MISMATCH-LIKE EVENT-RELATED POTENTIALS TO PITCH DEVIANCES IN THE CEREBELLAR INTERPOSITUS NUCLEUS AND THE EFFECT OF ITS TEMPORARY INACTIVATION IN RABBITS

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Herätepotentiaalit mitattiin kuudelta kanilta pikkuaivojen interpositustumakkeesta (IP) oddball-tilanteessa, jossa taajuudeltaan poikkeavia ääniä esitettiin toistuvien ääniärsykkeiden sarjassa (oddball-tilanne) sekä kontrollimittauksissa yksinään (deviant alone –tilanne). Lisäksi IP inaktivoitiin väliaikaisesti jäähdyttämällä se osassa sessioita. Poikkeavuusnegatiivisuuden (mismatch negativity, MMN) kaltaiset herätepotentiaalit, määriteltynä niiden tilastollisesti merkitsevänä erona poikkeavien äänien ja toistuvien äänien välillä oddball-tilanteessa, syntyivät latenssivälillä 100-148 ms ja 250-448 ms ärsykkeen esittämisestä. Herätepotentiaalit yksin esitettyihin, poikkeaviin ääniärsykkeisiin (deviant alone –tilanne), erosivat toistuviin ääniärsykkeisiin syntyvistä herätepotentiaaleista latenssivälillä 50-148 ms ja 300-448 ms. Tämän vuoksi MMN:n kaltaiset herätepotentiaalit latenssivälillä 250-300 ms vaativat poikkeavaa ärsykettä edeltävien toistuvien ärsykkeiden läsnäolon, ja siten muistuttivat ihmisillä esiintyvää MMN:ää. Jäähdytys ei poistanut MMN:n kaltaisia herätepotentiaaleja. Jäähdytystilanteessa merkitseviä eroja poikkeaviin ja toistuviin ääniärsykkeisiin syntyvien herätepotentiaalien välillä esiintyi latenssilla 100-148 ms. Tulokset osoittavat, että MMN:n kaltaisia herätepotentiaaleja, jotka ovat riippuvaisia toistuvien ärsykkeiden läsnäolosta, on havaittavissa IP:ssä. Tulokset kuitenkin osoittavat, että IP ei ole välttämätön MMN:n kaltaisten herätepotentiaalien syntymiselle, koska nämä herätepotentiaalit syntyvät myös jäähdytystilanteessa, ja siksi IP ei ole kriittinen alue ääniärsykkeiden analysoinnissa.

Mismatch-like event-related potentials to pitch deviances in the cerebellar interpositus nucleus and the effect of its temporary inactivation in rabbits

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Event-related potentials (ERPs) from the interpositus nucleus (IP) of the cerebellum were recorded in six rabbits during an oddball condition when pitch deviant tones occurred in a series of standard tones. In control recordings, the deviant tones were presented without the standard tones (deviant alone condition). Cooling was used in some sessions to temporarily inactivate the IP. MMN-like ERPs, defined as a significant difference between ERPs to deviant tones and those to standard tones in the oddball condition, were elicited at the latency range of 100-148 ms and 250-448 ms from a stimulus onset. ERPs to deviants in the deviant alone condition differed from those to standards in the oddball condition at the latency range of 50-148 ms and 300-448 ms. Therefore, MMN-like ERPs at the latency range of 250-300 ms were specific to preceding standards, and thus resembled MMN in humans. Cooling did not remove MMN-like ERPs. In the cooling condition significant differences between ERPs to deviants and those to standards in the oddball cooling condition were elicited at the latency range of 100-148 ms. The results suggest that MMN-like ERPs, which show dependence on the presence of standard stimuli, can be observed in the IP. However, the results suggest that because these MMN-like ERPs are elicited also in the cooling condition, the IP is not necessary for the generation of MMN-like ERPs, and therefore it is not an critical area in analysis of auditory stimuli.

Keywords: Mismatch negativity (MMN); Event-related potentials (ERP); Interpositus nucleus (IP); Oddball condition; Deviant alone condition; Cooling; Rabbit

Mismatch negativity (MMN) (irrespective of its polarity) is a component of auditory event-related potentials (ERPs) in humans. It is elicited at the latency range of 100-200 ms when infrequent (deviant) stimuli are presented in a sequence of frequent (standard) stimuli (oddball condition) (Näätänen, 1990). MMN is regarded as reflecting a neuronal comparison process initiated when an incoming stimulus does not match a memory trace of preceding standard stimuli (Näätänen, 1990). According to the comparison process theory, in the oddball condition the repetitive standard stimuli create a sensory (echoic) memory trace which is the neural representation of a standard stimulus. The deviant stimulus is compared according to its physical features to this memory trace and when it does not match, MMN is elicited. In studying MMN, so called deviant alone condition, in which deviant tones are presented without preceding standard tones, is used together with the oddball condition to control effect of standards on MMN elicitation to test the comparison process theory. Consistent with the comparison process theory, MMN is not elicited in the deviant alone condition. That is, there is no MMN when standard stimuli providing memory trace are not presented in a series (Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1989).

MMN has been mostly studied in the auditory modality and it is elicited by frequency (Näätänen, 1992), intensity (Näätänen et al., 1989), duration (Näätänen, Paavilainen and Reinikainen, 1989), spatial (Paavilainen, Karlsson, Reinikainen and Näätänen, 1989), phonemic (Sams, Aulanko, Aaltonen and Näätänen, 1990) and rise time changes (Lyytinen, Blomberg and Näätänen, 1992) and also with omission of a stimulus (Näätänen et al. 1989; Yabe, Tervaniemi, Reinikainen and Näätänen, 1997). It has been suggested that MMN is automatic and that it is not at all or only slightly dependent on attention. MMN can be elicited even if subject has been instructed to perform a task, for example to read a book and ignore the auditory stimuli (Näätänen, 1992). Furthermore, MMN can even be observed in comatose state (Kane, Rowlands, Curry, Butler and Cummings, 1994).

MMN has been localized to the auditory cortex, particularly in the supratemporal area (Alho, 1995; Giard, Lavikainen, Reinikainen, Perrin, Bertrand, Pernier and Näätänen, 1995). MMN has a potential value for example in diagnosing cerebral dysfunctions (Alho, Sainio, Sajaniemi, Reinikainen and Näätänen, 1990) and deficient auditory perception (Kraus, McGee, Micco, Sharma, Carrell and Nicol, 1993) and in predicting awakening of comatose patients (Kane et al., 1994). MMN has been found to be altered in the various disorders, such as schizophrenia (Javitt, Doneshka, Grochowski and Ritter, 1995), learning disabilities (Kraus, McGee, Carrell, Zecker, Nicol and Koch, 1996) and alcoholism (Jääskeläinen, Lehtokoski, Kujala, Pekkonen, Sinclair, Näätänen and Sillanaukee, 1995).

ERPs in stimulus conditions eliciting MMN in humans have also been studied in animals. Here the term "MMN-like" is used to refer to the statistically significant difference between ERPs to deviant tones and those to standard tones in the oddball condition in animals. MMN-like ERPs has been observed in various species, such as monkey (Javitt, Steinschneider, Schroeder, Vaughan Jr. and Arezzo, 1994), cat (Csepe, Karmos and Molnar, 1989; Ruusuvirta, Korhonen, Penttonen, Arikoski and Kivirikko, 1995a, 1995b), rat (Ruusuvirta, Penttonen and Korhonen, 1998), guinea pig (King, McGee, Rubel, Nicol and Kraus, 1995) and rabbit (Ruusuvirta, Korhonen, Arikoski and Kivirikko, 1996a, 1996b). In animals MMN-like ERPs appear earlier in latency than in humans, usually before 100 ms from stimulus onset (Ruusuvirta et al., 1998). MMN-like

ERPs has been observed not only in cortical areas (Karmos, Winkler, Molnar and Csepe, 1993) but also in subcortical areas such as thalamus (Kraus, McGee, Littman, Nicol and King, 1994), hippocampus and cerebellum (Ruusuvirta 1996; Ruusuvirta et al., 1996a). Some animal studies (Ruusuvirta, 1996) have demonstrated that the observed MMN-like ERPs do not depend on the preceding standard stimuli, as is the case with MMN in humans (Näätänen, 1990). Ruusuvirta (1996) has suggested that, instead of the comparison process, the different presentation rate of each type of stimulus *per se* might be sufficient to explain observed differences between ERPs to deviants and those to standards. In other words, if presentation rate is sufficient to explain the difference, then difference between ERPs to deviants and those to standards is the same irrespective of whether standards and deviants are presented in the same series or separately. Further, Ruusuvirta (1996) has also proposed that rather than neural refractoriness, this effect may represent an active process related to the formation of the short-term memory trace of repeated stimuli. This is because hippocampal multiple-unit activity (MUA) had been observed to increase to the standards and to decrease to the deviants, which suggested that brain responses to repetitive stimuli may not simply represent refractoriness in afferent pathways. Since the effect of the stimulus repetition rate can be related to the memory trace, the trace seems to be widely distributed in the brain.

Recently, however, Ruusuvirta et al. (1998) have demonstrated that also MMN-like ERPs resembling human-like MMN in terms of its standard specificity can be elicited in animals. They recorded ERPs from the auditory cortex in anesthetized rats in the oddball- and deviant alone conditions, and found that ERPs to deviant tones in the oddball condition differed significantly from ERPs to standard tones at the latency range of 63-243 ms. However, the difference between ERPs to deviant tones and those to standard tones at the 63-196 ms latency range could be detected only when standard tones precede deviant tones, and this result shows concordance with MMN in humans.

In the present study, we examined whether MMN-like ERPs are elicited in the interpositus (IP) nucleus of the cerebellum. The IP was a convenient area to study effect of auditory stimuli because it is a part of the secondary auditory pathway. In this pathway, auditory signal proceeds from the outer ear to the cochlea, the auditory nerve, the cochlear nucleus and via the lateral pontine nucleus to the interpositus nucleus (Lavond, Kim and Thompson, 1993). The IP has also been shown to be critical structure in the development of an association between two stimuli and it has been suggested to be the locus of the long lasting memory trace of an CS – UCS association in nictitating membrane conditioning studies (Clark, Zhang and Lavond, 1992; Steinmetz and Thompson, 1991). It would be interesting to know what kind of role the IP has in the processing that utilizes the short-term memory trace in the auditory modality, as revealed by MMN. Furthermore, previous studies (Ruusuvirta, 1996; Ruusuvirta et al., 1996a) have shown that MMN-like ERPs can be found in the cerebellar cortex in rabbits, and we assumed that similar ERPs could be found also in the IP of the cerebellum.

One part of present study was to clarify the effect of cooling on MMN responses. In the cooling procedure the cold probe (cooling electrode) is placed to the brain tissue and the cooling gas is conducted from the gas delivery system via the cold probe to the target area. The cooling procedure is used to locally inactivate the brain tissue by lowering temperature temporarily. Temperatures of 8.5-20.0 °C are reported to reversible inactivate cell bodies but not affect fibers of passage (Zhang, Ni and Harper, 1986). The cold probe is placed near the target rather than in it to avoid physically damaging the target. The effective range of cooling extends 2.5 mm from the center of the probe tip (Clark et al., 1992). In this study, the cold probe was placed into the dentate nucleus next to the IP to temporarily inactivate it. The effects of cooling on MMN have not been previously studied, but we supposed that if the IP is critical area in analysis of auditory stimuli cooling might remove MMN-like ERPs in the IP. On the other hand, if the IP has not so critical role in analysis of auditory stimuli cooling has probably no impact on MMN elicitation.

The purpose of this study is to test the following hypotheses emerged from the presented studies. Firstly, we expect that MMN-like ERPs can be observed in the IP of the cerebellum in rabbits. Secondly, we expect that these MMN-like ERPs are specific to preceding standard stimuli, that is, they are observed in the oddball condition but not in the deviant alone condition. Thirdly, we predict that cooling has an influence on these MMN-like responses in the IP so that these responses can not be observed in the cooling condition.

Methods

Subjects

Subjects were six adult New Zealand albino rabbits (one male and five female) weighting 2.7 - 4.1 kg at the time of the surgery. The animals were individually housed in about 1 x 1 meter metal cages. The temperature, humidity and a natural day-light cycle (12 h light / 12 h dark) were maintained stable and the rabbits were given free access to food and water. The animals were cared for by veterinarians, experimenters and animal caretakers of the University of Jyväskylä. The experiment was carried out according to the regulations of the European Union for animal health and care in laboratories. All procedures were carried out during the daylight portion of the cycle.

Surgery and electrodes

Before the surgery, the animals were anesthetized with intramuscular injections of ketamine-zylazine coctail (Ketalar, 2.4ml, 50mg/ml; 0.8ml Rompun, 20mg/ml; NaCl 0.8ml) and the anesthesia was maintained during the operation by repeated muscular injections (about every 20-30 minutes). The eyes were treated with Oftan to prevent infections and dryness during the operation.

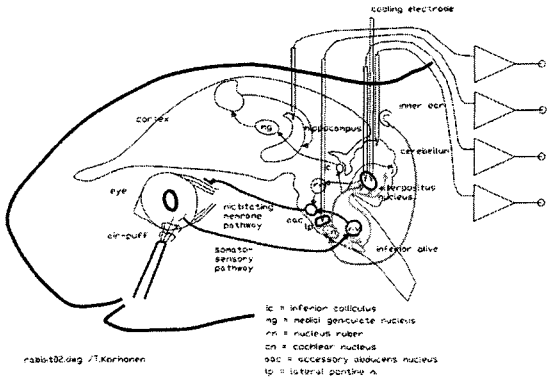

Figure 1. A schematic illustration of the cold probe (cooling electrode) in the dentate nucleus and the four recording electrodes (CA1 in the hippocampus, lateral pontine nucleus, HVI in the cerebellar cortex and IP in the cerebellum). Adapted from Korhonen (1997).

The head of the each rabbit was positioned in the stereotaxic device with bregma 1.5 mm above lambda. After drilling a hole overlying the cerebral and cerebellar cortex, seven teflon insulated stainless steel electrodes, tips about 70 μm (three stimulation electrodes and four recording electrodes) were lowered stereotaxically in their target areas. The final depths were determined by observing the activity on the oscilloscope. After implantation the electrodes were connected to two pin connectors which were cemented into place by dental acrylic mass together with four anchoring screws. Two interconnected scull screws were used as a reference electrode. For further details of the electrodes and the implantation procedure, see Korhonen (1991).

The stimulation electrodes were implanted into structures of the lateral hypothalamus (β -1.0mm, R 2.0mm; β +0.0mm, R 2.0mm; β +1.0mm, R 2.0mm), but they were not used in this study. The recording electrodes were implanted into the CA1 region of the hippocampus (β -5.0mm, R 5.0mm), the lateral pontine nucleus (λ +8.0mm, L 2.5mm), the cerebellar cortex (lobule HVI) (λ -0.5mm, R 5.0mm) and the interpositus nucleus of the cerebellum (λ +0.5mm, R 5.0mm) (Fig. 1). (In the given coordinates, β is used for bregma, λ for lambda, L for left, R for right and +/- for anterior/posterior). From these recording electrodes, the IP electrode were used in our study. In addition, the cold probe was implanted in the dentate nucleus in the cerebellum (λ +0.5mm, R 6.5mm) to cool and thus to temporarily inactivate the IP (Fig. 1.). The cold probe is able to inactivate tissue in an area of 2.5 mm around the tip, the distance about in which the IP is from the dentate nucleus. The electrodes and the cold probe were implanted using stereotaxic atlases of the rabbit brain (Sawyer, Everett and Green, 1954; Shek, Wen and Wisniewski, 1986).

Finally, after the surgery, the animals were given intramuscular injections of analgetics (Temgesic, 0.3 mg/ml). The animals were allowed to recover for at least one week before the experiments.

