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CEREBELLUM AND EMOTIONAL BEHAVIOR

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Abstract

Fear conditioning involves learning that a previously neutral stimulus (CS) predicts an aversive unconditioned stimulus (US). Lesions of the cerebellar vermis may affect fear memory without altering baseline motor/autonomic responses to the frightening stimuli. Reversible inactivation of the vermis during the consolidation period impairs retention of fear memory. In patients with medial cerebellar lesions conditioned bradycardia is impaired. In humans, cerebellar areas around the vermis are activated during mental recall of emotional personal episodes, if a loved partner receives a pain stimulus, and during learning of a CS–US association. Moreover, patients with cerebellar stroke may fail to show overt emotional changes. In such patients, however, the activity of several areas, including ventromedial prefrontal cortex, anterior cingulate, pulvinar and insular cortex, is significantly increased relative to healthy subjects when exposed to frightening stimuli. Therefore, other structures may serve to maintain fear response after cerebellar damage. These data indicate that the vermis is involved in the formation of fear memory traces. We suggest that the vermis is not only involved in regulating the autonomic/motor responses, but that it also participates in forming new CS–US associations thus eliciting appropriate responses to new stimuli or situations. In other words, the cerebellum may translate an emotional state elaborated elsewhere into autonomic and motor responses.

Key words

fear conditioning; learning and memory; cerebellar vermis; Purkinje cells; LTP

Abbreviations

CS, conditioned stimulus; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; PC, Purkinje cell; PF, parallel fiber; US, unconditioned stimulus

Emotions have a dominant role in controlling animal and human behavior; hence they are critically important for survival of individuals and of species. Most information on the brain circuitry underlying emotional processes is obtained by studying fear-related processes. Fear reactions represent not a single process, but a spectrum of responses that includes autonomic (heart rate and blood pressure variations, pupillary dilation), endocrine (pituitary-adrenal hormone) and behavioral (increased startle reflex, escape, immobility or freezing) responses. Dangerous environmental stimuli may elicit a fear response even without previous experience, by triggering an innate response that relies on an evolutionary memory. Previous innocuous stimuli may come to elicit a fear response if they are associated with harmful stimuli. During fear learning, the brain associates other stimuli and events that occur in individual experience with those that are innately set to cause emotions.

In a typical experiment, a neutral stimulus, like a sound acts as a conditioned stimulus (CS) and is repeatedly paired with a noxious unconditioned stimulus (US), typically an electric foot shock in laboratory animals, whereas in humans it is a loud noise or a wrist shock. Following pairing, the CS comes to elicit the defensive behavioral responses.

CEREBELLAR VERMIS AND FEAR CONDITIONING IN ANIMAL STUDIES

Early studies suggested a cerebellar involvement in the regulation of autonomic responses in aversive conditioning. Removal of the cerebellum was shown to impair performance of salivary, cardiac, and respiratory conditioning (Berntson and Torello 1982 and Sacchetti et al 2005). These effects on aversive conditioning can be localized to the cerebellar vermis. Dow and Moruzzi (1958) found that stimulation of the vermis, but not of the hemispheres, inhibited vasomotor tone which had been previously increased by peripheral stimulation. They also showed that vermal stimulation inhibited the increases in blood pressure, mydriasis and retraction of the lid as well as the struggling and lashing of the tail in sham rage in the decerebrate cat. Lesion of the vermis, but not of the hemispheres, impairs the acquisition of classically conditioned bradycardia in rabbits (Supple and Kapp, 1993) and rats (Supple et al 1987 and Supple and Leaton 1990). In apparent contradiction to these results, Hitchcock and Davis (1986) reported a robust conditioned fear potentiation of acoustic startle in subjects with complete section of all three cerebellar peduncles. As Leaton (2003) wrote, it would be premature to speculate about the precise role played by the vermis in fear learning.

