible MMN-like component in the visual modality needs to be distinguished from attention-dependent components.

In this dissertation thesis I first describe the methodological basis of event-related potentials (ERPs), as this method was used in all four studies, and the components of the ERPs related to the serially presented frequent and rare stimuli. Next, I review the MMN literature, including animal models. In the section Original findings and conclusions I briefly report the main results which I then evaluate and relate to the most recent findings in the field.

2 BACKGROUND OF THE STUDIES

2.1 Event-related potentials and detection of a change

Evolutionary the importance of the change detection mechanism is in signalling the appearance of danger or of an approachable entity. In addition, the most recently evolved abilities and predispositions in the evolution of the brain, language skills for example, are also based on the ability to discriminate correctly between auditory features.

Change detection research has obtained information, for example, from behavioural methods (auditory stimuli, e.g., Schröger & Wolff, 1998; visual stimuli, e.g., Pashler, 1988), and more recently, also from functional magnetic resonance imaging (fMRI, e.g., Sabri, Kareken, Dzemidzic, Lowe, & Melara, 2004) and positron emission tomography (PET, e.g., Müller, Jüptner, Jentzen, & Müller, 2002) recordings. The studies included in the present dissertation thesis are based on recordings of event-related potentials (ERPs). ERPs are summed neuronal membrane potentials which are time-locked to discrete sensory stimulus events. The advantage of the ERP method is its superior time resolution. In ERPs the brain responses to certain events can be studied on the millisecond scale whereas PET integrates brain activity over several seconds and fMRI over approximately 100 milliseconds. On the other hand, PET and fMRI allow better resolution than scalp-recorded ERPs in terms of the localisation of the activity. In scalp-recorded ERPs localisation of the signal is difficult to calculate, as the scalp, skull and membranes in the brain lead to its distortion. Magnetoencephalography (MEG), which is as accurate temporally as ERP, can obtain data only from the generators lying tangentially to the scalp, and does not, since they are otherwise oriented, scan the signal from these neurons (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). Intracranial ERP recordings, however, provide both accurate temporal and spatial information about brain processes. These recordings can be made from several brain areas, including the subcortical structures in animals, and also occasionally from restricted brain locations in clinical patients.

Different components (i.e. "peaks" and "deflections") [1] of ERPs have been studied extensively in the auditory and visual modality since the electroencephalography (EEG) method was developed. Until the 1960s ERPs were thought solely to be determined by the stimulus characteristics. Later on, psychological factors, such as the subject's state of arousal or attention, were also found to affect ERPs. Subsequently, a distinction was made between exogenous and endogenous components. The first-mentioned reflects the sensory processing of the physical features of the stimulus in afferent neuronal pathways within 100 ms from stimulus onset, and the second psychological factors related to stimulation elicited at latencies from 100 ms to 1 s after stimulus onset.

The oddball condition is a stimulus condition commonly employed in ERP studies, and it also provides a suitable tool for studying the detection of stimulus change. In the oddball condition a frequently presented (standard) stimulus is occasionally replaced by an infrequently presented (deviant) stimulus. These serially presented stimuli are separated by certain time intervals. Subjects can be instructed to respond to deviants or to a third stimulus type, targets, for example by pressing a button (active condition), or to ignore the stimuli and focus their attention on another task presented in the same or different modality as the oddball stimuli (passive condition).

Detection of a change in stimuli (for example a deviant stimulus in the oddball condition) elicits, after exogenous components, endogenous N2 and P3 deflections in ERPs. N2 deflections are of at least two types in the auditory modality: N2a, which is better known as mismatch negativity (MMN), and N2b. MMN was originally isolated from the N2 wave by Näätänen and colleagues (Näätänen et al., 1978, for a review, see e.g., Näätänen, 1990; Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001). Whereas N1 (for a review, see e.g., Näätänen & Picton, 1987), a late exogenous component, is elicited by an auditory *stimulus per se* and reflects strongly the physical characteristics of the stimulus, such as stimulus energy and presentation rate, MMN reflects pre-attentive detection of stimulus *change*. MMN is elicited even when the subject is unaware of the stimuli and does not consciously notice changes in them. Typically MMN has a latency of 100-250 ms from stimulus onset and fronto-central distribution. N2b, on the other hand, is optimally elicited in an active oddball condition in which subjects are responding to deviants (Näätänen, Simpson, & Loveless, 1982). N2b has an approximate latency of 200 ms, and like MMN, fronto-central distribution. Visual deviant stimuli also elicit N2b (e.g., Simson, Vaughan, & Ritter, 1977), but the evidence for N2a (MMN) has been less clear. However, recent findings seem to support the idea of a pre-attentive visual change detection mechanism (for a review see Pazo-Alvarez, Cadaveida, & Amenedo, 2003). In the somatosensory modality both MMN (Kekoni et al., 1997; Shinozaki et al., 1998) and N2b (usually labelled as N250, Kekoni, Hämäläinen, McCloud, Reinikainen, & Näätänen, 1996) have been reported. The P3 (or P300) component, on the other hand, has been interpreted to indicate attention switching to a change in the stimulus. P3 is modality non-specific and

has been observed in response to infrequent deviant stimuli (P3a, e.g., Courchesne, Hillyard, & Calambos, 1975) and to target stimuli which the subject is attending (P3b, e.g., Courchesne, 1978). The latency of P3 varies between 250-500 ms (e.g., Ochoa & Polich, 2000; Polich & Comanchero, 2003) and reflects the time required for the contextual evaluation of the stimulus (Polich & Herbst, 2000). Its amplitude is proportional to the amount of attentional resources devoted to the task in question (Kramer & Strayer, 1988).

In the next section MMN, which is a component of particular interest in the present studies, is considered in detail.

