Timo Ruusuvirta

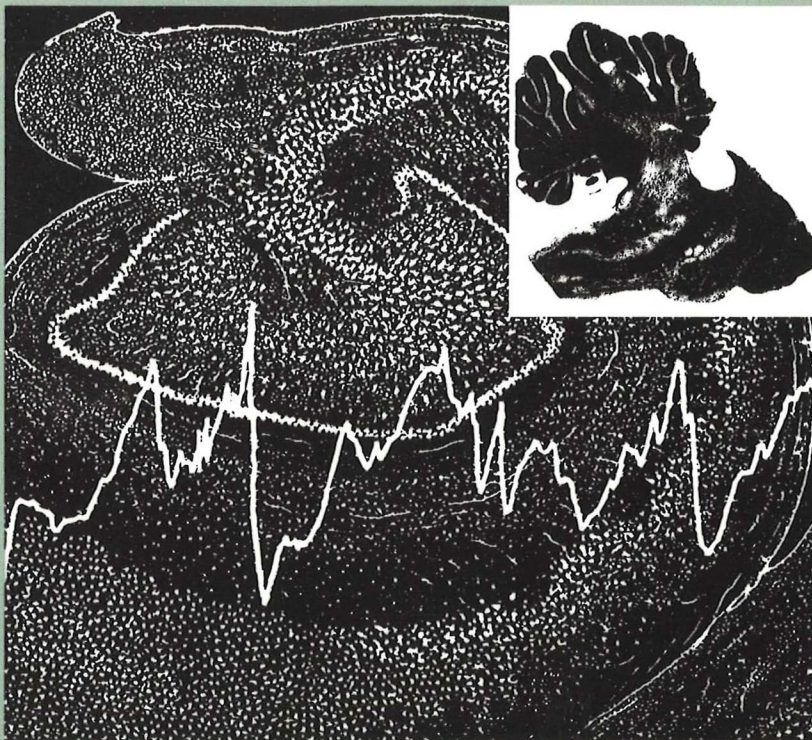# Brain Responses to Pitch Changes in an Acoustic Environment in Cats and Rabbits

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ABSTRACT

Brain responses to pitch changes were measured in cats and rabbits. Event-related potentials (ERPs) were recorded from the hippocampus (cats and rabbits), cerebellar cortex, and visual cortex (rabbits). Additionally, multiple-unit activity (MUA) was measured in rabbits from the same trials and through the same electrodes as the ERPs. Pitch changes were introduced by presenting pitch deviant tones (deviants) in a sequence of homogenous repeated tones (standards). Differences in ERPs to the deviants and those to the standards (MMN-like ERPs) were found in recordings from the hippocampus and cerebellar cortex but not from the visual cortex. They did not occur before 75 ms from tone onset. MMN-like MUA was, in turn, present within the 20 ms latency in the hippocampus. The MMN-like responses reflected the different presentation rates of the deviants and standards only. Therefore, the responses did not resemble the mismatch negativity (MMN) observed in the cerebral cortex in humans and thought to represent a comparison process detecting a mismatch between a sensory input by the deviant and a short-term memory trace of the preceding standards. The hippocampal MUA recordings revealed a fast (latency less than 20 ms) increase in spike activity, particularly to the standards, suggesting that the higher stimulus presentation rate did not result in refractoriness on the part of those neural ensembles that were activated by the stimulation, as has been proposed in the case of the reduced amplitude of the N1 deflection of ERPs in humans. Three main conclusions can be drawn. First, instead of a separate comparison process, the different presentation rate of each type of stimulus *per se* is sufficient to explain the observed differences between responses to the deviants and those to the standards. Second, rather than neural refractoriness, this effect may represent an active process related to the formation of the short-term memory trace of repeated stimuli. Thirdly, 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.

Keywords: cat, rabbit, habituation, orienting response, mismatch negativity, event-related potentials, multiple-unit activity

ACKNOWLEDGEMENTS

LIST OF PUBLICATIONS

I.   Ruusuvirta, T., Korhonen, T., Penttonen, M., Arikoski, J., & Kivirikko, K. (1995). Hippocampal evoked potentials to pitch deviances in an auditory oddball situation in the cat: Experiment I. *International Journal of Psychophysiology, 20,* 33-39.

II.   Ruusuvirta, T., Korhonen, T., Penttonen, M., Arikoski, J., & Kivirikko, K. (1995). Conditioned behavioral and hippocampal evoked responses in an auditory oddball situation in the cat: Experiment II. *International Journal of Psychophysiology, 20,* 41-47.

III.   Ruusuvirta, T., Korhonen, T., Penttonen, M., & Arikoski, J. (1995). Hippocampal evoked potentials to pitch deviances in an auditory oddball situation in the rabbit: no human mismatch-like dependence on standard stimuli. *Neuroscience Letters, 185,* 123-126.

IV.   Ruusuvirta, T., Korhonen, T., Arikoski, J., & Kivirikko, K. (1996). ERPs to pitch changes - a result of reduced responses to standard tones in rabbits? *NeuroReport, 7,* 413-416.

V.   Ruusuvirta, T., Korhonen, T., Arikoski, J., & Kivirikko, K. (1996). Multiple-unit responses to pitch changes in rabbits. *NeuroReport, 7,* 1266-1268.

CONTENTS

1 INTRODUCTION

The present thesis discusses responses of the central nervous system (CNS) to changes in an acoustic environment. It includes five publications (studies I-V) each of which concerns the application of an oddball situation where infrequently presented (deviant) tones occur in a train of frequently presented (standard) tones. The aim was to measure subcortical brain activity in situations which in humans elicit a scalp-recorded deflection of the event-related potential (ERP) known as mismatch negativity (MMN). MMN has been proposed to represent the detection of a mismatch between the memory trace of standard stimuli and an input by a deviant stimulus made by a comparison process (for a review, see Näätänen, 1990). However, as a difference between the presentation rates of standard and deviant stimuli in itself may lead to activity similar to MMN and as this possibility has not been controlled for in previous animal studies, one particular aim of the present study was to find out whether the observed subcortical activity fulfils the criterion for MMN, that is, its dependence on the presence of standard stimuli preceding a deviant stimulus. As it has been suggested that the effect of different rates of presentation of deviant and standard stimuli *per se* reflect the development of stronger refractoriness in those afferent neural elements that are related to more frequently presented stimuli, the focus was also on the nature of brain responses to these stimuli.

   The literature review focuses on two major theories of orienting and habituation that have been studied at the neural level. The relation of brain activity to these basic processes is examined together with a theory dissociating brain responses to novel stimuli and to stimulus changes. Finally, the term memory trace is defined.

2 REVIEW OF THE LITERATURE

2.1 Pitch, the auditory pathway, and its connections

The first stage in the analysis of pitch occurs as early as in the inner ear. The basilar membrane acts as a mechanical frequency analyzer which is based on the conversion from frequencies to places along the length of the membrane. This tonotopicity is maintained throughout the auditory system (for a review, see Harrison, 1978). For example, recordings from single neurons along the auditory pathway in anestethized cats (cochlear nucleus, inferior colliculus, medial geniculate body and auditory cortex) have shown that single neurons are sensitive to certain frequencies, forming a bank of band-pass filters with different but overlapping centre frequencies (for a review, see Moore, 1983). Typical of these filters is that the slope on the high-frequency side is usually greater than the slope on the low-frequency side. While some researchers have suggested that the neurons sharpen their tuning at the higher levels of the auditory system (for a review see Suga, 1995), there are studies that have not supported this view (e.g. Calford, Webster, & Semple, 1983).

Mainly from the association areas of the cerebral cortex, an auditory information flow proceeds towards the hippocampus via the entorhinal cortex (Gray, 1982; Lopes da Silva, Witter, Boeijinga, & Lohman, 1990). For example, it has been observed that when this connection is cut off in rats, they show less tendency to respond to novel auditory stimuli during tests of stimulus generalization following an auditory discrimination task. At the same time, hippocampal evoked potentials corresponding to the novelty of the stimulus disappear (Deadwyler, West, & Robinson, 1981).