Several lines of evidence support the view that the cerebellar role in learned fear may be more complex than a simple regulation of motor responses. Supple and Leaton (1990) found that while heart rate conditioned response was impaired by vermal lesion, baseline heart responses to CS and US were not affected. More recently, the capacity to learn and to retain fear conditioned responses has been investigated in hotfoot mutant mice (Sacchetti et al., 2004). These animals are characterized by a primary deficiency of the synapses made by the parallel fibers (PFs) onto the Purkinje cells (PCs) (Yamazaki et al 1992, Morando et al 2001, Yuzaki 2003 and Mandolesi et al 2009). In these mutant mice, although the cerebellar dysfunction does not affect acquisition of the conditioned motor response (Fig. 1A), conditioned response to the CS was significantly reduced 10 min and 24 h after learning trial (Fig. 1B, C). This suggests that the PF–PC synapses are probably involved in consolidation of fear memory.

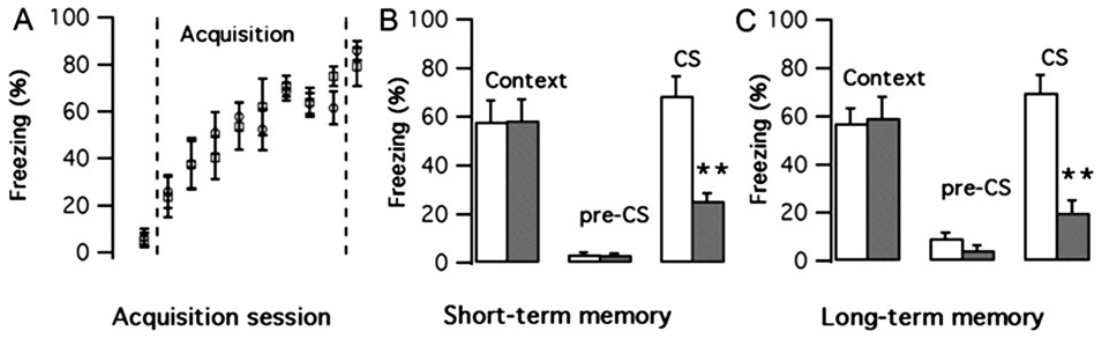

Fig. 1.
Cerebellar dysfunction impairs learned fear. (A) Freezing response, the index of fear behavior, was measured as percentage of immobility (i) 2 min before, (ii) during the presentation of 8 CS–US pairing and (iii) during 1 min immediately after the acquisition in the control (circle) and hotfoot mutant (square) mice. (B) Short-term memory was tested by measuring freezing response to the environment (context) and to CS 10 min after acquisition session in the control (empty columns) and in hotfoot (hatched columns) mice. Freezing in a new environment before CS retention is also shown (pre-CS). (C) Long-term memory 24 h after the acquisition session (from Sacchetti et al., 2004).

Reversible inactivation is a useful technique that allows dissociation of sensory and motor functions from memory. Drugs with reversible effects, like tetrodotoxin, lidocaine or muscimol, can be administered after acquisition and memory retention can be tested several days after its administration, long after the effect of the drugs are over. Several neural structures were tested during fear memory formation by means this post-trial blocking (Sacchetti et al 1999, Sacchetti et al 2003, Sacchetti et al 2005 and McGaugh 2000). In a recent study we found that tetrodotoxin injected into the vermis after CS–US pairing causes amnesic effects (Sacchetti et al., 2002a). Thus the vermis participates in emotional memory independently of its role in sensory or motor processes. Similarly, Yoshida et al. (2004) reported that reversible inactivation in goldfish severely impaired a conditioned cardiac response.

The same technique has been employed to inactivate the vermis after the recall of a fear memory trace (Sacchetti et al., 2007). In fact, fear memories are altered when amnesic agents are applied immediately after memory recall (Nader et al., 2000). The reversible block is made after memory recall, so post-retrieval manipulations can help to locate neural sites involved in the maintenance of long-term memories, independent of their involvement in motor responses or in innate fear behavior. Reversible inactivation of the vermis strongly affects fear memories that had been established several days before cerebellar manipulation (Sacchetti et al., 2007). Thus the vermis is also involved in the long-term maintenance of aversive memories. In the same study, it was found that stronger fear memories obtained by increasing the strength of conditioning are affected by the combined, but not independent, amygdala and cerebellar blockade. These findings indicate that strong aversive memories are resistant to cerebellar blockade. In addition, they suggest that under specific circumstances cerebellum supports the memory processes even in the absence of the amygdala. Strong fear memories represent essential information. Thus, the complementarity between amygdala and vermis might be evolutionarily developed in order to prevent the loss of the most essential traces.