Apparatus

The animals were kept in a Plexiglas restrainer during the experiments. The restrainer was located into a ventilated, electrically shielded and sound attenuated box. The animals were observed during the experiment through a video monitor. The apparatus which was attached to the animal´s head included pre-amplifier and connector. The tone was transmitted from the tone generator outside the box via the plastic tube to the animal´s ear. The tube was positioned approximately 2.5 cm in front of the left ear of the animal.

Sampling rate was 500 samples per second. The voltage changes were amplified, filtered (high pass 0.1-200 Hz) and fed to an A/D converter (Data Translation DT2831G). A microcomputer delivered the trials, randomized the inter-trial intervals, and controlled the signal generator and another computer has control over the whole experiment.

The cold probe (its inner cannula) was attached to gas delivery system. The cooling gas was freon-like 1,1,1,2-Tetrafluroethane (KLEA R-134-A). The part of the cold probe outside the animal´s head is covered with the plastic protector. Cooling temperature was about 10-12 °C.

Stimuli and procedure

The animals were given a 2-day adaptation period in the measurement box before the experiments. No stimuli were presented in these days.

The experiment consisted of two experimental conditions, the oddball condition and the deviant alone condition. The deviant alone condition was used as a control procedure. The recordings were made in four different days. Each experiment day consisted of five separate sessions: first deviant alone session, three consecutive oddball sessions and last deviant alone session. The cooling procedure were used in the middle (second) oddball session in second day and in the last deviant alone session in the last (that is, fourth) day. Each session included 84 trials (except with subject 45; in two sessions trials after 66 and 67 were missing) and lasted about ten minutes. Afterwards bad trials were rejected. Experimental situations and practices were same to all animals, except the subject 45 to whom the recordings were not made in fourth day because of technical problems. In this subject, the cold probe was broken, and thus cooling could not been used.

The experiment consisted of 1500 Hz standard tones and 2000 Hz deviant tones of 50 ms duration (90 dB, measured at a distance of 2,5 cm) presented at an interstimulus interval (ISI) of 500 ms. The occurrence of standard and deviant stimuli was randomized and the probability of the deviant tone was 5 %.

Cooling was used to inactivate the neural tissue in purpose to create a reversible lesion in the IP. Before the cooling sessions a little pause was placed to make sure that cooling has time to have an effect to the dentate

nucleus and the IP. The animals were allowed to recover about five minutes after the cooling session before the next session was started.

Histology

After the all experiments, the animals were given a lethal dose of sodium pentobarbital and perfused with physiological saline followed by 10 % formaline. The brains were removed and kept in formalin solution about two weeks. The brains were frozen and sectioned into 100 µm slices from the sites of the electrodes with microtome and stained with cresyl violet. The sectioning was also videorecorded. The position of the electrodes were determinated by viewing the stained sections and videotaped sectioning. Exact locations of the electrode tips were compared to the coordinates of the stereotaxic atlas of Shek et al. (1986) and Sawyer et al. (1954). The histological results are shown below.

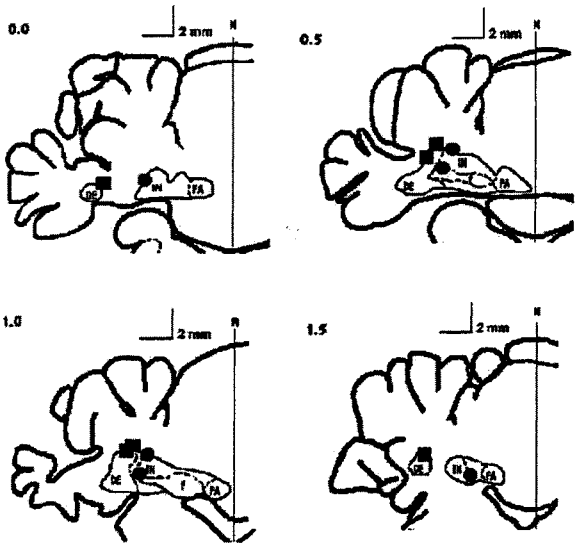

Figure 2. The histological results of the IP electrode tip locations are marked with circles and the cold probe tip locations with squares. The sections are taken from 0.0mm, 0.5mm, 1.0mm and 1.5mm anterior to lambda. Adapted from Thompson and McCormick (1980).

Data analysis

Data was collected using Brace computer program. In each trial, 1750 ms periods were collected. Statistical analyses were performed with SPSS 8.0 program (Windows).

An average of the sample points in 50 ms before each stimulus served as a baseline against which ERPs were corrected. The averages of all the trials in each sessions were used in t-tests. Blocks of sample points at 50 ms intervals were formed and used in analyses. All statistical analyses were performed by using paired t-tests.

The subject 46 had an erroneous wiring in consequence of false order of recording channel output and therefore the channel order was corrected in data analysis phase.

All animals were treated together in the t-tests and analyses were based on session types. The following comparisons were made: ERPs to standards and those to deviants in the oddball condition, ERPs to deviants in the deviant-alone condition and those to standards in the oddball condition, ERPs to deviants in the oddball condition and those to deviants in the deviant alone condition, ERPs to standards and those to deviants in the oddball cooling condition, ERPs to standards in the oddball cooling condition and those to deviants in the deviant alone cooling condition, ERPs to deviants in the oddball cooling condition and those to deviants in the deviant alone cooling condition, ERPs to standards in the oddball condition and those to standards in the oddball cooling condition, ERPs to deviants in the oddball condition and those to deviants in the oddball cooling condition, ERPs to deviants in the deviant alone condition and those to deviants in the deviant alone cooling condition.

Results

In the IP statistically significant differences ($p < 0.05$) were found between ERPs to deviants and those to standards in the oddball condition (MMN-like ERPs) at the latency range of 100-148 ms and 250-448 ms from stimulus onset (Fig. 3). These differences reflected ERPs to deviants being more positive than those to standards. Also there were significant differences between ERPs to deviants in the deviant alone condition and those to standards in the oddball condition at the latency range of 50-148 ms and 300-448 ms (Fig. 4). Thus, MMN-like ERPs at the latency range of 250-300 ms were elicited in the oddball condition only. ERPs to deviants in the oddball condition and those to deviants in the deviant-alone condition differed significantly at the latency range of 50-148 ms, ERPs to deviants in the deviant alone condition being more positive (Fig. 5).

Cooling did not remove MMN-like ERPs. In the oddball cooling condition significant differences were found between ERPs to deviants and those to standards at the latency range of 100-148 ms from stimulus onset (Fig. 6). These differences were at the same latency range than those in the oddball condition (Fig. 3) but in the cooling condition differences at later latencies (250-448 ms in the oddball condition) were missing. So, cooling had some impact on ERPs, but still MMN-like ERPs were elicited. When ERPs both to standards and deviants in the oddball cooling condition were compared to those in the oddball condition there were statistically significant differences only between ERPs to standards in these two conditions at the latency range of 150-198 ms from stimulus onset (See Fig. 7 and 8 in Appendix).

When ERPs to deviants in the deviant alone cooling condition were compared to those to standards in the oddball cooling condition the significant differences were found at the latency range of 100-198 ms from stimulus onset (See Fig. 9 in Appendix). ERPs to deviants in the

deviant alone cooling condition did not statistically differ from those to deviants in the deviant alone condition (See Fig. 10 in Appendix). There were no statistically significant differences between ERPs to deviants in the oddball cooling condition and those to deviants in the deviant alone cooling condition (See Fig. 11 in Appendix).

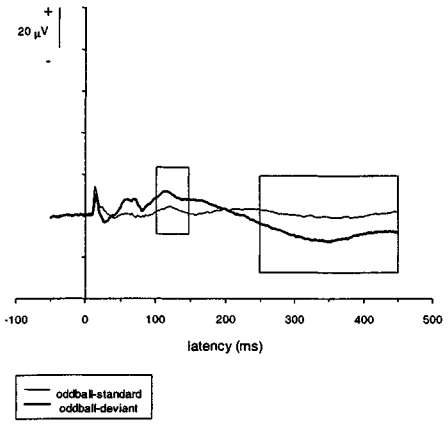

Figure 3. A grand average (N = 6) of ERPs to deviants (oddball-deviant) and ERPs to standards (oddball-standard) in the oddball condition. Rectangles superimposed on the pairs of curves indicate the latency range at which P-values of the paired t-tests were less than 0.05 (analyses are based on averaged 50-ms blocks of sample points).

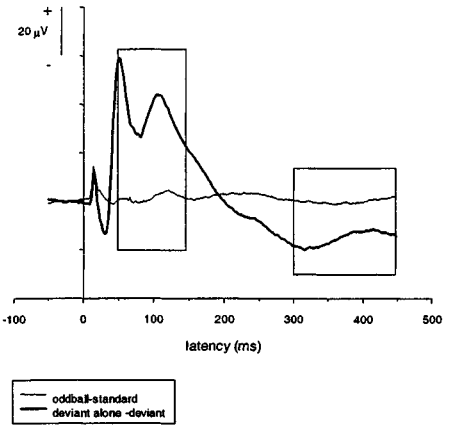

Figure 4. A grand average (N = 6) of ERPs to deviants in the deviant alone condition (deviant alone –deviant) and ERPs to standards in the oddball condition (oddball-standard). See Fig. 3. for further details.

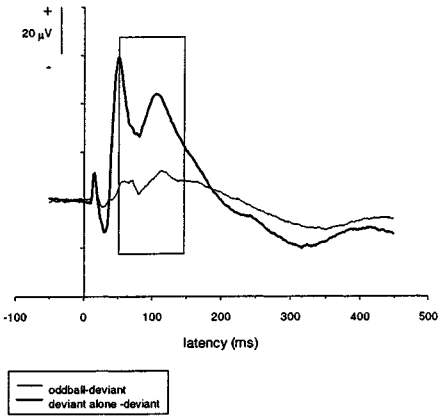

Figure 5. A grand average (N = 6) of ERPs to deviants in the oddball condition (oddball-deviant) and ERPs to deviants in the deviant alone condition (deviant alone –deviant). See Fig. 3. for further details.

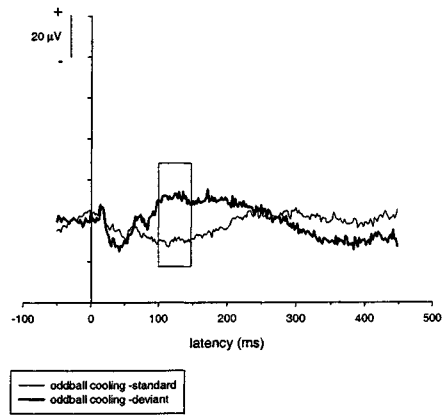

Figure 6. A grand average (N = 5) of ERPs to deviants (oddball cooling –deviant) and ERPs to standards (oddball cooling –standard) in the oddball cooling condition. See Fig. 3. for further details.

Discussion

In this study we found MMN-like ERPs, as revealed by the difference between ERPs to deviants and those to standards in the oddball condition in the IP of the cerebellum at the latency range of 100-148 ms and 250-448 ms (Fig. 3). This finding supports the first hypothesis which expected that such responses could be observed in the IP. The first differences (100-148 ms) seem to be elicited in the same latency range as MMN in human studies. The observed ERPs were specific to preceding

standards at the latency range of 250-300 ms, because they were elicited at this latency range between ERPs to deviants and those to standards in the oddball condition (Fig. 3) but not between ERPs to deviants in the deviant alone condition and those to standards in the oddball condition (Fig. 4), and in this respect they resemble MMN in humans (Näätänen, 1992). This supports the second hypothesis that the observed ERPs are specific to preceding standards. Therefore, at the latency range of 250-300 ms comparator process theory proposed by Näätänen (1990) could explain differences between ERPs to deviant and standard tones.

On the other hand, statistical differences between ERPs to deviants and those to standards in the oddball condition (Fig. 3) at the latency range of 100-148 ms and 300-448 ms were not specific to preceding standards, because differences at these same latencies were observed also between ERPs to deviants in the deviant alone condition and those to standards in the oddball condition (Fig. 4). In this respect the results do not support the hypothesis of standard specificity, and they are similar to those of Ruusuvirta (1996) who found that presentation rate *per se* was sufficient to explain the observed responses. So, in the present study, differences between ERPs to deviants and those to standards in the oddball condition (Fig. 3) included two kind of phenomena; the one that demanded the presence of standards (differences at the latency range of 250-300 ms) and the other in which presentation rate was sufficient to explain observed differences between deviant and standard ERPs (differences at the latency range of 100-148 ms and 300-448ms). These results thus resemble those of Ruusuvirta et al. (1998) who found that MMN-like ERPs observed at the latency range of 63-243 ms in rats were specific to preceding standards at the latency range of 63-196 ms and therefore showed concordance with MMN in humans. These MMN-like responses in rats were found from the auditory cortex. Our results showed that this same phenomenon can be found already in the deeper areas, such as the IP.

The first significant differences between ERPs to deviants in the deviant alone condition and those to standards in the oddball condition (Fig. 4) were found earlier than differences between ERPs to deviants and those to standards in the oddball condition (MMN) (Fig. 3), already at the latency range of 50 ms. Also differences between ERPs to deviants in the oddball condition and those to deviants in the deviant alone condition were found already at the latency range of 50 ms (Fig. 5). These findings might possible be linked with human-like N1 response, which in humans can usually appear already at 50-100 ms and have been shown to precede or overlap MMN (Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1989). N1 wave is exceptionally sensitive to the stimulus rate (Näätänen, 1990), so that when stimulus is repeated, N1 is reduced, and in the condition where stimuli are delivered alone (without standards) N1, even rather than MMN, is elicited (Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1989). So, in this study, rarely presented deviants in the deviant alone condition, when compared to ERPs to standards in the oddball condition, might have elicited response, which resemble NI in humans.

The finding that statistically significant differences were found between ERPs to deviants in the deviant alone condition and those to deviants in the oddball condition at the latency range of 50-148 ms (Fig. 5) conforms with the theory that, because of the difference in presentation rate between deviants and standards, afferent neural elements differ in terms of their level of refractoriness. In the course of the series, deviant related neurons will remain responsive, because of long ISIs between consecutive deviant stimuli. In contrast, neurons responsive to the standard stimulus frequency, as well as those responsive to both frequencies, will become strongly refractory because of the fast rate of the effective stimuli (Näätänen, 1992). In the oddball condition partly the same afferent paths are responsible for standard and deviant responses and neurons of these afferent paths become refractory because of fast presentation rate of standard stimuli. This might explain why ERPs to deviants in the oddball condition were weaker than in the deviant alone condition (Fig. 5). Because frequencies of standard and deviant tones are quite similar (1500 Hz and 2000 Hz), the same afferent paths take care of both standard and deviant responses. This can also be related to the overlapping representation areas of standard and deviant stimuli in the brain. Standard stimulus activates part of the representation area of the deviant stimulus and therefore ERPs to deviant stimulus is weaker in the oddball condition. The earlier study (Ruusuvirta et al., 1996a) suggested that an active neural process such as habituation rather than refractoriness could explain the decreased ERPs to repetitive standard stimuli. Thus, our finding that ERPs to deviants were weaker in the oddball condition than those in the deviant alone condition might be explained also according to habituation. Habituation is specific to repeated stimuli, and so in the oddball condition the repeated standard stimuli lead to habituation reaction. However, whatever the neural mechanisms behind our observation might be, whether they are active processes or represent the neuronal refractoriness can not be resolved with this data.

