

Jan Wikgren

Diffuse and Discrete Associations in Aversive Classical Conditioning

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ABSTRACT

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Diss.

The aim of the present study was to assess the role of the cerebellar interpositus nucleus (IPN) in different types of associations during classical eyeblink conditioning in rabbits. The techniques used were local cooling of the neural tissue together with both behavioral and neural recordings. In the first study, it was concluded that the IPN mediates conditioned eyeblink response (CR) irrespective of the modality of conditioned stimulus (CS). This result was accomplished by using an airpuff onto the back as the CS. In the second and third study, attention was paid to reflex facilitation during eyeblink conditioning and subsequent inactivation of the IPN. In conclusion of these studies, it can be said that the original unconditioned response (UR) is altered in an associative manner and that this CS-mediated reflex facilitation is not dependent on the discrete memory trace. Contrary to the CR proper, this kind of reflex facilitation was not affected by the inactivation of the IPN. In the fourth study, CS-evoked neural activity in the somatosensory cortex was found to increase as a function of learning. However, in occasional trials in which the rabbit failed to perform the CR also the neural response was absent even though the reflex facilitation was still seen. Thus, it is unlikely that the somatosensory cortex is the storage site for diffuse association in eyeblink conditioning. This dissertation includes also a review, in which, together with the original work presented, it is suggested that 1) discrete association is formed in the cerebellum, 2) reflex facilitation, as well as diffuse associations, is independent of the cerebellum, and 3) there is a possibility that these associations are interactive processes. In addition, possible neural mechanisms for such an interaction are suggested.

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Finally, I wish to thank my wife Minna for her support and understanding during all these years.

I would like to dedicate this dissertation to the memory of Carl Hagfors.

Jyväskylä, September 2002

Jan Wikgren

CONTENTS

1	INTRODUCTION	9
2	ASSOCIATIONS IN EYEBLINK CONDITIONING.....	12
2.1	Discrete associations in eyeblink conditioning	12
2.1.1	Pre-wired behavior and the cerebellum	13
2.2	Diffuse associations in eyeblink conditioning.....	16
2.2.1	Conditioned autonomic responses in eyeblink conditioning.....	16
2.2.2	Reflex modification in eyeblink conditioning	17
3	DIFFUSE AND DISCRETE ASSOCIATIONS: EPIPHENOMENA OR INTERACTIVE PROCESSES?	22
3.1	Possible Mechanisms	23
4	DISCUSSION.....	25
4.1	Original findings.....	25
4.2	Concluding remarks.....	25
	YHTEENVETO	27
	REFERENCES	29
	APPENDIX: SUMMARY OF THE ORIGINAL STUDIES	37

LIST OF PUBLICATIONS

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1 INTRODUCTION

A stimulus eliciting reflexive behavior usually elicits not only a single discrete response but a wide range of other reflexive responses. For example, a *startle stimulus* evokes, in humans, a reflexive eyeblink, which is called the *startle reflex* (e.g., Lang, Bradley, & Cuthbert, 1998). In addition to this discrete behavioral response, the startle stimulus alters activity of the autonomic nervous system (Turpin, Schaefer, & Boucsein, 1999). Further, a sudden, non-predicted occurrence disrupts ongoing behavior, which can be observed as a switch of attention from a task towards new, potentially significant information (the orienting response; Sokolov, 1990). Hence, the discrete stimulus, when it meets the requirements for the unconditioned stimulus, affects the functioning of the organism in a variety of ways.

A prominent feature of reflexive behavior is that it is not *critically* dependent on the functioning of the higher nervous system (Shik & Orlovsky, 1976). In the case of unconditioned stimulus in eyeblink conditioning, decerebellate-decerebrate animals produce quite normal reflexes to the US (Kelly, Zuo, & Bloedel, 1990). However, in the case of the decerebellate-decerebrate animals, behavior cannot be modified in other terms than simply that of the physical state of the reflex arc, such as muscular fatigue. The brain modifies reflexive behavior in ways other than through the simple physical properties of the directly available stimuli, i.e., as a structure by which complex associative learning becomes possible. When a reflex is elicited, it is not *emitted* by the brain, but the information from this occurrence is *projected to* the brain which also acquires information of the environment that were present when the reflex was elicited. Thus, innate behavioral abilities, and the accompanying neural activity, can be modified to match the requirements of the environment. In the process of learning, this would mean that the initially meaningless conditions that were present when and where the organism was required to respond to a biologically meaningful occurrence, prepare the organism to react to the same biologically meaningful stimuli when it encounters the same conditions the second time. That is, in the presence of the given conditions, the

organism is selectively attuned to certain information in order to detect the significant stimuli to which it is to respond (Milner, 1999; Weinberger, 1998). This would better prepare the organism to face the biologically meaningful stimuli, which, in turn, enhances its abilities to deal with them.

Diffuse responses that accompany the stimuli triggering pre-wired behavior can be seen to reflect two categories: those that prepare for approaching and those that prepare for avoidance (Greenwald, Bradley, Cuthbert, & Lang, 1998). The functional basis of these classes of reactions lies in their preparatory value in adjusting an animal's behavior better to suit a certain situation. For example, when the animal faces events that had previously been markers of potential hazards for its well being, it tends to avoid them.

The classical eyeblink conditioning paradigm in rabbits, originally introduced by Gormezano (e.g., Gormezano, Scheiderman, Deaux, & Fuentes, 1962), offers a valuable tool with which to study learning, in terms of both neural functioning and behavior. The amplitude of the original defensive response (extension of the nictitating membrane) to a noxious stimulus (airpuff directed at the eye) is a discrete and easily measured variable. In addition to the discrete response, the properties of the unconditioned stimulus causes the rabbit's autonomic nervous system to respond as well, which can be seen as changes in, for example, the rate of the heart beat (Powell & Kazis, 1976).

However, the most profound progress in localizing and identifying the neural structures essential for associative learning in eyeblink conditioning have concerned motor aspects of learning (e.g. Thompson, Thompson, Kim, Krupa, & Shinkman, 1998). Discrete sensorimotor learning seems to depend critically on cerebellar functioning (Thompson, Donegan, Clark, Lavond, Lincoln, Madden, Mamounas, Mauk, & McCormick, 1987), but the sensorimotor association is not the only association formed during eyeblink conditioning. This can be inferred both from the CS-evoked activity of the autonomic nervous system in conditioned animals and from the CS-evoked change in the eyeblink response itself. Namely, in addition to the development of the conditioned eyeblink response during this conditioning process, the original unconditioned reflex is augmented in the presence of the CS as well. This phenomenon is called *reflex facilitation* (e.g., Harvey, Gormezano & Cool-Hauser, 1985) and it can be seen after a few paired presentations of the given tone and the airpuff. The tone causes the subject to respond more vigorously to the airpuff than in a situation where the airpuff is presented alone (Weisz & LoTurco, 1988; Wikgren, Ruusuvirta, & Korhonen, 2002a).

There are, then, at least two types of associations that develop during the eyeblink conditioning: discrete and diffuse. These associations are formed either independently of each other or they might show some interaction. In the following, both possibilities are addressed. First, findings in favor for the view that the discrete association is formed and maintained by the cerebellar learning circuit are presented. Second, it is proposed that conditioned modification of the UR, of which reflex facilitation is used as an example, is not dependent on the cerebellar learning circuit. Third, related evidence is presented suggesting that diffuse associations could facilitate the formation of the discrete memory

trace in the cerebellum. Finally, two neural mechanisms are suggested for this interaction.