Vermis and amygdala may interact. Previous studies showed that vermal electrical stimulation modulates amygdala activity (Snider and Maiti 1976 and Heath et al 1978). These effects are mediated both by direct or indirect anatomical connections between cerebellum and limbic areas, and also by way of the paleocerebellar projections to ascending catecholamine neurons of the locus

coeruleus, the ventral tegmental area, and periaqueductal gray. In line with these findings, a recent study in human showed that cerebellar lesions are associated with a decrease in the activity of the amygdala (Turner et al., 2007).

HUMAN CEREBELLUM AND FEAR MEMORIES

Neuroimaging reveals a pattern of cerebellar activation in which pain response and learning activate different cerebellar regions (Ploghaus et al 1999 and Ploghaus et al 2000). Painful heat activates the anterior cerebellum around the vermis (see Fig. 2) while a sensory cue that anticipates the painful stimulation leads to activation of posterior cerebellar vermis (Fig. 2A) (Ploghaus et al 1999 and Ploghaus et al 2000). Therefore, nearby but separate regions are engaged during fear experience and associative learning, i.e. some regions of the human cerebellum are activated by associative processes independent of the direct regulation of motor/autonomic processes. A similar conclusion comes from another study in which fear conditioning activated the cerebellum (Fischer et al., 2000).

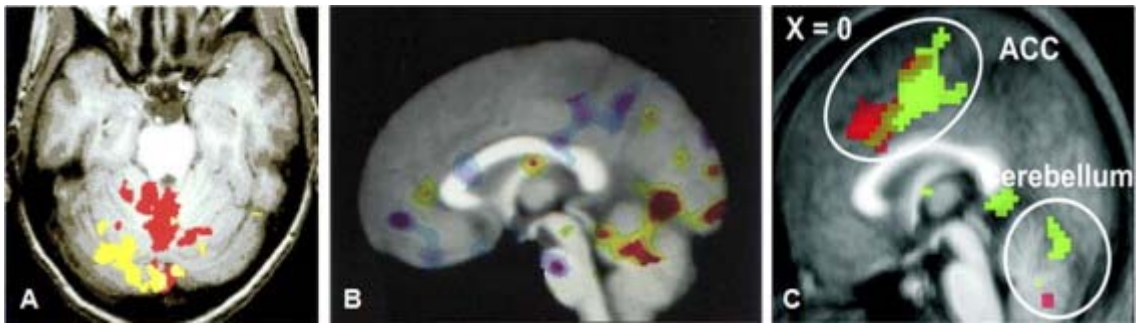

Fig. 2.
Cerebellar activity during human fear processes. (A) Cerebellar activation during pain perception (red) and anticipation of pain (yellow) (from Ploghaus et al. (1999) Science 274:1979–1981. Reprinted with permission from AAAS). (B) The recall of a fear personal event increases activity in the cerebellum, largely in midline structures. Reprinted by permission from Macmillan Publishers, Ltd.: Damasio et al. (2000), Nat Neurosci 3:1049–1056, copyright 2000. (C) Pain-related activation associated with either experiencing pain in oneself condition (green) or observing one's partner feeling pain (red) (from Singer et al., 2004 Science 303:1157–1162. Reprinted with permission from AAAS).

Damasio et al. (2000) reported a marked activation of midline cerebellum during mental recall of emotional personal episodes (Fig. 2B). The authors used functional imaging to compare brain regions activated by the recall of a neutral and an emotionally charged personal episode. They concluded that “although the cerebellum was not included in the hypothesis, we believe that the evolutionarily older components of the cerebellum probably are involved in the coordination of emotional responses and in the learned adjustment of those responses in a social setting.” More recently, Singer et al. (2004) used functional imaging to assess brain activity while healthy subjects experienced a painful stimulus and when they observed their loved partner receiving a similar pain stimulus. Among other structures, anterior cerebellum around the vermis was activated in subjects receiving the painful stimulation while posterior cerebellar vermis was activated in the same subjects when observing pain of others (Fig. 2C). In both conditions there was a concomitant activation of the lateral cerebellum. These results suggest that cerebellum is also involved in the empathic experience related to pain. According to the authors, “such decoupled representations—which are independent of the sensory inputs of the outside world—have been postulated to be

necessary for our ability to mentalize, that is, to understand the thoughts, beliefs, and intentions of others" (Singer et al., 2004).