Cooling did not remove MMN-like ERPs, because in the oddball cooling condition MMN-like ERPs were elicited at the latency range of 100-148 ms, which is the same latency range in which the MMN is normally elicited in humans. However, cooling removes in the oddball condition the differences between ERPs to deviants and those to standards at the latency range of 250-448 ms (Fig. 6 and 3), that is, also standard-specific MMN-like ERPs (250-300 ms). However, because MMN-like ERPs are still elicited in the cooling condition, results do not support the third hypothesis of this study, that cooling removes MMN-like ERPs. This would imply that the IP has not so critical role in the generation of MMN and that MMN is generated in other areas in the brain. In addition to the finding that cooling removes differences between ERPs to deviants and those to standards in the oddball condition at the latency range of 250-448 ms (Fig. 6), cooling also removes differences between ERPs to deviants in the deviant alone condition and those to standards in the oddball condition at the latency ranges 50-100 ms and 300-448 ms (See Fig. 9 in Appendix). Thus, cooling seems to affect to MMN-like

ERPs at later latencies. However, cooling had no impact on MMN-like ERPs. In the condition where cooling was used differences between ERPs to deviants in the deviant alone cooling condition and those to standards in the oddball cooling condition were found also at the latency range of 150-198 ms (See Fig. 9 in Appendix), which did not appear between ERPs to deviants in the deviant alone condition and those to standards in the oddball condition (Fig. 4). This is an interesting finding, but difficult to explain in this context. However, it seems that cooling changes a little ERPs to deviants after the first fast deflections.

Cooling had impact on ERPs to standards in the oddball condition: significant differences between ERPs to standards in the oddball condition and those to standards in the oddball cooling condition were found at the latency range 150-198 ms (See Fig. 7 in Appendix). Significant differences were not found between ERPs to deviants in the oddball condition and those to deviants in the oddball cooling condition (See Fig. 8 in Appendix), neither between ERPs to deviants in the deviant alone condition and those to deviants in the deviant alone cooling condition (See Fig. 10 in Appendix). The finding that cooling had an impact only on ERPs to standards could be linked to the fast presentation rate of standard stimuli (short ISI) in the oddball condition. Maybe processes underlying ERPs to stimuli at the short ISI (ERPs to standards) are more sensitive to the effect of cooling than those underlying ERPs to deviants at longer ISI.

Conclusively, the present results imply that deviant tones were neurophysiologically discriminated from standard tones in rabbits. The observed MMN-like ERPs were specific to preceding standards at the latency range of 250-300 ms implying that these ERPs resemble MMN in humans also in this respect. Our finding that the MMN-like ERPs can be elicited in the IP supports the earlier finding of the IP as a part of the secondary auditory pathway. Ruusuvirta (1996) and Ruusuvirta et. al (1996a) have also found the MMN-like ERPs in the cerebellar cortex. Along the same lines, this study indicated that MMN-like ERPs can be found also deeper areas of the cerebellum, that is, in the IP. Cooling affected only slightly to these MMN-like ERPs in the IP. This suggests that even if conditioning studies (Clark et al., 1992; Steinmetz and Thompson, 1991) have shown that the IP is the locus of the long lasting memory trace of an CS-UCS association, it is not the area where the short-term memory trace of MMN is elicited. Therefore, it seems that the IP is not an critical area in generation of MMN, even if MMN-like ERPs are observed in the IP.

More studies about effects of cooling on MMN with larger amount of trials would be needed, as well as studies about cooling using measurements before and after cooling with possible control group. This is the first study investigating the MMN-like ERPs in the IP, and also effect of cooling on these ERPs. It would be interesting to study these issues more in the future and further clarify the role of other deep structures in the generation of MMN.

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Appendix

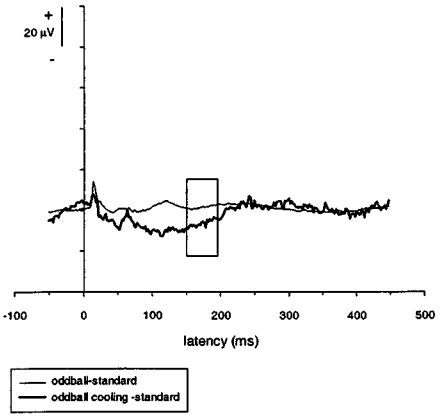

Figure 7. A grand average (N = 5) of ERPs to standards in the oddball condition (oddball-standard) and ERPs to standards in the oddball cooling condition (oddball cooling –standard). See Fig. 3. for further details.

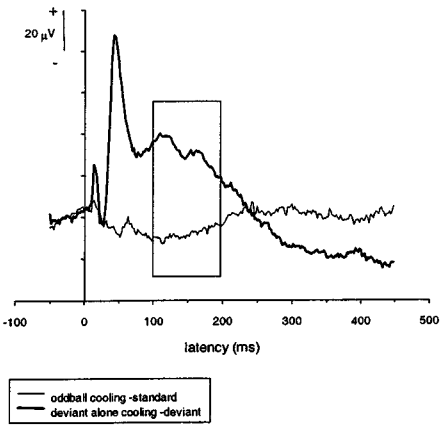

Figure 9. A grand average (N = 5) of ERPs to deviants in the deviant alone cooling condition (deviant alone cooling -deviant) and ERPs to standards in the oddball cooling condition (oddball cooling –standard). See Fig. 3. for further details.

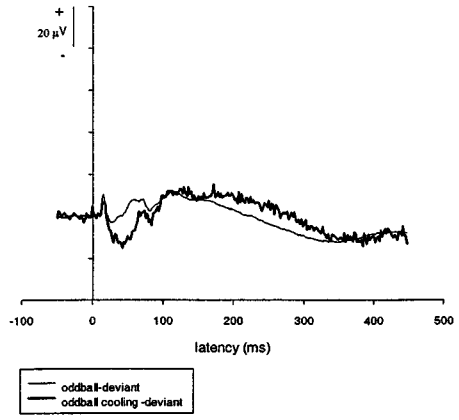

Figure 8. A grand average (N = 5) of ERPs to deviants in the oddball condition (oddball-deviant) and ERPs to deviants in the oddball cooling condition (oddball cooling –deviant). See Fig. 3. for further details.

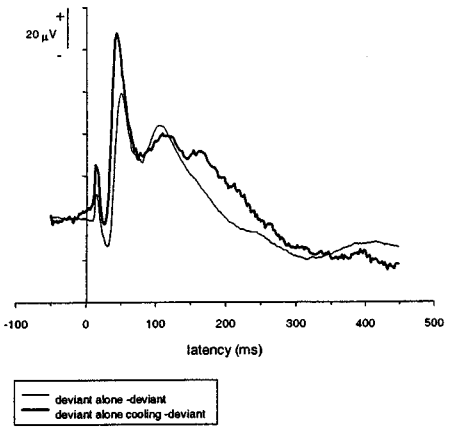

Figure 10. A grand average (N=5) of ERPs to deviants in the deviant alone condition (deviant alone –deviant) and ERPs to deviants in the deviant alone cooling condition (deviant alone cooling –deviant). See Fig. 3. for further details.

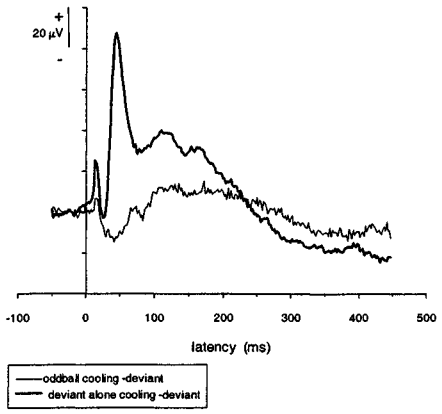

Figure 11. A grand average (N = 5) of ERPs to deviants in the oddball cooling condition (oddball cooling –deviant) and ERPs to deviants in the deviant alone cooling condition (deviant alone cooling –deviant). See Fig. 3. for further details.

MISMATCH NEGATIVITY IN AUDITORY SYSTEM

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CONTENTS

1. AUDITORY SYSTEM

Brain is a complicated system both structurally and functionally. There are excitatory and inhibitory effects in the brain, and brain function as a neural network system where different areas have huge amount of connections among each other. This is also true what comes to an auditory system. The auditory system provides both ipsilateral and contralateral inputs to the cortex, unlike the visual system. However, the majority of the input is contralateral (Kolb andWhishaw, 1990).

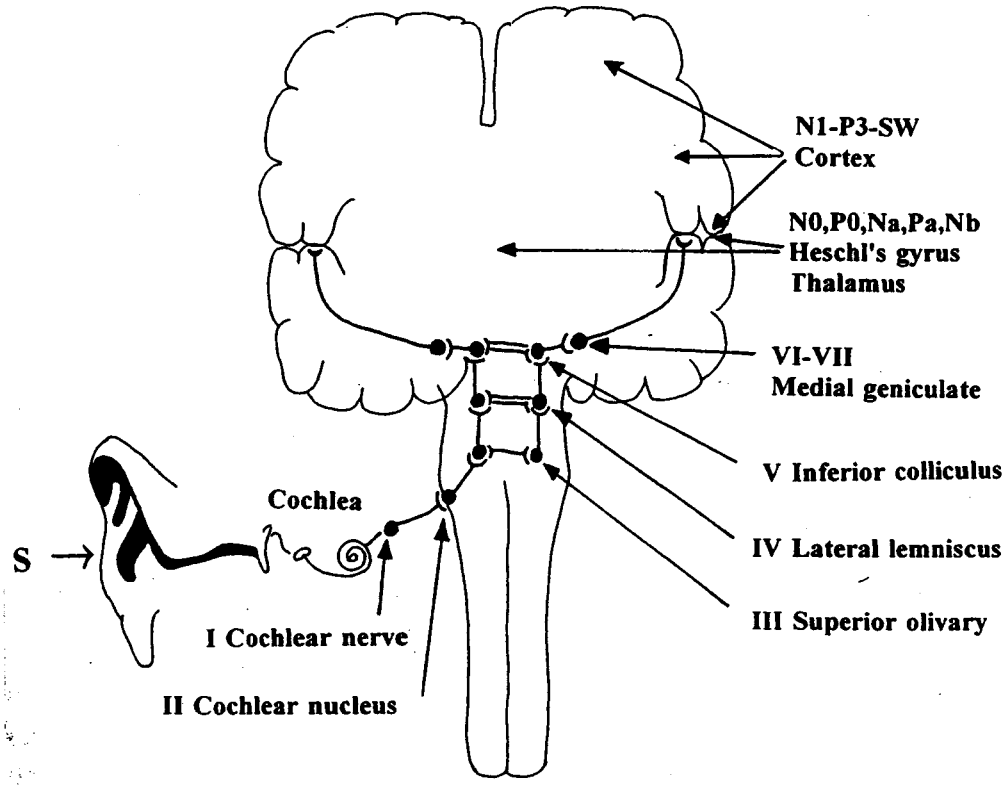

FIGURE 1. Auditory areas in the brain (From Hugdahl, 1995).

In this review we concentrate on two auditory pathways. The first, main pathway (like all other auditory pathways) begins from the **outer ear** (for this pathway, see Figure 1). The sound vibrations generate fluid waves in the **cochlea**, where they vibrate hair cells. These vibrations of the hair cells are transformed into electrical signals in the **auditory nerve**.

Auditory signal proceeds from auditory nerve to **cochlear nucleus (CN)**, which is located on the dorsolateral side of the brainstem between the spinal cord and pons and which has been suggested to be involved in the binaural analysis (Romand and Avan, 1997).

After cochlear nucleus auditory signal goes to the **superior olivary complex (SOC)** in the brainstem (the CN sends its projections also to the lateral lemniscus and the inferior colliculus). The SOC is a major binaural processing center and may play an important role in the localization of a sound source in space (Helfert, Snead and Altschuler, 1991; Rouiller, 1997).

Next step is the **lateral lemniscus (LL)**, which is major fiber pathway connecting the lower auditory brainstem with the **inferior colliculus (IC)** and the **medial geniculate nucleus (MGB)**. The inferior colliculus is the main structure of the mesencephalon and it is highly integrative center. The MGB is the principal thalamic relay of the auditory pathway. (In addition to the MGB, also two thalamic structures belong to the auditory pathways: the lateral part of the posterior complex of the thalamus, PO, and the posterolateral sector of the reticular nucleus of the thalamus, NRT).

From the MGB of the **thalamus** auditory information goes to the **auditory cortex**, which has many subareas having numerous interconnections among each other. The cortex has six layers, each of which has connections to the lower auditory nuclei. Layer I receives input from the medial division of the MGB. The deep layers (V and VI) has descending projections terminating in the inferior colliculus and auditory thalamus (Caspary and Finlayson, 1991; Ehret, 1997; Hugdahl, 1995; Helfert and Aschoff, 1997; Helfert, Snead and Altschuler, 1991; Kelly, 1991; Kolb and Whishaw, 1990; Phillips, Reale and Brugge, 1991; De Ribaupierre, 1997; Romand and Avan, 1997; Rouiller, 1997; Winer, 1991).

Another auditory pathway proceeds from the **outer ear** to **cochlea**, **auditory nerve** and **cochlear nucleus** and via **lateral pontine nucleus** to the **interpositus nucleus** in the cerebellum (Lavond, Kim, and Thompson, 1993). (For auditory areas in the cerebellum, see Figure 2)

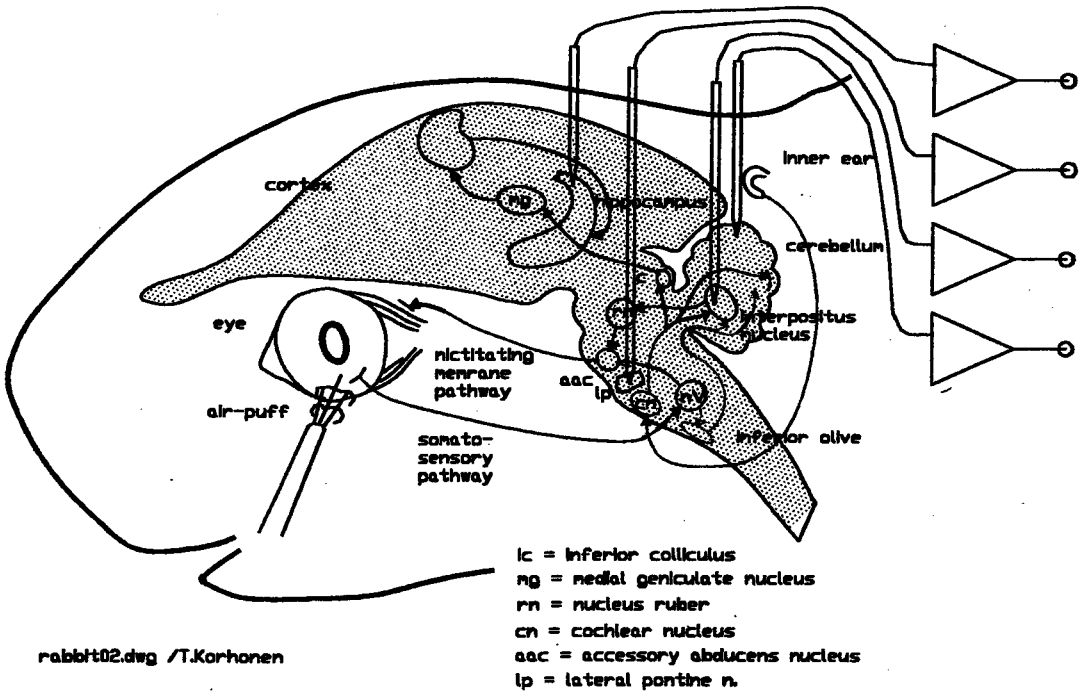

FIGURE 2. Electrodes in main auditory areas in the cerebellum (related to the another auditory pathway), hippocampus and lateral pontine nucleus. (T. Korhonen).

2. ERP COMPONENTS

The spontaneous electrical activity of the brain can be recorded for example by EEG on the surface of the skull or intracranially. Event-related potentials (ERPs) are changes in this electrical activity locked to a specific event or stimulus. ERP composes of electric fields which are generated by flow of current when huge amount of neurons are activated at the same time. The most frequently used method to extract ERPs is the technique of averaging (Galik and Conway, 1997).

Electrical activity on the surface of the skull picked up by the electrode is not necessarily from the area straight behind the electrode. Therefore, the spatial resolution of the EEG measurement is not quite exact because of the distance between the electrode and the generating area. Compared to these surface methods intracranial recordings are much more exact both spatially and temporally (only few milliseconds).

In early research involving these measures of brain potential, the term ´evoked potential´, or EP, was used. Nowadays the term ´event-related potential´ is preferred. However, in some studies we shall review, the term EP is still used.