2 ASSOCIATIONS IN EYEBLINK CONDITIONING

2.1 Discrete associations in eyeblink conditioning

The search for the neural circuit governing discrete associations has been linked to cerebellar function ever since the paper by McCormick, Lavond, Clark, Kettner, Rising & Thompson (1981). It has been shown that removal of the tissue rostral to the red nucleus, including the hippocampus and cerebral cortex, does not prevent acquisition or retention of the conditioned eyeblink response in the delayed conditioning paradigm (Moore, Yeo, Oakley, & Russell, 1980). Therefore, the essential circuitry for eyeblink conditioning can be located within the regions of the brainstem and cerebellum. In brief, this circuitry involves three components: 1) the CS pathway, that consists of sensory relay nuclei, the pontine nuclei and mossy fiber connections to the cerebellum, 2) the US pathway, which includes somatic sensory relay nuclei, the inferior olive and its climbing fiber connections to the cerebellum, and 3) the CR pathway, which includes the cerebellum, its projections from the interpositus nucleus via the superior cerebellar peduncle to the red nucleus and red nucleus projections to premotor and motor nuclei (for a review, see e.g., Anderson & Steinmetz, 1994 or Lavond, Kim & Thompson, 1993). Areas outside of this circuitry by no means are inactive during or futile for this kind of learning, but they are not *critically* necessary for the task. On the contrary, an animal with the discrete learning circuitry presented below is capable of learning the conditioned eyeblink response, but the rate of learning, as well as the timing of the response is compromised. Further, with this circuitry alone the animal does not experience aversiveness to the unconditioned stimulus (Thompson, Thompson, Kim, Krupa, & Shinkman, 1998), nor is it capable of learning if the situation is made even slightly more complex than is the case in classical delayed conditioning (e.g., trace conditioning: Kronforst-Collins & Disterhoft, 1998; Weiss, Bouwmeester, Power & Disterhoft, 1999). On the other hand, it is possible to successfully train decerebrated animals in the eyeblink conditioning paradigm

(Ivarsson & Svensson, 2000), which alone rules out the possibility that the cerebrum is a critical area for this kind of learning.

2.1.1 Pre-wired behavior and the cerebellum

Classical conditioning always involves conditioning of a pre-wired reflexive response. The notion 'eyeblink reflex' refers actually to a wide range of reflexive eye movements (Berthier, Desmond & Moore, 1987). The whole eyeblink response consists of eyeball retraction and eyelid movements in addition to movement of the nictitating membrane, whose amplitude is usually the dependent variable of interest. From here on, 'eyeblink reflex' is used to refer mainly to the nictitating membrane response.

Initially, the airpuff to the cornea causes the rabbit to elicit a defensive eyeblink reflex. The trigeminal nuclei in the brain stem are the primary sites for making such a response (Cegavske, Harrison & Torigoe, 1987). The tactile information from the cornea is relayed to the trigeminal complex (van Ham & Yeo, 1996a). Information is then projected to the accessory abducens which projects to the retractor bulbi muscle via the VIth nerve and to the area of the reticular formation caudal to the accessory abducens. These reticular formation cells then project to the accessory abducens thus completing the circuit with the long-latency element of the reflex (van Ham & Yeo, 1996b).

The trigeminal nuclei project also to the cerebellum via at least three routes. The most essential route in the case of eyeblink conditioning is the projection to the inferior olive, which in turn is the source of climbing fibers to the cerebellum (Yeo, Hardiman, & Glickstein, 1985; Courville, Faraco-Cantin, & Marcon, 1983; Akaike, 1988). Thus, the information about the reflexive occurrence is projected to the cerebellum via climbing fibers.

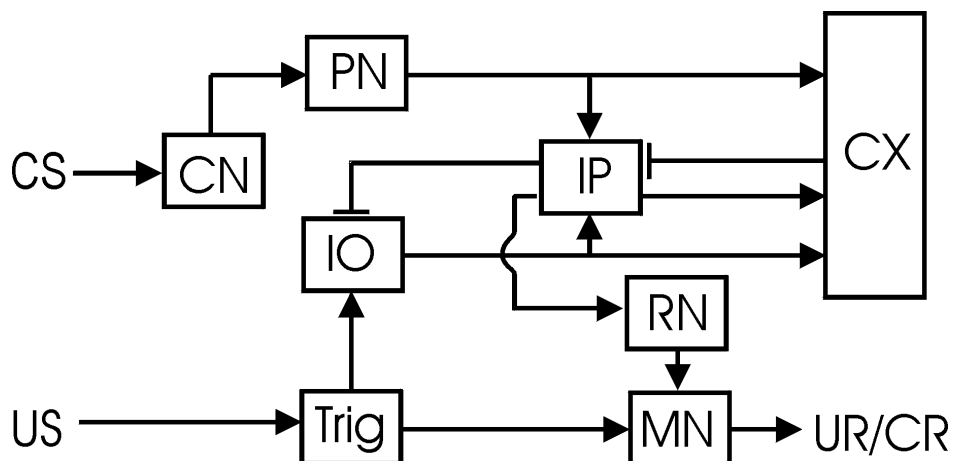


FIGURE 1 The critical neural circuit for eyeblink conditioning. Key: CN, cochlear nucleus, PN, pontine nuclei; IP, interpositus nucleus; CX, cerebellar cortex; IO, inferior olive; RN, red nucleus; Trig, trigeminal nuclei; MN, motor nuclei.

Auditory stimuli are the most often used conditioned stimuli in eyeblink conditioning. The tone evokes activity in the cochlear nucleus, which is the primary nucleus for auditory modality. The cochlear nucleus, in turn, projects primarily to the inferior colliculus, superior olive and higher auditory structures. The cochlear nucleus projects also to the lateral pontine nuclei, which in turn are the source of the mossy fibers to the cerebellum (Brodal & Bjaalie, 1992). Studies carried out in well-trained animals concerning the latencies of tone-evoked activity within the lateral pontine nucleus suggest that it represents two kinds of activity. First, acoustic-related activity occurs within the first 20-40 ms after the tone onset and, second, delayed activity that correlates with the conditioned response (Clark, Gohl, & Lavond, 1997). However, the latencies correlating with the learned response are more or less the same as those of the behavioral responses, making it unlikely that this region actually drives the CRs. Furthermore, during inactivation of the interpositus nucleus the learning-related activity, but not the acoustic-related activity, is abolished in the pontine-nuclei (Clark, Gohl, & Lavond, 1997). The pontine nuclei relay information from all sensory modalities to the cerebellum via the mossy fibers (Brodal & Bjaalie, 1992). Further, electrical stimulation of various sites in the pontine nuclei support conditioning when used as a CS (Steinmetz, Rosen, Chapman, Lavond, & Thompson, 1986). The qualitative differences between the climbing and mossy fibers are of crucial importance for theories of learning. These are the structures that, in terms of brain functioning, make the distinction between the CS and the US.