Imaging studies are correlational in nature, so they cannot establish whether a structure is necessary for emotional learning. The role of the cerebellum is better assessed by study of the effects of cerebellar damage. Conditioned bradycardia caused by pairing a tone with a painful stimulation is impaired in patients with medial cerebellar lesions (Maschke et al., 2002). Cerebellar stroke does not affect basal autonomic/motor responses to CS and US, in agreement with a similar result obtained in animals with vermal lesions (Supple and Leaton, 1990). Similarly, cerebellar stroke does not significantly affect baseline emotional responses in humans (Turner et al., 2007). In this study, the subjective response to emotional images as well as changes in heart rate before and after viewing a set of pictures was studied. Patients with cerebellar stroke did not differ from healthy subjects either in the subjective evaluation and the behavioral responses to these frightening stimuli. The studies by Maschke et al. (2002) and by Turner et al. (2007) suggest that the vermis in necessary to learn a new association between sensory stimuli and aversive ones, while it is not required for the regulation of baseline fear responses and for the cognitive evaluation of a dangerous situation. In line with this observation, animals with vermal lesion (Supple et al 1987 and Supple et al 1988) and the hotfoot mutant mice (Sacchetti et al., 2004) remember the environment (context) in which a painful stimulation is administered. Context representation is a form of hippocampal-dependent learning that resembles the human capacity to learn the declarative aspects of an emotional situation. Patients with selective bilateral damage to the amygdala did not acquire conditioned autonomic responses to visual or auditory stimuli, but are able to learn the declarative facts about which visual or auditory stimuli were paired with the US. By contrast, a patient with selective bilateral damage to the hippocampus failed to acquire the facts, but did acquire the conditioning (Bechara et al., 1995) On the basis of the previously reported complementarity between the vermis and the amygdala (Sacchetti et al., 2007) and on the anatomical connections between these two sites (see below), cerebellar vermis may interact with the amygdala in producing the unconscious, procedural responses related to a fear event.

To our knowledge, the report of Maschke et al. (2002) is the only study addressing the capacity to learn new fear-conditioned responses in patients after a cerebellar stroke. Further analysis would be necessary to clarify the role of the cerebellum in learned fear. Although the patients studied by Turner et al. (2007) did not show differences in emotion from controls, they did show less activity in dorsolateral prefrontal cortex, cingulate cortex, amygdala and thalamus, all structures that are thought to play a fundamental role in emotional behavior. In the same patients, frightening stimuli led to a significant increased activity of ventral medial prefrontal cortex, anterior cingulate, pulvinar and insular cortex with respect to that of healthy subjects. Therefore, alternative neural circuitry may become responsible for maintaining the evolutionarily critical fear response after cerebellar damage (Turner et al., 2007).

Under physiological conditions the vermis is involved in the formation of fear memory traces. We suggest that the cerebellar vermis not only regulates the autonomic/motor responses, but also participates in forming new CS–US association and in learning to respond appropriately to new stimuli or situations. The cerebellum may not participate directly in the elaboration of emotional states, like fear or anger. In fact, to our knowledge, no data indicate that patients with cerebellar lesions do not feel fear or anger. Moreover, the cerebellum has often been found to be involved not

only in aversive fear-related processes, but even in pleasant experience (Damasio et al 2000 and Turner et al 2007).

EMOTIONAL LEARNING AND EYE BLINKCONDITIONING

The cerebellum plays a crucial role in eye blink conditioning. The crucial sites in the cerebellum for such learning are the lobule HVI (Yeo et al 1985a and Yeo et al 1985b) and the interpositus nucleus (see for a review, Thompson and Steinmetz, 2009). Although most eye blink conditioning studies focus exclusively on the motor output of interest, subjects also learn about emotional aspects associated with the task (Lavond et al 1993 and Lee and Kim 2004). Fear responses (e.g. alterations in heart rate, blood pressure, papillary dilation) may be observed after only a few CS–US pairings, long before the conditioned eye blink appears (Lee and Kim, 2004). The developments of non-specific emotional and specific motor responses are referred to as the first phase and the second phase, respectively, of two-process models of conditioning (Rescorla and Solomon 1967 and Lennartz and Weinberger 1992). Lesion of the amygdala impairs the emotional responses related to eye blink conditioning (Lee and Kim, 2004), while lesion of the interpositus nucleus hampers the conditioned eye blink responses (McCormick and Thompson 1984 and Lee and Kim 2004) but did not affect the emotional responses (Lee and Kim, 2004).