ERPs have several negative and positive deflections, called components (see Figure 3). These components can be classified according to many factors, for example polarity of waveform (positive or negative), latency (milliseconds, for example P300), ordinal number (for example N1, N2, etc.), nature of the stimulated pathway or structure (sensory modality), cranial distribution or whether components occur before or after the stimulus. ERP components can be classified also along an exogenous – endogenous origin (Coles and Rugg, 1995; Hugdahl, 1995), the categorization which we will concentrate in this review. However, this classification is not so simple, because the same component can consist both exogenous and endogenous features. Identification and studying particular components of the scalp recorded ERPs as markers of specific aspects or stages of information processing is the important goal of cognitive psychophysiology (Karmos, Molnar, Csepe and Winkler, 1989).

2.1. Exogenous components

The exogenous ERP components usually occur within the first 100 – 200 ms after the stimulus onset (Hugdahl, 1995). They are evoked by the external stimulus features and reflect the first neural processing of the physical characteristics of a stimulus (Rockstoh, Elbert, Birbaumer and Lutzenberger, 1982; Hugdahl, 1995). They are relatively stable and have a short latency and modality specificity of scalp distribution. These components are obligatory and the magnitude of the response is not dependent of the cognitive processing of the stimulus (Coles and Rugg, 1995; Hugdahl, 1995). They are also independent of subject's state of arousal and they have high intraindividual stability (Rockstoh et al., 1982).

Auditory evoked potentials (AEPs), visual evoked potentials (VEPs) and somatosensory evoked potentials (SEPs) usually belong to exogenous ERP components, because they have primary sensory origin and therefore they occur quite erly after stimulus onset. The exogenous components can be divided into the subgroups by their latency into early components, middle latency components and long latency components (Näätänen, 1992; Hugdahl, 1995).

The early exogenous components occur after 8 ms from the stimulus onset and are generated by brainstem (Hugdahl, 1995). In auditory modality (AEPs) they are called the auditory brainstem responses (ABR or BAEPs). The ABR consist of seven peaks or waves within some 10 to 50 ms following the eliciting acoustic stimulus (see Figure 3). Wave I (P2) consist of the summated action potentials evoked by fibers of the auditory nerve; wave II (P3) most likely originates from the cochlear nucleus, wave III (P4) from the superior olivary complex, waves IV and V (P5, P6) from the midbrain, and wave VI (P7 – P12) from above the midbrain level (perhaps the medial geniculate nucleus) (Rockstroh et al., 1982).

A change in stimulus intensity changes the latency, amplitude and morphology of ABR. ABR have low amplitude and high frequency, and they are very sensitive to behavioral state or anesthesia. They have been found to have considerable clinical utility for noninvasively monitoring brainstem function and helping to localize brainstem lesions in humans.

The middle exogenous latency responses (MLR) N0, P0, Na, Pa and Nb appear 10 – 12 ms after stimulus onset (Näätänen, 1992) (see Figure 3). In auditory modality these middle latency responses are called auditory EPs (MLAEPs; latency 10 – 50 ms) (Halgren, 1990).

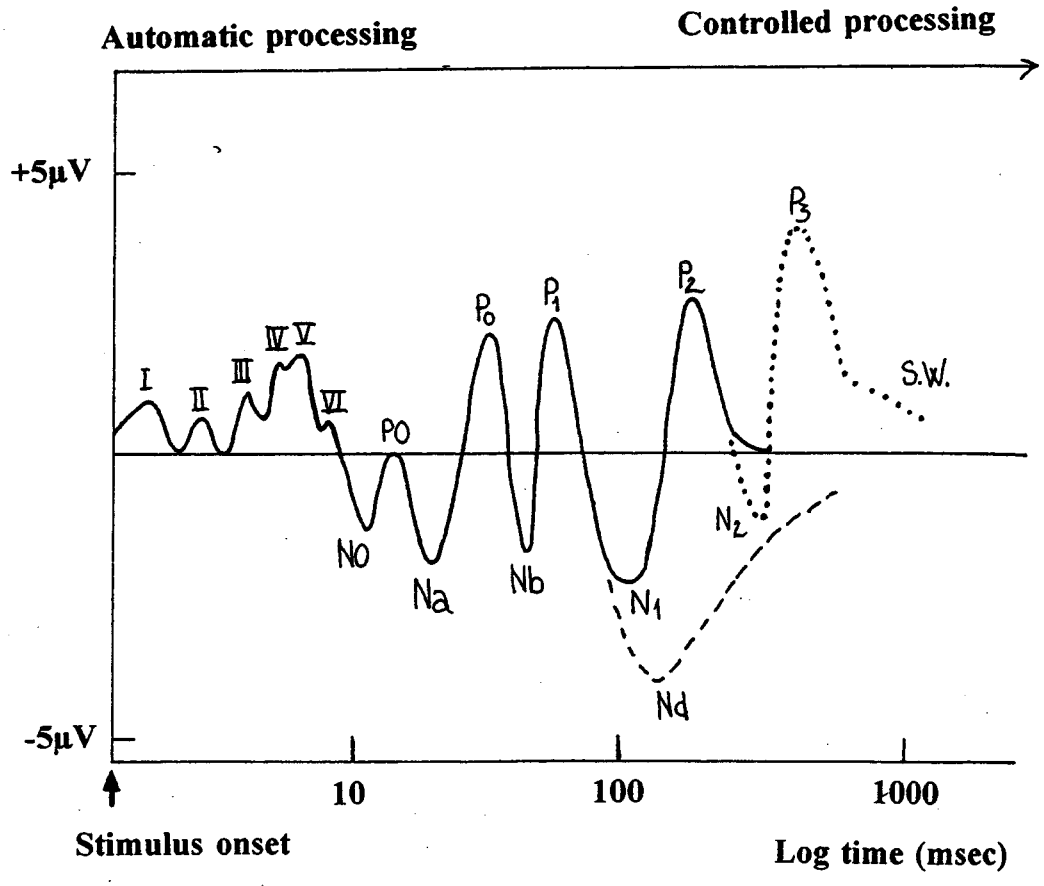

FIGURE 3. ERP components after the auditory stimulus. The waveforms of ABR are numbered I – VI. The other components are presented in the text (From Hugdahl, 1995).

The middle exogenous latency responses are recorded in the immediate vicinity of Heschl´s gyrus, and thus primary auditory cortex. They possibly reflect also the activity of auditory thalamus (Hugdahl, 1995; Näätänen 1992). When stimulus intensity is decreased, MLR decreases in amplitude and increases in latency (Näätänen 1992). MLR is quite similar to ABR; for example Makeig (1990) found that MLR amplitudes depend strongly on the interstimulus interval (ISI). MLR is also very sensitive to anesthesia and it has been proposed that MLR could be used in monitoring anesthetic depth (Näätänen 1992).

The long latency, or late (exogenous) ERP components N1 and P2 appear from 50 ms to 300 ms after stimulus onset (Coles and Rugg, 1995). The long latency auditory EPs are called LLAEPs and they occur in the same latency range (Halgren, 1990).

The late ERP components N1 and P2 and also P1 can be called "vertex potential" waves (Coles and Rugg, 1995) and also transient responses because they share characteristics with endogenous components. They are maximally present in frontocentral scalp regions. P2 component is closely related to N1 and they typically occur together in the auditory modality. Their scalp distributions are different: N1 is maximal over the vertex (Cz) of the scalp, whereas the P2 is not so focally localized (Hugdahl, 1995; Näätänen, 1992). The auditory N1 is possibly generated by the auditory cortex. On the other hand, N1 has been thought to have generation source in a deep occipito-temporal areas or a relatively more broadly distributed parietal site of generation (for a review, see Mangun and Hillyard, 1995). The scalp distribution of the P1 component shows an occipital maximum and thus is consistent with a generator in the visual cortex (Mangun and Hillyard, 1995).

The N1 response can be elicited both by onset and offset of a stimulus, and also by a change in the tonal frequency or intensity of a continuous auditory stimulus. The N1 wave is exceptionally sensitive to the stimulus rate. Also state factors, such as alertness and arousal, sleep and drugs have effects to N1 (Näätänen 1990). The N1 is related also to selective attention (Hugdahl, 1995). Several studies suggest that N1 amplitude also correlates with task performance, and that it is larger when the level of performance is higher (Näätänen 1990).

2.2. Endogenous components

Endogenous components occur from 100 – 200 ms and up to 500 –1000 ms (Hugdahl, 1995). According to Rockstoh et al. (1982), the peak latency of endogenous components varies between a minimum of some 100 ms and a maximum up to several seconds and they have modality-nonspecific scalp distribution. These components are quite independent from the physical parameters of the evoking events and are determinated by cognitive events or processes like attention or memory. They are elicited in complex experimental situations and often require active participation from the subject (Hugdahl, 1995).

The N2 (or N200) is a task-related endogenous component (for a review, see Coles and Rugg, 1995) occurring around 200 ms after the presentation of a deviant stimulus in a train of stimuli. N2 can be divided to two subcomponents, N2a (= MMN) and N2b. N2b is a endogenous component, but N2a is considered as exogenous component. (Hugdahl, 1995). The N2 is most reliably observed if a stimulus is omitted from time to time within a series of stimuli (Rockstroh et al., 1982). According to Rockstroh et al. (1982) the scalp distribution of the N2 differs, whether the omitted stimulus is visual or acoustic. Acoustic stimuli produce a precentral N2 maximum, visual stimulation a parieto-occipital maximum. Also the amplitude of N2 varies with stimulus modality. Furthermore, the N2 is influenced by the length of the interstimulus interval (ISI), showing decreased amplitude and increased latency with increasing ISIs. The N2 probably reflects the detection of a rare or complex, task relevant event which may also be the absence of an expected event. The component N2 seems to develop for attended, as well as unattended, stimuli as a "deviation" effect. That is why it is sometimes associated with the mismatch process (Rockstroh et al., 1982).

Like N2b, the late component called P3 (or P300) (see Figure 3) belongs to endogenous components. The P3 component is a cognitive (Javitt, Doneshka, Zylberman, Ritter, Vaughan, Jr., 1993) modality-nonspecific large positive wave that peaks around 300 ms (or 240 – 700 ms) after presentation of a stimulus when the subject is actively attending to that stimulus (Hugdahl, 1995; Halgren, 1990). It was first discovered by Sutton, Brauen, Zubin and John in 1965. It is probably the most studied wave of all ERP components (Hugdahl, 1995). The P3 is preceded by additional

cognitive components that index prior stages of auditory information processing (Javitt, Steinschneider, Schroeder, Vaughan and Arezzo, 1994). The scalp recordings have suggested that primary generator source of the P3 is the temporal parietal cortex. The depth recordings in humans have also suggested that components of the limbic system (e.g. hippocampus) are of major importance in P3 generation (Buchwald, 1990). At least some aspects of P3 seems to be generated in hippocampal areas. Thus it has been suggested that P3 is related to memory and learning (Hugdahl, 1995). The P3 consists of two distinct waveforms, P3a (with a latency around 250 ms) and P3b (with a peak latency around 300 ms). The P3a has a significantly shorter latency than the P3b and the P3a occurs to unattended rare stimuli whereas the P3b requires attention. The P3a has a more frontal scalp distribution (Hugdahl, 1995; Pineda, Foote, and Neville, 1987), whereas the P3b distribution is more parietal (Hugdahl, 1995). It has been thought that differences in the scalp distribution of the P3 suggest that a frontally pronounced P3 reflects passive attention and may be related to orientation and response inhibition, while a parietally pronounced P3 is associated with the different stages of recognition (Rocksroh et al., 1982). It has been also suggested that P3 in general is closely linked to the orienting response (OR) (Hugdahl, 1995).

The most typical paradigm in which the P3 can be observed is the oddball paradigm. Oddball paradigm is a stimulus condition in which an infrequent (deviant) auditory stimulus occurs in a sequence of repetitive (standard) auditory stimuli (Näätänen, 1990).

The determinants of the P3 are the probability, task relevance and the feedback value of a stimulus (Rockstroh et al., 1982). The amplitude of the P3 increases the more improbable the stimulus becomes. According to Hillyard and Woods (1979) the criteria for the P3 is that subjects must actively attend and discriminate targets from non-targets, that targets must require different responses or have different meanings than non-targets, and that the amplitude of the P3 is proportional to how expected the target is. There are several hypotheses about the functional significance of the P3 (Rockstroh et al., 1982). For example it has been concluded that P3 could reflect adjustments of memory representations. The P3 has been also considered to be a neural correlate of such cognitive functions as sequential information processing, short-term memory, and/or decision making. The P3 component can be missing or abnormal in various kinds of diseases or dysfunctions, e.g. schizophrenia (Javitt, Doneshka, Zylberman, Ritter and

Vaughan Jr., 1993), epilepsia, Alzheimer's disease, chronic alcoholism, childhood hyperactivity and autism (Kemner, Verbaten, Cuperus, Camfferman and van Engeland, 1995). The P3 has also possible use in differentiating depression from dementia.

The component called N4 (or N400) is one of the so called cognitive component and it can be regarded as the longest-latency processing negativity. The N4 is evoked at a latency-to-peak of about 400 ms by tasks requiring associative activation relation to semantic meaning, especially to the violation of semantic expectancies (Halgren, 1990; Coles, Gratton and Fabiani, 1990). However, subsequent studies have found that the N4 is evoked in many situations that do not appear to involve incongruity with the established context. The N4 is typically evoked by task-relevant words, faces, and meaningful line drawings. Effective tasks include reading, recognizing, naming, categorizing and rhyming.

Contingent negative variation, CNV is one of the so called movement-related potentials (MRP). It was first observed by Walter and his colleagues (Coles and Rugg, 1995). According to Picton and Stuss (1980) CNV describe the slow negative potential shift that develops during warned fore-period prior to an event such as the presentation of a motor or a mental task. The shift towards negativity starts approximately 400 ms after the onset of the warning stimulus and usually terminates with the imperative stimulus (Rockstroh et al., 1982). It has been suggested that CNV may be decomposed into two components: a sensory component, reflecting the effect of the warning stimulus and a motor or readiness component, reflecting the anticipation of the second imperative stimulus (for a review, see Hugdahl, 1995). The scalp distribution of the CNV is widespread and the CNV is maximal at moderate levels of arousal. The early CNV has a modality-specific distribution, being maximal frontocentrally to auditory stimuli (Coles and Rugg, 1995; Halgren, 1990). The late CNV has a topography that may vary with the task requirements. It has been suggested that CNV reflects various psychological functions, like expectancy, motivation, volition, arousal, attention, preparation, information processing and a scopeutic mode of action (scopeutic = something one wishes to effect or attain) (Rockstroh et al., 1982, Halgren, 1990).

Processing negativity (PN) is a slow endogenous negative component related to selective attention (Näätänen, Gaillard and Mäntysalo, 1978) and it can be seen as a earliest endogenous component. Näätänen has not mentioned the exact onset latency of the PN, but he proposes that this latency depends on the ISI. So, with short ISIs, PN

onset occurs early enough to overlap N1 peak (Näätänen, 1992). Näätänen et al. have suggested that PN might be generated in the auditory cortex. Näätänen has also proposed that early PN component is generated in the sensory specific cortex and late component in frontal regions (Näätänen, 1992).

3. MISMATCH NEGATIVITY (MMN)

Mismatch negativity (MMN) is a negative component of event-related brain potentials, specific to stimulus change. It is a cognitive (Javitt, Steinschneider, Schroeder, Vaughan and Arezzo, 1994; Schröger, Tervaniemi and Näätänen, 1995), short-latency context-dependent component (Näätänen, 1990) which is related to echoic memory. Because of these features the MMN is considered as a endogenous component. On the other hand, the MMN has some features typical to exogenous components, such as attention independence. Evidence that the MMN is an exogenous component can be found in literature. For example the N2a (MMN) has been referred as exogenous (Hugdahl, 1995). Anyway, it seems to us that different authors have different opinions about which of these two categories the MMN belongs to.