A prominent feature of learning-related neural activity during eyeblink conditioning is that not only can one measure activity occurring during presentation of the CS but that the neural activity measured from variety of regions actually forms a temporal model of conditioned behavior. That is, histograms of multiple unit activity have roughly the same shape as the NM movement. This is particularly true in the hippocampus (Berger, Alger, & Thompson, 1976), red nucleus and other brainstem nuclei (McCormick, Lavond & Thompson, 1983; Cartford, Gohl, Singson & Lavond, 1997) as well as in the somatosensory cortex (Wikgren, Ruusuvirta & Korhonen, 2002b), to name but a few. This pattern of activity develops before the first behavioral CR is seen, and within a trial the template precedes the behavioral response for about 30-40 ms. However, in every location studied to date, inactivation of the interpositus nucleus causes the abolition of such a template (Sears & Steinmetz, 1990; Clark & Lavond, 1996; Ryou, Cho & Kim, 1998; see also, Wikgren, Ruusuvirta, & Korhonen, 2002b). However, there has been a vigorous debate over the issue whether the cerebellar cortex or the deep nuclei is *the* critical site in this kind of conditioning (for cerebellar cortex theory, see e.g., Hesslow, Svensson & Ivarsson, 1999 or Gruart, Pastor, Armengo & Delgado-Garcia, 1997). This has remained a controversial issue mainly because lesions to the cerebellar cortex are very difficult to perform without damaging the underlying structures, such as the deep nuclei. On the other hand, lesions to the deep nuclei (as in the case of interpositus nucleus) are not easily done without damaging the cortex, at least to a small extent. Furthermore, lesion of the interpositus nucleus destroys the major efferent pathway of the cerebellar cortex, which increases confusion

about whether the critical area for learning lies in the cerebellar cortex or deep nuclei. Still, there is strong evidence that even a very small lesion to the anterior part of the interpositus nucleus would completely and permanently prevent expression and acquisition of the eyeblink CR. Steinmetz, Logue and Steinmetz (1992) gave paired eyeblink training for months to interpositus-lesioned rabbits without finding even a sign of learning.

The cerebellar cortex and interpositus nucleus might have different roles in eyeblink conditioning. It is known that learning related activity can be recorded from both areas, but the cerebellar cortex also shows learning-related activity to backward conditioning, which is not the case in the interpositus nucleus (Gould & Steinmetz, 1996). Gould and Steinmetz (1996) conclude that it seems possible that the interpositus nucleus is only able to exhibit changes in excitability when mossy fiber activation (CS) precedes climbing fiber activation (US). Therefore, even if the cerebellar cortex is able to form learning-related activity in backward conditioning, the association is not strong enough to drive a behavioral conditioned response. Further, lesions to these areas have different outcomes in eyeblink conditioning. Lesions of the relevant portion of the cerebellar cortex (Larsell's lobule HVI) retard CR acquisition but do not prevent it, and only temporarily affect performance of previously learned CRs (Lavond, Steinmetz, Yokaitis & Thompson, 1987; Lavond & Steinmetz, 1989). It has been suggested that the cerebellar cortex has a role in the timing and fine-tuning of the CR rather than a critical role in memory trace formation (Rosenfield & Moore, 1995). In line with this, subjects drawn from a mutant strain of mice, which lack Purkinje cells, the only output of the cerebellar cortex, can be eyeblink conditioned, although the rate of acquisition and amplitude of the CR are severely retarded (Chen, Bao, Lockard, Kim & Thompson, 1996).

During inactivation of the critical motor nuclei (accessory abducens nucleus, facial nucleus and surrounding reticular formation) the rabbit is completely unable to express behavioral CRs or URs. However, if eyeblink conditioning is administered to naïve rabbits with these areas inactivated, asymptotic learning is perceived immediately following termination of the inactivation (Krupa, Weng & Thompson, 1996). The same effect results from temporal inactivation of the red nucleus, but with one important exception. During inactivation or lesion of the red nucleus, the rabbit is able to perform the UR to the US as it normally would, but it cannot exhibit CRs (Rosenfield & Moore, 1985; Clark & Lavond, 1993). Therefore, the red nucleus is considered to be the primary motor output of the CR, but the inactivation of the red nucleus in itself does not prevent learning. Furthermore, electrical stimulation of the red nucleus produces eyeblinks, but such brain stimulation does not support conditioning when used as a US (Chapman, Steinmetz & Thompson, 1988). The site of the critical plasticity in eyeblink conditioning must therefore be afferent to the red nucleus.

In sum, plasticity in cerebellar structures (the interpositus nucleus and, possibly, the overlying cerebellar cortex) is responsible for the formation of the discrete association in eyeblink conditioning. There is no such instance where the discrete conditioned responding survives lesion to or inactivation of this area (Chapman, Steinmetz, Sears & Thompson, 1990; Nordholm, Thompson,

Dersarkissian & Thompson, 1993). This holds equally in other modalities of the CS (Wikgren & Korhonen, 2001a) and in different paradigms critically involving higher brain areas, as is the case in trace conditioning (Woodruff-Pak, Lavond & Thompson, 1985; Woodruff-Pak, Lavond, Logan, Steinmetz & Thompson, 1993).

2.2 Diffuse associations in eyeblink conditioning

While inactivation or lesion of the interpositus nucleus in naïve rabbits prevents acquisition of the CR and in trained rabbits abolishes the CR, some learning-related changes can still be seen. These learning-related changes involve responses of the autonomic nervous system (conditioned heart-rate response) and nonspecific responses (CS-mediated reflex facilitation; Wikgren, Ruusuvirta & Korhonen, 2002a) in the presence of the CS.

On the behavioral level, the work of Lang and his associates suggest that emotional responses are founded on two basic motivational systems, aversive and appetitive. In their studies of human and animal subjects (Lang, Bradley & Cuthbert, 1998; Greenwald, Cuthbert, Bradley & Lang, 1998) primed with either negative or positive stimuli different outcomes were observed to the reflex probes presented after or during these primed stimuli. For example, human subjects viewing images of unpleasant content (violence, mutilations, etc.) respond to startle stimulus more vigorously than when viewing images of neutral or pleasant content. Below, diffuse associations during eyeblink conditioning are presented. These would be manifested as changes in the functioning of the autonomic nervous system and conditioned reflex facilitation.

2.2.1 Conditioned autonomic responses in eyeblink conditioning

The corneal airpuff as a US, if the intensity used is strong enough, is sufficient to support conditioned bradycardia (McEchron, McCabe, Green, Llabre & Schneiderman, 1991). In the case of acoustical heart rate conditioning with the corneal airpuff as a US, it has been shown that auditory synaptic inputs to the medial subnucleus of the medial geniculate nucleus neurons increase in strength as a result of classical conditioning (McEchron, Green, Winters, Nolen, Schneiderman & McCabe, 1996). Further, lesions to this area disrupt the formation of autonomic associations when an auditory stimulus is used as a CS (LeDoux, Iwata, Pearl & Reis, 1986; McCabe, McEchron, Green & Schneiderman, 1993). This is in contrast with the results acquired in discrete eyeblink conditioning showing that stimulation of the thalamic auditory areas is a successful CS with one restriction; it does not support reflex facilitation (Nowak, Kehoe, Macrae, & Gormezano, 1999)

Using single-unit measures from various nuclei in the amygdalar complex, Richardson and Thompson (1984) were not able to find evidence for learning-related activity within the amygdala during eyeblink conditioning. More

recently, when the amygdala has been a subject for more extensive investigations, its role in fear conditioning has been clarified. Romanski, Clugnet, Bordi and LeDoux (1992) were able to register single units within the lateral nucleus of the amygdala, which showed responses to both auditory and aversive somatosensory (footshock) stimuli. Further, the response latencies for these units were < 30 ms, which suggests that the amygdalar lateral nucleus may have a role in forming the association between neutral and aversive stimuli.