Vermal lesions do not interfere with the conditioned eyelid response (McCormick and Thompson, 1984). However, more recent studies reported a significant, bilateral activation of both extracellular signal-regulated protein kinases and p38 mitogen-activated protein kinase (MAPK) in the anterior cerebellar vermis following eye blink conditioning (Zhen et al., 2001). In addition, a selective inhibitor of p38 MAPK produced a significant retardation of learning and blocked the learning-related activation of p38 MAPK in the anterior vermis (Zhen et al., 2001). Indeed, human eye-blink conditioning was found to produce a learning-related activation of the cerebellum, with the correlation between metabolic activation and learning being the highest for the anterior vermis (Logan and Grafton, 1995). Lobule HVI and the interpositus nucleus may be important for learning the conditioned motor responses (i.e. eye blink), while the vermis participates, together with the amygdala, to the regulation of the emotional conditioned responses that occur also during eye blink conditioning.

NEURAL BASIS OF THE CEREBELLAR INVOLVEMENT IN LEARNED FEAR

The involvement of the cerebellum in learned fear raises the question of whether this structure is also a site for plasticity related to the formation of a fear memory trace. Supple et al. (1993) showed that an acoustic CS that had been previously paired with an electric shock (US) elicited an increased firing of the PCs in vermal lobules III–V.

We have studied the cerebellar basis of plasticity related to a fear memory trace (Sacchetti et al 2004, Zhu et al 2006, Zhu et al 2007 and Scelfo et al 2008). Excitatory postsynaptic currents evoked in PCs following the activation of PF or climbing fibers were studied 24 h after fear learning in conditioned subjects and two control groups; unpaired animals, which received the CS and US in a temporally uncorrelated manner, and naïve animals, which were left in their home cage. In conditioned animals, the postsynaptic current produced by PFs, but not by climbing fibers, was

larger relative to the other two groups (Fig. 3A) (Sacchetti et al., 2004). Thus, long-term potentiation (LTP) is present in the vermis after fear learning which is strictly related to associative processes, since it is not present following unpaired CS and US presentation. This conclusion is in line with the behavioral studies showing the requirement of the vermis for CS–US association, but not for baseline responses to CS and US (Supple et al 1993, Ploghaus et al 1999, Ploghaus et al 2000 and Maschke et al 2002). Synaptic changes were localized to vermal lobules V and VI, an area that receives convergence of acoustic and nociceptive stimuli (Snider and Stowell 1944 and Saab and Willis 2003) and it is related to the expression of emotional behavior (Supple et al 1993 and Sebastiani et al 1992). Learning-induced synaptic plasticity has been described in amygdala (Rogan et al 1997 and McKernan and Shinnick-Gallagher 1997) and hippocampus (Sacchetti et al 2001, Sacchetti et al 2002b and Whitlock et al 2006). Thus, fear learning may be associated with similar neural mechanisms in several different brain structures.