In rabbits, it has been observed that the cerebellar cortex receives auditory input from auditory projections to the cerebellum at brain stem level. The cochlear nucleus has a connection to the pontine nucleus that, in turn, projects the mossy fibers to the cerebellar cortex (Steinmetz & Thompson, 1991).

2.2 Orienting and habituation

The orienting response (OR) was introduced by Pavlov (1927). He labelled it as a "what-is-it" reflex associated with a novel stimulus. At the behavioral level, the OR can be seen, for example, as eye or head movements towards the source of stimulation, though it has also been suggested that the OR is mediated by a system inhibiting behavior, and thereby could be reflected by an interruption of ongoing behavior (for a review, see Spinks & Siddle, 1983). Repeated stimulation leads to a response decrement, habituation of the OR (Harris, 1943). Since habituation is specific to stimulus features, it can be regarded as representing a form of non-associative learning. If a novel stimulus is embedded in a series of habituating stimuli, dishabituation occurs as there is a re-evocation of the OR to the succeeding stimulus.

A number of theories of the OR and habituation have been proposed and the level of explanation has varied between them. Some of them have defined the OR as a reflex resulting from a stimulus change or a novel stimulus, while others have applied more complex concepts describing human cognitive processes. In this study, the former will be emphasized.

Sokolov (1963, 1975) suggested that the sensory input is compared with a neural model formed by repeated stimulation. If there is a match between incoming stimulation and the model, no OR is evoked. In the case of a mismatch, the OR occurs. Sokolov (1975) located this neuronal model, formed due to repeated stimulation by the same stimuli, in the matrix of potentiated synapses of the hippocampus. He proposed that in the case of a stimulus differing from the model, this novel input interferes with the configuration of the matrix and consequently the excitatory hippocampal cells are no longer inhibited. As a consequence, the OR is evoked. According to Sokolov, the model of the stimulus includes all features of stimulation including its temporal aspects and relations between several successive stimuli.

Groves and Thompson (1970) presented a dual-process theory of habituation, according to which habituation is an outcome of the interaction between two independent processes: habituation in the stimulus-response (S-R) pathways, resulting in decreased transmission of synapses of these pathways, and non-specific sensitization increasing the overall excitability of the organism. Whereas Sokolov (1963, 1975) viewed dishabituation as representing disrupted habituation, Groves & Thompson interpreted it as a temporary masking of habituation by sensitization. The advantage of the dual-process theory has been its applicability to simple neural systems. Consequently, studies have been performed in invertebrates in order to reveal the cellular mechanisms of habituation and sensitization (e.g. Rankin & Carew, 1987; Broster & Rankin, 1994).

Observations concerning the stimulus specificity of sensitization have not accorded with the non-specificity assumption of sensitization made by the dual-process theory. That is, an increase in the overall excitability of the organism cannot explain facilitation, which is specific to a certain stimulus. Waters & Wright (1979) presented a habituation-sensitization model to explain

the influence of stimulus-specific factors affecting sensitization. They proposed that the degree to which a stimulus predicts or itself has effects on the physical integrity of the organism determines whether that stimulus is more likely to elicit the OR than others. Waters & Wright suggested that in humans, sensitization is modulated by neural interactions at the higher levels of the nervous system, such as the limbic-hypothalamic-frontal system. Consistently, human neuropsychological data have revealed that the limbic system, and cingulate and frontal lobes affect the OR and habituation (for a review, see Cohen, 1993). Pribram & McGuiness (1975) have also argued that the dual-process theory can not be applied higher than the collicular and thalamic levels.

In spite of the fact that significant stimuli have been observed to be more effective in eliciting ORs than non-significant stimuli (for a review, see Stephenson & Siddle, 1983) agreement has not been reached about the nature of the relationship between stimulus change and stimulus significance. Bernstein (1979) suggested that this relationship is multiplicative, whereas O'Gorman (1979) supported an additive view of the relationship. A recent study on electrodermal orienting (Ben-Shakhar, 1994) has stressed along the same lines as O'Gorman an interpretation according to which each stimulus in a sequence is independently compared, on the one hand, with representations of significant stimuli and, on the other hand, with the neural model of preceding stimuli.

The OR itself is also able to affect a process mediating stimulus significance, that is, associative learning. Korhonen & Penttonen (1989a, 1989b) found that when unpaired presentations of a conditioned stimulus (CS) and unconditioned stimulus (US) preceded their forward pairings in one group of cats, learning was much slower than in another group of animals in which the experiment started with forwardly paired trials. A stronger OR to novel CSs when the experiment started with forward CS-US pairings was interpreted to result in faster learning. In line with this, Pearce and Hall (1992) suggested that the OR and stimulus significance have a conditional relationship in that the former affects the latter. They emphasized that the strength of the OR, reflecting accuracy of prediction of the evoking stimuli, determines how susceptible the evoking stimulus is to conditioning.

2.3   Brain responses to repeated auditory stimuli

Response decrements to repeated tones have been observed along the auditory pathway. In their review of the literature, Buchwald & Humphrey (1973a) concluded that the higher the level of the pathway measured, the more observable the reductions of responses become. For example, Jaffe, Bourlier, & Hagamen (1969) recorded evoked potentials in auditory and nonauditory sites from the rostral forebrain to the pontine levels in unanesthetized spinal cats. They found rapid response decrements to clicks presented at 50-1000 ms inter-stimulus intervals (ISIs) in both auditory and nonauditory sites, the rostral sites being more susceptible to such decrements.

The foremost nucleus of the auditory pathway in which similar reductions in responsitivity have been observed is the cochlear nucleus. Reversible decreases in multiple-unit activity (MUA) at this location have been measured even when the stimulus field has been kept constant, ear muscles paralyzed, alterations in hair cell activity caused by the olivocochlear bundle blocked, and hair cell receptor discharges in the cochlea controlled by the round window microphonic recordings (Buchwald & Humphrey, 1973a). This implies that changes in the activity of the cochlear nucleus due to stimulus repetition seem not to reflect peripheral mechanisms but a mechanism intrinsic to the nucleus. Such decreases have been shown to be strongly dependent on the frequency of the stimulus (Buchwald & Humphrey, 1973b) and to be evident even when the cochlear nucleus has been surgically isolated from the brain stem (Brown & Buchwald, 1976).

In the superior colliculus, both the response decrease as a function of the repetition of an auditory stimulus and the pitch specificity of such a decrease were demonstrated in a study conducted by Horn and Hill (1964). They measured single units in rabbits and found that responses decreased due to the repetition of a 1000 Hz stimulus. Furthermore, if the repeated tone was suddenly changed to an otherwise identical but a 1500 Hz stimulus, the response of that particular unit was re-evoked. Thus, the decrease of responsitivity to 1000 Hz tones could not be attributed to the refractoriness of the recorded unit. Moreover, in the auditory cortex of cats, single neurons have been shown to have specificity to the position of a tone in a series of identical tones so that some neurons respond only to later stimuli in the series instead of there being a progressive decrease in activity of the responsive neurons due to stimulus repetition (McKenna, Weinberger, & Diamond, 1988). Accordingly, receptive field plasticity in the auditory cortex of the guinea pig to repetitive tones has been shown to be reflected by reduced responses to the repeated frequency that cannot be explained by neural fatigue (Condon & Weinberger, 1991).

Instead of refractoriness, a complex interaction between increases and decreases in brain activity to repeated stimuli seems to exist. By using monaural stimulation in paralyzed cats, Buchwald & Humphrey (1973a) found that in the lateral cochlear nucleus MUA increased to ipsilateral tones and decreased to contralateral tones as a response to a single tone. In contrast, at the level of the inferior colliculus and the medial geniculate body, responses to single tones were represented by increased spike activity to contralateral tones and decreased spike activity to ipsilateral tones. To repeated stimuli, the changes in these response modes consisted of an increase in the decreased spike activity and a decrease in the increased spike activity. Along the same lines, Vinogradova (1975) found two hippocampal cell types in rabbits: one active to novel stimuli and the other responding if a stimulus is repeated.