Further evidence about the role of the amygdala, as well as other limbic structures, in memory consolidation stems from the finding that amygdalar learning-related activity increases rapidly at the outset of conditioning but ceases as the conditioned responding becomes asymptotic. This decrease in neural activity within the limbic system can be seen even if the subject, after initial training, does not receive paired trials for several days. The limbic activity can only be seen as related to the consolidation process (Poremba & Gabriel, 1999). Amygdalar lesions prevent acquisition of learning-related neural activity within the thalamic nuclei and in related areas of the cingulate cortex (Poremba & Gabriel, 1997), which has been shown to be essential for discriminative avoidance learning (Gabriel, 1990). This suggests that the memory trace for such an event is not located in the amygdala but that this structure is needed in the initiation and consolidation of the memory trace. In amygdala-lesioned rats, long-latency learning-related activity in the auditory cortex is diminished, when a rat is fear-conditioned to a tone (Armony, Quirk & LeDoux, 1998). This line of evidence suggests that the amygdala has a critical role not only in expression of the learned response, but also in the formation of learning-relevant neural plasticity. However, this also suggests that there are yet unidentified areas of the brain that are capable of modifying learned behavior and memory no longer served by the limbic circuit (Poremba & Gabriel, 1999). This issue was addressed in our study where neural activity in the primary somatosensory cortex was recorded during eyeblink conditioning (Wikgren, Ruusuvirta, & Korhonen, 2002b). It was found that the somatosensory cortex shows learning-related activity which is related to the discrete memory trace (temporally preceding the template of the behavioral CR). However, this learning-related activity was not evoked by the tone in the case where trained rabbits failed to emit the discrete CR, even though the CS still affected the amplitude of the UR. Had there been learning-related activity in the absence of the CR, it would have supported the assumption that the somatosensory cortex had a role in the formation and/or storage of the diffuse associations in eyeblink conditioning.

2.2.2 Reflex modification in eyeblink conditioning

As stated previously, the unconditioned eyeblink reflex is modified long before the occurrence of the CR proper. More specifically, the amplitude and peak latency of the UR change very rapidly when the conditioning training is administered. The presence of the CS is a critical factor; when the CS precedes the US, the animal exhibits more vigorous and rapid eyeblink reflexes than in

the case of US-alone trials. This reflex facilitation (Harvey, Gormezano, & Cool-Hauser, 1985) can be observed very quickly during training, but it is notable that at the very outset of training, the CS does not have an effect on the UR amplitude in paired trials (Wikgren, Ruusuvirta & Korhonen, 2002a). This, along with observations in humans (Marcos & Redondo, 1999), suggests that the process of cumulative reflex facilitation is associative and therefore must be learned. It is known that the interpositus lesion does not interfere with conditioned reflex facilitation even though the lesion prevents acquisition of the CR proper (Weisz & LoTurco, 1988).

It could be argued that reflex facilitation is actually seen because of the early conditioned responses that are usually formed temporally in place of the UR. On this reasoning the reflex facilitation observed during the early phase of learning would in fact be the sum of the amplitudes of the UR and this early CR. This possibility is, however, ruled out because the CS does not evoke any CRs during this phase (Wikgren, Ruusuvirta, & Korhonen, 2002a). Donegan & Wagner (1987) cite the earlier work of Wagner (1979) who proposed that a signaled US (US preceded by a CS) generally results in a modified UR (UR'). The UR' will then be added to, or subtracted from the CR. This would mean that on CS+US trials, the measure of responding following the US would be a combination of a conditioned response and a modified unconditioned response (CS+US \rightarrow CR+UR', as they put it). In the light of our work (Wikgren, Korhonen & Ruusuvirta, 2002a) this, however, does not hold. Namely, from this interpretation it would follow that if the memory trace for the CR is blocked (as is the case in interpositus nucleus inactivation), the UR' should give way to the UR proper. But, on the contrary, during the inactivation of the interpositus nucleus, the discrete conditioned response abolishes, while the CS continues to affect the UR; the reflex facilitation is associative but it does not depend on the same structures as the conditioned eyeblink response (Wikgren & Korhonen, 2001b; Wikgren, Ruusuvirta, & Korhonen, 2002a). Nor is the conditioned response a sum of the CR and the UR as proposed by Clark, Zhang & Lavond (1992). Were this so, the UR to the signaled US would change during IPN inactivation, which is not the case.

The modulation of the UR during the learning process is not only of interest in its own right but may be representative of a larger class of phenomena (Donegan & Wagner, 1987). Therefore, classification of the types of reflex facilitation may serve as a useful basis for identifying the locations for nonspecific plasticity in the nervous system. Given that reflex facilitation exists even in the absence of the learned discrete response, as is the case during the inactivation of the IPN, some learning-related activity that it correlated with it should also be present. However, except for the altered receptive field plasticity in the auditory cortex (Weinberger, 1998), the learning-related activity identified in every location studied so far has been shown to cease during IPN inactivation.

Together, the results presented in the original publications underlying this dissertation indicate that three types of reflex facilitation accompany classical eyeblink conditioning in rabbits. These types are termed experience-related, CS-mediated, and CR-related reflex facilitation (see Figure 2).

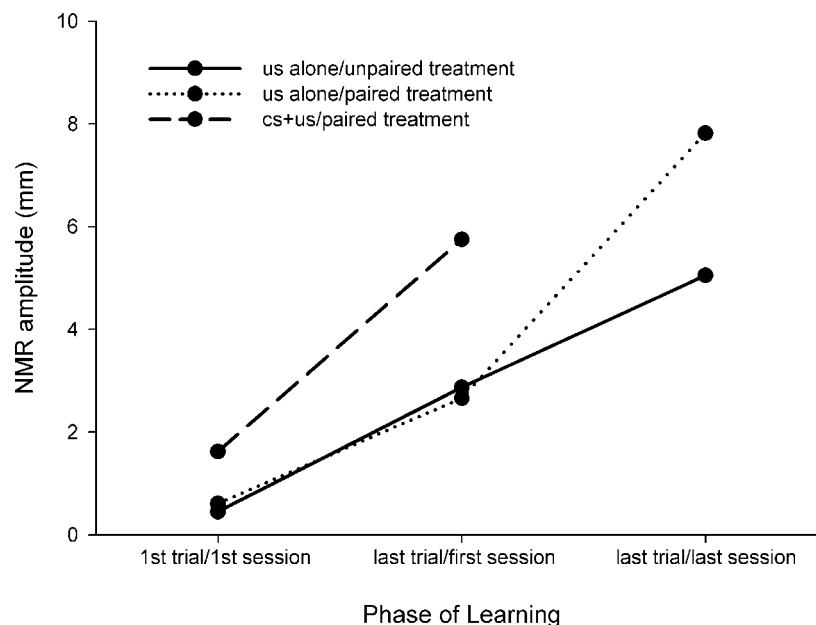


FIGURE 2 UR amplitudes in the three phases of the experiment. 1) the outset of the training, 2) the end of the first session and 3) after 5 sessions. Note that initially, the URs are of same amplitude in all three trial types (the difference was not significant). After one training session, presence of the CS facilitates the UR. When the URs in US alone trials between the unpaired and paired groups are compared, the paired group shows significantly more vigorous URs. See text for more detailed explanation.

Experience-related reflex facilitation can be inferred from the finding that irrespective of the temporal ordering of the stimuli (paired or unpaired), the UR amplitude increases as a function of the time spent in the experimental setting (Weisz & McInerney, 1990; Wikgren, Ruusuvirta & Korhonen, 2002a).

CS-mediated reflex facilitation was indicated by the finding that the UR in the paired group was facilitated more if the US was preceded by the CS, despite the fact that the initial level of responding was the same in both paired and US-alone trials (Wikgren, Ruusuvirta, & Korhonen, 2002a). The data suggest that CS-mediated reflex facilitation, at this phase of learning, reflects a conditioned change in the organism. Whatever this change might be, it affects the processing of the US in a facilitative manner.

CR-related reflex facilitation was seen as a relatively permanent increase in the UR amplitude in the US-alone trials, when the paired and unpaired groups were compared (Wikgren & Korhonen, 2001b; Wikgren, Ruusuvirta, & Korhonen, 2002a). This indicates a relatively permanent modification of the US/UR-circuit. This result is in accordance with those of Scheurs, Oh, Hirashima and Alkon (1995), who found CR-related reflex facilitation in US-alone trials when a robust level of CRs was achieved, but not when the extent of conditioning was low (17% CRs after the first day of conditioning in their data).