The MMN is one form of processing negativities and it is evoked by a stimulus that does not match preceding stimuli on simple sensory characteristics, even if that stimulus is neither attended nor detected (Näätänen, Simpson and Loveless, 1982). The MMN is elicited by a physically deviant stimulus occurring in a sequence with a series of homogenous, or standard, stimulus, so called typical oddball paradigm (Näätänen, Gaillard and Mäntysalo, 1978). MMN has also been recorded in atypical oddball paradigms where several deviants or standards are present (Kraus, McGee, Carrell and Sharma, 1995). However, the MMN occurs only when a deviant stimulus is presented in the context of a sequence of standard stimuli (Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1989). It has been observed that auditory cortical neurons of cat can exhibit stronger responses to a tone presented in a sequence of five tones than to the same tone presented alone (McKenna, Weinberger and Diamond, 1989).

Besides the typical and atypical oddball paradigm, Grau, Escera, Yago and Polo (1998) have proposed a new, faster paradigm to MMN elicitation. This paradigm is based on the use of trains of stimuli (three in this study) that are delivered at a very short interstimulus interval (ISI) (300 ms) to develop the sensory memory trace in the shortest possible time. In this paradigm trains started randomly with a deviant or standard stimulus (50% each) and the inter-train interval was varied according to so called memory probe interval (MPI). In this study, the MMN was obtained in young

people both at short and long ISIs at MPIs 0,4 and 4,0 s, but in older group the MMN suppressed at a MPI of 5,0 s. This suppression in MMN confirmed that this new paradigm is a useful tool for exploring auditory sensory memory decay. Also, the new paradigm has an advantage of obtaining the MMN in one-third the time of the conventional paradigm.

The MMN component was discovered by Risto Näätänen when he and his colleagues isolated it from auditory N2 wave. They divided the auditory N2 into two components (as mentioned earlier): an earlier-latency MMN (or sometimes referred as N2a) and a later N2b (Näätänen, 1992). The N2b usually follows and partly overlaps the MMN to deviant stimuli in an attended stimulus sequence (for a review, see Alho, 1995). In Scherg et al.'s study MMN was divided to two subcomponents, MMNa and MMNb (Scherg, Vajsar and Picton, 1989). MMNa preceeds MMNb in latency, but the two overlap. MMNa is observed in response to large differences between standard and deviant stimuli whereas MMNb is seen to small stimulus differences. These two components can be located at the different areas on the scalp, MMNb being located more anteriorly and orienting more frontally and laterally. MMN usually overlaps N1 and P2 components (Alho, Sainio, Sajaniemi, Reinikainen and Näätänen, 1990; Alho et al., 1993; Alho, 1995; Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1989), which usually appear from 50-300 ms after stimulus onset, N1 at about 100 ms and P2 about 200 ms. P3 and the other late endogenous components are supposed to be time-locked to MMN.

The MMN is usually isolated by subtracting the responses to standard tones from responses to deviant tones (Giard et al., 1995). MMN has been demonstrated to be largest frontally and larger over the right than left hemisphere (Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1989; Näätänen, Paavilainen and Reinikainen, 1989). The short-term memory store has thought to be the basis of the MMN and a crucial process prior to the higher level information processing (Csepe, Karmos and Molnar, 1987).

MMN is characterized by many features that distinguish it from other exogenous and endogenous ERP components that are sensitive to irregularities in repetitive stimulation, such as the P1, N1, N2b, P3a, P3b, or N400. These features are for example specificity to the auditory modality, its neural generation, automaticity, sensitivity to rather small deviations, relation to auditory sensory memory and its high correlation with behavioral discrimination performance (Schröger, 1998).

The auditory MMN is elicited at least by frequency, intensity, spatial, phonemic, rise time and duration changes. What comes to the duration and temporal changes, the MMN is elicited by duration decrements and also increments (Näätänen, Paavilainen and Reinikainen, 1989). MMN can be even elicited with a partial omission of a stimulus (Nordby, Hammerborg, Roth and Hugdahl, 1994; Näätänen, Paavilainen, Reinikainen, 1989), although the results of the omission studies have not been clear (Näätänen, 1992). However, Yabe, Tervaniemi, Reinikainen and Näätänen (1997) found a MMN even to a complete omission when the stimulus onset asynchrony (SOA, that is, the stimuli in the block starts at the different latency in different times) was shorter than 150 ms. In a later study (1998) Yabe et al. found that MMNm was elicited by stimulus omission with three different SOAs under 150 ms:100, 125, and 150 ms. MMN has even been elicited by synthesized instrumental tones (Vaz Pato and Jones, 1999).

MMN can be studied electrically as well as by measuring magnetic fields, when MMN is usually called MMNm or MMF. Kofoed, Bak, Rahn and Saermark (1995) studied magnetic mismatch field (MMF) in a tone-duration discrimination task. They also presented a new component, M2", which they proposed to indicate the beginning of the evaluation of the tone duration, while the MMF indicates the end of this process.

Mismatch negativity has also been observed in animals by intracranial and scalp recording studies. The term 'MMN-like' has been used to distinguish the MMN in animals from that in humans.

MMN has usually been found only in auditory modality. MMN and other later occurring auditory components (such as the P300) measure auditory and speech discrimination, processing, and cognition, while early and middle latency responses occurring before 50 ms measure hearing sensitivity (Stein, Kraus, McGee and Koch, 1995).

Besides auditory modality there are very few studies about MMN in other modalities. There have been attempts to record MMN in visual and somatosensory modalities, but a visual or somesthetic phenomenon analogous to the auditory MMN has not yet been satisfactorily demonstrated (Näätänen, 1992). However, later Kekoni et al. (1997) observed same kind of negativity than auditory MMN in human somatosensory system. Astikainen (1996) in her master's thesis tried to clarify the existence of visual MMN-like response in rabbit. She reported a MMN-like difference between standard and deviant stimuli in the cerebellum (75-225ms), visual cortex (25-

100 ms), dentate gyrus (0-100 and 125-200 ms) and CA1 of the hippocampal formation (75-175 ms). Deviant stimuli evoked similar ERPs with and without standards and thus the differences were not considered to represent similar comparison process suggested in human MMN studies.

3.1. Memory trace interpretation of MMN

The most influential explanation of MMN is a memory trace interpretation. In the oddball paradigm the repetitive standard stimuli create a sensory ('echoic') memory trace which is neural representation of standard stimulus. The deviant stimulus is compared according to its physical features to this memory trace and when it does not match, the MMN is elicited. The comparator mechanism underlying MMN analyzes stimuli by the difference between the gestalts of the deviant and the standard, and by the difference between the feature by which the deviant differed from the standards (Gomes, Ritter and Vaughan, 1995). This comparison process is automatic and the neuronal representation is likely to form the neurophysiological basis of the acoustic sensory memory (Alho et al., 1993; Alho, 1995; Giard et al. 1995; Näätänen, 1990, 1992; Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1989). Thus it has been proposed that the MMN indirectly represents the functioning of the short-term auditory memory (for a review, see Ruusuvirta, 1997). However, Winkler, Cowan, Csepe, Czigler and Näätänen (1996) have demonstrate longer-term effects on the MMN component, which suggest that some aspects of the sensory memory traces underlying this component are stored in a more durable representation.

The neural traces underlying MMN encode all auditory stimulus features, irrespective of their relevance to the possible task to be performed in experimental situations (Näätänen, 1992). According to the memory trace hypothesis the trace is reinforced by stimulus repetition, it has a decay time of about 10 sec and the frequently occurring deviants elicit weak MMN responses (Imada, Hari, Loveless, McEvoy and Sams, 1993). In the study of Ceponiene, Cheour and Näätänen (1998) the MMN data

suggested that neural traces of auditory sensory memory lasted for at least 1400 ms, probably considerably longer. The duration of the memory trace has been studied by varying the interstimulus interval (ISI). With longer ISIs the memory trace becomes weaker and the MMN smaller (Imada et al. 1993; Kujala et al., 1995). Kujala et al. (1995) studied MMN in the blind and sighted with a relatively long ISIs and they concluded that the auditory memory trace requires less sensory reinforcement or decays more slowly in the blind than in the sighted. However, the effect of the ISI on the amplitude of the MMN is unexpectedly small (Imada et al., 1993).

Näätänen et al. (1989) concluded that the MMN is a memory process. They also suggested that the MMN is a response to change, not repetition, and therefore is a reflection of memory trace. It has been shown that even two separate traces can be simultaneously present and participate in the mismatch process (Winkler, Paavilainen and Näätänen, 1992). In their study Winkler et al. (1992) used two different standard stimulus (600 Hz and 700 Hz), which were presented together with a deviant stimulus which was of different frequency in different blocs. These deviants elicited a MMN, though a smaller one than that obtained with only one standard stimulus. According to authors two aspects of the results from the blocks with two standards implicated that two parallell stimulus traces can be elicited simultaneously: 1) deviants elicited a MMN of approximately the same amplitude when preceded by sequences of four identical standards as when preceded by sequences of four stimuli containing both standards; 2) in contrast to the one-standard condition, the magnitude of stimulus deviance did not affect the MMN component elicited by the different deviants.

Näätänen, Paavilainen and Reinikainen (1989) demonstrated a MMN to occasional changes in stimulus duration, both decrements and increments. MMN was larger over the right than left hemisphere. They concluded that their results offer very strong evidence for the existence of memory trace of an auditory stimulus. Their data also indirectly demonstrated the existence of duration-specific neurons in the human brain.

Schröger, Tervaniemi and Näätänen (1995) investigated the neural mechanisms of intensity coding by presenting human subjects repetitively with tone pairs consisting of two tones differing in intensity. Infrequent order reversals of the two tones elicited the MMN. Authors interpreted this finding indicating that the human auditory system

automatically encodes information about the time course of intensity within tone patterns into neural representation.

Masking stimulus following a test stimulus at a short interval may erase or deteriorate the memory of the test stimulus, and thus eliminate MMN. Masking results belong to the strongest evidence for the involvement of memory traces in MMN generation (Näätänen, 1992). The recognition-masking paradigm was applied in study of Winkler, Reinikainen and Näätänen (1993) to test the memory trace hypothesis and their results strongly suggested that MMN provides a measure for a trace of sensory memory.

Due possibility is that the memory trace is located in the supratemporal auditory cortex, where the MMN is generated (Alho et al., 1993; Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1989). According to study by Mäkelä, Salmelin, Kotila and Hari (1994) lesions of the anteromedial thalamus may affect formation of sensory memory traces in the auditory cortex. Besides the auditory cortex it is possible that short-term memory trace can be located also subcortical sites, including the hippocampus and the cerebellar cortex, and thus, multiple sites in the brain (Ruusuvirta, 1996). Also results of Kraus, McGee, Littman, Nicol and King (1994) suggest that MMN might be a result of a process that can occur at lower levels of the auditory system. According to these authors a memory trace could be automatic, preattentive and could occur at low levels as well as cortically

Näätänen et al. (1997) demonstrated that memory traces are language-dependent. They made this observation when they studied different phoneme representations reflected by MMN in finnish and estonian subjects. It was found that both in finnish and in estonian subjects the MMN responses enhanced in reaction to phonemes in their own language, but not to phonemes in different languages. So, the results were interpreted as proving exictence of language-dependent memory traces. On the basis of the left-hemisphere dominance of the MMNm enhancement to phoneme prototypes, authors also suggested that the neural phoneme traces are located in the left auditory cortex. Results indicate that the left auditory cortex is involved in phonemic discrimination, because the phoneme traces are located there, whereas both the left and right auditory cortices serve acoustic discrimination.

Näätänen, Schröger, Karakas, Tervaniemi and Paavilainen (1993) studied the development of a memory trace for a complex, unfamiliar sound in the human brain.

Subjects were divided into subgroups according to their performance in the discrimination tests. The groups which were examined closer were ´good non-improvers´ who were good in discriminating deviants already in the beginning and ´improvers´ who improved their performance during the test. Within latter group deviant did not elicit MMN in the beginning but did later during the session. This result reflected, according to authors a gradual ´sharpening´ of sensory information encoded in the memory trace. In experiment 2, which was otherwise similar to experiment 1 but including no intervening blocks, the initially small MMN amplitude did not increase during the course of the session. This suggested that the trace improvement inferred as having occurred in experiment 1 depended on attention.

In a deviant-alone condition in which deviant stimuli are delivered without standard stimuli, MMN disappears because there is no memory trace created by standard stimuli (Näätänen, 1990). In human studies, a dependence of MMN on a memory trace has been demonstrated by this kind of deviant-alone condition, presenting deviant tones without intervening standard tones (Alho, Sainio, Sajaniemi, Reinikainen and Näätänen, 1990; Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1989). In this case, no MMN can be found. Ruusuvirta et al. (Ruusuvirta, Korhonen, Penttonen and Arikoski, 1995; Ruusuvirta, 1996) studied hippocampal auditory evoked potentials (AEPs) in oddball situation in rabbit using the deviant-alone situation as a control. They found that all AEP deflections observed in the oddball situation were found also in the deviant-alone situation and thus none of the AEP deflections to deviant tones in the oddball situation was specific to a memory trace of preceding standard tones. So the most crucial criteria for relating any of the observed AEPs to a MMN-like comparison process was not fulfilled.

3.2. The latency range of MMN

There are several opinions about MMN latency range in humans. For example Näätänen has suggested that MMN appears roughly 200 ms after stimulus onset (Näätänen et al.

1978), or 150 ms after stimulation (Näätänen, 1990), or about 100 ms from stimulus onset and lasts until about 250 ms after stimulus (Näätänen, 1992, see also Hugdahl, 1995). Alho, Sainio, Sajaniemi, Reinikainen and Näätänen (1990) proposed that MMN is peaking at around 100 and 180-200 ms from stimulus onset. Schröger, Tervaniemi and Näätänen (1995) has stated that MMN is usually peaking between 150 and 250 ms relative to onset of the deviation. According to Näätänen and Alho (1995), Ruusuvirta, Korhonen, Penttonen and Arikoski (1995) and Ruusuvirta, Penttonen and Korhonen (1998) the MMN is elicited at the latency range of 100-200 ms. Alho (1995) has mentioned that MMN peaks at 150 to 200 ms from stimulus onset. MMN has even been found as early as 50 ms following stimulus delivery (Javitt et al. 1993). The lifetime of the MMN effect is, according to Sokolov (1990), only about 10 seconds.

In animals the latency of MMN-like responses is somewhat different than in humans. Usually they have been observed to commence less than 100 ms from stimulus onset (Ruusuvirta, Penttonen and Korhonen, 1998). They have been observed in various species such as cat (Csepe, Karmos and Molnar, 1987, 1988a, 1988b, 1989; Karmos, Molnar, Csepe and Winkler, 1989; Karmos, Winkler, Molnar and Csepe, 1993; Ruusuvirta, 1996; Ruusuvirta, Korhonen, Penttonen, Arikoski and Kivirikko, 1995a; 1995b), guinea pig (King, McGee, Rubel, Nicol and Kraus, 1995; Kraus, McGee, Carrell, King, Littman and Nicol, 1994; Kraus, McGee, Littman, Nicol and King, 1994), rabbit (Ruusuvirta, 1996; Ruusuvirta, Korhonen, Arikoski and Kivirikko, 1996a, 1996b; Ruusuvirta, Korhonen, Penttonen and Arikoski, 1995), monkey (Javitt, Schroeder, Steinschneider, Arezzo and Vaughan Jr., 1992; Javitt, Steinschneider, Schroeder, Vaughan Jr. and Arezzo, 1994) and rat (Ruusuvirta et al. 1998). Studies have suggested that MMN-like responses in cats have been observed to occur at the latency range 30-70 ms (association cortex, vertex, AI and AII) (Csepe et al., 1987, 1988a) and 40 and 130 ms (hippocampus) (Ruusuvirta et al., 1995b; Ruusuvirta, 1996), in guinea pigs 30-80 and 135-170 ms (MGB), 30-180 ms (midline surface) and after 150 ms (temporal lobe) (Kraus, McGee, Littman, Nicol and King, 1994), in monkeys approximately 80 ms (AI) (Javitt et al., 1992) and 15-60 and 60-150 ms (AI) (Javitt et al., 1994), in rats 63-253 ms (auditory cortex) (Ruusuvirta et al., 1998) and in rabbits 0-20 ms, 60-80 and 100-160ms (hippocampus) (Ruusuvirta et al., 1996b; Ruusuvirta, 1996), 75-225 ms (cerebellar cortex), 125-175 and 200-250 ms (hippocampus) (Ruusuvirta et al., 1996a; Ruusuvirta, 1996) and 270 ms (Ruusuvirta et al., 1995; Ruusuvirta, 1996). We want to emphasize

that these latency ranges depend on the exact location where the ERPs are recorded in the brain. The responses in subcortical structures appear earlier than responses in higher cortical areas.