Surface ERPs in humans also show changes as a function of repeated auditory stimuli (Callaway, 1973). As the presentation rate increases but does not exceed 2/s, the decrease develops faster and reaches a lower asymptote. The N1 and P2 deflections of the human vertex potential are the major deflections that show a decrease in response to repeated stimuli. Opinions have differed

whether these ERP changes represent habituation or neuronal fatigue, i.e. refractoriness. Ritter, Vaughan, & Costa (1968) suggested that ISIs as short as 2 s result in neural refractoriness instead of habituation, since they did not find dishabituation of the vertex wave to changes in the pitch of the tone. Moreover, in an experiment (Roth, 1973) which applied an oddball-like 1000 Hz tone/noise paradigm (ISI 1 s), dishabituation was not present. A similar result could be found in a study by Wood & Elmasian (1986) in which tone sequences consisting of 6 tones were presented. In 50 % of the sequences, the fifth tone was replaced by a deviant stimulus. An increase in N1 amplitude to the deviant stimulus was found. However, no amplitude increase to the standard stimulus following the deviant stimulus was found. Consequently, Näätänen & Picton (1987) assumed that, instead of habituation, some kind of neural fatigue, probably based on complex neural circuits, must be responsible for N1 attenuation at short ISIs.

An opposite interpretation has been forwarded by Fruhstorfer, Soveri, & Järvilehto (1970). They proposed that a lack of dishabituation in the pitch change situation represents generalization of habituation over the pitches used rather than a lack of dishabituation. In fact, the refractoriness interpretation of decreased N1 deflection is not monotonously supported in the literature. Rothman, Davis, & Hay (1970) found that irregular ISIs (mean 2.5 s) resulted in slightly enhanced ERPs compared to those elicited when ISIs were kept constant. By keeping the ISI before the stimulus constant, they also found that, although the last ISI had the strongest effect on the response amplitude, the mean of the ISIs over the 10 seconds preceding the stimulus was also influential. Öhman, Kaye, & Lader (1972) also found a small increase in N1-P2 amplitude when the ISI was irregular. Näätänen & Picton (1987) distinguished different components of the N1 and suggested that temporal uncertainty partly affects the non-specific component of the N1, whereas its supratemporal component is affected by refractoriness alone. However, Budd & Michie (1994) recently observed that at ISIs of less than 500 ms, the amplitude of the N1 does not decrease, but instead increases, supporting a view according to which both facilitative and depressive processes rather than simple refractoriness underlie the decreased N1 deflections to repetitive stimuli.

2.4 Mismatch negativity

While habituation theories focus on mechanisms inducing habituation of responses to repetitive stimuli and those causing dishabituation, Näätänen, Gaillard, & Mäntysalo (1978) went a step further by assuming the existence of a specific mechanism detecting stimulus changes in an acoustic environment, a mechanism that compares sensory input to a short-term memory trace of preceding stimuli. Though, in principle such a comparison process appears similar to that proposed by Sokolov (1963, 1975), a critical difference exists. Näätänen (1986) regarded responses to the first stimulus in a series to reflect a mechanism that is different from that related to a stimulus change. At the level

of surface ERPs in humans, this is reflected by a large N1 deflection to the first stimulus, whereas a mismatch negativity (MMN) is elicited only when infrequent (deviant) stimuli are presented in a sequence of frequent (standard) stimuli. MMN can be identified by subtracting ERPs to standard stimuli from those to deviant stimuli. The specificity of MMN to preceding standard stimuli has been demonstrated by presenting deviant stimuli unaccompanied by standard stimuli. In this case, deviant stimuli elicit no MMN (Alho, Sainio, Sajaniemi, Reinikainen, & Näätänen, 1990; Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989; Sallinen, Kaartinen, & Lyytinen, 1992; Sams, Hämäläinen, Antervo, Kaukoranta, Reinikainen, & Hari, 1985). In human studies applying surface recordings of ERPs and their magnetic counterparts, it has been suggested that MMN is generated by activity of the auditory cortex (primary and non-primary) and, to some extent, by activity of the frontal lobe (for a review, see Alho, 1995).

MMN can be elicited to many types of deviance, such as pitch (Näätänen et al., 1978; Sams, Paavilainen, Alho, & Näätänen, 1985), intensity (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1987a), rise time (Lyytinen, Blomberg, & Näätänen, 1992), ISI (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1987b), duration (Näätänen, Paavilainen, & Reinikainen, 1989) and spatial location (Paavilainen, Karlsson, Reinikainen, & Näätänen, 1989). Even changes in abstract attributes have been shown to elicit MMN (Saarinen, Paavilainen, Schröger, Tervaniemi, & Näätänen, 1992). If a stimulus deviation is large MMN may be followed by N2b (Näätänen, Simpson, & Loveless, 1982) and/or P3a deflections (Squires, Squires, & Hillyard, 1975) which have been proposed to reflect the classical OR (Sokolov, 1975) following the OR to stimulus change (Näätänen & Gaillard, 1983). Consistent with this assumption, implying that the change OR may or may not lead to the classical OR, Lyytinen et al. (1992) found that MMN could be elicited without concomitant responses of the autonomic nervous system (ANS). Also, Tiitinen, May, Reinikainen, & Näätänen (1994) observed that MMN preceded attentive novelty detection (the reaction time of motor responses) by a constant interval.

There have also been attempts to model human MMN in animals. For present purposes the term "MMN-like" is used to refer simply to the difference between responses to deviant tones and those to standard tones in animals. A cortical MMN-like negativity to intensity-deviant clicks was reported to be elicited at a latency range of 80 ms in monkeys (Javitt, Schroeder, Steinschneider, Arezzo, & Vaughan, 1992). In a later study, Javitt, Steinschneider, Schroeder, Vaughan, & Arezzo (1994) located it in the supragranular laminae within the AI. Also, they found that intracortically the latency of MMN-like activity could be as short as 15 ms. In anesthetized guinea pigs, MMN-like ERPs to pitch-deviant tones (standards 2300 Hz, deviants 2450 Hz, tone duration of 50 ms) were observed to commence at a latency of 25 ms in epidural and medial geniculate body recordings (Kraus, McGee, Littman, Nicol, & King, 1994). In cats, MMN-like negativities were found to be elicited by pitch deviant 1-ms clicks (3000/4000 Hz) at a latency range of 30-70 ms in the AI and the AII areas of the auditory cortex, the vertex, and the association cortex (Csépe, Karmos, & Molnár, 1987). The responses in the association cortex

and vertex preceded those in the primary auditory cortex. At the same latency range as that of the MMN-like ERPs, a decrease MUA to standard tones and the absence of any such decrease to deviant tones has been observed in the AII area (Karmos, Winkler, Molnár, & Csépe, 1993). In addition, Csépe, Karmos, & Molnár (1988, 1989) also observed MMN-like negativity in the hippocampus to pitch deviant clicks (1 ms, 3600/4000 Hz) commencing at a latency of about 15 ms, preceding MMN-like responses in the cortex and medial geniculate body. Consequently, it was suggested that changes in pitch may be detected subcortically. The very early hippocampal ERPs imply that the hippocampus may participate in the detection of stimulus novelty, as has been proposed by Sokolov (1975).

The term "MMN-like" in animal studies, however, requires careful definition. In human studies a connection between MMN and a comparison process activated at the time of the deviant stimulus that detects the stimulus deviance has been unambiguously demonstrated. This has been done by presenting deviant tones in the presence and absence of intervening standard tones (Alho et al., 1990; Näätänen et al., 1989; Sallinen et al., 1994; Sams et al., 1985). The omission of standard tones has resulted in the absence of the wave form of responses to deviant tones that contributes to MMN elicited when standard stimuli are present. Control procedures used in animal studies (Csépe et al., 1987, 1988, 1989; Javitt et al., 1992; Kraus, McGee, Littman et al., 1994; Kraus, McGee, Carrel et al., 1994), including a reversal or change of probabilities of standard and deviant tones, or a presentation of deviant tones at the rate of standard tones, may only reveal the effect of different presentation rates within each stimulus type. These control procedures are, thus, not sufficient if the observed ERPs to deviant tones are meant to be defined as an index of a comparison process detecting a mismatch between a memory trace of standard stimuli and a sensory input by a deviant stimulus.