The relationship between the different types of reflex facilitation and the memory trace for the discrete CR was investigated by inactivating the IPN (Wikgren & Korhonen, 2001b; Wikgren, Ruusuvirta, & Korhonen, 2002a) and by comparing trials with or without overt CR (Wikgren, Ruusuvirta, & Korhonen, 2002b). Summarizing the results of these studies, it was shown that CS-

mediated reflex facilitation is independent of the memory trace for the discrete association and that CR-related reflex facilitation depends, at least to some extent on the cerebellar functioning. The CS, in trained animals, had an effect on the UR even when the IPN was inactivated (Wikgren & Korhonen, 2001b, Wikgren, Ruusuvirta, & Korhonen, 2002a) and when the animal failed to emit the discrete CR (Wikgren, Ruusuvirta, & Korhonen, 2002b). Further, the reversible inactivation of the IPN, after the unpaired treatment, was not found to affect UR amplitude in US-alone trials, but did so after the paired treatment (Wikgren & Korhonen, 2001b). This evidence further suggests that, in particular, the CS-US association formed by the IPN was also linked to the processing of the US presented alone.

Earlier studies suggest that reflex facilitation is specific to the physical features of the CS immediately preceding the US (Weisz & LoTurco, 1988; Weisz & McInerney, 1990), a key feature necessary for the CS acting as a signal. The exact nature of CS-mediated reflex facilitation remains to be seen. One possibility, however, is that this type of reflex facilitation might be related to a conditioned emotive state, referring to the ability of the US, not only to possess sensory and response-eliciting value as such, but also to induce aversiveness (Richardson & Thompson, 1984; Thompson, Thompson, Kim, Krupa, & Shinkman, 1998). This dissociation, at least in one direction, between the emotive and non-emotive value of the US has been further indicated by the finding that stimulation of the dorsal accessory olive as the US can be associated with the CS without accompanying signs of aversiveness (Mauk, Steinmetz, & Thompson, 1986). Thus, it is possible that the remaining, diffuse aspects of the US might have become associated with the CS independently of the behavioral response. This interpretation is further supported by the relative independence of CS-mediated reflex facilitation on the cooling of the IPN, indicating that the neural basis necessary for the related association must be other than the IPN.

What, then, might anatomically contribute to CS-mediated reflex facilitation? Earlier evidence suggests that the related pathways diverge from those necessary for the acquisition of the CR and maintenance already at the lower levels of the CS pathway. Whereas reflex facilitation can be induced by the electrical stimulation of the cochlear nucleus as the CS, this cannot be done when the nuclei later along this pathway (the superior olive, inferior colliculus or medial geniculate nucleus) are stimulated (Nowak, Kehoe, Macrae & Gormezano, 1999). This finding further converges with the findings on another line of research, the fear-potentiated startle effect (Davis, 1998), in which the amplitude of the UR to an intensive stimulus (the startle reflex), such as a loud tone, is modified by a state of fear. More specifically, pairing the neutral stimulus with the startle-eliciting noise, the startle reflex becomes stronger in paired trials, as measured by freezing behavior in rats or facial EMG responses in humans. Similarly to reflex facilitation, the startle-eliciting stimulus elicits the related behavior via the low levels of the CS pathway. The related neural circuit consists of the connection between the sensory neurons in the cochlear root nucleus and the neurons in the nucleus reticularis pontis caudalis (Rosen, Hitchcock, Sananes, Miserendino & Davis, 1991), which, in turn, has a connection with the motor nuclei and the amygdala. Particularly the central

nucleus of the amygdala seems to be a critical region for the acquisition and maintenance of the fear-potentiated startle effect, as suggested by lesions to the amygdala or its connections with the startle pathway (Hitchcock & Davis, 1991; Hitchcock, Sananes & Davis, 1989).

Given that both the CS-mediated reflex facilitation and the fear-potentiated startle effect reflect emotive aspects of learning and are contributed to by the early parts of the auditory pathway, they might also be similar in respect to both being dependent on the same critical region of the brain, the amygdala. Consistently, animals with amygdalar lesion are compromised in the CR acquisition and in exhibiting reflex facilitation during aversive conditioning (Weisz, Harden & Xiang, 1992), which indicates that the amygdala might be involved in learning the aversiveness of the US during eyeblink conditioning. The role of the amygdala in reflex facilitation is further supported by the finding that the electrical stimulation of the amygdala prior to presentation of the US facilitates the UR (Whalen & Kapp, 1991). The neural substrate for this effect seems to consist of the projections of the amygdalar central nucleus to the lateral tegmental field in the thalamus which, in turn, project to a variety of cranial motor nuclei (Hopkins & Holstege, 1978; Takeuchi, Satoda, Tashiro, Matsushima, & Uemura-Sumi, 1988). Thus, via these connections, the amygdala might modulate various reflexes, such as the nictitating membrane reflex (Whalen & Kapp, 1991; Kapp, Supple & Whalen, 1994) independently of the IPN.

3 DIFFUSE AND DISCRETE ASSOCIATIONS: EPIPHENOMENA OR INTERACTIVE PROCESSES?

In sum, the biologically significant US used in classical conditioning experiments evokes both a discrete unconditioned reflexive movement and diffuse reaction. Consequently, when the unconditioned stimulus is preceded by an initially meaningless, conditioned stimulus, both responses to the US become associated with the CS.

To make a distinction between two classes of associations during classical aversive conditioning is by no means a new idea. In 1967, Jerzy Konorski made such a distinction between preparatory and consummatory CRs (Konorski, 1967). Norman Weinberger (1998) has referred to nonspecific and specific responses to express roughly the same idea. Thompson and his co-workers (Thompson, Donegan, Clark, Lavond, Lincoln, Madden, Mamounas, Mauk, & McCormick, 1987; Lavond, Kim & Thompson, 1993) also distinguished between nonspecific and specific responses during conditioning. Moreover, it has for long been known that different brain areas encode different aspects of the learning task. This can be seen as a double dissociation between lesions in different brain areas: For example, lesions to the cerebellar vermis prevent heart-rate conditioning but not conditioned specific responses in rats (Supple & Leaton, 1990) whereas lateral cerebellar lesion in rabbits prevent eyeblink conditioning but not heart-rate conditioning (Lavond, Lincoln, McCormick & Thompson, 1984).

General idea behind these distinctions is more or less the same. Nonspecific, preparatory or diffuse associations are rapidly evolved, involve autonomic responses and are state-related in the sense that they prepare the organism to behave more congruently with the evoked state. Specific, consummatory or discrete associations, on the other hand, take time to develop, are learned responses to a certain local stimulation and involve skeletal muscles. In general, diffuse responses are the same to a wide variety of stimuli, whereas the aim of discrete responses is precisely aimed to deal with a certain stimulus. For example, an airpuff to the cornea and an electric shock to a leg

would evoke roughly the same diffuse responses but quite different discrete behavioral responses. The exact nature of the interaction between these types of associations is unclear, although correlative evidence supports the view that relevant diffuse associations are accompanied by enhanced formation of the discrete associations. For example, degree of reflex facilitation and learning rate correlate strongly when the learning rate is regulated by different stimulus parameters or pharmacological treatment (Harvey & Gormezano, 1981; Harvey, Gormezano, & Cool-Hauser, 1985).

On the basis of the original work associated with this dissertation it is proposed that the diffuse associations are not dependent on the cerebellum in the same way as is the discrete association in the case of eyeblink conditioning. It is also evident that the brain areas critically needed for formation of these associations are different. The crucial question, therefore, is whether these associations are independent or interactive processes.