2.2 Mismatch negativity and its animal models

MMN has been recorded to auditory deviant stimuli differing from standards with respect to several physical characteristics such as frequency, intensity, duration or inter-stimulus interval. In addition to a single deviant feature, MMN has also been elicited to infrequent combinations of stimulus features (in adults Gomes, Bernstein, Ritter, & Cheng, 1997, in infants Ruusuvirta, Huotilainen, Fellman, & Näätänen, 2003). Changes in the abstract features of stimulation also elicit MMN (e.g., Saarinen, Paavilainen, Schröger, Tervaniemi, & Näätänen, 1992). In the study by Saarinen et al. changes within pairs of tones were presented as an ascending or descending change in frequency while all the pairs of tones were presented randomly across several frequency levels. Along the same lines, MMN has been found to stimuli violating the rules by which stimulus features are combined (e.g., Paavilainen, Simola, Jaramillo, Näätänen, & Winkler, 2001, where the rule was "the higher the frequency, the louder the intensity" or the reverse rule). Even in these cases, MMN elicitation does not require voluntary attention, and the primary task subjects are engaged on can be in a modality other than the auditory, e.g. watching a video without sound (Paavilainen et al., 2001), or even be asleep (Ruusuvirta et al., 2003).

ERPs analogous to MMN have been documented in cats, rabbits and rats to frequency changes (Csépe, Karmos, & Molnar, 1987, 1988, 1989; Pincze, Lakatos, Rajkai, Ulbert, & Karmos, 2001, 2002; Ruusuvirta, Korhonen, Arikoski, & Kivirikko, 1996a,b; Ruusuvirta, Korhonen, Penttonen, & Arikoski, 1995; Ruusuvirta, Korhonen, Penttonen, Arikoski, & Kivirikko, 1995; Ruusuvirta, Penttonen, & Korhonen, 1998) and in guinea pigs and monkeys to intensity changes (Javitt, Schroeder, Steinschneider, Arezzo, & Vaughan, 1992; Javitt, Steinschneider, Schroeder, Vaughan, & Arezzo, 1994; Kraus, McGee, Littman, Nicol, & King, 1994). Interestingly, MMN-like ERPs to changes in speech-sounds have been found in guinea pigs (Kraus, McGee, Littman et al., 1994). Animal studies are important as they can yield information about the evolutionary continuum of the change detection mechanism and of the locations in the brain where MMN-like ERPs can be elicited.

2.2.1 Memory-based process or neural refractoriness?

The concept of the memory trace was first introduced by Pavlov (1927) in order to describe information storage during the inter-stimulus interval between the conditioned (CS) and the unconditioned stimulus (US). He suggested that a neural representation of the CS permits its association with the US. Trace conditioning studies in rabbits have reported that with an interval of 800 ms (Smith, Coleman, & Gormezano, 1969), but not 2000 ms (Solomon, Vander Schaaf, Thompson, & Weisz, 1986), between a tone CS offset and the US, a conditioned response (CR) has been found to develop.

The concept of MMN is also based on an assumption about the formation of the memory trace. Namely, MMN is assumed to be elicited as a discrepancy between the neuronal trace formed by a repetitive standard stimulus and a subsequent sensory input (Näätänen, 1992). If the new input differs from the representation of the repeated stimulus in the memory, as in the case of deviants, and arrives during the lifetime of that memory trace, MMN is elicited (the memory trace explanation, Näätänen, 1990). In principle, there is another possible explanation of MMN which, in turn, does not require the concept of the memory trace. It proposes that standards activate the afferent pathway more frequently than deviants and that the higher neural refractoriness in neurons activated by standards than deviants leads to MMN (the refractoriness explanation, Näätänen, 1990).

Consistent with the memory trace explanation, MMN has not been elicited by the first stimulus in a series (Cowan, Winkler, Teder, & Näätänen, 1993). At least two different stimulus types or a stimulus omission within a temporal integration window (Yabe et al., 1998) is needed to observe MMN. Omission-elicited MMN clearly shows that MMN does not reflect the physical characteristics of the stimulus. In addition, MMN is found only when the one stimulus type is presented frequently and thus forms a memory trace which the other, infrequently presented, stimulus type violates. The memory trace explanation has also been supported by multiple unit activity (MUA) recordings in animals (Ruusuvirta et al., 1996b). The results have suggested that MMN generation is an active process, not one of neural refractoriness, because the hippocampal MUA responses to standards increased compared to those of deviants. Further evidence against the refractoriness explanation has been provided by human studies in which the changes have been present in the combinations of the stimulus features (e.g., Gomes et al., 1997; Ruusuvirta et al., 2003). In these, MMN has been observed even when the features in infrequently presented deviants have already been present in the standards. These finding demonstrates that MMN does not reflect neuronal refractoriness, because both stimulus types (e.g. two types of standards and two types of deviants in the study by Ruusuvirta et al.) activate with equal frequency the afferent pathways related to the processing of the physical features of the stimuli.

When the standards and deviants have had different physical features, however, the traditional control procedure to test the memory-trace hypothesis in auditory MMN studies has been the condition which I refer to as the deviant-

alone condition (e.g., Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989). In this condition, deviant stimuli (alone-deviants) are presented without standard stimuli, but at the same inter-deviant interval as in the oddball condition (figure 1). By this control condition the memory trace explanation can be tested by comparing ERPs to alone-deviants with those to oddball-deviants. If a (statistically significant) difference between these two can be found, the difference between ERPs to oddball-standards and oddball-deviants would better be considered to reflect memory-based processing than neural refractoriness. This is due to the expectation that ERPs to deviant stimuli and those to alone-deviant stimuli are different because the ERPs to oddball deviants capture not only the physical features of this stimulus but also the relation between the two types of stimuli (standards and deviants). An alternative version of the traditional oddball-deviant versus alone-deviant comparison was introduced by Ruusuvirta et al. (1998). This also utilises the deviant-alone condition, but the comparison is made between alone-deviant ERPs and oddball-standard ERPs. If these two are significantly different, the difference found in the oddball condition should be considered to reflect neural refractoriness instead of a memory-based process, because no memory trace of standards is needed. However, if the alone-deviant and standard stimuli are incapable of eliciting differential ERPs, the differential ERPs found in the oddball condition should be considered to be memory-based.