2.5 Memory trace

In the context of non-associative learning, the memory trace of the stimulus refers to a prolonged neural representation of the stimulus following its offset. According to Sokolov (1975), a neural model of a stimulus is represented by the matrix of potentiated synapses of hippocampal cells. Näätänen (1984) presented a memory trace hypothesis relating MMN to changes in pitch. According to the hypothesis, a pitch-specific cortical neural population is in a state of homogenous inhibition when the first stimulus is introduced (No MMN), activating only the afferent neurons (N1 elicited). A few repetitions of the stimuli release the neurons related to other frequencies from inhibition (MMN is elicited if a pitch change occurs) at the same time as neurons affected by the stimuli become refractory (no MMN if there is no change). This refractoriness has been proposed to represent the neural model of repetitive stimuli (Näätänen & Picton, 1987). Common to Näätänen's and Sokolov's proposals is that they assume the model of the stimulus to be located in specific

parts of the brain. However, no anatomically separate parts of the brain are attributed to the neural representations of the stimulus by the dual-process theory of habituation. Instead, according to Thompson, Berry, Rinaldi, & Berger (1979), the neural model of the stimulus is represented by a decrease in the transmission of all of those synapses that are activated by stimulation.

3   AIMS OF THE STUDIES

Generally, the present experiments (Studies I to V) aim at resolving those behavioral and, especially, neural responses that occur in situations in which there are changes in the acoustic environment. Such an environment is provided in all cases by an oddball situation consisting of pitch deviant tones in a sequence of standard tones. A modified version based on an experimental setting used in conditioning studies (Korhonen & Penttonen, 1989a,b; Penttonen, Korhonen, & Arikoski, 1993; Penttonen, Korhonen, & Hugdahl, 1991; Penttonen, Korhonen, Arikoski, Ruusuvirta, & Hugdahl, 1993) in which a US follows the deviant tones was also applied.

Studies I and II were carried out in cats, and Studies III to V in rabbits. In Study I, an attempt was made to confirm earlier observations of hippocampal responses to pitch changes in cats by measuring activity from several hippocampal electrode sites. Also, the ability of the deviant stimulus to act as a dishabituating stimulus was examined. Study II was carried out in the same animals to define the latency range at which the conditioned responses (CRs) to the deviant tones are elicited when the US is presented after each deviant tone. Since the CRs represented conditioned ORs (orienting head turns towards the tone source) elicited at the same latency range as "novelty" ORs (Korhonen & Penttonen, 1989a,b), they allowed a definition of the maximum latency range at which the MMN-like process should have occurred in Study I. This is because MMN in humans has been shown to be elicited before the latency range of the attentive novelty detection (Tiitinen et al., 1994). In Study III the focus was on whether any deflection of hippocampal ERPs to deviant tones shows the kind of specificity to the preceding standard tones as is required for the ERPs to be considered MMN-like. Consequently, control sessions consisting of the omission of the standard tones were added to the experiment. On the basis of the results of Study III, Study IV attempted to resolve whether ERPs to pitch changes can already be observed in the cerebellum. In that study, recordings were made, not only from the hippocampus, but also from the cerebellar cortex. For Study V, MUA indexing the net spike activity of neurons in the vicinity of the recording electrode (Buchwald, Holstein, & Weber, 1973) was recorded

during the same trials and through the same electrodes as were the ERPs reported in Study IV.

4 METHODS

Cats were anesthetized with sodium pentobarbital (40 mg/kg). In rabbits, anesthesia was initiated and maintained with a Ketalar® (50 mg/ml)-Rompune ® (20 mg/ml) cocktail. Atropin (0.2 mg/kg) inhibited salivation. Temgesic® (0.01 mg/kg) was administered as an analgesic for two days. In surgery, a stereotaxic instrument was used. The general procedure followed a method described by Korhonen (1991a). Monopolar recording electrodes were implanted into the dorsal hippocampus and, in the case of the cats in Studies I-II, bipolar stimulation electrodes into the lateral hypothalamus. In Study IV, electrodes were implanted also into the visual and cerebellar cortices. During implantation, signals from the electrodes were monitored to detect typical hippocampal activity and to determine the depth needed for penetration through the skull and dura in the cortical recordings (Studies IV and V). The animals were allowed to recover for at least a week after surgery.

The recording and stimulation electrodes were made of teflon-coated stainless steel wire of 50 µm diameter surrounded by a hypothermic tube (0.41 mm). After inserting and fixing the wire in the tube, the tip of the wire was sharpened to a conical shape and exposed up to a length of 300-500 µm. The recording electrodes were referred to the skull screws at both sides of the midline. All the electrodes were connected to two 15-pin D-type connectors that were fixed with dental acrylic to the anchoring screws in the skull.

In Study II, a head movement acceleration transducer was used to measure head movements (Korhonen, 1991b). Its sensitivity was 10 mV/g and resonance frequency 1000 Hz. A plastic tube transmitting tones from a loudspeaker located outside the measurement box was also attached to a holder fixed to dental acrylic. The distance to the left ear was 2 cm. For the cats in Study II, the effect of the stimulation of the lateral hypothalamus (US) was tested. The US consisted of a 100 Hz pulse train of 500 ms in duration. The pulse amplitude and the electrode were selected on the basis of the rewarding effects obtained when the US was applied (orienting, approach movements).

During the measurements, the cats were unrestrained in a ventilated, sound attenuated, and electrically shielded box. The animals were monitored

by a video camera through the experiments. The rabbits were in a Plexiglas restrainer located in a ventilated, sound attenuated, and electrically shielded box. They were also monitored by a video camera. A computer controlled the presentation of the trials and the generator delivering pulse trains for brain stimulation. A second computer was used for recording the signals.

After the measurements, the animals were anesthetized with a lethal dose of anesthetic and perfused with physiological saline followed by 10% formalin. A 10-μA direct current was delivered through the electrodes for 20 s in order to mark the locations of the electrode tips. The brains, together with the electrode assembly, were kept in formalin for a week. After this period, the electrodes were removed and, to enable the location of the hippocampal and hypothalamic sites, 40-μm slices were cut and stained with cresyl violet and potassium ferrocyanide. Since the contact of the cortical electrodes with the tissue could be verified by their penetration through the dura, the surface locations of the electrodes in the visual and cerebellar cortices were visually detected when removing the skull. Subsequently, the locations of the electrodes were defined according to brain atlases (Fifková & Maršala, 1967; Snider & Niemer, 1961; Shek, Wen, & Wisniewski, 1986).

5 SUMMARY OF THE STUDIES

5.1 Study I

The purpose of Study I was to verify earlier observations of MMN-like hippocampal ERPs commencing at a latency range of about 20 ms in cats (Csépe et al., 1988, 1989). The ability of deviant tones to act as dishabituating stimuli was also studied. Whereas Csépe et al. used 1 ms clicks (3600/4000 Hz) delivered through a bone conductor, Study I used longer stimuli that were delivered through a loudspeaker in order to model more closely studies in humans. The recordings were made from different sites of the hippocampus including the CA1, CA3 and dentate fascia.

5.1.1 Methods

The subjects were 4 freely moving adult cats. The stimuli consisted of 2500 Hz deviant tones presented in a series of 2000 Hz standard tones (65 dB). The probability of a deviant tone occurring was 4.3 % and the ISI was 500 ms. The tones were delivered via a plastic tube to the front of the left ear (at a distance of 2 cm). The experiment consisted of three blocks of 80 trials separated by a few minutes. The animals were videotaped together with a signal indicating of the timing of the delivered stimuli in order to allow observation of the orienting head movements towards the tone source.