3.1 Possible mechanisms

There are two possible mechanisms by which the diffuse association could affect the formation of the discrete association. These could be referred to as potentiated processing of either the US or the CS. It should be noted, however, that these proposed mechanisms are not mutually exclusive, i.e., they could both be equally valid.

According to the first of these, US potentiation hypothesis, the neural functioning related to the CS-mediated reflex facilitation seen in the early phase of eyeblink conditioning augments the error signal in the inferior olive nucleus compared to the US-alone trials. The Rescorla-Wagner model of classical conditioning is based on the 'surprise value' of the US. If the US occurs as a non-predicted phenomenon to the subject, it is likely to contain maximal surprise value. In contrast, an expected and predicted unconditioned stimulus would have minimal surprise value. Thompson and his co-workers (Thompson, Thompson, Kim, Krupa, & Shinkman, 1998) put this very simply:

$$IO = US - CR$$

where IO refers to activity in the inferior olive (value of the error signal), US is the surprise value of the US and CR is the amount of learning. Thus, the error output from the IO equals the surprise value minus the amount of learning. In a naïve animal the US would be 1 and the CR would be 0. When learning is maximal it would be vice versa. Thus, it is assumed that the amount of activity in the inferior olive during a paired trial would directly reveal whether there is something to be learned or not. This addresses nicely not only the formation of the memory trace but also the blocking effect (Kamin, 1969), both theoretically (Gluck, Allen, Myers & Thompson, 2001) and empirically (Kim, Krupa & Thompson, 1998).

A diffuse, state-related change could then have an effect on the formation of the discrete association in the cerebellum by increasing the error signal given by the inferior olive. Thus far, this possibility has not been addressed.

The second possibility for interaction between CS-mediated reflex facilitation and an enhanced learning rate would include increased responsiveness to the specific properties of the tone. The receptive field patterns in the auditory cortex ("physiological memory", Weinberger, 1998) and response patterns in associative cortex (Kraus & Disterhoft, 1982) are quickly modified by a tone in classical conditioning. Further, as it has been shown that direct pontine nuclei stimulation can be used as a 'supernormal' CS in classical conditioning (Steinmetz, Rosen, Chapman, Lavond, & Thompson, 1986), the cortical projections to the pontine nuclei could increase their activity thus leading to an enhancement in discrete learning. In line with this notion, Knowlton and Thompson (1992) showed that, as in the case of normal, peripheral tone-CS, the interpositus nucleus and pontine nuclei are critical for the sensorimotor learning when stimulation of the auditory cortex is used as a CS. They also suggested that the projections from the auditory cortex to the pontine nuclei may form the route along which the possible associations formed in the cerebral cortex may modulate classical conditioning in the cerebellum (Knowlton & Thompson, 1992; Knowlton, Thompson, & Thompson, 1993). Further, as indicated by Tracy, Thompson, Krupa, and Thompson (1998), the pontine nuclei not only relay information to the cerebellum but their stimulation threshold is also lowered as a function of conditioning. Therefore the CS-potential hypothesis could be studied by recording pontine nucleus activity, particularly during the early phase of learning.

Recent evidence indicates that the amygdala is involved also in eyeblink conditioning. More specifically, Neufeld and Mintz (2001) first presented a tone CS paired with a startle tone US and then switched to eyeblink conditioning. It was found that this group of rats learned the eyeblink CR faster than the control group which had no prior emotional conditioning treatment. The same was then done with amygdala-lesioned rats, which showed no such superiority over the control group. This suggests not only that the diffuse association affects the formation of the discrete association but also that it is the amygdala that is the critical site for this kind of learning. The projections from the amygdala to the cerebellum, then, are the crucial connection when postulating a brain mechanism responsible for the interaction of diffuse and discrete associations. Projections of the amygdalar central nucleus (ACe) to the lateral tegmental field in the thalamus, which project onto a variety of cranial motor nuclei, may form the substrate by which the ACe contributes to the conditioned modulation of various reflexes, such as the nictitating membrane reflex (Whalen & Kapp, 1991; Kapp, Supple & Whalen, 1994).

4 DISCUSSION

4.1 Original findings

The original findings associated with this dissertation lend support to an idea that discrete and diffuse associations are formed in relative independence, and differ in their temporal manifestation in the learning process. However, they may be interrelated phenomena in the sense that diffuse associations affect the formation of the discrete association by enhancing the processing of the relevant stimulus. This can be concluded from the findings that a) the rabbit responds more vigorously to the US if it is preceded by a CS which has previously been paired with the US before (study III); b) inactivating the discrete association does not interfere with the facilitative effect of the CS (studies II and III); and c) this facilitation can also be seen during trials where a trained rabbit sometimes fails to emit the CR (study IV).

The view that the cerebellum, and especially the interpositus nucleus, is a critical area for the discrete association in eyeblink conditioning was supported by the finding that its temporal inactivation abolishes the discrete conditioned responses in the case of the somatosensory CS as well (Study I). This shows that the role of the interpositus nucleus in the formation of the discrete association is not related to the physical properties of the CS.

4.2 Concluding remarks

Some more or less speculative remarks can be made regarding the use of the eyeblink conditioning paradigm in learning studies. From an evolutionary perspective, it is reasonable to assume that the diffuse and discrete associations serve to accomplish the same adaptive goal as interactive processes. Therefore, it is hard to believe that even though these associations show some

independence, they do not affect each other. The crucial question, however, is whether conditioned reflex facilitation is a good dependent variable for the measurement of the diffuse association. The evidence presented in the present dissertation indicates that reflex facilitation might well reflect diffuse associations during eyeblink conditioning and thus provide an index of the state-related changes in the subject.

Learning does not take place in isolation but as a process of adjusting to the environment. Even though the performance vs. learning debate has consistently come down on the side of the view that they are not critically dependent on each other (Steinmetz, Lavond, Ivkovich, Logan, & Thompson, 1992), this does not mean that learning in normal conditions would not involve gradual improvement in performance. The work of Thompson and his colleagues has shown that performance is not necessary for learning, but this hardly allows the conclusion that better performance would not lead to better learning. Better performance, for its part, could be defined as those actions taken to obtain information more selectively with regard to the task the organism is engaged on. In normal conditions, of which the rabbit eyeblink conditioning paradigm is hardly a natural example, performance is needed in order to selectively attend to those stimuli and conditions, which previously led to biologically significant occurrences. Thus, it is possible that the reflex facilitation seen during the rabbit eyeblink conditioning paradigm offers a tool by means of which the circular nature of the natural learning process can be studied.

YHTEENVETO

Täsmälliset ja laaja-alaiset ehdollistumat klassisessa aversiivisessä ehdollistumisessa

Tutkimus keskittyy eri tyyppisiin opittuihin reaktioihin aversiivisen klassisen ehdollistamisen aikana. Käytetty tutkimusasetelma oli kanin silmäniskuehdollistaminen, jossa kania opetetaan tekemään vilkkuluomirefleksi sinänsä neutraaliin ääneen, johon ei alun perin liity käyttäytymisvastetta. Vilkkuluomirefleksi aiheutettiin ilmapuhalluksella silmään, joka on luonteeltaan välttämisyrefleksin aiheuttava tapahtuma. Ilmapuhallus aiheuttaa vilkkuluomirefleksin (täsmällisen reaktion) lisäksi autonomisen hermoston aktivaation muutoksia (laaja-alaisia reaktioita), joita puolestaan voi mitata esim. sydämen syketiheyden muutoksina. Ehdollistamisvaiheessa kanille esitetään neutraali ärsyke (esim. ääni) ennen ilmapuhallusta, jonka seurauksena kani vähitellen oppii räpättämään silmäänsä reaktiona pelkkään ääneen. Tämän lisäksi äänellä voidaan havaita myös vaikutus alkuperäisen ehdottoman refleksin voimakkuuteen. Jo kauan ennen täsmällisen ehdollistuman oppimista kani reagoi voimakkaammin ilmapuhallukseen ääneen yhdistettynä kuin siinä tapauksessa että ilmapuhallus esitettäisiin yksinään. Tätä ilmiötä kutsutaan refleksifasilitaatioksi.