In study of Csepe et al. (1987) the latency of MMN-like negativity showed dependence both on the location of the recording site and on the probability of the deviant tones. Csepe et al. (1989) investigated whether small frequency differences would elicit an MMN. They found that the smaller the difference the larger the latency range and the cortical area showing a significant MMN.

3.3. Determinants of MMN

Determinants of MMN are magnitude and probability of stimulus deviation, interstimulus interval (ISI), predictability, stimulus significance, sleep and drug effects, long-term response decrement, constancy of the standard stimulus, masking effects and generators of MMN (Näätänen, 1992).

Stimulus intensity or magnitude effects on the MMN so that with an increasing intensity of stimulus deviation MMN gets larger and earlier and its duration may be shortened. Dependency of MMN on stimulus intensity can be seen in the observation that the weaker the stimulus intensity, the larger is the response elicited. On the other hand the MMN gradually decreases in amplitude and increases in latency as the deviant stimulus becomes more intense. In general the MMN amplitude is a curvilinear function of intensity (Näätänen, 1992). Also number of differences between standard and deviant stimuli affects to MMN. When a deviant is different from the standard in more than one stimulus dimension, MMN is larger than when it differs in only one feature (Schröger, 1998).

It has been shown that the lower probability of deviant stimuli produce a larger MMN (see for example Csepe, Karmos and Molnar, 1987). However, a low probability of deviant stimulus is not necessary for MMN elicitation. Both event and temporal probabilities affect MMN. The MMN amplitude also strongly depends on the local probability of the immediately preceding sequence of stimuli (Näätänen, 1992). In their

study in cat Csepe, Karmos and Molnar (1988b, 1989) varied probability of deviant stimuli (33, 20, 10 and 5 %) and they found that changes of the middle-latency negative wave both of the cortical and of the subcortical EPs were closely related to the changes of the probability of deviant stimuli in the series of standard stimuli. In their study (1988b) also the cortical distribution of MMN was partly dependent on the probability of the deviant tones. The subcortical MMN could be observed in sleep only at the lowest probability. The MMN on the MGB responses was identified first at 20 % probability.

When ISI is prolonged or shortened enough, MMN is no longer elicited by deviants. This may reflect the decay of neural trace in time generated by standard stimuli. Näätänen and colleagues tried to determine the shortest ISI at which MMN can still be elicited (Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1989). They found MMN even with an ISI of 101 ms (possibly even with an ISI of 51 ms). In another study it was found MMN with an ISI of 60 ms. The longest ISI, at which MMN has been elicited in adults, is 10 s (Sams, Hari, Rif, and Knuutila, 1993). A similar estimate in children is unknown. The rate of both standard and deviant stimuli is of importance in ISI effects on MMN. The ISI between deviant stimuli might be important because it determines whether a trace of a previous similar deviant stimulus is still present in the system at the arrival of the sensory input from the next deviant stimulus (Näätänen, 1992).

Schröger (1996a) has studied the influence of intensity and ISI both on the frequency-MMN and intensity-MMN. He found that the frequency-MMN was not influenced by the intensity and ISI whereas the intensity-MMN was modulated both these elements. Results indicated that there is functional differences between the neural traces underlying the frequency-MMN and the intensity-MMN.

Predictability and significance of deviant stimuli have no effect on MMN (Näätänen, Gaillard and Mäntysalo, 1978; Näätänen, Simpson and Loveless, 1982; Scherg, Vajsar and Picton, 1989). However, according to Sussman, Ritter and Vaughan Jr. (1998b) under certain conditions, when the predictability can be detected by the brain within the estimated limits of sensory memory, predictable occurrence of deviant stimuli affects the MMN process.

Constancy of the standard stimulus has also effect on MMN. In studies examining the tolerance of MMN generation to slight variations in the intensity of the

standard stimulus it has been found that MMN occurs when the standard stimulus is varied, but at a reduced amplitude, and, further, that the MMN attenuation is proportional to the range of variation (Näätänen, 1992).

Validity of MMN response has been studied by McGee, Kraus and Nicol (1997). Best indicators are, according to authors, criteria based on measurements of response area, onset latency, and duration. Statistical methods which utilize response subaverages were the poorest indicators of the response validity.

Several studies have investigated generators of MMN and many brain areas have been proposed to contribute to elicitation of the MMN. These issues are discussed next.

3.4. Generators of MMN

The early studies of MMN indicated a midline distribution with an amplitude maximum over frontal areas. Also recordings over temporal cortices yielded large MMNs. According to these findings it has been proposed that MMN is actually composed of two subcomponents: a sensory-specific one, generated in the auditory cortices, and a frontal one. The sensory-specific mechanism detects the stimulus deviance preconsciously and then activates frontal mechanism, which is related to conscious discrimination of stimulus deviation and the orienting response. The sensory-specific subcomponent of MMN has larger responses contralaterally and frontal MMN over right hemisphere irrespective of the ear of stimulation (Giard et al., 1995; Näätänen, 1992).

Various methods have been applied to determine MMN generators, for example MMN scalp distribution using a dipole-modeling method, magnetoencephalographic (MEG) data, intracranial MMN recordings in animals and humans, and effects of local brain lesions on MMN (Alho, 1995).

The MMN arises in the supragranular cortical layers and is dependent upon both exitatory NMDA receptor activation and GABAergic inhibitory mechanisms (Ritter, Deacon, Gomes, Javitt and Vaughan Jr., 1995). In most studies MMN is localized to the auditory cortex, particularly in supratemporal area in the vicinity of Heschl´s gyrus

(Alho et al., 1993; Alho et al., 1996; Alho et al., 1998; Cornwell, Nudo, Straussfogel, Lomber and Payne, 1998; Csepe, 1995; Csepe, Karmos and Molnar, 1987; Giard et al., 1995; Halgren et al., 1995; Huotilainen et al., 1998; Javitt, Doneshka, Zylberman, Ritter and Vaughan Jr., 1993; Javitt, Schroeder, Steinschneider, Arezzo and Vaughan Jr., 1992; Javitt, Steinschneider, Schroeder, Vaughan and Arezzo, 1994; Karmos, Molnar, Csepe and Winkler, 1986; Karmos, Winkler, Molnar and Csepe, 1993; King, McGee, Rubel, Nicol and Kraus, 1995; Kraus, McGee, Carrell and Sharma, 1995; Kraus, McGee, Littman, Nicol and King, 1994; Kropotov, Näätänen, Sevostianov, Alho, Reinikainen and Kropotova, 1995; Näätänen, 1990; Näätänen, 1992; Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1989; Näätänen, Paavilainen and Reinikainen, 1989; Ruusuvirta, 1997; Ruusuvirta, Penttonen and Korhonen, 1998; Scherg, Vajsar and Picton, 1989; Schröger, Tervaniemi, Näätänen, 1995; Woldorff, Hillyard, Gallen, Hampson and Bloom, 1998; Yabe et al., 1998. For a review, see Alho, 1995). It has been also proposed that there are two major sources for the MMN, the supratemporal plane and the frontal cortex (Javitt, Schroeder, Steinschneider, Arezzo and Vaughan, Jr., 1992). Besides the primary auditory cortical areas, the MMN has also been observed in the non-primary auditory pathway (Csepe, 1995; King, McGee, Rubel, Nicol and Kraus, 1995; Kraus, McGee, Carrell, King, Littman and Nicol, 1994; Kraus, McGee, Littman, Nicol and King, 1994; Scherg, Vajsar and Picton, 1989. For a review, see Alho, 1995), as well as in subcortical areas, such as hippocampus and thalamus (Csepe, Karmos and Molnar, 1988b, 1989; Ruusuvirta, 1996; Ruusuvirta et al, 1995; Ruusuvirta et al., 1995a, 1995b; Ruusuvirta et al., 1996a, 1996b; Ruusuvirta et al. 1998. For a review, see Alho, 1995 and Ruusuvirta, 1997). MMN can also be observed in cerebellum (Ruusuvirta, 1996; Ruusuvirta et al. 1996a). It has even been suggested that the detection of different pitches of tones may not require cerebral structures at all (for a review, see Ruusuvirta et al. 1996a).

According to review of Alho (1995), studies indicate that a major MMN source is located in the auditory cortex. However, Alho proposes that the exact location of this MMN generator appears to depend on which feature of the sound is changed, as well as on the complexity of the sound. Therefore memory traces of different acoustic features, as well as for sounds of different complexity, might be located in different regions of auditory cortex. This is supported by study of Alho et al. (1996) in which processing of complex sounds in the human auditory cortex was studied by MEG. The results

suggested that at least partially different supratemporal neuron populations are involved in processing changes in simple and complex sounds and that sensory-memory representations for these sounds may be located in different fields of the auditory cortex.

Also Giard et al. (1995) received same kind of results. They analyzed the neural correlates of acoustic stimulus representation in echoic sensory memory using the MMN. The scalp topographies of the MMNs elicited by pure tones deviating from standard tones by either frequency, intensity, or duration varied according to the type of stimulus deviance. This indicates, according to authors that the MMNs for different attributes originate, at least in part, from distinct neural populations in the auditory cortex. This result was supported by dipole-model analysis. The differences in MMN topographic distribution were larger in the left than in the right hemisphere. The hypothesis that the frequency, intensity, and duration of acoustic stimuli have separate neural representations in human auditory cortex is consistent with findings from animal studies. Also studies by McGee, Kraus, King, Nicol and Carrell (1996) who measured acoustic evoked potentials from the guinea pig temporal lobe, suggest that the various acoustic elements that distinguish speech stimuli are processed at different locations along the auditory pathway. Also Kraus et al. (1994) concluded that, because an MMN was recorded from the thalamus in response to some stimuli but not others, distinct generators for MMN responses to different stimulus contrasts may exist.

Kropotov et al. (1995) recorded MMN intracranially from the human temporal cortex of patients (Parkinsonian patients and patients with obsessive-compulsive disorder) with electrodes implanted in the brain for diagnosis and therapy. The MMN was present in the temporal cortex in Broadman areas 21 and 42. The MMN was absent in other recording sites including the caudate nucleus, the globus pallidus, ventrolateral nucleus of the thalamus, cingulate gyrus, amygdala, hippocampus and white matter 2 cm below the temporal cortex. The MMN was found to be attention independent and modality specific. Also Halgren et al. (1995) had an opportunity to study ERPs intracranially in humans. Electrodes were implanted in the superior temporal plane and parietal lobe of 41 epileptic patients localize seizure origin prior to surgical treatment. They found a component in superior temporal plane (STP) which they called STP-MMN, mainly in the posterior superior temporal plane (pSTP).

Also studies in monkeys have demonstrated that MMN is generated within auditory cortex. Javitt et al. (1992) first demonstrated MMN in monkey. They found

that MMN had a frontal maximum and concluded that the primary generators of MMN are within auditory cortex. Javitt et al. (1994) studied intracortical mechanisms of MMN generation in monkey. Their main findings were that AI contributes substantially to scalp recorded MMN and within AI, MMN reflects activation primarily of supragranular cortical laminae. Data demonstrated, according to these authors, that in monkeys, AI provides a major contribution to surface MMN and may constitute primary generator.

Ruusuvirta et al. (1998) recorded ERPs from the auditory cortex in anesthetized rats and they found MMN-like response. Results also suggested that thalamus may contribute to MMN-like activity in the auditory cortex.

The study of Cornwell, Nudo, Straussfogel, Lomber and Payne (1998) has indirectly shown that TI (temporo-insular) area of the cortex has a important role in auditory discrimination in cat. These authors studied the impact of lesions in auditory and visual tasks in cat and found that lesions of TI cortex profoundly impaired performance at discriminating complex sounds but had no effect on visual discrimination. Authors therefore concluded that TI cortex might possibly participate in selective attention.

According Csepe (1995) the primary system plays an active role in the comparison processes reflected by the MMN and the non-primary pathway acts only as a modulating influence. These primary and secondary auditory cortical processing are occurring in parallel (Csepe, 1995). In their study Csepe et al. (1987) recorded MMNs from the cat auditory cortex. Their studies showed that in addition to responses of the primary auditory area AI, an MMN also is observed in area AII. The EPs recorded from the AI and AII areas of the auditory cortex show more dynamic changes than the vertex and association cortical responses. Csepe et al. (1987) suggested that both the primary and secondary areas take part in the comparing process but their role may be different.

King et al. (1995) studied MMN in guinea pig using oddball paradigm. On the basis of the results they suggested that the primary and non-primary auditory pathways appear to provide distinctly different contributions to encoding of changes in binaural phase. The representation of intrinsic stimulus properties seems to be reflected principally in the primary auditory pathway, the representation of stimulus change appears to have a strong non-primary auditory pathway contribution. It seems that both pathways are necessary, but neither is sufficient alone.

The study of Kraus et al. (Kraus, McGee, Littman, Nicol and King, 1994) investigated the role of the thalamus and contribution of primary and non-primary pathways to the generation of MMN in guinea pigs. Electrodes were placed in the caudomedial (non-primary) and ventral (primary) subdivisions of auditory thalamus (medial genigulate nucleus). Surface epidural electrodes were placed at the midline and over the temporal lobe. Tone-evoked MMN was observed in non-primary thalamus (caudomedial geniculate nucleus, MGcm) but not in the primary thalamus (ventral geniculate nucleus, MGv). MMN was also observed at the midline (non-primary) but not over the temporal lobe (primary). Results indicated that the thalamic contribution involves the non-primary, not the primary subdivision of the medial geniculate body. However, MMN was observed in the surface temporal response 150 ms after stimulus onset. So we are surprised that authors do not consider this finding important and therefore are overlooking the role of the temporal lobe as a generator of MMN.

A same kind of study was performed by Kraus, McGee, Carrell, King, Littman and Nicol (1994). They studied discrimination of speech-like contrasts in the auditory thalamus (MGB) and cortex. Also in this study MMN was not elicited in the ventral portion of MGB (primary) by either stimulus contrasts. In caudomedial portion of the MGB (non-primary) one contrast elicited strong MMN, whereas the other did not. In the midline surface (non-primary) MMN was elicited by both stimulus contrasts, but neither contrasts elicited an MMN from the surface over the temporal lobe (primary). Thus, also this study supported the idea that non-primary portions of the auditory pathway contribute substantially to the MMN.

Scherg et al. (1989) studied MMN generators in human and also they demonstrated nonprimary origins for the MMN. This is interesting because most human studies of the MMN generating system have pointed to a cortical origin for the response. Authors also suggested that the subcomponents of MMN have different origins. The origin of MMNa is from primary auditory cortex, whereas MMNb is localized to nonprimary auditory cortex.

In their studies, Csepe et al. (1988b) recorded subcortical evoked potentials in cats both in wakefullness and in slow wave sleep. The MMN of different latency was observed in different cortical areas, in the medial geniculate body (MGB) and in the hippocampus. The hippocampal MMN, appearing in slow wave sleep was smaller than

that in wakefulness. The hippocampal data suggested that MMN might also be generated outside of the auditory system.