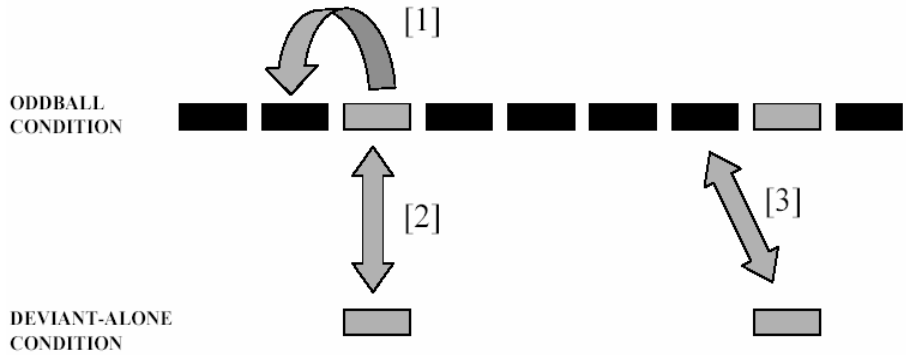

FIGURE 1 Semantic illustration of the presentation of the stimuli in the oddball condition and in the deviant-alone condition. The black quadrangles refer to standard stimuli and the grey ones to (alone-)deviant stimuli. The mismatch negativity is typically demonstrated as a difference wave (ERPs to standards preceding the deviants subtracted from ERPs to deviants, [1]). Whether this difference wave reflects the memory trace explanation or the refractoriness explanation can be tested, for example, by applying the traditional control procedure [2] or the alternative procedure [3] which both utilise the deviant-alone condition. These control procedures have been explained in detail in the text.

Most of the MMN studies which have applied the traditional control procedure have supported the memory trace explanation (e.g., Näätänen et al.,1989; Sallinen, Kaartinen, & Lyytinen, 1994). On the other hand, in a few studies the memory trace explanation has failed to obtain support in the light of this traditional control procedure (infants as subjects, Alho, Sainio, Sajaniemi, Reinikainen, and Näätänen, 1990; rabbits as subjects, Ruusuvirta et al., 1996a). However, it is possible that the alternative control procedure is more sensitive, since Ruusuvirta et al. (1998) found that the memory trace explanation obtained support when it was applied but not when they applied the traditional procedure.

Because the majority of studies seem to suggest that MMN elicitation is dependent on the memory trace formed by standards, it can be used as a tool for studying the sensory memory. In the oddball condition, by gradually prolonging the stimulus onset asynchrony (SOA), the decay time of the memory trace for standards can be approximated by examining the length of SOA required to lose the MMN. By using this type of method, Mäntysalo and Näätänen (1987) found that a pitch-deviant tone evoked MMN with SOA of 2 s but not of 4 s. Data by Näätänen et al. (1987) showed, however, that MMN can be elicited with SOA of 4 s. These approximations (2-4 s) of the decay time of the auditory sensory memory are well in line with the findings of behavioral studies (Cowan, 1984; Darwin, Turveu, & Crowder, 1972) but contradict the results obtained by Böttcher-Gandor and Ullsperger (1992) and Sams et al. (1993), which suggest a decay time as long as 10 s.

2.2.2 Auditory modality specificity?

The possibility of the pre-attentive detection of change in the visual modality has been the subject of debate recently. On the one hand, it has been suggested that changes in visual stimuli may not be *seen* if they are not attended to (for inattentional blindness see, e.g., Most et al., 2001; for a review of change blindness, see Rensik, 2002). In the same vein it has been argued that aware visual perception is not possible without attention (e.g., Joseph, Chun, & Nakayama, 1997). Wolfe (1999) has suggested that instead of inattentional blindness a failure in visual perception is due to inattentional amnesia; i.e. he supposed that unattended visual stimuli can be *seen* but will be instantly *forgotten* if they are not attended to. Wolfe thus made a distinction between seeing and remembering the stimuli. On the other hand, there is data indicating that very sensitive measures can reveal pre-attentive processing and that it seems to occur in the visual modality (Thornton & Fernandez-Duque, 2000), although it may not lead to aware perception. MMN as a sensitive measure and pre-attentive change detection indicator may also be a useful tool to study information processing in the visual modality.

However, only a few studies had been conducted prior to the 21st century to examine whether the mechanism underlying MMN also operates outside the auditory modality. For the visual modality, the results were first negative, while data by Nyman et al. (1990) and Csibra and Czigler (1990) suggested that

visual deviants were not pre-attentively detected. Moreover, other data, showing differential ERPs to standards and deviants, indicated that the refractoriness explanation, rather than the memory trace explanation, seems to be sufficient to account for these ERPs (Alho et al., 1992). A similar finding was obtained from a study demonstrating the analogous visual MMN-like ERPs in animals (Prechtl & Bullock, 1993). Czigler and Csibra (1992) in turn found that a MMN-like negativity in ERPs was related only to more salient deviant stimuli – a finding similar to that reported by Alho et al. (1992). In sum, the results obtained from these early studies led to the conclusion that even if visual deviants and standards elicit differential ERPs, these may not be analogous to the auditory MMN, which has been found to be memory-based and also sensitive to minor changes (e.g., Tervaniemi, Schröger, & Näätänen, 1997). On the other hand, there were also data suggesting the existence of visual MMN-like ERPs (Cammann, 1990; Tales, Newton, Troscianko, & Butler, 1999). However, the memory-trace hypothesis was not tested in these studies.