Täsmällisen ehdollistuman (vilkkuluomen liike vasteena ääneen) ”muistijälki” on voitu paikantaa pikkuaivojen interpositus-tumakkeeseen. Tämän tumakkeen tuhoaminen estää täydellisesti täsmällisen vasteen muistijäljen syntymisen ja jo ehdollistuneilla eläimillä tehdyt leesiot aiheuttavat opitun vasteen täydellisen katoamisen. Kuitenkaan kyseisen tumakkeen tuhoamisella ei ole vaikutusta refleksiiviseen käyttäytymiseen tai aistitoimintoihin sinänsä. Koska muistijälki on näin voitu paikantaa, voidaan hyvin tutkia muita mahdollisia ehdollistumia vilkkuluomiehdollistamisen aikana. Aiemmin on havaittu, että pikkuaivojen leesio ei estä refleksifasilitaatiota tai laaja-alaisen ehdollistumien syntymistä. Tämä näkyy mm. siinä että pikkuaivoleesioitujen kani sydämen syketiheyden muutokset voidaan ehdollistaa. Toisaalta taas tiedetään, että etuaivojen (erityisesti mantelitumakkeen) vauriot estävät laaja-alaisen ehdollistumien syntymisen estämättä kuitenkin esim. vilkkuluomirefleksin ehdollistumista. Mantelitumakkeen vauriot kylläkin hidastavat oppimista ja estävät refleksifasilitaation, mikä antaa aiheutta olettaa että refleksifasilitaatio sekä on yhteydessä laaja-alaisiin ehdollistumiin että heijastaa prosessia jolla oppiminen tehostuu.

Ensimmäisessä tutkimuksessa tutkittiin interpositus-tumakkeen toiminnan yhteyttä klassiseen ehdollistamiseen silloin kun ehdollisena ärsykkeenä käytetään yleisesti käytetyn äänen sijasta neutraalia somatosensorista ärsykettä. Ilmapuhallus silmään yhdistettiin pitkään ilmapuhallukseen annettuna keskelle selkää, jonka seurauksena kani oppi tekemään vilkkuluomirefleksin jo ehdollisen ärsykkeen aikana. Tämän jälkeen kanin interpositus-tumakkeeseen etukäteen leikkauksessa sijoitetun jäähdytysputken avulla tumakkeen lämpötila laskettiin alle 20 asteen, jolloin tumakkeen solut eivät enää toimineet. Jäähdytyk-

tekemään vilkkuluomirefleksin jo ehdollisen ärsykkeen aikana. Tämän jälkeen kanin interpositus-tumakkeeseen etukäteen leikkauksessa sijoitetun jäähdytysputken avulla tumakkeen lämpötila laskettiin alle 20 asteen, jolloin tumakkeen solut eivät enää toimineet. Jäähdytyksen aikana myös opittu vaste hävisi, mistä voidaan päätellä interpositus-tumakkeen olevan välttämätön täsmällisen ehdollistuman syntymiselle riippumatta siitä, mikä aistipiiri välittää ehdollisen ärsykkeen. Voidaan myös päätellä, että interpositus-tumakkeen tasolla ärsyкkeitä käsitellään paremminkin informaation kuin aistienergian muodossa.

Toisessa ja kolmannessa tutkimuksessa tutkittiin alkuperäisen refleksin muokkautumista klassisen ehdollistamisen aikana ja muokkautumisen yhteyttä interpositus-tumakkeen toimintaan. Tumake jäähdytettiin edellä mainitulla tavalla näennäisehdollistamisen (jossa ärsyкkeitä esitettiin toisistaan irrallaan) ja klassisen ehdollistamisen jälkeen. Yhteenvetona näistä voi todeta, että refleksin muokkautuminen (fasilitaatio) liittyy kolmeen asiaan: Ensinäkin refleksi voimistuu jo pelkästä altistuksesta ilmapuhallukselle, tätä kutsuttiin kokemukseen liittyväksi refleksi-fasilitaatioksi (experience-related reflex facilitation). Toiseksi voitiin havaita refleksin voimistuminen, joka oli yhteydessä opitun täsmällisen vasteen voimakkuuden kanssa (CR-related reflex facilitation). Kolmanneksi voitiin luokitella ehdollisesta ärsyкkeestä riippuvainen refleksin voimistuminen (CS-mediated reflex facilitation). Interpositus-tumakkeen jäähdytyksen aikana äänellä oli yhä vaikutus ehdottomaan refleksiin, josta voitiin päätellä ehdollisesta ärsyкkeestä riippuvaisen refleksifasilitaation riippumattomuus täsmällisten muistijälkien kannalta välttämättömistä aivorakenteista.

Neljännessä tutkimuksessa tarkasteltiin tuntoaivokuoren hermostollista aktiivisuutta (monisoluaktiivisuus) vilkkuluomiehdollistamisen aikana. Tarkempana tavoitteena oli tutkia, liittyykö tämän alueen aktiivisuus täsmälliseen vai laaja-alaiseen muistijälkeen. Tämän takia oppineiden kaniin tuntoaivokuoren aktiivisuutta verrattiin tilanteissa jossa kani joko tuottaa ehdollisen täsmällisen vasteen tai jostain syystä jättää sen tekemättä (on yleisesti tiedossa, että hyvinkin opetettu kani silloin tällöin jättää reagoimatta ehdolliseen ärsyкkeeseen). Koe osoitti että tuntoaivokuorella esiintyy samanlaista oppimiseen liittyvää hermostollista toimintaa kuin on havaittu monella muulla alueella aiemmin. Tämä oppimiseen liittyvä aktiivisuus jäi kuitenkin pois silloin kun kani ei tuottanut opittua täsmällistä vastetta, vaikka edellä mainittu refleksifasilitaatio havaittiin näilläkin kerroilla. Tästä voidaan päätellä että tuntoaivokuoren aktiivisuus liittyy täsmälliseen muistijälkeen eikä laaja-alaiseen ehdollistumaan.

Kokonaisuutena näiden kokeiden tulokset tukevat katsausosassa esitettyä näkemystä, jonka mukaan eri aivoalueet ovat eri määrin tekemisissä erilaisten ehdollistumien synnyssä. Refleksifasilitaatio, joka nähdään oppimisen aikana voi edustaa prosessia, joka tehostaa nisäkkäiden oppimista, sillä refleksifasilitaation suuruuden on todettu korreloivan voimakkaasti täsmällisten assosiaatioiden muodostumisnopeuden kanssa.

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APPENDIX: SUMMARY OF THE ORIGINAL STUDIES

General methodology

Animals. New Zealand albino rabbits were used as subjects in all experiments. The animals were individually housed in metal cages on a 12:12 hr light-dark cycle with free access to food and water. All the experimental procedures were performed during the light portion of the cycle. Experiments were carried out in accordance with the European Communities Council Directive (86/609/EEC) regarding the care and use of animals for experimental procedures.

Surgery. The animals were anesthetized with an i.m. injection of ketamine-xylazine cocktail. The anesthetized animals were placed in a stereotaxic instrument (Kopf Instruments) with the bregma 1.5 mm above the lambda. A longitudinal incision was made to reveal the skull onto which the headstage designed to hold the minitorque potentiometer was cemented with dental acrylic using four stainless steel anchoring screws. The electrode implantation procedure (Study IV) has been described earlier in detail (Korhonen, 1991). In studies I, II and III, these guidelines were applied to the implantation of the cold probe. The tip of the cold probe was targeted at the vicinity of the interpositus nucleus (see Figure 3). At the end of the surgery, a nylon loop was sutured into, but not through the nictitating membrane (NM) of the right eye. Analgesics were provided 2 hours after surgery and additionally if needed. The animals were given at least one week to recover after surgery before the actual experimental procedures.