In a further study in cat Csepe, Karmos and Molnar (1989) recorded MMN in the auditory and association cortices, at the vertex, in the MGB of the thalamus and in the dorsal hippocampus in quiet waking state and in slow wave sleep. Data demonstrated that MMN could be elicited in the auditory cortex, but also in the MGB and in the hippocampus. In the MGB and in the hippocampus MMN appeared quite early, about 25-30 ms from the stimulus onset and in SWS it was observed only at the lowest probability. On the basis of the study hippocampus have been shown to be a system which may take part in the comparison of different signals. According to results, the comparison process may start in subcortical level.

Ruusuvirta et al. (1996a; see also Ruusuvirta, 1996) recorded ERPs and found MMN-like responses in the hippocampus and cerebellum of rabbit. The MMN was elicited 50 ms earlier in cerebellum than in hippocampus. According to authors, these earlier cerebellar responses to pitch changes provide evidence that the neural circuit capable of detecting pitch changes may be located at the brain stem level. In another same kind of study Ruusuvirta et al. (1996b; see also Ruusuvirta, 1996) recorded MUA in same recording sites as in previous study. This time they found a significant MMN-like response only in hippocampus.

However, the role of the hippocampus is not necessarily so clear in generation of the MMN as suggested by some studies. Ruusuvirta, Korhonen, Penttonen, Arikoski and Kivirikko (1995b) interpreted the poor detectability of the MMN-like negativity in their studies indicating that the hippocampus may not necessarily generate the neural process contributing to the hippocampal MMN-like ERPs and that process reflected by the MMN-like negativity has possible extra-hippocampal source. They also suggested that those ERPs may reflect an input of the neural process being present cortically.

3.5. Attention and MMN

Attention is the focusing of perception leading to heightened awareness of a limited range of stimuli which has both overt behavioral component and internal components (Atkinson, Atkinson, Smith and Bem, 1993).

Attention can be either active or passive. Passive attention is forced by qualities of the stimulus itself; attention is not maintained unless the stimulus possesses some significance for the organism, but wanes rapidly upon repetition of the stimulus (Ritter, Vaughan Jr. and Costa, 1968). MMN is related to passive attention (Tiitinen, May and Näätänen, 1997). Passive attention and orienting are important and vital processes found as well lower species as higher species, like human beings. Frontal areas are important in attention processes, especially the right prefrontal cortex. Attention effects on ERPs have been analyzed first in the oddball paradigm. Attention in the oddball situation is usually introduced by instructing the subject to discriminate deviants stimuli among standard stimuli. In audition, a good deal of sounds are initially received in the absence of attention (Näätänen, 1992).

Attention has been studied since –50´s. The early studies of ERPs and selective attention in humans was centered around the N1 wave (Alho, video-lecture 3.2. 1999).

Hillyard et al. studied attention with dichotic listening method in humans. They found that when auditory stimulus were attended there were responses in ERP 20-50 ms after the stimulus and these responses also increased. The N1 component was increased to attended stimuli in comparison with unattended stimuli. Hillyard et al. suggested that these findings support the Broadbent´s filter theory, according to which first all stimuli briefly are stored and analyzed in parallel for their elementary physical properties and is followed by a higher-level processing stage into which only a subset of stimuli, allowed by the filter, enter (Alho, video-lecture 3.2.1999; Näätänen, 1992).

Also Näätänen et al. begun to study attention in 70´s. Näätänen concluded that there is a separate selection mechanism which picks up attended stimuli. These stimuli generate a attentional trace (which resembles a memory trace) in auditory cortex, possibly in secondary sensory areas which is controlled by frontal activity (Alho, video-lecture 3.2. 1999). Näätänen (1982) defined attentional trace in his attentional trace theory as a voluntarily maintained representation of the physical features of the relevant

stimulus which separate it from the irrelevant stimulus. On the theory, only stimulus features that are frequently presented can be incorporated into the attentional trace. The initial selection performed with the attentional trace was described as a self-terminating matching (comparison) process on-line generating the early processing negativity (PN). The PN is a slow endogenous negative component related to selective attention and it is full dependent on attention (Näätänen, Gaillard and Mäntysalo, 1978; Näätänen 1992). The PN is elicited only when auditory stimuli have similar physical features with preceding stimuli (Näätänen, 1992).

Näätänen (1992) has proposed that passive attention is based on a) automatic brain mechanisms with a special sensitivity to onset, offset, or change in acoustic input rather than to any specific sensory information, and b) a high-priority access of signals generated by these processing mechanisms to that controlling the direction of attention. According to Näätänen (1992) automatic processing in audition has three different functions, first to produce sensory stimulus representations containing specific sensory contents for percepts, second to course attention switching and conscious perception, and third to provide arousal.

Näätänen et al. found the response which they called mismatch negativity (MMN) in experimental situations in which there was a change in a series of auditory stimuli and, most importantly, in which the subjects did not pay attention to those stimuli (Alho, video-lecture 3.2. 1999). MMN are thought to be not at all or slightly dependent on attention and thus it represents an automatic form of sensory analysis (Mangun and Hillyard, 1995; Näätänen, 1992; Näätänen and Alho, 1995). However, scalp MMN may be modulated by attention, but only if the attention is highly focal and the deviation is rather small. It has been suggested that the automaticity of MMN is dependent on the feature being changed (Schröger, 1998).

MMN causes directing of attention towards new stimuli. Stimulus change is initially and preconsciously detected by a sensory-specific mechanism of auditory cortex, the generator of the sensory-specific MMN subcomponent, which in turn triggers the frontal process that generates the frontal MMN subcomponent (Giard et al., 1990). In the oddball task, MMN generator processor represents the first, preconscious, stage in discriminating stimulus deviation and to trigger the chain of further cerebral processes, which lead to conscious discrimination of stimulus deviation (Näätänen,1992). MMN is often followed by many endogenous components, for

example large positive wave P3a. Therefore P3a is considered to reflect attention switch (Alho, video-lecture, 3.2. 1999). Whereas MMN usually is elicited independently of attention, P3a elicitation often depends on attention. Other components that are dependent on attention are CNV, PN and N2b. It has been suggested that N2b component reflects an orienting of attention. The endogenous components that follow MMN are triggered even by very weak MMN process.

Studies have shown that MMN does not depend on attention. For example in oddball paradigm MMN can be elicited even by slight, threshold-level deviations in an auditory stimulus block, while the subject is intensely concentrating on reading. Also drug effects provide indirect evidence for the attentional insensitivity of frequency MMN. MMN is either enhanced or attenuated depending on whether the drugs have activating or deactivating effects. The fact that the memory trace duration is not affected by attention provides further evidence for MMN independence of attention.

Also existence of MMN in sleep, anesthesia and in comatose state prove that attention do not affect to MMN (sleep effects in cats reviewed in Csepe, Karmos and Molnar, 1987, 1988a, 1988b, 1989). MMN may only occur during certain moments of sleep but not consistently. It was found that MMN appears during stage 2 sleep preceeding a K-complex (Sallinen, Kaartinen and Lyytinen, 1994). The MMN can occur also for example in REM-sleep.

Csepe, Karmos and Molnar (1987) studied auditory evoked potentials in oddball paradigm in six freely moving cats during wakefulness and sleep. The auditory stimuli were short tones generated by sine wave bursts of 1 ms duration. The standard tones were 4 kHz and the deviant tones 3 kHz. In their studies, MMN was evoked by the unattended low probability deviant tones. These MMN-like changes could be identified both in wakefulness and slow wave sleep (same result was also replicated in study by Csepe et al. 1989). The evoked potentials recorded from AI (middle ectosylvian gyrus) and AII (ventral region of the ectosylvian gyrus) areas of the auditory cortex showed more dynamic changes than the vertex and association cortical (middle suprasylvian gyrus) responses. The amplitude of the MMN was inversely proportional to the probability of deviant tones and the latency of the MMN showed dependence both on the location of the recording site and on the probability of deviant tones. The latency of the MMN-like negativity was longer during slow wave sleep than in wakefulness. During slow wave sleep the MMN of increased latency could be evoked only at the

lowest probabilities and the cortical distribution of the MMN changed. These results are in agreement with the data on humans. Näätänen found that the amplitude of the MMN depends on the probability of the deviant stimulus. On the other hand Näätänen did not found MMN during sleep in humans in his studies in 1986. The results of Csepe et al. (1987) suggests that MMN may be related to those automatic and parallel information processes which are independent not only on the conscious perception but also on the vigilance. Therefore it seems possible that a genuine comparing process is active during the whole sleep-waking cycle which may be the neuronal background for the awaking effect of the relevant stimuli during sleep. On the basis of their findings Csepe et al. (1987) suggested that the short-term memory which is the basis of the MMN must be a crucial process prior to the higher level information processing.

Karmos, Molnar, Csepe and Winkler (1986) have also shown attention effects in cortical layers in cat. They observed that the negative EP component (50-60 ms) in the attentive animal had its largest amplitude in the uppermost layer of the cortex and this component gradually decreased toward the depth.

MMN has been recorded also under anesthesia, though with a very small amplitude and only from a very limited cortical area. At the same time, no MMN had been observed over the association cortex, and the only detectable MMN-like negativity had appeared over the primary auditory cortex. MMN had been recorded if the deviants differed from the standards by at least 10% of the standard frequency and at a very low deviant probability. This suggests that the comparison processes are suppressed and can be activated only by large and low probability deviations (Csepe, 1995).

Also dichotic listening studies have suggested that attention has no effect on MMN. MMNs elicited by frequency deviants within the attended and ignored inputs in dichotic stimulus presentation are very similar in amplitude and latency when a relatively slow stimulus rate is used (Näätänen et al. 1978). However, it has also been reported that when attention is very strongly focused on input to one ear, MMN is almost eliminated for intensity decrements in the input for the opposite ear. Also deviant-standard negativities has been shown to be much larger for the attended than unattended channel, especially at the midline. It has been suggested that the frequency MMN does not depend on attention, whereas the intensity MMN can indeed be modulated by attention (Näätänen, 1992).

Kaukoranta et al. (1989) and Lounasmaa, Hari, Joutsiniemi, and Hämäläinen (1989) recorded MEG responses in the oddball paradigm by comparing MMNm (MEG equivalent of the MMN) to deviant stimuli in attended and ignore conditions. Kaukoranta et al. (1989) investigated MEG responses to duration decrements and Lounasmaa et al. (1989) to intensity decrements. Both studies found a very similar MMNm under target-discrimination and reading conditions, providing evidence for attentional insensitivity of MMN in the oddball paradigm.

Also Alho et al. (1998) and Woldorff, Hillyard, Gallen, Hampson and Bloom (1998) studied attention using MEG recordings. In study of Alho et al. (1998) deviant tones and novel sounds elicited the MMN and its MEG counterpart MMNm both when the auditory stimuli were attended to and when they were ignored. So, also these results prove that MMN does not depend on attention. On the basis of their study, Woldorff et al. (1998) suggested that the feature encoding, memory-trace formation, and mismatch-registration processes reflected in the MMN do not depend on attention being directed to the eliciting stimuli, but they can be suppressed or gated if attention is strongly focused elsewhere.

Sussman, Ritter and Vaughan Jr. (1998a) demonstrated that attention affects the organization of auditory input associated with the MMN system. Their study supports the notion that both pre-attentive and attentive mechanisms play a role in auditory stream segregation.

Näätänen (1990) also proposed attention model in audition. On this model, auditory stimuli receive complete processing of all their physical features (for example frequency, intensity and duration) by the "permanent feature-detector system". This is very rapid sensory processing and a good deal of it occurs at the subcortical level. Näätänen suggested that this processing stage does not depend on attention and that is automatic, parallel and preconscious. After this the outcomes of this stage enter sensory memory without attention but no higher forms of memory. Outcomes of these sensory processes do not themselves cause conscious perception. Whether a conscious percept also occurs depend on the sensory attention-triggering characteristics of the stimulus: besides the permanent feature-detector system, sensory input also activates a parallel system of sensory analysis, one sensitive only to onset and offset of stimulus energy. This is the "transient-detector system", detecting the occurrence of sensory events. Thus conscious perception follows when the transient-detector system is activated strong

enough to cause "executive mechanisms" to "look at" the output of the permanent feature-detector system. The model also suggested a second, memory-dependent route to attention switch which is via MMN-generator mechanism (Näätänen, 1992).

Much in the same way Escera, Alho, Winkler and Näätänen (1998) have distinguished two separate neural mechanisms in triggering involuntary attention to acoustic novelty and change. These are a transient-detector mechanism activated by novel sounds and reflected in the N1 and a stimulus-change detector mechanism activated by deviant tones and novel sounds and reflected in the MMN. Schröger (1996b) has collected the most important features of the change-detection system. First, it is a low-level system that operates rather independently of other ongoing mental activities. Second, it is a system that is not largely influenced by high-level systems and third it is a system that is sensitive to the amount of deviation. A particular memory-related change-detection mechanism, which is indicated by MMN, has also been proposed to be involved in distraction conditions, in which rather small deviations in acoustic environment may cause reliable impairment in behavioral performance (Schröger and Wolff, 1998).

Supratemporal and nonspecific N1 have some dependence on attention but possibly no selective-attention effect. There is evidence that exogenous components (for example the supratemporal N1 and MMN) do not seem to be enhanced by attention. In turn, T-complex N1 is probably affected by selective attention. Elicitation of frontal N1 is probably attention-independent and it has hardly no selective-attention effect (Näätänen,1992). In situations where stimuli is not attended auditory cortex is activated first and this courses activation of the frontal lobes. This is in contradiction with attended situations, in which frontal lobes become activated before auditory areas (Alho, video-lecture, 3.2. 1999).

3.6. MMN in different age and patient groups

MMN has been studied also in children, even in newborn babies (Alho, Sainio, Sajaniemi, Reinikainen and Näätänen, 1990; Leppänen, 1999) although more MMN-data are available in adults. Alho et al. (1990) recorded ERPs of human newborns to pitch changes in a repetitive sequence of tone pips. The data showed that in newborns, deviant tones appearing among standard tones elicit a negative component resembling the MMN obtained in adults. Because this MMN-type negativity can be found already at early ontogenetic stage, it might provide a new way to test the development of the central nervous system and to diagnose cerebral dysfunction at a very early stage.

Kraus et al. (1993) studied MMN in school-age children. They used just perceptibly different variants of the speech phoneme, which elicited the MMN. Child and adult MMNs were similar with respect to peak latency and duration. However, MMN magnitude (peak-to-offset amplitude and area) was significantly larger in children than in adults. On the other hand, the MMN onset-to-peak amplitude was not significantly different in adults and children. The larger amplitude in peak-to-offset response may be partially related to an early developing´P3a-like´ component. Also results of this study supported using the MMN as a tool, for example in the study of deficient auditory perception in children.

Karayanidis, Andrews, Ward and Michie (1995) compared the performance of normal 20-76 year old subjects in three age groups and Parkinson´s disease patients on auditory selective attention processes. On the part of the MMN the results indicated that the MMN amplitude was reduced in the old group.

MMN can be altered in different disorders, such as in different kind of learning disabilities (Kraus et al., 1996), hearing impairments (Alho et al., 1990; Kraus, McGee, Carrell and Sharma, 1995), blindness (Kujala et al., 1995), schizophrenia (Catts et al., 1995; Javitt, Doneshka, Grochowski and Ritter, 1995; Javitt, Doneshka, Zylberman, Ritter and Vaughan Jr., 1993; Kathmann, Wagner, Rendtorff and Engel, 1995), alcoholism (Jääskeläinen et al., 1995; Kathmann et al., 1995), aphasia and frontal-lobe damages (for a review, see Näätänen, 1992).

Children with learning problems often cannot discriminate rapid acoustic changes that occur in speech (Kraus et al., 1996). On the basis of Kraus et al.´s (1996)

study of normal children and children with learning problems impaired behavioral discrimination of a rapid speech change was correlated with diminished magnitude of MMN. Results indicated that some children´s discrimination deficit originate in the auditory pathway before conscious perception and it have implications for differential diagnosis and targeted therapeutic strategies for children with learning disabilities and attention disorders. The MMN can be useful tool also in those patients who have hearing impairments (Näätänen, 1992) or who have cochlear implants. MMN can for example provide a means to distinguish those children with central sensory deficits from children whose auditory and other communication deficits arise from other causes (Kraus, McGee, Carrell and Sharma, 1995).