Recently, there has been a proliferation of human studies related to visual MMN-like ERPs (for a review, see Pazo-Alvarez et al., 2003) but, unfortunately, some of them have not tested the memory-trace hypothesis. On the other hand, those which have tested it have reported inconsistent results. That is, in these studies both the refractoriness explanation (Kenemans, Jong, & Verbaten, 2003) and the memory-trace explanation (Czigler, Balázs, & Winkler, 2002; Pazo-Alvarez, Amanedo, & Cadaveida, 2004), have obtained support. Recently also Stagg, Hindley, Tales, and Butler (2004) have argued that the MMN-like ERPs they observed were memory-based because the standards and deviants they applied differed from each others only in their brightness (perceptually grey or white colour), and they found that a decrease as well as increase in brightness elicits a MMN-like difference wave. This might be regarded as somewhat bold conclusion, however. Namely, as different colours are processed by different neuronal populations in monkeys (Dow, 2002) it is possible that the MMN-like ERPs found by Stagg et al. were contaminated by neural refractoriness. In addition, the data by Czigler et al. (2002) have suggested that colour-specific refractoriness may exist. They reported that the anterior activity they found was related to this refractoriness effect and only the posterior activity was related to the memory-based MMN-like processing.

Although several studies have recently searched for a visual counterpart of the MMN, comparison of these ERPs to the auditory MMN is problematic. That is, ERPs have been recorded while subjects were attending to stimuli presented only to different locations in the visual field than the oddball stimuli, (Czigler et al., 2002; Fu, Fan, & Chen, 2003; Heslenfeld, 2003; Kenemans et al., 2003; Pazo-Alvarez et al., 2004; Tales et al., 1999) or to auditory stimuli presented mutually exclusively with the oddball stimuli (Alho et al., 1992; Cammann, 1990; Horimoto, Inagaki, Yano, Sata, & Kaga, 2002; Wei, Chang, & Luo, 2002). These kinds of primary tasks may be problematic considering that attentional resources can easily be switched to stimuli that should be ignored. It

is thus not clear whether memory-based visual MMN-like ERPs can be elicited without attention when subjects are engaged on a task in a non-visual modality.

In the somatosensory modality, MMN-like ERPs in humans have been found and these seem also to be memory-based (Kekoni et al., 1997; Shinozaki et al., 1998). No animal studies have been conducted, however. In addition to visual and somatosensory MMN-like ERPs there is evidence of such processing in the chemosensory modality as well (for a review of chemosensory ERPs, see Pause & Krauel, 2000). A MMN-like deflection to olfactory stimuli has been found at latency of 400-500 ms from the deviant stimulus (Krauel, Schott, Sojka, Pause, & Ferstl, 1999). Furthermore, this deflection was elicited when oddball stimuli were presented at 15 s intervals but not when this interval was 30 s (Krauel, Pause, Sojka, & Ferstl, 1999, cited in Pause & Krauel, 2000). Thus there seems to be a transient sensory store also for the chemosensory modality.

2.2.3 Generators

The brain locations of MMN generators have been investigated using multiple EEG-electrodes with dipole-models, magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and intracranial recordings directly from the brain. In the MEG studies the main generator of the magnetic counterpart of MMN (MMNm) in humans has been found in the supratemporal plane near the auditory cortex (e.g., Hari et al., 1984; Sams et al., 1985). The generator of MMNm was different from that of N1m (magnetic counterpart of N1), approximately 1 cm further away from it (Huotilainen et al., 1993; Rosburg, 2003), supporting the view that these components are involved in different types of processing (as previously described in the section 2.1). The location of the MMNm generator varies slighty depending on the type of the deviant stimulus; frequency, intensity and duration deviants at least have been found to have different generators (Rosburg, 2003). In addition to a temporal generator, MMN also has a frontal sub-component (e.g., Giard, Perrin, Pernier, & Bouchet, 1990) which reflects involuntary switching of attention towards an acoustic change (Näätänen, 1992). This frontal component has been found to be preceded by the temporal component (Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000). In their fMRI study, Opitz, Rinne, Mecklinger, Cramon, and Schröger (2002) located the frontal MMN component to the opecular part of the right inferior gyrus.

Animal studies in the auditory modality have replicated the finding of a cortical generator of MMN (Csépe et al., 1987, 1988, 1989; Javitt et al., 1992; Javitt et al., 1994; Pincze et al., 2001, 2002; Ruusuvirta et al., 1998). In addition, previous animal studies have suggested that several subcortical regions, such as the hippocampus (Csépe et al., 1988, 1989; Ruusuvirta et al., 1996a), thalamus (Csépe et al., 1988, 1989; Kraus, McGee, Carrell et al., 1994; Kraus, McGee, Littman et al., 1994) and cerebellum (Ruusuvirta et al., 1996a) are involved in MMN elicitation.

In humans, only a few studies of MMN applying subcortical recordings either with intracranial electrodes or brain imaging techniques have been

reported. However, recent PET data indicate a possible subcortical generator of MMN in the parahippocampal gyrus (Müller et al., 2002). Other human studies have only been able to replicate the findings regarding the cortical generators while no evidence of a MMN generator in subcortical structures has been obtained (Kropotov et al., 2000; Kropotov et al., 1995). In addition, unilateral hippocampal lesions in humans have not been found to affect scalp recorded MMN amplitude (Alain, Woods, & Knight, 1998).