Procedure. During the experiments, the loop sutured to the NM was linked by a rigid stainless steel hook to the swivel arm of the minitorque potentiometer

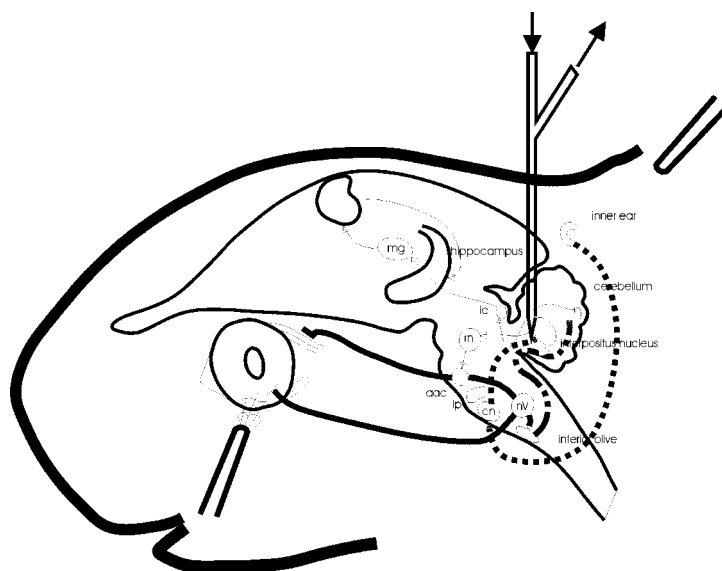


FIGURE 3 Cold probe implantation and functioning.

Delayed Classical Conditioning

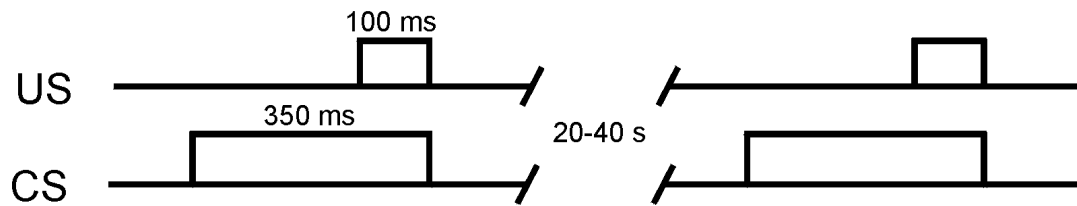


FIGURE 4 Schematic illustration of the paired treatment.

to measure the movement of the NM. The extension of the NM was transduced to voltage by the potentiometer (1 mm equalled 1 V). On the first day, the animals were adapted to the experimental situation by placing them in a Plexiglas restraining box (Gormezano et al, 1962) located in a soundproof conditioning chamber.

The rabbits were subjected to either unpaired or paired treatment. The CS used was an airpuff on the back (Study I) or a tone (Studies II, III and IV). The duration of the CS was always 350 ms. The US was an airpuff towards the cornea. The duration of the airpuff was 100 ms, and when presented in paired trials the CS and the US co-terminated (delayed conditioning paradigm, see Figure 4). In unpaired treatment the stimuli were presented pseudorandomly so that they never occurred together. In paired treatment one session consisted of 60 paired presentations and 10 US-alone and 10 CS-alone test trials.

Data Analysis. In the analyses, *t*-tests for paired samples and analyses of variance (ANOVA) for repeated measures were used. In the ANOVAs, Greenhouse-Geisser-adjusted degrees of freedom for the averaged tests of significance were used whenever the sphericity assumption was violated.

Histology. After the experiments, the animals were anesthetized with i.m. injection of ketamine-xylazine cocktail and then overdosed by an i.v. injection of pentobarbital. The rabbits were then perfused via the ascending aorta with saline followed by 10 % formalin. The brain was removed and fixed in 10% formalin solution for at least one week. Locations of the electrode or cold probe tips were determined according to the stereotaxic brain atlas for rabbits.

Study I: Somatosensory CS and IPN inactivation

Earlier studies suggest that the memory trace for the conditioned eyeblink reflex is formed and maintained in the interpositus nucleus (IPN) in the deep cerebellar nuclei when either an auditory or visual stimulus is used as a conditioned stimulus (CS). It is also presumed that IPN functioning in the formation of the discrete association is not specific to the modality of the CS. Therefore, in this study, the basic procedure for eyeblink conditioning was replicated but a somatosensory CS (an airpuff onto the back) was used. In well-trained animals, the IPN was reversibly inactivated by a cold probe and the existence of the learned responses to the CS was then tested.

The reversible IPN inactivation blocked the memory trace to the somatosensory CS. The finding further supports the view that IPN-mediated memory trace formation is not dependent on the modality of the CS.

Study II: UR amplitude and IPN inactivation

The role of the IPN in the formation of discrete associations is well known. It is also known that UR amplitude is facilitated as a function of the extent of conditioning. The aim of this study was to test whether IPN inactivation has an effect on UR amplitudes after unpaired and paired treatments.

The amplitude of unconditioned responses (URs) in presentations of the unconditioned stimulus (US) alone were measured in six rabbits during explicitly unpaired and classical conditioning treatments. After both phases of the experiment, the interpositus nucleus (IPN) was reversibly inactivated by a cold probe.

URs after unpaired treatment were unaffected by inactivation, but after acquisition of a robust level of conditioned responses URs in US-alone test trials were reduced in amplitude compared with URs immediately before and after inactivation. The results suggest that the IPN has a role in CR-related reflex modification.

Study III: Reflex facilitation in eyeblink conditioning

Reflex facilitation of the UR and its associative and non-associative properties were studied in more detail.

In Experiment 1, by comparing unconditioned responses (URs) in the unpaired and paired groups, three types of reflex facilitation were distinguished. One type was linked to the mere exposure to the unconditioned stimuli (USs) and/or experimental setting (experience-related reflex facilitation). The second type was related to the formation of the memory trace for conditioned eyeblink (CR-related reflex facilitation). The third type was linked to the immediate precedence of the conditioned stimulus (CS) in the paired group (CS-mediated reflex facilitation). In Experiment 2, reversible inactivation of the interpositus nucleus (IPN, the plausible core of the sensorimotor learning system) abolished the CR and reduced the CR-related reflex facilitation, indicating that it depends, at least to some extent, on the plasticity of the IPN. It was concluded that the CS-mediated reflex facilitation could be seen as an index of the diffuse associations taking place in eyeblink conditioning.

Study IV: SCx activity linked to sensorimotor memory trace

Behavioral and neural responses of the somatosensory cortex were recorded in nine rabbits during explicitly unpaired and subsequent paired classical eyeblink conditioning treatments. Furthermore, the activity in the somatosensory cortex in CR-failure trials were compared to those with successful CRs and to US-alone trials.

During the unpaired treatment, neither behavioral responses exceeding the criterion for conditioned response (CR) nor neural responses to the tone were found. During the classical conditioning, both neural responses and behavioral CRs emerged. However, even after obtaining behavioral responses exceeding the CR criterion, such responses occasionally failed to occur. In these trials, neural responses to the tone could not be found either. The results suggest that learning-related plasticity in the somatosensory cortex is linked to sensorimotor learning and thus reflects the widely distributed efferent copy of the discrete, cerebellar memory trace.

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