In early blind humans the MMN has been shown to be larger than in the sighted, although all studies have not found this kind of result (Kujala et al., 1995).

In schizophrenia MMN amplitude is decreased (Catts et al., 1995; Javitt et al., 1995; Javitt et al., 1993). On the basis of their study Javitt et al. (1995) further suggested that the neurophysiological dysfunction associated with schizophrenia is widespread and extends to the level of the sensory cortex. They also concluded that impairments of short-duration working-type memories may play a crucial role in the neurophysiology of schizophrenia and that schizophrenia is associated with a deficit in the sensory memory underlying MMN generation. Also Catts et al. (1995) studied MMN in schizophrenia and the effect of medication on MMN. They found, as did Javitt et al. (1995), that MMN amplitude is significantly lower in schizophrenia than in healthy subjects. They also found a significant negative correlation between age and MMN amplitude. MMN amplitude was significantly correlated with ratings of negative symptoms of schizophrenia but not with positive symptoms, which indicated that MMN may be a chronicity marker or reflect a predisposition to the development of schizophrenia. Subjects with bipolar affective disorder did not show lower MMN amplitude. Results implicate the auditory cortex in the pathophysiology of schizophrenia. According to Kathmann et al. (1995) in medicated schitzophrenics MMN peak latency is delayed. Javitt et al. (1993) studied schizophrenics in a passive auditory oddball paradigm and they found that schizophrenic subjects showed a significant reduction in MMN amplitude relative to controls. A deficit was greater on the left than the right side. Also these authors suggested that information processing is impaired even at the level of auditory cortex and that the pathophysiological processes

underlying information processing dysfunction in schizophrenia are widespread throughout the cortex.

Like in schizophrenics also in alcoholics the peak latency of the MMN is delayed (Kathmann et al., 1995). On the basis of study by Jääskeläinen et al. (1995) MMN is significantly diminished by alcohol and its latency is increased after alcohol ingestion.

MMN can also be used to predict awakening of comatose patients from coma. If MMN is present, patients have hope to return to consciousness (Kane, Rowlands, Curry, Butler and Cummins, 1994).

Training can affect to performance and it causes changes in MMN: training may enlarge MMN. So, MMN may serve as an objective indicator of neuropsychologic changes in central auditory system resulting from learning or auditory experience, for example it can help to evaluate the efficacy of auditory rehabilitation strategies, hearing aids, and cochlear implants (Kraus, McGee, Carrell, King, Tremblay and Nicol, 1995; Kraus, McGee, Carrell and Sharma, 1995). Training and rehabilitation effects are usually more efficient in children than in adults, because plasticity is stronger in young age. Because of the good short-term replicability at the group level, the MMN is useful in studying the effectiveness of rehabilitation and treatments in clinical groups (Escera and Grau, 1996).

3.7. Alternative explanation to comparison process

In human studies the MMN has been proposed to reflect the detection of a mismatch between the memory trace of standard stimuli and an input by a deviant stimulus. This detection is made by a specific comparison process (for a review, see Näätänen, 1990).

In animal studies performed by Ruusuvirta et al. (Ruusuvirta et al., 1995; Ruusuvirta et al., 1996a, 1996b; Ruusuvirta, 1996) the so called "deviant-alone" situation has been used as a control procedure to find out whether the standard stimuli are needed in elicitation of the MMN. These studies have revealed that the observed

ERP responses are not specific to preceding standards, that is, the same kind of MMN-like reflection than in oddball situation is elicited also in deviant-alone situation. So, the observed ERP deflections were not analogous to MMN in human. Instead of comparison process the studies indicated that MMN-like responses reflected a difference in the presentation rates *per se* of the deviant and standard stimuli (Ruusuvirta, 1996). Further, rather than neural refractoriness, this effect may represent an active process related to the formation of the short-term memory trace of repeated stimuli. Studies demonstrated that also subcortical areas have important role in these processes.

4. HABITUATION, SENSITIZATION AND ORIENTATION

Habituation and sensitization are elementary forms of reflexive learning (Kandel, Schwartz and Jessel, 1991). They occur in nearly all species and response systems. Habituation and sensitization effects reflect how one ends up sorting out what to ignore and what to respond to. They are some of the most simple means based on neural structural properties to adapt themselves to the variable conditions in environment (Arikoski, Korhonen and Ruusuvirta, 1998). Habituation and sensitization effects are closely related to the intensity and frequency of the eliciting stimulus. (Domjan, 1998). Orientation is response towards new stimuli in the environment. The OR is a preparatory, information-catching mechanism used for switching on specific behavioral acts (Sokolov, 1990).

4.1. Habituation

Habituation is the simplest form of learning. It is a decrease in a behavioral response to a repeated stimulus and it is response- and stimulus-specific (Kandel, Scwartz and Jessel, 1991; Domjan, 1998). It is a nonassociative form in which an animal learns about the properties of a novel, innocuous stimulus when that stimulus is repeated. So, habituation processes are highly specific to the repeated stimulus. An animal first responds to a new stimulus with a series of orienting reflexes. When the stimulus is repeated, the animal learns to recognize it and, if the stimulus is neither rewarding nor noxious, the animal learns to suppress its responses. An organism may stop responding to a stimulus in one aspect of its behavior while continuing to respond to the stimulus in other ways. The learned suppression of the response to a repeated stimulus is called habituation. Habituation has also a characteristic of stimulus generalization. For example, the person who has become habituated to a particular clock chime may also

fail to respond to another clock chime that is similar to the original one. Changing the nature of eliciting stimulus can produce recovery of a habituated response. The habituated response can also be restored by sensitizating the organism with exposure to an extraneous stimulus. This phenomenon is called dishabituation. Habituation can be short lasting (lasting minutes) and long lasting (lasting several weeks). Short-term habituation effect has identifiable characteristic of spontaneous recovery (Domjan, 1998).

Habituation was first investigated in animals by Pavlov and Sherrington. According to their studies Sherrington concluded that habituation is due to a functional decrease in the synaptic effectiveness of the pathways to the motor neurons that have been repeatedly activated. The same problem was later investigated at the cellular level by Spencer and Thompson. In the intracellural recordings they found that habituation leads to a decrease in the synaptic activity between interneurons and motor neurons (Kandel, Schwartz and Jessell, 1991). One of the basic studies has been performed with the marine snail Aplysia, which have a simple nervous system. Also other simple organisms have been found to have same kind of neuronal structures than mammals, for example structures that match pyramidal cells in hippocampus in rabbits (Arikoski, Korhonen and Ruusuvirta, 1998). Aplysia has set of defensive reflexes for withdrawing its tail, gill and siphon. With repeated stimulation these reflex withdrawals habituate which is due to decrease in synaptic transmission. This synaptic decrease seems to be a general mechanism of habituation.

4.2. Sensitization

Sensitization is an increase in responsiveness to a wide variety of stimuli following an intense or noxious stimulus. In sensitization an animal learns about the properties of a noxious stimulus and as a result it remembers to respond more effectively to a variety of other stimuli. A sensitizing stimulus can override the effects of habituation. Sensitization involves enhancement of synaptic transmission. Like habituation

sensitization has both a short-term form lasting minutes and a long-term form lasting days and weeks (Kandel, Schwartz and Jessel, 1991). The duration of sensitization effects is determined by the intensity of the sensitizing stimulus (Domjan, 1998). Unlike habituation, sensitization is not highly stimulus-specific.

4.3. The dual process theory of habituation and sensitization

The dual-process theory of habituation and sensitization assumes that different types of underlying neural processes are responsible for increases and decreases in responsiveness to stimulation (Domjan, 1998). One category of changes in the nervous system produces decreases in responsiveness, or habituation process. Another category of changes in the nervous system produces increases in responsiveness. Such changes constitute the sensitization process. The habituation and sensitization processes are not mutually exclusive. The behavioral outcome of these underlying processes depends on which processes is stronger. The changes in the elicited behavior that actually occur in a particular situation represent the net effect of habituation and sensitization processes. The dual-process theory has been very influential in the study of the plasticity of elicited behavior (although it has not been successful in explaining all habituation and sensitization effects) (Domjan, 1998). The advantage of the dual-process theory has also been its applicability to simple neural systems (for a review, see Ruusuvirta, 1996).

Groves and Thompson (1970) suggested on the basis of neurophysiological research that habituation and sensitization processes occur in different parts of nervous system. Habituation processes are assumed to occur in what is called the S-R system. This system consist of the shortest neural path that connects the sense organs stimulated by the eliciting stimulus and the muscles involved in making the elicited response. By contrast, sensitization processes are assumed to occur in what is called the state system. This consists of other parts of the nervous system that determine the organism´s general level of responsiveness or readiness to respond. The state system is also altered by emotional experiences. The state and S-R systems are activated differently by repeated

presentations of a stimulus. The S-R system is activated every time a stimulus elicits a response because it is the neural circuit that conducts impulses from sensory input to response output. By contrast, the state system becomes involved only in special circumstances. First, some extraneous event may increase subject´ s alertness and sensitize the state system. Second, the state system may be sensitized by the repeated stimulus presentations if the stimulus is sufficiently intense or excitatory (Domjan, 1998).

4.4. Orientation

The orienting response (OR) is a specific behavioral act directed towards extraction of information from the environment (Sokolov, 1990). It has been hypothesized that infrequent events tend to elicit an orienting response whose activity is more pronounced in the right hemisphere (Pineda, Footer and Neville, 1987). Novel targets provoke an orienting response that habituates during training and when stimulus becomes familiar (Honey, Watt and Good, 1998). However, recent studies of Honey et al. (1998) have demonstrated that the OR in rats is not solely dependent on stimulus novelty.

Orientation includes many behavioral and neurophysiological responses such as head and eye movements, vascular modifications, EEG changes, and event-related potentials (Sokolov, 1990). Most of the physiological effects occurring in the orienting response can be understood as resulting from a sudden increase in reticular or thalamic nonspecific activation, thus suggesting that the principal center of the OR release might be located in the nonspecific activating systems of the brain such as the reticular formation (Näätänen 1992).

OR was first described by Pavlov in 1927, and later Sokolov has developed a theory about orienting response. According to his theory, the repetitive stimulus results in the development of its cortical "neuronal model", a neuronal representation of the physical features of the repetitive stimulus, and this development parallels the orienting-response habituation. However, no direct empirical evidence for the neuronal-model

construct was obtained in humans, but Sokolov´s hippocampal recordings in rats seemed to support the neuronal-model concept (Sokolov, 1990; Näätänen, 1992). Single-unit studies have shown that hippocampal neurones are simulating specific features of the OR as a response to novelty. Repeated presentation of stimuli results in a selective habituation of novelty detectors in hippocampus and of the OR. The trace of a standard stimulus formed at the level of hippocampal neurones matches the features of the standard stimulus and can be called a "neuronal model of the stimulus". The OR is triggered by mismatch between the test stimulus and the elaborated neuronal model (Sokolov,1990). There are two outputs from the hippocampus which regulate the basic components of the OR and the level of arousal: inhibitory and activating. The activating units are responsible for the generation of different components of the orienting response and reticular arousal. The inhibitory neurons are responsible for identification of similarity of conditions and for relaxation during repeated stimulus presentation (Sokolov, 1990).

Sokolov´s orienting-response theory has also met criticism. It has been argued that the theory cannot explain the orienting response to a stimulus that is neither novel nor different. Another criticism challenges the basic assumption that a physical stimulus change per se is sufficient to elicit an orienting response (Näätänen, 1992).

Sokolov (1990) divides OR to two mechanisms, voluntary and involuntary. In the event-related potential, such a differentiation is expressed in mismatch negativity (involuntary effect) and processing negativity (voluntary effect). Näätänen (1992) has also proposed that the OR have two components which are the arousal component of the OR (arousal-related effects which facilitate sensory and motor functions) and the attentional (informational) component of the OR (which consists of a reflex-like attention switch to the eliciting stimulus and the accompanying bodily effects specifically associated with an attention switch).

Orienting response have been studied for example in somatosensory conditioning studies with painful reinforcement, studies in color vision and experiments recording eye movements (Sokolov, 1990). The classical and most commonly used experimental paradigm to study the OR is the so called repetition-change paradigm. It consists of a sequence of homogenous stimuli usually presented with rather long interstimulus intervals (ISI) (Näätänen, 1992).

Ruusuvirta, Korhonen, Penttonen, Arikoski and Kivirikko (1995a; see also Ruusuvirta, 1996) recorded ERPs in the different areas of the hippocampus during an oddball situation in the cat. They also observed orienting head movements towards the tone source. A rewarding electrical stimulation of the lateral hypothalamus was paired with deviant tones. The conditioned orienting head turns to deviant tones were found when they were paired with the electrical stimulation of the lateral hypothalamus and the amplitude of the hippocampal ERPs at the latency range more than 50 ms were increased parallel to the development of the conditioned OR. The mean onset and peak latencies of the ERPs corresponded to those of the head movement acceleration signals. Authors suggested that the hippocampal negativity N130d observed in the previous cat study (Ruusuvirta at al., 1995b; Ruusuvirta, 1996) may reflect the neural OR.

OR have many effects on ERP components, like an increase in MMN and a decrease in processing negativity (PN). MMN and PN can be seen as two mechanisms of the OR (Sokolov, 1990). It has been proposed that the scalp MMN / P3a represents the cortical component of the OR. However Csepe, Karmos and Molnar (1987) and Csepe (1995) have suggested that there is no direct link between the orientation reaction (OR) and MMN. The P3 component in OR is elicited in response to new surprising stimulus and it decreases in amplitude after several trials (habituation). According to Ritter et al. (1968) the P3 component reflects a shift of attention associated with the orienting response.

N2a / P3a / SW has been interpreted as the cortical component of the orientation of attention. The supramarginal gyrus, (sMg) and the posterior cingulate gyrus (pCg) have been hypothesized to constitute the cerebral network for this orientation of attention (Halgren et al., 1995).

Habituation of the OR have the selective nature. After habituation of the responses to a specific stimulus, a presentation of a stimulus characterized by those specific parameters evokes no response. Still, we get responses to deviations from that stimulus.

5. DISCUSSION

MMN has been studied already about two decades both in human and animal studies. MMN was discovered in human studies by Risto Näätänen, who proposed that the MMN is related to a comparison process. However, recent animal studies by Ruusuvirta, Korhonen, Arikoski, Kivirikko and Penttonen have shown that, instead of a comparison process, the MMN-like activity rather reflects process that is related to the different presentation rates of standard and deviant stimuli in itself. According to our view this representation rate theory looks probable because there is hardly any separate comparing mechanisms in the brain. Instead, stimulus properties and representation rate appear to be more significant determinants in the elicitation of the MMN.

Animal studies have provided an opportunity to study MMN intracranially and thus clarify the role of different brain areas in elicitation of MMN. We think that this is important because it significantly extends the view of the neural mechanisms of the MMN we can get on the basis of the human studies, which have usually localized MMN in the auditory cortex. It is very interesting that MMN and thus memory trace in animals can be found in so many brain areas, such as cerebellum and hippocampus. However, in one human intracranial study (Kropotov et al., 1995) where electrodes were placed in several areas in the brain (also for example in hippocampus) the MMN was found only in auditory cortex but not in other structures. This seems unexpected in the frame of the many findings in animal studies. Although some quantitive differences between human and animal brain can be found, the basic structures and functions are similar. However, in the study of Kropotov et al. (1995) the subjects were not normal healthy adults because they suffered from Parkinson´s disease and obsessive-compulsive disorder. This could have had some effect on the results because MMN amplitude has been observed to decrease in some diseases.

Fortunately, MMN has not remained only as an abstract concept but it has been applied in many ways in clinical use. For example in coma, hearing disorders and dyslexia MMN is a significant tool. MMN is a interesting phenomenon and nowadays new studies are being made and thus new applications can be found in the future.

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