Recordings were made from the CA1, CA3 and dentate fascia of the hippocampus. ERPs were filtered (0.1 - 100 Hz) and digitized at the rate of 200 samples per second with a microcomputer. The amplitude averages were calculated from the post-stimulus averages of 30-60 ms (N40) and 100-170 ms (N130) and corrected against the baseline (the mean amplitude of the pre-stimulus period of 50 ms). Each trial of each cat/electrode location was treated as an individual case in the statistical analyses, which were performed using ANOVA for repeated measures.

5.1.2 Results

The animals oriented towards the tone source by turning their heads only to the first stimuli of the first trial block. Within a few first trials the animals were typically sitting quietly in the middle of the box. When the difference ERPs (deviant ERPs - standard ERPs [N40d, N130d]) were calculated, no clear N40d could be seen (it was statistically significant in only two out of four cats). In contrast, the 130d was clearly observed, being statistically significant in all animals and hippocampal locations. No difference in ERPs was observed when responses to standard tones following deviant tones were compared to responses to standard tones preceding deviant tones.

5.1.3 Discussion

The results of Study I partly verified earlier observations of the existence of MMN-like hippocampal ERPs in cats (Csépe et al., 1988, 1989), since such ERPs were found. However, the MMN-like deflections were only slightly reflected by the ERPs at a latency range of less than 100 ms (N40d), corresponding to the MMN-like ERPs observed by Csépe et al.. Instead, the main MMN-like deflection was elicited at more than 100 ms from stimulus onset (N130d). Consequently, it was suggested that, instead of MMN, N130d might be analogous to ERPs following MMN in humans, such as N2b or P3a (Näätänen, Simpson, & Loveless, 1982; Squires, Squires, & Hillyard, 1975).

5.2 Study II

The aim of this study was to define the maximum latency range for MMN-like potentials according to the latency of conditioned ORs elicited by deviant tone-US pairings.

5.2.1 Methods

The subjects were the same 4 cats as in Study I. The stimulus parameters and the general experimental setting were analogous to those in Study I, except that each deviant stimulus was followed by electrical stimulation of the lateral hypothalamus as the US. It was delivered 500 ms from the onset of each deviant stimulus. In addition to ERPs, head turn acceleration signals were also recorded in order to gain an index of the amplitude of the conditioned ORs. The amplitude averages were calculated from the post-stimulus averages of 60-100 ms (N80) for ERPs and 100-200 ms for the acceleration signals, and corrected against the baseline (the mean amplitude/acceleration of the pre-stimulus average of 50 ms). Each trial of a single cat/electrode location was treated as an individual case in statistical analyses, which were performed using ANOVA for repeated measures.

5.2.2 Results

The animals developed conditioned ORs towards the deviant tones as a function of the paired deviant tone-US presentations. In the averaged wave form, the onset latency of both behavioral and neural responses was about 50 ms. The hippocampal N80 deflection was developed and reflected ERPs that, in an average, had time-amplitude characteristics similar to the time-acceleration characteristics of the behavioral ORs. In fact, the ERPs developed before the head turns, and their onset and peak latencies preceded slightly those of the head turns.

5.2.3 Discussion

The onset of the conditioned ORs (50 ms) was in accordance with earlier observations of MMN-like ERPs in cats elicited before 50 ms from stimulus onset (Csépe et al., 1988, 1989). This is because MMN in humans has been shown to precede attentive novelty detection (Tiitinen et al., 1994). The MMN-like ERPs at more than 100 ms from tone onset in Study I may, therefore, reflect ERPs analogous to N2b or P3a deflections in humans (Näätänen, Simpson, & Loveless, 1982; Squires, Squires, & Hillyard, 1975).

5.3   Study III

This study aimed at resolving whether in rabbits hippocampal ERPs to deviant tones contributing to MMN-like responses in the oddball situation are specific to the preceding standard tones.

5.3.1 Methods

The subjects were 8 adult rabbits. Deviant tones of 2500 Hz were presented in a series of 2000 Hz standard tones (85 dB). The probability of the occurrence of a deviant tone was 5 % and the ISI was 500 ms. Both of the tones were delivered via a plastic tube to the front of the left ear (at a distance of 2 cm). The experiment consisted of five blocks of 80 trials separated by a few minutes. In trial blocks 2 to 4, the standard stimuli were present (the oddball situation). In trial blocks 1 and 5 (the deviant-alone situation) the standard stimuli were removed.

Recordings were made from the CA1, CA3, and dentate fascia (Df) of the hippocampus. In addition, in two rabbits, the electrodes were also implanted into the corpus callosum. ERPs were filtered (0.1 - 100 Hz) and digitized at the rate of 200 samples per second with a microcomputer. The amplitude averages were calculated from the post-stimulus averages of 50-70 ms (N60), 100-130 ms (N110), 180-220 ms (P200), 250-280 ms (P270) and 330-360 ms (P340), and corrected against the baseline (the mean amplitude of the pre-stimulus period of 50 ms). The statistical analyses were performed using ANOVA for repeated measures.

5.3.2 Results

In the oddball situation, significant differences between ERPs to the deviant tones and those to the standard tones were observed in the CA1 and Df. The amplitude of the P270 deflection was higher to the deviant tones than to the standard tones. In the deviant-alone situation, the amplitudes of ERPs to the deviant tones were not lower than those in the oddball situation. Polarity reversals between ERPs to the deviant tones measured from the hippocampus and corpus callosum occurred in both types of situation.

5.3.3 Discussion

Hippocampal MMN-like ERPs (significant differences between ERPs to the deviant tones and those to the standard tones) were observed, although they appeared as a rather late positivity (P270) to the deviant tones. By controlling the effect of the standard tones (a comparison was made between deviant ERPs when the standard tones were present and when they were absent), it was shown that the MMN-like ERPs reflected a difference between the presentation rates of the two stimulus types rather than an outcome of the neuronal comparison process detecting the stimulus change (for a review, see Näätänen, 1990). This is because none of the ERP deflections to the deviant tones in the oddball situation was specific to the preceding standard tones.

5.4   Study IV

This study in rabbits was methodologically similar to Study III except that recordings were made, in addition to those from the hippocampus, also from the visual and cerebellar cortices.

5.4.1 Methods

The subjects were 7 adult rabbits. The 85 dB tones consisted of pitch-deviant tones incorporated in a series of standard tones (The pitches of the tones, 1500 Hz and 2000 Hz, were balanced within each animal). The probability of the occurrence of a deviant tone was 5 % and the ISI was 500 ms. Both of the tones were delivered to the left ear. The experiment consisted of five blocks of 80 trials presented twice on separate days in order to reverse the pitches of each type of stimulus. In blocks 2 to 4, the standard stimuli were present (the oddball situation). In blocks 1 and 5 (the deviant-alone situation), the standard tones were removed.

Recordings were made from the hippocampus, visual cortex and cerebellar cortex. ERPs were filtered (0.1 - 200 Hz) and digitized at the rate of 400 samples per second with a microcomputer. The amplitude averages were calculated and corrected against the baseline (the mean amplitude of the pre-stimulus period of 50 ms) for 25 ms time segments from the onset of the tones. Statistical analyses were performed using a paired t-test.

5.4.2 Results

In the oddball situation, significant differences between ERPs to the deviant stimuli and to the standard stimuli were observed at 125-175 and 200-250 ms from stimulus onset in the hippocampus and at 75 - 225 ms from stimulus onset in the cerebellar cortex but not in the visual cortex. The differences consisted of higher ERP amplitudes to deviant stimuli than to standard stimuli. When the standard stimuli were removed (the deviant-alone situation), it was found that the amplitudes of ERPs to the deviant stimuli were higher than they were when the standard stimuli were present (the oddball situation).

5.4.3 Discussion

MMN-like ERPs (differences between ERPs to the deviant and standard tones) both in the hippocampus and cerebellar cortex imply that the detection of pitch changes may already take place in the cerebellum. This assumption is supported by an earlier observation of conditioned auditory discrimination in decerebrate cats when a shock US was presented after a CS (Norman, Buchwald, & Villablanca, 1977). In such a case, the neural trace of the CS, including the physical features of the CS, is obligatory in order to establish an association between the CS and US.