One may wonder why subcortical MMN generators have not been found more often in humans, despite being shown to exist in several animal studies. First, it is possible that the differential ERPs recorded subcortically in animals represent different brain process than human MMN. Indeed, the identification of MMN-like ERPs among other long-latency components can be problematic. This separating out can be done, for example, as demonstrated by Pincze et al. (2001, 2002). They separated the N1 from MMN-like ERP component by varying the degree of deviance between standard and deviant tones in separate stimulus blocks. Proper experimental control conditions are thus needed in all future animal studies. A second possibility is that this discrepancy is caused by different methodologies. When intracortical electrodes are used in patients they are placed in the brain on a strictly clinical basis, and thus the locations of the electrodes may vary considerably between subjects, possibly causing statistically non-significant MMN due the large amount of variability between the subcortical recording sites. It may be also that the brain processes of patients differ from those of normal subjects to the extent that they do not show MMN. For example, Pekkonen, Jousmäki, Reinikainen, and Partanen (1995) found that MMN amplitude was significantly smaller in patients with Parkinson's disease. This fact alone could explain the negative result of Kropotov et al. (1995) concerning hippocampal MMN (half of their subjects were Parkinsonian patients). It is also uncertain how much evidence lesion studies in human patients can provide about MMN generators. For example, Alain et al. (1998) found that MMN amplitude in patients was not affected by unilateral hippocampal lesions compared that in control subjects. However, it may be possible that a unilateral and partial lesion in the hippocampal formation is not sufficient to affect MMN elicitation. The result could be different in the case of bilateral and wider lesions. In addition, some sub-areas of the hippocampus may be involved in MMN elicitation while others are not (for example, CA 3 area is found to be related to novelty detection, see e.g., Vinogradova, 1975, 2001). Moreover, the intact cortical structures in these patients alone could enable the elicitation of MMN of equally large amplitude to that found in controls since the recordings were made from the scalp.

3 AIMS OF THE STUDIES

In studies I and II, we sought to clarify whether MMN-like ERPs can be observed to visual or somatosensory changes in rabbits. Only one study of visual MMN-like processing in animals had previously been conducted (in turtles) and no such animal studies in the somatosensory modality had been reported. In study I, the visual changes concerned the orientation of a light bar. In turn, the somatosensory changes in study II concerned the location of an air-puff stimulus presented to the rabbits' muzzle. We hypothesised that changes in both of these physical features may elicit MMN-like ERPs. This assumption was based on the previous findings of a few human studies suggesting the existence of pre-attentive MMN-like processing outside the auditory modality (Alho et al., 1992; Cammann, 1990; Czigler & Csibra, 1992; Kekoni et al., 1997; Shinozaki et al., 1998; Tales et al., 1999). We expected, similarly, to find this processing in non-human mammals.

In study I, two control procedures based on deviant-alone recording to test the memory trace hypothesis of the MMN were compared: the traditional control condition and the alternative one introduced by Ruusuvirta et al. (1998) (described in detail in section 2.2.1). We hypothesised that the previous negative results concerning the memory-trace explanation in the case of visual MMN-like ERPs (Alho et al., 1992; Prechlt & Bullock, 1993) would be overturned by this alternative procedure. This had previously been found in the study by Ruusuvirta et al. in the case of MMN-like ERPs to frequency changes in rats. The alternative control procedure was also applied in studies II and IV.

In our studies of the visual (study I) and somatosensory (study II) modalities in rabbits we hypothesised that because in the auditory modality in animals MMN-like ERPs have been found cortically in the auditory projection area (Csépe et al., 1988, 1989; Javitt et al., 1992; Ruusuvirta et al., 1998), corresponding ERPs would be found in the visual and somatosensory cortex to changes in these modalities. This expectation was also based on findings in humans suggesting the elicitation of MMN (or MMN-like ERPs) in the cortical projection areas to the changes in auditory (e.g., Sams et al., 1985), visual (e.g., Tales et al., 1999) and somatosensory (Kekoni et al., 1997; Shinozaki et al., 1998) stimuli.

In study III, we compared the decay time of the auditory and visual sensory memory in rabbits by applying three different SOAs (500, 1500 and 3000 ms) in the oddball condition. Although several animal studies have reported auditory MMN-like ERPs, none of them have detected the duration of the sensory memory. These studies have typically applied SOAs of 500 ms, which can hardly be considered the limit of duration of the sensory memory. We hypothesised that the sensory memory for auditory information would last longer than the memory for visual information, as this has been previously suggested by human behavioural studies (visual sensory memory decay time 0.3 - 1.0 s: Averbach & Coriell, 1961; Eriksen & Collins, 1967; Sakitt, 1976; Sperling, 1960, auditory sensory memory decay time 1.5 - 4.0 s: Cowan, 1984; Crowder, 1982; Darwin et al., 1972).

In study IV, our aim was to determine whether visual MMN-like ERPs can be found in human subjects with the stimuli nearly similar to used in our previous rabbit study (study I). Because in previous studies of human visual MMN-like ERPs the control of attention may have been insufficient (this issue is explained in the section 2.2.2), in this study our aim was to bind the subjects' attentional resources to a demanding non-visual primary task. In addition, the primary task was presented asynchronously with the visual deviants. That is, the subjects were given the task of listening to a radio play consisting of an oral narrative in Finnish with musical elements and counting the vowel sounds in it. Despite this attention-catching task, we hypothesised that MMN-like ERPs can be elicited.

4 ORIGINAL FINDINGS AND CONCLUSIONS

The results of the present studies suggest that MMN-like processing is multi-modal in nature as differential ERPs were found to auditory, visual and somatosensory changes in rabbits (studies I, II and III) and to visual changes in humans (study IV). The findings in the visual modality were expected because previous studies of MMN-like ERPs in animals (Prechtl & Bullock, 1993) and humans (Alho et al., 1992; Cammann, 1990; Czigler & Csibra, 1992; Tales et al., 1999) have also demonstrated a visual counterpart of the MMN. Recently several studies have supported the idea of visual MMN-like processing in humans (Czigler et al., 2002; Fu et al., 2003; Heslenfeld, 2003; Horimoto et al., 2002; Pazo-Alvarez et al., 2004; Stagg et al., 2004, for a review, see Pazo-Alvarez et al., 2003). In animals, somatosensory MMN-like ERPs have not been reported previously. However, our finding of such ERPs to somatosensory changes in rabbits was in line with similar ERPs previously identified in humans (Kekoni et al., 1997; Shinozaki et al., 1998).