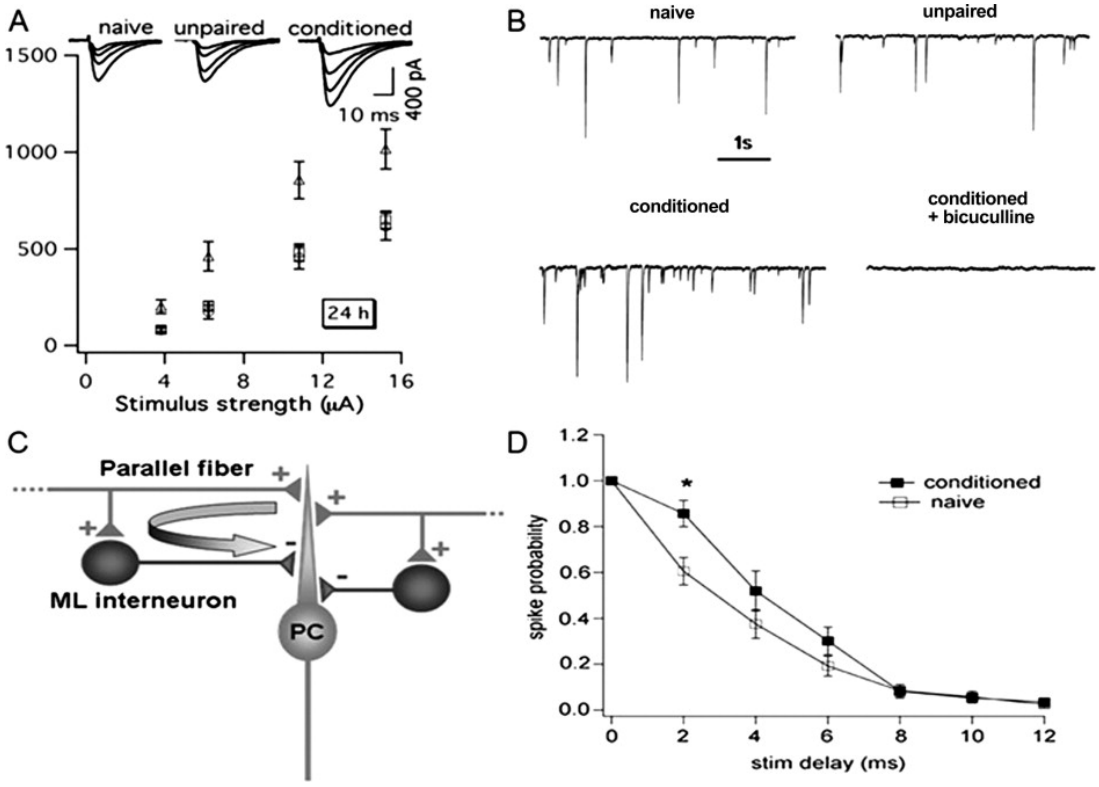

Fig. 3.
Cerebellar plasticity related to fear memories. (A) In the vermal lobules V–VI, 24 h after fear conditioning there is an increase of excitatory PF–PC transmission in conditioned subjects (triangle) with respect to naive (circle) and unpaired (square) groups (from Sacchetti et al., 2004). (B) Learned fear increases GABAergic synaptic activity onto the PC in respect to unpaired and naive subjects. The inhibitory activity was totally abolished by the GABA antagonist bicuculline. (C) Schematic of the cerebellar circuit of feed-forward inhibition. Activation of a beam of PFs is rapidly followed by synaptic inhibition. A PC may be both directly excited and then inhibited with disynaptic delay via molecular layer (ML) interneurons activated by the same set of active PFs. (D) The significance of the simultaneous potentiation of both the inhibitory and excitatory synapses on PCs was assessed through the probability distribution of spike generation as a function of PFs stimulation delay. The filled squares represent the spike probability of conditioned animals while empty squares refer to the same probability for naïve animals (B, D: from Scelfo et al., 2008. Copyright 2008, National Academy of Sciences, USA).

In a subsequent study, excitability properties of the PCs were measured: input resistance, inward rectification, maximal firing frequency, the first inter-spike interval, post-burst after-hyperpolarization and action potential threshold and amplitude. None of the evaluated parameters was significantly different between conditioned and control subjects (Zhu et al., 2006), indicating that fear learning does not affect the intrinsic membrane properties involved in PC firing. Therefore, at the level of the PC, the plastic change associated with fear conditioning is specifically restricted to synaptic efficacy.

Learning-induced PF–PC LTP shares common features with the LTP which can be electrically induced at these synapses by repetitive PFs stimulation (Lev-Ram et al., 2002). In fact, the electrically-induced LTP is occluded in cerebellar slices from conditioned animals (Zhu et al., 2007). Given that LTP is produced in vitro by PFs repetitive stimulation, it is possible that learning-induced LTP is the result of conjunctive activation of two separate PFs channels conveying CS and US stimuli, consistent with the fact that PFs carry acoustic inputs, as well as nociceptive information (Saab and Willis, 2003).