In accordance with Study III, both the hippocampal and cerebellar MMN-like ERPs seem to reflect the difference in the presentation rates between the deviant and standard stimuli *per se.*

5.5   Study V

For this study, MUA was recorded in parallel with ERPs (Study IV) in order to obtain an index of the firing of a local neuronal population from ERP recording sites.

5.5.1 Methods

MUA was recorded in parallel with the ERPs reported in Study IV. It was filtered (500 - 6000 Hz) and digitized at the rate of 15 000 samples per second with a microcomputer. Spikes were detected by using a special computer program. After setting a threshold for the spike amplitude needed for their detection, spikes exceeding this threshold were counted per 10 ms-bins. Subsequently, the standard scores for each bin were computed by subtracting the activity of the baseline (an average of 50 ms pre-stimulus spike frequency) from the activity of each bin and dividing the residual by the standard deviation of the baseline activity over the trials. The statistical analyses were based on the averages of two consecutive bins and performed using a paired t-test.

5.5.2 Results

In the oddball situation, significant differences between MUA responses to the deviant stimuli and those to the standard stimuli were observed only in the hippocampus. The first difference could be found at a latency of less than 20 ms from the tone onset. It mainly reflected an increase in MUA to the standard stimuli. Later differences (at 60-80 and 100-160 ms) reflected a prominent decrease in MUA to deviant stimuli. Differences between the MUA to deviant and standard stimuli were not found in the visual or cerebellar cortices.

When the standard stimuli were removed (the deviant-alone situation), it was found that the decrease in hippocampal MUA to the deviant stimuli at latency ranges of 60-80 and 100-120 ms was significantly more pronounced than that in the oddball situation. In the visual cortex, the MUA to the deviant stimuli was significantly higher in the oddball situation than in the deviant-alone situation at a latency of 100-120 ms. No such differences were found in the cerebellar cortex.

5.5.3 Discussion

The absence of cerebellar MMN-like MUA, in spite of the prominent MMN-like ERPs recorded in parallel through the same electrodes (Study IV), implies that ERPs may be a better indicator of MMN-like activity than MUA in the cerebellar cortex.

In contrast, the hippocampal MMN-like MUA was prominent and could be seen at an earlier latency range (< 20 ms) than the simultaneously recorded MMN-like ERPs (Study IV). Thus, the difference between the physical features of standard compared to deviant stimuli seems to be rapidly detected by the hippocampus.

In accordance with Studies III and IV, the hippocampal MMN-like activity merely reflected the difference in presentation rates between the deviant and standard stimuli. Although the standard stimuli did have an effect on the deviant responses, this effect did not favor MMN-like activity (the difference between MUA to the standard and deviant stimuli).

6   GENERAL DISCUSSION

In Studies I to IV, significant hippocampal MMN-like ERPs commenced not less than 100 ms from tone onset. In this respect, the present results in cats (Study I) were in contrast to earlier observations of MMN-like negativity in the cat auditory cortex 40-70 ms from stimulus onset and a similar type of hippocampal activity commencing as early as about 20 ms from stimulus onset (Csépe et al., 1988, 1989). The wider pitch difference and longer stimulus duration used in Study I should rather have resulted in a shorter latency of responses than those observed by Csépe et al. (Näätänen & Gaillard, 1983). In fact, in Study II, it was found that ERPs at a latency longer than 50 ms in cats were related to concurrent behavioral conditioned ORs (head turns in the direction of the tone source) elicited by the deviant tone-US pairings. It seemed evident that, instead of MMN, the MMN-like ERPs observed in Study I rather reflected responses related to the OR that may correspond to human N2b (Näätänen, Simpson, & Loveless, 1982) and/or P3a deflections (Squires, Squires, & Hillyard, 1975) that may follow MMN.

   Similarly in rabbits, MMN-like hippocampal ERPs were not found before a latency range of 100 ms from stimulus onset (studies III and IV). However, a very different result was provided by Study V. It was found that MMN-like MUA, recorded from the same animals and trials, and through the same electrodes as the ERPs in Study IV, commenced as early as within 20 ms from stimulus onset. It is possible that the absence of MMN-like ERPs at this latency can be explained by two different types of hippocampal neurons: one activated by infrequently presented (deviant) stimuli and the other by frequently presented (standard) stimuli (Vinogradova, 1975). As activity of both of these neurone types may be represented by a negative ERP deflection, it is possible that the MMN-like ERP in the hippocampus (a difference between the ERPs to deviants and standards) may markedly diminish or, as has been observed in humans, even be absent (Kropotov et al., 1995). A very interesting result concerning the speed of hippocampal responses in humans was provided by a study applying magnetic field tomography (MFT, Ioannides et al., 1995). In that study, signs of an activity at a latency of less than 30 ms were found in the

depth of the medial temporal lobe in the oddball situation. Though, this activity was similar regardless of the stimulus type and led to the loss of the difference between responses to the deviant and standard stimuli.

Latency differences similar to those observed between ERPs and MUA in the hippocampus (Studies IV and V) have also been found in the cerebral cortex. Recent intracortical recordings in monkeys have shown that whereas in surface recordings MMN-like responses are elicited at a latency of longer than 50 ms in the AI area (Javitt et al., 1992), intracortically their latency can be as short as 15 ms (Javitt et al., 1994). Despite the fact that intracortical ERP recordings have been made in humans (Kropotov et al., 1995), the measures of brain activity used have been different from those applied in monkeys by Javitt et al. (1994). While in humans analyses have been based on plain ERPs, current source density (CSD) analyzed data have been applied in monkeys. Consequently, it remains to be seen whether similar differences in latencies between surface MMN and its intracortical correlates as observed in monkeys exist in humans. If so, then they would suggest that surface MMN may not represent the moment of detection of stimulus change but, instead, an outcome of such a process.

Study IV showed that MMN-like ERPs can be observed in the cerebellar cortex. The observed MMN-like deflection was stronger and of a shorter latency than that recorded from the hippocampus. In contrast, MMN-like MUA was not statistically significant in the cerebellar cortex, whereas it commenced very early and was statistically significant in the hippocampus (Study V). Thus, it seems that, in contrast to the hippocampus, the cerebellar MMN-like response is best represented by the summation of postsynaptic potentials, in contrast to MUA, which has been suggested to be produced by presynaptic potentials (spikes) (Coles, Gratton, & Fabiani, 1990). To what extent cerebellar activity was influenced by input from the cerebral structures remains a puzzle. However, earlier studies on habituation (e.g. Buchwald & Humphrey, 1973a,b) have shown that two essential features needed for the observed responses are present already at brain-stem level. These features are the changes in response to repetitive stimuli and their selectivity regarding the pitch of the stimuli (see Chapter 6.3). Also, the ability of decerebrate cats (Norman, Buchwald, & Villablanca, 1977) or cats with ablated auditory cortices (Butler, Diamond, & Neff, 1957; Thompson, 1960) to make pitch discriminations suggest that pitch discrimination-related responses are possible even without the dorsal part of the auditory system. Ravizza & Belmore (1978) reviewed studies indicating that the auditory cortex is not necessary for pitch discrimination. Rather, they concluded that the auditory cortex contributes to the processing of more complex attributes of auditory stimuli. Accordingly, Diamond & Neff (1957) found that the ablation of the temporal cortices in cats impaired the discrimination of tonal patterns. On the basis of these findings, it seems likely, or at least possible, that the cerebellar responses observed in Studies IV and V reflected activity along the auditory pathway at the brain-stem level that arrives at the cerebellar cortex via the mossy fibers (Steinmetz & Thompson, 1991).

The effect of the different presentation rates of the auditory stimuli on the MUA in the visual cortex (Study V) may reflect prewired connections to the

visual cortex similar to those enabling the plasticity needed for visual-cortex participation in auditory discrimination in blind humans (Kujala et al., 1995). However, the effect of the stimulus presentation rate was shown not to be specific to the pitch of the stimuli, leading therefore to the loss of the difference between responses to deviant and standard tones in the oddball situation, that is, the absence of a MMN-like response. This is in accordance with observations that MMN is elicited mainly in the auditory cortex (for reviews, see Näätänen, 1990; Alho, 1995).