In order to test the memory-trace hypothesis with respect to MMN-like ERP, we used the alternative control condition suggested by Ruusuvirta et al. (1998). In study I, we found that only this control procedure was able to show evidence of memory-based processing, the traditional procedure proving less sensitive to this phenomenon. Indeed, in all three studies (I, II, IV) applying control condition differential ERPs found in the oddball condition were memory-based, as no statistically significant ERPs were elicited between alone-deviants and oddball-standards in those latencies where the oddball-deviants and oddball-standards were, however, found to differ. In other words, the intervening standards in the series (and the memory trace formed by them) were needed for the elicitation of the differential ERPs. In this respect the differential ERPs in rabbits and humans in the present studies resembled the auditory MMN.

Recently, a new control procedure has been introduced to test the memory trace hypothesis of the MMN (Jacobsen & Schröger, 2001). This procedure, termed the equal probability condition, aims to test for the contamination of neural refractoriness in differential ERPs by embedding the stimulus type used

as a deviant in the oddball condition among several types of stimuli such that its rate of presentation is the same as that of a deviant in the oddball condition and also the same as that of the other stimuli in this control condition (later this stimulus type is referred to as equal probability deviant). The advantage of the equal probability condition is that it eliminates neural refractoriness by presenting all the stimulus types at the same frequency (none of them can be less refractory than the other) and at the same inter-stimulus interval as in the oddball condition. Genuine MMN can be estimated by subtracting the ERPs to equal probability deviant from the ERPs to oddball-deviants.

Of the published visual MMN-like studies those by Czigler et al. (2002) and Pazo-Alvarez et al. (2004) have utilised the equal probability condition and shown that the resulting MMN-like responses to visual deviants (Czigler et al., colour deviants; Pazo-Alvarez et al., motion direction deviants) were dependent on the existence of a memory-trace. However, it is unclear whether different visual features are processed similarly as there are data suggesting that neural refractoriness accounts for differential ERPs found to changes in spatial frequency (Kenemans et al., 2003).

As expected, we found MMN-like ERPs in rabbits to visual deviants in the visual cortex (study I) and to somatosensory deviants in the somatosensory cortex (study II). Somatosensory deviants did not elicit differential ERPs in the visual cortex, which further confirmed our assumption of a modality-specific generator. In humans (study IV), we found MMN-like deflection occipitally. In this study, visual standards and deviants did not elicit differential ERPs frontally as usually found in the case of auditory MMN. Our finding of the absence of frontal distribution is probably explained by the difficulty of the primary task. This conclusion is additionally supported by the fact that no P3 component was found (for auditory modality, see Duncan & Kaye, 1987; Gaeta, Friedman, Ritter, & Cheng, 2001; Lyytinen, Blomberg, & Näätänen, 1992). It thus seems to be that the difficulty of the primary task was able to prevent involuntary attentional shift towards the visual stimuli, and it can be argued that the processing of the visual stimuli was done pre-attentively.

The elicitation of subcortical (hippocampal and cerebellar) MMN-like ERPs in study I is in line with results showing visual MMN-like processing subcortically in turtles (Prechtl & Bullock, 1993). In rabbits also we found MMN-like ERPs to auditory deviants in the hippocampus (study III) and to somatosensory deviants in the cerebellar cortex (study II). These findings together with the previous findings in animals (Csépe et al., 1988, 1989; Kraus, McGee, Carrell et al., 1994; Kraus, McGee, Littman et al., 1994; Ruusuvirta et al., 1996a;) demonstrate that MMN-like ERPs are elicited in several deep structures in the animal brain. It is unlikely that cortical feedback alone could explain the subcortical findings, since in the present studies (I and II) subcortical activation was found at the same time as the cortical activation or even earlier. The various animal studies suggest that it would be needful to further address this issue in humans. Crucial to such a study would be the development of a suitable methodology for human subcortical recordings. Combination of

temporally accurate measures, such as ERP or MEG recordings, with measures which can detect signals in the deeper brain structures, such as PET or fMRI, may provide a workable method. Also improved PET and fMRI resolution may contribute to the success of such efforts, as has recently been shown (subcortical MMN generator in the parahippocampal gyrus, Müller et al., 2002).

Because the memory-trace explanation seemed to be sufficient to explain the differential ERPs recorded in rabbits in the auditory and visual conditions (Study I; Ruusuvirta et al., 1996b), in study III the decay times of the sensory memory trace in these modalities were compared as indexed by MMN-like ERPs. We addressed this issue by varying the inter-stimulus interval between the oddball stimuli to determine the point at which differential ERPs are no longer elicited – reason for this being decay of the memory trace. We found differential ERPs in rabbits to auditory pitch-deviant stimuli at the stimulus onset asynchronies (SOAs) of 500 and 1500 ms but to visual orientation deviant stimuli only at the SOA of 500 ms. The results resemble the suggested difference in duration between auditory (Cowan, 1984; Crowder, 1982; Darwin et al., 1972) and visual (Averbach & Coriell, 1961; Eriksen & Collins, 1967; Sakitt, 1976; Sperling, 1960) sensory memory in humans studied previously by behavioral methods. Of the neurophysiological studies in humans utilising the MMN-paradigm to estimate visual sensory memory decay time, the study by Fu et al. (2003) applied 200 and 400 ms intervals between stimuli but without finding the limit for this memory. Kenemans et al. (1989), on the other hand, applied two inter-stimulus intervals, 2.45 s and 8.45 s, both of which were found to elicit differential ERPs to standards and deviants. However, no primary task was applied in the ignore-condition, which leads one to suspect that attentive processing may have contributed to the elicitation of the ERPs found. Studies conducted in the auditory modality in humans, in turn, have shown a decay time of approximately 10 s (e.g. Sams et al., 1993). Recently, Winkler et al. (2002), using somewhat different stimulus conditions, found that the sensory memory trace can last as long as 30 s and suggested that after the auditory sensory buffer the information may be stored as longer lasting traces. However, further studies are needed to compare sensory memory responses to different types of stimulation and in different modalities. It is also probable that the time span for animal and human memory may not be the same.