Cerebellar PCs exhibit sustained inhibitory inputs due to the massive GABAergic innervation from basket and stellate cells in the molecular layer and from neighboring PCs via their collaterals (Eccles et al., 1967). Very recently we investigated the possibility that also inhibitory synapses in the cerebellar cortex could be modified in relation to fear learning. We found that the frequency, but not the amplitude, of spontaneous and miniature GABAergic events onto the PCs was significantly greater 24 h after conditioning (Fig. 3B) (Scelfo et al., 2008), implying a form of inhibitory LTP mediated by an increase in the presynaptic activity of the inhibitory synapses onto the PC.

The fact that fear learning is accompanied by an LTP of both the excitatory and inhibitory inputs to PCs raised the question of the possible significance of this concomitant potentiation. In several brain structures it has been shown that precisely timed signal processing depends on direct monosynaptic excitation and underlying disynaptic inhibition (feed-forward inhibition) (Pouille and Scanziani 2001 and Mittmann et al 2005). All theories of timing concerning the cerebellum require that the output of the cerebellar cortex, encoded in the axons of PCs, be precisely tuned in response to sensory stimulation. This is achieved through effective integration of correlated activity onto the PCs which must be able to act as coincidence detector. The precision of time spiking in PCs is strongly regulated by GABAergic synapses through feed-forward inhibition and because effective summation for spike generation of multiple asynchronous PFs inputs can occur within a time window of only a few milliseconds (Mittmann et al., 2005). Therefore, we explored the possibility that fear-related long-term plastic changes may affect this time window and thereby influence the output of the whole neuronal network. We found that the probability for excitatory inputs to summate and reach the threshold for spike generation in the PC is changed following emotional learning in such a way to facilitate the summation of temporarily close related events. On the other hand, the presence of GABAergic potentiation maintains the temporal accuracy (Fig. 3C) (Scelfo et al., 2008). These results show that excitatory LTP ensures a more effective detection while inhibitory potentiation serves to maintain the coincidence detection unchanged ensuring that the temporal fidelity of the network is maintained.

The presence in the vermis of synaptic changes related to learned fear as well as the behavioral data showing the involvement of this site in the formation of a fear memory trace raises the question to which target site(s) the vermis sends its information. In the 1938 and 1940, Dow and Moruzzi (1958)

found that stimulation of the vermis, but not of the hemispheres, inhibited vasomotor tone which had been previously increased by peripheral stimulation. The late respiratory as well as the autonomic components of these reflexes, which are partly due to adrenaline secretion, were also inhibited. They proposed that "these autonomic cerebellar effects may be part of a more complex behavioral reaction." Subsequent studies showed that the vermis is connected to the spinal cord, brainstem and the hypothalamus by way of the fastigial nucleus, thus it can regulate the cardiovascular tone, respiration and gastrointestinal functions, as well as other autonomic processes (Berntson and Torello, 1982). The vermis is also connected with brain sites that are associated with affective and learning processes. Snider showed that vermian and fastigial stimulation in the cat induces electrophysiological responses in the basolateral amygdala, a crucial site for fear behavior, and in septum and hippocampus (Snider and Maiti, 1976). These results have been confirmed in rats (Heath et al., 1978) and monkeys (Heath and Harper, 1974). In addition, the vermis by way of fastigial nucleus projects (i) to periaqueductal gray area, a region that has anatomical bidirectional connections with amygdala and septum and (ii) to the locus coeruleus and the ventral tegmental area, the centers of catecholaminergic systems (Berntson and Torello, 1982). Therefore, given its anatomical and functional connections with several structures involved either in somatosensory perception (as the brainstem, thalamus), in emotional state (amygdala, septum and locus coeruleus) and in the control of motor responses, the vermis may represent an interface between the sensory stimuli, the emotional state of the subject and the motor responses. This raises the issue of whether the cerebellum participates in the subjective feeling of emotions or whether it regulates only its expression. Patients with cerebellar lesions appear to experience fear or anger normally. Thus, such emotional processing may be elaborated elsewhere without requiring cerebellar activity. We propose that the vermis learns and retains CS–US association in order to set the more appropriate responses to a new stimuli and/or situations.

Acknowledgments

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