6.1 Is a comparison process needed to explain the observed brain responses to pitch changes?

Studies I to V showed that MMN-like responses (differences between responses to deviants and standards) can be seen subcortically. However, these responses dramatically differed from those observed in surface recordings in humans (for a review, see Näätänen, 1990). It was found in the present studies that MMN-like responses did not reflect responses to deviant stimuli that would depend on the preceding standard stimuli, as is the case with MMN. Instead, they reflected the faster rate of repetition of the standard stimuli compared with the deviant stimuli. The standard stimuli affected responses to the deviant stimuli only in so far as the responses to the deviant stimuli began to resemble the responses to the standard stimuli and therefore did not actually support a prominent MMN-like activity (Fig. 1).
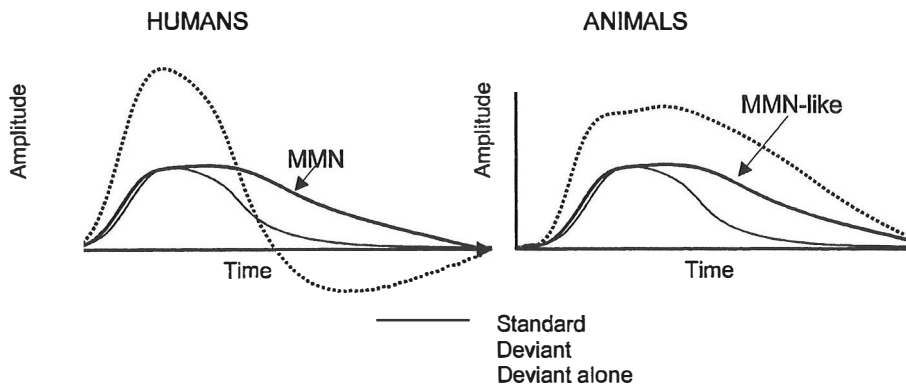
FIGURE 1. A simplified illustration of scalp recorded ERPs in humans (adapted from Näätänen et al., 1989) and subcortical ERPs in animals. "Standard" and "Deviant" refer to averaged responses to corresponding stimulus types in the oddball situation. "Deviant alone" refers to averaged responses to deviant tones presented in the absence of standard tones.

Consequently, the most crucial criterion for relating the observed MMN-like responses to the comparison process activated by the deviant stimuli was not fulfilled. Instead, two factors seemed to be needed to account for the observed

MMN-like activity. The first was an effect of the stimulus-repetition rate and the second the specificity of this effect to those stimulus features that differentiate the standard stimuli from the deviant stimuli. A contribution by these factors to MMN-like responses could be seen in Study V. In that study, the absence of cerebellar MMN-like unit activity seemed to be due to the absence of the stimulus-repetition effect at that recording site. Responses to deviant tones did not differ from those to preceding standard tones (the oddball situation), despite the fact that the standard tones had no effect on the responses to the deviant tones. The stimulus repetition effect could be seen in the visual cortex. Responses to deviant tones when standard ones were present differed from those when standard tones were absent. However, there were no differences between responses to the deviant tones and those to the preceding standard tones (oddball situation). Thus, the stimulus-repetition effect was not specific to the pitch of stimuli, resulting in the absence of MMN-like activity in the visual cortex as well. In the hippocampus, both the stimulus repetition effect and its pitch specificity were present, leading to significant MMN-like activity at that recording site.

One of the most surprising results was a prominent MMN-like ERP in the cerebellar cortex. However, earlier studies (Buchwald & Humphrey, 1973a,b; Moore, 1983) on the auditory system indicate that both the effect of the stimulus-repetition rate and its specificity to the pitch of the stimulus are present already at that level of the auditory system. Also in line with these findings are studies demonstrating the ability of decerebrate cats (Norman, Buchwald, & Villablanca, 1977) or cats with ablated auditory cortices (Butler, Diamond, & Neff, 1957; Thompson, 1960) to make pitch discriminations.

In conclusion, since the MMN-like responses can be ascribed to represent a difference in the presentation rates *per se* of the deviant stimuli and standard stimuli, such responses in either the hippocampus or cerebellar cortex cannot be considered to represent responses analogous to MMN in humans. To some extent, those responses resembled the supratemporal component of the N1 deflection in humans (Näätänen & Picton, 1987). This is because the N1 deflection is reduced by stimulus repetition, partially recovered when the stimulus is changed, and elicited by both the first and embedded stimulus in a series. In fact, Näätänen & Picton suggested that the supratemporal component of the N1 deflection could be related to the readout of the neural model of the stimulus. However, they assumed that the model reflected by the N1 deflection is represented by refractoriness of its cortical generator mechanism and, thereby, unaccompanied by increased neuronal activity such as found in Study V.

Any of Studies did not apply recordings from the auditory cortex, thus permitting the suggestion that the observed subcortical MMN-like activity is different of its nature than such activity in the auditory cortex. However, our latest recordings in cats (Korhonen, Ruusuvirta, & Arikoski, 1996) revealed that MMN-like activity observed in the auditory cortex could also be ascribed, as in Studies III-IV, to a difference in the presentation rates *per se* of the deviant and standard stimuli. Further studies are needed, not only in order to verify the

present results but also to reveal the relation between subcortical responses and those in the auditory cortex.

6.2 The nature of the change in brain responses to repetitive stimuli

Study I showed that despite the difference between ERPs to deviant stimuli and those to standard stimuli (the MMN-like response), deviant tones could not act as dishabituating stimuli. In that respect, one could suggest, as Näätänen & Picton (1987) did in the context of the human N1 deflection, that the MMN-like responses simply indexed the more pronounced refractoriness of the standard-related neural pathways compared to the deviant-related neural pathways due to a difference between the presentation rates of the deviant and standard stimuli. However, the increase in hippocampal MUA to frequently presented (standard) stimuli and the decrease to infrequently presented (deviant) stimuli in rabbits (study V; see also, Vinogradova, 1975) suggested that more complex changes in brain responses than a decrease in neuronal activity are caused by an increase in the stimulus repetition rate. Thus, the absence of dishabituation reflected by ERPs does not necessarily mean that a decrease in ERPs to a stimulus when its repetition rate is increased reflects neural refractoriness at least at the brain site under investigation.

6.3 The short-term memory trace

It has been suggested that the short-term memory trace for auditory stimuli is located at the same site as that where MMN is generated, i.e. in the cerebral cortex (Näätänen, 1984). In this context, the observed MMN-like activity (Studies I to V) is in two respects rather confusing. Firstly, MMN-like responses were observed at subcortical sites, including the hippocampus (Studies I to V) and the cerebellar cortex (Study IV), indicating that the memory trace of repeated auditory stimuli may also exist at those locations and, thus, at multiple sites in the brain. Such a conclusion was also drawn by Csépe et al. (1988, 1989) on the basis of the thalamic and hippocampal MMN-like ERPs. Accordingly, a trace formed elsewhere than in the auditory cortex must, for example, have been required for learning to discriminate pitch changes on the basis of the shock following them in animals with ablated auditory cortices (Butler, Diamond, & Neff, 1957). Secondly, according to Studies III to V, this trace does not seem to be connected to the MMN-like comparison process between an incoming stimulus and the trace, but to responses reflecting the difference in presentation rates between deviant and standard stimuli. In line with this, Csépe et al. (1989) connected hippocampal MMN-like ERPs to the neural mechanism described by Sokolov (1975).

In the case of the present data two memory trace-interpretations remain to be considered. The responses in the cerebellar and visual cortices (Studies IV and V) are in accordance with the memory-trace assumption of the dual-process theory of habituation (Thompson et al., 1979), which states that the trace is represented by the depressed transmission of the synapses in the stimulus-response pathways (note that the cerebellar cortex has an auditory input from the auditory pathway at brain-stem level [Steinmetz & Thompson, 1991]). This is because repetitive stimuli are expected to induce either a reduction or no change in brain activity at any level of the pathways. However, the increased hippocampal MUA does not support this theory, since no increase in brain activity should occur. In this case, a close connection to the stimulus-comparator theory (Sokolov, 1975) and related hippocampal recordings (Vinogradova, 1975) is indicated. However this, in turn, is only on condition that we ignore the assumption about the memory trace being located solely in the hippocampus. In any case, neural fatigue alone does not seem to explain the observed changes in brain activity to repeated auditory stimuli as has been suggested in the context of the N1 deflection in humans (Näätänen & Picton, 1987). Instead, an active neural process would seem to be related to these changes.