In conclusion, the results of the present studies together with other previous studies suggest that MMN-like processing occurs not only in the auditory modality but also in the visual and somatosensory modalities. It is thus possible that the mechanisms behind MMN are multi-modal, in much the same way as those behind the P3 component. Since human MMN-like ERPs have rarely been studied in the somatosensory modality, this issue should be further clarified to find out, for example, what types of changes in this modality elicit MMN-like differences and what the decay times for their short-term memory traces are. The present rabbit study implies that the visual sensory memory is shorter than its auditory counterpart, but its decay time in humans as indexed by MMN-like ERPs is not known. Most importantly, because the

memory trace explanation of MMN (Näätänen, 1990) has been tested widely (and found sufficient) only in the auditory modality in humans, this issue needs to be studied carefully in future experiments in the other modalities.

Footnotes

1 ERP "peaks" and "deflections" are visually observable in the ERP waveform as oscillations in the positive or negative polarities. The concept "component" refers to deflection, which is a unitary event in the brain and has a specific generator (Näätänen, 1992, pp. 80-83). Components can be revealed by experimental manipulation.

YHTEENVETO

Muutoksen esitietoinen havaitseminen sarjallisesti esitetyissä ärsykkeissä kaneilla ja ihmisillä

Väitöskirjaan sisältyvissä artikkeleissa on tutkittu poikkeavan ärsykkeen havaitsemista toistettujen ärsykkeiden sarjassa. Tiedetään, että tällainen ärsykkeen muutos voidaan havaita kuulojärjestelmässä myös esitietoisesti, ja sitä ilmentää aivojen herätevasteena mitattava poikkeavuusnegatiivisuusvaste (mismatch negativity, MMN). Poikkeavuusnegatiivisuus esiintyy reaktiona ärsykemuutokseen, joka voi ilmetä esimerkiksi äänen taajuudessa, intensiteetissä tai kestossa. Tyypillisessä ärsykejärjestelyssä, ns. oddball-tilanteessa, esitetään tiettyä ärsykettä toistuvasti ja välillä (satunnaisesti, esimerkiksi 10 % todennäköisyydellä) sen korvaa hieman tästä poikkeava ärsyke. Poikkeavuusnegatiivisuuden oletetaan syntyvän hermostollisessa vertailuprosessissa, jossa hermostoon saapuvan äänen representaatio ei vastaa edellisten äänien muodostamaa muistijälkeä. Komponentti heijastaa tällä tavoin sensorista muistia ja tarjoaa siksi käyttökelpoisen työkalun kuuloaistijärjestelmän ja sensorisen muistin tutkimiseen. Koska poikkeavuusnegatiivisuus syntyy myös silloin kun tutkittava ei tarkkaile ärsykkeitä, se mahdollistaa myös sellaisten potilasryhmien tutkimisen, joille vaativien ohjeiden seuraaminen koetilanteessa on vaikeaa.

Ensimmäisessä tutkimuksessa mitattiin herätevasteita visuaalisiin ärsykemuutoksiin kaneilla. Tutkimuksen tarkoitus oli selvittää esiintyykö poikkeavuusnegatiivisuuden kaltainen komponentti myös näköjärjestelmässä. Aiemmissa tutkimuksissa oli saatu viitteitä siitä, että poikkeavuusnegatiivisuuden kaltainen komponentti voisi olla mitattavissa niin ihmisillä kuin eläimilläkin visuaalisiin ärsykkeisiin. Niissä tutkimuksissa, joissa käytettiin kontrollimittausta, ilmeni kuitenkin, että tämä vaste ei kenties heijastaisikaan vertailuprosessia toistuvasti esitettyjen ärsykkeiden muodostaman muistijäljen ja poikkeavan ärsykkeen representaation välillä, mitä pidetään poikkeavuusnegatiivisuuden keskeisenä ominaisuutena. Mittasimme pysyvästi asetetuilla kallon sisäisillä elektrodeilla kanin hippokampuksesta, pikkuaivokuorelta ja visuaaliselta aivokuorelta herätevasteita valoärsykkeen orientaatiossa tapahtuviin muutoksiin. Havaitsimme, että poikkeavuusnegatiivisuuden kaltainen vaste esiintyi kaikilla mittausalueilla aivoissa. Lisäksi kontrollimittaus, jossa esitettiin poikkeavia ärsykkeitä ilman toistettuja ärsykkeitä, osoitti, että vaste oli oletuksemme mukaisesti myös riippuvainen toistetusti esitettyjen ärsykkeiden muodostamasta muistijäljestä. Käyttämämme kontrollimenettely, jolla tutkimme poikkeavuusnegatiivisuuden riippuvuutta muistijäljestä, oli erilainen kuin aiemmin näköjärjestelmän poikkeavuusnegatiivisuuden tutkimuksessa käytetty kontrollimenettely. Siksi onkin mahdollista, että aiemmat negatiiviset tulokset visuaalisen poikkeavuus-

negatiivisuuden muistiperustaisuuteen liittyen johtuisivat niissä käytetystä ilmiölle vähemmän herkästä kontrollimenettelystä.