It is crucial that a distinction is made in the context of diminished ERPs to repetitive stimuli between interpretations of refractoriness vs. an active brain process (reflected by both decreases and increases of brain activity when the stimulus repetition rate is increased). This is because these two interpretations lead to very different conclusions concerning the neural representation of the stimulus. If changes in ERPs to repetitive stimuli are regarded as reflecting refractoriness, then it is difficult to see a connection with the neural model of the stimulus, also including the temporal features of stimulation. In this case, amplitude changes would simply represent the limits of the recovery speed of the afferent pathways of the organism. In the opposite case, such a connection is very easy to make. Only a process consisting of both facilitative and depressive components would be able to retain the temporal features of the stimulus environment, thereby forming the true short-term memory trace needed, for example, for MMN to ISI deviances (Näätänen et al., 1987b). Interestingly, it seems possible that coding these features does not seem to require cerebral structures. In fact, the cerebellar cortex has already been related to response timing in nictitating membrane conditioning in rabbits (Steinmetz, 1990).

7 CONCLUSIONS

The present results together with those of earlier studies provide evidence that brain responses to pitch changes can be observed in animals and that such responses are not limited to the structures of the cerebral cortex. In addition to the hippocampus (Studies I to V), responses to pitch changes were also observed in the cerebellar cortex (Study V). For the cerebellar cortex, only summated post-synaptic activity (ERPs) was able to reflect MMN-like responses that could not be represented by the pre-synaptic activity of a small group of neurons (MUA).

However, it became evident that none of the MMN-like responses (Studies III to V) fulfilled the criterion of MMN. The observed responses to pitch changes did not reflect a mismatch between an input by the deviant tones and a memory trace of the preceding standard tones detected by the stimulus-comparison process (for a review, see Näätänen, 1990). Instead, they reflected a process that is related to the different presentation rates of the stimuli and is selective to the pitch of the stimuli. This interpretation was found to be applicable to the MMN-like activity observed at all latencies, including the hippocampal MMN-like MUA at a latency range of less than 20 ms (Study V).

The increased spike activity, particularly to frequently presented standard stimuli, is counter to the suggestion that the refractoriness of the afferent neurons could have been responsible for the effect of the different stimulus presentation rates on the hippocampal MMN-like MUA (Study V). Instead, an active brain process seems to be involved in changes, at least in hippocampal responses, when an auditory stimulus is repeated. Unlike refractoriness, such a process can be related to the short-term memory trace of auditory stimuli, including the temporal aspects of stimulation. In contrast to human studies, which have detected MMN in the cerebral cortex, thereby assuming that the short-term memory trace of standard tones is located in the cerebral cortex, the appearance of MMN-like activity in the hippocampus and the cerebellar cortex in the cat and rabbit may reflect the presence of auditory short-term memory at those locations and, therefore, at multiple sites in the brain.

YHTEENVETO

Tutkimuksen tavoitteena oli tarkastella sähköisiä aivovasteita kuuloärsykemuu-
toksiin kissoilla ja kaneilla. Tutkimus painottui selvittämään erityisesti kahta
kysymystä: (a) onko kuuloärsykemuutoksiin liittyviä vasteita havaittavissa isoai-
vokuoren alapuolisissa rakenteissa kuten hippokampuksessa sekä pikkuaivo-
kuorella, ja (b) ovatko mahdolliset havaitut vasteet ominaisuuksiltaan samankal-
taisia kuin aiemmin ihmisen pään pinnalta mitatut vasteet. Aiemmin rapor-
toiduissa eläintutkimuksissa on kyllä havaittu vasteita kuuloärsykepoikkeamien
yhteydessä mm. hippokampuksessa ja talamuksessa, mutta näiden vasteiden
suhdetta ärsykepoikkeamien rekisteröintiin liittyviin aivoprosesseihin ei olla
selvitetty. Tämän suhteen selvittäminen on kuitenkin tärkeää, sillä aivovasteet
ärsykepoikkeamiin voivat selittyä kahdella eri tavalla. Aiemmat ihmiskokeet
ovat viitanneet siihen, että vasteet voivat edustaa erityisen hermostollisen vertai-
luprosessin toimintaa silloin kun se rekisteröi sisääntulevan sensorisen tiedon
vastaamattomuuden aiemmasta ärsykekentästä muodostuneeseen lyhytkestoi-
seen muistijälkeen. Toisaalta vasteet ärsykepoikkeamiin voivat myös heijastaa
taustaärsykkeiden ja ärsykepoikkeamaa edustavien ärsykkeiden eri esiintymisti-
heyttä.

Ärsykepoikkeamien aikaansaamia aivovasteita havaittiin hippokampukses-
sa sekä pikkuaivokuorella. Havaitut hippokampaaliset vasteet kissoilla olivat
latenssiltaan myöhäisempiä kuin mitä aiemmissa tutkimuksissa oli havaittu.
Myös kaneilla nämä vasteet esiintyivät verraten myöhäisellä latenssilla. Nämä
havainnot johtivatkin aluksi oletukseen, jonka mukaan havaitut vasteet edustai-
sivat ärsykepoikkeamasidonnaisia vasteita seuraavia vasteita, kuten N2b tai P3a
vasteet ihmisillä. Oletusta tukivat lisäksi samanaikaisesti havaitut vasteet kanien
pikkuaivokuorella, jotka olivat latenssiltaan lyhyempiä kuin hippokampaaliset
vasteet. Kuitenkin viimeisimmässä koesarjassa kävi ilmi, että hippokampaaliset
vasteet ärsykepoikkeamiin solujen laukeamistiheyden muutoksina mitattaessa
voivat olla niin nopeita, että niiden rinnastaminen ihmisillä havaittuihin N2b tai
P3a vasteisiin on vaikeaa.

Pikkuaivokuorirekisteröinnit viittasivat lisäksi siihen, että hermostollinen
mekanismi, joka johtaa ärsykepoikkeamien kirvoittaviin vasteisiin, voisi esiintyä
jo pikkuaivojen tasolla. Tähän viittaavat myös aiemmat havainnot hermoston
muovautuvuudesta ja sen valikoivuudesta kuuloärsykkeiden fysikaalisten
piirteiden mukaan eläimillä, joilta ylemmät kuuloradan rakenteet tai yhteydet

niihin on tuhottu.

Tutkimuksessa käytetty kontrollimenettely osoitti, että havaitut ärsykepoikkeamien kirvoittamat aivovasteet eivät heijastaneet sen kaltaisen hermostollisen vertailuprosessin toimintaa, jonka on ihmiskokeiden perusteella esitetty sijaitsevan isoaivokuorella. Sen sijaan, vasteiden muutokset ärsykkeen toiston seurauksena sekä näiden muutosten valikoivuus toistettavan ärsykkeen piirteiden suhteen näytti selittävän havaitut vasteet. Lisäksi tuloksista kävi ilmi, että ärsykkeen toiston vaikutus sinänsä aivovasteisiin ei näyttäisi heijastavan, kuten aiemmin on esitetty, toistettavan ärsykkeen piirteiden aktivoimien afferenttien ratojen väsymistä. Sen sijaan se todennäköisesti liittyy aktiiviseen hermostolliseen prosessiin, joka voi toimia lyhytkestoisen muistin perustana. Näinollen on mahdollista, että isoaivokuoren alapuolisissa osissa havaitut vasteet kuuloärsykepoikkeamiin heijastavat taustaärsykkeiden toiston vaikutusta
ja sitä, että lyhytkestoinen muistijälki kuuloärsykekentästä on aivoissa edustettuna sen monissa eri osissa.

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