Toisessa tutkimuksessa mittasimme herätevasteita tuntoärsykkeisiin kanin iso- ja pikkuaivokuorelta. Oddball-tilanteessa ärsykkeet olivat ilmapuhalluksia esitettynä kahteen eri kohtaan kanin kuonossa: toiseen kohtaan ilmapuhallus esitettiin toistetusti ja toiseen harvoin. Havaitsimme, että tämä poikkeavaan kohtaan esitetty ilmapuhallus aiheutti jälleen poikkeavuusnegatiivisuuden kaltaisen vasteen, joka oli lisäksi riippuvainen toistuvien ärsykkeiden aiheuttamasta muistijäljestä. Sama tulos oli raportoitu myös aiemmin somatosensorisissa järjestelmässä ihmisillä. Tuloksemme tutkimuksesta II viittasivat siihen, että ärsykkeiden neurofysiologinen erottelu tapahtuu spesifisti ärsykkeiden edustaman aistikanavan vastaanottoalueella aivokuorella, muttei muiden aistien vastaanottoaluilla, sillä havaitsimme vasteen tuntoaivokuorella, muttemme näköaivokuorella. Kuten tutkimuksessa I, myös tutkimuksessa II, oli poikkeavuusnegatiivisuuden kaltainen vaste mitattavissa pikkuaivokuorelta.

Kolmannessa tutkimuksessamme muuntelimme ärsykkeiden välistä aikaa oddball-tilanteessa tarkoituksenamme tutkia muistijäljen kestoa kuulo- ja näköjärjestelmässä. Ensimmäisen tutkimuksemme tavoin käytimme näköärsykkeen muutoksena sen orientaatiota. Kuuloärsykkeen muutos ilmeni sen taajuuden vaihtumisena. Koska poikkeavuusnegatiivisuus vaatii muistijäljen ja hermostoon saapuvan ärsykkeen vertailuprosessia, voidaan muistijäljen kestoa arvioida pidentämällä ärsykkeiden välistä aikaa (joka muistijäljen tulee säilyä vertailun mahdollistamiseksi) asteittain, kunnes poikkeavuusnegatiivisuusvastetta ei enää synny. Ärsykkeitä esitettiin sarjallisesti 0.5, 1.5 ja 3.0 sekunnin välein, siten että näkö- ja kuuloärsykkeet esitettiin erillisinä sarjoina. Aiemmissa ihmisillä tehdyissä käyttäytymisvastemittauksissa on havaittu, että sensorinen muisti on kestoltaan lyhempi näköjärjestelmässä (ikoninen muisti) kuin kuulojärjestelmässä (kaikumuisti), joten oletimme että sama voisi olla havaittavissa hermostollisissa rekisteröinneissä kanilla. Tulokset osoittivatkin, että käyttämällä poikkeavuusnegatiivisuutta muistijäljen keston mittarina, muistijälki näyttäisi heikkenevän hypoteesin mukaisesti nopeammin näkö- kuin kuulojärjestelmässä. Kun kuulojärjestelmässä poikkeavuusnegatiivisuus havaittiin vielä ärsykkeiden välisen ajan ollessa 1.5 sekuntia, esiintyi se näköjärjestelmässä ainoastaan 0.5 sekunnin ärsykevälillä. Näiden tulosten perusteella näyttää siltä, että nisäkäslajien välillä on samankaltaisuutta ärsykkeiden prosessointikyvyssä ja sensorisessa muistissa.

Neljäs tutkimus oli ihmistutkimus, jossa mittasimme aikuisilta koehenkilöiltä visuaalisia herätevasteita pään pinnalta. Kuten tutkimuksessa I, ärsykemuutos ilmeni valopalkin orientaatiossa. Visuaalisten herätevasteiden mittauksen aikana koehenkilöiden tehtävänä oli tarkkailla kuulokkeista esitettyä radiokuunnelmaa ja laskea siinä esiintyviä vokaaleja, jolloin voitiin olettaa, että visuaalisia ärsykkeitä kyettiin prosessoimaan lähinnä vain esitietoisesti. Herätevasteet osoittivat, että tarkkaillusta tehtävästä huolimatta, koehenkilöt kykenivät erottamaan poikkeavat ärsykkeet toistetuista

ärsykkeistä. Tätä ilmentävä poikkeavuusnegatiivisuuden kaltainen herätevaste heijasti muistiperustaista informaation käsittelyä takaraivolohkolla, mikä sopii siihen jo tutkimuksessa I tehtyyn havaintoon, että tämän kaltainen tarkkaavuudesta riippumaton aistiärsykkeiden prosessointi tapahtuu kyseessä olevaan aistijärjestelmään erikoistuneella aivokuoren vastaanottoalueella.

Kokonaisuudessaan tuloksemme viittaavat siihen, että poikkeavuusnegatiivisuuden esiintyminen ei rajoitu vain kuulojärjestelmään. Tutkimuksissamme havaittu poikkeavuusnegatiivisuutta muistuttava vaste näkö- ja tuntojärjestelmässä näyttäisi ilmentävän sensorista muistia kuten poikkeavuusnegatiivisuuskin. Lisäksi, yhdenmukaisesti poikkeavuusnegatiivisuuden ominaisuuksien kanssa, havaitsemamme vasteet näkö- ja tuntojärjestelmässä ilmenivät, vaikkei tutkittavat tarkkailleet ärsykkeitä. Tutkimustuloksemme tukevat myös aiempia eläintutkimuksia, joiden nojalla on voitu esittää, että poikkeavuusnegatiivisuuden taustalla oleva hermostollinen mekanismi on yhteinen eri nisäkäslajeille.

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